Haemodynamics

Modern applications of basic physiological concepts

Wijnberge, M.

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HAEMODYNAMICS

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Marije Wijnberge

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Haemodynamics
Modern applications of basic physiological concepts

ACADEMISCH PROEFSCHRIFT

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ten overstaan van een door het College voor Promoties ingestelde commissie,
in het openbaar te verdedigen in de Agnietenkapel
op woensdag 18 januari 2023, te 13.00 uur

door Marije Wijnberge
geboren te Landsmeer

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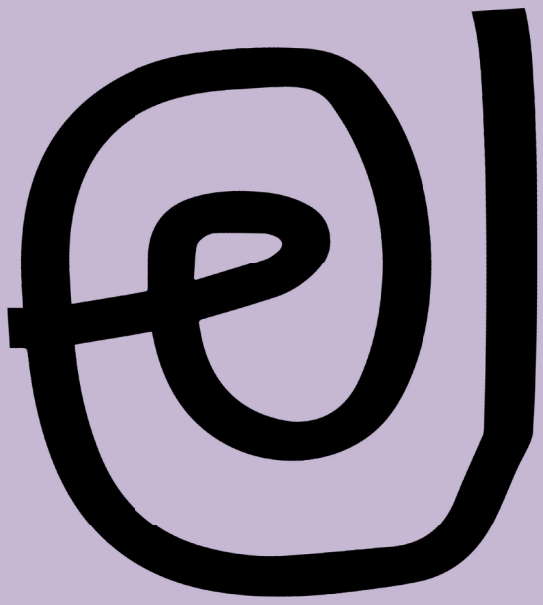
‘and those who were seen dancing were thought to
be insane by those who could not hear the music’

CONTENTS



1

General introduction and thesis outline

GENERAL INTRODUCTION

Haemodynamics is defined as the study of the forces involved in blood circulation. The goal of blood circulation is to carry oxygen and nutrients close to the cells and to remove waste products. Effective haemodynamics require sufficient myocardial contractility, and adequate filling and tonus of the circulatory system. Perioperatively, in the operating theatre, at the postoperative anaesthesia care unit and at the Intensive Care Unit (ICU), patients often need support of their circulatory system. Maintaining stable haemodynamics is challenging and at present our treatments are mostly reactive. Furthermore, selecting the correct treatment modality can be difficult as a proper pathophysiological diagnosis of the cause of the haemodynamic instability might be inapparent.

In Part I of this thesis we primarily focus on patients admitted to the intensive care unit (ICU) and aim to implement a physiological theory on venous return in clinical practice. In Part II we focus on prediction and prevention of haemodynamic instability (defined as perioperative hypotension) with the use of machine learning.

Part I – Mean systemic filling pressure

A decade ago, it became possible to derive mean systemic filling pressure (MSFP) at the bedside. MSFP has the potential to help guide haemodynamic care but the estimation is not yet implemented in common clinical practice.

MSFP or mean circulatory filling pressure (MCFP) is considered the combined upstream pressure that drives blood into the right atrium. In animals, it was demonstrated that when right atrial pressure (RAP) is gradually increased, venous return (VR) is reduced until blood flow ultimately ceases, Figure 1.[1, 2] MCFP is defined as the equilibrated vascular pressure of all compartments at zero blood flow.[3, 4] MCFP was translated from the laboratory to clinical care by obtaining VR curves based on heart-lung interaction with inspiratory holds.[5-8] The stop-flow MCFP and inspiratory hold MSFP showed to be linear and correlation between the two methods was high.[7] Although MCFP and MSFP are used interchangeably, MSFP is most often used when it refers to a technique without the necessity for a stop of the blood flow.[9]

From MSFP derived parameters can be calculated that provide insight into the haemodynamic status of an individual patient. These parameters include the driving pressure for venous return (VRdp), compliance (Csys) and stressed volume (Vs).[10-14] Vs is thought to be the effective circulating volume, and previous studies have shown it to be around 25-30% of total blood volume.[10-14] As accurate and feasible clinical assessment of the intravascular volume status of ICU patients is a challenge, MSFP and its derived parameters might be of guidance.[15, 16] Previous studies have shown MSFP to be a marker of fluid loading responsiveness and to aid in the understanding of the working

mechanisms of vasoactive drugs[17-21] and into the effects of hyperoxia.[22, 23] In this thesis we describe the current available methods to estimate MSFP in clinical care, assess the normal range of MSFP for different patient categories and ultimately study the feasibility of implementing MSFP in clinical care.

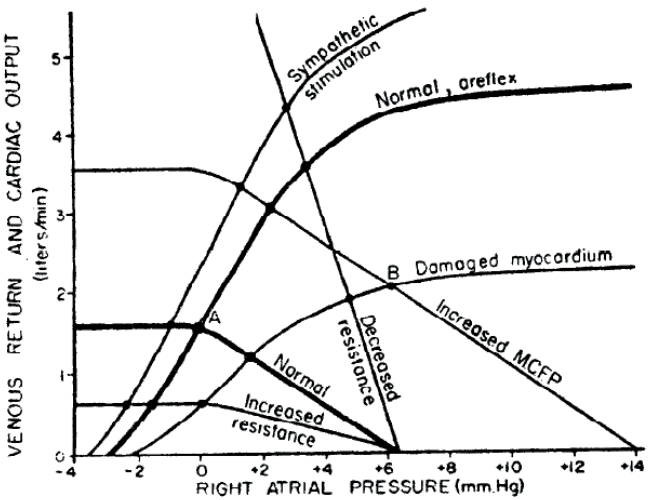


Figure 1. Equilibration of various venous return curves with different cardiac response curves.[1] Reproduced with permission from the American Physiological Society.

Part II – Hypotension

In recent decades, improvements in anaesthesia have markedly reduced anaesthesia-related intraoperative mortality.[24] In striking contrast, 30 day postoperative mortality is relatively high.[25] Recent attention has been drawn to intraoperative hypotension (IOH) as a potential risk factor for postoperative morbidity and mortality.[26-34] Blood pressure at the level of the macrocirculation might be needed to match the metabolic demands at the level of the microcirculation. Hypotension can be a sign of hypo-perfusion of vital organs and can demonstrate a mismatch of oxygen delivery and demand.[35-37]

Anaesthetised patients are at risk for hypotension as most anaesthetic agents reduce sympathetic activity and suppress cardiovascular regulatory mechanisms.[38-43] Older patients and patients undergoing major surgery are at particular risk of IOH.[44,45] As the surgical population is predicted to keep ageing and the percentage of major surgery is only increasing, delving into this potentially modifiable risk factor is of interest.[46]

Machine learning

Adapted from Pinsky's view on the chaos theory; chaos (in this case hypotension) is not random but rather a highly structured behaviour that is dependent on earlier states.[47]

Hypotension is most often preceded by cardiovascular compensation mechanisms that can be detected in the arterial blood pressure (ABP) waveform.[36] The ABP waveform is a composite, consisting of both forward and reflected waves.[48, 49] Subtle changes in the waveform can be recognised timely with the use of machine learning.[50, 51]

Pressure and flow

To diagnose the underlying cause of the impending hypotension additional information is needed. From the arterial waveform, haemodynamic variables can be extracted that provide information on contractility, flow and resistance.[52-54] In this thesis, cardiac output, stroke volume, stroke volume variation, dynamic arterial elastance (Eadyn) and delta pressure over delta time of the left ventricle (dP/dt) were utilized. Blood pressure is measured during all surgeries; blood flow, on the other hand, is very rarely measured.[55] Optimally, both are used to provide insight into the haemodynamic status of a patient and to guide treatment.[56] [37]

Invasive versus non-invasive blood pressure monitoring

The gold standard to measure blood pressure is invasive, with a cannula in the radial or femoral artery.[57, 58] In current clinical practice, invasive ABP monitoring is mainly restricted to high-risk surgeries and high-risk patients.[59-62] In the vast majority of surgical patients BP is monitored intermittently using an oscillometric method with a non-invasive cuff around the upper arm (NIBP-arm).[63] As IOH occurs frequently, this could lead to a delay in recognition or even in missed hypotensive events.[64-66] In this thesis we will study a non-invasive yet continuous method to monitor and predict hypotension.[67-70]

AIMS OF THIS THESIS:

In this thesis, we focus on perioperative haemodynamics. The key aims of this thesis are:

1. Describe the current available methods to estimate MSFP in clinical care
2. Assess the normal range of MCFP for ICU patients and study the influence of patient characteristics on MCFP
3. Study the feasibility of implementing MSFP in clinical care
4. Study the association of intraoperative hypotension and postoperative morbidity and mortality
5. Predict and reduce intraoperative hypotension using invasively measured arterial waveforms
6. Assess a non-invasive continuous alternative for hypotension detection and prediction

OUTLINE OF THIS THESIS:

Part I – Mean systemic filling pressure

Chapter 2 summarises the current methods to estimate MSFP in ICU patients.

Chapter 3 describes the range of MCFP in ICU patients and studies the influence of patient characteristics on MCFP. We hypothesized fluid balance, the use of vasoactive medication, being on mechanical ventilation and the level of positive end-expiratory pressure that would be positively associated with MCFP.

Chapter 4 represents a study assessing the feasibility to implement MSFP derived with inspiratory holds ($MSFP_{hold}$) in clinical practice. We measured $MSFP_{hold}$ and derived parameters before and after a fluid bolus and exploratory assessed a potential difference in response between colloids and crystalloids.

Part II – Hypotension

In **Chapter 5** we perform a systematic review with meta-analysis to assess the association of intraoperative hypotension with postoperative morbidity and mortality.

Chapter 6 contains the study protocol for our randomised clinical trial presented in Chapter 7. In order to go from prediction to prevention, the prediction of hypotension needs to be followed by a timely treatment. As study team, we created a flow diagram to diagnose the underlying cause of the impending hypotension. Dynamic haemodynamic variables such as cardiac output, stroke volume, stroke volume variation (SVV), Eadyn and dP/dt were used.

In **Chapter 7** we assess whether use of a machine-learning derived early warning system to predict hypotension results in a reduction of the time weighted average in hypotension. In order to reduce hypotension, the treating anaesthetists need to change treatment behaviour from reactive to proactive.

Chapter 8 reports on the immediate postoperative effects of reducing intraoperative hypotension. We aim to answer the following question: does reduction of intraoperative hypotension leads to a reduction in postoperative hypotension? Postoperative hypotension is defined as hypotension measured in the post-anaesthesia care unit (PACU).

In **Chapter 9** we shift from invasive to non-invasive blood pressure monitoring. In this cohort study, we validate whether the machine learning derived early warning system to predict hypotension is also suitable for non-invasive continuous arterial waveforms.

Chapter 10 contains a sub-study of the cohort study presented in Chapter 9; in this sub-study, we assess whether intermittent blood pressure monitoring results in missed or delayed recognition of hypotensive events.

In **Chapter 11** we describe our experience working with one of the first machine learning algorithms of its kind for clinical use in the operating room.

The results of this thesis are summarised in **Chapter 12.**
Chapter 13 bevat een Nederlandse samenvatting van dit proefschrift.
A discussion of the results and future perspectives can be found in **Chapter 14**.

REFERENCES

1. Guyton AC. Determination of cardiac output by equating venous return curves with cardiac response curves. *Physiol Rev*. Jan 1955;35(1):123-9. doi:10.1152/physrev.1955.35.1.123
2. Guyton AC, Lindsey AW, Abernathy B, Richardson T. Venous return at various right atrial pressures and the normal venous return curve. *Am J Physiol*. Jun 1957;189(3):609-15. doi:10.1152/ajplegacy.1957.189.3.609
3. Bayliss WM, Starling EH. Observations on Venous Pressures and their Relationship to Capillary Pressures. *J Physiol*. Apr 17 1894;16(3-4):159-318.7. doi:10.1113/jphysiol.1894.sp000498
4. Patterson SW, Starling EH. On the mechanical factors which determine the output of the ventricles. *J Physiol*. Sep 8 1914;48(5):357-79. doi:10.1113/jphysiol.1914.sp001669
5. Den Hartog EA, Versprille A, Jansen JR. Systemic filling pressure in intact circulation determined on basis of aortic vs. central venous pressure relationships. *Am J Physiol*. Dec 1994;267(6 Pt 2):H2255-8. doi:10.1152/ajpheart.1994.267.6.H2255
6. Versprille A, Jansen JR. Mean systemic filling pressure as a characteristic pressure for venous return. *Pflugers Arch*. Oct 1985;405(3):226-33. doi:10.1007/bf00582565
7. Pinsky MR. Instantaneous venous return curves in an intact canine preparation. *J Appl Physiol Respir Environ Exerc Physiol*. Mar 1984;56(3):765-71. doi:10.1152/jappl.1984.56.3.765
8. Maas JJ, Geerts BF, Jansen JR. Evaluation of mean systemic filling pressure from pulse contour cardiac output and central venous pressure. *Journal of clinical monitoring and computing*. Jun 2011;25(3):193-201. doi:10.1007/s10877-011-9294-0
9. Guyton AC, Polizo D, Armstrong GG. Mean circulatory filling pressure measured immediately after cessation of heart pumping. *Am J Physiol*. Nov 1954;179(2):261-7. doi:10.1152/ajplegacy.1954.179.2.261
10. Maas JJ, Pinsky MR, Aarts LP, Jansen JR. Bedside assessment of total systemic vascular compliance, stressed volume, and cardiac function curves in intensive care unit patients. *Anesthesia and analgesia*. Oct 2012;115(4):880-7. doi:10.1213/ANE.0b013e31825fb01d
11. Peters J, Mack GW, Lister G. The importance of the peripheral circulation in critical illnesses. *Intensive Care Med*. Sep 2001;27(9):1446-58. doi:10.1007/s001340101034
12. Gelman S. Venous function and central venous pressure: a physiologic story. *Anesthesiology*. Apr 2008;108(4):735-48. doi:10.1097/ALN.0b013e3181672607
13. Parkin WG. Volume state control - a new approach. *Crit Care Resusc*. Sep 1999;1(3):311-21.
14. Magder S, De Varennes B. Clinical death and the measurement of stressed vascular volume. *Crit Care Med*. Jun 1998;26(6):1061-4. doi:10.1097/00003246-199806000-00028
15. Vincent JL, Pinsky MR. We should avoid the term “fluid overload”. *Critical care (London, England)*. Sep 11 2018;22(1):214. doi:10.1186/s13054-018-2141-7
16. Arshed S, Pinsky MR. Applied Physiology of Fluid Resuscitation in Critical Illness. *Crit Care Clin*. Apr 2018;34(2):267-277. doi:10.1016/j.ccc.2017.12.010
17. Maas JJ, Pinsky MR, de Wilde RB, de Jonge E, Jansen JR. Cardiac output response to norepinephrine in postoperative cardiac surgery patients: interpretation with venous return and cardiac function curves. *Crit Care Med*. Jan 2013;41(1):143-50. doi:10.1097/CCM.0b013e318265ea64
18. Geerts BF, Maas JJ, Aarts LP, Pinsky MR, Jansen JR. Partitioning the resistances along the vascular tree: effects of dobutamine and hypovolemia in piglets with an intact circulation. *Journal of clinical monitoring and computing*. Oct 2010;24(5):377-84. doi:10.1007/s10877-010-9258-9

19. Geerts BF, Maas J, de Wilde RB, Aarts LP, Jansen JR. Arm occlusion pressure is a useful predictor of an increase in cardiac output after fluid loading following cardiac surgery. *European journal of anaesthesiology*. Nov 2011;28(11):802-6. doi:10.1097/EJA.0b013e32834a67d2
20. Maas JJ, Geerts BF, van den Berg PC, Pinsky MR, Jansen JR. Assessment of venous return curve and mean systemic filling pressure in postoperative cardiac surgery patients. *Crit Care Med*. Mar 2009;37(3):912-8. doi:10.1097/CCM.0b013e3181961481
21. Cecconi M, Aya HD, Geisen M, et al. Changes in the mean systemic filling pressure during a fluid challenge in postsurgical intensive care patients. *Intensive Care Med*. Jul 2013;39(7):1299-305. doi:10.1007/s00134-013-2928-6
22. Helmerhorst HJF, de Wilde RBP, Lee DH, et al. Hemodynamic effects of short-term hyperoxia after coronary artery bypass grafting. *Ann Intensive Care*. Dec 2017;7(1):20. doi:10.1186/s13613-017-0246-9
23. de Wit F, van Vliet AL, de Wilde RB, et al. The effect of propofol on haemodynamics: cardiac output, venous return, mean systemic filling pressure, and vascular resistances. *British journal of anaesthesia*. Jun 2016;116(6):784-9. doi:10.1093/bja/aew126
24. Bartels K, Karhausen J, Clambey ET, Grenz A, Eltzschig HK. Perioperative organ injury. *Anesthesiology*. Dec 2013;119(6):1474-89. doi:10.1097/aln.0000000000000022
25. Noordzij PG, Poldermans D, Schouten O, Bax JJ, Schreiner FA, Boersma E. Postoperative mortality in The Netherlands: a population-based analysis of surgery-specific risk in adults. *Anesthesiology*. May 2010;112(5):1105-15. doi:10.1097/ALN.0b013e3181d5f95c
26. Sessler DI, Khanna AK. Perioperative myocardial injury and the contribution of hypotension. *Intensive Care Med*. Jun 2018;44(6):811-822. doi:10.1007/s00134-018-5224-7
27. van Waes JA, van Klei WA, Wijeysundera DN, van Wolfswinkel L, Lindsay TF, Beattie WS. Association between Intraoperative Hypotension and Myocardial Injury after Vascular Surgery. *Anesthesiology*. 2015-01-01 2015;124(1):35-44.
28. Xu L, Yu C, Jiang J, et al. Major adverse cardiac events in elderly patients with coronary artery disease undergoing noncardiac surgery: A multicenter prospective study in China. *Archives of Gerontology and Geriatrics*. 2015-01-01 2015;61(3):503-509.
29. Sun LY, Wijeysundera DN, Tait GA, Beattie WS. Association of intraoperative hypotension with acute kidney injury after elective noncardiac surgery. *Anesthesiology*. 2015-01-01 2015;123(3):515-523.
30. Hallqvist L, Granath F, Huldt E, Bell M. Intraoperative hypotension is associated with acute kidney injury in noncardiac surgery: An observational study. *European journal of anaesthesiology*. Apr 2018;35(4):273-279. doi:10.1097/eja.0000000000000735
31. Monk TG, Bronsert MR, Henderson WG, et al. Association between Intraoperative Hypotension and Hypertension and 30-day Postoperative Mortality in Noncardiac Surgery. *Anesthesiology*. Aug 2015;123(2):307-19. doi:10.1097/ALN.0000000000000756
32. Bijker JB, van Klei WA, Vergouwe Y, et al. Intraoperative hypotension and 1-year mortality after noncardiac surgery. *Anesthesiology*. 2009-01-01 2009;111(6):1217-1226.
33. Gregory A, Stapelfeldt WH, Khanna AK, et al. Intraoperative Hypotension Is Associated With Adverse Clinical Outcomes After Noncardiac Surgery. *Anesthesia and analgesia*. Jun 1 2021;132(6):1654-1665. doi:10.1213/ane.0000000000005250
34. Futier E, Lefrant JY, Guinot PG, et al. Effect of Individualized vs Standard Blood Pressure Management Strategies on Postoperative Organ Dysfunction Among High-Risk Patients Undergoing Major Surgery: A Randomized Clinical Trial. *JAMA*. Oct 10 2017;318(14):1346-1357. doi:10.1001/jama.2017.14172
35. Harten J KJ. Perioperative optimisation. *Scot Med J* 2004;49(1):6-9.

36. Pinsky MR. Functional hemodynamic monitoring. *Crit Care Clin*. Jan 2015;31(1):89-111. doi:10.1016/j.ccc.2014.08.005
37. Pinsky MR. Both Perfusion Pressure and Flow Are Essential for Adequate Resuscitation. *Sepsis*. 2001/05/01 2001;4(2):143-146. doi:10.1023/A:1011406921372
38. Aditianingsih D, Sukmono B, Agung TA, Kartolo WY, Adiwongso ES, Mochtar CA. Comparison of the Effects of Target-Controlled Infusion of Propofol and Sevoflurane as Maintenance of Anesthesia on Hemodynamic Profile in Kidney Transplantation. *Anesthesiol Res Pract*. 2019;2019:5629371. doi:10.1155/2019/5629371
39. Tanaka M, Nishikawa T. Arterial baroreflex function in humans anaesthetized with sevoflurane. *British journal of anaesthesia*. Mar 1999;82(3):350-4. doi:10.1093/bja/82.3.350
40. Ogawa Y, Iwasaki K, Shibata S, Kato J, Ogawa S, Oi Y. Different effects on circulatory control during volatile induction and maintenance of anesthesia and total intravenous anesthesia: autonomic nervous activity and arterial cardiac baroreflex function evaluated by blood pressure and heart rate variability analysis. *J Clin Anesth*. Mar 2006;18(2):87-95. doi:10.1016/j.jclinane.2005.06.004
41. Ebert TJ, Muzi M, Lopatka CW. Neurocirculatory responses to sevoflurane in humans. A comparison to desflurane. *Anesthesiology*. Jul 1995;83(1):88-95. doi:10.1097/00000542-199507000-00011
42. Bristow JD, Prys-Roberts C, Fisher A, Pickering TG, Sleight P. Effects of anesthesia on baroreflex control of heart rate in man. *Anesthesiology*. Nov 1969;31(5):422-8. doi:10.1097/00000542-196911000-00009
43. Carter JA, Clarke TN, Prys-Roberts C, Spelina KR. Restoration of baroreflex control of heart rate during recovery from anaesthesia. *British journal of anaesthesia*. Apr 1986;58(4):415-21. doi:10.1093/bja/58.4.415
44. Tritapepe L. Hypotension during surgery for high risk patients: Cause or consequence of pathology? *Minerva Anestesiologica*. 2013-01-01 2013;79(9):978-980.
45. Cheung CC, Martyn A, Campbell N, et al. Predictors of intraoperative hypotension and bradycardia. *The American journal of medicine*. May 2015;128(5):532-8. doi:10.1016/j.amjmed.2014.11.030
46. Fowler AJ, Abbott TEF, Prowle J, Pearse RM. Age of patients undergoing surgery. *Br J Surg*. Jul 2019;106(8):1012-1018. doi:10.1002/bjs.11148
47. Pinsky MR. Complexity modeling: identify instability early. *Crit Care Med*. Oct 2010;38(10 Suppl):S649-55. doi:10.1097/CCM.0b013e3181f24484
48. Segers P, O'Rourke MF, Parker K, Westerhof N, Hughes A. Towards a consensus on the understanding and analysis of the pulse waveform: Results from the 2016 Workshop on Arterial Hemodynamics: Past, present and future. *Artery Res*. Jun 2017;18:75-80. doi:10.1016/j.artres.2017.03.004
49. Saugel B, Kouz K, Scheeren TWL, et al. Cardiac output estimation using pulse wave analysis-physiology, algorithms, and technologies: a narrative review. *British journal of anaesthesia*. Jan 2021;126(1):67-76. doi:10.1016/j.bja.2020.09.049
50. Samuel AL. Some Studies in Machine Learning Using the Game of Checkers. IBM Journal of Research and Development1959.
51. Jiang T, Gradus JL, Rosellini AJ. Supervised Machine Learning: A Brief Primer. *Behav Ther*. Sep 2020;51(5):675-687. doi:10.1016/j.beth.2020.05.002
52. Booth J. A short history of blood pressure measurement. *Proc R Soc Med*. Nov 1977;70(11):793-9.
53. Thiele RH, Durieux ME. Arterial waveform analysis for the anesthesiologist: past, present, and future concepts. *Anesthesia and analgesia*. Oct 2011;113(4):766-76. doi:10.1213/ANE.0b013e31822773ec
54. Chantler PD, Lakatta EG. Arterial-ventricular coupling with aging and disease. *Front Physiol*. 2012;3:90. doi:10.3389/fphys.2012.00090

55. Chilkoti G, Wadhwa R, Saxena AK. Technological advances in perioperative monitoring: Current concepts and clinical perspectives. *J Anaesthesiol Clin Pharmacol*. Jan-Mar 2015;31(1):14-24. doi:10.4103/0970-9185.150521
56. Ackland GL, Brudney CS, Cecconi M, et al. Perioperative Quality Initiative consensus statement on the physiology of arterial blood pressure control in perioperative medicine. *British journal of anaesthesia*. May 2019;122(5):542-551. doi:10.1016/j.bja.2019.01.011
57. Saugel B, Kouz K, Meidert AS, Schulte-Uentrop L, Romagnoli S. How to measure blood pressure using an arterial catheter: a systematic 5-step approach. *Critical care (London, England)*. Apr 24 2020;24(1):172. doi:10.1186/s13054-020-02859-w
58. Picone DS, Schultz MG, Otahal P, et al. Accuracy of Cuff-Measured Blood Pressure: Systematic Reviews and Meta-Analyses. *J Am Coll Cardiol*. Aug 1 2017;70(5):572-586. doi:10.1016/j.jacc.2017.05.064
59. Nuttall G, Burckhardt J, Hadley A, et al. Surgical and Patient Risk Factors for Severe Arterial Line Complications in Adults. *Anesthesiology*. Mar 2016;124(3):590-7. doi:10.1097/aln.0000000000000967
60. Brzezinski M, Luisetti T, London MJ. Radial artery cannulation: a comprehensive review of recent anatomic and physiologic investigations. *Anesthesia and analgesia*. Dec 2009;109(6):1763-81. doi:10.1213/ANE.0b013e3181bbd416
61. Scheer B, Perel A, Pfeiffer UJ. Clinical review: complications and risk factors of peripheral arterial catheters used for haemodynamic monitoring in anaesthesia and intensive care medicine. *Critical care (London, England)*. Jun 2002;6(3):199-204. doi:10.1186/cc1489
62. Cousins TR, O'Donnell JM. Arterial cannulation: a critical review. *AANA journal*. Aug 2004;72(4):267-71.
63. Wijnberge M, van der Ster BJP, Geerts BF, et al. Clinical performance of a machine-learning algorithm to predict intra-operative hypotension with noninvasive arterial pressure waveforms: A cohort study. *European journal of anaesthesiology*. Jun 1 2021;38(6):609-615. doi:10.1097/eja.0000000000001521
64. Salmasi V, Maheshwari K, Yang D, et al. Relationship between Intraoperative Hypotension, Defined by Either Reduction from Baseline or Absolute Thresholds, and Acute Kidney and Myocardial Injury after Noncardiac Surgery. *Anesthesiology*. 2017-01-01 2017;126(1):47-65.
65. Stapelfeldt WH, Yuan H, Dryden JK, et al. The SLUScore: A Novel Method for Detecting Hazardous Hypotension in Adult Patients Undergoing Noncardiac Surgical Procedures. *Anesthesia and analgesia*. Apr 2017;124(4):1135-1152. doi:10.1213/ane.0000000000001797
66. Davies SJ, Vistisen ST, Jian Z, Hatib F, Scheeren TWL. Ability of an Arterial Waveform Analysis-Derived Hypotension Prediction Index to Predict Future Hypotensive Events in Surgical Patients. *Anesthesia and analgesia*. Mar 20 2019;doi:10.1213/ane.0000000000004121
67. Bogert LW, van Lieshout JJ. Non-invasive pulsatile arterial pressure and stroke volume changes from the human finger. *Experimental physiology*. Jul 2005;90(4):437-46. doi:10.1113/expphysiol.2005.030262
68. Martina JR, Westerhof BE, van Goudoever J, et al. Noninvasive continuous arterial blood pressure monitoring with Nexfin(R). *Anesthesiology*. May 2012;116(5):1092-103. doi:10.1097/ALN.0b013e31824f94ed
69. Vos JJ, Poterman M, Mooyaart EA, et al. Comparison of continuous non-invasive finger arterial pressure monitoring with conventional intermittent automated arm arterial pressure measurement in patients under general anaesthesia. *British journal of anaesthesia*. Jul 2014;113(1):67-74. doi:10.1093/bja/aeu091

70. Heusdens JF, Lof S, Pennekamp CW, et al. Validation of non-invasive arterial pressure monitoring during carotid endarterectomy. *British journal of anaesthesia*. Sep 2016;117(3):316-23. doi:10.1093/bja/aew26

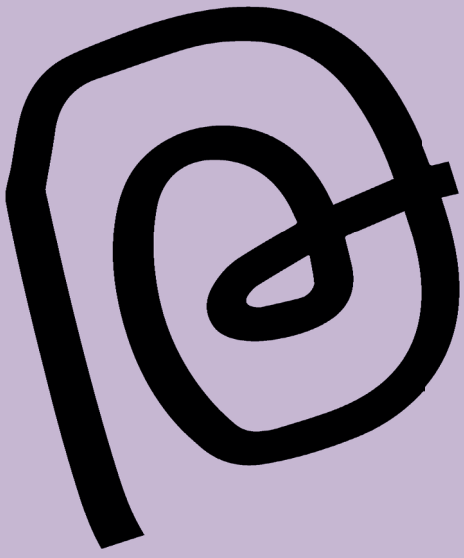
Part I

Mean systemic filling pressure

krvavo crven
stvorena sam
od hladnog severnog mora

blood red
and still I'm made
from the cold North Sea

Shira Wolfe 2022



2

Estimating mean systemic filling pressure in clinical practice: A systematic review comparing three bedside methods in the critically ill

Marije Wijnberge
Daniko P. Sindhunata
Michael R. Pinsky
Alexander P. Vlaar
Else Ouweneel
Jos R. Jansen
Denise P. Veelo MD
Bart F. Geerts

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ABSTRACT

The bedside hemodynamic assessment of the critically ill remains challenging since blood volume, arterial-venous interaction and compliance are not measured directly. Mean systemic filling pressure (MSFP) is the blood pressure throughout the vascular system at zero flow. Animal studies have shown MSFP provides information on vascular compliance, volume responsiveness and enables the calculation of stressed volume. It is now possible to measure MSFP at the bedside. We performed a systematic review of the current MSFP measurement techniques and compared their clinical applicability, precision, accuracy and limitations. A comprehensive search strategy was performed in PubMed, Embase and the Cochrane databases. Studies measuring MSFP in heart-beating patients at the bedside were included. Data were extracted from the articles into predefined forms. Quality assessment was based on the Newcastle-Ottawa Scale for cohort studies. A total of 17 prospective cohort studies were included. Three techniques were described: $MSFP_{hold}$, based on inspiratory hold-derived venous return curves, $MSFP_{arm}$, based on arterial and venous pressure equilibration in the arm as a model for the entire circulation, and $MSFP_{analogue}$, based on a Guytonian mathematical model of the circulation. The included studies show MSFP to accurately follow intravascular fluid administration and vascular compliance following drug-induced hemodynamic changes. Bedside MSFP measures allow for more direct assessment of circulating blood volume, venous return and compliance. However, studies are needed to determine normative MSFP values and their expected changes to therapies if they are to be used to guide clinical practice.

Keywords

Blood pressure; Blood volume; Critical care; Hemodynamics; Intensive care; Venous pressure.

BACKGROUND

It is difficult to determine the cause for hemodynamic instability in patients and to predict the best treatments. Currently, cardiovascular resuscitation options are triggered by arterial pressure and cardiac output (CO) measures, focusing on the oxygen delivery side of the circulation. However, primary determinants of CO reside on the venous side. Veins are 30–50 times more compliant than arteries and contain approximately 75% of the total blood volume.[1-5] Mean systemic filling pressure (MSFP) provides vital information on this "forgotten venous side of the circulation".[6]

In 1894, MSFP was defined as the equilibrium pressure throughout the circulation during circulatory arrest.[7] In the 1950s, Guyton and colleagues described a linear relationship between venous return (V_R) and right atrial pressure (P_{ra}), described as: $V_R = (MSFP - P_{ra})/(RVR)$.[8-9] RVR is resistance to V_R and defines the slope of the V_R curve. This linearity has been confirmed in intact circulations in animal studies and is not affected by hypo- or hypervolemia.[10-15] V_R curves enable to determine the equilibrium point of the circulation, which is the intersection between the CO and V_R curve. Central venous pressure (CVP) is a surrogate of P_{ra} used in clinical practice. CVP at zero flow equals MSFP (Figure 1).

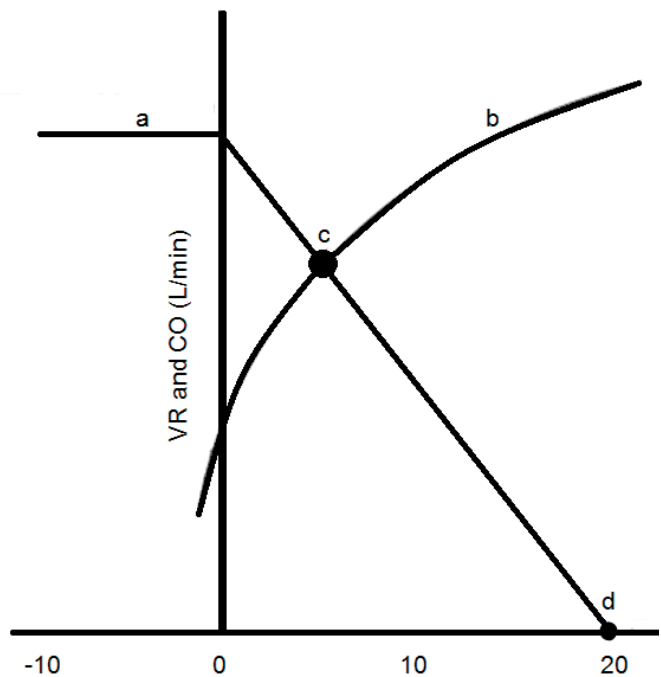

Figure 1. The venous return curve (*a*) combined with the cardiac output curve (*b*). The intersection of these two curves (*c*) is the working point of the circulation. The central venous pressure when venous return equals zero is the MSFP (d). The slope of the V_R is determined by the resistance to venous return

Vascular volume requires a minimal volume before its distending pressure becomes positive. The amount of blood not causing pressure on the vessels is called unstressed volume (V_u) and reflects intravascular volume present with MSFP of zero. Stressed volume (V_s) is the additional blood causing a distending pressure on the vascular walls and reflects the effective circulating volume. V_u and V_s together define the total blood volume. V_s is approximately 25% of the total blood volume.[3-5] V_s and vascular compliance (Csys) define MSFP.[16] An increase in V_s increases MSFP, and an increase in Csys decreases MSFP. Fluid loading should increase MSFP, but V_R only increases if the pressure gradient for V_R (i.e., MSFP - CVP) increases, RVR decreases, or both. Since in the steady state V_R = CO, knowing the determinants of V_R is relevant to understanding cardiovascular state.

Recently, methods have emerged to enable clinicians to estimate MSFP at the bedside. Our objectives for this review were to describe the techniques and to highlight their clinical applicability, precision, accuracy and limitations in critically ill patients.

MATERIALS AND METHODS

Publication selection

This review was performed according to PRISMA guidelines[17](Additional files) and methodology outlined in the Cochrane Handbook for systematic reviews.[18] No study protocol was published. A PubMed, Embase and Cochrane Library database search was performed with help of a clinical librarian with no restriction on publication date. The search was performed up to May 18, 2017. The search strategy combined the following concepts: (1) “mean systemic filling pressure” or “mean circulatory filling pressure” or “static filling pressure” and (2) “intensive care” or “critical care” or “perioperative” or “intraoperative” (Additional files). Titles, abstracts and full-texts were independently screened by two reviewers for relevance (MW and DPS), and discrepancies were resolved by a third reviewer (BFG). The references of the selected articles were examined for additional eligible articles. Studies were included when available in English and full-text, described prospective studies in which MSFP estimation methods were examined in heart-beating ICU patients and contained a description of their clinical applicability, precision and accuracy or limitations.

Data extraction and analysis

Data were extracted into predefined forms. No additional analyses were performed. Critical appraisal was based on the Newcastle–Ottawa Scale for cohort studies[19] to assess the quality of non-randomized studies at study level. A modified version of the scale was used since only five out of nine questions were applicable, resulting in a possible highest score of five stars (Additional files).

Study	Method	N	Patient population (all adult ICU patients)	Age	Male	Timeframe MSFP measurement
Maas (21) 2009	MSFP-hold	12	Postoperative cardiac surgery 10 CABG 2 AVR	64 (10)	10 (83%)	Not described
Keller (23) 2011	MSFP-hold	9	Postoperative cardiac surgery 3 CABG 6 AVR	Median 61 IQR 55-75	4 (44%)	Not described
Maas (22) 2012	MSFP-hold	10	Postoperative cardiac surgery 2 AVR 1 MVP +TVP 7 CABG	64 (11)	9 (90%)	Within 1 hour after ICU admission
Persichini (27) 2012	MSFP-hold	16	Septic shock	67 (16)	8 (50%)	Not described
Maas (25) 2013	MSFP-hold	16	Postoperative cardiac surgery 1 MVP 15 CABG	64 (11)	Not described	Within 1 hour after ICU admission
Guerin (28) 2015	MSFP-hold	30	Shock	65 (12)	21 (70%)	Not described
De Wit (24) 2016	MSFP-hold	17	Postsurgical gastroinstestinal 16 oesophageal resection 1 pancreaticoduodenectomy	62 (9)	14 (82%)	Not mentioned
Helmerhorst (26) 2017	MSFP-hold	22	Postoperative cardiac surgery 22 CABG	63 (59-66)	17 (85%)	1 hour after ICU admission
Geerts (43) 2011	MSFP-arm	24	Postoperative cardiac surgery 17 CABG 7 CABG plus valve repair	64 (10)	19 (79%)	Within 2 hours after ICU admission
Aya (41) 2014	MSFP-arm	20	Postoperative cardiac surgery 13 CABG 4 AVR 4 MVR	63 (11)	17 (85%)	Initial period at ICU (not further defined)
Aya (42) 2017	MSFP-arm	80	Postoperative cardiac surgery 36 CABG 27 AVR+CABG 12 MVR+CABG 5 Other	70 Range 52-80	62 (78%)	Initial period at ICU (not further defined)
Parkin (49) 1994	MSFP-analogue	10	Multi-organ failing patients receiving CVVH for acute renal failure	65 Range 24-77	7 (70%)	Not described

Study	Method	N	Patient population (all adult ICU patients)	Age	Male	Timeframe MSFP measurement
Cecconi (48) 2013	MSFP-analogue	39	22 Cardiac surgery 8 Shock 6 Non cardiac surgery 3 Other	68 (12)	26 (67%)	Not described
Gupta (20) 2015	MSFP-analogue	61	Postoperative cardiac surgery 40 CABG 8 CABG + valve replacement 8 Valve replacement 5 Bentall's procedure 7 DDD pacing	63 (11)	46 (75%)	Within 6 hours after ICU admission
Aya (51) 2016	MSFP-analogue	26	Postoperative fluid challenge 7 Cardiac surgery 19 Noncardiac surgery	68 Range 53-80	16 (62%)	Initial period at ICU (not further defined)
Maas (16) 2012	MSFP-hold MSFP-arm MSFP-analogue	11 11 11	Postoperative cardiac surgery 9 CABG 2 AVR	64 Range 50-80	9 (82%)	Within 2 hours after ICU admission
Maas (30) 2012	MSFP-arm MSFP-hold	15 12	Postoperative cardiac surgery 9 CABG 5 Valve 1 CABG+ valve	64 (11)	Not described	Within 1 hour after ICU admission

Table 1. Baseline characteristics for included studies. CABG= coronary artery bypass, MVR= mitral valve replacement, MPV= mitral valve prolapse, AVR= aortic valve replacement, TVP= tricuspid valve prolapse. CVVH= continuous veno-venous hemodiafiltration. Age is presented as mean with standard deviation (SD) or median with range or interquartile range (IQR). Number of males per study is presented as counts with percentage

RESULTS

Study selection and characteristics

The initial search identified 369 articles, of which 300 were excluded after screening title and abstract. A total of 53 articles were excluded based on full-text. Two relevant articles were found by citation tracking. Consequently, 17 prospective cohort studies estimating MSFP in heart-beating ICU patients were included (Additional files). Three different bedside measurement techniques were found. Eight studies estimated MSFP applying inspiratory hold maneuvers ($MSFP_{hold}$), three studies during a circulatory stop-flow in the arm ($MSFP_{arm}$) and four studies using a mathematical algorithm ($MSFP_{analogue}$). Two studies compared multiple techniques.

Eleven studies were performed in postoperative cardiac surgery patients (Table 1). All patients were hemodynamically stable without alteration in vasopressor use or fluid therapy during the study protocol. All patients were sedated and mechanically

ventilated. In one study, spontaneous breathing efforts were observed.[20] The number of included patients ranged from nine to 80. In all studies, CVP was measured via a catheter in the right internal jugular vein. CO measurement techniques differed between studies (Additional files).

$MSFP_{hold}$

Technique description

$MSFP_{hold}$ is based on the linear relation between CVP and V_R ($V_R = (MSFP - CVP)/RVR$). CVP is raised by performing a series of end-inspiratory hold maneuvers. In 2009, the method was first studied in humans.[21] Inspiratory hold maneuvers at 5, 15, 25 and 35 cmH_2O incremental ventilatory plateau pressures (P_{vent}) were performed, and CO was measured in the last 3 seconds of the 12 seconds inspiratory hold. They validated that after 7–10 seconds a steady state consists when $V_R = CO$. By plotting the CVP and CO values, a V_R curve is constructed and the zero-flow pressure (MSFP) extrapolated. Seven studies[16,21-26] estimated $MSFP_{hold}$ using these four plateau pressures. Two studies[27,28] used two points (P_{vent} 5 and 30 cmH_2O) at 15-s inspiratory and expiratory hold plateau phase. Between the $MSFP_{hold}$ measurements, either 1-min pauses were used to re-establish the initial hemodynamic steady state[16,21,22, 24, 28] or the consecutive inspiratory hold was performed when CO had returned to baseline.[23, 26, 27]

Clinical applicability

The average baseline $MSFP_{hold}$ values found in the eight included studies range from 19 to 33 mmHg with a wide standard deviation (Tables 2, 3). Five studies[21-23, 26, 28] demonstrated fluid administration caused an increase in MSFP hold, confirming that in humans, as in animals before[14,15] $MSFP_{hold}$ follows hemodynamic changes (Table 2). One of these studies found passive leg raising (PLR) to significantly increase MSFP hold values.[28] RVR was not significantly affected by different volumetric conditions nor by PLR. V_s was calculated from MSFP as a measure for effective circulating volume.[22] In one study, MSFP was used to assess the hemodynamic effects of arterial hyperoxia ($FiO_2 = 90\%$ for 15 min) in ICU patients.[26] During this hyperoxia, left ventricular afterload increased and contractility remained similar; however, CO did not decrease. Both MSFP and RVR increased significantly (Table 3), explaining why V_R (thus CO) remained unaltered.

Studies have used $MSFP_{hold}$ to describe hemodynamic changes caused by propofol[24] and norepinephrine[25, 27] (Table 3). In septic shock patients, decreasing the dose of norepinephrine decreased both MSFP and RVR.[27] Further, after increasing norepinephrine CO decreased in ten patients and CO increased in six patients.[25] In all patients, MSFP and RVR increased, though the “balance” between the two values determined whether CO increased. One study showed an increase in propofol caused a decrease in MSFP without a change in CO.[24] These studies show MSFP behaves within the framework of

Study	Method	N	Patient population	Baseline position	Baseline MSFP	Hypervolemia (induced by fluid administration)	p-value*	Amount of fluid administered to induce hypervolemia	Hypovolemia (induced by HUT)	p-value†
Maas (21) 2009	MSFP-hold	12	Cardiac surgery	Supine	18.7 (4.5)	29.1 (5.2)	=0.001	500 mL colloid in 15-20 min	14.5 (3.0)	=0.005
Keller (23) 2011	MSFP-hold	9	Cardiac surgery	Semirecumbent	19.7 IQR 17.0-22.6	26.9 IQR 18.4-31.0	<0.05	500 mL colloid	-	-
Maas (22) 2012	MSFP-hold	10	Cardiac surgery	Not described	18.7 (4.0)	26.4 (3.2)	<0.001	500 mL colloid	-	-
Guerin (28) 2015	MSFP-hold	30	Shock	Semirecumbent	Responder: 25 (13) Non-responders: 24 (10)	 32 (17) 28 (12)	 <0.01 <0.01	500 mL saline in 10 min		
Geerts (43) 2011	MSFP-arm	24	Cardiac surgery	Supine	Responders: 16.2 (6.3) Non-responders: 24.3 (8.2)	 22.0 (7.6) 29.9 (9.1)	 <0.001 <0.001	500 mL colloid	-	-
Aya (41) 2014	MSFP-arm	20	Cardiac surgery	Supine	22.4 (7.7)	-	-	-	-	-
Aya (42) 2017	MSFP-arm	80	Cardiac surgery	Supine	23.0 Range: 17.3-29.8	-	-	-	-	-
Parkin (49) 1994	MSFP-analogue	10	CVVH	Not described	Target state= 15.9	-	-	CVVHD	-	-
Cecconi (48) 2013	MSFP-analogue	39	Heterogenous	Not described	Responders: 17.8 (5.1) Non-responders: 17.9 (5.1)	 20.9 (5.1) 21.0 (4.9)	 <0.001 <0.001	Mean 252 (8.9) mL 52.5 % crystalloid 37.6 % colloid 8.8 % FFP & RBC	-	-

Gupta (20) 2015	MSFP-analogue	61	Cardiac surgery	Supine	Responders: 17 (3.7) Non-responders: 17 (3.6)	19 (4.3) 19 (4.1)	=0.02 =0.03	Mean 264 (16) mL 50 % saline. Other 50%: mix of FFP, platelets, albumin, packed RBC, return of pump blood	-	-
Aya (51) 2016	MSFP-analogue	26	Heterogenous	Not described	Responders: 13.7 IQR: 10.9-16.9 Non-responders: 16.7 IQR: 10.5-18.9			250 mL crystalloid		
Maas (16) 2012	MSFP-hold MSFP-arm MSFP-analogue	11	Cardiac surgery	Supine	19.7 (3.9) 18.4 (3.7) 14.7 (2.7)	28.3 (3.6) 27.1 (4.0) 19.2 (1.1)	<0.001 <0.001 <0.001	500 mL colloid	16.2 (3.0) 15.4 (3.1) 10.9 (2.0)	=0.001 =0.001 <0.001
Maas (30) 2012	MSFP-arm MSFP-hold#	15	Cardiac surgery	Supine	21.0 (6.8)	27.7 (7.4)	<0.001	500 mL colloid (10 steps of 50 mL)	-	-

Table 2. Mean systemic filling pressure during different volumetric states. Data presented as mean with SD or median with interquartile range (IQR). MSFP in mmHg. p-value*= difference between baseline and hypervolemia induced by fluid administration, p-value†= difference between baseline and hypovolemic state. Hypovolemic state induced by head up tilt (HUT) to 30 degrees. Responders= fluid responsiveness was defined by a 10% increase in CO

hemodynamic reasoning and lends itself to being used as a less invasive method to assess drug-induced physiology. Since MSFP exists at the intersection of arterial and venous flow, it enables to calculate arterial and venous resistance by calculating the critical closing pressure (P_{cc}). P_{cc} is the mean arterial pressure (MAP) to zero CO-intercept. Arterial resistance is calculated as (MAP − P_{cc})/CO.[22]

Precision and accuracy

The technique precision has not yet been assessed in humans. However, in an animal study the averaged coefficient of variation for repeated measurements of $MSFP_{hold}$ was 6%.[29] Comparing the techniques' accuracy, no significant differences between $MSFP_{hold}$ and $MSFP_{arm}$ existed, whereas $MSFP_{analogue}$ values were significantly lower.[16,30]

Study	Method	n	Situation A	Situation B	p-value*	Situation C	p-value#
Persichini (27) 2012		16	NE 0.30 Range 0.10-1.40	NE 0.19 Range 0.08-1.15			
	MSFP-hold (in mmHg)		33 (12)	26 (10)	p=0.003		
Maas (25) 2013		16	Baseline 1 NE 0.04 (0.03)	NE increase of 0.04 (0.02)		Baseline 2 NE 0.04 (0.03)	
	MSFP-hold (in mmHg)		21.4 (6.1)	27.6 (7.4)	p<0.001	22.0 (5.3)	
De Wit (24) 2016		17	Propofol low Cb 3.0 (0.90) ug/mL	Propofol medium Cb 4.5 (1.0) ug/mL		Propofol high Cb 6.5 (1.2) ug/mL	
	MSFP-hold (in mmHg)		27.9 (5.4)	24.6 (4.9)	p=0.01	21.4 (4.2)	p<0.001
Helmerhorst (26) 2017		22	FiO2 21-30%	FiO2 90%			
	MSFP-hold (in mmHg)		20.8 (3.5)	23.1 (4.0)	p<0.001		

Table 3. MSFP and pharmacodynamics. NE= norepinephrine dose in ug/kg/min presented as mean with range or mean with standard deviation. p-value*= p-value for situation A compared to B. p-value#= p-value for situation A compared to C. MSFP values are presented as mean with standard deviation. Cb= target blood concentration of propofol in ug/mL. MSFP-hold values presented in mmHg. FiO_2= fractional oxygen concentration.

Limitations

The use of $MSFP_{hold}$ is restricted to mechanically ventilated and sedated patients with a central venous catheter. The procedure of the inspiratory hold maneuvers is not yet automated and requires a direct link between monitor and ventilator, or advanced monitor analytics to detect the inspiratory holds and to perform the instantaneous CO calculations. Furthermore, it is not suitable during cardiac arrhythmia. This method is

not suitable to measure rapid changes in hemodynamic status since it takes a couple of minutes to perform the multiple end-inspiratory (and end-expiratory) holds. Potentially, this technique is operator-dependent because a proper inspiratory plateau pressure is needed. CVP can be altered due to incorrect catheter placement. An absolute CO value is not necessary for $MSFP_{hold}$ as the technique extrapolates to zero CO. If the trend measurements are accurate, the RVR slope might change, but the intersection MSFP point remains constant. The latter holds only true for the MSFP itself, the RVR is dependent of the slope of the curve. In clinical practice, a physician would use MSFP together with RVR; therefore, for clinical use of the MSFP an accurate CO value is needed.

Potentially, the inspiratory hold maneuver overestimates MSFP by the blood translocation from the pulmonary into the systemic circulation.[31,32,33,34] During inspiratory hold maneuvers, arterial pressure decreases. If sustained, baroreflex-induced increased sympathetic tone may cause MSFP to increase.[35, 36] Indeed one study performed in pigs found the $MSFP_{hold}$ overestimating compared to a method using right atrial balloon occlusion in euvolemic conditions, in bleeding and hypervolemia; however, the values found between the two methods were similar.[34] Two clinical studies[16, 30] have shown $MSFP_{hold}$ and $MSFP_{arm}$ values not being significantly different, debating the former result found in pigs. Future studies in humans are needed. Moreover, all patients undergoing inspiratory holds are on neuro-humoral suppressive agents, probably dampening the baroreflex and other autonomic influences.[37,38,39]

$MSFP_{arm}$

Technique description

As MSFP is defined as the steady-state blood pressure during no-flow conditions, instantaneously MSFP should mainly be similar for different vascular compartments even though each compartment may have different V_u and V_s.[2, 40] Four studies[16, 41–43] used the arm to estimate MSFP. For arm occlusion, a rapid cuff inflator (inflates in 0.3 s)[16, 43] or a pneumatic tourniquet (inflates in 1.4 s)[41, 42] was inflated around the upper arm to 50 mmHg above systolic blood pressure. Arterial and venous pressures were measured via a radial artery catheter and a peripheral venous cannula in the forearm. When these two pressures equalize, $MSFP_{arm}$ values are achieved. An initial study determined that a 25–30 s stop-flow time was adequate to achieve this equilibration.[16] Following this, in two studies $MSFP_{arm}$ was measured as the average radial arterial pressure at 30 s after stop-flow.[16, 43] One study found the smallest difference between venous and arterial pressure after 60 s of stop-flow.[41] This discrepancy could be explained by different inflation time, i.e., induction of stop-flow.

Clinical applicability

The average baseline $MSFP_{arm}$ values found in the included studies range from 16 to 24 mmHg (Table 2). $MSFP_{arm}$ can be performed in spontaneously breathing subjects and requires only one measure. $MSFP_{arm}$ was assessed as a predictor of fluid loading responsiveness (FLR). One study showed that a low $MSFP_{arm}$ (< 22 mmHg) predicts FLR with 71% sensitivity and 88% specificity, where responders were defined when CO increased > 10% after 500 mL colloid administration.[43] Another study showed changes in circulating volume (500 mL colloid) are tracked well by changes in $MSFP_{arm}$.[16] Finally, one study indicated a minimum of 4 mL/kg fluid challenge was needed to define FLR.[42]

Precision and accuracy

Repeated measurements of $MSFP_{arm}$ showed no significant differences.[41] The coefficient of variation for a single measurement was 5%, which reduced to 3% after four measurements. Bland–Altman analysis showed a bias of − 0.1 ± 1.68 mmHg for the first two measurements. The least significant change[44] for a single measurement was 14% (i.e., ± 3 mmHg for a $MSFP_{arm}$ of 22 mmHg). One study observed a negligible bias of two $MSFP_{arm}$ determinations at baseline position and after fluid expansion.[16] Two studies[16, 30] found no significant differences in $MSFP_{arm}$ to $MSFP_{hold}$ measures.

Limitations

Theoretically, a limitation of the technique is the influence of an auto regulatory hypoxia-induced response causing arterial vasodilation. The time of measuring MSFP after arm occlusion should be enough for arterial and venous pressures to equilibrate, but before hypoxia-induced vasodilation causes an underestimation of MSFP .[45] One study observed plateau pressures after 20–30 s and saw a further decrement after 35–40 s which indicates hypoxia-induced vasodilation.[16] Potentially, arm occlusion causes a small accumulation of blood volume because the venous outflow stops before the arterial inflow stops.[16] Though, this potential overestimation is negligible since the inflow is small compared to the total distal arm volume as long as cuff inflation is rapid. To note, $MSFP_{arm}$ is only reliable when a stable plateau pressure is achieved.[2]

In contrast to $MSFP_{hold}$, $MSFP_{arm}$ measures can be made in non-sedated patients with cardiac arrhythmias. However, the possible influence of the rapid cuff inflator on reflex mechanisms needs to be studied. In septic patients, central and peripheral vasomotor tone might be altered differently.[46] Shortly after cardiac surgery differences between aortic and radial pressure can occur,[47] still, the original validation studies were on postoperative cardiac surgery patients.

$MSFP_{analogue}$

Technique description

Based on a Guytonian model of the systemic circulation ($CO = V_R = (MSFP - CVP)/RVR$), an analogue of *MSFP* can be derived using a mathematical model: $MSFP_{analogue} = axCVP + bxMAP + cxCO$.[5,20,48,49] In this formula, *a* and *b* are dimensionless constants ($a + b = 1$). Assuming a veno-arterial compliance ratio of 24:1, $a = 0.96$ and $b = 0.04$; c resembles arteriovenous resistance and is based on a formula including age, height and weight.[5,48,49,50]

Clinical applicability

The average baseline $MSFP_{analogue}$ values found in the included studies range from 14 to 18 mmHg (Table 2). One study compared fluid replacement based on target $MSFP_{analogue}$ compared to conventional treatment in continuous veno-venous hemodiafiltration.[49] Fluid replacement based on target $MSFP_{analogue}$ led to significantly less fluid administration with stable cardiovascular variables (CVP, MAP, CO) and no complications. So, $MSFP_{analogue}$ measurement adequately follows intravascular volume status in patients. $MSFP_{analogue}$ measurements are automatic making it an attractive alternative to to $MSFP_{hold}$ and $MSFP_{arm}$.

More recently, the $MSFP_{analogue}$ dynamics, measured with the Navigator™ device (Applied Physiology, Pty Ltd, Australia), were observed.[20, 48, 51] Patients were defined as responders with an increase in stroke volume or CO > 10% after 250 mL fluid administration. $MSFP_{analogue}$ increased after fluid administration; however, baseline $MSFP_{analogue}$ did not differ between responders and non-responders[20, 45, 48] (Table 2). This is contrary to results of another study[43] using $MSFP_{arm}$, possibly due to different fluid volume (250 vs. 500 mL).[42] Although the driving pressure for V_R (MSFP - CVP) was different between responders and non-responders, it showed low sensitivity (79%) and specificity (56%) to predict FLR. [20, 48]

Precision and accuracy

Precision has not been assessed for analogue (Table 4). Comparing measurement techniques revealed a lower $MSFP_{analogue}$ value compared to $MSFP_{hold}$.[16] However, a significant regression of $MSFP_{analogue}$ and $MSFP_{hold}$ was observed enabling to adjust the $MSFP_{analogue}$ value using a calibration factor.[5]

Limitations

The mathematical model is based on CVP, MAP and CO measurements. As CVP values vary during ventilation, usually end-expiratory CVP-recordings can be used. Furthermore, CVP values depend on the position of the transducer. Accurate CO values are needed for this

method. The limitation of $MSFP_{analogue}$ is that the algorithm is based on a mathematical model with mathematical coupling between CO and MSFP and fixed Csys and resistance parameters,[5] therefore presumably not applicable for all patient populations or clinical conditions. We are unable to assess the availability of the Navigator™ for routine care.

DISCUSSION

We found three bedside techniques to measure MSFP: $MSFP_{hold}$, $MSFP_{arm}$ and $MSFP_{analogue}$. They were used to follow volumetric state and to study drug-induced hemodynamic changes in patients.

The interpretation of V_R curves and MSFP in clinical practice is subject to debate.[52-59] The values found in heart-beating ICU patients are higher (14–33 mmHg) than in deceased ICU patients (12.8 ± 5.6 mmHg, mean ± sd), probably because of alteration of vasomotor tone after dying.[53] Furthermore, ICU patients often receive vasopressors which increase MSFP and the study populations differed making it not one-to-one comparable. It is also speculated that the pressure described by Guyton is not measurable in heart-beating patients and the extrapolated pressure of the curve represents a different physiological parameter. Nevertheless, in two studies $MSFP_{arm}$ was interchangeable with $MSFP_{hold}$.[16, 30] Furthermore, although MSFP values may differ, the CVP values do as well, which may account for a similar driving pressure for V_R. The reviewed studies illustrate the possible clinical benefits of using the bedside derived MSFP values.

This review is limited since we were unable to pool the data because of the variety in used conditions and interventions. The 16 included studies were performed by only a few research groups with a limited amount of included patients. In most of the studies, each patient served as their own control since it is not clear what would be an appropriate outside control group.

Still, all studies testing the accuracy of MSFP to follow intravascular changes and pharmacodynamics found significant results. Therefore, it is unlikely that a larger number of patients will show different outcomes. It is possible only positive studies were published, indicating publication bias. MSFP values differ between the studies and have a wide range within studies (Table 2). Normal values for different patient populations need to be defined before MSFP can be implemented into standard (ICU) care. The increase in MSFP values after fluid administration depends on vascular redistribution, vasomotor tone and fluid loss into the interstitial space. Studies focusing on clinical decision-making based on MSFP, driving pressure for V_R, V_s or Csys have not yet been performed. Study designs need to be created to see if using these measures improves outcomes. Also, no precision studies examining $MSFP_{hold}$ or $MSFP_{analogue}$ exist yet.

	MSFP-hold	MSFP-arm	MSFP-analogue
	CO=VR=(MSFP-CVP)/RVR	**Pa=Pv**	**MSFP= axCVP+bxMAP+cxCO**
Applicability to a broad patient population	**-**	**+/-**	**+/-**
	Restricted to fully sedated and mechanically ventilated patients	In theory applicable in all patients (sedated or awake) with an radial artery catheter	In theory applicable in all patients (sedated or awake)
	Restricted to patients without a contraindication for inspiratory holds (such as COPD with bullae)		Continuous and accurate CO, MAP and CVP measurements needed
	Continuous and accurate CO and CVP measurements needed		Not suitable in cardiac arrhythmia
	Not suitable in cardiac arrythmia		
Accuracy	**+**	**+**	**-**
	Values interchangeable with MSFP-arm	Values interchangeable with MSFP-hold	Values significantly lower than derived with MSFP-hold
	When sedated baroreflex probably of little influence	Dependent on time of measurement: > Pa and Pv equilibration.< hypoxia-induced vasodilatation	MSFP-anologue can be transformed to MSFP-hold values (constant error)
	Mechanical ventilation may overestimate MSFP value	Possible influence rapid cuff inflator on reflex mechanism altering MSFP value in non-sedated patients. This is not studied.	Mathematical coupling and the equation is based on assumptions that may not be generalizable to all patient populations in ICU
Precision	**?**	**+**	**?**
	Not studied	No significant differences during repeated measurements. LSC for a single measurement is 14%.	Not studied
Outcome operator independent	**-**	**+/-**	**+**
	Inspiratory holds	Timing of measurement	CVP transducer position and CO measurement technique
	CVP transducer position and CO measurement technique		
	Extrapolation of curve		
Responding time	**-**	**+**	**+**
	>4 minutes	30-60 seconds	Fast, no exact times mentioned
Costs	**-**	**+**	**+**

	MSFP-hold	MSFP-arm	MSFP-analogue
	CO=VR=(MSFP-CVP)/RVR	**Pa=Pv**	**MSFP= axCVP+bxMAP+cxCO**
	Theoretically no extra devices needed than standard present in ICU	Rapid Cuff Inflator (Hokanson E20, Bellevue, Washington, USA) =3000 euro	NavigatorTM (Applied Physiology, Pty Ltd, Sydney, Australia). Price unknown.
Risk of complications	**+**	+/-	**-**
	No complications reported in published studies. In theory:	No complications reported in published studies. In theory:	No complications reported in published studies. In theory:
	Barotrauma from inspiratory holds	In sedated patients, attention should be paid deflating the rapid cuff before hypoxemia induced damage can occur	Complications associated with central venous catheters and CO measurement
	Severe hemodynamic instability induced by inspiratory holds	In awake patients, local pain could be caused by inflating the rapid cuff inflator	
	Complications associated with central venous catheters and CO measurement		

Table 4. Comparison of bedside MSFP measurement techniques.CO= cardiac output. CVP= central venous pressure. RVR = resistance to venous return. MAP= mean arterial pressure. Pa= arterial pressure. Pv= venous pressure (the latter two measured in the arm).

CONCLUSIONS

Presently, three bedside MSFP-measurement techniques are available. All require invasive hemodynamic monitoring. Though MSFP-measures allow for more direct assessment of circulating blood volume, VR and Csys, studies are needed to determine cut-off values to allow MSFP to trigger therapeutic interventions and to determine its value in clinical practice.

List of abbreviations

CO= cardiac output
Csys= vascular compliance
CVP= central venous pressure
FiO_2= fractional oxygen concentration
FLR= fluid loading responsiveness
ICU= intensive care unit
MAP= mean arterial pressure
MCFP = mean circulatory filling pressure
MSFP= mean systemic filling pressure
Pcc= critical closing pressure
Pra= right atrial pressure
RVR= resistance for venous return
VR= venous return
Vs= stressed volume
Vu= unstressed volume

Author's contributions

All authors contributed to the manuscript. MW, DV and BG designed the study. MW performed a systematic search of the literature. MW and DS independently screened articles for relevance and subsequently performed data extraction into predefined forms. Quality assessment of the included articles was also independently performed by MW and DS. MW, DV, BG and MP wrote the manuscript. JJ, EO and AV critically reviewed and revised the manuscript. All authors read and approved the final manuscript.

Competing interests

None of the authors have relevant conflict of interest present for any aspect of the submitted work. Denise Veelo performed consultancy work for Edwards Lifesciences, Hemologic and Merck outside the submitted work. Bart Geerts performed consultancy work for Edwards Lifesciences and Philips outside the submitted work. Michael Pinsky is a consultant for Cheetah Medical, Edwards Lifesciences, Exotstat Medical, LiDCO Ltd and Cyberonics outside the submitted work.

Ethics approval and consent to participate

Not applicable.

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REFERENCES

1. Hainsworth R. The importance of vascular capacitance in cardiovascular control. News Physiol Sci. 1990;5:250-4.
2. Maas JJ. Mean systemic filling pressure: its measurement and meaning. Neth J Crit Care. 2015;19:6-11.
3. Peters J, Mack GW, Lister G. The importance of the peripheral circulation in critical illnesses. Intensive Care Med. 2001;27:1446-58.
4. Gelman S. Venous function and central venous pressure: a physiologic story. Anesthesiology. 2008;108:735-48.
5. Parkin WG. Volume state control: a new approach. Critical Care Resusc. 1999;1:311-21.
6. Jansen JR, Maas JJ, Pinsky MR. Bedside assessment of mean systemic filling pressure. Curr Opin Crit Care. 2010;16:231-6.
7. Bayliss WM, Starling EH. Observations on venous pressures and their relationship to capillary pressures. J Physiol. 1894;16:159-318.
8. Guyton AC, Polizo D, Armstrong GG. Mean circulatory filling pressure measured immediately after cessation of heart pumping. Am J Physiol. 1954;179:261-7.
9. Guyton AC, Lindsey AW, Abernathy B, Richardson T. Venous return at various right atrial pressures and the normal venous return curve. Am J Physiol. 1957;189:609-15.
10. Versprille A, Jansen JR: Mean systemic filling pressure as a characteristic pressure for venous return. Pflugers Arch. 1985;405:226-33.
11. Pinsky MR. Instantaneous venous return curves in an intact canine preparation. J Appl Physiol Respir Environ Exerc Physiol. 1984;56:765-71.
12. Hiesmayr M, Jansen JR, Versprille A. Effects of endotoxin infusion on mean systemic filling pressure and flow resistance to venous return. Pflugers Arch. 1996;431:741-7.
13. den Hartog EA, Versprille A, Jansen JR. Systemic filling pressure in intact circulation determined on basis of aortic vs. central venous pressure relationships. Am J Physiol. 1994;267:H2255-8.
14. Yamamoto J, Trippodo NC, Ishise S, Frohlich ED. Total vascular pressure-volume relationship in the conscious rat. Am J Physiol. 1980;238:H823-8.
15. Samar RE, Coleman TG. Measurement of mean circulatory filling pressure and vascular capacitance in the rat. Am J Physiol. 1978;234:H94-100.
16. Maas JJ, Pinsky MR, Geerts BF, de Wilde RB, Jansen JR. Estimation of mean systemic filling pressure in postoperative cardiac surgery patients with three methods. Intensive Care Med. 2012;38:1452-60.
17. Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gøtzsche PC, Ioannidis JP, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. PLoS Med. 2009;6:e1000100.
18. Higgins JPT, Green S. Cochrane handbook for systematic reviews of interventions (version 5.1.0). 2011. http://handbook.cochrane.org. Accessed 16 March 2017.
19. Wells G, Shea B, O'Connell J, Peterson J, Welch V, Losos M, et al: The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp. 2009. Accessed 20 February 2017.
20. Gupta K, Sondergaard S, Parkin G, Leaning M, Aneman A. Applying mean systemic filling pressure to assess the response to fluid boluses in cardiac post-surgical patients. Intensive Care Med. 2015;41:265-72.

21. Maas JJ, Geerts BF, van den Berg PC, Pinsky MR, Jansen JR. Assessment of venous return curve and mean systemic filling pressure in postoperative cardiac surgery patients. Crit Care Med. 2009;37:912-8.
22. Maas JJ, de Wilde RB, Aarts LP, Pinsky MR, Jansen JR. Determination of vascular waterfall phenomenon by bedside measurement of mean systemic filling pressure and critical closing pressure in the intensive care unit. Anesth Analg. 2012;114:803-10.
23. Keller G, Desebbe O, Benard M, Bouchet JB, Lehot JJ Bedside assessment of passive leg raising effects on venous return. J Clin Monit Comput. 2011;25:257-63.
24. de Wit F, van Vliet AL, de Wilde RB, Jansen JR, Vuyk J, Aarts LP, et al. The effect of propofol on haemodynamics: cardiac output, venous return, mean systemic filling pressure, and vascular resistances. Br J Anaesth. 2016;116:784-9.
25. Maas JJ, Pinsky MR, de Wilde RB, de Jonge E, Jansen JR. Cardiac output response to norepinephrine in postoperative cardiac surgery patients: interpretation with venous return and cardiac function curves. Crit Care Med. 2013;41:143-50.
26. Helmerhorst HJ, de Wilde RB, Lee DH, Palmen M, Jansen JR, van Westerloo DJ, et al. Hemodynamic effects of short-term hyperoxia after coronary artery bypass grafting. Ann Intensive Care. 2017;7:20.
27. Persichini R, Silva S, Teboul JL, Jozwiak M, Chemla D, Richard C, et al. Effects of norepinephrine on mean systemic pressure and venous return in human septic shock. Crit Care Med. 2012;40:3146-53.
28. Guerin L, Teboul JL, Persichini R, Dres, M, Richard C, Monet X. Effects of passive leg raising and volume expansion on mean systemic pressure and venous return in shock in humans. Critical Care. 2015; 19:411
29. Maas JJ, Geerts BF, Jansen JR. Evaluation of mean systemic filling pressure from pulse contour cardiac output and central venous pressure. J Clin Monit Comput. 2011;25:193-201.
30. Maas JJ, Pinsky MR, Aarts LP, Jansen JR. Bedside assessment of total systemic vascular compliance, stressed volume, and cardiac function curves in intensive care unit patients. Anesth Analg. 2012;115:880-7.
31. Fessler HE, Brower RG, Wise RA, Permutt S. Effects of positive end-expiratory pressure on the gradient for venous return. Am Rev Respir Dis. 1991;143:19-24.
32. Hedenstierna G. Pulmonary perfusion during anesthesia and mechanical ventilation. Minerva Anestesiol. 2005;71:319-24.
33. Jellinek H, Krenn H, Oczenski W, Veit F, Schwarz S, Fitzgerald RD. Influence of positive airway pressure on the pressure gradient for venous return in humans. J Appl Physiol. 2000;88:926-32.
34. Berger D, Moller PW, Weber A, Bloch A, Bloechlinger S, Haenggi M, et al. Effect of PEEP, blood volume and inspiratory hold maneuvers on venous return. Am J Physiol Heart Circ Physiol. 2016; 311: H794-H806.
35. Borst C, Karemaker JM. Time delays in the human baroreceptor reflex. Journal of the Autonomic Nervous System. 1983; 9:399-409.
36. Peters JK, Lister G, Nadel ER, Mack GW. Venous and arterial reflex responses to positive-pressure breathing and lower body negative pressure. J Appl Physiol. 1997; 82(6):1889-1896.
37. Sato M, Tanaka M, Umehara S, Nishikawa T. Baroreflex control of heart rate during and after propofol infusion in humans. Br J Anaesth. 2005;94:577-8.1
38. Ebert TJ. Sympathetic and hemodynamic effects of moderate and deep sedation with propofol in humans. Anesthesiology. 2005;103:20-4.

39. Lennander O, Henriksson BA, Martner J, Biber B. Effects of fentanyl, nitrous oxide, or both, on baroreceptor reflex regulation in the cat. Br J Anaesth. 1996;77:399-403.
40. Anderson RM. Appendix: clinical determination of mean cardiovascular pressure. In: Anderson RM, editor. The gross physiology of the cardiovascular system (second edition). Tucson, Arizona: Racquet Press; 1993, p. 61-2.
41. Aya HD, Rhodes A, Fletcher N, Grounds RM, Cecconi M. Transient stop-flow arm arterial-venous equilibrium pressure measurement: determination of precision of the technique. J Clin Monit Comput. 2016;30:55-61.
42. Aya HD, Rhodes A, Chis Ster I, Fletcher N, Grounds RM, Cecconi M. Hemodynamic effect of different doses of fluids for a fluid challenge: a quasi-randomized controlled study. Crit Care Med. 2017;45:e161-8.
43. Geerts BF, Maas J, de Wilde RB, Aarts LP, Jansen JR. Arm occlusion pressure is a useful predictor of an increase in cardiac output after fluid loading following cardiac surgery. Eur J Anaesthesiol. 2011;28:802-6.
44. Kawalilak CE, Johnston JD, Olszynski WP, Kontulainen SA. Least significant changes and monitoring time intervals for high-resolution pQCT-derived bone outcomes in postmenopausal women. J Musculoskelet Neuronal Interact. 2015;15:190-6.
45. Betik AC, Luckham VB, Hughson RL. Flow-mediated dilation in human brachial artery after different circulatory occlusion conditions. Am J Physiol Heart Circ Physiol. 2004;286:H4428.
46. Hatib F, Jansen JR, Pinsky MR. Peripheral vascular decoupling in porcine endotoxic shock. J Appl Physiol. 2011;111:853-60.
47. Stern DH, Gerson JI, Allen FB, Parker FB. Can we trust the direct radial artery pressure immediately following cardiopulmonary bypass? Anesthesiology. 1985;62:557-61.
48. Cecconi M, Aya HD, Geisen M, Ebm C, Fletcher N, Grounds RM, et al. Changes in the mean systemic filling pressure during a fluid challenge in postsurgical intensive care patients. Intensive Care Med. 2013;39:1299-305.
49. Parkin G, Wright C, Bellomo R, Boyce N. Use of a mean systemic filling pressure analogue during the closed-loop control of fluid replacement in continuous hemodiafiltration. J Crit Care. 1994;9:124-33.
50. Crozier TM, Wallace EM, Parkin WG. Haemodynamic assessment in pregnancy and pre-eclampsia: a Guytonian approach. Pregnancy Hypertens. 2015;5:177-81.
51. Aya HD, Ster IC, Fletcher N, Grounds RM, Rhodes A, Cecconi M. Pharmacodynamic analysis of a fluid challenge. Crit Care Med. 2016;44:880-91.
52. Brengelmann GL. A critical analysis of the view that right atrial pressure determines venous return. J Appl Physiol. 2003;94:849-59.
53. Repessé X, Charron C, Fink J, Beauchet A, Deleu F, Slama M, et al. Value and determinants of the mean systemic filling pressure in critically ill patients' *Am J Physiol Heart Circ Physiol* 309: H1003–H1007, 2015.
54. Brengelmann GL. Letter to the editor: comments on "Value and determinants of the mean systemic filling pressure in critically ill patients". Am J Physiol Heart Circ Physiol. 2015;309:H1370-1.
55. Repessé X, Vieillard-Baron A. Reply to "Letter to the editor: comments on 'Value and determinants of the mean systemic filling pressure in critically ill patients'". Am J Physiol Heart Circ Physiol. 2015;309:H1372-3.
56. Beard DA, Feigl EO. Understanding Guyton's venous return curves. *Am J Physiol Heart Circ Physiol.* 2011;301:H629-33.

57. Teboul JL. Mean systemic filling pressure: we can now estimate it, but for what? Intensive Care Med. 2013;39:1487-1488.58. Parkin G. Re: mean systemic filling pressure: we can now estimate it but for what? Intensive Care Med. 2014;40:139.
59. Teboul JL. Mean systemic filling pressure: we can now estimate it, but for what? Response to comment by Parkin. Intensive Care Med. 2014;40:140.

LEGENDS ADDITIONAL FILES

I: Search in EMBASE, MEDLINE and Cochrane Library: Description of the used search terms per database.

II: Quality assessment according to a modified version of the Newcastle-Ottowa scale for cohort studies: Including representativeness, ascertainment, demonstration, comparability and outcome.

III: PRISMA Flowchart: Description of results of systematic literature search, reasons for excluding studies and the amount of included studies.

IV: Expanded baseline characteristics for included studies: Authors, described MSFP measurement method, patient population, exclusion criteria, age and sex of included patients, type of cardiac output measurement, used vasopressors, sedation and anesthesia techniques and timeframes of MSFP measurements.

V: PRISMA 2009 Checklist: an evidence-based minimum set of items for reporting in systematic reviews and meta-analysis.

ADDITIONAL FILE I. SEARCH IN EMBASE, MEDLINE AND COCHRANE LIBRARY

The specific search terms were as follows:

EMBASE (Ovid) 133 hits**.** Database(s): **Embase Classic+Embase** 1947 to 2017 May 18

Search Strategy:

#	Searches	Results
1	(mean systemic filling pressure* or MSFP or PMSF or mean circulatory filling pressure* or static filling pressure* or mean static filling pressure* or mean systemic pressure*).ti,ab,kw.	2384
2	exp intensive care/ or exp intensive care unit/ or exp intensive care nursing/ or perioperative period/ or surgery/ or perioperative period/ or surgery/ or perioperative nursing/ or peroperative care/ or exp intraoperative period/ or exp intraoperative monitoring/ or (surgery or surgical or IC or ICU* or intensive care or critical care or perioperat* or peri-operat* or intraoperat* or intra-operat* or intravascular).ti,ab,kw.	2975277
3	1 and 2	133

MEDLINE (Pubmed) 193 hits

(mean systemic filling pressure*[tiab] OR MSFP[tiab] OR PMSF[tiab] OR mean circulatory filling pressure*[tiab] OR static filling pressure*[tiab] OR mean systemic pressure*[tiab]) AND ("Critical Care"[Mesh] OR "Intensive Care Units"[Mesh] OR "Critical Care Nursing"[Mesh] OR "Perioperative Period"[Mesh] OR "Perioperative Care"[Mesh] OR "Perioperative Nursing"[Mesh] OR "Intraoperative Care"[Mesh] OR "Intraoperative Period"[Mesh] OR "Monitoring, Intraoperative"[Mesh] OR "Surgical Procedures, Operative"[Mesh] OR "General Surgery"[Mesh] OR "surgery" [Subheading] OR surgery OR surgical OR IC OR ICU* OR intensive care OR critical care OR perioperat* OR intraoperat* OR peri-operat* OR intra-operat*OR intravascular)

Cochrane Library 53 hits

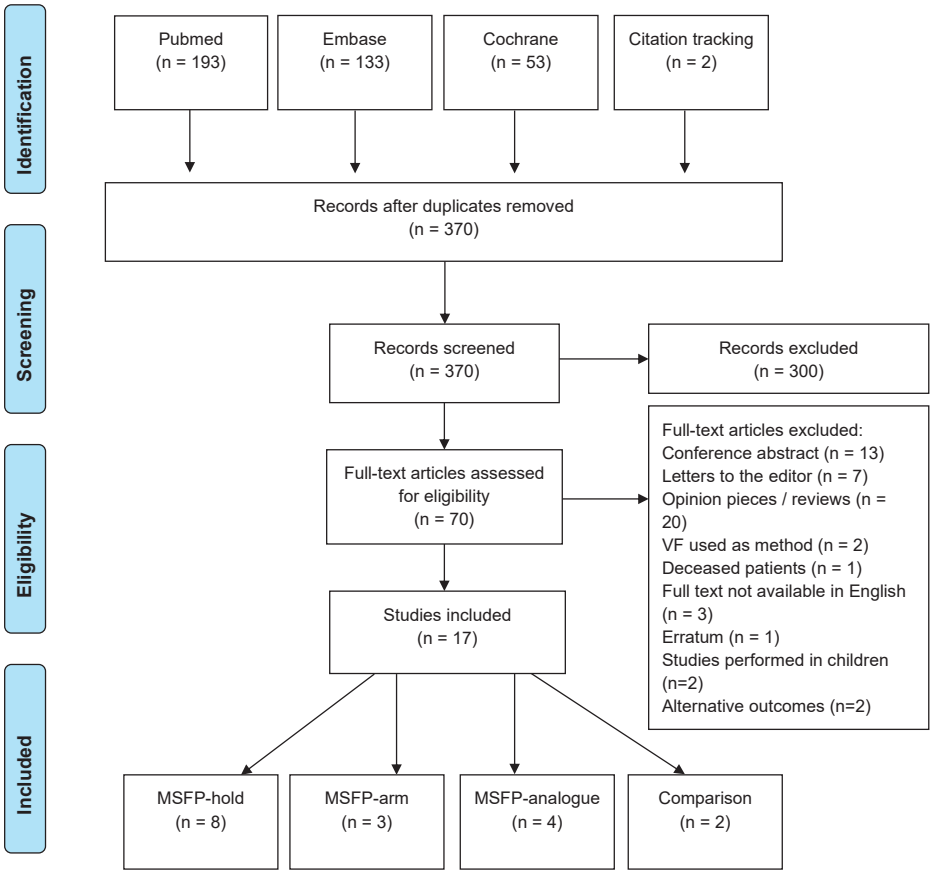
ID	Search	Hits
#1	mean systemic filling pressure* or MSFP or PMSF or mean circulatory filling pressure* or static filling pressure* or mean static filling pressure*: ti, ab, kw (Word variations have been searched)	136
#2	MeSH descriptor: [Critical Care] explode all trees	2131
#3	MeSH descriptor: [Intensive Care Units] explode all trees	3301
#4	MeSH descriptor: [Critical Care Nursing] explode all trees	22
#5	MeSH descriptor: [Perioperative Period] explode all trees	7342
#6	MeSH descriptor: [Perioperative Care] explode all trees	11730
#7	MeSH descriptor: [Perioperative Nursing] explode all trees	130
#8	MeSH descriptor: [Intraoperative Care] explode all trees	1476
#9	MeSH descriptor: [Intraoperative Period] explode all trees	2018
#10	MeSH descriptor: [Monitoring, Intraoperative] explode all trees	1514
#11	MeSH descriptor: [Surgical Procedures, Operative] explode all trees	116933
#12	MeSH descriptor: [General Surgery] explode all trees	365
#13	surgery or surgical or IC or ICU* or intensive care or critical care or perioperat* or peri-operat* or intraoperat* or intra-operat* or intravascular: ti, ab, kw (Word variations have been searched)	157285
#14	#2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13	213997
#15	#1 and #14	53

ADDITIONAL FILE II. QUALITY ASSESSMENT ACCORDING TO A MODIFIED VERSION OF THE NEWCASTLE- OTTOWA SCALE

Study	Method	Representativeness	Ascertainment	Demonstration	Comparability	Outcome	Total stars
Maas (1) 2009	MSFP-hold	*	*	*		*	**4**
Keller (2) 2011	MSFP-hold	*	*	*		*	**4**
Maas (3) 2012	MSFP-hold	*	*	*		*	**4**
Persichini (4) 2012	MSFP-hold	*	*	*		*	**4**
Maas (5) 2013	MSFP-hold	*	*	*		*	**4**
Guerin (6) 2015	MSFP-hold	*	*	*		*	**4**
De Wit (7) 2016	MSFP-hold	*	*	*		*	**4**
Helmerhorst (8) 2017	MSFP-hold	*	*	*		*	**4**
Geerts (9) 2011	MSFP-arm	*	*	*		*	**4**
Aya (10) 2014	MSFP-arm	*	*	*		*	**4**
Aya (11) 2017	MSFP-arm	*	*	*		*	**4**
Parkin (12) 1994	MSFP-analogue		*	*		*	**3**
Cecconi (13) 2013	MSFP-analogue	*	*	*		*	**4**
Gupta (14) 2015	MSFP-analogue	*	*	*		*	**4**
Aya (15) 2016	MSFP-analogue	*	*	*		*	**4**
Maas (16) 2012	MSFP-hold MSFP-arm MSFP-analogue	*	*	*	*	*	**5**
Maas (17) 2012	MSFP-hold MSFP-arm	*	*	*	*	*	**5**

Additional file II. Quality assessment based on a modified version of the Newcastle-Ottowa scale for cohort studies.[18]

ADDITIONAL FILE III. PRISMA FLOWCHART



Additional file III. PRISMA flowchart.[19]

ADDITIONAL FILE IV. BASELINE CHARACTERISTICS FOR INCLUDED STUDIES

Study	Method	N	Patient population (all adult ICU patients)	Exclusion criteria	Age
Maas (1) 2009	MSFP-hold	12	Postoperative cardiac surgery 10 CABG 2 AVR	CHF NYHA IV Aortic aneurysm Extensive PAOD Valvular insufficiency Arrhythmia Artificial pacing Cardiac assist device	64 (10)
Keller (2) 2011	MSFP-hold	9	Postoperative cardiac surgery 3 CABG 6 AVR	LVEF<45% Aortic aneurysms PAOD Valvular insufficiency Arrhythmia Artificial pacing Cardiac assist device	Median 61 IQR 55-75
Maas (3) 2012	MSFP-hold	10	Postoperative cardiac surgery 2 AVR 1 MVP +TVP 7 CABG	CHF NYHA IV Aortic aneurysm Extensive PAOD Valvular insufficiency Arrhythmia IABP	64 (11)
Persichini (4) 2012	MSFP-hold	16	Septic shock	Pregnancy PLR contraindicated	67 (16)
Maas (5) 2013	MSFP-hold	16	Postoperative cardiac surgery 1 MVP 15 CABG	Previous myocardial infarction LVEF<45% Aortic insufficiency Aortic aneurysm Extensive PAOD	64 (11)
Guerin (6) 2015	MSFP-hold	30	Shock aetiology 9 Septic Shock 4 Cardiogenic Shock 2 Hypovolemic Shock	PLR contraindicated	65 (12)
De Wit (7) 2016	MSFP-hold	17	Postsurgical 16 oesophageal resection 1 pancreaticoduodenectomy	Aberrant cardiovascular anatomy Significant valvular regurgitation Severe arrhythmias	62 (9)

Male	Cardiac output measurement	Vasopressor use	Sedation/ Anaesthesia	Timeframe MSFP measurement
10 (83%)	Beat-to-beat CO Modelflow pulse contour analysis Calibrated with thermodilution	9 patients Dobu NE NPN Enox	All patients Propofol Sufentanil	Not described
4 (44%)	Beat-to-beat CO Pulse contour analysis (PiCCO) Calibrated with thermodilution	None	All patients Propofol Sufentanil	Not described
9 (90%)	Beat-to-beat CO Modelflow pulse contour analysis Calibrated with thermodilution(*)	8 patients NE NPN Dobu	All patients Propofol Sufentanil	Within 1 hour after ICU admission
8 (50%)	Beat-to-beat CI pulse contour analysis (PiCCO2) Calibrated with thermodilution.	All patients NE	All patients received sedation (not specified)	Not described
Not described	Beat-to-beat CO Modelflow pulse contour analysis Calibrated with lithium indicator dilution method (LiDCO)	All patients NE 1 patient Dobu	All patients Propofol Sufentanil	Within 1 hour after ICU admission
21 (70%)	Beat-to-beat CI pulse contour analysis (PiCCO2) Calibrated with thermodilution.	23 patients NE 3 patients Dobu	29 patients Propofol 13 patients Remifentanil	Not described
14 (82%)	Beat-to-beat CO Modelflow pulse contour analysis Calibrated with thermodilution (*)	1 patient NE	All patients Propofol	Not described

Study	Method	N	Patient population (all adult ICU patients)	Exclusion criteria	Age
Helmerhorst (8) 2017	MSFP-hold	22	Postoperative cardiac surgery 22 CABG	CHF Severe arrhythmias Intracardiac shunts Extensive PAOD Pulmonary disease Aortic aneurysm Significant valvular disease	63 (59-66)
Geerts (9) 2011	MSFP-arm	24	Postoperative cardiac surgery 17 CABG 7 CABG plus valve repair	Aortic aneurysm Extensive PAOD Arrhythmias Postoperative valvular insufficiency Artificial pacing Cardiac assist device	64 (10)
Aya (10) 2014	MSFP-arm	20	Postoperative cardiac surgery 13 CABG 4 AVR 4 MVR	Extensive PAOD Postoperative valve regurgitation Tachyarrhythmia IABP Pregnancy Body weight below 50kg	63 (11)
Aya (11) 2017	MSFP-arm	80	Postoperative cardiac surgery 36 CABG 27 AVR+CABG 12 MVR+CABG 5 Other	Extensive PAOD Postoperative valve regurgitation Tachyarrhythmia IABP Pregnancy Body weight below 50kg Active bleeding Sepsis	70 Range 52-80
Parkin (12) 1994	MSFP-analogue	10	Multi-organ failing patients receiving CVVH for acute renal failure	Not described	65 Range 24-77
Cecconi (13) 2013	MSFP-analogue	39	Postoperative fluid challenge 22 Cardiac surgery 8 Shock 6 Non cardiac surgery 3 Other	Aortic regurgitation Tachyarrhythmia IABP Pregnancy Body weight below 50 kg	68 (12)
Gupta (14) 2015	MSFP-analogue	61	Postoperative cardiac surgery 40 CABG 8 CABG + valve replacement 8 Valve replacement 5 Bentall's procedure 7 DDD pacing	Not described To note: patients with arrhythmia, paced rhythms and spontaneous breathing efforts were included	63 (11)

Male	Cardiac output measurement	Vasopressor use	Sedation/ Anaesthesia	Timeframe MSFP measurement
17 (85%)	Beat-to-beat CO obtained by Modelflow pulse contour analysis. Hemodynamics also monitored by LiDCO*plus*	2 patients NE	All patients Propofol Sufentanil	1 hour after ICU admission
19 (79%)	CO not required for MSFP measurement	16 NE 9 Dobu 1 NPN	All patients Propofol Sufentanil	Within 2 hour after ICU admission
17 (85%)	CO not required for MSFP measurement	13 NE 4 Dopa 3 Milrinone	16 propofol 11 morphine 2 alfentanyl	Initial period at ICU (not further defined)
62 (78%)	CO not required for MSFP measurement	43 patients Dopa or NE	26 patients Propofol or Morphine	Initial period at ICU (not further defined)
7 (70%)	Thermodilution CO measured **each hour**	All patients inotropic or vasoactive medication. (not specified)	Not described	Not described
26 (67%)	Beat-to-beat CO Pulse contour analysis with LiDCO plus. Calibrated with lithium-dilution	2 NE 5 Dopa 4 Milrinone	Not described	Not described
46 (75%)	PAC thermodilution (not continuous)	27 NE 6 Dobu 10Milnirone 9 NPN 6 Glyceryl trinitrate	All patients Propofol Fentanyl or Morphine	Within 6 hours after ICU admission

Study	Method	N	Patient population (all adult ICU patients)	Exclusion criteria	Age
Aya (15) 2016	MSFP-analogue	26	Postoperative fluid challenge 7 Cardiac surgery 19 Noncardiac surgery	Extensive PAOD Postoperative valve regurgitation Tachyarrhythmia IABP Pregnancy Body weight below 50kg Active bleeding Sepsis	68 Range 53-80
Maas (16) 2012	MSFP-hold MSFP-arm MSFP-analogue	11 11 11	Postoperative cardiac surgery 9 CABG 2 AVR	LVEF<40% Aortic aneurysm Extensive PAOD Postoperative arrhythmia Postoperative valvular insufficiency Artificial pacing Cardiac assist device	64 Range 50-80
Maas (17) 2012	MSFP-arm MSFP-hold	15 12	Postoperative cardiac surgery 9 CABG 5 Valve 1 CABG + valve	NYHA IV Aortic aneurysm Extensive PAOD Arrhythmias	64 (11)

Additional file IV. Baseline characteristics for included studies. CHF= congestive heart failure. CABG= coronary artery bypass, MVR= mitral valve replacement, MPV= mitral valve prolapse, AVR= aortic valve replacement, TVP= tricuspid valve prolapse, NYHA=New York Heart Association scoring system, PAOD= peripheral arterial occlusive disease, LVEF= left ventricular ejection fraction. CO= cardiac output, CVVH=continuous veno-venous hemodiaflitration, IABP= intra-aortic balloon pump, Dobu= dobutamine, NE= norepinephrine, NPN= nitroprusside sodium, Dopa= dopamine, Enox= enoximone, GI= gastrointestinal. (*) Calibration techniques not available in the articles, authors contacted. Age is presented as mean with standard deviation (SD) or median with range or interquartile range (IQR). Number of males per study is presented as counts with percentage.

Male	Cardiac output measurement	Vasopressor use	Sedation/ Anaesthesia	Timeframe MSFP measurement
16 (62%)	Beat-to-beat CO LiDCOplus pulse power analysis Calibrated with lithium dilution	9 NA 1 Dopa 2 Dopexamine 1 Dobu 3 Milrinone 1Adrenaline	14 patients Propofol	Initial period at ICU (not further defined)
9 (82%)	Beat-to-beat CO Modelflow pulse contour analysis Calibrated with thermodilution.	4 Dobu 1 Enox 5 NE 1 NPN	All patients Propofol Sufentanil	Within 2 hours after ICU admission
Not described	Beat-to-beat CO Modelflow pulse contour analysis Calibrated with thermodilution (*)	8 Dobu 1 Enox 7 NE 1 Epinephrine 1 NPN	Propofol Sufentanil	Within 1 hour after ICU admission

Additional file V. PRISMA 2009 Checklist.[20] This additional file can be downloaded from the journal website.

REFERENCES ADDITIONAL FILES

1. Maas JJ, Geerts BF, van den Berg PC, Pinsky MR, Jansen JR. Assessment of venous return curve and mean systemic filling pressure in postoperative cardiac surgery patients. Crit Care Med. 2009;37:912-8.
2. Keller G, Desebbe O, Benard M, Bouchet JB, Lehot JJ Bedside assessment of passive leg raising effects on venous return. J Clin Monit Comput. 2011;25:257-63.
3. Maas JJ, de Wilde RB, Aarts LP, Pinsky MR, Jansen JR. Determination of vascular waterfall phenomenon by bedside measurement of mean systemic filling pressure and critical closing pressure in the intensive care unit. Anesth Analg. 2012;114:803-10.
4. Persichini R, Silva S, Teboul JL, Jozwiak M, Chemla D, Richard C, et al. Effects of norepinephrine on mean systemic pressure and venous return in human septic shock. Crit Care Med. 2012;40:3146-53.
5. Maas JJ, Pinsky MR, de Wilde RB, de Jonge E, Jansen JR. Cardiac output response to norepinephrine in postoperative cardiac surgery patients: interpretation with venous return and cardiac function curves. Crit Care Med. 2013;41:143-50.
6. Guerin L, Teboul JL, Persichini R, Dres, M, Richard C, Monet X. Effects of passive leg raising and volume expansion on mean systemic pressure and venous return in shock in humans. Critical Care. 2015; 19:411
7. de Wit F, van Vliet AL, de Wilde RB, Jansen JR, Vuyk J, Aarts LP, et al. The effect of propofol on haemodynamics: cardiac output, venous return, mean systemic filling pressure, and vascular resistances. Br J Anaesth. 2016;116:784-9.
8. Helmerhorst HJ, de Wilde RB, Lee DH, Palmen M, Jansen JR, van Westerloo DJ, et al. Hemodynamic effects of short-term hyperoxia after coronary artery bypass grafting. *Ann Intensive Care.* 2017;7:20.
9. Geerts BF, Maas J, de Wilde RB, Aarts LP, Jansen JR. Arm occlusion pressure is a useful predictor of an increase in cardiac output after fluid loading following cardiac surgery. Eur J Anaesthesiol. 2011;28:802-6.
10. Aya HD, Rhodes A, Fletcher N, Grounds RM, Cecconi M. Transient stop-flow arm arterial-venous equilibrium pressure measurement: determination of precision of the technique. J Clin Monit Comput. 2016;30:55-61.
11. Aya HD, Rhodes A, Chis Ster I, Fletcher N, Grounds RM, Cecconi M. Hemodynamic effect of different doses of fluids for a fluid challenge: a quasi-randomized controlled study. Crit Care Med. 2017;45:e161-8.
12. Parkin G, Wright C, Bellomo R, Boyce N. Use of a mean systemic filling pressure analogue during the closed-loop control of fluid replacement in continuous hemodiafiltration. J Crit Care. 1994;9:124-33.
13. Cecconi M, Aya HD, Geisen M, Ebm C, Fletcher N, Grounds RM, et al. Changes in the mean systemic filling pressure during a fluid challenge in postsurgical intensive care patients. Intensive Care Med. 2013;39:1299-305.
14. Gupta K, Sondergaard S, Parkin G, Leaning M, Aneman A. Applying mean systemic filling pressure to assess the response to fluid boluses in cardiac post-surgical patients. Intensive Care Med. 2015;41:265-72.
15. Aya HD, Ster IC, Fletcher N, Grounds RM, Rhodes A, Cecconi M. Pharmacodynamic analysis of a fluid challenge. Crit Care Med. 2016;44:880-91.

16. Maas JJ, Pinsky MR, Geerts BF, de Wilde RB, Jansen JR. Estimation of mean systemic filling pressure in postoperative cardiac surgery patients with three methods. Intensive Care Med. 2012;38:1452-60.
17. Maas JJ, Pinsky MR, Aarts LP, Jansen JR. Bedside assessment of total systemic vascular compliance, stressed volume, and cardiac function curves in intensive care unit patients. Anesth Analg. 2012;115:880-7.
18. Wells G, Shea B, O'Connell J, Peterson J, Welch V, Losos M, et al: The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp. 2009. Accessed 20 February 2017.
19. Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gøtzsche PC, Ioannidis JP, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. PLoS Med. 2009;6:e1000100
20. Moher D Liberati A, Telzlaff J, Altman DG, the PRISMA Group. Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA statement. PLoS Med.2009;6;e1000097

3

Defining human mean circulatory filling pressure in the Intensive Care Unit

Marije Wijnberge
Jaap Schuurmans
Rob B.P. de Wilde
Martijn K. Kerstens
Alexander P. Vlaar
Markus W. Hollmann
Denise P. Veelo
Michael R. Pinsky
Jos R.C. Jansen
Bart F. Geerts

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ABSTRACT

Introduction

Potentially, mean circulatory filling pressure (MCFP) could aid hemodynamic management in patients admitted to the intensive care unit (ICU). However, data regarding the normal range for MCFP do not exist challenging its clinical use. We aimed to define the range for MCFP for ICU patients and also calculated in what percentage of cases equilibrium between arterial blood pressure (ABP) and central venous pressure (CVP) was reached. In patients in which no equilibrium was reached, we corrected for arterial to venous compliance differences. Finally, we studied the influence of patient characteristics on MCFP. We hypothesized fluid balance, the use of vasoactive medication, being on mechanical ventilation and the level of positive end-expiratory pressure would be positively associated with MCFP.

Methods

We retrospectively studied a cohort of 311 patients that had cardiac arrest in ICU whilst having active recording of ABP and CVP one minute after death.
Results: Median MCFP was 15 mmHg (IQR 12-18). ABP and CVP reached an equilibrium state in 52% of the cases. Correction for arterial to venous compliances differences resulted in a maximum alteration of 1.3 mmHg in MCFP. Fluid balance over the last 24 hours, the use of vasoactive medication and being on mechanical ventilation were associated with a higher MCFP.

Conclusion

Median MCFP was 15 mmHg (IQR 12-18). When ABP remained higher than CVP, correction for arterial to venous compliance differences did not result in a clinically relevant alteration of MCFP. MCFP was affected by factors known to alter vasomotor tone and effective circulating blood volume.

Key words

hemodynamics, critical care, physiology, arterial pressure, venous pressure.

New and Noteworthy

In a cohort of 311 ICU patients, median MCFP measured after cardiac arrest was 15 mmHg (IQR 12-18). In 48% of cases ABP remained higher than CVP but correction for arterial to venous compliance differences did not result in clinically relevant alterations of MCFP. Fluid balance, use of vasopressors or inotropes and being on mechanical ventilation were associated with a higher MCFP.

INTRODUCTION

Mean circulatory filling pressure (MCFP) is of clinical interest because it provides information on intravascular effective circulatory blood volume or stressed volume (Vs) and circulatory vascular compliance (Csys).[1-8] Potentially, MCFP could be used to guide hemodynamic treatment in patients admitted to the Intensive Care Unit (ICU). [9,10]

MCFP can be estimated by several techniques. The inspiratory hold method (MCFP-hold) is most commonly used to determine MCFP in patients in whom the heart is beating.[11] However, MCFP-hold data for different patient populations are lacking. Absence of a range of MCFP values in ICU patients hampers the clinical use of MCFP.

The 'gold standard' MCFP is determined during a no-flow state vascular equilibrium pressure where arterial pressure (ABP) equals central venous pressure (CVP).[9,12-14] This MCFP value can be determined in deceased patients shortly after cardiac arrest.

MCFP at equilibrium, defined as ABP equals CVP, is not reached in all cases. No-flow ABP greater than no-flow CVP can occur if arterioles collapse when arterial pressure decreases. This no-flow ABP is usually referred to as the critical closing pressure (CCP). [14,15] The presence of an ABP to CVP gap is hypothesized to be caused by a self-regulating vascular mechanism, or 'vascular waterfall'; which functions to keep arterial pressure slightly elevated potentially sustaining blood flow to vital organs.[15] In the presence of an ABP (CCP) to CVP gap, MCFP can be calculated using the correction formula: MCFP = CVP+1/c*(CCP-CVP), where 1/c is the arterial to venous compliance ratio.[16]

We describe MCFP in ICU patients one-minute following cardiac arrest. Our main objective was to define the range for MCFP for patients admitted to the ICU. Secondly, we determined the percentage of patients for which an equilibrium of ABP and CVP was reached within one minute after cardiac arrest. In patients in whom no equilibrium was reached, we determined the impact of correcting for a CCP to CVP gap. Lastly, we determined the influence of patient characteristics and clinical conditions on MCFP. We hypothesized fluid balance, being on mechanical ventilation, the level of positive end-expiratory pressure (PEEP) and use of vasoactive medication (vasopressors or inotropes) to be associated with a higher MCFP. The effect of gender, age, ICU length of stay, hospital length of stay, APACHE IV score and APACHE IV admission diagnosis were studied in an exploratory fashion.

METHODS

Study design and ethics: This was a retrospective observational study. The study protocol was assessed by the Medical Ethics Committee of the Leiden University Medical Center (LUMC). A waiver to perform the study was obtained (P15.144/NV/nv; 2 September 2015).

Patient population and data acquisition: All adult patients that died in the LUMC ICU between 2007 and 2015 while having continuous ABP and CVP monitoring at the time of cardiac arrest were included for data acquisition. ABP was measured via an arterial catheter (Arrow, 20-22G Arrow International Inc, Reading PA, USA) in the radial artery or femoral artery and CVP was measured via a central venous catheter (Vygon MultCath 3, Vygon GmbH Aachen, Germany) in the internal jugular vein. Hewlett and Packard blood pressure modules were used (M1006B, Boeblingen, Germany) and both arterial and venous pressure monitors were zeroed to the patient's phlebostatic point.
A data query employing the patient digital management system (Metavision, PDMS, IMDSoft vers 5.0, Needham, MA, USA) was performed to collect data. ABP and CVP measurements were extracted one minute after cardiac arrest. Cardiac arrest was defined by a flat line on the monitor. Data were reviewed for validity by two researchers (MW and MK).

Patients were included for data analysis if both ABP and CVP measurements were present one minute after cardiac arrest. Patient data were excluded if no CVP recordings were present or CVP values were reported as less than -1 mmHg. Patient data were also excluded when CVP was higher than ABP since accuracy of the measured pressures in these cases can be questioned. Patients on mechanical assist devices were excluded.

For our second objective, we determined the percentage of patients in which equilibrium of ABP and CVP after cardiac arrest was reached. Equilibrium pressure was defined as a difference between ABP and CVP of less than 2 mmHg. The 2 mmHg cut-off was decided upon taking into account the accuracy of the disposable pressure transducers and the pressure modules (connected to the bedside patient monitor).[17] The group in which no equilibrium pressure was reached (ABP to CVP gap of more than 2 mmHg) was described as the CCP group. In this CCP group, MCFP was calculated using the formula: MCFP = CVP x 1/c*(CCP-CVP), where 1/c is the arterial to venous compliance ratio. MCFP was calculated for three different c values (c=16, 30 and 60) since the reported arterial to venous compliance ratio varies.[9,18-21]

For our third objective, the influence of patient characteristics and clinical conditions on MCFP was determined. Before start of the study, we hypothesized that fluid balance, use of vasopressors or inotropes, mechanical ventilation of the lungs and the level of PEEP to be associated with a higher MCFP value. Fluid balance was analyzed over the last 24 hours and for the cumulative total during ICU stay. Vasoactive medication was defined as noradrenaline, adrenaline, dopamine and dobutamine. Exploratory studied were the effect of patient characteristics such as gender and age, ICU length of stay, hospital length of stay, APACHE IV score and APACHE IV admission diagnosis.

Statistical analyses: Descriptive statistics were used for objective one and two. Continuous data were presented as median with range and/or IQR or mean with standard deviation when normally distributed (assessed by inspection of the histogram). Categorical data were given as frequencies with percentages.

Inferential statistics were used for our third objective. Linear regression analyses were used to assess the effect of fluid balance, vasoactive medication (vasopressors or inotropes), being on mechanical ventilation and the level of PEEP on MCFP. For these analyses, a probability value of $p<0.05$ was considered statistically significant. The effect of gender and age, ICU length of stay, hospital length of stay, APACHE IV score, APACHE IV admission were studied in an exploratory fashion. First scatterplots were made to visually assess the correlations; subsequently univariate analyses were performed. Categorical variables (e.g., APACHE IV admission diagnosis) were transformed into dummy variables.

All analyses were performed using IBM SPSS Statistics version 23.0.

RESULTS

The data query resulted in data on 1,341 patients, 907 patients were excluded for having no CVP measurement and 90 patients were excluded for not having an ABP measurement one minute after cardiac arrest (Figure 1). Exclusion of evidently false ABP or CVP (extremely high or low), exclusion of one patient being below 18 years of age and exclusion of four patients on mechanical circulatory assist devices resulted in 311 patients for final analysis.

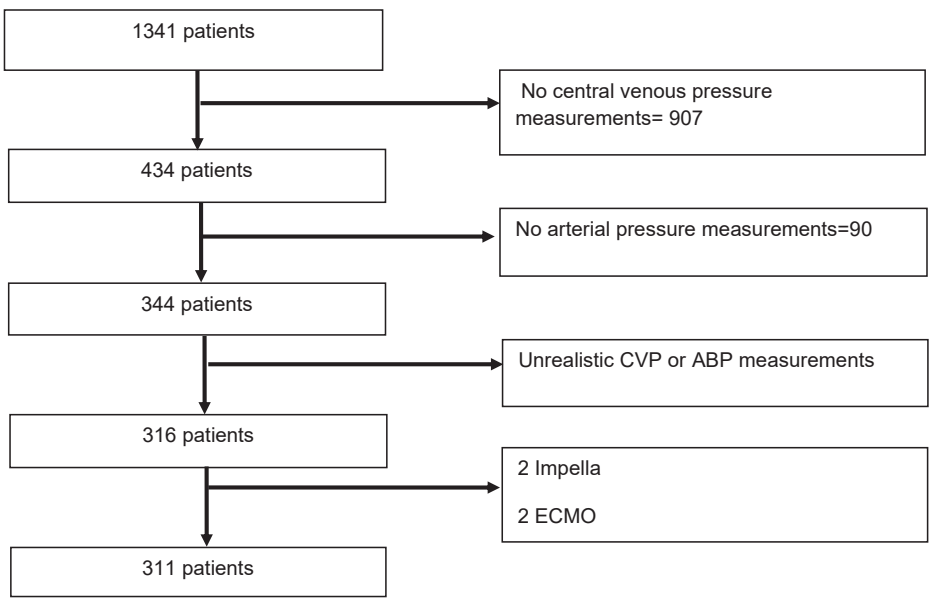


Figure 1. Flowchart of patient exclusion.

Baseline characteristics: Table 1 shows the baseline characteristics. The median age of included patients was 67 years and 64% were male. The primary reason for ICU admission was cardiovascular pathology (31%). Median MCFP for all patients was 15 mmHg (IQR 12-18).

	n= 311	n=162 (ABP=CVD)	n=149 (ABP>CVD)
	100.0%	52.1 %	47.9 %
MCFP (one minute)	15 [12-18]	16 [14-18]	13 [9-18]
Male (n, %)	198 (63.7%)	99 (61.5%)	99 (66.4%)
Age (years)	67 [59-75]	68 [60-75]	67 [57-75]
Length (meters)	1.74 +/- 0.10	1.74 +/- 0.09	1.75 +/- 0.09
Weight (kg)	80 +/- 17	80 +/- 17	81 +/- 17
BMI	26 +/- 5	26 +/- 5	26 +/- 5
ICU length of stay (days)	3 [1-8]	2 [1-8]	3 [1-9]
Hospital length of stay (days)	6 [2-16]	6 [2-17]	6 [2-16]
Fluid balance 24 hr before dying (in ml)	3949 [2262-6619]	4022 [2535-6802]	3846 [1912-6463]
Vasoactive medication	137 (44.1%)	80 (49.7%)	57 (38.3%)
Mechanical ventilation	194 (62.4%)	110 (67.9%)	85 (56.4%)
Underlying diagnosis (APACHE IV)			
-Cardiac surgical	39 (12.5%)	26 (16.0%)	13 (8.7%)
-Cardiovascular	96 (30.9%)	47 (29.0%)	49 (32.9%)
-Sepsis	51 (16.4%)	29 (17.9%)	17 (11.4%)
-Respiratory	46 (14.8%)	26 (16.0%)	25 (16.8%)
-Neurology	17 (5.5%)	5 (3.1%)	12 (8.1%)
-Gastro-intestinal	53 (17.0%)	24 (14.8%)	29 (19.5%)
-Hematology	9 (2.9%)	5 (3.1%)	4 (2.7%)

Table 1. Baseline characteristics. MCFP in mmHg, the MCFP represents the CVP one minute after cardiac arrest. Continuous data are presented median with interquartile range, or mean with standard deviation (+/-) when normally distributed. Categorical data are given as frequencies with percentages. ABP = arterial blood pressure at zero flow, BMI= body mass index, CVP = central venous pressure at zero flow, ICU = intensive care unit, MCFP = mean circulatory filling pressure.

Proportion of patients for which equilibrium between ABP and CVP was reached: In 162 patients (52%) an equilibrium pressure was reached one minute after cardiac arrest. In the remaining 149 patients (48%) ABP remained higher than CVP. In this CCP group the median difference between ABP and CVP was 8 mmHg (IQR 5-13). Median MCFP in the CCP group was lower compared to the equilibrium (non-CCP) group (13 mmHg, IQR 9-18 versus 16 mmHg IQR 14-18). In the CCP group less vasopressors and inotropes were used and fewer patients were on mechanical ventilation (Table 1). Correction for arterial to venous compliance differences with c-values of 16, 30 and 60, respectively, resulted in a 1.3, 1.1 and 0.9 mmHg difference (Table 2).

MCFP related to patient characteristics: Table 3 demonstrates median MCFP per Apache IV admission diagnosis. Patients who underwent cardiac surgery had the highest median MCFP (17 mmHg, IQR 14-21) compared to the other subgroups.

Subset ABP>CVP	n=149
CVP	13.0 [9.0-18.0]
ABP	23.0 [17.0-30.0]
Difference	8.0 [5.0-13.0]
MCFP for c = 16	14.3 [10.2-18.3]
MCFP for c = 30	14.1 [9.8.1-18.1]
MCFP for c = 60	13.9 [9.4-18.1]

Table 2. MCFP in mmHg in the subset of patients reaching no equilibrium pressure (ABP>CVP). The correction factors for critical closing pressure MCFP = CVP + 1/c*(CCP-CVP) where c is the arterial to venous compliance ratio (see text for details). Continuous data are presented as median with interquartile range. ABP = arterial blood pressure at zero flow, CVP = central venous pressure at zero flow, ICU = intensive care unit, MCFP = mean circulatory filling pressure.

Apache IV admission diagnosis	n (%)	MCFP
Cardiosurgical	39 (12.5%)	17 [14-21]
Cardiovascular	96 (30.9%)	14 [11-18]
Respiratory	51 (16.4%)	14 [12-17]
Sepsis	46 (14.8%)	14 [11-18]
Gastrointestinal	53 (17.0%)	16 [14-20]
Neurology	17 (5.5%)	13 [8 -17]
Haematology	9 (2.9%)	16 [12-21]

Table 3. MCFP values (in mmHg) per Apache IV admission diagnosis presented in median with interquartile range [] and range. APACHE: Acute Physiology and Chronic Health Evaluation

The univariate regression analysis (Table 4) revealed fluid balance within the last 24 hours, use of vasoactive medication (vasopressors or inotropes), mechanical ventilation to be associated with a higher MCFP. Specifically, MCFP was higher (16.4 mmHg +/- 5.8 versus 14.6 mmHg +/- 5.7) in patients on vasopressors or inotropes and in patients on mechanical ventilation (16.3 mmHg +/- 5.9 versus 14.1 mmHg +/- 5.4). The level of PEEP was not associated with a higher MCFP value. The cumulative fluid balance was not associated with a higher MCFP value. The exploratory analyses demonstrated admission diagnosis to be associated with MCFP

The multivariate regression analysis (Table 5) revealed use of vasoactive medication, mechanical ventilation and admission diagnosis to be associated with MCFP. Fluid balance and mechanical ventilation showed high co-linearity. Patients on mechanical ventilation had a significantly higher fluid balance. Therefore, only one of the two variables could be incorporated in the multivariate model. The best model was chosen.

	R^2	Beta	95% CI	p-value
APACHE score IV	0.00	0.00	-0.17 to 0.02	0.96
Length	0.01	-4.44	-11.37 to 2.48	0.21
Weight	0.00	0.02	-0.21 to 0.05	0.39
BMI	0.01	0.09	-0.34 to 0.21	0.16
ICU length of stay	0.00	0.00	-0.00 to 0.00	0.81
Hospital length of stay	0.00	0.00	0.00 to 0.00	0.92
Age	0.01	-0.03	-0.08 to 0.02	0.18
Gender	0.00	0.08	-1.27 to 1.43	0.91
APACHE IV admission diagnosis				
Cardiovascular	Baseline*			
Cardiothoracic surgery		3.01	0.89 to 5.12	**<0.01**
Gastrointestinal		2.02	0.11 to 3.92	**0.04**
Sepsis		-0.30	-2.30 to 1.69	0.77
Respiratory		-1.20	-3.13 to 0.73	0.22
Haematology		1.65	-2.23 to 5.53	0.40
Neurological		-2.14	-5.07 to 0.79	0.15
Fluid balance in L (24 hours)	0.03	0.26	0.10 to 0.42	**<0.01**
Cumulative fluid balance	0.01	0.00	0.00 to 0.00	0.15
Vasoactive medication	0.02	1.79	0.50 to 3.08	**<0.01**
Mechanical ventilation	0.03	2.17	0.86 to 3.49	**<0.01**
Level of PEEP	0.01	0.17	-0.04 to 0.37	0.11

Table 4. Univariate regression analysis. *= Statistical Baseline chosen based on largest group. Beta = unstandardized Beta. APACHE = Acute Physiology and Chronic Health Evaluation scoring system. ICU = Intensive Care Unit. PEEP = positive end-expiratory pressure.

	Beta	95% CI	p-value
Vasoactive medication	1.43	0.16 – 2.70	0.03
Mechanical ventilation	1.55	0.23 – 2.86	0.02
APACHE IV admission diagnosis			
Cardiothoracic surgery	2.90	0.97 – 4.83	<0.01
Gastrointestinal	2.25	0.55 – 3.93	<0.01

Table 5. Multivariate regression analysis. APACHE = Acute Physiology and Chronic Health Evaluation scoring system. Beta = unstandardized Beta. CI= confidence interval.

DISCUSSION

In this study, we determined MCFP one minute after cardiac arrest in a cohort of 311 ICU patients. Our main findings were: 1) Median MCFP in this population was 15 mmHg (IQR 12-18); 2) ABP and CVP reached equilibrium within one minute after cardiac arrest in 52% of patients. In the remaining 48% of patients ABP was higher than CVP, indicating presence of a critical closing pressure. 3) Fluid balance over the last 24 hours, use of vasopressors or inotropes and being on mechanical ventilation were associated with

a higher MCFP. Cardiac surgical patients had the highest MCFP 17 mmHg (IQR 13-21) compared to the other subgroups.

The first insights in human MCFP measurements date from 1940, when cardiovascular physician-physiologist Isaac Starr measured MCFP in deceased patients.[13,22] The method in our study is similar to the method Starr used with one important distinction; our measurements were set at one minute after cardiac arrest, whereas in Starr his experiments the measurements were made within 30 minutes of death.[13,22] Repessé et al. reported a mean MCFP of 13 ± 6 mmHg in 202 ICU patients one minute after cardiac arrest.[23] In our study both ABP and CVP had to be present for patient inclusion whereas Repessé et al. extended inclusion to patients in which only one of the two pressures (ABP or CVP) was available. In that study, both ABP and CVP were present in 157 out of 202 patients.

Strikingly, all 157 cases reached one-minute equilibrium whereas in our cohort only 52% of patients reached an equilibrium. Differences in the cohorts studied (e.g. medical versus surgical patients, differences in underlying pathology) and a possibly more conservative definition of equilibrium in our study might explain the diverging results. The latter is an assumption, since Repessé et al. did not give their definition of equilibrium. In our study, we defined equilibrium as pressure differences between ABP and CVP smaller than or equal to 2 mmHg.

Median ABP (or CCP) to CVP pressure gap in patients who did not reach equilibrium was 8 mmHg. This closely resembles the pressure gap reported during ventricular fibrillation for pacemaker implantation.[18,24] However, in that population duration of no-flow was not long enough for pressures to equilibrate. The persistence of a low level of flow in the left carotid artery for up to four minutes has been described in pigs during ventricular fibrillation.[25] Waiting longer for the pressures to equilibrate in deceased patients poses the risk of confounding MCFP measurements by vasodilation due to energetic loss of vasomotor tone or reflex vasoconstriction due to loss of vascular pulsatility. Measuring CVP at one minute after cardiac arrest currently represents the uniform standard for determination of MCFP in deceased patients.

Maas et al. explain the existence of CCP as part of a self-regulating vascular mechanism referred to as the vascular waterfall.[15] Potentially, CCP could impede measurement of no-flow MCFP, However, attempting to correct for arterial to venous compliance differences (1/16, 1/30 and 1/60) did not result in different MCFP values. Existing literature on MCFP measurements during induced cardiac arrest have reported similar findings, with most studies describing a negligible increase for MCFP of 0.3-0.5 mmHg and 1.2 mmHg in animal and human studies respectively. [18,20,21,26] This difference is within the 2 mmHg accuracy cut-off we used to define equilibrium pressure, and thus not considered to be clinically relevant. CVP is considered the main determinant of

MCFP in a no-flow state, suggesting that measuring no-flow CVP alone at one-minute after cardiac arrest is sufficient to determine MCFP.

Animal studies show a large variety in arterial to venous vascular compliance ratios and in humans, hypertension and comorbidity affect this ratio.[19,27,28] [20] We therefore explored compliance correction using three physiological plausible potential ratios (16,30 and 60).

Influencing factors: We found that fluid balance within the last 24 hours, use of vasoactive medication, mechanical ventilation and admission diagnosis were associated with MCFP in the univariate regression analysis. MCFP behaves in a predictable fashion in line with known physiologic mechanisms.

A higher MCFP was found in patients with a more positive fluid balance over the last 24 hours. An increase in stressed volume (Vs) given a constant circulatory compliance (Csys) leads to a higher MCFP (MCFP = Csys x Vs). The univariate positive correlation found between fluid balance and MCFP is consistent with existing literature. Guérin et al., also found an increase in MCFP values after volume expansion. [29] An important note is that fluid overload does not equal a high MCFP. MCFP takes into account the intravascular volume status; a patient may have anasarca, be hypovolemic at the same time and thus have a low MCFP. This probably explains why the cumulative fluid balance was not associated with MCFP in the univariate analysis. In our multivariate analysis, fluid balance over the last 24 hours was no longer found to significantly associate with MCFP. Fluid balance and mechanical ventilation showed high co-linearity. Patients receiving mechanical ventilation had a significantly higher fluid balance.

Vasopressors (e.g. norepinephrine) alter MCFP by increasing Csys or by recruitment of unstressed volume. Unstressed volume (Vu) is the blood contained in the system at zero transmural pressure. Animal research has suggested that with increased sympathetic activity splanchnic resistance (a part of the circulation with a high proportion of unstressed volume) increased proportionally more than total vascular resistance. This results in blood flow redistribution away from larger unstressed vascular beds in the splanchnic region leading to an increase in Vs, and thereby increasing MCFP without a change in total blood volume (Vs +Vu).[30,31] Repesse et al. also found the use of norepinephrine ($p<0.01$) to be associated with increased MCFP. [23]

Mechanical ventilation increases MCFP by shifting blood from the pulmonary to the systemic circulation.[18] Additionally, the increase in intrathoracic pressure by mechanical ventilation leads to an increase in CVP and a decrease in ABP. If sustained, both baroreflex-induced increased sympathetic tone and the reaction of fluid loading to a decrease in ABP may also increase MCFP.[32,33] We expected the level of PEEP to be also correlated with MCFP, since PEEP shifts the diaphragm in a more caudal position increasing abdominal pressure, thereby increasing pressure in the splanchnic compartment, compressing splanchnic vasculature, and consequently increasing stressed volume resulting in

elevated MCFP.[34] Furthermore, in clinical practice, decreases in cardiac output by increasing PEEP is often compensated for by fluid resuscitation. Surprisingly, in our univariate analysis the level of PEEP alone was not correlated with MCFP.

Rothe stated 'MCFP is a measure of the fullness of the circulation'.[30] Both filling the container but also decreasing the cross-sectional area of the container increases fullness. Our study validates his statement and demonstrates that MCFP behaves in a fashion predictable from known physiologic mechanisms. Currently it is extremely difficult to determine the fullness of the vascular system, even in critically ill patients who regularly have invasive hemodynamic monitoring. The current hemodynamic variables do not provide a complete picture, MCFP might aid to guide hemodynamic management in ICU patients. Clinical studies should determine whether integrating MCFP in clinical practice proves to be beneficial.

The exploratory analyses of the influence of the admission diagnosis demonstrated that cardiac surgical patients and gastrointestinal patients had a higher MCFP. Hypothetically, cardiac surgery patients have less decreased diastolic compliance leading to an increased CVP for the same ventricular filling and requiring a higher driving pressure for venous return to sustain cardiac output. For blood to flow back from the periphery to the right atrium there needs to be a pressure gradient such that MCFP exceeds CVP. Thus, if CVP is elevated, MCFP must be higher for blood to flow and for cardiac output to sustain.[35] A considerable number of the gastrointestinal patients had hepatic failure (45%). Moreover, liver dysfunction and cardiac dysfunction often co-exists and they both result in RAAS-driven fluid retention.[36,37]

We report on the influence of the admission diagnosis. It may be that a fraction of the patients died from a cause different than their admission diagnosis. Unfortunately, we could not extract the cause of death from the patient files. However, the time from ICU admission till death was relatively short with a median of 3 days, therefore we think it is justifiable to use the admission diagnosis for these exploratory analyses.

This study has several limitations, all related to the retrospective design of the study. Most importantly, we were obliged to adhere to strict inclusion criteria in order to guarantee valid measurements. Prior to data collection we decided to only include patients when both ABP and CVP were present. As a result, we had to exclude 1030 out of 1341 patients limiting the size of our cohort and our results need to be confirmed in a larger study. However, we report on the biggest cohort available.

CONCLUSION

Our database study is one of the first defining normal MCFP values. In a cohort of 311 patients who died in ICU we found that the median MCFP was 15 mmHg (IQR 12-18). CVP

and ABP reached an equilibrium state in 52% of cases. In the remaining 48% of cases the ABP remained higher than the CVP illustrating the existence of a vascular waterfall. Correction for arterial to venous compliance differences did however not result in clinically relevant alterations of MCFP in those patients. Fluid balance over the last 24 hours, use of vasopressors or inotropes and being on mechanical ventilation were associated with a higher MCFP.

Disclosures

None of the authors have conflicts of interest, financial or otherwise, for the submitted work

Author contributions

J.R.J. and B.F.G. conceived and designed research; M.W., R.B.d.W., and M.K.K. performed experiments; M.W. and J.S. analyzed data; M.W., R.B.d.W., A.P.V., M.W.H., M.R.P., J.R.J., and B.F.G. interpreted results of experiments; M.W. prepared figures; M.W., J.S., M.W.H., and B.F.G. drafted manuscript; M.W., R.B.d.W., M.K.K., A.P.V., M.W.H., D.P.V., M.R.P., J.R.J., and B.F.G. edited and revised manuscript; M.W., J.S., R.B.d.W., M.K.K., A.P.V., M.W.H., D.P.V., M.R.P., J.R.J., and B.F.G. approved final version of manuscript.

REFERENCES

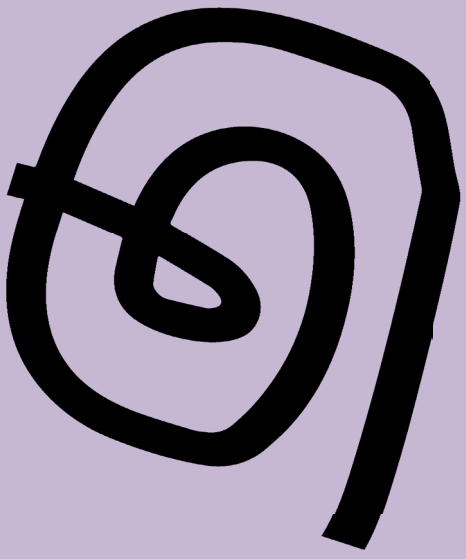
1. Chawla LS, Ince C, Chappell D, et al. Vascular content, tone, integrity, and haemodynamics for guiding fluid therapy: a conceptual approach. *Br J Anaesth.* 2014;113(5):748-755.
2. Chappell D, Jacob M, Hofmann-Kiefer K, Conzen P, Rehm M. A rational approach to perioperative fluid management. *Anesthesiology.* 2008;109(4):723-740.
3. Magder S. Fluid status and fluid responsiveness. *Curr Opin Crit Care.* 2010;16(4):289-296.
4. Cherpanath TG, Geerts BF, Lagrand WK, Schultz MJ, Groeneveld AB. Basic concepts of fluid responsiveness. *Neth Heart J.* 2013;21(12):530-536.
5. Bentzer P, Griesdale DE, Boyd J, MacLean K, Sirounis D, Ayas NT. Will This Hemodynamically Unstable Patient Respond to a Bolus of Intravenous Fluids? *JAMA.* 2016;316(12):1298-1309.
6. Yang X, Du B. Does pulse pressure variation predict fluid responsiveness in critically ill patients? A systematic review and meta-analysis. *Critical care (London, England).* 2014;18(6):650.
7. Marik PE, Cavallazzi R, Vasu T, Hirani A. Dynamic changes in arterial waveform derived variables and fluid responsiveness in mechanically ventilated patients: a systematic review of the literature. *Crit Care Med.* 2009;37(9):2642-2647.
8. Zhang Z, Lu B, Sheng X, Jin N. Accuracy of stroke volume variation in predicting fluid responsiveness: a systematic review and meta-analysis. *J Anesth.* 2011;25(6):904-916.
9. Guyton AC, Polizo D, Armstrong GG. Mean circulatory filling pressure measured immediately after cessation of heart pumping. *Am J Physiol.* 1954;179(2):261-267.
10. Maas JJ, Pinsky MR, Geerts BF, de Wilde RB, Jansen JR. Estimation of mean systemic filling pressure in postoperative cardiac surgery patients with three methods. *Intensive Care Med.* 2012;38(9):1452-1460.
11. Wijnberge M, Sindhunata DP, Pinsky MR, et al. Estimating mean circulatory filling pressure in clinical practice: a systematic review comparing three bedside methods in the critically ill. *Ann Intensive Care.* 2018;8(1):73.
12. Bayliss WM, Starling EH. Observations on Venous Pressures and their Relationship to Capillary Pressures. *J Physiol.* 1894;16(3-4):159-318.157.
13. Starr I. Role of the 'static blood pressure' in abnormal increments of venous pressure, especially in heart failure. Part II. clinical and experimental studies. In. Vol 199:40-55. *.Am J Med Sci* 1940.
14. Versprille A, Jansen JRC. Mean systemic filling pressure as a characteristic pressure for venous return. *Pflugers Archiv European Journal of Physiology.* 1985;405(3):226-233.
15. Maas JJ, de Wilde RB, Aarts LP, Pinsky MR, Jansen JR. Determination of vascular waterfall phenomenon by bedside measurement of mean systemic filling pressure and critical closing pressure in the intensive care unit. *Anesth Analg.* 2012;114(4):803-810.
16. Maas JJ. Mean systemic filling pressure: its measurement and meaning. *Netherlands Journal of Critical Care.* 2015;19(1).
17. Gardner RM. Accuracy and reliability of disposable pressure transducers coupled with modern pressure monitors. *Crit Care Med.* 1996;24(5):879-882.
18. Jellinek H, Krenn H, Oczenski W, Veit F, Schwarz S, Fitzgerald RD. Influence of positive airway pressure on the pressure gradient for venous return in humans. *J Appl Physiol (1985).* 2000;88(3):926-932.
19. Mitzner W, Goldberg H. Effects of epinephrine on resisitive and compliant properties of the canine vasculature. *J Appl Physiol.* 1975;39(2):272-280.
20. Samar RE, Coleman TG. Mean circulatory pressure and vascular compliances in the spontaneously hypertensive rat. *Am J Physiol.* 1979;237(5):H584-589.

21. Yamamoto J, Trippodo NC, Ishise S, Frohlich ED. Total vascular pressure-volume relationship in the conscious rat. *Am J Physiol.* 1980;238(6):H823-828.
22. Starr I. and Rawson AJ. Role of the 'static blood pressure' in abnormal increments of venous pressure, especially in heart failure. Part I. Theoretical studies on an improved circulation schema whose pumps obey Strarling's law of the heart. In. Vol 199: 27-39. *Am J Med Sci* 1940.
23. Repessé X, Charron C, Fink J, et al. Value and determinants of the mean systemic filling pressure in critically ill patients. *American journal of physiology Heart and circulatory physiology.* 2015;309(5):H1003-1007.
24. Schipke JD, Heusch G, Sanii AP, Gams E, Winter J. Static filling pressure in patients during induced ventricular fibrillation. *American journal of physiology Heart and circulatory physiology.* 2003;285(6):H2510-2515.
25. Steen S, Liao Q, Pierre L, Paskevicius A, Sjoberg T. The critical importance of minimal delay between chest compressions and subsequent defibrillation: a haemodynamic explanation. *Resuscitation.* 2003;58(3):249-258.
26. Lee RW, Lancaster LD, Gay RG, Paquin M, Goldman S. Use of acetylcholine to measure total vascular pressure-volume relationship in dogs. *Am J Physiol.* 1988;254(1 Pt 2):H115-119.
27. Shoukas AA, Brunner MC. Epinephrine and the carotid sinus baroreceptor reflex. Influence on capacitive and resistive properties of the total systemic vascular bed of the dog. *Circ Res.* 1980;47(2):249-257.
28. Shoukas AA, Sagawa K. Control of total systemic vascular capacity by the carotid sinus baroreceptor reflex. *Circ Res.* 1973;33(1):22-33.
29. Guerin L, Teboul JL, Persichini R, Dres M, Richard C, Monnet X. Effects of passive leg raising and volume expansion on mean systemic pressure and venous return in shock in humans. *Critical care (London, England).* 2015;19:411.
30. Rothe CF. Mean circulatory filling pressure: Its meaning and measurement. *Journal of Applied Physiology.* 1993;74(2):499-509.
31. Maas JJ, Pinsky MR, de Wilde RB, de Jonge E, Jansen JR. Cardiac output response to norepinephrine in postoperative cardiac surgery patients: interpretation with venous return and cardiac function curves. *Crit Care Med.* 2013;41(1):143-150.
32. Borst C, Karemaker JM. Time delays in the human baroreceptor reflex. *Journal of the autonomic nervous system.* 1983;9(2-3):399-409.
33. Peters JK, Lister G, Nadel ER, Mack GW. Venous and arterial reflex responses to positive-pressure breathing and lower body negative pressure. *Journal of applied physiology (Bethesda, Md : 1985).* 1997;82(6):1889-1896.
34. Berger D, Moller PW, Weber A, et al. Effect of PEEP, blood volume, and inspiratory hold maneuvers on venous return. *American journal of physiology Heart and circulatory physiology.* 2016;311(3):H794-806.
35. Guarracino F, Bertini P, Pinsky MR. Cardiovascular determinants of resuscitation from sepsis and septic shock. *Critical care (London, England).* 2019;23(1):118.
36. Xanthopoulos A, Starling RC, Kitai T, Triposkiadis F. Heart Failure and Liver Disease: Cardiohepatic Interactions. *JACC Heart failure.* 2019;7(2):87-97.
37. El Hadi H, Di Vincenzo A, Vettor R, Rossato M. Relationship between Heart Disease and Liver Disease: A Two-Way Street. *Cells.* 2020;9(3).

The vessels, for in a circle you can find neither commencement nor end, they are like rivers that purl through the body and supply the human body with life; the heart and the vessels perpetually moving, like courses of rivers returning to their sources after a passage through numerous channels.

Hippocrates and Cardiology, American Heart Journal, 2001

Selected by Daphne Psaltaki



4

Feasibility to estimate mean systemic filling pressure with inspiratory holds

Marije Wijnberge
Jos R.C. Jansen
Michael R. Pinsky
Robert Klanderman
Lotte Terwindt
Joachim Bosboom
Nikki Lemmers
Alexander P. Vlaar
Denise P. Veelo
Bart F. Geerts

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ABSTRACT

Background

A decade ago, it became possible to derive mean systemic filling pressure (MSFP) at the bedside using the inspiratory holds maneuver. MSFP has the potential to help guide hemodynamic care but the estimation is not yet implemented in common clinical practice. In this study, we assessed the ability of MSFP, vascular compliance (Csys) and stressed volume (Vs) to track fluid boluses. Second, we assessed the feasibility of implementation of MSFP in the intensive care unit (ICU). Exploratory, a potential difference in MSFP response between colloids and crystalloids was assessed.

Methods

This was a prospective cohort study in adult patients admitted to the ICU after cardiac surgery. MSFP was determined using 3-4 inspiratory holds with incremental pressures (maximum 35 cm H_2O) to construct a venous return curve. Two fluid boluses were administered; 100 mL and 500 mL, enabling to calculate Vs and Csys. Patients were randomized to crystalloid or colloid fluid administration. Trained ICU consultants acted as study supervisors and protocol deviations were recorded.

Results

20 patients completed the trial. MSFP was able to track the 500 mL bolus ($p<0.001$). In 16 patients (80%), Vs and Csys could be determined. Vs was median 2029 ml (IQR 1605-3164) and Csys was median 73 ml $mmHg^{-1}$ (IQR 56-133). A difference in response between crystalloids and colloids was present for the 100 mL fluid bolus ($p=0.019$), and in a post-hoc analysis also for the 500 mL bolus ($p=0.010$).

Conclusion

MSFP can be measured at the bedside and provides insights into the hemodynamic status of a patient that are currently missing. Clinical feasibility of Vs and Csys was judged ambiguous based on the lack of required hemodynamic stability. Future studies should address the clinical obstacles found in this study and less invasive alternatives to determine MSFP should be further explored.

Trial registration

ClinicalTrials.gov Identifier NCT03139929, registered the 4th of May 2017.

Keywords

Hemodynamics, venous return, mean circulatory filling pressure, physiology.

INTRODUCTION

At present, a decade after it became possible to estimate mean systemic filling pressure (MSFP) at the bedside, the parameter has not yet been implemented in (routine) clinical care. MSFP is considered the combined upstream pressure that drives blood flow into the right atrium and MSFP allows calculation of additional hemodynamic parameters such as the driving pressure for venous return (VRdp), stressed volume (Vs) and total systemic vascular compliance (Csys).[1] Vs provides information on the effective circulating volume, a hemodynamic variable that is missing in current clinical practice. MSFP has helped to better understand the effects of vasopressors, propofol and hyperoxia.[2-5] MSFP and the derived parameters could potentially be beneficial to guide hemodynamic care in patients admitted to the intensive care unit (ICU).[6-8]

MSFP can be determined in sedated and ventilated patients by extrapolating central venous pressure (CVP) versus cardiac output (CO) at different ventilatory plateau pressures during inspiratory holds.[9] Previous studies showed MSFP to predict fluid loading responsiveness.[10, 11] Although MSFP sounds promising, studies describing clinical guidance based on MSFP and the derived parameters are lacking.[12] Also, in previous MSFP studies,[13-15] colloids were used limiting clinical translatability of results and feasibility since in ICU patients crystalloids are the preferred choice of fluids.[1]

In this study, our first aim was to asses the ability of MSFP, Csys and Vs to track two fluid boluses. Our second aim was to assess the feasibility of clinical implementation of MSFP in the ICU. Exploratory, as a third aim, a potential difference in response between colloids and crystalloids was assessed. As the intravascular half-life for crystalloids is around 20-40 minutes and for colloids 2-3 hours we hypothesized a difference in the delta MSFP after a fluid bolus.[16] If present, this would question the use of crystalloids for Csys and Vs determination.

METHODS

Participants

This was a prospective cohort study in post-surgical patients after coronary artery bypass grafting (CABG). The study is written according to the Strobe guidelines for cohort studies and was conducted in accordance with the Declaration of Helsinki.[17, 18] The study took place at the ICU of the Amsterdam University Medical Centers, location Academic Medical Center (AMC). The study was approved by the medical ethics committee (NL5531.018.15) and was registered at clinicaltrials.nl before start of the study (NCT03139929). Written informed consent was obtained prior to surgery. Patients were included between 2017 and 2019. Adult patients (>18 years old) scheduled to undergo elective CABG surgery

were included. Exclusion criteria before surgery were morbid obesity (BMI>40), right or left sided heart failure, significant valvular regurgitation or stenosis, arrhythmias, intra-cardiac shunts, symptomatic peripheral vascular disease, and symptomatic pulmonary disease.

During surgery, anesthesia was provided as per routine care. At the end of surgery noradrenalin, propofol and/or sufentanil were continued for transport to the ICU. Exclusion criteria at the ICU were a contraindication for fluid loading and persistent hemodynamic instability. Hemodynamic instability was defined as a persistent mean arterial pressure (MAP) below 55 mmHg, a cardiac index below 1.5 L/min/m^2 or patients in which the MAP remained highly fluctuating (delta 40 mmHg in 10 minutes) after optimizing initial treatment. A maximum of one hour was allowed for patients to fulfil the hemodynamic stability criteria after arrival in the ICU. During study measurements no alterations in respiratory rate, positive end expiratory pressure (PEEP), fraction of inspired oxygen (FiO_2) and position of the patient were allowed. Also, the rate of anesthetic, analgesic and vasoactive drugs were set before the start of study and could not be altered during study measurements.

Study measurements

Study measurements were performed by a dedicated study team consisting of one member to control the ventilator (inspiratory holds), one member for circulation (administering fluid bolus), one member as annotator and one supervising ICU consultant.

Arterial blood pressure (ABP) was monitored via a catheter in the radial artery and CVP was monitored via a catheter inserted in the right internal jugular vein. Both were connected to a pressure transducer and both pressure transducers were referenced to the intersection of the anterior axillary line and the fifth intercostal space. Beat-to-beat CO was obtained by Modelflow pulse contour analysis.[19] Measurements were recorded at a sample frequency of 100 hertz and 0.2 mmHg resolution.

MSFP was measured employing successive inspiratory holds as previously published.[1, 20] In short, four inspiratory holds were executed at different pressure levels namely 5, 15, 25 and 35 cmH_2O above PEEP. The CVP and CO data at those inspiratory holds were fitted by linear regression. A previous animal study demonstrated three holds sufficient to reliably assess MSFP.[21] Therefore, a MSFP measurement was judged successful if at least 3 holds were performed. If the third inspiratory hold (25 cmH2O above PEEP) resulted in a significant decrease in MAP (defined as a MAP below 50 mmHg) the fourth inspiratory hold (35 cmH2O above PEEP) could be ommited as decided by the supervising ICU consultant.

For this study, MSFP was measured on three timepoints; at baseline (T=0), after 100 mL of fluid loading (T=1) and after a second bolus of 500 mL (T=2), Figure 1. Both fluid

bolus sizes were chosen based on previous studies[1, 22] and given at the same infusion speed of 50 mL/min. The supervising ICU consultant could terminate fluid infusion if the ABP increased excessively. No blood pressure cut-off values were defined as the allowed maximum systolic blood pressure (SBP) could differ per patient.

To assess the effect of type of fluid on MSFP, 50% of the patients which fulfilled hemodynamic stability criteria prior to start the study were randomized between crystalloid (Sterofundin, BBraun), or colloid infusion (Tetraspan, BBraunn).[16]

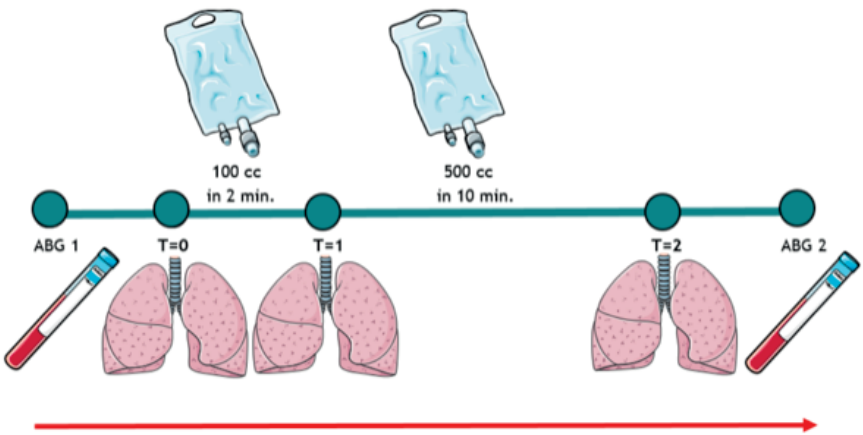

Figure 1. Visual study protocol. ABG = arterial blood gas.

Outcomes

MSFP was determined as explained above, by extrapolating CO versus CVP at different inspiratory plateau pressures to CVP is zero. CVP was used as a surrogate for right atrial pressure. The driving pressure for venous return (VRdp) was defined as MSFP - CVP. Venous return (VR) was defined as VRdp divided by resistance to venous return (RVR). RVR is the reciprocal of the slope of the VR curve or RVR=(MSFP-CVP)/CO. The total systemic vascular resistance (Rsys) was calculated as the ratio between the pressure difference of MAP and CVP with CO.[1, 14, 23]

With MSFP measured before and after fluid administration, a pressure-volume relationship could be constructed. Csys is the slope of this relation, or delta volume/ delta MSFP. [1] Csys = fluid bolus / (MSFP after bolus – MSFP before bolus). Vs = Csys x MSFP.

Since Vs and Csys may vary widely if sympathetic tone or blood flow distribution varies, hemodynamic stability was required during the two volume challenges. Hemodynamic instability during the study was defined as a change in heart rate exceeding 10 beats per minute between two time points (T=0, T=1, T=2), a decrease in MAP despite fluid administration or a change in respiratory rate.

Protocol deviations, to assess feasibility, were defined as any deviation from the study protocol. The supervising ICU consultant was asked to clarify the rationale for the protocol deviation.

Statistical analysis

Continuous data are presented as means with standard deviations when normally distributed or as medians with interquartile ranges (IQR 25-75th) when the data were not normally distributed. Distribution was assessed visually based on Q-Q plots and histograms. Categorical data are presented as frequencies with percentages. Paired T-tests or the non-parametric Wilcoxon signed rank test were used for comparison of hemodynamic variables on T=0, T=1 and T=2. Independent T-test or the non-parametric Mann-Whitney U test were used for differences between colloid and crystalloid groups. A post-hoc analysis was performed to correct for patients who did not receive the total amount of 500 mL during the second fluid bolus. The post-hoc analysis was performed by dividing the planned fluid administration (=500 mL) by the actual administered fluids (in mL), times the delta MSFP.

A p value of <0.05 was considered to indicate significance. All analyses were performed using Matlab version 14 and SPSS version 28.

Sample size analysis

To detect the 500 mL bolus, a sample size of 7 patients was calculated to have 90% power to detect a difference in Vs means of 500 mL, assuming a standard deviation of 400 mL, using a paired t-test with a 0.05 two-sided significance level.

To detect the 100 mL bolus, a sample size of 38 patients was calculated to have 90% power to detect a difference in Vs means of 100 mL, assuming a standard deviation of 210 mL, using a paired t-test with a 0.05 two-sided significance level.

Assuming a drop-out rate of 10%, a sample size of 42 patients was calculated based on the first 100cc fluid bolus, between T=0 and T=1. As this was the smallest fluid bolus this required the largest number of patients.

Sample sizes were calculated with nQuery Advanced, version 8.5.1.

RESULTS

Study population

For this prospective cohort study, 121 patients were assessed for eligibility, 44 patients had undergone solely CABG surgery and were enrolled in the ICU. A total of 20 patients completed the trial. Exclusion of 24 patients before start of study measurements at ICU was because of hemodynamic instability (n=18) or because of logistic reasons (n=6) e.g.

night-time or incomplete study team, Supplemental Material 1. The median age was 65 years and 100% were men. Table 1 and Supplemental Material 2 show the baseline characteristics. Four out of 20 (20%) patients were judged fluid loading responsive (FLR) defined as 12% increase in CO after the second fluid bolus. [24] No serious adverse events occurred in both the colloid and crystalloid group.

	n= 20
Age	66 +/- 8.7
Men	20 (100%)
Height (in cm)	178.7 +/- 6.5
Weight (in kg)	88.6 +/- 11.2
BMI	27.8 +/- 3.7
ASA I	0
ASA II	0
ASA III	16 (80%)
ASA IV	4 (20%)
Medical history	
Hypertension	9 (45%)
Heart failure	0
COPD	0
OSAS	1 (5%)
Obesity	4 (20%)
Diabetes	6 (30%)
Renal insufficiency	1 (5%)
Hypothyroidism	2 (10%)
Relevant medication	
Beta-blocker	16 (80%)
Type of surgery	
CABG on pump	20 (100%)
Surgery duration (min)	252.5 (237.8-324.5)
CPB duration (min)	87.5 (72.0-132.3)
Aortic clamp time (min)	61.5 (45.0-73.5)
TEE after cardiac bypass by cardiac anesthesiologists	
Good LVF and RVF	18 (90%)
Moderate LVF	2 (10%)

Table 1. Baseline characteristics
ASA: American Society of Anesthesiologists. BMI: body mass index. COPD: chronic obstructive pulmonary disease. OSAS: obstructive sleep apnea syndrome. CABG: coronary artery bypass grafting. CPB: cardiopulmonary bypass. TEE: transesophageal echocardiography. LVF: left ventricular function. RVF: right ventricular function. Min: minutes. Continuous data are presented as mean with standard deviation (+/-), or median with interquartile ranges (IQR 25^{th}-75^{th}). Categorical data are presented as numbers with percentages (%). ASA classifications were as follows: 1: a healthy person. 2: a patient with mild systemic disease. 3: a patient with severe systemic disease and 4: a patient with severe systemic disease that is a constant threat to life.

	T=0	T=1	T=2	p1	p2
MSFP	20.08 +/- 3.77	21.88 +/- 4.72	26.82 +/- 5.58	**0.005**	**<0.001**
Fluid bolus		100 +/- 0 100 (100-100)	465 +/- 103 500 (425 – 500)		
HR	69 +/- 11	68 +/- 10	66 +/- 9	**0.028**	**0.049**
MAP	72 +/- 6	79 +/- 7	88 +/- 11	**<0.001**	**<0.001**
CO	5.25 +/- 1.53	5.12 +/- 1.26	5.40 +/- 1.35	0.397	**0.003**
CVP	6.86 +/- 2.62	7.24 +/- 2.70	8.63 +/- 3.35	**0.004**	**<0.001**
SVR	1158 (934 – 1450)	1322 (1067 – 1607)	1393 (1169 – 1617)	**0.025**	0.478
VRdp	13.22 +/- 2.38	14.97 +/- 3.50	18.19 +/- 3.63	**0.012**	**<0.001**
RVR	2.53 (1.89-3.27)	2.78 (2.37-3.66)	3.38 (2.94-4.11)	**0.044**	**0.004**
Rsys	13.15 (9.45-16.62)	14.65 (11.33-17.90)	15.44 (11.35-19.46)	**0.004**	0.204
PPV	8.94 (7.72 – 11.48)	7.99 (5.69 – 10.51)	5.29 (3.26 – 8.33)	0.351	**<0.001**
SVV	7.96 (5.92 – 9.19)	5.98 (4.87 – 8.00)	3.35 (2.58 – 6.28)	**0.030**	**<0.001**

Table 2. Hemodynamic changes after two fluid boluses.
MSFP: mean systemic filling pressure. HR: heart rate. MAP: mean arterial pressure. CO: cardiac output. CVP: central venous pressure. SVR: systemic vascular resistance (80*(MAP-CVP)/CO). VRdp: driving pressure for venous return (MSFP-CVP). RVR: resistance to venous return ((MSFP-CVP)/CO). Rsys: total systemic vascular resistance (MAP-CVP)/CO. Data are presented as mean with standard deviation (+/-) or median with IQR (25^{th}-75^{th}) depending on normality. P-values 1 and 2 are determined with paired T-test or the non-parametric related-samples Wilcoxon Signed Rank test, depending on normality of the data. p1 demonstrates timepoint 0 versus timepoint 1. p2 demonstrates timepoint 1 versus timepoint 2.

MSFP

Providing a fluid bolus increased MSFP as expected, with mean MSFP at T=0 20.08 mmHg +/- 3.77, at T=1 21.88 mmHg +/- 4.72 and at T=2 26.82 mmHg +/- 5.58, Table 2.

Stressed volume and compliance

16 patients (80%) fit the inclusion criteria for hemodynamic stability (i.e. stable heart-rate and no change in respiratory rate during the study period) and were used for Vs and Csys calculations, Table 3 and Supplemental Material 3.

Since, Vs after 100 mL of crystalloid did not consistently result in an increase in MSFP, it was judged not reliable to present mean/median Vs and Csys at T=1, Supplemental Material 3. Following T=2 was median 2028.95 ml (IQR 1605.08-3163.51) and Csys at T=2 was median 72.74 ml $mmHg^{-1}$ (IQR 55.77-132.58). Corrected for body weight this translates to a median Vs of 24.17 ml kg^{-1} (IQR 15.68-38.48) and median Csys of 0.87 ml $mmHg^{-1}$ kg^{-1} (IQR 0.54 – 1.49).

Protocol deviations and clinical feasibility

Table 3 summarizes the protocol deviations and reasons. In all 20 patients (100%), the predefined minimum of three holds could be performed, thus in all patients MSFP determination was possible. In 10 out of 20 patients (50%) the total of four holds could be executed (at 5,15,25 and 35 cmH2O above PEEP). The reason for not performing a

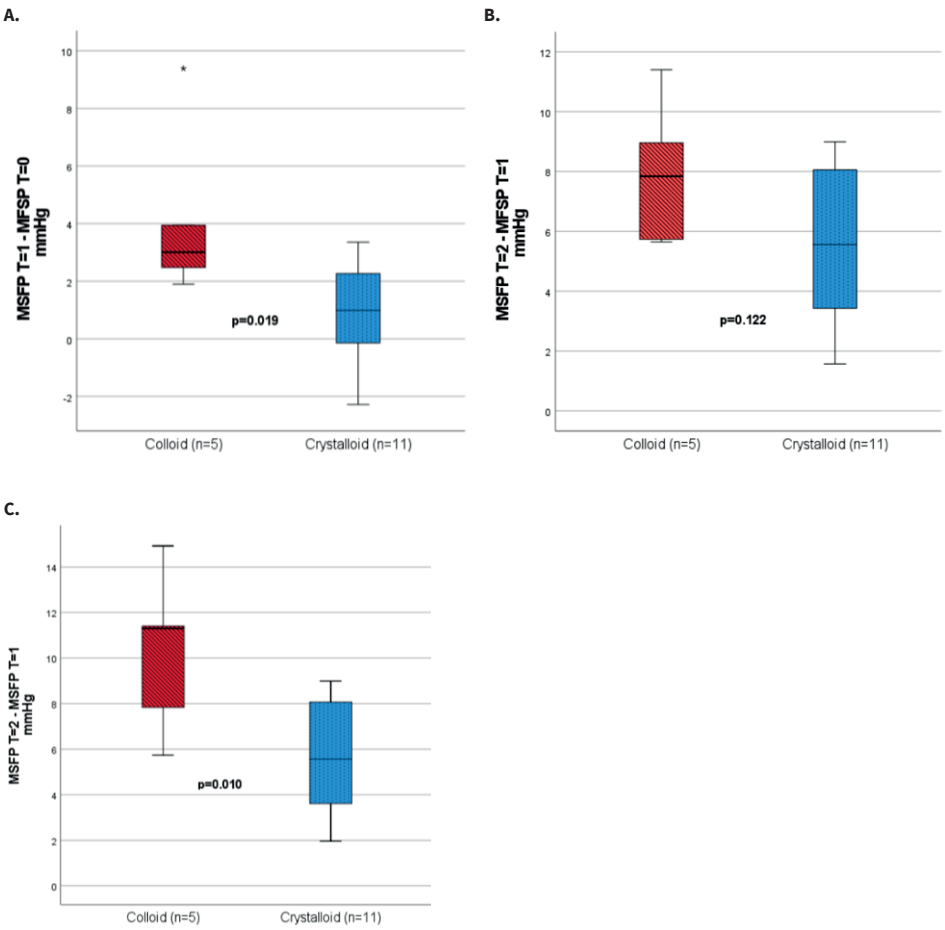

Figure 2. Delta MSFP
Figure 2A: delta first fluid bolus, 100 mL; Figure 2B: delta second fluid bolus planned to be 500 mL, but in 40% of the colloid group the fluid infusion was ceased prematurely; Figure 2C: post-hoc analysis for a hypothetical delta MSFP if the total of 500 mL would have been administered. MSFP= mean systemic filling pressure. mmHg: millimetres of mercury. Thin vertical black stripe represents the minimum and maximum MSFP. Boxplot represents 25th to 75th quartile. Horizontal thick black stripe: median. P-values for independent t-test. Red and slash to the right= colloid. Blue and dots = crystalloid.

fourth hold was a significant temporary decrease in MAP (mean lowest MAP 49 mmHg +/-5.81, for less than 20 seconds) after the third hold, as judged by the supervising ICU physician.

In 5 out of 20 patients, the supervising ICU physician decided the second fluid bolus (500 cc) to be terminated before the total volume was infused because of a considerable increase in the systolic blood pressure (mean highest systolic blood pressure 169 mmHg +/- 11.97).

Supplemental material 4 summarizes this single center experience concerning feasibility for MSFP, Vs and Csys calculation in ICU.

Exploratory analyses: colloid vs crystalloid

Dissecting type of fluids, the choice to cease the infusion of fluids between T=1 and T=2 was 3 out of 15 (20%) in the crystalloid group and 2 out of 5 (40%) in the colloid group.

Independent T-test demonstrated a significant difference in the response on the first fluid bolus (100 mL) between crystalloids and colloids (p=0.019), Figure 2. Paired T-test demonstrated the first colloid bolus resulted in a significant increase in MSFP (p=0.038), whereas the first crystalloid bolus infusion did not (p=0.110). For the second fluid bolus, no significant difference in delta MSFP between type of fluids was found (p=0.122), Figure 2. However, as the administered amount of fluid during the second bolus of colloid was lower than the administered bolus of crystalloid (Table 3), this was not a fair comparison. A post-hoc analysis demonstrated that when the ceased fluid infusions were extrapolated to the planned 500 mL bolus there was a significant difference in delta MSFP between crystalloid and colloid infusion, p=0.01, Figure 2 and Supplemental Material 5.

DISCUSSION

This prospective study demonstrated the expected increase in MSFP, derived with 3-4 successive inspiratory holds, after fluid loading. Clinical feasibility for MSFP determination was deemed sufficient – although labor intensive – but clinical feasibility for Vs and Csys was judged ambiguous. The results of this study demonstrate the potential of MSFP and might partly explain why MSFP, Vs and Csys, derived with inspiratory holds, are not yet widespread implemented in clinical care.

Previous studies

Our results are in line with previous studies demonstrating the effect of a fluid bolus on MSFP. [11, 13] Although MSFP is thought central for the characterization of the circulation, the subsequent derived values such as Vss and Csys are subject to physiologic variability, though if accurate of potentially greater clinical value.[6-8]

In 1990, Vs was calculated to represent 30 +/- 17% of the total predicted blood in patients on cardiac bypass for major vascular sugery.[25] During hypothermic cardiac arrest the cardiac bypass pump was turned off and the blood that drained passively into a reservoir represented a mean Vs of 1,290 mL +/- 296, which equaled 20.2 mL kg^{-1} +/- 1.0.[25] This is close to the 19.5 mL kg^{-1} +/- 12.1 previously found in intact patients with the inspiratory hold technique,[20] where Vs was mean 1,677 mL at baseline. In the present

Fluid administration	
Complete first bolus (100 mL)	20/20 (100%)
Complete second bolus (500 mL)	15/20 (75%)
Crystalloid complete second bolus	12/15 (80%)
Crystalloid infused	mean 483.67 mL +/- 92.78 median 500 IQR 500-500
Colloid complete second bolus	3/5 (60%)
Colloid infused	mean 410.00 mL +/- 124.50 median 500 IQR 275-500
Reason ceasing infusion?	Considerable increase in blood pressure
ABP at which infusion was ceased:	
Maximum SBP	169 mmHg +/- 11.97
Δ SBP	47 mmHg +/- 6.58
MAP	97 mmHg +/- 4.10
Δ MAP	24 mmHg +/- 4.24
Inspiratory holds	
5, 15 and 25 cmH2O above PEEP	20/20 (100%)
5, 15, 25 and 35 cmH2O above PEEP	10/20 (50%)
Reasons not performing fourth hold	Considerable decrease in MAP during third hold
Lowest MAP during third hold	49 mmHg +/- 5.81
Δ MAP during third hold	25 mmHg +/- 5.78
Lowest CO during third hold	2.27 L +/- 0.95
Vs and Csys calculations	
Haemodynamic instability during study	4/20 (20%)
Reasons	
Δ HR more than 10 bpm between two timepoints (T=0, T=1, T=2)	2/20 (10%) MSFP 18 and MSFP 19
Starting to trigger ventilator after the 35 mmHg hold	1/20 (5%) MSFP 26
Decrease in MAP after fluid administration	1/20 (5%) MSFP 23

Table 3. Protocol deviations + reasons
Continuous data are presented as mean with standard deviation (+/-) or median with inter quartile ranges (IQR 25^{th}-75^{th}). Categorical data are presented as frequencies with percentages. SBP: systolic blood pressure. MAP: mean arterial pressure. PEEP: positive end expiratory pressure. CO: cardiac output. HR: heart rate. Vs: stressed volume. Csys: compliance. Δ = delta.

study, the median Vs was 2,028.95 mL at T=2 (median 24.17 mL kg^{-1}), after in total 600 mL fluid loading.

Previous clinical studies have found Csys to be 80 ml $mmHg^{-1}$ and 64.3 ml $mmHg^{-1}$.[1, 20] In the present study the median Csys was 72.74 ml $mmHg^{-1}$. Thus, the present Vs and Csys values are in line with previous studies.

Clinical feasibility

An MSFP measurement takes around 4-5 minutes. Estimating Vs and Csys thus requires at least 10 minutes (including fluid loading time) and it assumes the administered fluid is added to the stressed volume compartment.[16,26] Interestingly, a 100 mL of colloids did significantly increase MSFP whereas 100 mL of crystalloids did not. A previous study also found the response on crystalloid variable in post-CABG patients.[27] Perhaps a capillary leak syndrome with endothelial glycocalyx shedding can partly explain our results or that the expected transudation of crystalloid into the interstitium occurred rapidly in patients after cardiac surgery.[28] Furthermore, Vs and Csys calculation are based upon the assumption that the fluid administered adds directly to the stressed compartment (Vs) without alterations in the unstressed compartment. This assumption might not always be true if fluid administration also results in a shift of blood flow distribution across vascular beds with differing proportions of unstressed and stressed vascular volumes. We conclude a 100 mL bolus of crystalloids to be insufficient to reliable calculate Csys and Vs in this specific ICU population. [29,30]

Further scrutiny of the MSFP measurement, in the present study, shows that supervising ICU physicians were less inclined to allow the fourth hold (35 cmH_2O) compared to previous studies because of (transient) hypotension.[1, 20] Excluding the final 35 cm H2O inspiratory hold step in the patients in whom the total of four holds could be executed, no significant change in the MSFP estimate was found; p=0.696. This demonstrates that using high inspiratory hold levels may not be necessary. We noted that for executing the inspiratory holds a deep level of sedation is necessary, exceeding the common level of sedation in ICU patients. Lastly, although inspiratory holds have shown to prevent postoperative pulmonary complications in non-ARDS patients[31] they should not be performed in ARDS patients.[32]

Limitations

In only 20 patients, instead of the planned 42, study measurements could be performed. For the 20 patients, we were sufficiently powered (>90%) to detect a difference in Vs means of 500 mL but a post-hoc sample size analysis demonstrated this to reduce the power for detection of the 100 mL to 56%. The majority of patients were excluded because they did not meet the hemodynamic stability criteria to start the study in the ICU. Our criteria could be too strict, or our cardiac surgery population more severely ill. Comparison with previous studies was not possible, as these numbers were not reported.

The colloid versus crystalloid analyses should be regarded as exploratory, however could be used as a stepping stone for new trials. The post-hoc analysis requires for MSFP to increase linearly with infused fluids, as suggested by previous data.[33] Still, we cannot prove this linear association to be true for the presented data, thus future studies should confirm our results.

The high number of protocol deviations in of study protocol might not solely describe clinical feasibility but can also illustrate that the supervising ICU consultants in the study hospital were respectively more conservative.

In this study, we used Modelflow pulse contour to calculate CO. For MSFP, Vs and Csys absolute CO values are not necessary, trends are sufficient, Supplemental Material 6. However, for RVR absolute values become relevant. Modelflow can be calibrated with thermodilution and echocardiography.[34-37]

An unintended but important finding is that all the patients studied were men. All initially included women were deemed hemodynamically unstable in the ICU. Aiming to include women in order to obtain a study population that is reflective of the clinical population and in order to translate findings across genders remains important.[38-40]

What needs to happen to bring MSFP to clinical care, and what for?

MSFP determined with inspiratory holds is of great interest for research purposes, but based on this study not yet ready for clinical use. Yet, less invasive alternatives for determining MSFP do exist. [4] MSFP analogue is based on a model of the circulation, it is a calculation with CO, CVP and MAP as input data. MSFP analogue is much simpler to measure but was thought to suffer from greater inaccuracies, probably because of the assumptions in the calculation.[15,41] The calculation uses standard arterial and venous compliances and resistances that might be inaccurate during acute disease states. However, a recent animal study concluded MSFP analogue to be the most reliable method to indirectly measure MSFP.[42] The jury is still out, and this contradiction in results invites for future research. A third method to estimate MSFP is based on a stop flow principle, determined with a rapidly inflating cuff (halting blood flow) around the upper arm. A previous study demonstrated all three methods to track a fluid bolus.[15]

If MSFP determined with inspiratory holds are to become more commonly used, studies need to define the minimum number of inspiratory holds for accurate MSFP determination and should assess whether holds with lower plateau pressures also result in accurate MSFP values.[11,43] Furthermore, if knowing accurate Vs and Csys are required, then defining the optimal fluid type (colloid vs crystalloid) and the minimal volume challenge needed to determine Vs and Csys needs to be assessed. Being able to quickly and reliably calculate MSFP, Csys and Vs could be beneficial in guiding hemodynamic care in various types of patients.[6-8] For example in current sepsis resuscitation first fluids are administered and subsequently (after >2 Liters of fluids is added in a normal size

adult patient) a vasopressor is started. Based on a Guytonian approach to the circulation, however, it would make more sense to start a vasopressor earlier in the treatment to recruit unstressed to the stressed volume.[2,8] Recruiting unstressed to stressed volume is an important survival mechanism of the human body. Measuring MSFP, Vs and Csys might lead to a reduction in the total amount of fluids administered for resuscitation.[8,44] Despite the use of invasive hemodynamic monitoring options available in the ICU, we still lack direct and repetitive estimation of the effective circulating volume (Vs). Working with MSFP might enable to go beyond fluid loading responsiveness and help us better understand the physiology during various clinical scenario's.[8,45,46] Future studies should study whether adding MSFP, Vs and Csys to our clinical arsenal actually results in improved patient outcomes.

CONCLUSIONS

Mean systemic filling pressure estimated with inspiratory holds behaves predictably conform known physiologic mechanisms. Clinical feasibility for Csys and Vs calculation was judged ambiguous based on the lack of required hemodynamic stability and on the assumption of administered fluids to stay intravascular. Future studies should address the clinical obstacles found in this study and less invasive alternatives to determine MSFP should be further explored.

Declarations

Ethics Approval and Consent to participate

The study was conducted in accordance with the Declaration of Helsinki. The study was approved by the medical ethics committee (NL5531.018.15) and was registered at clinicaltrials.nl before start of the study (NCT03139929). Written informed consent was obtained from all patient at least a day prior to surgery.

Data Availability Statement

Study data is anonymized and securely stored at the Amsterdam UMC.

Competing interests

The authors have no competing interests as defined by BMC, or other interests that might be perceived to influence the results and/or discussion reported in this paper.

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No funding was received.

Authors' contributions

Study conception: Bart Geerts. Data collection: Marije Wijnberge, Robert Klanderman, Lotte Terwindt, Joachim Bosboom, Nikki Lemmers, Alexander Vlaar, Denise Veelo, Bart Geerts. Data analyses: Marije Wijnberge and Jos Jansen. Statistical analyses: Marije Wijnberge. Interpretation of the data: all authors. Drafting the manuscript: Marije Wijnberge, Jos Jansen, Michael Pinsky and Bart Geerts. Revision of the manuscript: all authors.

REFERENCES

1. Maas JJ, Pinsky MR, Aarts LP, and Jansen JR. Bedside assessment of total systemic vascular compliance, stressed volume, and cardiac function curves in intensive care unit patients. *Anesthesia and analgesia* 115: 880-887, 2012.
2. Adda I, Lai C, Teboul JL, Guerin L, Gavelli F, and Monnet X. Norepinephrine potentiates the efficacy of volume expansion on mean systemic pressure in septic shock. *Critical care (London, England)* 25: 302, 2021.
3. Maas JJ, Pinsky MR, de Wilde RB, de Jonge E, and Jansen JR. Cardiac output response to norepinephrine in postoperative cardiac surgery patients: interpretation with venous return and cardiac function curves. *Crit Care Med* 41: 143-150, 2013.
4. de Wit F, van Vliet AL, de Wilde RB, Jansen JR, Vuyk J, Aarts LP, de Jonge E, Veelo DP, and Geerts BF. The effect of propofol on haemodynamics: cardiac output, venous return, mean systemic filling pressure, and vascular resistances. *British journal of anaesthesia* 116: 784-789, 2016.
5. Helmerhorst HJ, de Wilde RB, Lee DH, Palmen M, Jansen JR, van Westerloo DJ, and de Jonge E. Hemodynamic effects of short-term hyperoxia after coronary artery bypass grafting. *Annals of intensive care* 7: 20, 2017.
6. Rothe CF. Mean circulatory filling pressure: Its meaning and measurement. *Journal of Applied Physiology* 74: 499-509, 1993.
7. Vos JJ, Kalmar AF, and Scheeren TWL. Bedside assessment and clinical utility of mean systemic filling pressure in acute care. *Journal of Emergency and Critical Care Medicine* 4: 2020.
8. Persichini R, Lai C, Teboul JL, Adda I, Guérin L, and Monnet X. Venous return and mean systemic filling pressure: physiology and clinical applications. *Critical care (London, England)* 26: 150, 2022.
9. Wijnberge M, Sindhunata DP, Pinsky MR, Vlaar AP, Ouweneel E, Jansen JR, Veelo DP, and Geerts BF. Estimating mean circulatory filling pressure in clinical practice: a systematic review comparing three bedside methods in the critically ill. *Annals of intensive care* 8: 73, 2018.
10. Cooke K, Sharvill R, Sondergaard S, and Aneman A. Volume responsiveness assessed by passive leg raising and a fluid challenge: a critical review focused on mean systemic filling pressure. *Anaesthesia* 73: 313-322, 2018.
11. Guerin L, Teboul JL, Persichini R, Dres M, Richard C, and Monnet X. Effects of passive leg raising and volume expansion on mean systemic pressure and venous return in shock in humans. *Critical care (London, England)* 19: 411, 2015.
12. Vincent JL, and Pinsky MR. We should avoid the term "fluid overload". *Critical care (London, England)* 22: 214, 2018.
13. Keller G, Desebbe O, Benard M, Bouchet JB, and Lehot JJ. Bedside assessment of passive leg raising effects on venous return. *Journal of clinical monitoring and computing* 25: 257-263, 2011.
14. Maas JJ, de Wilde RB, Aarts LP, Pinsky MR, and Jansen JR. Determination of vascular waterfall phenomenon by bedside measurement of mean systemic filling pressure and critical closing pressure in the intensive care unit. *Anesthesia and analgesia* 114: 803-810, 2012.
15. Maas JJ, Pinsky MR, Geerts BF, de Wilde RB, and Jansen JR. Estimation of mean systemic filling pressure in postoperative cardiac surgery patients with three methods. *Intensive care medicine* 38: 1452-1460, 2012.
16. Hahn RG, and Lyons G. The half-life of infusion fluids: An educational review. *Eur J Anaesthesiol* 33: 475-482, 2016.

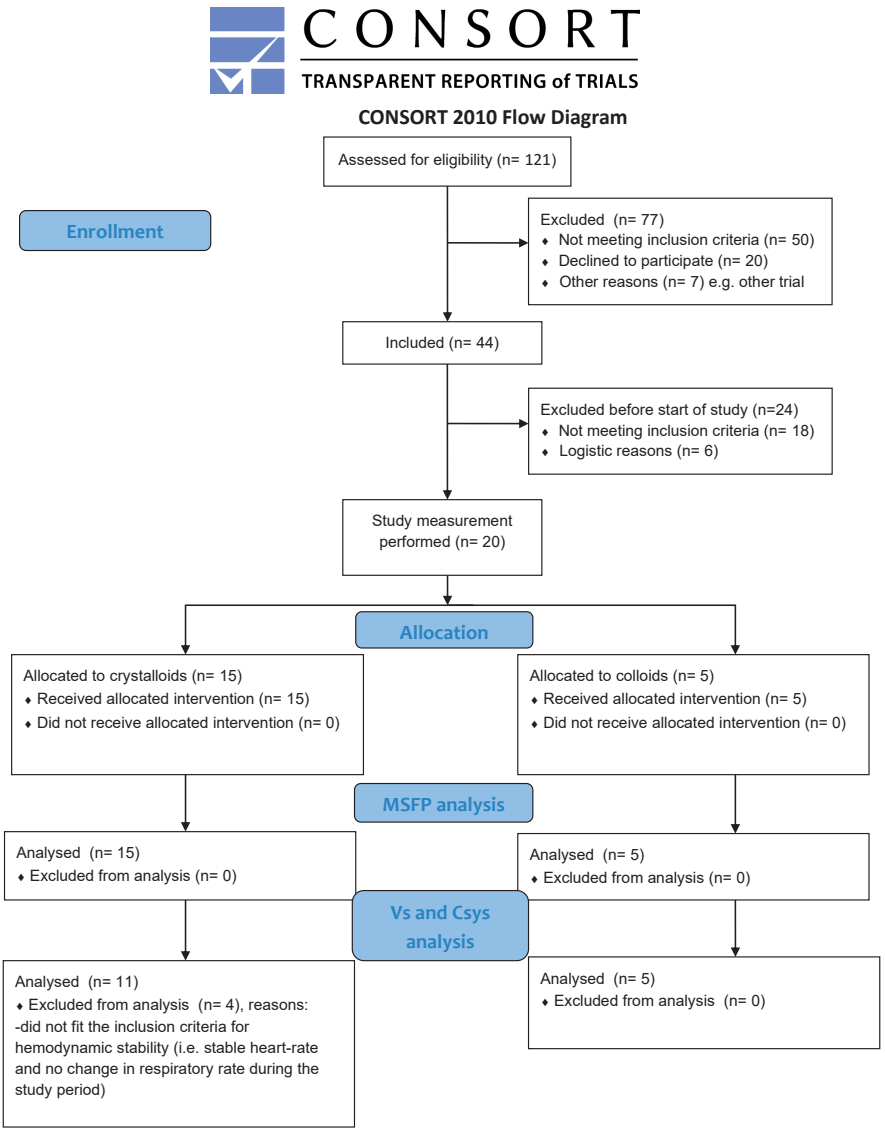
17. von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, and Vandenbroucke JP. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. *Lancet (London, England)* 370: 1453-1457, 2007.
18. Cuschieri S. The STROBE guidelines. *Saudi J Anaesth* 13: S31-s34, 2019.
19. de Wilde RB, Schreuder JJ, van den Berg PC, and Jansen JR. An evaluation of cardiac output by five arterial pulse contour techniques during cardiac surgery. *Anaesthesia* 62: 760-768, 2007.
20. Maas JJ, Geerts BF, van den Berg PC, Pinsky MR, and Jansen JR. Assessment of venous return curve and mean systemic filling pressure in postoperative cardiac surgery patients. *Crit Care Med* 37: 912-918, 2009.
21. Maas JJ, Geerts BF, and Jansen JRC. Evaluation of mean systemic filling pressure from pulse contour cardiac output and central venous pressure. *Journal of Clinical Monitoring and Computing* 25: 193-201, 2011.
22. Smorenberg A, Cherpanath TGV, Geerts BF, de Wilde RBP, Jansen JRC, Maas JJ, and Groeneveld ABJ. A mini-fluid challenge of 150mL predicts fluid responsiveness using Modelflow(R) pulse contour cardiac output directly after cardiac surgery. *J Clin Anesth* 46: 17-22, 2018.
23. Jansen JR, Maas JJ, and Pinsky MR. Bedside assessment of mean systemic filling pressure. *Current opinion in critical care* 16: 231-236, 2010.
24. Cherpanath TG, Geerts BF, Lagrand WK, Schultz MJ, and Groeneveld AB. Basic concepts of fluid responsiveness. *Neth Heart J* 21: 530-536, 2013.
25. Magder S, and De Varennes B. Clinical death and the measurement of stressed vascular volume. *Crit Care Med* 26: 1061-1064, 1998.
26. Hahn RG, Drobin D, and Zdolsek J. Distribution of crystalloid fluid changes with the rate of infusion: a population-based study. *Acta Anaesthesiol Scand* 60: 569-578, 2016.
27. Sondergaard S, Larsson JS, and Möller PW. The haemodynamic effects of crystalloid and colloid volume resuscitation on primary, derived and efficiency variables in post-CABG patients. *Intensive Care Med Exp* 7: 13, 2019.
28. Dekker NAM, Veerhoek D, Koning NJ, van Leeuwen ALI, Elbers PWG, van den Brom CE, Vonk ABA, and Boer C. Postoperative microcirculatory perfusion and endothelial glycocalyx shedding following cardiac surgery with cardiopulmonary bypass. *Anaesthesia* 74: 609-618, 2019.
29. Aya HD, Ster IC, Fletcher N, Grounds RM, Rhodes A, and Cecconi M. Pharmacodynamic Analysis of a Fluid Challenge. *Crit Care Med* 44: 880-891, 2016.
30. Aya HD, Rhodes A, Chis Ster I, Fletcher N, Grounds RM, and Cecconi M. Hemodynamic Effect of Different Doses of Fluids for a Fluid Challenge: A Quasi-Randomized Controlled Study. *Crit Care Med* 45: e161-e168, 2017.
31. Hartland BL, Newell TJ, and Damico N. Alveolar recruitment maneuvers under general anesthesia: a systematic review of the literature. *Respir Care* 60: 609-620, 2015.
32. Cavalcanti AB, Suzumura É A, Laranjeira LN, Paisani DM, Damiani LP, Guimarães HP, Romano ER, Regenga MM, Taniguchi LNT, Teixeira C, Pinheiro de Oliveira R, Machado FR, Diaz-Quijano FA, Filho MSA, Maia IS, Caser EB, Filho WO, Borges MC, Martins PA, Matsui M, Ospina-Tascón GA, Giancursi TS, Giraldo-Ramirez ND, Vieira SRR, Assef M, Hasan MS, Szczeklik W, Rios F, Amato MBP, Berwanger O, and Ribeiro de Carvalho CR. Effect of Lung Recruitment and Titrated Positive End-Expiratory Pressure (PEEP) vs Low PEEP on Mortality in Patients With Acute Respiratory Distress Syndrome: A Randomized Clinical Trial. *Jama* 318: 1335-1345, 2017.
33. Maas JJ, Pinsky MR, Aarts LP, and Jansen JR. Bedside assessment of total systemic vascular compliance, stressed volume, and cardiac function curves in intensive care unit patients. *Anesthesia and analgesia* 115: 880-887, 2012.

34. Swan HJ, Ganz W, Forrester J, Marcus H, Diamond G, and Chonette D. Catheterization of the heart in man with use of a flow-directed balloon-tipped catheter. *The New England journal of medicine* 283: 447-451, 1970.
35. Harvey S, Harrison DA, Singer M, Ashcroft J, Jones CM, Elbourne D, Brampton W, Williams D, Young D, and Rowan K. Assessment of the clinical effectiveness of pulmonary artery catheters in management of patients in intensive care (PAC-Man): a randomised controlled trial. *Lancet (London, England)* 366: 472-477, 2005.
36. Tuggle D. Obtaining pulmonary artery catheter data is too labor intense to be reliable. *Crit Care Med* 37: 1833; author reply 1833, 2009.
37. de Vaal JB, de Wilde RB, van den Berg PC, Schreuder JJ, and Jansen JR. Less invasive determination of cardiac output from the arterial pressure by aortic diameter-calibrated pulse contour. *British journal of anaesthesia* 95: 326-331, 2005.
38. Bybee KA, and Stevens TL. Matters of the heart: cardiovascular disease in U.S. women. *Mo Med* 110: 65-70, 2013.
39. Garcia M, Mulvagh SL, Merz CN, Buring JE, and Manson JE. Cardiovascular Disease in Women: Clinical Perspectives. *Circ Res* 118: 1273-1293, 2016.
40. Gulati M, Hendry C, Parapid B, and Mulvagh SL. Why We Need Specialised Centres for Women's Hearts: Changing the Face of Cardiovascular Care for Women. *Eur Cardiol* 16: e52, 2021.
41. Meijs LPB, van Houte J, Conjaerts BCM, Bindels A, Bouwman A, Houterman S, and Bakker J. Clinical validation of a computerized algorithm to determine mean systemic filling pressure. *J Clin Monit Comput* 36: 191-198, 2022.
42. Werner-Moller P, Sondergaard S, Jakob SM, Takala J, and Berger D. Effect of volume status on the estimation of mean systemic filling pressure. *J Appl Physiol (1985)* 126: 1503-1513, 2019.
43. Persichini R, Silva S, Teboul JL, Jozwiak M, Chemla D, Richard C, and Monnet X. Effects of norepinephrine on mean systemic pressure and venous return in human septic shock. *Crit Care Med* 40: 3146-3153, 2012.
44. Ospina-Tascón GA, Hernandez G, Alvarez I, Calderón-Tapia LE, Manzano-Nunez R, Sánchez-Ortiz AI, Quiñones E, Ruiz-Yucuma JE, Aldana JL, Teboul JL, Cavalcanti AB, De Backer D, and Bakker J. Effects of very early start of norepinephrine in patients with septic shock: a propensity score-based analysis. *Critical care (London, England)* 24: 52, 2020.
45. Moller PW, Hana A, Heinisch PP, Liu S, Djafarzadeh S, Haenggi M, Bloch A, Takala J, Jakob SM, and Berger D. The Effects of Vasoconstriction And Volume Expansion on Veno-Arterial ECMO Flow. *Shock* 51: 650-658, 2019.
46. Crozier TM, Wallace EM, and Parkin WG. Haemodynamic assessment in pregnancy and pre-eclampsia: A Guytonian approach. *Pregnancy Hypertension* 5: 177-181, 2015.

LEGENDS SUPPLEMENTAL CONTENT

Supplemental Material 1: Consort flowdiagram
Supplemental Material 2: Study characteristics
Supplemental Material 3: Delta MSFP, stressed volume and compliance
Supplemental Material 4: Clinical feasibility
Supplemental Material 5: Post-hoc analysis delta MSFP, corrected for differences in infused fluids
Supplemental Material 6: Importance absolute CO values

SUPPLEMENTAL MATERIAL 1. CONSORT FLOWDIAGRAM



SUPPLEMENTAL MATERIAL 2. STUDY CHARACTERISTICS

	Start study	End study
Temperature (°C)	36.1 +/- 0.44	36.2 +/- 0.52
Fluid balance (mL)	1890 (IQR 1769-2685)	2251 (IQR 1881-3020)
Hb (mmol/L)	7.53 +/- 1.01	7.23 +/- 0.97
pH	7.39 +/- 0.05	7.41 +/- 0.05
Lactate	1.31 +/- 0.61	1.29 +/- 0.52
FiO2 (%)	30 (IQR 30-40)	
Tidal volumes (mL)	528.14 +/- 57.1	
Tidal volume (ml/kg) TBW	6.0 +/- 0.96	
Tidal volume (ml/kg) IBW	6.7 +/- 0.7	
PEEP (cmH2O)	5 +/- 0	
Plateau pressure (cmH2O)	11.6 +/- 2.6	
Respiratory rate (per minute)	12 (IQR 12-14.5)	
Sufentanil	11 (60%)	
Mcg/hr	40 (IQR 20-41) 35 +/- 12	
In mcg/kg/hr	0.45 (0.25-0.48) 0.40 +/- 0.15	
In mcg/kg/min	-	
Propofol	20 (100%)	
Mg/hr	400 (IQR 303-400) 368 +/- 53.50	
in mg/kg/hr	4.48 (IQR 3.48-4.80) 4.21 +/- 0.80	
In mg/kg/min	0.08 (IQR 0.06-0.08) 0.07 +/- 0.01	
Noradrenalin	20 (100%)	
Mcg/hr	325 (IQR 300-500) 368.0 +/- 176.5	
Mcg/kg/hr	3.71 (IQR 1.18-5.31) 4.18 +/- 2.10	
Mcg/kg/min	0.06 (IQR 0.05-0.09) 0.07 +/- 0.035	

°C: degrees Celsius. mL: milliliters. Hb: haemoglobin. mmol=millimol, L=liter, FiO2: fraction of inspired oxygen. IBW: ideal body weight. TBW: total body weight. Medication dosage calculated with total body weight. Continuous data are presented as mean with standard deviation (+/-) or median with inter quartile ranges (IQR 25^{th}-75^{th}). Categorical data are presented as frequencies with percentages.

SUPPLEMENTAL MATERIAL 3. DELTA MSFP, STRESSED VOLUME AND COMPLIANCE.

	Crystalloid (n=15)								
	Bolus1	Bolus2	Δ MSFP T=1 – T=0	Δ MSFP T=2– T=1	Csys1	Csys2	Vs1	Vs2	Δ / Δ MSFP
MSFP10	100	500	-2.28	8.89	-43.86	56.24	-879.82	1628.23	-3.90
MSFP12	100	400	2.74	1.57	36.50	254.78	530.66	4104.46	0.57
MSFP13	100	705	-1.01	5.21	-99.01	135.32	-1614.85	2912.02	-5.16
MSFP14	100	500	-1.06	2.34	-94.34	213.68	-1544.34	3997.86	-2.21
MSFP16	100	500	0.85	8.28	117.65	60.39	2337.65	1699.88	9.74
MSFP17	100	500	0.99	4.02	101.01	124.38	2241.41	3259.95	4.06
MSFP18	*100*	*500*	*3.48*	*6.90*	*28.74*	*72.46*	*710.63*	*2292.03*	*1.98*
MSFP19	*100*	*500*	*10.29*	*-2.07*	*9.72*	*-241.55*	*276.97*	*-6384.06*	*-0.20*
MSFP20	100	500	0.74	5.56	135.14	89.93	2185.14	1954.14	7.51
MSFP23	*100*	*500*	*0.67*	*1.02*	*149.25*	*490.20*	*3529.85*	*12093.14*	*1.52*
MSFP25	100	500	3.20	7.84	31.25	63.78	543.44	1586.73	2.45
MSFP26	*100*	*250*	*0.16*	*0.28*	*625.00*	*892.86*	*15175.00*	*22169.64*	*1.75*
MSFP28	100	500	1.29	8.99	77.52	55.62	2054.26	1899.89	6.97
MSFP37	100	500	1.79	6.14	55.87	81.70	1213.41	2103.76	3.42
MSFP44	100	400	3.36	2.83	29.80	141.13	691.18	3247.34	0.84
	Colloids (n=5)								
MSFP36	100	300	3.01	8.96	33.26	33.49	655.11	922.14	2.98
MSFP38	100	500	9.39	7.84	10.65	63.78	361.24	2379.46	0.83
MSFP39	100	250	1.90	5.65	52.63	44.25	1221.58	1232.74	2.97
MSFP41	100	500	3.94	11.40	25.38	43.86	662.69	1597.37	2.89
MSFP42	100	500	2.48	5.74	40.32	87.11	1042.34	2621.08	2.31

Δ MSFP = delta MSFP. Δ / Δ MSFP = second delta/first delta. Italics: 4 patients that did not fit the delta MSFP, Csys and Vs hemodynamic stability criteria: MSFP 18, MSFP 19, MSFP23 and MSFP 26. Csys: compliance. Vs: stressed volume. MSFP: mean systemic filling pressure.

SUPPLEMENTAL MATERIAL 4. CLINICAL FEASIBILITY

MSFP derived with inspiratory holds method	Clinical implementation in ICU	Rationale	Potential solution
Restricted to fully sedated and mechanically ventilated patients	+/-	Requires a level of sedation higher than standard of care in ICU	Inspiratory holds with smaller incremental pressures
		Not all patients in ICU are mechanically ventilated	
Restricted to patients with continuous and accurate CO and CVP measurements	+	Patients in which the treating ICU consultant is interested in MSFP usually have a central venous catheter to receive vasoactive drugs	
		The majority of patients in ICU have an arterial catheter for ABP monitoring, a CO measurement device can be connected	
		For MSFP,Vs and Csys calculation CO trends are sufficient. For RVR absolute values are required.	
Restricted to patients whom are hemodynamically stable for at least 4- 5 minutes	+	For most patients achievable	Inspiratory holds with smaller incremental pressures
Duration of Vs and Csys measurements	+/-	For a Vs or Csys measurement two MSFP measurements are required (=at least 10 minutes)	
Assumption that 100% of fluid administered remains in the intravascular compartment for the duration of the measurement	?	Crystalloids are the default fluids in the study ICU. We found a difference between colloids and crystalloids.	Future studies should aim to find the correct type of fluid (colloid/crystalloid) for Csys and Vs calculation
Hazardous?	?	Not known; only speculative	
		In this study in 50% of patients the fourth hold was withheld because of a too large decrease in MAP. However, three holds seem sufficient.	Inspiratory holds with smaller incremental pressures
		In the study hospital, executing inspiratory holds is restricted to ICU consultants only	
Number of people needed for one MSFP measurement	+	In the present study the inspiratory holds were manually executed	Computerized MSFP measurement

ABP: arterial blood pressure. CO: cardiac output. CVP: central venous pressure. Csys: compliance. ICU: Intensive Care Unit. Vs: stressed volume. MSFP: mean systemic filling pressure.

SUPPLEMENTAL MATERIAL 5. POST-HOC ANALYSIS DELTA MSFP, CORRECTED FOR DIFFERENCES IN INFUSED FLUIDS

	Bolus2	Δ MSFP T=2– T=1	Δ MSFP T=2– T=1 Corrected
Crystalloid (n=15)			
MSFP10	500	8.89	8.89
MSFP12	400	1.57	1.96
MSFP13	705	5.21	3.70
MSFP14	500	2.34	2.34
MSFP16	500	8.28	8.28
MSFP17	500	4.02	4.02
MSFP18	*500*	*6.90*	*6.90*
MSFP19	*500*	*-2.07*	*-2.07*
MSFP20	500	5.56	5.56
MSFP23	*500*	*1.02*	*1.02*
MSFP25	500	7.84	7.84
MSFP26	*250*	*0.28*	*0.56*
MSFP28	500	8.99	8.99
MSFP37	500	6.14	6.14
MSFP44	400	2.83	3.54
15 patients, mean +/-		4.52 +/- 3.43	4.51 +/- 3.36
11 patients, mean +/-*		5.61 +/-2.68	5.57 +/- 2.63
Colloids (n=5)			
MSFP36	300	8.96	14.93
MSFP38	500	7.84	7.84
MSFP39	250	5.65	11.30
MSFP41	500	11.40	11.40
MSFP42	500	5.74	5.74
Mean +/-		7.92 +/- 2.40	10.24 +/- 3.55

A post-hoc analysis to correct for the patients who did not receive the total of 500 mL of fluids during the second fluid bolus. The post-hoc analysis was performed by dividing the planned amount of fluid administered (=500 mL) by the actual amount of fluids administered (in mL), times the delta MSFP.

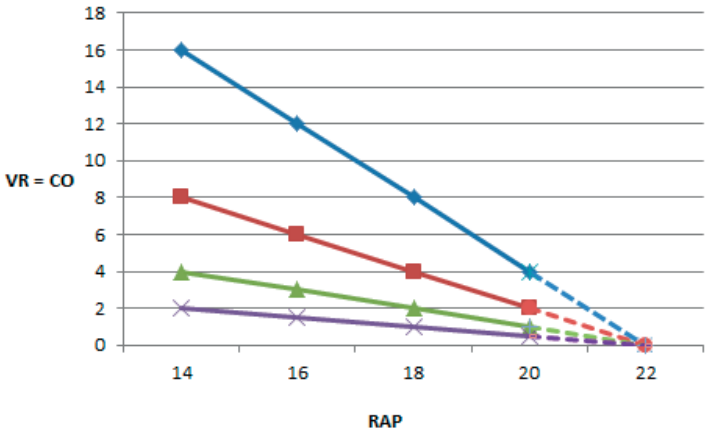
For example: MSFP 12, planned = 500 mL. Provided = 400 mL. 500/400= 1,25. Delta found = 1.57 mmHg. Corrected delta MSFP = 1.57 * 1.25 = 1.96.

Δ MSFP = delta MSFP. Italics: 4 patients that did not fit the delta MSFP, Csys and Vs hemodynamic stability criteria: *MSFP 18, MSFP 19, MSFP23 and MSFP 26*. Csys: compliance. Vs: stressed volume. MSFP: mean systemic filling pressure.

Utilizing all 20 patients, mean delta MSFP crystalloid 4.51 sd 3.36 and mean delta MSFP colloid 10.24 sd 3.55, using the independent t-test, p <0.01

Utilizing the 16 patients who fulfilled the hemodynamic stability criteria, using the independent t-test, mean delta MSFP crystalloid 5.57 sd 2.63 and mean delta colloid 10.24 sd 3.55, p = 0.01

SUPPLEMENTAL MATERIAL 6. ABSOLUTE VALUES



A correct absolute cardiac output (CO) value is needed for the slope of the line, defining the resistance to venous return (RVR). However, if the uncalibrated CO values are consistent too high or too low (i.e. if the trend is correct), the intersection point will be similar, resulting in a similar mean systemic filling pressure (MSFP), compliance (Csys) and stressed volume (Vs). RAP: right atrial pressure.

Part II

Hypotension

5

Association of intraoperative hypotension with postoperative morbidity and mortality: systematic review and meta-analysis

Marije Wijnberge
Jimmy Schenk
Esther Bulle
Alexander P. Vlaar
Kamal Maheshwari
Markus W. Hollmann
Jan M. Binnekade
Bart F. Geerts
Denise P. Veelo

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ABSTRACT

Background

Intraoperative hypotension, with varying definitions in literature, may be associated with postoperative complications. The aim of this meta-analysis was to assess the association of intraoperative hypotension with postoperative morbidity and mortality.

Methods

MEDLINE, Embase and Cochrane databases were searched for studies published between January 1990 and August 2018. The primary endpoints were postoperative overall morbidity and mortality. Secondary endpoints were postoperative cardiac outcomes, acute kidney injury, stroke, delirium, surgical outcomes and combined outcomes. Subgroup analyses, sensitivity analyses and a meta-regression were performed to test the robustness of the results and to explore heterogeneity.

Results

The search identified 2931 studies, of which 29 were included in the meta-analysis, consisting of 130 862 patients. Intraoperative hypotension was associated with an increased risk of morbidity (odds ratio (OR) 2.08, 95% confidence interval 1.56 to 2.77) and mortality (OR 1.94, 1.32 to 2.84). In the secondary analyses, intraoperative hypotension was associated with cardiac complications (OR 2.44, 1.52 to 3.93) and acute kidney injury (OR 2.69, 1.33 to 5.55). Overall heterogeneity was high with an I^2 of 88%. When hypotension severity, outcome severity and study population variables were added to the meta-regression, heterogeneity was reduced to 50%.

Conclusions

Intraoperative hypotension during non-cardiac surgery is associated with postoperative cardiac and renal morbidity, and mortality. A universally accepted standard definition of hypotension would facilitate further research into this topic.

INTRODUCTION

During surgery, most patients suffer from at least one episode of hypotension. The reported incidence varies, depending on the definition of intraoperative hypotension (IOH) used. IOH defined as a mean arterial pressure (MAP) below 65 mmHg occurred in approximately 65% of operations and IOH defined as a 20% decrease in the MAP from baseline occurred in 94%.[1] More than 100 definitions of hypotension are mentioned in the literature, all using slightly different cut-off values, complicating research into IOH.[1] IOH is usually caused by the vasodilatory and cardiodepressive effects of anaesthetics or absolute hypovolemia during surgery.[2] Older patients or patients undergoing major surgery are at particular risk of IOH.[3]

Hypotension can reduce perfusion of vital organs and result in a mismatch of oxygen delivery and demand.[4] Clinical cohort studies have shown an association of IOH with postoperative complications such as acute kidney injury (AKI) and myocardial infarction (MI).[5,6] A systematic review showed that optimizing perioperative haemodynamics using fluids and vasopressors lowered the incidence of postoperative AKI.[7] However, not all studies reported an association between IOH and postoperative morbidity.[8-10]

A comprehensive review of studies on the effect of IOH on outcome in non-cardiac surgery is currently lacking. The primary aim of this meta-analysis was to critically appraise the association of IOH with postoperative morbidity and mortality in patients undergoing non-cardiac surgery. Secondary aims are to analyse its association with cardiac outcomes, AKI, stroke, delirium, surgical outcomes and combined outcomes.

METHODS

Study selection

This meta-analysis was performed following the MOOSE checklist,[11] PRISMA guidelines[12] and methodology outlined in the Cochrane Handbook for systematic reviews.[13] This was a systematic review of risk, testing for the association of exposure with outcome. The study protocol was registered in the Prospero registry (number CRD42017079398). MEDLINE, Embase and Cochrane Library databases were searched with guidance of a clinical librarian, between January 1990 and August 2018. Search terms contained both Medical Subject Headings (MeSH) terms and free text to define patient population (type of surgery), event (IOH), and postoperative outcomes (mortality and morbidity). The complete search strategy is available in Supplemental Text Document 1 (Text S1) Titles, abstracts, and full-texts were independently screened by two reviewers for relevance with use of the review program Rayyan.[14] Disagreements were discussed with a third reviewer. Reference lists of the selected articles were examined for additional eligible

articles. Studies were included when IOH was incorporated as a predictive variable for postoperative mortality or organ damage in adult patients undergoing elective non-cardiac surgery. Exclusion criteria were non-availability of full texts or language other than English. In case of non-availability, authors were not contacted. Reviews and case reports were excluded. Finally, studies describing IOH in combination with low bispectral index and low minimum alveolar concentration, the so called 'triple low state',[15, 16] were excluded from this review as the effect of hypotension alone could not be studied.

Outcomes

The prespecified primary outcomes were overall morbidity and mortality. Prespecified secondary outcome measures were cardiac adverse outcomes, AKI, neurological outcomes (i.e. stroke), delirium, surgical complications such as surgical-site infection or anastomotic leakage, and combined outcomes.

Data-extraction

Data were extracted using predefined tables for data collection. Data extraction was done in duplicate. Extracted data consisted of study design, patient characteristics, methods, definition of IOH, type of blood pressure measurement (non-invasive or arterial), and postoperative patient outcomes.

Quality assessment

Critical appraisal was based on the Newcastle-Ottawa Scale (NOS) for cohort studies to assess the quality of non-randomized studies.[17] The NOS is a grading system with scores given for selection (maximum 4 points), comparability (maximum 2 points) and outcome (maximum 3 points), with a highest possible score of 9. Studies with a NOS score higher than 3 were included in the quantitative meta-analysis, to reduce possible bias introduced by low-quality studies.

Meta-analysis

The included studies were analysed in an overall meta-analysis. For each study, only one definition of IOH and one outcome in terms of morbidity or mortality were used in the analysis. Considering that both the predictive variable IOH and the outcome measures morbidity and mortality are dichotomous, data were extracted into 2x2 tables. When studies presented results using multiple definitions of IOH or multiple outcome variables, one of each was selected to be incorporated in the analysis. The selection procedure for the definitions of IOH and outcome variables was predefined and agreed upon by all reviewers without knowledge of the potential effect of their selection on the results.

First, an overview of all IOH definitions and outcomes used in the various articles was made. If more than one definition of hypotension was present in the study, the definition that was most frequently used in all studies was chosen. To illustrate, a MAP of 60 mmHg was used more frequently to define hypotension than a MAP of 50 mmHg, so that when a study reported both, results for MAP of 60 mmHg were extracted.
Second, the same method was applied to select and extract outcome variables. To illustrate, myocardial infarction was reported more frequently than myocardial injury. Therefore, if a study reported results for both myocardial injury and myocardial infarction, the myocardial infarction data were extracted.

Studies were categorised based on postoperative outcomes in the following groups: mortality, cardiac, renal, stroke, delirium, and any postsurgical complication. The postsurgical complication category included all studies that did not fit into the other categories, and included surgical-site infection, postsurgical complications graded according to the Clavien-Dindo classification,[18] anastomotic leakage, any postoperative complication and headache.

A random-effect meta-analysis was conducted, using inverse variance weighting to pool studies. Between-study variance (tau, τ) was estimated using the Der Simonian-Laird method. The percentage of the variability in effect estimates between studies that is due to heterogeneity rather than due to sampling error (chance) was expressed as the I^2 value. To assess possible publication bias, a funnel plot was constructed and inspected visually. Egger's test was performed to test for asymmetry of the funnel plot.

Subgroup Analysis

Subgroup analysis, based on severity of hypotension, was performed to evaluate whether the definition of hypotension influenced the association found. Hypotension severity was ranked considering both duration and depth of hypotension. A panel of anaesthetists was used to rank the 29 included definitions of hypotension, starting from the most severe definition. The same rank could be used for different definitions if these definitions were thought to be of equal severity (Text S2). All questionnaires were collected, recalculated and averaged into a 1-9 scale. Based on this 1-9 scale, studies were divided into three groups: mild, moderate and severe hypotension.

Sensitivity Analyses

Sensitivity analyses were performed to test the robustness of the association found, with the aim of assessing whether the decisions made during the review process affected the overall odds ratio (OR). Pooled odds ratios in the sensitivity analyses were inspected visually to assess whether they showed the same direction of association as the result of the primary meta-analysis. If the odds ratio of a sensitivity analysis aligned with that found in the primary meta-analysis, the overall result and conclusions were

not influenced by including or excluding particular studies and thus regarded as robust. Predefined factors for sensitivity analyses were outcome severity, generalizability of the study population and methodological quality of the studies.

The outcome severity of each included study was scored based on the Clavien-Dindo classification,[18] which provides a validated grading system for the severity of postoperative complications. In this sensitivity analysis, the overall effect in studies with Clavien-Dindo grade IV and V was analysed.

To assess the influence of differences in study sample populations (generalizability) on the association between IOH and postoperative morbidity and mortality, the studies were divided based on the first question (S1) of the NOS scale; '*Representativeness of the exposed cohort'*. Studies that were classified as generalizable were selected for the sensitivity analysis.

To assess the influence of study quality on the association between IOH and postoperative morbidity and mortality, studies were divided based on low (NOS score 4-5) or high (NOS score 6-8) study quality. For this sensitivity analysis, high quality studies were selected. To test ultimately the robustness of the meta-analysis, the studies initially excluded because of low study quality (NOS score below 4), were included in the final sensitivity analysis.

Meta-regression

A meta-regression was performed to account for the heterogeneity in the effect of IOH on postoperative mortality and morbidity. Before the analysis, it was hypothesized that hypotension severity, outcome severity and the generalizability of the patient population accounted for (part of) the heterogeneity. As subgroups based on outcome (primary analysis) and subgroups based on outcome severity have overlapping properties, only outcome severity was included as a factor in the meta-regression. Hypotension severity was assessed as described above. The amount of heterogeneity in the meta regression was estimated using the maximum likelihood method.

Data analysis was performed using the statistical program R.[19, 20] The overall meta-analysis, sensitivity analyses, subgroup analysis and meta-regression were composed using the *meta* package in R.

RESULTS

The initial search in MEDLINE, Embase, and Cochrane Library resulted in 2931 articles. Eight articles were found via citation tracking. Selection based on titles and abstracts resulted in 177 eligible articles. After screening of full texts, 133 articles were excluded. As a result, 44 articles were included in the qualitative synthesis, Supplemental Table 1

(Table S1). Two articles[21, 22] used the same cohort of patients; both reported a (similar) secondary analysis of the VISION cohort.[23] As this would introduce an overestimation of the weight of the VISION cohort, the article with the most severe outcome parameter was included.[22] Fourteen articles[24-37] were excluded based on low study quality based on the NOS scale (Figure 1).

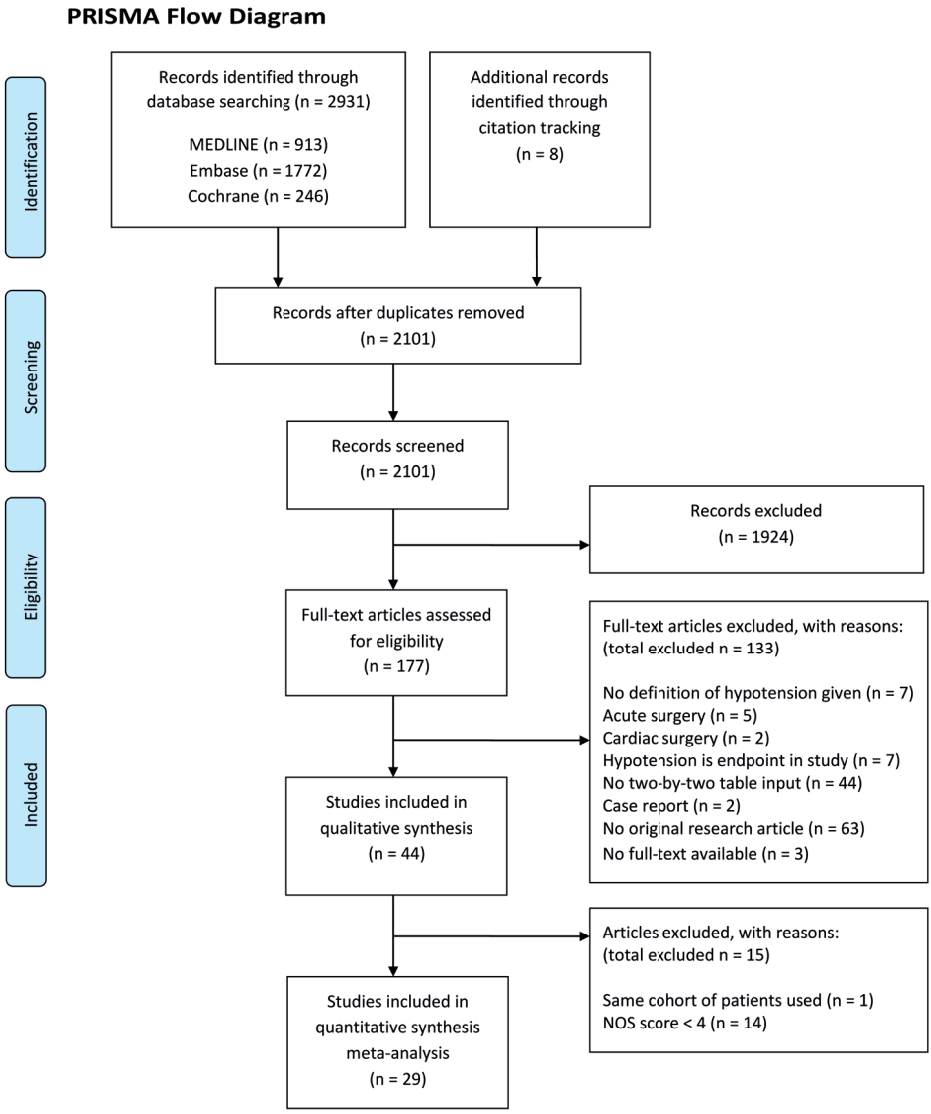

Figure 1. PRISMA diagram showing the selection of articles for review

Study-characteristics

In total, 29 studies[8-10,22,38-62] were included in the meta-analysis, a combined total of 130 862 patients. Mean age was 63 sd 8 years and 54% of studied patients were men. Of the 29 studies, 25 studied morbidity and four studied mortality. Among the included morbidity studies, one was a case-control study.[8] This study used propensity score matching in a large cohort, resulting in a high study quality.[38] Table 1 shows the quality of the studies included in the meta-analysis. The different definitions of IOH used are shown in Supplemental Figure 1 (Figure S1).

Author	Year	S1	S2	S3	S4	Comparability	O1	O2	O3	Total NOS
Babazade[10]	2016	1	1	1	1	0	1	0	0	**5**
Bijker[9]	2009	1	1	1	1	1	1	1	1	**8**
Brinkman[38]	2015	0	1	1	1	0	1	0	0	**4**
Ellis[39]	2018	0	1	1	1	0	1	1	1	**6**
Hallqvist[40]	2017	1	1	1	1	0	1	1	1	**7**
Hallqvist[41]	2016	1	1	0	0	0	1	1	1	**5**
Hirsch[42]	2014	1	1	1	1	0	1	1	1	**7**
Hsieh[8]	2016	1	1	1	0	1	1	1	1	**7**
Kheterpal[43]	2009	1	1	1	0	0	0	1	0	**4**
Marcantonio[44]	1998	1	1	1	1	0	1	1	1	**7**
Matsota[45]	2016	1	1	1	1	0	1	0	0	**5**
McLean House[46]	2016	1	1	1	0	0	1	1	0	**5**
Mizota[47]	2017	1	1	1	1	1	1	1	1	**8**
Monk[48]	2015	0	1	1	1	0	1	1	1	**6**
Patti[49]	2011	1	1	0	0	0	1	1	0	**4**
Post[50]	2012	1	1	1	1	0	1	1	0	**6**
Roshanov[22]	2017	1	1	0	1	0	1	1	1	**6**
Sabate[51]	2011	1	1	0	0	0	1	0	1	**4**
Santiago Lastra[52]	2017	0	1	1	0	0	1	1	1	**5**
Sessler[53]	2018	1	1	1	0	0	1	1	1	**6**
Sun[54]	2015	1	1	1	1	0	1	0	0	**5**
Tallgren[55]	2006	0	1	0	1	0	1	1	1	**5**
Thakar[56]	2007	0	1	1	1	0	0	1	1	**5**
van Waes[57]	2016	1	1	1	0	1	1	1	0	**6**
von Knorring[58]	1992	0	1	1	1	0	0	1	1	**5**
White[59]	2016	0	1	0	1	0	1	1	0	**4**
Xu[60]	2015	0	1	1	1	0	1	1	1	**6**
Yu[61]	2018	0	1	1	1	0	1	1	1	**6**
Ziser[62]	1999	0	1	0	0	0	1	1	1	4

Table 1. Quality of the studies included in the meta-analysis according to the NewCastle-Ottowa Scale. S1, representativeness of the exposed cohort; S2, selection of the non-exposed cohort; S3, ascertainment of exposure; S4, demonstrating that outcome of interest was not present at start of study; C, comparability of cohorts on the basis of the design or analysis; O1, assessment of outcome; O2, was follow-up long enough for outcomes to occur; O3, adequacy of follow-up of cohorts. NOS, Newcastle–Ottawa Scale.

Meta-analysis

The meta-analysis showed an overall significant association between IOH and postoperative morbidity and mortality (Figure 2). Associations between IOH and postoperative complications were seen regarding cardiac outcomes (OR 2.44, 95% confidence interval 1.52 to 3.93), acute kidney injury (OR 2.69, 1.31 to 5.55), and mortality (OR 1.94, 1.32 to 2.84). An association was found for IOH and the outcome subgroup "any postsurgical complication" (OR 1.76, 1.04 to 2.98). There was no association between IOH and stroke (OR 0.81, 0.49 to 1.33) or delirium (OR 1.32, 0.47 to 3.71).

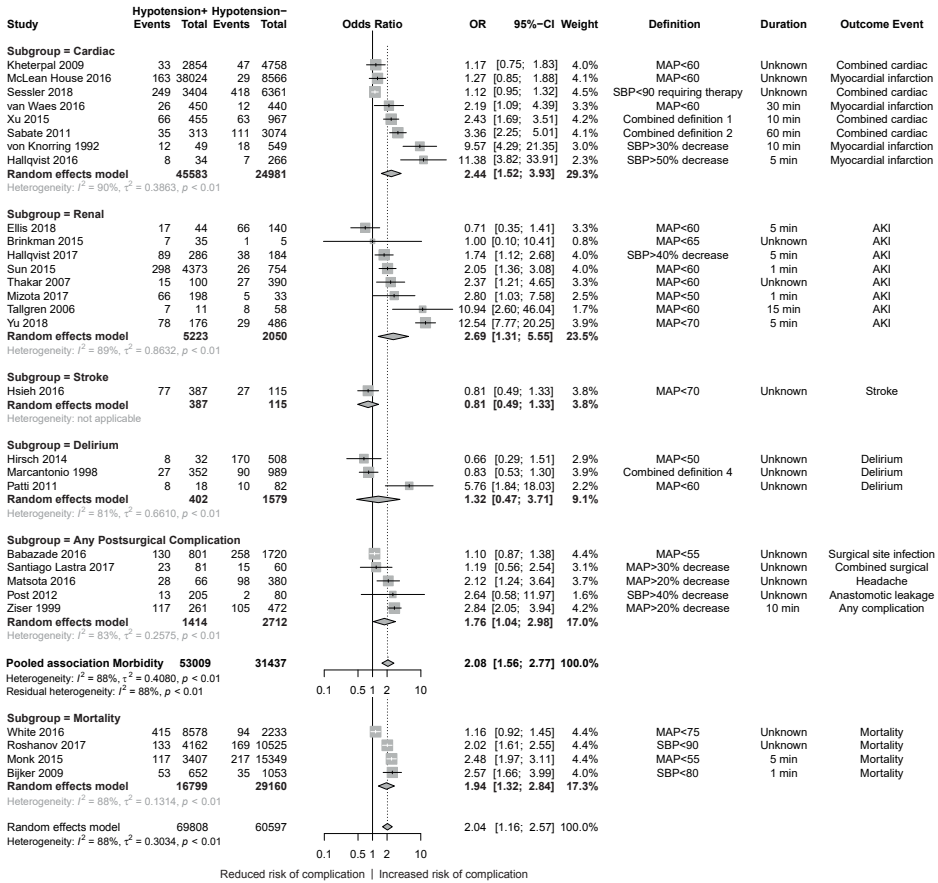

Figure 2. A random-effects model was used for all meta-analyses. Odds ratios (ORs) are shown with 95 % confidence intervals. *Units for mean arterial pressure (MAP) are mmHg. MI, myocardial infarction; SBP, systolic BP; SSI, surgical-site infection.

Heterogeneity

All studies assessed the effect of IOH on postoperative morbidity or mortality, however, study designs varied. Heterogeneity between studies was high (I^2 = 88%). Visual

inspection of the funnel plot showed that, for both larger and smaller studies negative as well as positive results were published. The Egger's test to test for asymmetry in the funnel plot showed that there was no indication for publication bias, p= 0.106 (Figure 3).

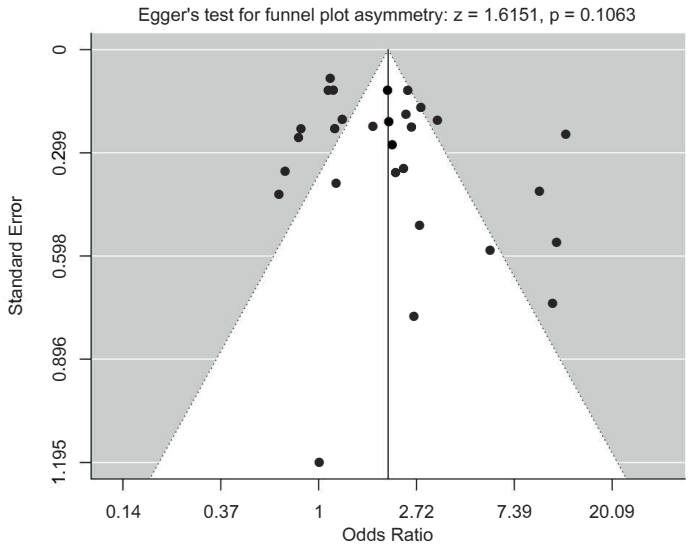

Figure 3. Funnel plot of all included studies. Egger's test for funnel asymmetry: z=1.62,p=0.106.

Subgroup analysis

Table S2 shows the hypotension severity ranking per study. Visual inspection demonstrated the OR's per subgroup to increase with the severity of hypotension, Figure S1. The subgroup 'mild hypotension' showed an overall OR of 1.99 (95% CI 0.52-7.69), 'moderate hypotension' showed an overall OR of 1.59 (1.23-2.07) and the subgroup 'severe hypotension' showed an OR of 2.62 (1.83-3.76).

Sensitivity analyses

All four sensitivity analyses indicated that the results of the meta-analysis were robust. Table S2 demonstrates the Clavien-Dindo grade per study outcome. Figure S2 shows that studies with Clavien-Dindo grade III-V had a pooled association in the same direction as the overall pooled OR in the primary meta-analysis. Figure S3 and Figure S4 show that the effect found in this meta-analysis remained when analysing solely studies classified as generalizable and when selecting only studies with the highest study quality. Figure S5 demonstrates that including studies with a very low study quality did not alter the overall results.

Meta-regression

Random-effects meta-regression revealed an association between the predefined factors and the amount of heterogeneity in the effect of IOH on postoperative morbidity and mortality. When the hypotension severity scale was included in the meta-regression, heterogeneity was reduced to 75%, (p=0.0001). Figure 4 visualizes the association between hypotension severity and outcome in a bubble plot. Adding the outcome severity scale as a second factor in this meta-regression, reduced heterogeneity to 61% (p<0.0001). Finally, the generalizability of the studies was added to the meta-regression, further reducing the heterogeneity to 50% (Text S3).

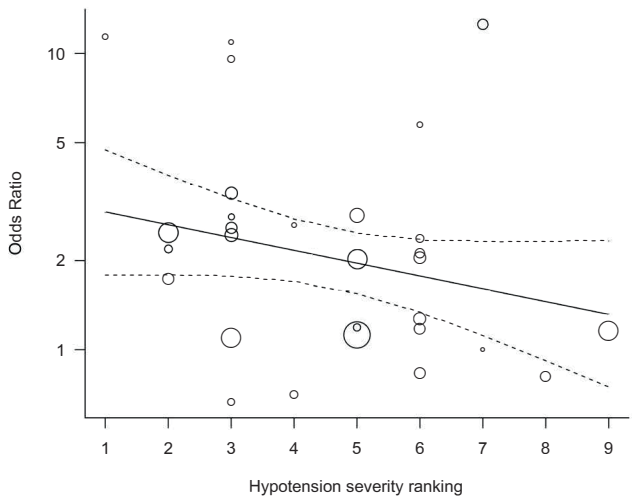

Figure 4. Meta-regression: bubble plot visually demonstrating a relationship between severity of hypotension and odds ratio (OR) found in the 29 included studies. Each bubble represents the OR for an included study. The size of each bubble corresponds with the study weight attributed in the meta-analysis. The regression line denotes the best fit with 95% confidence intervals.

DISCUSSION

IOH was associated with an increased risk of postoperative morbidity and mortality. This effect was most notable in studies with cardiac events, AKI and mortality as endpoints, indicating that these outcomes seem most susceptible to IOH.

These findings are in line with a recently published meta-analysis by Gu and colleagues, [64] which showed that IOH alone (compared with the triple low state of IOH with low bispectral index and low minimum alveolar concentration) increased the risk of postoperative mortality and morbidity. However, these authors included only studies published to May 2016, excluding recently published articles. Moreover, they only

extracted the results based on the most severe definition of hypotension, which might not provide the most clinically relevant effect estimation.

Wesselink and colleagues[65] performed a systematic review without meta-analysis including all studies that reported on intraoperative outcome and hypotension, regardless of the possibility of extracting two by two tables. The authors reported that the association between IOH and outcome becomes stronger when the MAP was lower. However, various assumptions were made to translate the severity of different definitions of IOH leading to debatable results.

Randomized trials are rare because it is difficult to maintain patients in predefined blood pressure groups and such trials are costly. Recently, the first randomised controlled trial (n=292) studying the effect of IOH on a composite postoperative outcome of systemic inflammatory response syndrome and dysfunction of at least one organ system was published.[66] This trial evaluated the effect of an individualized blood pressure strategy aiming at a systolic blood pressure within 10% of the patients resting blood pressure as compared to standard of care. The authors reported reduced risk of organ dysfunction with strict management of blood pressure, in patients undergoing abdominal surgery. In line with the results of the current meta-analysis, these results stress the importance of the prevention of hypotension during surgery.

IOH was not associated with stroke in this meta-analysis, although only one article reporting stroke could be included preventing definite conclusions from being drawn.[8] Furthermore, the *a priori* risk of postoperative stroke is extremely low with a reported incidence of 0.1% in non-cardiac, non-neurological surgery.[8] As such, the study might have been underpowered.

IOH was not associated with delirum. However, a recently published RCT found a significantly lower rate of an altered level of consciousness in the individualized blood pressure group (5.4% *versus* 15.9%, p = 0.007).[66]

This meta-analysis provides an overview of the effect of IOH on multiple postoperative outcomes, aggregating all available evidence up to date. Despite heterogeneity found between studies, the majority of studies show IOH to be associated with worse postoperative outcomes.

The debate about the importance of blood flow *versus* blood pressure is long-lived. Both flow and pressure are required for adequate delivery of oxygen to tissues.[67] Blood pressure is a parameter measured during all surgeries; blood flow, on the other hand, is very rarely measured.

Studies reporting on the effect of IOH on postoperative morbidity and mortality were only included in this study if a two-by-two table could be constructed. This resulted in exclusion of some large studies showing a positive association between IOH and outcomes.[6, 68] Inclusion of these studies would probably have led to a stronger association between IOH and postoperative outcomes.

Despite this, the inclusion criteria resulted in a relatively large number of included studies and an extensive overall study population. Unfortunately, heterogeneity was high. Studies differed with respect to the chosen definitions of IOH and the reported postoperative outcomes. Definitions of IOH were mostly based on either absolute thresholds like MAP and systolic blood pressure or a relative threshold, i.e., a decrease in blood pressure relative to patients' baseline blood pressure. Different definitions of IOH may lead to different associations with adverse postoperative outcomes.[1, 65, 69] Currently, the intraoperative consensus statement advises to maintain a MAP above the 60-70 threshold.[70] A universally accepted threshold will facilitate easier comparison between studies in the future.

The sensitivity analyses performed in this study indicated a robust pooled effect of IOH on postoperative outcomes, and a large part of the heterogeneity found in the meta-analysis was explained by a combination of hypotension severity, outcome severity and study population. Despite the fact that articles published in languages other than English were not included in this meta-analysis, the funnel plot and Egger's test revealed no indication for publication bias.

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REFERENCES

1. Bijker JB, van Klei WA, Kappen TH, van Wolfswinkel L, Moons KGM, Kalkman C. Incidence of intraoperative hypotension as a function of the chosen definition: literature definitions applied to a retrospective cohort using automated data collection. *Anesthesiology* 2007; 107(2):213-220.
2. Tritapepe L. Hypotension during surgery for high risk patients: Cause or consequence of pathology? *Minerva Anestesiologica* 2013; 79(9):978-980.
3. Cheung CC, Martyn A, Campbell N, Frost S, Gilbert K, Michota F, et al. Predictors of intraoperative hypotension and bradycardia. *American Journal of Medicine* 2015; 128(5):532-538.
4. Harten J KJ. Perioperative optimisation. *Scot Med J* 2004; 49(1):6-9.
5. Sharma SK, McCauley J, Cottam D, Mattar SG, Holover S, Dallal R, et al. Acute changes in renal function after laparoscopic gastric surgery for morbid obesity. *Surgery for Obesity and Related Diseases* 2006; 2(3):389-392.
6. Salmasi V, Maheshwari K, Yang D, Mascha EJ, Singh A, Sessler DI, et al. Relationship between intraoperative hypotension, defined by either reduction from baseline or absolute thresholds, and acute kidney and myocardial injury after noncardiac surgery. *Anesthesiology* 2017; 126(1):47-65.
7. Brienza N, Giglio MT, Marucci M, Fiore T. Does perioperative hemodynamic optimization protect renal function in surgical patients? A meta-analytic study. *Critical Care Medicine* 2009; 37(6):2079-2090.
8. Hsieh JK, Dalton JE, Yang D, Farag ES, Sessler DI, Kurz AM. The association between mild intraoperative hypotension and stroke in general surgery patients. *Anesthesia and Analgesia* 2016; 123(4):933-939.
9. Bijker JB, van Klei WA, Vergouwe Y, Eleveld DJ, van Wolfswinkel L, Moons KGM, et al. Intraoperative hypotension and 1-year mortality after noncardiac surgery. *Anesthesiology* 2009; 111(6):1217-1226.
10. Babazade RH, O. Yilmaz, Nicole, M, Stocchi L, Gorgun E, Kessler H, et al. Association between intraoperative low blood pressure and development of surgical site infection after colorectal surgery. *Annals of Surgery* 2016; 264(6):1058-1064.
11. Stroup DF, Berlin JA, Morton SC, Olkin I, Williamson GD, Rennie D, et al. Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis Of Observational Studies in Epidemiology (MOOSE) group. *Jama* 2000; 283(15):2008-12.
12. Liberati A AD, Tetzlaff J, Mulrow C, Gøtzsche PC, Ioannidis JP, Clarke M, Devereaux PJ, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: explanation and elaboration. *BMJ* 2009; 339:2700.
13. Higgins JPT, Green S. Cochrane handbook for systematic reviews of interventions. *Cochrane Collaborations* 2017.
14. Ouzzani M, Hammady H, Fedorowicz Z, Elmagarmid A. Rayyan - a web and mobile app for systematic reviews. *Systematic Reviews* 2016; 5(210).
15. Kertai MD, White WD, Gan TJ. Cumulative duration of “triple low” state of low blood pressure, low bispectral index, and low minimum alveolar concentration of volatile anesthesia is not associated with increased mortality. *Anesthesiology* 2014; 121(1):18-28.
16. Sessler DI, Sigl JC, Kelley SD, Chamoun NG, Manberg PJ, Saager L, et al. Hospital stay and mortality are increased in patients having a triple low of low blood pressure, low bispectral index, and low minimum alveolar concentration of volatile anesthesia. *Anesthesiology* 2012; 116(6):1195-1203.

17. Wells GA, Shea B, O'Connell D, Peterson J, Welch V, Losos M, et al. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. 2017.
18. Dindo D, Demartines N, Clavien PA. Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. *Ann Surg* 2004; 240(2):205-13.
19. R Core Team (2017): R: A language and environment for statistical computing. R foundation for statistical computing V, Austria. Available from https://www.R-project.org/, Accessed at: 31-10-2018.
20. Stiglic G, Watson R, Cilar L. R you ready? Using the R programma for statistical analysis and graphics. *Res Nurs Health,* 2019; 42 (6): 494-499
21. Abbott TEF, Pearse RM, Archbold RA, Ahmad T, Niebrzegowska E, Wragg A, et al. A prospective international multicentre cohort study of intraoperative heart rate and systolic blood pressure and myocardial injury after noncardiac surgery: results of the VISION study. *Anesth Analg* 2018; 126(6):1936-1945.
22. Roshanov PS, Rochwerg B, Patel A, Salehian O, Duceppe E, Belley-Cote EP, et al. Withholding versus continuing angiotensin-converting enzyme inhibitors or angiotensin ii receptor blockers before noncardiac surgery: an analysis of the vascular events in noncardiac surgery patients cohort evaluation prospective cohort. *Anesthesiology* 2017; 126(1):16-27.
23. Devereaux PJ, Biccard BM, Sigamani A, Xavier D, Chan MTV, Srinathan S, et al. Association of postoperative high-sensitivity troponin levels with myocardial injury and 30-day mortality among patients undergoing noncardiac surgery. *JAMA* 2017; 317(16):1642-1651.
24. Charlson ME, MacKenzie CR, Gold JP, Ales KL, Topkins M, Shires GT. Risk for postoperative congestive heart failure. *Surg Gynecol Obstet* 1991; 172(2):95-104.
25. Pipanmekaporn T, Punjasawadwong Y, Charuluxananan S, Lapisatepun W, Bunburaphong P, Patumanond J, et al. Incidence of and risk factors for cardiovascular complications after thoracic surgery for noncancerous lesions. *Journal of Cardiothoracic and Vascular Anesthesia* 2014; 28(4):960-965.
26. Barone JE, Bull MB, Cussatti EH, Miller KD, Tucker JB. Perioperative myocardial infarction in low-risk patients undergoing noncardiac surgery is associated with intraoperative hypotension. *Journal of Intensive Care Medicine* 2002; 17(5):250-255.
27. Sposato LA, Suarez A, Jauregui A, Riccio PM, Altounian M, Andreoli MG, et al. Intraoperative hypotension, new onset atrial fibrillation, and adverse outcome after carotid endarterectomy. *Journal of the Neurological Sciences* 2011; 309(1):5-8.
28. Yang L, Sun DF, Han J, Liu R, Wang LJ, Zhang ZZ, et al. Effects of intraoperative hemodynamics on incidence of postoperative delirium in elderly patients: a retrospective study. *Med Sci Monit* 2016; 22:1093-1100.
29. Duane DT, Howard SJ, Kraayenbrink M. Incidence and predictors of bulbar palsy after surgery for acoustic neuroma. *Journal of Neurosurgical Anesthesiology* 1997; 9(3):263-268.
30. Guarino M, Stracciari A, Di Alessandro R, Borghi A, Gardella E, Pazzaglla P, et al. A prospective study on the neurological complications after liver transplantation. *Gastroenterology International* 1999; 12(3):140-145.
31. Xu X, Ling Q, Wei Q, Wu J, Gao F, He ZL, et al. An effective model for predicting acute kidney injury after liver transplantation. *Hepatobiliary and Pancreatic Diseases International* 2010; 9(3):259-263.
32. Li Q, Yao G, Ge Q, Yi M, Gao J, Xi Z. Relevant risk factors affecting time of ventilation during early postoperative period after orthotopic liver transplantation. *Journal of Critical Care* 2010; 25(2):221-224.

33. Lauterio A, Di Sandro S, Gruttadauria S, Spada M, Di Benedetto F, Baccarani U, et al. Donor safety in living donor liver donation: An Italian multicenter survey. *Liver Transplantation* 2017; 23(2):184-193.
34. Chen Y, He L, Qu W, Zhang C. Predictors of intraoperative pressure injury in patients undergoing major hepatobiliary surgery. *J Wound Ostomy Continence Nurs* 2017; 44(5):445-449.
35. Balci MK, Vayvada M, Salturk C, Kutlu CA, Ari E. Incidence of early acute kidney injury in lung transplant patients: a single-center experience. *Transplantation Proceedings* 2017; 49(3):593-598.
36. Chen X, Ding X, Shen B, Teng J, Zou J, Wang T, et al. Incidence and outcomes of acute kidney injury in patients with hepatocellular carcinoma after liver transplantation. *Journal of Cancer Research and Clinical Oncology*; 143(7):1337-1346.
37. Vasivej T, Sathirapanya P, Kongkamol C. Incidence and risk factors of perioperative stroke in noncardiac, and nonaortic and its major branches surgery. *J Stroke Cerebrovasc Dis* 2016; 25(5):1172-1176.
38. Brinkman R, HayGlass KT, Mutch WA, Funk DJ. Acute kidney injury in patients undergoing open abdominal aortic aneurysm repair: A pilot observational trial. *J Cardiothorac Vasc Anesth.* 2015; 29:1212-9.
39. Ellis RJ, Del Vecchio SJ, Kalma B, et al. Association between preoperative hydration status and acute kidney injury in patients managed surgically for kidney tumours. *International Urology and Nephrology.* 2018; 50:1211-1217
40. Hallqvist L, Granath F, Huldt E, Bell M. Intraoperative hypotension is associated with acute kidney injury in noncardiac surgery. *Eur J Anaesthesiol*. 2017; 34:1-7.
41. Hallqvist L, Martensson J, Granath F, Sahlen A, Bell M. Intraoperative hypotension is associated with myocardial damage in noncardiac surgery. *Eur J Anaesthesiol.* 2016; **33** : 450–6.
42. Hirsch J, DePalma G, Tsai TT, Sands LP, Leung JM, Impact of intaoperative hypotension and blood pressure fluctuations on early postoperative delirium after non-cardiac surgery. *Br J Anaesth*. 2015;115(3):418-26.
43. Kheterpal S, O'Reilly M, Englesbe MJ, et al. Preoperative and intraoperative predictors of cardiac adverse events after general, vascular and urological surgery. *Anesthesiology.* 2009; 110: 58–66
44. Marcantonio ER, Goldman L, Orav EJ, Cook EF, Lee TH. The association of intraoperative factors with the development of postoperative delirium. *Am J Med.* 1998; 105 : 380–4
45. Matsota PK, Christodoulopoulou TC, Batistaki CZ, Arvaniti CC, Voumvourakis KI, Kostopanagiotou GG. Factors associated with the presence of postoperative headache in elective surgery patients: a prospective single center cohort study. *J Anesth.* 2017:31; 225–36
46. McLean House, Marolen KN, St Jacques PJ, McEvoy MD, Ehrenfeld JM. Surgical Apgar score is associated with myocardial injury after noncardiac surgery. *J Clin Anesth.* 2016; 34:395-402.
47. Mizota T, Hamada M, Matsukawa S, Seo H, Tanaka T, Segawa H. Relationship between intraoperative hypotension and acute kidney injury after living donor liver transplantation: A retrospective analysis. *J Cardiothoracic Vasc Anesth.* 2017; 31:582-9.
48. Monk TG, Bronsert MR, Henderson WG, et al. Association between intraoperative hypotension and hypertension and 30-day postoperative mortality in noncardiac surgery. *Anesthesiology.* 2015;123:307–19.
49. Patti R, Saitta M, Cusumano G, Termine G, Di Vita G. Risk factors for postoperative delirium after colorectal surgery for carcinoma. *Eur J Oncol Nurs.* 2011; 15:519-23
50. Post IL, Verheijen PM, Pronk A, Siccama I, Houweling PL. Intraoperative blood pressure changes as a risk factor for anastomotic leakage in colorectal surgery. *Int J Colorectal Dis.* 2012; 27:765-72.

51. Sabate S, Mases A, Guilera N, et al. Incidence and predictors of major perioperative adverse cardiac and cerebrovascular events in non-cardiac surgery. *Br J Anaesth.* 2011; 107(6):879-90.
52. Santiago-Lastra Y, Mathis MR, Andraska E, et al. Extended Case Duration and hypotension are associated with higher-grade postoperative complications after urinary diversion for non-oncological disease. *Reconstructive Urology.* 2017; 111: 189-196.
53. Sessler DI, Meyhoff CS, Zimmerman NM, et al. Period-dependent Associations between Hypotension during and for four days after noncardiac surgery and a composite of myocardial infarction and death: a substudy of the POISE-2 Trial. *Anesthesiology.* 2018; 128:317-27.
54. Sun LY, Wijeysundera DN, Tait GA, Beattie WS. Association of intraoperative hypotension with acute kidney injury after elective noncardiac surgery. *Anesthesiology.* 2015; 123:515–23
55. Tallgren M, Niemi T, Poyhia R, et al. Acute renal injury and dysfunction following elective abdominal aortic surgery. *Eur J Vasc Endovasc Surg.* 2007; 33:550-5
56. Thakar CV, Kharat V, Blanck S, Leonard AC. Acute kidney injury after gastric bypass surgery. *Clin J Am Soc Nephrol.* 2007; 2:426-30
57. van Waes JA, van Klei WA, Wijeysundera DN, van Wolfswinkel L, Lindsay TF, Beattie WS. Association between intraoperative hypotension and myocardial injury after vascular surgery. *Anesthesiology.* 2015; 124:35-44
58. von Knorring J, Lepantalo M, Lindgren L, Lindfors O. Cardiac arrhythmias and myocardial ischemia after thoracotomy for lung cancer. *Ann Thorac Surg.* 1992; 53:642-7
59. White SM, Moppet IK, Griffiths R, et al. Secondary analysis of outcomes after 11,085 hip fracture operations from the prospective UK Anaesthesia Sprint Audit of Practice (ASAP-2). *Anaesthesia*. 2016; 71(5):506-14
60. Xu L, Yu C, Jiang J, et al. Major adverse cardiac events in elderly patients with coronary artery disease undergoing noncardiac surgery: a multicenter prospective study in China. *Arch Gerontol Geriatr.* 2015;61:503-9
61. Yu J, Keun Park H, Kwon H, et al. Risk factors for acute kidney injurty after percutaneous nephrolithotomy implications of intraoperative hypotension. *Medicine.* 2018; 97 (30)
62. Ziser A, Plevak DJ, Wiesner RH, Rakela J, Offord KP, Brown DL. Morbidity and mortality in cirrhotic patients undergoing anesthesia and surgery. *Anesthesiology.* 1999; 90:42-53
63. Austin PC. An introduction to propensity score methods for reducing the effects of confounding in observational studies. *Multivariate Behav Res* 2011; 46(3):399-424.
64. Gu WJ, Hou BL, Kwong JSW, Tian X, Qian Y, Cui Y, et al. Association between intraoperative hypotension and 30-day mortality, major adverse cardiac events, and acute kidney injury after non-cardiac surgery: a meta-analysis of cohort studies. *Int J Cardiol* 2018.
65. Wesselink EM, Kappen TH, Torn HM, Slooter AJC, van Klei WA. Intraoperative hypotension and the risk of postoperative adverse outcomes: a systematic review. *Br J Anaesth* 2018; 121(4):706-721.
66. Futier E, Lefrant JY, Guinot PG, Godet T, Lorne E, Cuvillon P, et al. Effect of individualized vs standard blood pressure management strategies on postoperative organ dysfunction among high-risk patients undergoing major surgery: a randomized clinical trial. *JAMA* 2017; 318(14):1346-1357.
67. Pinsky MR. Both perfusion pressure and flow are essential for adequate resuscitation. *Sepsis* 2000; 4: 143-146. 10.1023/A:1011406921372'
68. Walsh M, Devereaux PJ, Garg AX, Kurz A, Turan A, Rodseth RN, et al. Relationship between intraoperative mean arterial pressure and clinical outcomes after noncardiac surgery: toward an empirical definition of hypotension. *Anesthesiology* 2013; 119(3):507-515.

69. Vernooij LM, van Klei WA, Machina M, Pasma W, Beattie WS, Peelen LM. Different methods of modelling intraoperative hypotension and their association with postoperative complications in patients undergoing non-cardiac surgery. *Br J Anaesth* 2018; 120(5):1080-1089.
70. Sessler DI, Bloomstone JA, Aronson S, Berry C, Gan TJ, Kellum JA, et al. Perioperative quality initiative consensus statement on intraoperative blood pressure, risk and outcomes for elective surgery. *British journal of anaesthesia.* 2019;122(5):563-574.

SUPPLEMENTAL DIGITAL CONTENT

Text S1. Complete search strategy
Text S2. Format used for ranking the hypotension severity of the definitions used for hypotension, in the included studies
Text S3. Meta-regression using the maximum likelihood estimator method
Table S1. Overview of all studies
Table S2. Ranking of the included articles for the sensitivity analyses
Figure S1. Subgroup analysis using the hypotension severity ranking
Figure S2. Sensitivity analysis using the Clavien-Dindo grading scale (Grade I-V)
Figure S3. Sensitivity analysis based on study population (S1 from NOS score)
Figure S4. Sensitivity analysis using the study quality based on NOS score
Figure S5. Sensitivity analysis adding studies which were excluded based on low study quality (NOS <4)

TEXT S1. COMPLETE SEARCH STRATEGY

Last search performed on 01-08-2018. Searches were made with the advice of a clinical librarian.

PUBMED

("Intraoperative Period"[Mesh] OR intraoperative[tiab] OR intra-operative[tiab] OR peroperative[tiab] OR per-operative[tiab]) AND ("Hypotension"[Mesh] OR hypotens*[tiab] OR low blood pressure[tiab] OR low mean arterial pressure[tiab] OR low systolic blood pressure[tiab]) AND ("mortality" [Subheading] OR "Fatal Outcome"[Mesh] OR "Mortality"[Mesh] OR "Morbidity"[Mesh] OR "Heart Failure"[Mesh] OR "Stroke"[Mesh] OR mortalit*[tiab] OR morbidit*[tiab] OR fatal outcome*[tiab] OR organ damage[tiab] OR organ failure[tiab] OR stroke[tiab] OR kidney injury[tiab] OR heart failure[tiab] OR myocardial damage[tiab] OR renal failure OR cerebrovascular accident[tiab])

EMBASE

(intraoperative period/ or operation duration/ or (intraoperative or intra-operative or peroperative or per-operative).ti,ab,kw.) AND (exp hypotension/ or (hypotens* or low blood pressure or low mean arterial pressure or low systolic blood pressure).ti,ab,kw.) AND (fatality/ or mortality/ or cardiovascular mortality/ or hospital mortality/ or surgical mortality/ or exp mortality rate/ or morbidity/ or heart failure/ or cerebrovascular accident/ or (mortalit* or morbidit* or fatal outcome* or organ damage or organ failure or stroke or kidney injury or heart failure or myocardial damage or renal failure or cerebrovascular accident).ti,ab,kw.)

Cochrane Central Register of Controlled Trials

http://on0linelibrary.wiley.com/cochranelibrary/search/advanced/shared/searches/2334847973302740272

ID Search Hits

#1 intraoperative or intra-operative or peroperative or per-operative:ti,ab,kw (Word variations have been searched) 15445

#2 hypotens* or low blood pressure or low mean arterial pressure or low systolic blood pressure:ti,ab,kw (Word variations have been searched) 30612

#3 mortalit* or morbidit* or fatal outcome* or organ damage or organ failure or stroke or kidney injury or heart failure or myocardial damage or renal failure or cerebrovascular accident:ti,ab,kw (Word variations have been searched) 99288

#4 #1 and #2 and #3 in Trials 246

TEXT S2. FORMAT USED FOR RANKING THE HYPOTENSION SEVERITY OF THE DEFINITIONS USED FOR HYPOTENSION, IN THE INCLUDED STUDIES.

Definitions	Hypotension severity	Duration of hypotension	Measuring Method
MAP>20% decrease		Unknown	Unknown
MAP>20% decrease		10 min	Unknown
MAP>20% decrease or MAP>20 mmHg decrease		60 min	Unknown
MAP>30% decrease		Unknown	Unknown
SBP>30% decrease		10 min	Unknown
SBP>40% decrease		Unknown	Unknown
SBP>40% decrease		5 min	Arterial
SBP>50% decrease		5 min	Arterial
Combined definition: delta MAP>30% decrease /SBP<90		Unknown	Unknown
Combined definition: SBP<90 DBP<60 of SBP>30% decrease		10 min	Arterial
MAP<50		Unknown	Arterial & NIBP
MAP<50		1 min	Arterial
MAP<55		Unknown	Unknown
MAP<55		5 min	Arterial & NIBP
MAP<60		Unknown	Arterial & NIBP
MAP<60		Unknown	Arterial & NIBP
MAP<60		30 min	Arterial & NIBP
MAP<60		Unknown	Unknown
MAP<60		5 min	Arterial & NIBP
MAP<60		1 min	Arterial
MAP<60		Unknown	Unknown
MAP<60		15 min	Unknown
MAP<65		Unknown	Arterial
MAP<70		Unknown	Unknown
MAP<70		5 min	Arterial
MAP<75		Unknown	Unknown
SBP<80		1 min	Arterial & NIBP
SBP<90		Unknown	Arterial & NIBP
SBP<90 requiring therapy		Unknown	Unknown

Please rate the definitions of hypotension combined with the duration of hypotension into one severity scale. If you think definitions are equal in severity, you are free to use the same rank.
Start by rating the most severe definition of hypotension as number 1.

TEXT S3. META-REGRESSION USING THE MAXIMUM LIKELIHOOD ESTIMATOR METHOD

Step 1: Hypotension severity added to baseline

tau^2 (estimated amount of residual heterogeneity):	0.1457 (SE = 0.0571)
tau (square root of estimated tau^2 value):	0.3817
I^2 (residual heterogeneity / unaccounted variability):	**75.02%**
H^2 (unaccounted variability / sampling variability):	4.00
R^2 (amount of heterogeneity accounted for):	68.44%

Step 2: Both hypotension severity and Clavien-Dindo Grade added to baseline

tau^2 (estimated amount of residual heterogeneity):	0.0984 (SE = 0.0427)
tau (square root of estimated tau^2 value):	0.3137
I^2 (residual heterogeneity / unaccounted variability):	**61.43%**
H^2 (unaccounted variability / sampling variability):	2.59
R^2 (amount of heterogeneity accounted for):	78.68%

Step 3: Hypotension severity, Clavien-Dindo Grade and Study population added to baseline

tau^2 (estimated amount of residual heterogeneity):	0.0638 (SE = 0.0315)
tau (square root of estimated tau^2 value):	0.2526
I^2 (residual heterogeneity / unaccounted variability):	**49.69%**
H^2 (unaccounted variability / sampling variability):	1.99
R^2 (amount of heterogeneity accounted for):	86.18%

TABLE S1.

First author	Year	Country	Study design	n	Study population	Definition of hypotension	Outcome	Definition of outcome	OR [95% CI]	NOS-score
					Studies not included in primary meta-analysis					
Abbott	2017	International Multicenter	Prospective cohort	16079	Non-cardiac surgery	SBP<100	Myocardial infarction	Serum troponin elevation in the presence of at least one ischemic symptom (ECG or echocardiogram)	0.97 [0.80; 1.17]	6
Balci	2017	Turkey	Retrospective cohort	30	Lung transplantation	MAP<70	AKI	AKIN guidelines	3.00 [0.78; 13.31]	3
Barone	2002	United States of America	Case control study	60	Non-cardiac surgery	SBP<100	Myocardial infarction	Postoperative ischemic ECG changes, CKMB >2,5% of total CK and documentation in the medical record of ischemia by an internist of cardiologist	6.15 [1.89; 20.05]	2
Charlson	1991	United States of America	Prospective cohort	254	Patients with either hypertension or diabetes	Decrease MAP >40mmHg from baseline	Heart failure	Congestive heart failure seven days postoperative	1.39 [0.68; 2.83]	2
Duane	1997	United Kingdom	Retrospective cohort	102	Acoustic neuroma	Decrease MAP >30% or decrease SBP>30%	Bulbar palsy	New postoperative bulbar palsy	4.87 [1.19; 19.90]	2

First author	Year	Country	Study design	n	Study population	Definition of hypotension	Outcome	Definition of outcome	OR [95% CI]	NOS-score
Guarino	1999	Italy	Prospective cohort	114	Liver transplantation	MAP<50	Combined neurological	Central nervous complications in the first month postoperative, consisting of stupor, tremor, coma and seizures	2.46 [1.08; 5.60]	3
Lauterio	2017	Italy	Retrospective cohort	246	Living liver donation patients	SBP<100	Postoperative complications	Surgical complications graded by the Clavien-Dindo system	25.98 [3.28; 204.70]	2
Li	2010	China	Prospective cohort	96	Orthotopic liver transplantation	SBD<90 or DBP<50	Time ventilated in ICU	Postoperative ventilation >24 hours	2.60 [1.02; 6.61]	3
Pipanmekaporn	2014	Thailand	Retrospective cohort	719	Thoracotomy or thoracoscopy for non-cancerous lesions	MAP<60 or SBP<80	Combined cardiac	Combined cardiac outcome, consisting of cardiac arrhythmias, cardiac arrest, pulmonary embolism, myocardial ischemia and heart failure, 30 days postoperative	4.41 [1.80; 10.80]	2
Sposato	2011	Argentin	Retrospective cohort	186	Patients undergoing carotid endarterectomy	SBP<80	Combined cardiac	New atrial fibrillation on ECG during continuous monitoring during hospital stay	9.58 [1.93; 47.43]	3
Vasivej	2016	Thailand	Case-control		Non-cardiac, non-aortic surgery	MAP<65	Stroke	TOAST classification up to 30 days postoperative	1.20 [0.42; 3.46]	3

First author	Year	Country	Study design	n	Study population	Definition of hypotension	Outcome	Definition of outcome	OR [95% CI]	NOS-score
X Chen*	2017	China	Retrospective cohort	566	Liver transplant for hepatocellular carcinoma	SBP<90	AKI	Increase of sCr≥26.4 µmol/L or increase sCr >50% within the first 48 hours postoperatively	59.15 [24.49; 144.00]	3
Xu	2010	China	Retrospective cohort	102	Liver transplantation	SBP<90	AKI	sCr >1.5 mg/dl with an increase of 50% above the baseline level and/ or the need for renal replacement therapy in the first week after surgery	5.60 [2.19; 14.33]	3
Y Chen#	2017	China	Retrospective cohort	803	Hepatobiliary surgery	DBP<60	Pressure injury	Diagnosed using the 2014 Staging System for pressure ulcers/injuries promulgated by the National Pressure Ulcer Advisory Panel	3.96 [1.77; 8.86]	2
Yang	2016	China	Retrospective cohort	480	Elderly patients, elective surgery with general anesthesia	Decrease MAP >30%	Delirium	Postoperative delirium 1-3 days after surgery	0.91 [0.41; 2.20]	2
Studies included in primary meta-analysis										
Babazade	2016	United States of America	Retrospective cohort	2521	Colorectal surgery	MAP<55	Surgical site infection	Postoperative infection of surgical wound	1.10 [0.87; 1.38]	5
Bijker	2009	Netherlands	Retrospective cohort	1705	General and vascular surgery	SBP<80	Mortality	1 year postoperative mortality	2.57 [1.66; 3.99]	8

First author	Year	Country	Study design	n	Study population	Definition of hypotension	Outcome	Definition of outcome	OR [95% CI]	NOS-score
Brinkman	2015	Canada	Prospective cohort	40	Open repair of an infrarenal aneurysm	MAP<65	AKI	Increase of sCr≥26.4 µmol/L or increase sCr >50% within the first 48 hours post-operatively	1.00 [0.10; 10.41]	4
Ellis	2018	Australia	Retrospective cohort	184	Urologic	MAP<60	AKI	Increase in serum creatinine level by ≥0.3mg/dL within 2 days or ≥1.5 times baseline value within 7 days (KDIGO)	0.71 [0.35; 1.41]	6
Hallqvist	2016	Sweden	Prospective cohort	300	Elective, non-cardiac surgery, for overnight admission	Decrease SBP >50%	Myocardial infarction	Ischaemic ECG changes, ischaemic symptoms or regional wall motion abnormalities	11.38 [3.82; 33.91]	5
Hallqvist	2017	Sweden	Retrospective cohort	470	Elective, major, non-cardiac surgery	Decrease SBP >40%	AKI	Increase in serum creatinine level by ≥0.3mg/dL within 2 days or ≥1.5 times baseline value within 7 days (KDIGO)	1.74 [1.12; 2.68]	7
Hirsch	2014	United States of America	Prospective cohort	594	Non-cardiac surgery	MAP<50	Delirium	Confusion assessment method (CAM) at 9 am and 12 pm	0.66 [0.29; 1.51]	7
Hsieh	2016	United States of America	Case control study	502	Non-cardiac, non-neurological, non-carotid surgery, under general anesthesia	MAP<70	Stroke	Identification by ICD-codes in electronic patient system	0.81 [0.49; 1.33]	7

First author	Year	Country	Study design	n	Study population	Definition of hypotension	Outcome	Definition of outcome	OR [95% CI]	NOS-score
Kheterpal	2009	United States of America	Prospective cohort	7740	General, vascular and urological surgery	MAP<60	Combined cardiac	Combined cardiac outcome, consisting of cardiac arrest, acute myocardial infarction or a new atrial flutter, atrial fibrillation or second or third degree AV block	1.17 [0.75; 1.83]	4
Marcantonio	1998	United States of America	Retrospective cohort	1341	>50 years old, for major elective non-cardiac surgery	Decrease MAP>30% or SBP<90	Delirium	Delirum diagnosed with the the confusion assessment method	0.83 [0.53; 1.30]	7
Matsota	2016	Japan	Prospective cohort	446	Elective, non-cardiac, nonneurological surgery	Decrease MAP >20%	Headache	International headache society criteria	2.12 [1.24; 3.64]	5
McLean House	2016	United States of America	Retrospective cohort	46590	Non-cardiac surgery	MAP<60	Myocardial infarction	cTn-I>1.5 ng/mL or cTnt-T> 0.3ng/nL	1.27 [0.85; 1.88]	5
Mizota	2017	Japan	Retrospective cohort	231	Living donor liver transplantation	MAP<50	AKI	100% increase in sCr or urine output of <0.5 ml/kg/h for >12 hours during the first seven postoperative days	2.80 [1.03; 7.58]	8
Monk	2015	United States of America	Retrospective cohort	18756	Non-cardiac surgery	MAP<55	Mortality	30 day postoperative mortality	2.48 [1.97; 3.11]	6
Patti	2011	Italy	Prospective cohort	100	>65 years old, elective non-laparoscopic colorectal cancer surgery	MAP<60	Delirium	Diagnosed with the delirium rating scale	5.76 [1.84; 18.03]	4

First author	Year	Country	Study design	n	Study population	Definition of hypotension	Outcome	Definition of outcome	OR [95% CI]	NOS-score
Post	2012	Netherlands	Prospective cohort	285	Elective or emergency colorectal surgery	Decrease SBP >40%	Anastomotic leakage	Confirmed with a CT scan or ultrasound or by operative evidence	2.64 [0.58; 11.97]	6
Roshanov	2017	International Multicenter	Prospective cohort	14687	Non-cardiac surgery	SBP<90	Mortality	30 day postoperative mortality	2.02 [1.61; 2.55]	6
Sabate	2011	Spain	Prospective cohort	3387	Non-cardiac surgery	MAP> 20 mmHg decrease or MAP >20% decrease	Combined cardiac	Non-fatal cardiac arrest, myocardial infarction, congestive heart failure, new cardiac arrhythmia, angina, stroke, cardiac death, cerebrovascular death	3.36 [2.25; 5.01]	4
Santiago Lastra	2017	United States of America	Retrospective cohort	141	Urologic	Decrease MAP >30%	Postoperative complications	Surgical complications graded by the Clavien-Dindo system	1.19 [0.56; 2.54]	5
Sessler	2018	International Multicenter	Retrospective cohort	9765	Patients at risk for cardiovascular disease	SBP<90 requiring therapy	Combined myocardial infarction and mortality	Third universal definition of myocardial infarction criteria and 30 day mortality	1.12 [0.95; 1.32]	6
Sun	2015	Canada	Retrospective cohort	5127	Non-cardiac surgery	MAP<60	AKI	Increase in serum creatinine level by ≥0.3mg/dL within 2 days or ≥1.5 times baseline value within 7 days	2.05 [1.36; 3.08]	5
Talgren	2006	Finland	Prospective cohort	69	Elective abdominal aortic surgery	MAP<60	AKI	>50% increase in sCr or oliguria <0,5ml/kg/h for 24 hours or anuria	10.94 [2.60; 46.04]	5

First author	Year	Country	Study design	n	Study population	Definition of hypotension	Outcome	Definition of outcome	OR [95% CI]	NOS-score
Thakar	2007	United States of America	Retrospective cohort	491	Gastric bypass surgery	MAP<60	AKI	>50% increase in sCr during the first three days postoperatively or requirement for dialysis during the postoperative period	2.37 [1.21; 4.65]	5
van Waes	2016	Netherlands	Prospective cohort	890	Vascular surgery, >60 years old	MAP<60	Myocardial infarction	Elevated troponin and symptoms of ischemia, ischaemic ECG changes, new myocardial loss, new wall motion abnormalities or an intracoronary thrombus	2.19 [1.09; 4.39]	6
von Knorring	1992	Finland	Retrospective cohort	598	Thoracic surgery for lung cancer	Decrease SBP>30%	Myocardial infarction	ECG changes, CKMB elevation	9.57 [4.29; 21.35]	5
White	2016	United Kingdom	Retrospective cohort		Hip surgery	MAP<75	Mortality	30 day postoperative mortality	1.16 [0.92; 1.45]	4
Xu	2015	China	Prospective cohort	1422	Non-cardiac surgery, >60 years old	SBP<90 or DBP<60 or decrease SBP>30%	Combined cardiac	Combined cardiac outcome, consisting of cardiac death, non-fatal cardiac arrest, acute myocardial infarction, congestive heart failure and angina	2.43 [1.69; 3.51]	6
Yu	2018	Korea	Retrospective cohort	662	Urologic	MAP<70	AKI	Increase in serum creatinine level by ≥0.3mg/dL within 2 days or ≥1.5 times baseline value within 7 days (KDIGO)	12.54 [7.77; 20.25]	6

First author	Year	Country	Study design	n	Study population	Definition of hypotension	Outcome	Definition of outcome	OR [95% CI]	NOS-score
Ziser	1999	United States of America	Retrospective cohort	733	Liver cirrhosis	Decrease MAP>20%	Postoperative complications	Any postoperative complications occurring in 30 days postoperatively	2.84 [2.05; 3.94]	4

Supplemental table 1. Overview of all studies. The first part shows an overview of the 15 studies that were not included in the meta-analysis. 14 of these studies were excluded because of low study quality (NOS-score). The study by Abbott et al could not be included because it used the same cohort of patients as the study by Roshanov. The second part shows an overview of the 29 studies that were included in the meta-analysis. In supplemental sensitivity figure 5, we combined the studies of our meta-analysis with the 14 studies that were excluded, to test the robustness of the result in our meta-analysis.

Chen# = Chen Y. *J Wound Ostomy Continence Nurs.* 2017.

Chen* = Chen X. *J Cancer Res Clin Oncol.* 2017.

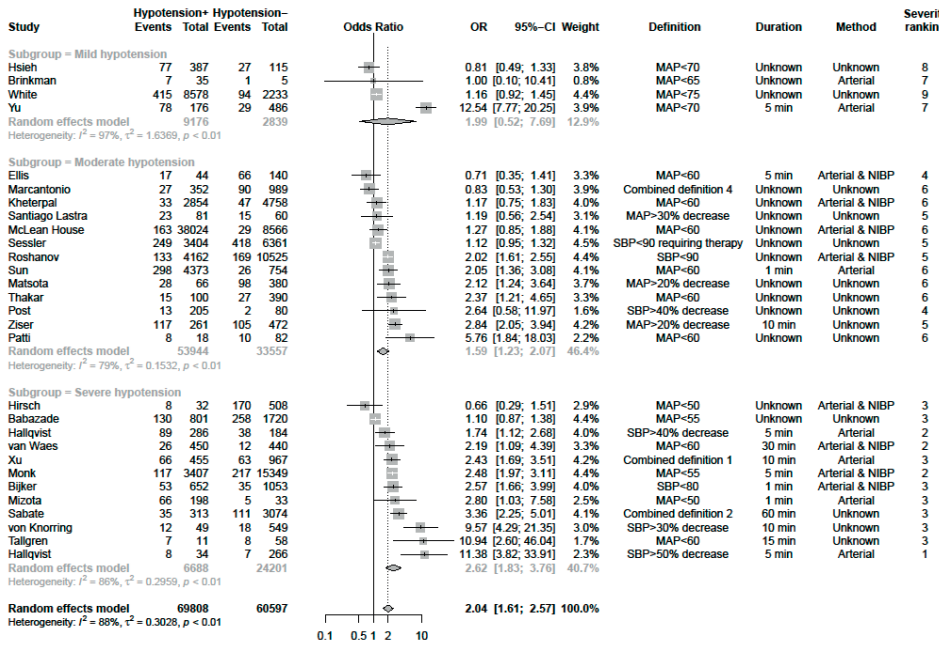
TABLE S2.

Authors	Year	Outcome event	Clavien-Dindo Scale	Hypotension definition	Hypotension duration	Bloodpressure measuring method	Hypotension severity ranking	Total NOS score	Generalizability
Kheterpal	2009	Combined cardiac	Grade III	MAP<60	Unknown	Arterial & NIBP	6	4	Generalizable
McLean House	2016	Myocardial infarction	Grade IV	MAP<60	Unknown	Arterial & NIBP	6	5	Generalizable
Sessler	2018	Combined cardiac	Grade IV	SBP<90 requiring therapy	Unknown	Unknown	5	6	Generalizable
van Waes	2016	Myocardial infarction	Grade IV	MAP<60	30 min	Arterial & NIBP	2	6	Generalizable
Xu	2015	Combined cardiac	Grade IV	SBP<90 or DBP<60 or SBP>30% decrease	10 min	Arterial	3	6	Non-Generalizable
Sabate	2011	Combined cardiac	Grade III	MAP>20% decrease or MAP>20 mmHg decrease	60 min	Unknown	3	4	Generalizable
von Knorring	1992	Myocardial infarction	Grade IV	SBP>30% decrease	10 min	Unknown	3	5	Non-Generalizable
Hallqvist	2016	Myocardial infarction	Grade IV	SBP>50% decrease	5 min	Arterial	1	5	Generalizable
Ellis	2018	AKI	Grade II	MAP<60	5 min	Arterial & NIBP	4	6	Non-Generalizable
Brinkman	2015	AKI	Grade II	MAP<65	Unknown	Arterial	7	4	Non-Generalizable
Hallqvist	2017	AKI	Grade II	SBP>40% decrease	5 min	Arterial	2	7	Generalizable
Sun	2015	AKI	Grade II	MAP<60	1 min	Arterial	6	5	Generalizable
Thakar	2007	AKI	Grade II	MAP<60	Unknown	Unknown	6	5	Non-Generalizable
Mizota	2017	AKI	Grade II	MAP<50	1 min	Arterial	3	8	Generalizable
Tallgren	2006	AKI	Grade II	MAP<60	15 min	Unknown	3	5	Non-Generalizable
Yu	2018	AKI	Grade II	MAP<70	5 min	Arterial	7	6	Non-Generalizable
Hsieh	2016	Stroke	Grade IV	MAP<70	Unknown	Unknown	8	7	Generalizable
Hirsch	2014	Delirium	Grade II	MAP<50	Unknown	Arterial & NIBP	3	7	Generalizable
Marcantonio	1998	Delirium	Grade II	SBP<90 or MAP>30% decrease	Unknown	Unknown	6	7	Generalizable

Authors	Year	Outcome event	Clavien-Dindo Scale	Hypotension definition	Hypotension duration	Bloodpressure measuring method	Hypotension severity ranking	Total NOS score	Generalizability
Patti	2011	Delirium	Grade II	MAP<60	Unknown	Unknown	6	4	Generalizable
Babazade	2016	Surgical site infection	Grade II	MAP<55	Unknown	Unknown	3	5	Generalizable
Santiago Lastra	2017	Combined surgical	Grade III	MAP>30% decrease	Unknown	Unknown	5	5	Non-Generalizable
Matsota	2016	Headache	Grade I	MAP>20% decrease	Unknown	Unknown	6	5	Generalizable
Post	2012	Anastomotic leakage	Grade III	SBP>40% decrease	Unknown	Unknown	4	6	Generalizable
Ziser	1999	Any complication	Grade III	MAP>20% decrease	10 min	Unknown	5	4	Non-Generalizable
White	2016	Mortality	Grade V	MAP<75	Unknown	Unknown	9	4	Non-Generalizable
Roshanov	2017	Mortality	Grade V	SBP<90	Unknown	Arterial & NIBP	5	6	Generalizable
Monk	2015	Mortality	Grade V	MAP<55	5 min	Arterial & NIBP	2	6	Non-Generalizable
Bijker	2009	Mortality	Grade V	SBP<80	1 min	Arterial & NIBP	3	8	Generalizable

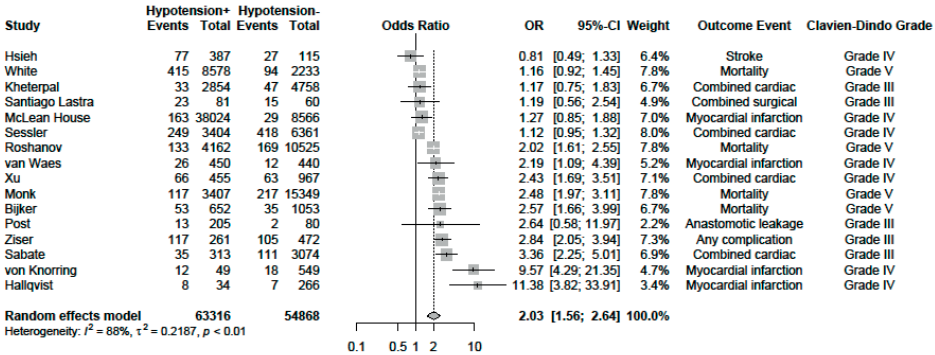
Supplemental Table 2. Ranking of the included articles for the sensitivity analyses. This table shows the severity ranking of the studied outcome based on the Clavien-Dindo Scale, the hypotension severity ranking, and the total NOS-score for each study. It also shows an overview of the generalizability of the studied population per study, which was based on the S1 question of the NOS-score.

FIGURE S1.



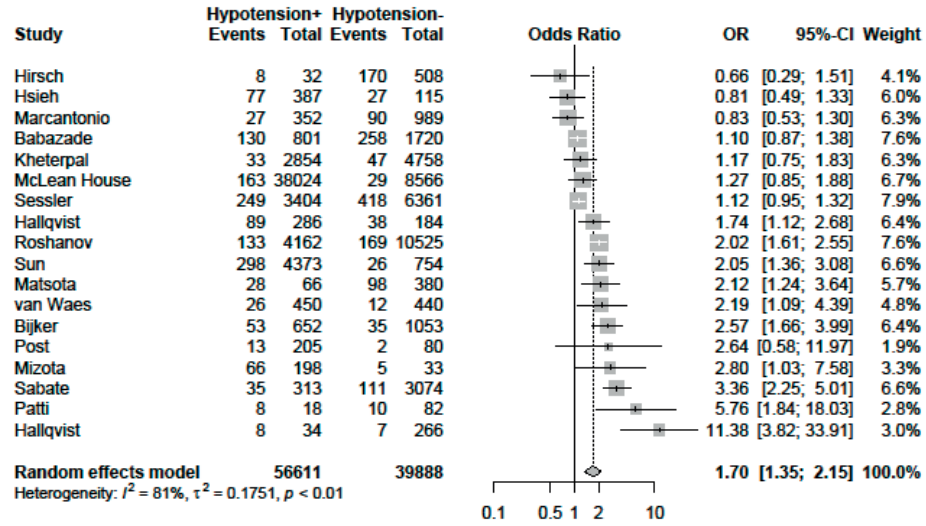
Supplemental figure 1. Subgroup analysis using the hypotension severity ranking. The influence of hypotension severity was assessed comparing differences between subgroups. The most severe definition was ranked 1, the least severe was ranked 9. Three subgroups were created based on the severity of the hypotension definition used. The odds ratio's in the subgroups moderate hypotension (OR=1.59, 95%CI=1.23-2.07) and severe hypotension (OR=2.62, 95%CI=1.83-3.76) show an association in the same direction as the overall odds ratio in the primary meta-analysis (OR=2.04, 95%CI=1.61-2.57).

FIGURE S2.



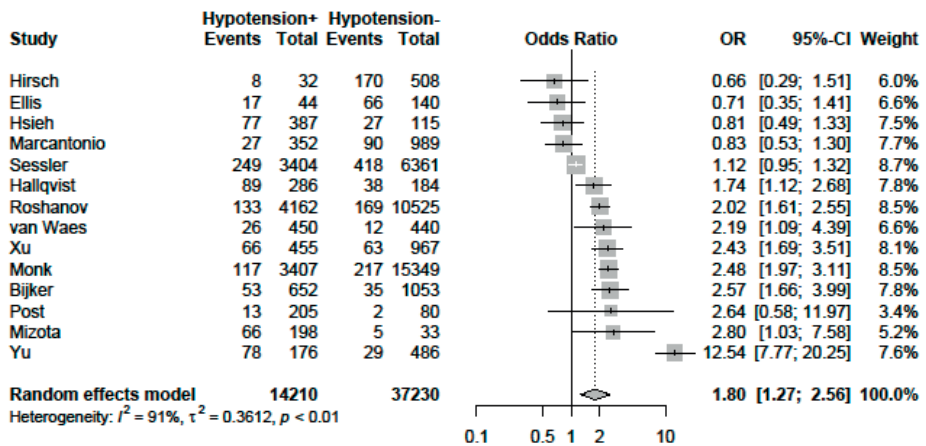
Supplemental figure 2. Sensitivity analysis using the Clavien-Dindo grading scale (Grade I-V). Studies with an outcome event graded as Clavien-Dindo 3 or above were selected, to assess the influence of excluding studies with a lower outcome event grade on the overall odds ratio in the primary meta-analysis. The odds ratio in this sensitivity analysis shows an association (OR=2.03, 95%CI=1.56-2.64) in the same direction as the overall odds ratio in the primary meta-analysis (OR=2.04, 95%CI=1.61-2.57).

FIGURE S3.



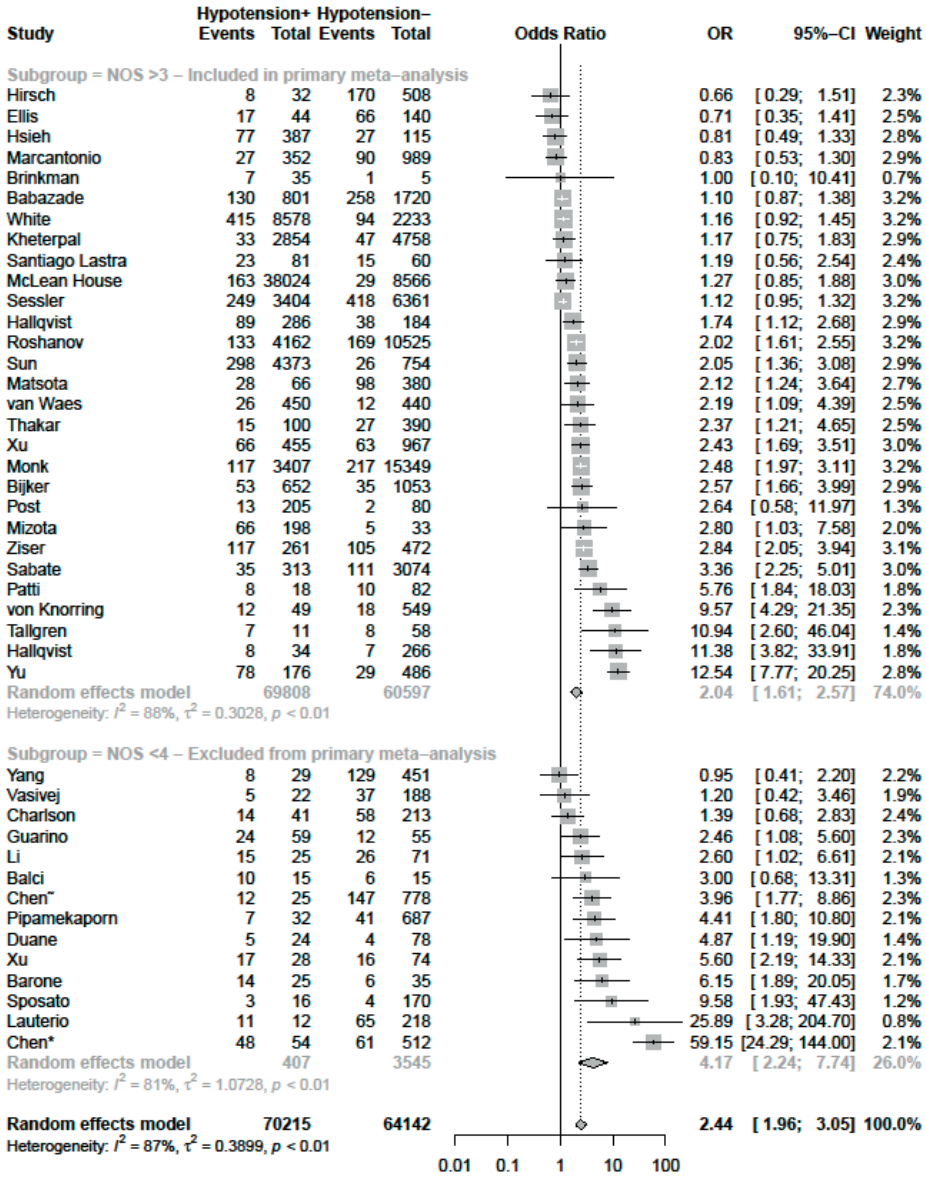
Supplemental figure 3. Sensitivity analysis based on study population (S1 from NOS score). Studies that were classified as generalizable were selected to assess the possible influence of the generalizability of the study population on the overall odds ratio. A study population was classified as generalizable when it scored a point on the first question of the NOS scale (S1); '*Representativeness of the exposed cohort*'. The odds ratio in this sensitivity analysis shows an association (OR=1.70, 95%CI=1.35-2.15) in the same direction as the overall odds ratio in the primary meta-analysis (OR=2.04, 95%CI=1.61-2.57)

FIGURE S4.



Supplemental figure 4. Sensitivity analysis using the study quality based on NOS score. Studies that were graded with a NOS score 6 and above were selected to assess the possible influence of the study quality on the overall odds ratio. The odds ratio in this sensitivity analysis shows an association (OR=1.80, 95%CI=1.27-2.56) in the same direction as the overall odds ratio in the primary meta-analysis (OR=2.04, 95%CI=1.61-2.57)

FIGURE S5.



Supplemental figure 5. Sensitivity analysis adding studies which were excluded based on low study quality (NOS <4). The influence of adding low quality studies on the overall odds was assessed. The first group shows the pooled results of the studies included in the primary meta-analysis, the second group shows the pooled results of the studies that were excluded from the meta-analysis based on study quality. This sensitivity analysis shows that excluding these studies did not change the association found in the primary meta-analysis (OR=2.44, 95%CI=1.96-3.05 versus OR=2.04, 95%CI=1.61-2.57).

M’affaccio alla finestra, e vedo il mare: vanno
le stelle, tremolano l’onde.

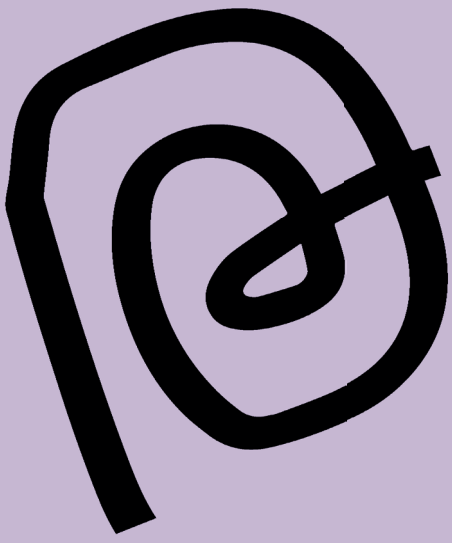
Vedo stelle passare, onde passare:
un guizzo chiama, un palpito risponde.

Ecco sospira l’acqua, alita il vento:
sul mare è apparso un bel ponte d’argento.

Ponte gettato sui laghi sereni,
per chi dunque sei fatto e dove meni?

Il mare
Giovanni Pascoli

Selected by Valeria Guglielmi



6

The use of a machine-learning algorithm that predicts hypotension during surgery in combination with personalized treatment guidance: study protocol for a randomized clinical trial

Marije Wijnberge
Jimmy Schenk
Lotte E. Terwindt
Marijn P. Mulder
Markus W. Hollmann
Alexander P. Vlaar
Denise P. Veelo
Bart F. Geerts

Trials 2019 Oct 11;20(1):582. PMID: 31601239

ABSTRACT

Background

Intraoperative hypotension is associated with increased morbidity and mortality. Current treatment is mostly reactive. The hypotension prediction index (HPI) algorithm is able to predict hypotension minutes before the blood pressure actually decreases. Internal and external validation of this algorithm has shown good sensitivity and specificity. We hypothesize that the use of this algorithm will reduce the time weighted average (TWA) in hypotension during surgery.

Methods

We aim to include 100 adult patients undergoing non-cardiac surgery with an anticipated duration of more than 2 h, necessitating the use of an arterial line, and an intraoperatively targeted mean arterial pressure (MAP) of > 65 mmHg. This study is divided into two parts; in phase A baseline TWA data from 40 patients will be collected prospectively. A device (HemoSphere) with HPI software will be connected but fully covered. Phase B is designed as a single-center, randomized controlled trial were 60 patients will be randomized with computer-generated blocks of four, six or eight, with an allocation ratio of 1:1. In the intervention arm the HemoSphere with HPI will be used to guide treatment; in the control arm the HemoSphere with HPI software will be connected but fully covered. The primary outcome is the TWA in hypotension during surgery.

Discussion

The aim of this trial is to explore whether the use of a machine-learning algorithm intraoperatively can result in less hypotension. To test this, the treating anesthesiologist will need to change treatment behavior from reactive to proactive.

Trial registration

This trial has been registered with the NIH, U.S. National Library of Medicine at ClinicalTrials.gov, ID:NCT03376347. The trial was submitted 04 November 2017 and accepted for registration 18 December 2017.

Keywords

Artificial intelligence, Blood pressure, Perioperative care, Anesthesiology, Hemodynamics

BACKGROUND

Worldwide, an estimated 313 million people have to undergo surgical procedures every year.[1] Intraoperatively, patients often suffer from episodes of hypotension. Hypotension, defined as a mean arterial pressure (MAP) < 65 mmHg, occurs in 65% of surgeries.[2] Intraoperative hypotension is usually caused by anesthetics, preoperative use of medication, existing comorbidities or by the surgery itself.[3]

Since both pressure and flow are required to deliver oxygen to the tissues, hypotension can negatively affect organ function.[4] Clinical cohort studies and one randomized controlled clinical trial have shown intraoperative hypotension to be associated with postoperative complications such as myocardial ischemia, renal insufficiency and increased mortality.[5-11] Not only the time spent in hypotension but also the severity (the depth) of hypotension may be important for postoperative outcome.[12] The time weighted average (TWA) combines the time and depth of hypotension.[13, 14]

Hypotension is most often preventable; however, current management of the hypotensive episodes is predominantly reactive and often occurs with some delay. Machine learning was used to develop an algorithm to predict hypotension minutes before the blood pressure actually decreases, the Hypotension Probability Indicator (HPI).[15] The HPI algorithm is developed using continuously measured waveform data from 1334 patients, internally validated on a cohort of 350 patients and externally validated on a cohort of 204 patients. The HPI algorithm was able to predict hypotension with 88% sensitivity and 87% specificity minutes before a hypotensive event occurs.[15]

We hypothesize that the use of the HPI algorithm in combination with a personalized treatment protocol will reduce the amount of time spent in hypotension measured by the TWA during non-cardiac surgery.

METHODS/DESIGN

Study design

This investigator –initiated trial is divided into two phases. Phase A consists of prospective data collection in 40 patients to gain insight in the normal TWA in our study population. Phase A data is collected to check our sample size for phase B and to verify if the control group is a representative sample. Phase B is a single-center randomized controlled (1:1) superiority trial including 60 patients. The study takes place in the Academic Medical Center (AMC) Amsterdam, The Netherlands, a tertiary academic center. The study started with inclusion of the first patient in November 2017, the planned duration of the trial is 18 months. This trial has been registered with the NIH, U.S. National Library of Medicine at ClinicalTrials.gov (NCT03376347). This manuscript was written in accordance with the

Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) guideline (Additional File 1) on reporting of intervention trial protocols.[16]

Eligibility criteria

Adult patients (aged 18 years or older) scheduled to undergo an elective, clinical, non-cardiac, surgical procedure under general anesthesia and requiring an arterial line will be eligible for inclusion. A desired target MAP of 65 mmHg during surgery is used as an inclusion criterion, to ensure that both study arms will be similar in this aspect. Patients undergoing emergency surgery are not eligible. Patients with cardiac failure, severe cardiac shunts, severe aortic stenosis and severe cardiac arrhythmias will be excluded in accordance with the summary of product characteristics of the HPI algorithm. Patients enduring significant hypotension before surgery and patients requiring dialysis will be excluded. Patients planned to undergo liver surgery or vascular surgery will be excluded because of the use of vascular clamping. For this trial, anesthesiologists are not allowed to use a different hemodynamics treatment protocol besides our study protocol; therefore, an exclusion criterion is the planned usage of a perioperative Goal Directed Fluid Therapy (GDFT) protocol.

Researchers will screen all patients presenting for elective, non-cardiac, non-day-case surgery. Patients will be contacted and informed in case of eligibility. Patient informed consent will be obtained the day prior to surgery.

Study outline

Patients will be contacted on the surgical ward or at the pre-operative assessment clinic, and written information and oral explanation will be provided. Patient characteristics, medical history, medication use and American Society of Anesthesiologists (ASA) physical score classification will be collected from the medical records. Blood pressure measured at the outpatient clinic, blood pressure measured the day before surgery on the ward and blood pressure measured in the operating theater before induction will also be registered.

Phase A: TWA and normal treatment behavior of anesthesiologists in the AMC will be collected prospectively as baseline data. These data will be used to verify our sample size calculation for phase B and to study whether our control group is representative for the study population by comparing the baseline group versus the control group. During this phase of the study the treating anesthesiologist and anesthesia nurse will not be informed about the aim of the study or the endpoints measured.

Phase B: in this phase, patients will be randomized. The treating anesthesiologist and the anesthesia nurse will be informed about the study protocol and the usage of the HPI algorithm (with the secondary screen) the day before the surgery. All study interventions are to be performed by trained study personnel or the treating anesthesiologist, following instructions from the researchers.

In both study phases a researcher will be present – continuously – during all surgeries to note surgical and anesthetic details.

For a Consolidated Standards of Reporting Trials (CONSORT) flow diagram of the study see Figure 1. All data will be entered using an electronic Clinical Report Form build in Castor EDC, a Good-Clinical-Practice-compliant data management system.[17]

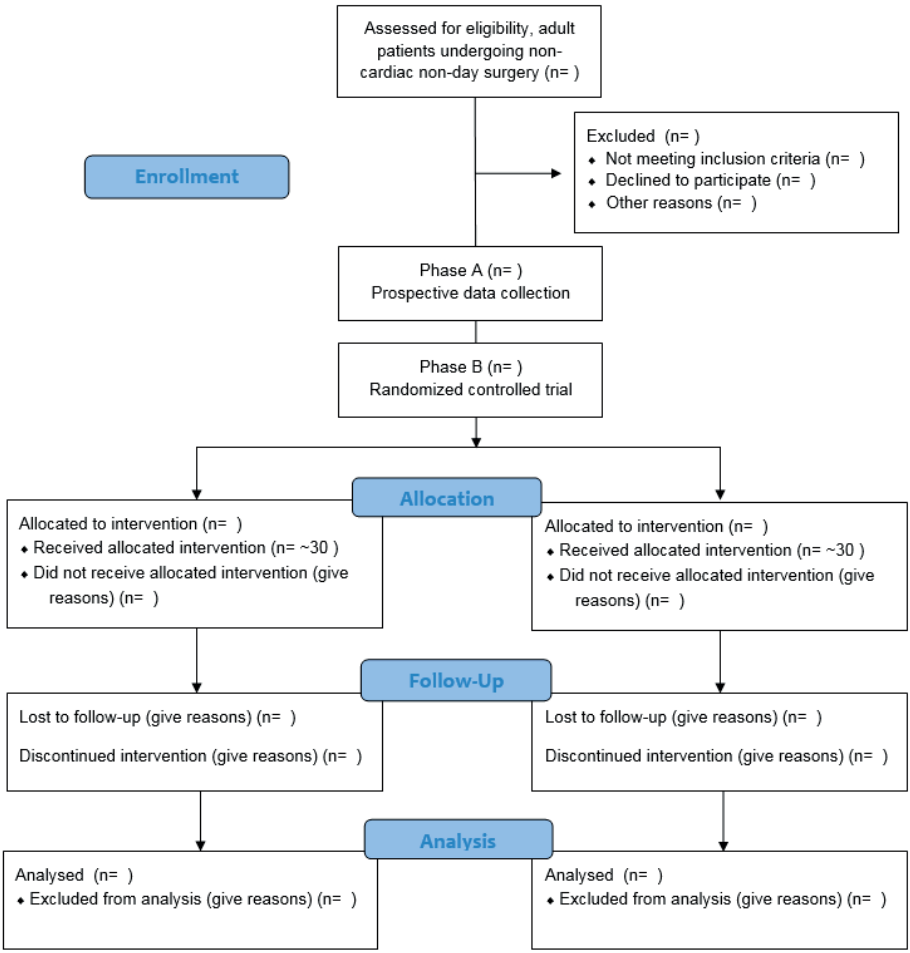


Figure 1. Consort Flow diagram

Randomization and blinding

In phase B, patients will be randomized to either use of the HPI algorithm intraoperatively (intervention arm) or standard care (control arm). We will use a computer-generated permutated block randomization, with a 1:1 allocation ratio. This will result in concealed and varying permutated block sizes of four, six or eight patients.

Randomization will be performed by a designated researcher. An independent researcher (not involved in collecting study data), blinded for the randomization, will perform the statistical analysis for the primary outcome.

Study procedures and interventions

The HPI algorithm was previously internally and externally validated.[15] The HPI algorithm is only available on the HemoSphere and Flotrac monitoring systems and requires the use of a FlotracIQ sensor connected to an arterial line (Edwards Lifesciences Corp., Irvine, CA, USA). The FlotracIQ sensor has a splitter which enables the splitting of the arterial blood pressure signal to facilitate a blood pressure signal on both the Philips monitor (standard care) and the HemoSphere monitor (study).

In all study participants, this system will be connected to both the HemoSphere and the Philips monitor. The Philips monitor displays the MAP, systole, diastole and the pulse pressure variation as per standard care protocol in our hospital. In the baseline group (phase A) and in the control arm (phase B) the HemoSphere with HPI software will be connected; however, the screen will be fully covered. In the control arm the anesthesiologist solely uses the variables visible on the Philips monitor to guide hemodynamic treatment. In the intervention arm the HemoSphere with HPI software will be visible and the perioperative hemodynamic management will be based on both the Philips monitor and the HemoSphere monitor. Use of the HPI software is additional to standard care, it is not used as a replacement of standard care. In the intervention arm we will ask the anesthesiologist and anesthesia nurse to use the study treatment flowchart (Figure 2). If the HPI alarm goes off, which entails both a sound and a flickering light, we ask the anesthesiologist to act upon this alarm preferably within 2 minutes. Use of the study treatment flowchart ensures that the anesthesiologist has to think about the underlying cause. The HemoSphere with HPI software has a second screen (Figure 3) with variables that provide information about the underlying cause of the predicted hypotension.

Outcome measures

Our primary outcome measure is the TWA in hypotension during surgery. The TWA is a calculation of the depth (in millimeters of mercury) of hypotension below the “threshold” MAP of 65 mmHg multiplied by the time spent in hypotension in minutes, this results in an area under the threshold AUT, see Figure 4.

To better compare this value between different operations this AUT will be divided by the total duration of the operation:

Time weighted average= (depth of hypotension x time spent in hypotension) / total surgery time)

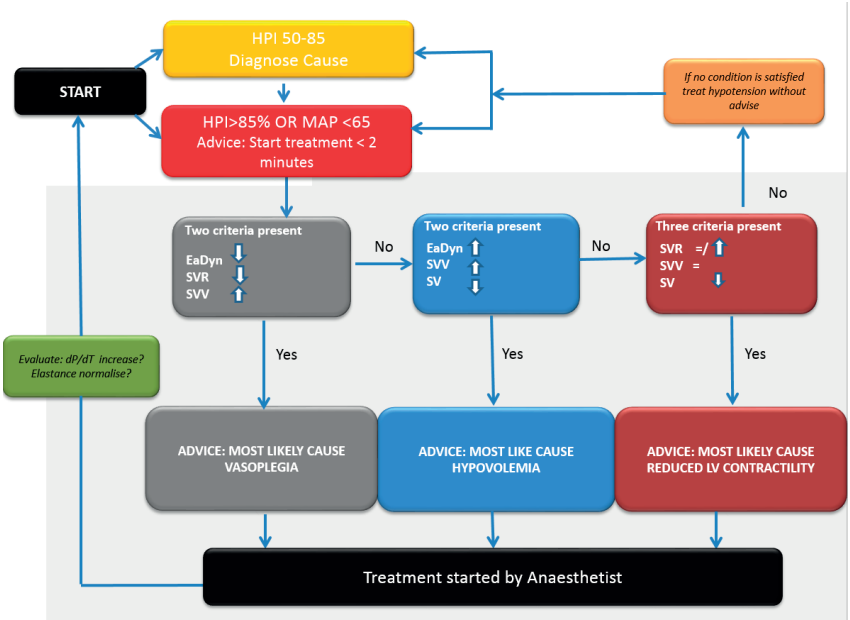


Figure 2. HYPE personalized treatment guidance protocol. HPI=hypotension prediction index. MAP= mean arterial pressure. EaDyn= dynamic arterial elastance. SVR= systemic vascular resistance. SVV= stroke volume variation. SV=stroke volume. dP/dT= delta pressure/delta time, measure for left ventricular function

Figure 3. HemoSphere with HPI and secondary screen. P↓BP= probability of hypotension, this is a prediction ranging from 0-100%. MAP= mean arterial pressure. CO= cardiac output. SVR= systemic vascular resistance. PR= pulse rate. SV= stroke volume. SVV= stroke volume variation. dP/dt= delta pressure/delta time. Eadyn= dynamic arterial elastance

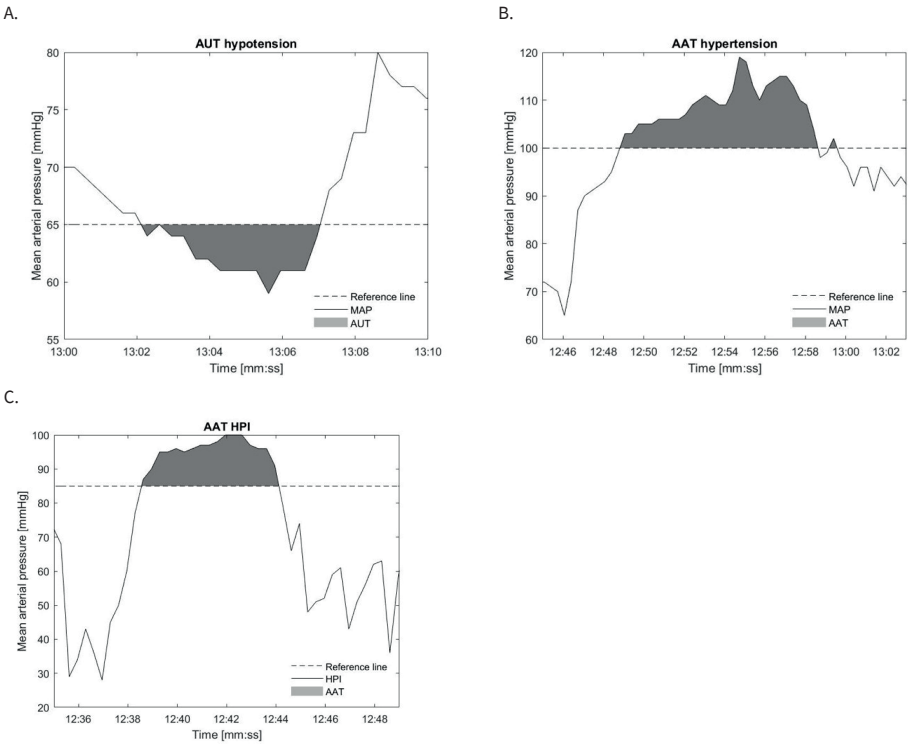


Figure 4. AUT and AAT calculations. **A** demonstrates the calculation of the area under (AUT) the curve used to calculate the TWA in hypotension. *TWA= (depth hypotension below MAP 65 threshold in mmHg x time spent below MAP 65 threshold in minutes, the AUT) / total duration operation in minutes)*. **B** and **C** demonstrate the calculation area above the curve (AAT) used to calculate the TWA in hypertension and the TWA of HPI alarm

Example: a MAP of 50 mmHg for 5 min results in an AUC of 75 (15 × 5). The total duration of the operation in minutes is 120 min. TWA = 75/120 = 0.625.

Hypotension is defined as a MAP < 65 mmHg for 1 min. An HPI alarm is defined as an HPI value of 85% and above during at least 1 min. A subsequent hypotensive episode, as well as an HPI alarm only counts as two separate events when respectively the MAP or the HPI will be normal for at least 1 min.

The secondary outcome measures include incidence of hypotension, time in hypotension, the percentage of time in hypotension and the AUC of a MAP < 65 mmHg. The above-mentioned parameters including TWA will also be assessed for hypertension (defined as MAP > 100 mmHg for at least 1 min) and for the HPI alarms. For hypertension and HPI alarm the area above the curve (AAT) will be calculated instead of the AUC, see Figure 4. We will assess the treatment behavior of hypotension and HPI. This includes treatment choice (i.e., vasopressors, fluids, inotropes, position changes), treatment dose, time to treatment and feasibility of working with HPI based on the number of protocol violations.

Exploratory outcomes include underlying cause(s) of intraoperative hypotension and we will assess whether the use of HPI intraoperatively will result in less hypotension (measured in TWA) postoperatively at the Post Anesthesia Care Unit (PACU).

For an overview of outcome assessment see Figure 5.

TIMEPOINT	Pre-intervention	Study intervention			Follow-up
		Baseline	*During surgery*	*PACU*	
ENROLMENT:					
Project information: written and oral communication	X				
Eligibility screen	X				
Written informed consent	X				
Randomization	X				
Inform treating Anesthesiologist	X				
ASSESSMENTS:					
Baseline characteristics					
Patient characteristics					
Medical history					
Medication use					
ASA score					
Blood pressure		X	X	X	
Heart rate		X	X	X	
Primary outcome					
TWA in hypotension			X		
Secondary outcomes					
TWA in hypertension			X		
Treatment behavior			X		
Exploratory outcomes					
Underlying causes hypotension			X		
TWA in hypotension				X	
TWA in hypertension				X	
Safety outcomes					
Adverse events					X

Figure 5. Schedule of enrollment, interventions and assessments. *PACU* Post Anesthesia Care Unit, *ASA* American Society of Anesthesiologists, *TWA* time-weighted average

Safety

All adverse and serious adverse events, irrespective of causality, will be collected and reviewed by the principal investigator and reported to the Medical Ethics Committee of the AMC Amsterdam. Adverse events are defined as any undesirable experience occurring to a subject during the study, whether or not considered related to the experimental intervention. All adverse events reported spontaneously by the subject or observed by the investigator or his staff will be recorded.

Serious adverse events are defined as any untoward medical occurrence or effect that: results in death; is life-threatening (at the time of the event); requires hospitalization or prolongation of existing inpatients' hospitalization; results in persistent or significant disability or incapacity; is a congenital anomaly or birth defect; or any other important medical event that did not result in any of the outcomes listed above due to medical or surgical intervention but could have been based upon appropriate judgment by the investigator. An elective hospital admission will not be considered as a serious adverse event.

We cover the potential harm of overtreatment by assessing the cumulative treatment dose during surgery and by assessing the amount of hypertension (in TWA, AUT, incidence, total time and percentage of time spent in hypertension). We will compare the outcomes between the control and intervention groups.

Insurance is provided for all participating subjects by the AMC Amsterdam.

Sample size calculation (phase B)

Difference in primary outcome will be compared using the Student's *t* test or the Mann-Whitney *U* test, based on normality. A statistician performed the sample-size analysis. Based on previously published blood pressure data during surgery, it was estimated that our control group would have a TWA of 0.50 and a difference of 0.38 or larger between two study groups would be clinically relevant.[18] An effect size of 0.74 was calculated by dividing the estimated difference of 0.38 (mean experimental group − mean control group) by the standard deviation of 0.51. A sample size of 30 in each group in the randomized phase will have 80% power to detect an effect size of 0.74 using a two-group *t* test with a 0.05 two-sided significance level. Sample size was calculated using R 2017.[19]

The baseline data collection enables us to calculate the normal TWA spent in hypotension in our hospital and will be used to verify our sample-size analysis.

Patients who are randomized but in whom no study measurement was started, no arterial line was placed or when technical failure of the HemoSphere device prevented data collection will be excluded and replaced.

Statistical analyses

We will analyze the data based on an intention-to-treat principle. The intention-to-treat population is defined as all patients who meet the inclusion criteria at the end of the study period.

Continuous data will be presented as median with range and/or interquartile range (IQR), or mean with standard deviation and range when normally distributed. Normality of distribution will be assessed visually with histograms and Q-Q plots. Categorical data were given as frequencies with percentages. For each of the analyses a probability value of $p < 0.05$ will be considered statistically significant.

Our primary outcome is TWA in hypotension (phase B). We will compare the TWA of each arm using the Student's *t* test or Mann-Whitney *U* test, depending on the distribution of the data. The baseline data collection enables us to calculate the normal TWA spent in hypotension in our hospital and will be used to verify the representativeness of our control group. We will compare the TWA in the baseline group (phase A) to the TWA in the control arm (phase B).

The secondary and exploratory research questions involving categorical data will be analyzed using the χ^2 test/Fisher's exact test and secondary research questions involving continuous (numerical) data will be analyzed using the Student's *t* test or the Mann-Whitney *U* test. Feasibility of working with HPI will be analyzed using qualitative research methods, reporting the number of protocol violations with reasons. Underlying causes of intraoperative hypotension will be analyzed using our study flowchart (Figure 2) on all 100 patients. To assess whether use of HPI intraoperatively results in less postoperative hypotension at the PACU the TWA in hypotension during PACU stay will be analyzed. The exploratory questions will not be addressed in the primary article. All analyses for the primary article will be done using Matlab (R2018b) and SPSS (version 25).

Monitoring

In accordance with the decision of our Medical Ethics Committee this trial is scored "low risk" and will, therefore, not need to be monitored by a Data Monitoring Committee.

Ethical approval and registration

This study protocol has been approved by the Medical Ethics Committee of the AMC in Amsterdam. All protocol amendments will be communicated to the Medical Ethics Committee. The study protocol is in adherence with the Declaration of Helsinki and the guideline of Good Clinical Practice. Written informed consent will be obtained by trained researchers the day prior to surgery. A subject-screening and enrollment log will be kept on a secure server only accessible to study personnel. This trial has been registered with the NIH, U.S. National Library of Medicine at ClinicalTrials.gov (NCT03376347).

DISCUSSION

Definition of intraoperative hypotension

Intraoperative hypotension is clearly associated with adverse postoperative outcomes.[11] Controversially, a universally accepted definition for intraoperative hypotension does not yet exist.[2] In this study, we define hypotension as a MAP below 65 mmHg which is in line with some large clinical trials and with our hospital's protocol.[14]

Treatment behavior

For a machine-learning algorithm based tool to help prevent intraoperative hypotension the treating anesthesiologists need to be willing to change their treatment behavior from reactive to proactive. Furthermore, the anesthesiologists will need to get used to diagnosing the underlying cause of hypotension based on the extra hemodynamic variables.

Clinical relevance

The algorithm was developed using continuously measured waveform data from 1334 patients, internally validated on a cohort of 350 patients and externally validated on a cohort of 204 patients.[15] This is the first randomized controlled trial using this algorithm intraoperatively. This trial is powered on the TWA in hypotension. If this trial is successful in reducing intraoperative hypotension, future studies are needed and they will need to be powered to anticipated changes in clinical outcomes.

Abbreviations

AAT: Area above the threshold
AMC: Academic Medical Center
ASA: American Society of Anesthesiologists
AUT: Area under the threshold
GDFT: Goal Directed Fluid Therapy
HPI: Hypotension Prediction Index
IQR: Interquartile range
MAP: Mean arterial pressure
PACU: Post Anesthesia Care Unit
TWA: Time-weighted average

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Affiliations

Department of Anesthesiology, Amsterdam UMC, location Academic Medical Center, University of Amsterdam, Meibergdreef 9, Postbus 22660, 1105 AZ, Amsterdam, The Netherlands
M. Wijnberge, J. Schenk, L. E. Terwindt, M. P. Mulder, M. W. Hollmann, D. P. Veelo & B. F. Geerts

Department of Intensive Care Medicine, Amsterdam UMC, location Academic Medical Center, University of Amsterdam, Meibergdreef 9, Postbus 22660, 1105 AZ, Amsterdam, The Netherlands
M. Wijnberge & A. P. Vlaar

Department of Technical Medicine, University of Twente, Drienerlolaan 5, 7522 NB, Enschede, The Netherlands
M. P. Mulder

Contributions

MW: design of study, writing of the manuscript, future acquisition and interpretation of study data. JS and LET: future acquisition of study data and critically reviewing the manuscript. MPM: independent blinded analysis of study data. MWH, BFG, APV and DPV: conception and design of study, critically reviewing the manuscript and interpretation of study data. All authors approved this final version of the manuscript to be published and are accountable for all aspects of the work. There will be no use of professional writers.

Ethics approval and consent to participate

This study protocol has been approved by the Medical Ethics Committee of the AMC in Amsterdam. The study protocol is in adherence with the Declaration of Helsinki and the guideline of Good Clinical Practice. Informed consent will be obtained by trained researchers the day prior to surgery. A subject screening and enrollment log will be kept on a secure server only accessible to study personnel. This trial has been registered with the NIH, U.S. National Library of Medicine at ClinicalTrials.gov (NCT03376347).

Consent for publication

As noted in the study protocol, study participants will consent to having their data and results published anonymously.

Competing interests

The Department of Anesthesiology of the Academic Medical Center (AMC) received financial support for this project from Edwards Lifesciences. DPV, APV, MW and BFG receive consultancy fees from Edwards Lifesciences.

Additional file 1. Spirit 2013 Checklist. Download available at journal website.

REFERENCES

1. Weiser TG, Haynes AB, Molina G, et al. Estimate of the global volume of surgery in 2012: an assessment supporting improved health outcomes. *Lancet (London, England)*. Apr 27 2015;385 Suppl 2:S11. doi:10.1016/s0140-6736(15)60806-6
2. Bijker JB, van Klei WA, Kappen TH, van Wolfswinkel L, Moons KG, Kalkman CJ. Incidence of intraoperative hypotension as a function of the chosen definition: literature definitions applied to a retrospective cohort using automated data collection. *Anesthesiology*. 2007-01-01 2007;107(2):213-220.
3. Tritapepe L. Hypotension during surgery for high risk patients: Cause or consequence of pathology? *Minerva Anestesiologica*. 2013-01-01 2013;79(9):978-980.
4. Harten J KJ. Perioperative optimisation. *Scot Med J* 2004;49(1):6-9.
5. van Waes JA, van Klei WA, Wijeysundera DN, van Wolfswinkel L, Lindsay TF, Beattie WS. Association between Intraoperative Hypotension and Myocardial Injury after Vascular Surgery. *Anesthesiology*. 2015-01-01 2015;124(1):35-44.
6. Xu L, Yu C, Jiang J, et al. Major adverse cardiac events in elderly patients with coronary artery disease undergoing noncardiac surgery: A multicenter prospective study in China. *Archives of Gerontology and Geriatrics*. 2015-01-01 2015;61(3):503-509.
7. Sun LY, Wijeysundera DN, Tait GA, Beattie WS. Association of intraoperative hypotension with acute kidney injury after elective noncardiac surgery. *Anesthesiology*. 2015-01-01 2015;123(3):515-523.
8. Hallqvist L, Granath F, Huldt E, Bell M. Intraoperative hypotension is associated with acute kidney injury in noncardiac surgery: An observational study. *European journal of anaesthesiology*. Apr 2018;35(4):273-279. doi:10.1097/eja.0000000000000735
9. Monk TG, Bronsert MR, Henderson WG, et al. Association between Intraoperative Hypotension and Hypertension and 30-day Postoperative Mortality in Noncardiac Surgery. *Anesthesiology*. Aug 2015;123(2):307-19. doi:10.1097/ALN.0000000000000756
10. Bijker JB, van Klei WA, Vergouwe Y, et al. Intraoperative hypotension and 1-year mortality after noncardiac surgery. *Anesthesiology*. 2009-01-01 2009;111(6):1217-1226.
11. Futier E, Lefrant JY, Guinot PG, et al. Effect of Individualized vs Standard Blood Pressure Management Strategies on Postoperative Organ Dysfunction Among High-Risk Patients Undergoing Major Surgery: A Randomized Clinical Trial. *JAMA*. Oct 10 2017;318(14):1346-1357. doi:10.1001/jama.2017.14172
12. Wesselink EM, Kappen TH, Torn HM, Slooter AJC, van Klei WA. Intraoperative hypotension and the risk of postoperative adverse outcomes: a systematic review. *British journal of anaesthesia*. Oct 2018;121(4):706-721. doi:10.1016/j.bja.2018.04.036
13. Hsieh JK, Dalton JE, Yang D, Farag ES, Sessler DI, Kurz AM. The Association Between Mild Intraoperative Hypotension and Stroke in General Surgery Patients. *Anesthesia and analgesia*. Oct 2016;123(4):933-9. doi:10.1213/ane.0000000000001526
14. Salmasi V, Maheshwari K, Yang D, et al. Relationship between Intraoperative Hypotension, Defined by Either Reduction from Baseline or Absolute Thresholds, and Acute Kidney and Myocardial Injury after Noncardiac Surgery. *Anesthesiology*. 2017-01-01 2017;126(1):47-65.
15. Hatib F, Jian Z, Buddi S, et al. Machine-learning Algorithm to Predict Hypotension Based on High-fidelity Arterial Pressure Waveform Analysis. *Anesthesiology*. Oct 2018;129(4):663-674. doi:10.1097/aln.0000000000002300

16. Chan AW, Tetzlaff JM, Gotzsche PC, et al. SPIRIT 2013 explanation and elaboration: guidance for protocols of clinical trials. *BMJ (Clinical research ed)*. Jan 8 2013;346:e7586. doi:10.1136/bmj.e7586
17. Castor Electronic Data Capture CB, Amsterdam, The Netherlands, 2018.
18. Maheshwari K, Khanna S, Bajracharya GR, et al. A Randomized Trial of Continuous Noninvasive Blood Pressure Monitoring During Noncardiac Surgery. *Anesthesia and analgesia*. Aug 2018;127(2):424-431. doi:10.1213/ane.0000000000003482
19. R Core Team (2017): R: a language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. Available from https://www.R-project.org/

7

Effect of a Machine Learning-Derived Early Warning System for Intraoperative Hypotension versus Standard Care on Depth and Duration of Intraoperative Hypotension During Elective Noncardiac Surgery
THE HYPE randomized clinical trial

Marije Wijnberge
Bart F. Geerts
Liselotte Hol
Nikki Lemmers
Marijn P. Mulder
Patrick Berge
Jimmy Schenk
Lotte E. Terwindt
Markus W. Hollmann
Alexander P. Vlaar
Denise P. Veelo

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ABSTRACT

Importance

Intraoperative hypotension is associated with increased morbidity and mortality. A machine learning–derived early warning system to predict hypotension shortly before it occurs has been developed and validated.

Objective

To test whether the clinical application of the early warning system in combination with a hemodynamic diagnostic guidance and treatment protocol reduces intraoperative hypotension.

Design, Setting, and Participants

Preliminary unblinded randomized clinical trial performed in a tertiary center in Amsterdam, the Netherlands, among adult patients scheduled for elective noncardiac surgery under general anesthesia and an indication for continuous invasive blood pressure monitoring, who were enrolled between May 2018 and March 2019. Hypotension was defined as a mean arterial pressure (MAP) below 65 mm Hg for at least 1 minute.

Interventions

Patients were randomly assigned to receive either the early warning system (n = 34) or standard care (n = 34), with a goal MAP of at least 65 mm Hg in both groups.

Main Outcomes and Measures

The primary outcome was time-weighted average of hypotension during surgery, with a unit of measure of millimeters of mercury. This was calculated as the depth of hypotension below a MAP of 65 mm Hg (in millimeters of mercury) × time spent below a MAP of 65 mm Hg (in minutes) divided by total duration of operation (in minutes).

Results

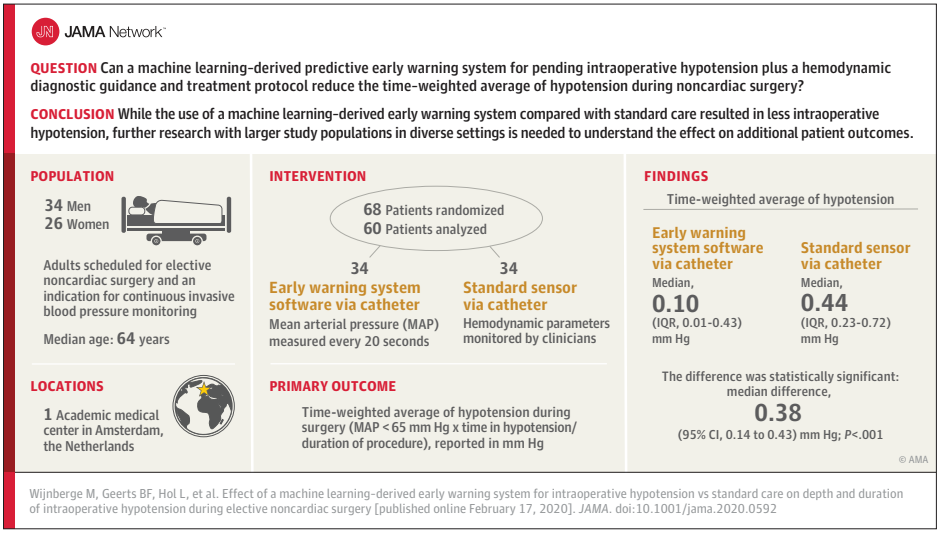
Among 68 randomized patients, 60 (88%) completed the trial (median age, 64 [interquartile range (IQR), 57-70] years; 26 [43%] women). The median length of surgery was 256 minutes (IQR, 213-430 minutes). The median time-weighted average of hypotension was 0.10 mm Hg (IQR, 0.01-0.43 mm Hg) in the intervention group vs 0.44 mm Hg (IQR, 0.23-0.72 mm Hg) in the control group, for a median difference of 0.38 mm Hg (95% CI, 0.14-0.43 mm Hg; *P* = .001). The median time of hypotension per patient was 8.0 minutes (IQR, 1.33-26.00 minutes) in the intervention group vs 32.7 minutes (IQR, 11.5-59.7 minutes) in the control group, for a median difference of 16.7 minutes (95% CI,

7.7-31.0 minutes; $P < .001$). In the intervention group, 0 serious adverse events resulting in death occurred vs 2 (7%) in the control group.

Conclusions and Relevance

In this single-center preliminary study of patients undergoing elective noncardiac surgery, the use of a machine learning–derived early warning system compared with standard care resulted in less intraoperative hypotension. Further research with larger study populations in diverse settings is needed to understand the effect on additional patient outcomes and to fully assess safety and generalizability.

Trial Registration ClinicalTrials.gov Identifier: NCT03376347



Visual Abstract. Machine Learning–Derived Early Warning System for Intraoperative Hypotension During Elective Noncardiac Surgery

KEY POINTS

Question

Can a machine-learning derived predictive early warning system for pending intraoperative hypotension in combination with a hemodynamic diagnostic guidance and treatment protocol reduce the time-weighted average (TWA) in hypotension during non-cardiac surgery?

Findings

In this single-center preliminary randomized clinical trial that included 68 patients undergoing elective non-cardiac surgery, the time-weighted average in hypotension for those randomized to the early warning system versus those receiving standard care was 0.10 mmHg vs 0.44 mmHg, a difference that was statistically significant.

Meaning

While the use of a machine-learning derived early warning system compared with standard care resulted in less intraoperative hypotension, further research with larger study populations in diverse settings is needed to understand the effect on patient outcomes and fully assess safety and generalizability.

Please find the accompanying Editorial by prof. dr. Angus at the journals's website: Randomized Clinical Trials of Artificial Intelligence | Anesthesiology | JAMA | JAMA Network

INTRODUCTION

An estimated 266 million operations were performed worldwide in 2015.[1] One of the risks patients commonly face is intraoperative hypotension. A previous study involving 255 patients reported that 87% experienced one or more hypotensive episodes intraoperatively (with hypotension defined as a mean arterial pressure [MAP] <65 mmHg).[2] Reported causes are anesthetic drugs, existing comorbidities and surgical manipulation.[3, 4]

Clinical cohort studies have shown intraoperative hypotension in non-cardiac surgery to be associated with postoperative complications such as renal insufficiency, myocardial injury and increased mortality.[5-10]

Current management of intraoperative hypotensive episodes is predominantly reactive. Recently, Hatib et al.[11] developed an algorithm with the use of machine learning to predict hypotension minutes before the blood pressure actually decreases, the Hypotension Prediction Index (also called the Hypotension Probability Index). This algorithm (hereafter referred to as the early warning system) was developed using the arterial waveform data of 1344 patients, and it has been internally and externally validated, showing a sensitivity of 88% and a specificity of 87%.[2, 11] This early warning system is fixed, meaning that it does not include dynamic learning changes evolving during patient care. Using an early warning system to predict hypotension does not necessarily lead to less hypotension. Associated factors to consider are feasibility of working with this tool and the possibility of performing a timely and correct intervention. Hemodynamic variables, in combination with a hemodynamic diagnostic guidance and treatment protocol, allow for determination of the underlying cause of the impending hypotension.

A preliminary single-center randomized clinical trial (RCT) was performed. It was hypothesized that use of the early warning system would reduce the amount of hypotension (MAP <65 mm Hg) as measured by time-weighted average during major noncardiac surgery.[12]

METHODS

Participants

The HYpotension PrEdiction (HYPE) trial was a preliminary investigator-initiated single-center RCT. The study took place at the Amsterdam University Medical Centers, Location AMC, a tertiary academic center in the Netherlands. The study was approved by the institutional review board of the AMC (NL62115.018.17).

Written informed consent was obtained from all patients the day prior to surgery by a designated researcher. The first participant was enrolled in May 2018, and the last follow-up was in March 2019. The trial protocol has been published previously[13] and is available online (Supplement 1).

Adult patients (≥18 years old) scheduled to undergo an elective noncardiac surgical procedure under general anesthesia with need for continuous invasive blood pressure monitoring per arterial line were included. A target MAP of at least 65 mm Hg during surgery was obligatory to ensure both study groups to be similar in this aspect. Patients for whom the attending anesthesiologists requested a target MAP higher or lower than 65 mm Hg were excluded prior to surgery. Patients undergoing emergency surgery were not eligible. Patients with cardiac failure, severe cardiac shunts, severe aortic stenosis, or severe cardiac arrhythmias were excluded in accordance with the summary of product characteristics of the early warning system. Patients with hypotension (MAP <65 mm Hg) before surgery and patients requiring dialysis were also excluded. Patients planned to undergo liver surgery or vascular surgery were excluded because of the use of vascular clamping. During the trial, anesthesiologists were not allowed to use perioperative goal-directed fluid therapy because the study hemodynamic diagnostic guidance and treatment protocol has blood pressure as a starting point, while a goal-directed fluid therapy protocol typically starts with flow evaluation as the main concept.

Randomization

Patients were randomized to either the intraoperative early warning system (intervention group) or standard care (control group) (Figure 1). A computer-generated permutated block randomization (concealed and varying permutated block sizes of 4, 6, or 8 patients) was used with a 1:1 allocation ratio. The researcher performing statistical analyses was blinded to patient group allocation.

Intervention

In all study participants, an arterial catheter was placed in the radial artery and connected to the Flotrac IQ sensor with the early warning system software (Edwards Lifesciences). The arterial pressure waveform was measured continuously with a sample frequency of 100 Hz. The HemoSphere monitor (Edwards Lifesciences) displayed hemodynamic parameters calculated from the waveform every 20 seconds. The value calculated by the early warning system was updated every 20 seconds as well.[11]

The Flotrac IQ pressure transducer was connected to the HemoSphere monitor (hereafter referred to as the study monitor), and the resulting electrical signal was transmitted to the Philips monitor (hereafter referred to as the standard monitor). The standard monitor displayed the MAP, systole, diastole, and pulse pressure variation per standard care in the study hospital. The quality of the arterial waveform signal was

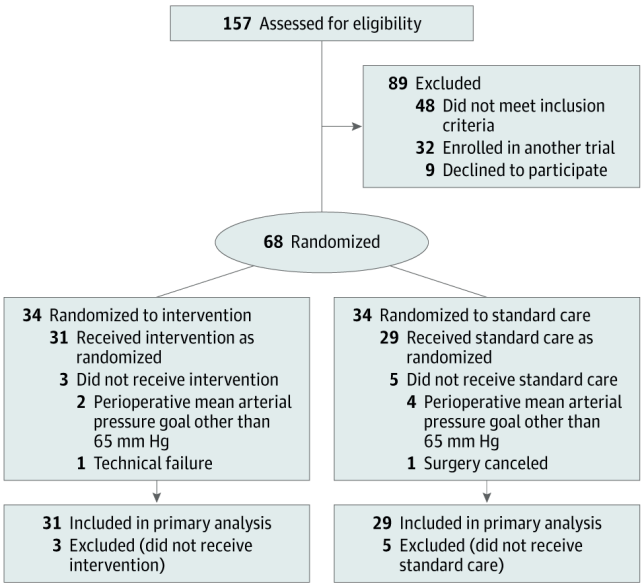


Figure 1. Participant Flow in the **Hy**potension **PrE**diction (HYPE) Trial

visually checked by the treating anesthesiologist for overdamping and underdamping after placement of the arterial line and during surgery.

Attending anesthesiologists and anesthesia nurses were informed about the study protocol and the use of the early warning system the day before surgery. Intraoperatively, an observer was present to record surgery- and anesthesia-related details.

Use of the study monitor was additional to standard care monitoring. The early warning system detects deteriorations in cardiovascular compensatory mechanisms that could lead to hypotension. The early warning system consists of 23 variables that are extracted from the arterial pressure waveform.[11] When the value of the early warning system alarm (hereafter referred to as the alarm) exceeds 85, the likelihood of occurrence of a hypotensive event within the next 15 minutes is about 85%.[2] The time to hypotension is not fixed; the progression into hypotension depends on the underlying physiological mechanisms causing the hypotension and on individual patient characteristics.[11] The performance of the early warning system regarding prediction of hypotension was analyzed on patient data collected in the short observational study according to methods previously described by Hatib et al[11] and presented in eFigure 1 in Supplement 2.

In this study, when the value of prediction of hypotension exceeded 85 (eFigure 2 in Supplement 2), which entailed both a sound and a flickering light, the anesthesiologist was reminded to act, preferably within 2 minutes. The study monitor with the early warning system software has a secondary screen (eFigure 2) with variables (heart

rate, cardiac output, change in pressure over change in time, stroke volume, stroke volume variation, dynamic arterial elastance, and systemic vascular resistance) that provide information about the underlying cause of the predicted hypotension.[14] The hemodynamic diagnostic guidance and treatment protocol (Figure 2 and eFigure 3 in Supplement 2) was designed by the authors to help treating anesthesiologists interpret the changes of the variables visible on the secondary screen.[13] For example, the combination of an increase (arrow up) in stroke volume variation and a decrease (arrow down) in systemic vascular resistance results in the diagnosis of vasoplegia (Figure 2 and eFigure 3). The hemodynamic diagnostic guidance and treatment protocol was adapted from Pinsky and Payen.[15]

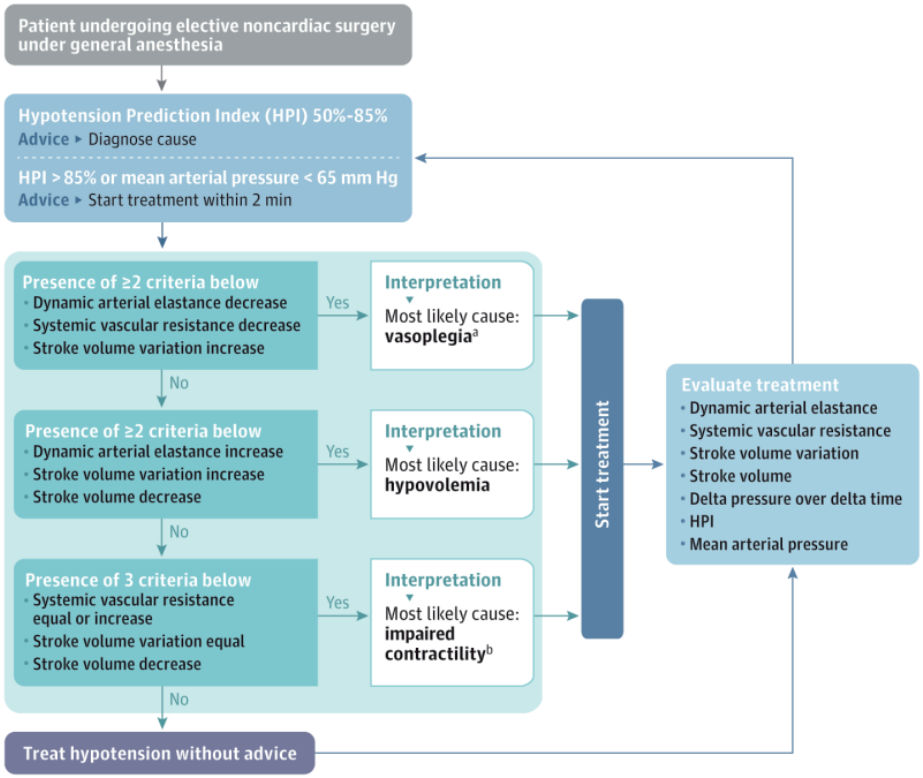


Figure 2. Hemodynamic Diagnostic Guidance and Treatment Protocol
[a]Vasoplegia indicates decreased systemic vascular resistance.
[b]Impaired left ventricular contractility.

Control

In the control group, the study monitor was connected, but the screen was fully covered and the alarms were silenced; anesthesiologists solely used the variables visible on the standard monitor to guide hemodynamic treatment.

Prior to launching the RCT, we conducted a short observational study to ensure that the care the control group received was representative of standard care in the study hospital (eTables 1 and 2 in Supplement 2). The only difference between the control group and the observational study group was that anesthesiologists were unaware of the aim of the study (to assess hypotension) in the observational study group.

All data were entered using an electronic clinical report form build in Castor EDC, a Good Clinical Practice–compliant data management system.[16]

Outcomes

The primary outcome measure was the time-weighted average of hypotension during surgery. The outcome assessor was blinded to participants' group randomization. The time-weighted average combines the duration and severity (the minimal MAP reached) of hypotension, corrected for the total time of surgery.[12] Hypotension was defined as a MAP less than 65 mm Hg for at least 1 minute. A hypotensive event ended when the value normalized (MAP ≥65 mm Hg) for at least 1 minute. The time-weighted average is measured by calculating the area under the threshold (AUT) divided by the total duration of surgery (eFigure 4 in Supplement 2).[12,13]

Time-weighted average = (depth of hypotension in millimeters of mercury below a MAP of 65 mm Hg × time in minutes spent below a MAP of 65 mm Hg) ÷ total duration of operation in minutes. The units for AUT are millimeters of mercury × minutes and the units for time-weighted average are millimeters of mercury.[13]

As an example, a patient undergoes a surgery that lasts 180 minutes, in which they experience 10 episodes of hypotension, all lasting for 1 minute and all with a minimal MAP of 60 mm Hg. The AUT = 10 minutes × (65 − 60 = 5 mm Hg under the MAP threshold of 65 mm Hg) = 10 × 5 = 50 mm Hg per minute. The time-weighted average = 50 mm Hg per minute ÷ 180 minutes = 0.28 mm Hg.

The secondary outcome measures included incidence of hypotension (the number of hypotensive events per patient), total time with hypotension, and percentage of time spent with hypotension during surgery. To assess the risk of overtreatment, the above-mentioned variables were also assessed for hypertension (defined as a MAP >100 mm Hg for at least 1 minute). To be able to calculate the time-weighted average for hypertension, first the area above the curve needed to be calculated (eFigure 4 in Supplement 2). These time and incidence variables were also assessed post hoc for the alarms. An alarm was deemed present when the early warning system prediction value reached 85 or higher

for at least 1 minute. An alarm ended when the value normalized (<85) for at least 1 minute.

Clinicians' behavior regarding treatment of alarms (intervention group) and hypotension (control group) was assessed. We noted (1) treatment choice (ie, vasopressor, fluids, inotropes, Trendelenburg position, and decrease in anesthetics); (2) cumulative dose; and (3) time from alarm to start of treatment in the intervention group and from onset of hypotension to start of treatment in the control group. All alarms or hypotensive events per patient were used for this analysis. If an alarm or hypotensive event had more than 1 treatment, the time to first treatment was used. In post hoc analyses, control group clinicians' treatment behavior after silent alarms to which they were blinded was also assessed and compared with treatment behavior after alarms in the intervention group. We calculated (1) total number of silent alarms; (2) number of alarms per patient; (3) number of alarms that led to treatment; (4) number of treatments per alarm; (5) time from alarm to treatment in the intervention group compared with time from silent alarm to treatment in the control group (all alarms per patient were used for this analysis; if an alarm had more than 1 treatment, the time to first treatment was used); and (6) time from first alarm to first treatment in the intervention group compared with time from first silent alarm to first treatment in the control group. The last analysis was performed because all actions after the first alarm might be influenced by and correlated with the first alarm.

The feasibility of working with the hemodynamic diagnostic guidance and treatment protocol was based on the number of protocol violations.

Primary and secondary endpoints were analyzed for the intraoperative period only. Intraoperative and postoperative adverse events and serious adverse events were documented (for definitions see eTable 3 in Supplement 2).

Sample size calculation

Time-weighted average is a relatively novel end point such that only an estimation could be made of what difference would be clinically relevant. Prior to the study, an expert panel familiar with the potential effect of intraoperative hypotension was consulted, and it was decided that a 75% reduction of hypotension in terms of combined depth and duration (time-weighted average) was considered to be clinically relevant. Prior to this study, the mean time-weighted average of hypotension in the study clinic was estimated to be 0.5 mm Hg. Thus, the estimated mean difference between groups for the calculation of the sample size was considered to be 0.38 mm Hg. Based on preliminary results from a trial[12], the standard deviation of time-weighted average of hypotension was estimated to be 0.51 mm Hg. Dividing the mean difference by the standard deviation resulted in an effect size of 0.74. It was calculated that a sample size of 60 patients, 30 in each group, would have 80% power to detect this effect using a 2-group *t* test with

an α = .05 2-sided significance level. R version 3.3.3 (R Foundation) was used to perform these calculations.[17]

Patients who were randomized but for whom no study measurements were performed were excluded (Figure 1).

Statistical analyses

All patients who met the inclusion criteria at the end of the study period were analyzed according to their randomization group. If data was missing, the amount of missing data and the reason was assessed.

Continuous data are presented as medians with interquartile ranges (IQRs) or as means with standard deviations when normally distributed. The confidence intervals for the median differences were calculated with the Hodges-Lehmann method. Normality of distribution was assessed visually with histograms and Q-Q plots. Categorical data are presented as frequencies with percentages. Differences between categorical data were analyzed using the χ^2 test.

For each of the analyses, a 2-sided probability value of $P < .05$ was considered to be statistically significant. An exploratory regression analysis was performed to assess possible effects of confounders on the primary end point (eFigure 5 in Supplement 2). Because of the potential for type I error due to multiple comparisons, findings for analyses of secondary end points and post hoc end points should be interpreted as exploratory.

All analyses were performed using Matlab version R2018b (MathWorks Inc) and SPSS version 25 (IBM Corp).

RESULTS

Study population

For the preliminary RCT, 157 patients were assessed for eligibility. A total of 68 patients were enrolled, of whom 34 were randomly assigned to the intervention group and 34 to the control group (Figure 1). Of these 68 patients, 60 (88%) completed the trial. The median age was 64 (interquartile range, 57-70 years); 26 patients (43%) were women. The majority of patients completing the trial (n = 54 [90%]) underwent oncologic gastrointestinal surgery. Table 1 shows the baseline characteristics of the intervention group and the control group. The short observational study conducted prior to launching the RCT consisted of 40 patients (eTables 1 and 2 in Supplement 2). None of the analyzed determinants had any missing values.

Primary endpoint

The median time-weighted average of hypotension was 0.10 mm Hg (IQR, 0.01-0.43 mm Hg) in the intervention group vs 0.44 mm Hg (IQR, 0.23-0.72 mm Hg) in the control group, for a median difference of 0.38 mm Hg (95% CI, 0.14-0.43 mm Hg; $P = .001$) (Table 2).

Secondary endpoints

Hypotension

In the intervention group, 26 patients (84%) experienced 1 or more hypotensive episode during surgery compared with 28 (97%) in the control group, for a difference of 13% (95% CI, −2% to 28%; $P = .09$). The median incidence of hypotension was 3.00 (IQR, 1.00-8.00) hypotensive episodes per patient in the intervention group vs 8.00 (IQR, 3.50-12.00) in the control group, for a median difference of 4.00 (95% CI, 1.00-7.00) episodes per patient ($P = .004$). The median incidence of hypotension was calculated including patients who had 0 hypotensive episodes. The median total time of having hypotension per patient was 8.00 (IQR, 1.33-26.00) minutes in the intervention group vs 32.67 (IQR, 11.50-59.67) minutes in the control group, for a median difference of 16.67 (95% CI, 7.67-31.00) minutes ($P < .001$).

There were no significant differences for hypotension end points between the control group and the observational study group (eTable 2 in Supplement 2).

Treatment behavior

Comparing treatment choice, ephedrine was chosen 38 of 596 times (6%) in the intervention group vs 37 of 258 times (14%) in the control group, for a difference of 8% (95% CI, 6%-14%; $P < .001$). Phenylephedrine was chosen 110 of 596 times (19%) in the intervention group compared with 61 of 258 times (24%) in the control group, for a difference of 5% (95% CI, 1% to 11%; $P = .04$). Fluid boluses were chosen 96 of 596 times (16%) as treatment of choice in the intervention group compared with 16 of 258 times (6%) in the control group, for a difference of 10% (95% CI, 6%-14%; $P < .001$) (eTable 4 in Supplement 2).

There was no significant difference in the cumulative dose of vasopressors or fluids given during surgery (Table 3). The median cumulative dose of noradrenaline was 1034 µg (IQR, 770-1720 µg) in the intervention group compared with 925 µg (IQR, 428-2131 µg) in the control group (median difference, 118 µg; 95% CI, −418 to 534 µg; $P = .67$). The median dose of fluids was 1800 mL (IQR, 1500-2700 mL) in the intervention group vs 1800 mL (IQR, 1450-2650 mL) in the control group (median difference, 150 mL; 95% CI, −470 to 600 mL; $P = .58$).

The median time from alarm (intervention group) or hypotension (control group) to first treatment was 53 seconds (IQR, 24-99 seconds) in the intervention group vs 87 seconds (IQR, 53-173 seconds) in the control group (median difference, 34 seconds; 95% CI, 23-47 seconds; $P < .001$).

Patient characteristics	Intervention (n=31)	Control (n=29)
Age, years	68.0 [61 – 73]	62.0 [56 – 67]
Men, No (%)	21 (68)	13 (45)
Women, No (%)	10 (32)	16 (55)
Body mass index, kg/m^2	24.2 [21 – 26]	24.7 [22 – 27]
ASA classification, No.(%)[a]		
1 – normal, healthy	1 (3)	3 (10)
2 – mild systemic disease	24 (77)	24 (83)
3 – severe systemic disease	6 (19)	2 (7)
4 – life-threatening disease	0 (0)	0 (0)
WHO classification, No.(%)[b]		
0 – fully active	20 (65)	17 (59)
1 – ambulatory and light work	6 (19)	6 (21)
2 – ambulatory but unable to work	4 (13)	5 (17)
3 - >50% confined to bed or chair	1 (3)	1 (3)
4 –Totally confined to bed or chair	0 (0)	0 (0)
MAP outpatient clinic, mmHg	100 [93 – 106]	92 [81 – 98]
MAP day before, mmHg	98 [88 – 105]	92 [82 – 102]
MAP before induction, mmHg	104 [95 – 112]	93 [85 – 104]
Type of surgery, No.(%)		
Gynaecological	1 (3)	3 (10)
Gastrointestinal	30 (97)	24 (83)
Pancreas	*19 (63)*	9 (38)
Esophagus	*9 (30)*	8 (33)
Other[c]	0 (0)	2 (7)
Surgical approach, No.(%)		
Laparotomy	19 (61)	13 (45)
Laparoscopic	2 (7)	5 (17)
Conversion	1 (3)	3 (10)
Combined	9 (29)	8 (28)
Duration of surgery, minutes[d]	256 [194 – 425]	259 [223 – 442]
Duration of anesthesia, minutes[e]	302 [230 – 475]	300 [259 – 487]

Table 1. Baseline table

Abbreviations: ASA, American society of Anesthesiologists; MAP, mean arterial pressure; WHO, World Health Organization. Continuous data are presented as median with IQR. Categorical data are given as number with percentages. [a] The ASA classifications were as follows: 1: a healthy person; 2: a patient with mild systemic disease; 3: a patient with severe systemic disease; and 4: a patient with severe systemic disease that is a constant threat to life.[18,19] [b] The WHO classifications were as follows: 0: fully active, able to carry on all predisease performance without restriction; 1: restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, eg, light housework, office work; 2: ambulatory and capable of all self-care but unable to carry out any work activities, mobile for more than 50% of waking hours; 3: capable of only limited self-care, confined to bed or chair more than 50% of waking hours; 4: completely disabled, unable to carry out any self-care, totally confined to bed or chair.[20,21]

[c] Including excision of a recurrent abdominal wall carcinoma and a deep inferior epigastric perforator breast reconstruction. [d] duration of surgery was calculated in minutes form the time of incision until closure of the surgical wound. [e] Calculated in minutes from the time of first anesthetic drug administration (sufentanil, lidocaine, or propofol) until extubation. If extubation was not in the operating room but in the intensive care unit or postanesthesia care unit, the time of leaving the operating room was noted as the end of anesthesia administration.

	Intervention (n=31)	Control (n=29)	Median difference (95 %CI)[a]	p-value[b]
Primary endpoint				
Time-weighted average in hypotension, mmHg	0.10 [0.01 – 0.43]	0.44 [0.23 – 0.72]	0.38 (0.14 to 0.43)	**.001**
Secondary endpoints				
Hypotension				
AUT, mmHg*min[c]	20.0 [2.2 – 148.3]	142.2 [64.67 – 258.92]	74.0 (33.0 to 137.7)	**.002**
Incidence	3.0 [1.0 – 8.0]	8.0 [3.5 – 12.0]	4.0 (1.0 to 7.0)	**.004**
Total time, min	8.0 [1.3 – 26.0]	32.7 [11.5 – 59.7]	16.7 (7.7 to 31.0)	**.001**
% of surgery time	2.8 [0.8 – 6.6]	10.3 [4.6 – 15.6]	5.6 (3.0 to 9.4)	**<.001**
Hypertension				
Time-weighted average, mmHg	0.09 [0.00 – 0.21]	0.05 [0.00 – 0.13]	0.00 (-0.85 to 0.17)	.47
AAT, mmHg*min[c]	33.3 [0.0 – 88.0]	13.3 [0.0 – 44.3]	-3.5 (-29.0 to 5.5)	.40
Incidence	2.0 [0.0 – 3.0]	1.0 [0.0 - 2.0]	0.0 (-1.0 to 0.0)	.23
Total time, min	4.0 [0.0 – 10.7]	3.0 [0.0 – 6.8]	-0.7 (-4.3 to 0.7)	.40
% of surgery time	1.5 [0.0 – 3.3]	0.9 [0.0 – 1.9]	-0.2 (-1.4 to 0.3)	.40
Treatment behavior				
Reaction time, seconds[d]	53.0 [24.0 – 99.0]	87.3 [53.0 – 172.5]	34.3 (22.8 to 47.3)	**<.001**
Post-hoc endpoints				
Treatment behavior				
Treatments per patient[e]	15.0 [5.0 – 29.0]	9.0 [3.5 – 13.0]	-6.0 (-13.0 to -1.0)	**.02**
Early warning system alarms				
Time-weighted average, HPI	1.99 [1.12 – 3.17]	4.31 [2.50 – 5.79]	1.79 (0.74 to 2.95)	**.001**
AAT, HPI*min[c]	529.7 [196.3 – 1315.0]	1231.0 [701.5 – 1966.3]	629.3 (229.3 to 1012.3)	**.002**
Incidence	11.0 [7.0 – 16.0]	11.0 [8.0 – 14.5]	0.0 (-4.0 to 3.0)	.84
Total time, min	56.7 [21.7 – 122.7]	116.3 [68.3 – 170.3]	51.7 (20.7 to 91.0)	**.002**
% of time	20.9 [14.5 – 35.6]	41.1 [23.9 – 56.4]	15.8 (5.8 to 25.9)	**.002**

Table 2. Primary and secondary endpoints

[a] All end points are medians per patient. Incidence rates of hypotension, hypertension, and early warning system alarms are median number of events per patient.

[b] Median differences and their 95% confidence intervals were calculated with the Hodges-Lehmann method.

[c] P values were measured with the Mann-Whitney U test.

[d] See Supplement 7 for details on calculation of area under the threshold and area above the threshold.

[e] In the intervention group, reaction time was measured as the time (in seconds) from the onset of the early warning system alarm to treatment. In the control group, reaction time was defined as the time from start of hypotension to treatment.

[f] Treatments per patient were calculated as median number of treatments related to hypotension or early warning system alarm per patient.

[g] The Hypotension Prediction Index (referred to in this article as the early warning system) is an algorithm developed with the use of machine learning to predict hypotension.

In post hoc analyses, the median time from alarm to treatment (intervention group) or the median time from silent alarm (blinded for clinicians) to treatment (control group) was 53 seconds (IQR, 24-99 seconds) in the intervention group vs 161 seconds

(IQR, 73-391 seconds) in the control group (median difference, 48 seconds; 95% CI, 13-97 seconds; *P* < .001). The median time from solely the first alarm in all patients (silent alarm in the control group) to first treatment was 57 seconds (IQR, 22-81 seconds) in the intervention group vs 108 (IQR, 44-204 seconds) in the control group (median difference, 91 seconds; 95% CI, 70-117 seconds; *P* = .01) (eTable 5 in Supplement 2).

	Intervention (n=31)	Control (n=29)	Median differences with 95%CI	p-value
Noradrenaline, µg	1034.0 [770.7 – 1720.0]	925.7 [428.7 – 2131.0]	-118.0 (-534.3 to 418.0)	.67
Noradrenaline, γ (µg/kg/min)[a]	0.057 [0.033 – 0.071]	0.040 [0.021 – 0.066]	-0.010 (-0.025-0.005)	.18
Ephedrine, mg	10.0 [0.0 – 22.5]	10.0 [10.0 – 16.3]	0.0 (-5.0 to 5.0)	.52
Phenylephrine, µg	200.0 [100.0 – 600.0]	300.0 [100.0 – 500.0]	0.0 (-200.0 to 100.0)	.84
Given amount of fluids, ml	2100.0 [1750.0 – 3000.0]	1800.0 [1550.0 – 2950.0]	-150 (-600.0 to 470.0)	.58
Given amount of colloids, ml	250.0 [0.0 – 500.0]	0.0 [0.0 – 500.0]	0.0 (-250.0 to 0.0)	.09
Given amount of crystalloids, ml	1800.0 [1500.0 – 2700.0]	1800.0 [1450.0 – 2650.0]	100.0 (-550.0 to 300.0)	.72
Fluid balance, ml[b]	1180.0 [680.0 – 1650.0]	1150.0 [582.5 – 1552.5]	-80.00 (-480.00 to 300.00)	.62
Propofol, mg[c]	100 [60 – 1647]	125 [50 – 2568]	20 (-1430 to 1467)	.90
Sevoflurane, vol %	1.67 [1.48 – 1.73]	1.57 [1.42 – 1.75]	-0.02 (-0.80 to 0.17)	.66
Sufentanil i.v., µg	80.0 [50.0 – 85.0]	70.0 [53.8 – 85.0]	-5.0 (-25.0 to 15.0)	.51
Morphine, mg[d]	10.00 [8.50 -11.25]	10.00 [8.75 – 15.00]	0.00 (-2.50 to 6.00)	.83
Epidural analgesia, No.(%)	21 (68)	13 (45)	-	.07

Table 3. Cumulative dose of medications given during surgery
Continuous data are presented as median with interquartile range [IQR]. Median differences are presented with their 95% confidence intervals (CI). Categorical data are given as counts with percentages.
[a]Noradrenaline dose corrected for patient body weight.
[b] Fluid balance at the end of surgery.
[c]Calculated for the patients who received propofol (n=7 in the intervention group and n=12 in the control group).
[d]Calculated for the patients who received morphine (n=6 in the intervention group and n=13 in the control group).

Hemodynamic diagnostic guidance and treatment protocol violations

In total, 377 predictive alarms with a duration of more than 1 minute were present in the intervention group. Among the 377 alarms, 81% (304 alarms) led to treatment within 2 minutes. In 5% (20 alarms), treatment was not according to study treatment protocol, and 14% of alarms (53 alarms) were ignored by anesthesiologists.

There were several reasons for ignoring alarms (protocol violations). In 36% (19 alarms), the current treatment modality was exhausted or treatment was provided just before the alarm (indicating a high [>85%] chance of hypotension occurring) was triggered. In 36% (19 alarms), the anesthesiologist did not want to act on the alarm

because of alarm fatigue, ie, the anesthesiologist refused to treat because of the frequency of the alarms. Alarm fatigue is a phenomenon described in more detail in the literature.[22] In 26% (14 alarms), there was a temporary reason for the (predicted) hypotension, such as lung recruitment or brief surgical obstruction of the vena cava. In the remaining 2% (1 alarm), the anesthesiologist had a different priority, namely an airway problem.

Hypertension

The median time-weighted average of hypertension was 0.09 mm Hg (IQR, 0.00-0.21 mm Hg) in the intervention group vs 0.05 mm Hg (IQR, 0.00-0.13 mm Hg) in the control group (median difference, 0.00 mm Hg; 95% CI, −0.85 to 0.17 mm Hg; $P = .47$).

Adverse events

In the intervention group, 0 serious adverse events resulting in death occurred versus 2 (7%) in the control group. In total, 33 adverse events occurred in the intervention group versus 30 in the control group (eTable 3 in Supplement 2).

DISCUSSION

This preliminary study demonstrated that application of a machine learning–derived early warning system for pending intraoperative hypotension in combination with a hemodynamic diagnostic guidance and treatment protocol significantly reduced the time-weighted average of hypotension during surgery. Hypotension was prevented without increasing the number of hypertensive events. Neither the cumulative dose of vasoactive medication given nor the fluid balance was significantly higher in the intervention group. Among all alarms, 81% were treated according to protocol. In post hoc analyses, the time from alarm to treatment was significantly lower in the intervention group.

This study extends on the work by Hatib et al. and Davies et al. who showed that the early warning system was able to predict hypotension with good sensitivity and specificity.[2, 11] This study adds the translation from prediction to actual prevention of hypotension.

Several studies have demonstrated intraoperative hypotension to be associated with myocardial injury, acute kidney injury, and mortality.[5-10, 23] Based on these studies, the 2019 perioperative Quality Initiative consensus statement concluded with the notion that anesthesiologists should maintain a MAP threshold of greater than 60 to 70 mm Hg during surgery.[24] Furthermore, it states that that postoperative injury is a function of both time spent in hypotension and the depth of hypotension, making the

time-weighted average in hypotension an end point of particular interest.[24] Futier et al. demonstrated in a RCT that maintaining a higher blood pressure during abdominal surgery reduced the risk of postoperative organ dysfunction.[25] In all cases, a vasopressor (norepinephrine) was used to maintain the higher blood pressure. In this current study, hypotension prevention was taken a step further by predicting hypotension and preventing it through diagnosing and treating the specific cause of the impeding hypotension (preload, afterload, or contractility).

Limitations

This study has several limitations. First, the definition of hypotension (MAP <65 mm Hg) was similar for all patients. Maintaining this threshold is current best practice.[23,24] However, every patient may have a personal minimal MAP to be maintained during surgery.[26,27] In the future, the optimal hypotension threshold per patient might be determined using a machine learning tool, further personalizing intraoperative hemodynamic treatment.

Second, in the trial, the depth of anesthesia was not measured. In a recent RCT, a significant reduction in norepinephrine dose was observed by using electroencephalographic monitoring in patients under anesthesia.[17] However, because patients were randomized, the anesthesia depth was expected to be similar between the groups. Indeed, the cumulative dose of propofol and sevoflurane did not statistically differ between the groups.

Third, because the early warning system is validated only for invasive continuous blood pressure monitoring, patients in this study were more severely ill and had a higher risk of hypotension than in a more general population. The study population mainly entailed oncologic gastrointestinal patients. In addition, the time-weighted average of 0.44 mm Hg in the control group is quite high compared with a US study reporting a time-weighted average of hypotension of 0.30 mm Hg in noncardiac surgery.[23] The selection of patients in this trial, and possibly a lack of awareness of the importance of intraoperative hypotension in the study hospital, might explain this difference. Accordingly, a different study population might not—or not to this extent—benefit from the use of the early warning system.

Fourth, an observer being present in the operating room may have influenced protocol adherence. In future trials, a more pragmatic approach without an observer present in the operating room should be used.

Fifth, this was a preliminary study, a single-center RCT with a small sample size. In this trial, a physiological rather than clinical outcome was assessed. Future trials should be powered on clinical and economic outcomes such as disability-free survival (World Health Association Disability Assessment Schedule 2.0), organ injury, mortality, and costs.[20]

CONCLUSIONS

In this single-center preliminary study of patients undergoing elective noncardiac surgery, the use of a machine learning–derived early warning system for pending hypotension compared with standard care resulted in less intraoperative hypotension. However, further research with larger study populations in diverse settings is needed to understand the effect on additional patient outcomes and to fully assess safety and generalizability.

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Authors' contributions
Concept and design: Wijnberge, Geerts, Hollmann, Vlaar, Veelo.
Acquisition, analysis, or interpretation of data: All authors.
Drafting of the manuscript: Wijnberge, Geerts, Hollmann, Vlaar, Veelo.
Critical revision of the manuscript for important intellectual content: All authors.
Statistical analysis: Wijnberge, Lemmers, Mulder, Schenk.
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Administrative, technical, or material support: Wijnberge, Geerts, Hol, Lemmers, van den Berge, Schenk, Terwindt, Hollmann, Vlaar, Veelo.
Supervision: Geerts, Hollmann, Vlaar, Veelo.

Conflict of Interest Disclosures
Dr Wijnberge reported receipt of consultancy fees from Edwards Lifesciences outside the submitted work. Dr Geerts reported receipt of grants from Edwards Lifescience outside the submitted work and consultancy fees and research grants from Philips. Dr Hollmann reported serving as executive section editor of pharmacology for *Anesthesia & Analgesia* and as section editor of anesthesiology for the *Journal of Clinical Medicine* and receipt of speakers' fees from CSL Behring and Eurocept BV and consultancy fees from Eurocept BV. Dr Vlaar reported receipt of personal fees from AKPA. Dr Veelo reported receipt of personal fees and other from Edwards Lifesciences outside the submitted work as well as consultancy fees and research grants from Philips and Hemologic. No other disclosures were reported.

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Role of the Funder/Sponsor
Edwards Lifesciences, the manufacturer of the Hypotension Prediction Index, the early warning system, was contacted after design of the trial. Edwards Lifesciences was not involved in the design and conduct of the study; collection, management, analysis, or interpretation of the data; or preparation and review of the manuscript. Edwards Lifesciences did not approve the manuscript and had no input in the decision to submit the manuscript for publication. Edwards Lifesciences read the manuscript before submission. However, no publication restrictions apply.

Meeting Presentations

The results of this study were presented at the European Society of Intensive Care Medicine conference, September 30, 2019, Berlin, Germany; and at the Society of Critical Care Medicine's 49th Annual Critical Care Congress, February 17, 2020, Orlando, Florida.

Data Sharing Statement

Supplement 3, available from JAMA website

REFERENCES

1. Weiser TG, Haynes AB, Molina G, et al. Estimate of the global volume of surgery in 2012: an assessment supporting improved health outcomes. *Lancet (London, England)*. Apr 27 2015;385 Suppl 2:S11. doi:10.1016/s0140-6736(15)60806-6
2. Davies SJ, Vistisen ST, Jian Z, Hatib F, Scheeren TWL. Ability of an Arterial Waveform Analysis-Derived Hypotension Prediction Index to Predict Future Hypotensive Events in Surgical Patients. *Anesthesia and analgesia*. Mar 20 2019;doi:10.1213/ane.0000000000004121
3. Tritapepe L. Hypotension during surgery for high risk patients: Cause or consequence of pathology? *Minerva Anestesiologica*. 2013-01-01 2013;79(9):978-980.
4. Cheung CC, Martyn A, Campbell N, et al. Predictors of intraoperative hypotension and bradycardia. *The American journal of medicine*. May 2015;128(5):532-8. doi:10.1016/j.amjmed.2014.11.030
5. van Waes JA, van Klei WA, Wijeysundera DN, van Wolfswinkel L, Lindsay TF, Beattie WS. Association between Intraoperative Hypotension and Myocardial Injury after Vascular Surgery. *Anesthesiology*. 2015-01-01 2015;124(1):35-44.
6. Xu L, Yu C, Jiang J, et al. Major adverse cardiac events in elderly patients with coronary artery disease undergoing noncardiac surgery: A multicenter prospective study in China. *Archives of Gerontology and Geriatrics*. 2015-01-01 2015;61(3):503-509.
7. Sun LY, Wijeysundera DN, Tait GA, Beattie WS. Association of intraoperative hypotension with acute kidney injury after elective noncardiac surgery. *Anesthesiology*. 2015-01-01 2015;123(3):515-523.
8. Hallqvist L, Granath F, Huldt E, Bell M. Intraoperative hypotension is associated with acute kidney injury in noncardiac surgery: An observational study. *European journal of anaesthesiology*. Apr 2018;35(4):273-279. doi:10.1097/eja.0000000000000735
9. Monk TG, Bronsert MR, Henderson WG, et al. Association between Intraoperative Hypotension and Hypertension and 30-day Postoperative Mortality in Noncardiac Surgery. *Anesthesiology*. Aug 2015;123(2):307-19. doi:10.1097/ALN.0000000000000756
10. Bijker JB, van Klei WA, Vergouwe Y, et al. Intraoperative hypotension and 1-year mortality after noncardiac surgery. *Anesthesiology*. 2009-01-01 2009;111(6):1217-1226.
11. Hatib F, Jian Z, Buddi S, et al. Machine-learning Algorithm to Predict Hypotension Based on High-fidelity Arterial Pressure Waveform Analysis. *Anesthesiology*. Oct 2018;129(4):663-674. doi:10.1097/aln.0000000000002300
12. Maheshwari K, Khanna S, Bajracharya GR, et al. A Randomized Trial of Continuous Noninvasive Blood Pressure Monitoring During Noncardiac Surgery. *Anesthesia and analgesia*. Aug 2018;127(2):424-431. doi:10.1213/ane.0000000000003482
13. Wijnberge M, Schenk J, Terwindt LE, et al. The use of a machine-learning algorithm that predicts hypotension during surgery in combination with personalized treatment guidance: study protocol for a randomized clinical trial. *Trials*. Oct 11 2019;20(1):582. doi:10.1186/s13063-019-3637-4
14. Dindo D, Demartines N, Clavien PA. Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. *Ann Surg*. Aug 2004;240(2):205-13.
15. Pinsky M Pcmbov-acIFHMUilCaEMS-V, Berlin, 381 - 395. ISBN 3540223495.
16. Castor Electronic Data Capture CB, Amsterdam, The Netherlands, 2018.
17. Sponholz C, Schuwirth C, Koenig L, et al. Intraoperative reduction of vasopressors using processed electroencephalographic monitoring in patients undergoing elective cardiac surgery: a randomized clinical trial. *Journal of clinical monitoring and computing*. Feb 19 2019;doi:10.1007/s10877-019-00284-1

18. Doyle DJ, Goyal A, Bansal P, Garmon EH. American Society of Anesthesiologists Classification. *StatPearls*. StatPearls Publishing
19. Knuf KM, Maani CV, Cummings AK. Clinical agreement in the American Society of Anesthesiologists physical status classification. *Perioper Med (Lond)*. 2018;7:14. doi:10.1186/s13741-018-0094-7
20. Federici S, Bracalenti M, Meloni F, Luciano JV. World Health Organization disability assessment schedule 2.0: An international systematic review. *Disabil Rehabil*. Nov 2017;39(23):2347-2380. doi:10.1080/09638288.2016.1223177
21. Oken MM, Creech RH, Tormey DC, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. *Am J Clin Oncol*. Dec 1982;5(6):649-55.
22. Wilken M, Huske-Kraus D, Klausen A, Koch C, Schlauch W, Rohrig R. Alarm Fatigue: Causes and Effects. *Studies in health technology and informatics*. 2017;243:107-111.
23. Salmasi V, Maheshwari K, Yang D, et al. Relationship between Intraoperative Hypotension, Defined by Either Reduction from Baseline or Absolute Thresholds, and Acute Kidney and Myocardial Injury after Noncardiac Surgery. *Anesthesiology*. 2017-01-01 2017;126(1):47-65.
24. Sessler DI, Bloomstone JA, Aronson S, et al. Perioperative Quality Initiative consensus statement on intraoperative blood pressure, risk and outcomes for elective surgery. *British journal of anaesthesia*. May 2019;122(5):563-574. doi:10.1016/j.bja.2019.01.013
25. Futier E, Lefrant JY, Guinot PG, et al. Effect of Individualized vs Standard Blood Pressure Management Strategies on Postoperative Organ Dysfunction Among High-Risk Patients Undergoing Major Surgery: A Randomized Clinical Trial. *JAMA*. Oct 10 2017;318(14):1346-1357. doi:10.1001/jama.2017.14172
26. Wesselink EM, Kappen TH, Torn HM, Slooter AJC, van Klei WA. Intraoperative hypotension and the risk of postoperative adverse outcomes: a systematic review. *British journal of anaesthesia*. Oct 2018;121(4):706-721. doi:10.1016/j.bja.2018.04.036
27. Ackland GL, Brudney CS, Cecconi M, et al. Perioperative Quality Initiative consensus statement on the physiology of arterial blood pressure control in perioperative medicine. *British journal of anaesthesia*. May 2019;122(5):542-551. doi:10.1016/j.bja.2019.01.011

LEGENDS SUPPLEMENTAL CONTENT

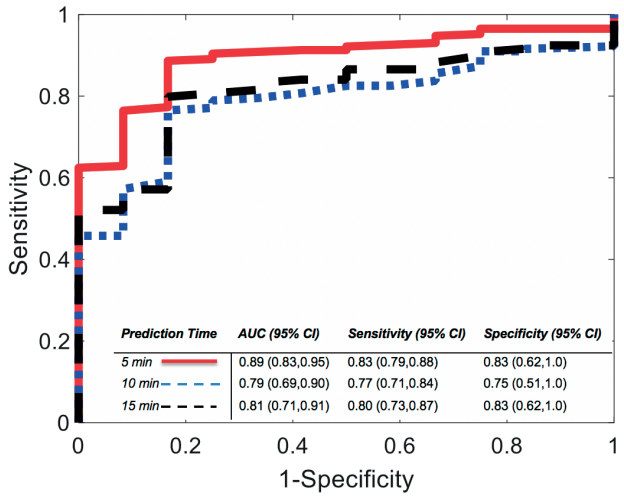
Supplement 1. Trial protocol, JAMA website.

Supplement 2.

eFigure 1. Performance of the Early Warning System in the Observational Study Group (ROC Analysis)
eFigure 2. HemoSphere Monitor And Secondary Screen
eFigure 3. Hemodynamic Diagnostic Guidance and Treatment Protocol Explanation
eTable 1. Observational Study Baseline Characteristics
eTable 2. Observational Study Versus Control Group RCT
eFigure 4. AAT and AUT to Calculate TWA
eTable 3. Adverse and Serious Adverse Events
eFigure 5. Post Hoc Regression Analysis
eTable 4. Treatment Choice RCT
eTable 5. Treatment Behavior Silent Alarms

Supplement 3. Data sharing agreement, JAMA website.

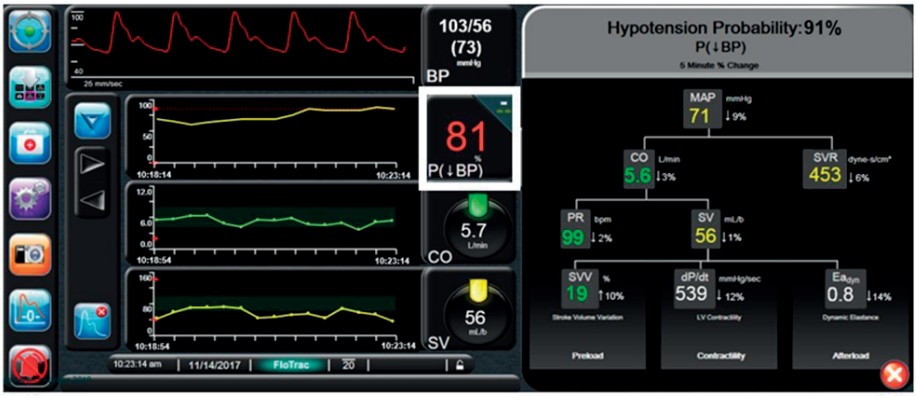
EFIGURE 1. PERFORMANCE OF THE EARLY WARNING SYSTEM IN THE OBSERVATIONAL STUDY GROUP (ROC ANALYSIS)



Receiver under the operating curve (ROC) plot in the observational study group.
In this figure we show the performance of the early warning system in our observational study population (n=40 patients, including 360 hypotensive events and 183 hours of surgery). The exact same methods were used as published by Hatib et al.[1] First the early warning system (the hypotension prediction index) Youden Index was calculated at the three timepoints. The Youden Index at 5 minutes prior to hypotension was 50, the Youden Index at 10 minutes prior to hypotension was 39 and the Youden Index 15 minutes prior to hypotension was 40. Second the ROC curves were plotted at 5, 10 and 15 minutes before a hypotensive event. The sensitivity and specificity at these specific time points were calculated. Of note, these results should be interpreted with caution due to the limited sample size.

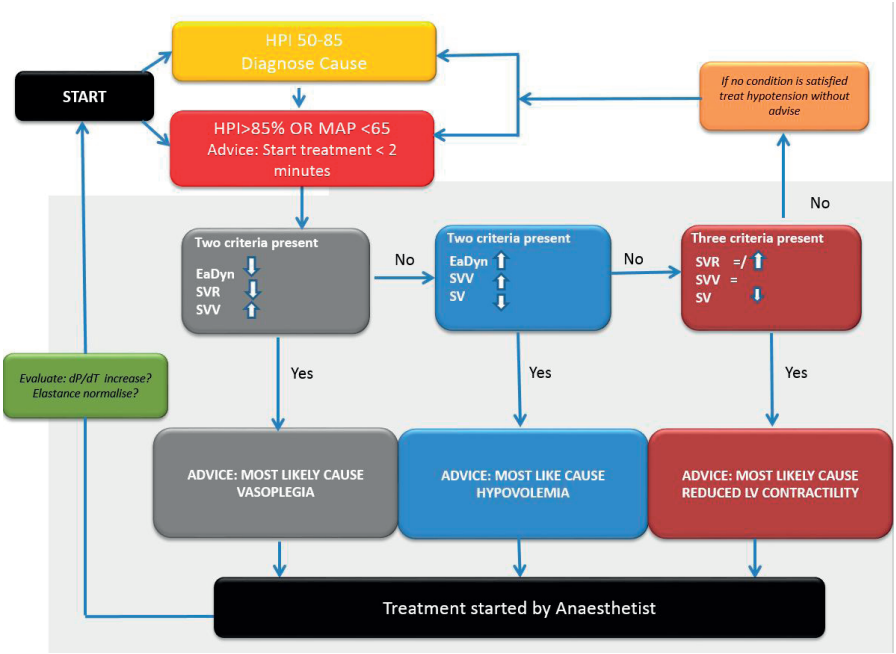
1. Hatib F, Jian Z, Buddi S, et al. Machine-learning Algorithm to Predict Hypotension Based on High-fidelity Arterial Pressure Waveform Analysis. *Anesthesiology.* 2018;129(4):663-674.

EFIGURE 2. HEMOSPHERE MONITOR AND SECONDARY SCREEN



The early warning system is able to predict hypotension before it occurs. An early warning alarm value (the red number in the figure) above 85 translates approximately to an 85% chance of hypotension to occur in the following minutes. The variables in the secondary screen provide information about the underlying cause of the (predicted) hypotension. These variables include: mean arterial blood pressure (MAP), cardiac output (CO), systemic vascular resistance (SVR), pulse rate (PR), stroke volume (SV), stroke volume variation (SVV), a measure of left ventricular contractility from an arterial pressure waveform (dP/dt) and dynamic arterial elastance (Eadyn). Interpretation of these variables requires in depth hemodynamic knowledge, knowledge that anesthesiologists possess. Furthermore, the attending anesthesiologist is provided with a diagnostic flowchart to help diagnose the underlying cause. Every 20 seconds, the early warning system alarm value (visible in the figure as the red number 81) is recalculated. When the early warning system alarm value exceeds 85%, an alarm indicates that a patient may be trending towards a hypotensive event (MAP < 65 mmHg). The attending anesthesiologist will then use the variables on the second screen and the hemodynamic diagnostic guidance and treatment flowchart (Supplement 4) to diagnose and treat the underlying cause of the predicted hypotension.

EFIGURE 3. HEMODYNAMIC DIAGNOSTIC GUIDANCE AND TREATMENT PROTOCOL EXPLANATION



The hemodynamic variables continuously inform the anesthesiologist about the patient's hemodynamic status. When the early warning system alarm exceeds the value 85 or if the Mean Arterial blood Pressure (MAP) drops below 65 mmHg, the treating anesthesiologist actively searches for the underlying cause of the predicted hypotension. Broadly, hypotension can be caused by a preload (hypovolemia), contractility or afterload (vasoplegia) problem. The behavior of the various hemodynamic variables over time can be screened and by making combinations (presence of at least two or three criteria) the most likely cause of hypotension can be diagnosed. For example, the combination of an increase (arrow up) in stroke volume variation, and a decrease (arrow down) in systemic vascular resistance results in the diagnosis of vasoplegia.

The suggested treatment advice for vasoplegia are vasopressors, the suggested treatment advice for hypovolemia are fluids (crystalloid of colloids) and the suggested treatment advice for reduced contractility is to administer inotropes. If more than one underlying cause was present based on the criteria the advice was to treat both underlying problems and administer a combination of treatments. The anesthesiologists were free to choose the dose of the fluids and drugs they wanted to administer.

The hemodynamic diagnostic guidance and treatment protocol was based on previous published research[1]

1. Pinsky M Protocolized cardiovascular management based on ventricular-arterial couping. In: Functional Hemodynamic Monitoring. Update in Intensive Care and Emergency Medicine. Springer-Verlag, Berlin, 381 - 395. ISBN 3540223495

ETABLE1. OBSERVATIONAL STUDY BASELINE CHARACTERISTICS

Patient characteristics	Observational study(n=40)
Male, No.(%)	20 (50)
Age, years	67.0 [59 - 72]
Male, No. (%)	20 (50)
Female, No. (%)	20 (50)
BMI, kg/m^2	24.3 [22 – 27]
ASA classification, No.(%)[a]	
1 – normal, healthy	2 (5)
2 – mild systemic disease	24 (60)
3 – severe systemic disease	13 (33)
4 – life-threatening disease	1 (3)
WHO classification, No.(%)[b]	
0 – fully active	12 (30)
1 – ambulatory and light work	20 (50)
2 – ambulatory but unable to work	7 (18)
3 - >50% confined to bed or chair	0 (0)
4 –Totally confined to bed or chair	1 (3)
MAP outpatient clinic, mmHg	100 [92 – 110]
MAP day before, mmHg	97 [92 -107]
MAP before induction, mmHg	98 [90 – 111]
Type of surgery, No.(%)	
Gynaecological	3 (8)
Gastrointestinal	36 (90)
Pancreas	*12 (33)*
Oesophagus	*14 (39)*
Other	1 (3)
Surgical approach, No.(%)	
Laparotomy	16 (40)
Laparoscopic	6 (15)
Conversion	4 (10)
Combined	14 (35)
Duration of surgery, min[c]	272 [197 – 377]
Duration of anesthesia, min[d]	323 [238-436]

Prior to launching the RCT, a short observation study was conducted to ensure to control group was a representative sample of standard care in our hospital. The data collected including time-weighted average in hypotension was collected (see Supplement 6). The only difference in methods between the control group in the RCT and the short observational was that the anesthesiologist was not aware of the aim of the study (to assess hypotension) in the observational study group.

ASA= American society of Anesthesiologists. WHO= World Health Organization. MAP= mean arterial pressure. Continuous data are presented as median with interquartile range [IQR]. Categorical data are given as number with percentages.

[a] The ASA classification was defined as ASA 1: a normal healthy person, ASA 2: a patient with mild systemic disease, ASA 3: a patient with severe systemic disease, ASA 4: a patient with severe systemic disease that is constant threat to life. [1,2]

[b] The WHO classification was defined as WHO 0: Fully active, able to carry on all pre-disease performance without restriction, WHO 1: Restricted in physically strenuous activity but ambulatory and able to carry

out work of a light or sedentary nature, e.g. light house work, office work, WHO 2: Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours, WHO3: Capable of only limited self-care, confined to bed or chair more than 50% of waking hours, WHO4: Complete disabled. Cannot carry on any self-care. Totally confined to bed or chair.[3,4]

[c] duration of surgery was calculated in minutes form the time of incision until closure of the surgical wound.

[d] duration of anesthesia was calculated in minutes from administration of first anesthetic drug (sufentanil, lidocain, propofol) until extubation. If extubation was not in the operation room but at the ICU of PACU the time of leaving the operation room was noted as end of anesthesia.

1. Doyle DJ, Garmon EH. American Society of Anesthesiologists Classification (ASA Class). In: *StatPearls.* Treasure Island (FL): StatPearls Publishing. StatPearls Publishing LLC.; 2019.
2. Knuf KM, Maani CV, Cummings AK. Clinical agreement in the American Society of Anesthesiologists physical status classification. *Perioperative medicine (London, England).* 2018;7:14.
3. Federici S, Bracalenti M, Meloni F, Luciano JV. World Health Organization disability assessment schedule 2.0: An international systematic review. *Disability and rehabilitation.* 2017;39(23):2347-2380.
4. Oken MM, Creech RH, Tormey DC, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. *American journal of clinical oncology.* 1982;5(6):649-655.

ETABLE 2. OBSERVATIONAL STUDY VS CONTROL GROUP RCT

	Observational study	**Control group RCT**	Median differences with 95%CI[a]	P-value[b]
Primary endpoint Hypotension				
Time-weighted average in hypotension, mmHg	0.44 [0.16 – 0.76]	0.44 [0.23 – 0.72]	-0.5 (-0.22 to 0.14)	.48
Hypotension				
AUT, mmHg*min[c]	80.00 [27.92 – 248.96]	142.17 [64.67 – 258.92]	35.58 (-21.00 to 86.50)	.24
Incidence	6.00 [2.00 – 11.00]	8.00 [3.50 – 12.00]	2.00 (-1.00 to 5.00)	.22
Total time, min	17.50 [7.58 – 47.58]	32.67 [11.50 – 59.67]	6.17 (-5.33 to 19.00)	.31
% of time	8.89 [2.71 – 16.83]	10.34 [4.59 – 15.55]	0.86 (-3.13 to 4.46)	.67
Hypertension				
TWA, mmHg	0.01 [0.00 – 0.22]	0.05 [0.00 – 0.13]	0.00 (0.00 to 0.05)	.39
AAT, mmHg*min[c]	1.92 [0.00 – 54.67]	13.33 [0.00 – 44.25]	2.17 (0.00 to 13.33)	.20
Incidence	1.00 [0.00 -1.75]	1.00 [0.00 -2.00]	0.00 (-1.00 to 0.00)	.18
Total time, min	0.83 [0.00 – 5.17]	3.00 [0.00 – 6.83]	0.33 (0.00 to 2.33)	.24
% of time	0.30 [0.00 – 2.80]	0.85 [0.00 – 1.91]	0.00 (-0.20 to 0.76)	.45
Treatment behavior				
Reaction time, seconds[d]	95.5 [42.8 – 170.7]	87.3 [53.0 – 172.5]	-1.8 (-18.9 to 16.6)	.86
Post-hoc endpoints				
Treatments				
Incidence treatments[e]	5.00 [2.00 – 7.75]	9.00 [3.50 – 13.00]	3.00 (1.00 to 6.00)	**.02**
Early warning system alarms				
TWA, HPI	4.03 [2.10 – 6.78]	4.31 [2.50 – 5.79]	0.13 (-1.12 to 1.50)	.87
AAT, HPI*min[c]	908.67 [423.83 – 2255.67]	1231.00 [701.50 – 1966.33]	160.17 (-301.33 to 599.33)	.46
Incidence	9.50 [6.00 – 14.00]	11.00 [8.00 – 14.50]	1.00 (-2.00 to 4.00)	.44
Total time, min	95.83 [43.00 – 187.50]	116.33 [68.33 – 170.33]	13.00 (-26.33 to 50.67)	.39
% of time	41.96 [22.99 – 59.11]	41.14 [23.93 – 56.35]	-0.65 (-12.44 to 9.40)	.89

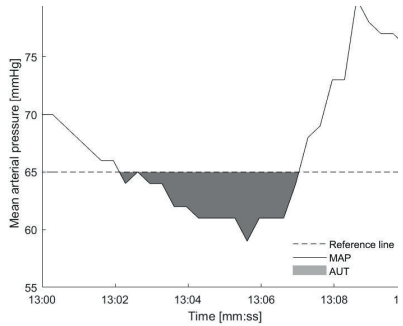
Prior to launching the RCT, a short observation study was conducted to ensure to control group was a representative sample of standard care in our hospital. The only difference in methods between the control group in the RCT and the short observational was that the anesthesiologist was not aware of the aim of the study (to assess hypotension) in the observational study group. There are no significant differences in hypotension or hypertension endpoints between the observational study group and the control group. This table illustrates that our control group was indeed a representative sample of standard care.

All endpoints are medians per patient. The incidence of hypotension, hypertension and early warning system alarms presents the median number of events per patient. Continuous data are presented as median with interquartile range [IQR] and median differences with their 95% confidence intervals (CI). HPI= hypotension prediction index, the variable of the early warning system illustrating the prediction of hypotension. MAP = mean arterial pressure. TWA = time-weighted average. AUT = area under the

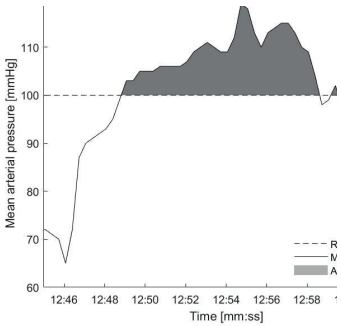
threshold. AAT = area above the threshold. [a] The median differences and their 95% confidence intervals were calculated with the Hodges-Lehmann method [b] The p-value was measure with the Mann-Whitney U test [c] See Supplement 7 for illustration of the AUT and AAT [d] In the intervention group, the reaction time was measured as the time (in seconds) from the onset of the early warning system alarm until treatment. In the control group, reaction time was defined as the time from start of hypotension untill treatment. [e]Treatment incidence was calculated as the median treatments related to hypotension or the alarm.

EFIGURE4. FIGURE AUT AND AAT TO CALCULATE TWA

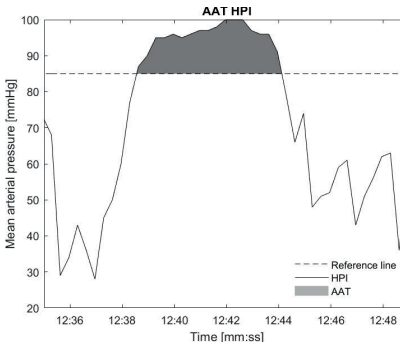
A.



B.



C.



Not only the time spent in hypotension but also the severity (minimum MAP reached) of hypotension is important for associations with postoperative outcome.[1] The time-weighted average (TWA) in hypotension combines the time and depth of hypotension and is therefore a good outcome parameter. To calculate the TWA of hypotension the AUT is needed. The AUT is calculated as the 'depth of hypotension below the threshold – defined as a Mean Arterial blood Pressure (MAP) of 65 mmHg' x 'time spent below MAP 65 mmHg in minutes'. Subsequently the formula of TWA in hypotension is as follows: 'AUT' / 'total duration operation in minutes'. The AAT is required to calculate the TWA in hypertension. The AAT is calculated by multiplying the 'depth of hypertension – defined as a MAP above 100 mmHg' by the 'time spent above a MAP of 100 mmHg in minutes'. The TWA of hypertension is calculated by dividing the AAT by the 'total duration operation in minutes'.

1. Sessler DI, Bloomstone JA, Aronson S, et al. Perioperative Quality Initiative consensus statement on intraoperative blood pressure, risk and outcomes for elective surgery. *British journal of anaesthesia.* 2019;122(5):563-574.

ETABLE3. ADVERSE AND SERIOUS ADVERSE EVENTS

	Intervention (*n=31 patients)*	Control (*n=29 patients)*	*p*-value[a]
Total number of adverse events	33	30	
Pulmonary complications			.38
Pneumonia	-	2	
Pneumothorax	1	-	
Other	1	1	
Cardiac events			.81
Myocardial infarction	1	-	
Arrhythmia	2	1	
Pericardial effusion	1	1	
Surgical complications			.37
Post-surgical bleeding	2	1	
Mediastinal or abdominal abscess	3	1	
Anastomotic leakage	-	5	
Chylothorax	6	6	
Ileus	4	1	
Wound infection	3	2	
Bile leakage	1	1	
Reoperations	2	1	
Urologic			>.99
Increase of > 50% in creatinine	1	1	
Trombo-embolic event	-	1	.97
Neurologic event			>.99
CVA/TIA	-	-	
Postoperative cognitive dysfunction	1	-	
Re-admittance ICU	2	2	>.99
Re-admittance hospital	2	1	>.99
30-day mortality	-	2	.44

Frequencies are given as numbers. ICU = intensive care unit. [a] P-values were calculated using the Chi-square test

According to our study protocol and local ethical committee guidelines adverse events were defined as any undesirable experience occurring to a subject during the study, whether or not considered related to the experimental intervention. Serious adverse events were defined as any untoward medical occurrence or effect that 1. resulted in death 2. was life threatening 3. required hospitalization or prolongation of hospitalization, 4. resulted in persistent or significant disability or incapacity. 5 was a congenital anomaly or birth defect; 6. any other important medical event - that did not result in any of the outcomes listed above- due to medical or surgical intervention. An elective hospital admission was not considered to be a serious adverse event.

Definitions of postoperative outcomes

Pulmonary complications:

Pneumonia; radiologic confirmation of an infiltrate, combined with positive cultures (when available) and clinical signs of infection (above 38.5 degrees Celsius or elevated leucocytes or elevated C-reactive protein). Pneumothorax; collection of air between the visceral and parietal pleural surfaces, requiring drainage. Other was defined as reintubation, pleural effusion (collection of fluid between the visceral and parietal pleural surfaces, requiring drainage) and acute respiratory failure (partial pressure of arterial oxygen<60 mmHg or oxygen saturation <90% while breathing ambient air).
Surgical complications:

Intraoperative surgical complications are defined as any complication that has a lasting harmful effect on the patient and is not part of the normal surgical procedure. Postoperative surgical bleeding was defined as postoperative blood loss requiring blood transfusion and/or leading to hemodynamic instability. Mediastinal abscess was scored when an abscess was identified by radiologic imaging or intraoperative visualization and required interventional or antibiotic treatment. Anastomotic leakages were recorded when they were clinically manifest and confirmed by physical examination, radiologic imaging, or intraoperative/endoscopic visualization. Chylothorax was recorded when elevated levels of triglycerides in intrathoracic fluid ([1 mmolL-1 [89 mg per dL]) were found. Wound infection was defined as a contaminated wound requiring any type of intervention.

Thrombo-embolic complications:

Thrombo-embolic events were recorded when a (pulmonary or other) embolus was detected on computed tomography or by duplex ultrasound.

Neurologic complications

Neurologic events included delirium and cerebrovascular events.

Cardiac complications

Cardiac complications were arrhythmia (any change in rhythm on the electrocardiogram, requiring treatment), myocardial infarction (electrocardiographic changes suggesting myocardial infarction and / or enzyme changes suggesting myocardial infarction), and left ventricular failure (marked pulmonary edema on a chest radiograph).

Urologic complications:

Kidney function disorder was defined as 50% elevation of preoperative creatinine.

EFIGURE 5. POST HOC REGRESSION ANALYSIS

In order to post-hoc test for the possible confounding effect of the pre-induction blood pressure on the time-weighted average (TWA) of hypotension, the following statistical procedures were performed.

1. The normality of time-weighted average in hypotension was visually inspected (figure 1 and 2)

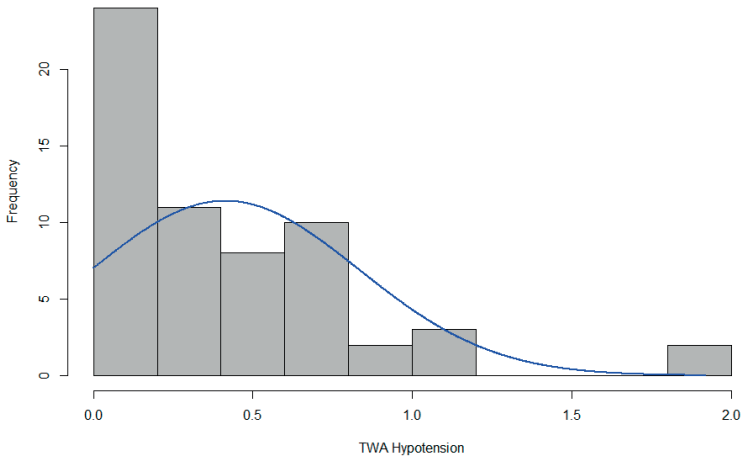


Figure 1. Histogram of the time-weighted average in hypotension

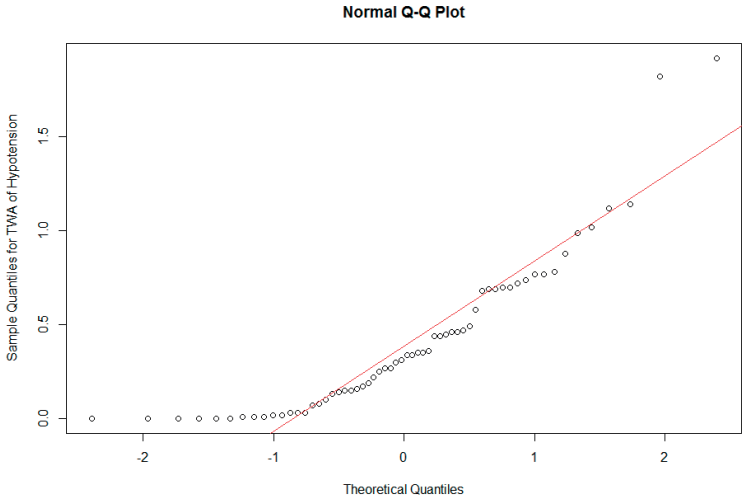


Figure 2. Q-Q Plot of the time-weighted average in hypotension

2. The normality of the pre-induction Mean Arterial Pressure (MAP) was visually inspected (figure 3 and 4)

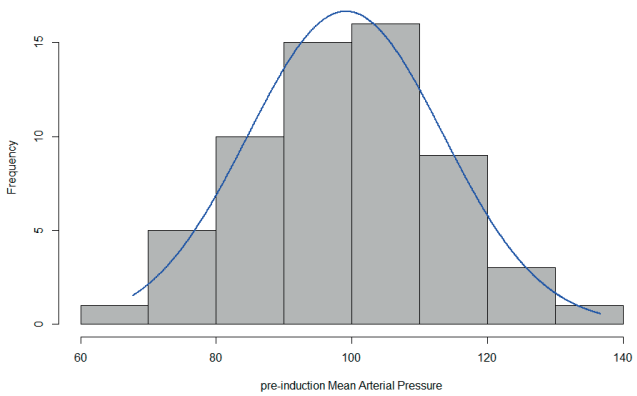


Figure 3. Histogram of the pre-induction MAP

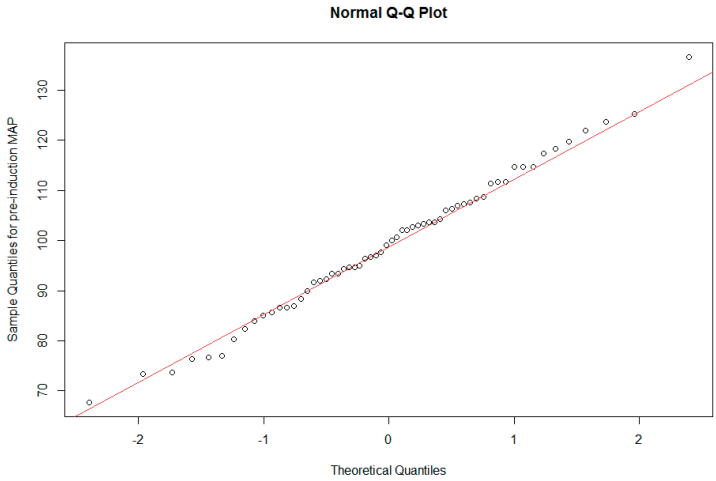


Figure 4. Q-Q Plot of the pre-induction MAP

3. To correct for the non-normality of time-weighted average in hypotension, data was transformed to normality using the box-cox function. Optimum lambda for transformation was calculated at 0.3 (Figure 5)

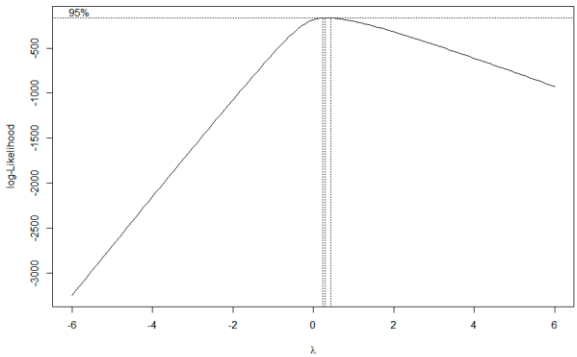


Figure 5. Optimum lambda cut-off for transformation to normality

4. The time-weighted average in Hypotension was log-transformed using the optimum lambda of 0.3. After transformation the normality was inspected visually. (Figure 6 and 7)

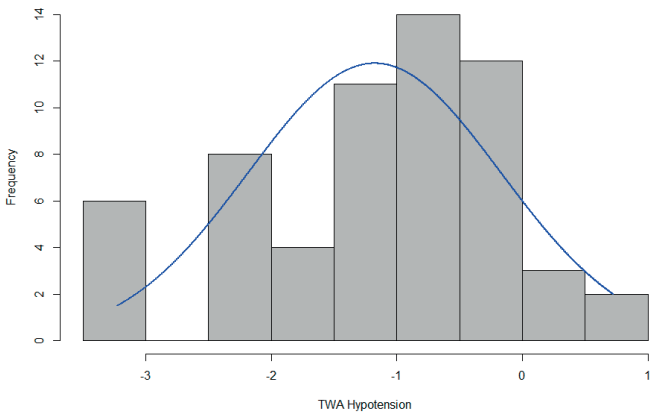


Figure 6. Histogram of the time-weighted average in hypotension after transformation

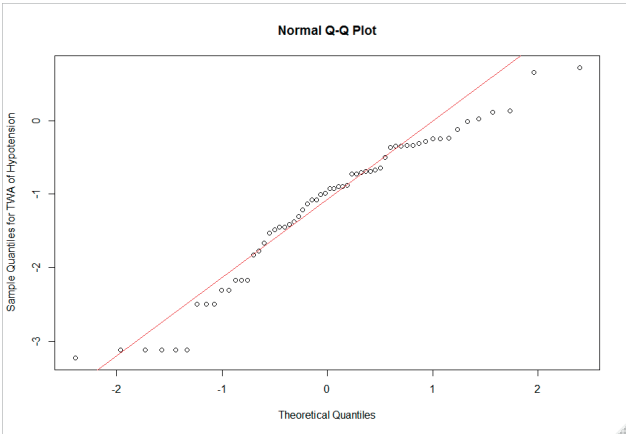


Figure 7. Q-Q Plot of the time-weighted average in hypotension after transformation

5. A linear regression model was composed to assess the effect of the early warning system usage on the time weighted average in hypotension:

Residuals:
Min 1Q Median 3Q Max
-2.38621 -0.59293 0.05263 0.52641 2.31166
Coefficients:
Estimate Std. Error t value Pr(>|t|)
(Intercept) -0.7368 0.1702 -4.328 6.02e-05 ***
randomized_group -0.8543 0.2368 -3.607 0.000646 ***

Signif. codes: 0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
Residual standard error: 0.9168 on 58 degrees of freedom
Multiple R-squared: 0.1832, Adjusted R-squared: 0.1691
F-statistic: 13.01 on 1 and 58 DF, p-value: 0.0006456

6. A multi-variate linear regression model was composed to assess the confounding effect of MAP before induction on the relationship between early warning system usage and the time-weighted average in hypotension.

Residuals:
Min 1Q Median 3Q Max
-2.39984 -0.59703 0.03883 0.52480 2.32360
Coefficients:
Estimate Std. Error t value Pr(>|t|)
(Intercept) -0.853754 0.846990 -1.008 0.317721
randomized_group -0.864287 0.249087 -3.470 0.000999 ***
MAP_before_induction 0.001232 0.008736 0.141 0.888359

Signif. codes: 0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
Residual standard error: 0.9247 on 57 degrees of freedom
Multiple R-squared: 0.1835, Adjusted R-squared: 0.1549
F-statistic: 6.405 on 2 and 57 DF, p-value: 0.003095

ETABLE4. TREATMENT CHOICE RCT

	Intervention	Control	Proportional difference (95%CI)[b]	p-values[c]
Total number of treatments [a]	N = 596	N = 258		
Treatment choice No. (%)				
Noradrenaline	263 (44)	102 (40)	0.04 (-0.03 – 0.12)	.21
Ephedrine	38 (6)	37 (14)	0.08 (0.06 – 0.14)	**<.001**
Phenylephrine	110 (19)	61 (24)	0.05 (-0.01 – 0.11)	**.04**
Dobutamine	3 (0.5)	0 (0)	0.01 (-0.00 – 0.01)	.25
Decrease anesthetics	44 (7)	17 (7)	0.01 (-0.03 - 0.04)	.68
-Sevoflurane	*42 (7)*	*17 (7)*	0.01 (-0.03 – 0.04)	.81
-Propofol	*2 (0.3)*	*0 (0)*	0.00 (0.00 – 0.01)	.35
Decrease analgesics	9 (2)	4 (2)	0.00 (-0.02 – 0.02)	.96
-Sufentanil intravenous	*3 (0.5)*	*1 (0.4)*	0.00 (-0.01 – 0.01)	.82
-Sufentanil epidural	*2 (0.3)*	*0 (0)*	0.00 (0.00 – 0.01)	.35
-Bupivacaine epidural	*1 (0.2)*	*2 (1)*	0.01 (-0.01 – 0.02)	.17
-Lidocain epidural	*0 (0)*	*0 (0)*	-	-
-Ketamin intravenous	*3 (0.5)*	*1 (0.4)*	0.00 (-0.01 – 0.01)	.82
Fluid bolus	96 (16)	16 (6)	0.10 (0.06 – 0.14)	**<.001**
-Colloid	*29 (5)*	*3 (1)*	0.04 (0.02 – 0.06)	**.009**
-Crystalloid	*67 (11)*	*13 (5)*	0.06 (0.03 – 0.10)	**.004**
Increase speed of fluid infusion	23 (4)	16 (6)	0.02 (-0.01 – 0.06)	.30
Blood products	0 (0)	0 (0)		-
Trendelenburg	9 (2)	5 (2)	0.00 (-0.02- 0.02)	.80

The results are presented as frequencies with percentage (%) [a] Total number of treatments means the total number of treatments for hypotension in the control group (because the early warning system alarm was blinded) and the total number of treatments for the early warning system alarms and hypotension in the intervention arm. [b] Proportional differences were calculated with use of the poisson distribution [c]P-values were calculated using the Chi-square test

ETABLE5. TREATMENT BEHAVIOR SILENT ALARMS CONTROL GROUP

Early warning system alarms	Intervention (n=31)	Control (n=29)	Proportional difference or median difference (95% CI)[a]	p-value[b]
Total alarms, n	377	356		-
Alarms per patient	11 [7 - 16]	11 [8 – 15]	0 (-4 to 3)	.84
Total treated alarms, n (%)	324 (86%)	117 (33%)	53 (47 to 59)	**< .001**
Treatments per alarm	1 [1 - 2]	0 [0 - 1]	1 (0 to 1)	**< .001**
Time from alarm to first treatment action (seconds)	53 [24 - 99]	161 [73 - 391]	48 [13 to 97]	**< .001**
Time from first alarm to first treatment action (seconds)	57 [22 – 81]	108 [44 - 204]	91 [70 to 117]	**0.01**

This table demonstrates the results of a post-hoc analyses. Results presented in median with IQR [ ], or frequencies with %. This table shows the total number of treatments after an early warning system alarm (referred to as 'alarm') but before hypotension occurred. In the intervention group the alarms were visible to the treating anesthesiologists. In the control group the alarms were not visible to the treating anesthesiologists. The results show that in the control group in 117 out of 356 alarms the treating anesthesiologist started treatment before hypotension occurred. The median time to treatment was significantly longer in the control group. [a]For continuous data the median differences and their 95% confidence intervals were calculated with the Hodges-Lehmann method. For categorical data the proportional differences were calculated with use of the poisson distribution. [b]Mann-Whitney U test for continuous data and chi-square for categorial data.

Känslor är som vågor, vi kanske inte kan stoppa dem från att komma men vi kan välja vilka vi vill surfa på

Feelings are much like waves. We can't stop them from coming, but you can choose which ones to surf

Jonathan Mårtensson

Selected by Jasmijn Wijnberge

8

The effect of Hypotension Prediction Index-guided intraoperative haemodynamic care on depth and duration of postoperative hypotension: a sub-study of the Hypotension Prediction trial

Jimmy Schenk
Marije Wijnberge
Jolanda M. Maaskant
Markus W. Hollmann
Liselotte Hol
Rogier V. Immink
Alexander P. Vlaar
Bart F. Geerts
Denise P. Veelo

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ABSTRACT

Background

Intraoperative and postoperative hypotension are associated with morbidity and mortality. The Hypotension Prediction (HYPE) trial showed that the Hypotension Prediction Index (HPI) reduced the depth and duration of intraoperative hypotension (IOH), without excess use of intravenous fluid, vasopressor, and/or inotropic therapies. We hypothesised that intraoperative HPI-guided haemodynamic care would reduce the severity of postoperative hypotension in the PACU.

Methods

This was a sub-study of the HYPE study, in which 60 adults undergoing elective noncardiac surgery were allocated randomly to intraoperative HPI-guided or standard haemodynamic care. Blood pressure was measured using a radial intra-arterial catheter, which was connected to a FloTracIQ sensor. Hypotension was defined as MAP <65 mm Hg, and a hypotensive event was defined as MAP <65 mm Hg for at least 1 min. The primary outcome was the time-weighted average (TWA) of postoperative hypotension. Secondary outcomes were absolute incidence, area under threshold for hypotension, and percentage of time spent with MAP <65 mm Hg.

Results

Overall, 54/60 (90%) subjects (age 64 (8) yr; 44% female) completed the protocol, owing to failure of the FloTracIQ device in 6/60 (10%) patients. Intraoperative HPI-guided care was used in 28 subjects; 26 subjects were randomised to the control group. Postoperative hypotension occurred in 37/54 (68%) subjects. HPI-guided care did not reduce the median duration (TWA) of postoperative hypotension (adjusted median difference, *vs* standard of care: 0.118; 95% confidence interval [CI], 0–0.332; *P*=0.112). HPI-guidance reduced the percentage of time with MAP <65 mm Hg by 4.9% (adjusted median difference: –4.9; 95% CI, –11.7 to –0.01; *P*=0.046).

Conclusions

Intraoperative HPI-guided haemodynamic care did not reduce the TWA of postoperative hypotension.

Keywords

Anaesthesia, Anaesthesiology, Blood pressure, Machine Learning, Perioperative care, Surgery

EDITOR'S KEY POINTS

- Perioperative hypotension is associated with a greater risk of cardiorenal morbidity and mortality.
- Using an arterial catheter, the Hypotension Prediction Index (HPI) may alert clinicians to the short-term risk of hypotensive events.
- The authors hypothesised that haemodynamic care guided by intraoperative use of the HPI would reduce the depth and duration of postoperative hypotension.
- Intraoperative HPI-guided haemodynamic care did not reduce the time-weighted average of postoperative hypotension.

BACKGROUND

One-fifth of all surgical patients experience at least one episode of postoperative hypotension (POH), defined as MAP below 65 mm Hg for at least 1 min in the first 24 h after surgery.[1] In line with findings for intraoperative hypotension (IOH),[2,3,4,5,6,7] POH is associated with acute kidney and myocardial injury,[8,9,10] doubling the relative risk of morbidity and mortality.[1] Despite the widely recognised negative outcome associated with POH,[1,8] absence of clinically overt side-effects during or immediately after a postoperative hypotensive event often results in more liberal BP management. There is a lack of strong evidence and consensus regarding optimal BP targets.

Recently, the Hypotension Prediction Index (HPI) has been developed, enabling projection of a hypotensive event to occur within the next minutes. The HPI predicts an intraoperative hypotensive event, minutes before it occurs, with 88% sensitivity and 87% specificity.[11] HPI-guided haemodynamic care during surgery resulted in a reduction in depth and duration of IOH, without an increased use of i.v. fluids, vasopressors, or inotropes.[12] However, it is unknown whether the proactive treatment of potential causes of IOH using HPI-guided haemodynamic care also results in a change in the depth and duration of POH.

In this sub-study of the Hypotension Prediction (HYPE) trial,[12,13] we hypothesised that intraoperative HPI-guided haemodynamic care would reduce the severity of POH in the PACU. The primary aim was to determine whether the time-weighted average (TWA) of POH in the PACU is affected by intraoperative HPI-guided haemodynamic care.

METHODS

Study design

This was a single-centre, prospective cohort sub-study of the HYPE trial,[12,13] conducted at the PACU of the Amsterdam University Medical Centers, location 'AMC', in Amsterdam, The Netherlands. Patients were recruited on the day before their surgery, from June 2018 to February 2019. The parent trial protocol (HYPE trial) was approved by the local ethics committee on October 5, 2017 (B2017568). The sub-study amendment was approved on March 16, 2018 (B2018150), before recruitment of the first patient. The trial was registered with the National Institutes of Health, United States National Library of Medicine at ClinicalTrials.gov(NCT03376347), was conducted in accordance with the ethical principles as set out in the Declaration of Helsinki and followed the ICH Harmonised Tripartite Guideline for Good Clinical Practice. Written informed consent was obtained from each patient. A password-protected subject log was kept on a secure

server. Participation in the trial was recorded in the electronic patient record, visible for all other care providers.

Study participants

The parent HYPE trial was a pilot RCT, conducted at the same medical centre.[12] The parent study included subjects ≥18 yr old scheduled for elective noncardiac surgery under general anaesthesia with a target MAP ≥65 mm Hg, using continuous invasive BP monitoring. The aim was to assess the impact of HPI-guided haemodynamic care on IOH. Patients were randomly allocated to an intervention or a control arm, using a permuted block randomisation. Patients who were randomised but for whom no study measurements were performed, were excluded. Subjects in the intervention arm were treated by the attending anaesthesiologist with access to the HPI algorithm and a haemodynamic guidance and treatment protocol during surgery. Subjects in the control arm received institutional standard care, with a target MAP ≥65 mm Hg. Summarised, the HYPE trial showed a 77% reduction in IOH in terms of both depth and duration.[12,13]

Measurements

Hypotension was defined as MAP <65 mm Hg, measured invasively with a radial arterial catheter. A hypotensive event was defined as a MAP <65 mm Hg for at least 1 min. An event ended when MAP >65 mm Hg for 20 s. Both the time spent in hypotension and the depth of the hypotensive episode have been associated with postoperative outcome.[14,15] To assess the severity of hypotension, the area under threshold (AUT) was calculated for each event by summation of the difference between MAP and the threshold, multiplied by the event duration (Supplementary Figure S1). The total AUT was divided by the observed time, which differed per patient. This resulted in a TWA of POH.[15]

Study procedures and blinding

After surgery, all study participants were transferred to the PACU where they received standard care, with an intention to keep MAP ≥65 mm Hg. BP was monitored with an arterial catheter in the radial artery. The arterial line was connected to a FloTracIQ sensor, which was connected to a HemoSphere monitor (both obtained from Edwards Lifesciences, Irvine, CA, USA). The monitor was fully covered with a non-transparent sheet, to ensure that the displayed data could not influence care. Alarms and sounds were disabled. The HemoSphere monitor was used to collect haemodynamic data. To facilitate postoperative care, the invasive BP signal was also transmitted to a Philips IntelliVue MX550 patient monitor (Koninklijke Philips NV, Amsterdam, The Netherlands), displaying MAP, systolic and diastolic pressure to the attending physicians and nurses at the PACU. Postoperative invasive BP monitoring was continued until discharge to a

general ward, according to standard clinical practice. The medical team providing care at the PACU and all included patients were blinded to group allocation.

Data collection

Arterial pressure waveform was measured continuously with the FloTracIQ sensor (Edwards Lifesciences), using a sample frequency of 100 Hz. Using a low pass filter to exclude artifacts, the HemoSphere monitor averages and stores haemodynamic variables every 20 s. Subject characteristics, medical history, pre-procedural medication, type of surgery, intraoperative medication, intraoperative fluid balance, duration of the surgery, duration of general anaesthesia, postoperative medication, postoperative fluid balance, duration of postoperative monitoring, usage of epidural anaesthesia, postoperative mechanical ventilation and its duration, and postoperative complications at the PACU were collected from the electronic patient record by a research nurse, who was blinded to group allocation. The severity of a postoperative complication was graded using the Clavien–Dindo Classification.[16] Complications graded III or higher were defined as severe. All data were entered into an electronic Clinical Report Form built in Castor EDC, a Good Clinical Practice compliant data management system.[17]

Primary outcome

The primary outcome of this study was the difference in TWA of POH, between subjects with HPI-guided haemodynamic care and subjects with standard haemodynamic care during surgery. Change in TWA of POH over time was plotted in 2 h time frames.

Secondary outcomes

Secondary outcomes were the differences in incidence of hypotension; AUT of POH; total time (in minutes) spent in hypotension and percentage of total observed time spent in hypotension.

Sample size

Sample size was fixed, and the calculation was based on the main endpoint of the parent study, in which the mean TWA of IOH was estimated at 0.5 mm Hg. A 75% reduction of hypotension in terms of both depth and duration was considered clinically relevant for both the parent and the sub-study. Thus, the mean difference between groups was estimated at 0.38 mm Hg. Sixty subjects would provide 80% power to detect an effect size of at least 0.74 at an estimated difference of 0.38 in the mean TWA in HPI-guided haemodynamic care *vs* standard haemodynamic care subjects, using Student's *t*-test with a 0.05 two-sided significance level.

Statistical analyses

Continuous data are presented as median with inter-quartile range (IQR), or as a mean with standard deviation (SD) when normally distributed. Normality of distribution was assessed visually using boxplots, histograms, and Q–Q plots, and statistically using the Shapiro–Wilkinson normality test. Differences between continuous data were analysed using the Student's *t*-test when normally distributed. Differences between non-normally distributed continuous data were analysed using the Wilcoxon rank-sum test. Categorical data are presented as frequencies with percentages. Differences between categorical data were analysed using the Fisher's exact test. For each of the analyses, a *P* value <0.05 was considered statistically significant.

As haemodynamic guidance with the HPI algorithm was randomised during the parent HYPE trial, confounding variables are likely to be distributed equally between groups. However, owing to the smaller sample size of this sub-study, statistically significant differences for potentially confounding and effect modifying variables could still occur by chance. Therefore, the effect of statistically significant differences in baseline characteristics was analysed using logistic regression. Confounding variables were corrected for using multivariate logistic regression. During the planning stage of this study, continued mechanical ventilation and severe postoperative complications were identified as potential effect modifiers. When significant, an adjusted estimate of effect was calculated by stratifying the data into a subgroup. Statistical analyses were performed by a statistician blinded to treatment allocation, using R, version 3.5.1. (R Foundation for Statistical Computing, Vienna, Austria).[18]

RESULTS

Study participants

Data were analysed for 54 (90%) of 60 recruited subjects (Figure 1). Three patients in each group were lost to follow-up, because of technical failure of the FloTracIQ device (Edwards Lifesciences). Participants randomised to HPI-guided haemodynamic care and standard of care shared similar characteristics before surgery (Table 1). The duration and depth of IOH was reduced by HPI-guided haemodynamic care. Postoperative care was similar between HPI guidance and standard of care groups (Supplementary Table S1).

Primary outcome: severity of POH during PACU stay

There was no difference in unadjusted estimated median difference in TWA of POH between HPI-guided haemodynamic care *vs* standard care during surgery (–0.03; 95% confidence interval [CI], –0.31 to 0.04; *P*=0.295; Table 2). Continuation of mechanical ventilation did not affect the TWA of POH (β = 0.27, 95%CI −0.92 – 1.45, *P* = 0.66), but

Participant characteristics	Standard haemodynamic care during surgery (*n*=26)	HPI-guided haemodynamic care during surgery (n=28)	*p*-value
Age (yr)	62 [57, 66]	69 [61, 73]	**0.032**
Male (*n*; %)	11 (42.3)	19 (67.9)	0.107
BMI (kg m^2)	25.0 (4.2)	24.4 (4.1)	0.599
ASA physical status (%)			**0.020**
1	3 (11.5)	1 (3.6)	
2	23 (88.5)	21 (75.0)	
3	0 (0.0)	6 (21.4)	
MAP day before surgery (mm Hg)	92.9 (14.2)	96.7 (12.8)	0.302
Type of surgery (*n*; %)			0.160
Gastrointestinal	21 (80.8)	27 (96.4)	
Gynaecological	3 (11.5)	1 (3.6)	
Other	2 (7.7)	0 (0.0)	
Surgical approach (*n*; %)			0.344
Open	12 (46.2)	18 (64.3)	
Laparoscopic	5 (19.2)	2 (7.1)	
Combined lap and open	6 (23.1)	7 (25.0)	
Conversion from lap to open	3 (11.5)	1 (3.6)	
Epidural (*n*; %)	12 (46.2)	19 (67.9)	0.181
Duration of surgery (min)	247 [222, 402]	254 [194, 409]	0.749
Blood loss during surgery (ml)	325 [150, 445]	275 [188, 388]	0.814
Fluid balance end of surgery (ml)	1153 (793)	1252 (730)	0.633
Mechanical ventilation in PACU (%)	4 (15.4)	2 (7.1)	0.596
Intraoperative medication (cumulative doses)			
Norepinephrine (µg)	810 [422, 2135]	1060 [840, 1615]	0.436
Ephedrine (mg)	12 [10, 17]	10 [0, 20]	0.301
Phenylephrine (µg)	225 [100, 400]	300 [75, 625]	0.406
Sevoflurane (volume%)	1.55 [1.40, 1.74]	1.64 [1.49, 1.73]	0.426
Intraoperative hypotension			
Average MAP	74.7 [71.8, 78.3]	77.7 [75.5, 80.9]	**0.017**
TWA hypotension	0.45 [0.26, 0.72]	0.14 [0.02, 0.45]	**0.004**
AUT hypotension	132 [63, 208]	34 [3.0, 154]	**0.013**
Incidence	8.0 [3.2, 11.0]	3.0 [1.0, 7.2]	**0.019**
Time in hypotension (min)	28.0 [12.8, 52.3]	9.3 [1.9, 26.9]	**0.004**
% of surgery time	10.25 [4.83, 15.80]	3.48 [1.03, 7.27]	**0.002**

Table 1. Characteristics of subjects at PACU arrival. Continuous data are given as median [IQR] unless reported as mean (SD). Bold values denote statistical significance at the $p < 0.05$ level. TWA, time-weighted average; AUT, area under threshold; IQR, inter-quartile range

having a severe postoperative complication did (β = 2.75, 95%CI 1.54 – 3.96, *P* = <0.001). HPI-guided haemodynamic care during surgery did not alter the TWA of POH when we adjusted for postoperative complications (adjusted estimated median difference in TWA: –0.12; 95% CI, –0.33 to 0.0; *P*=0.112; Table 3).

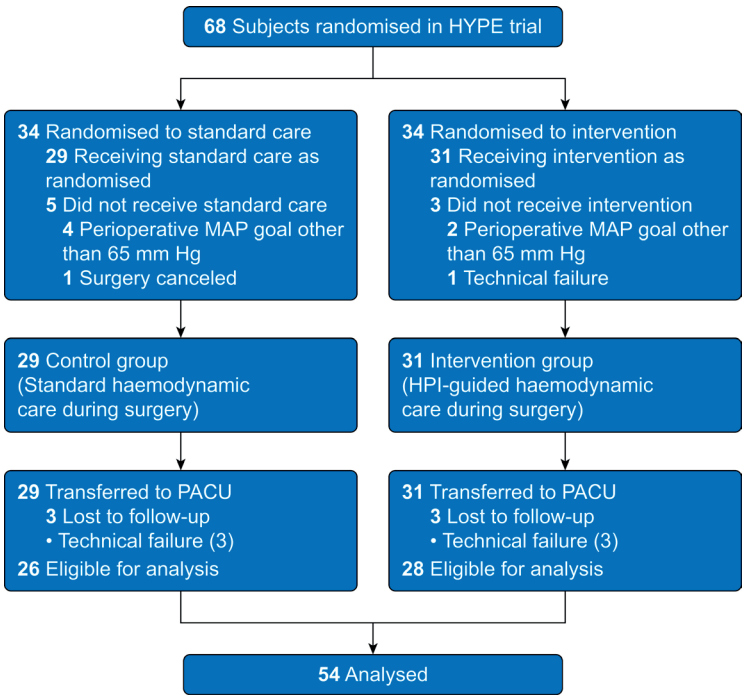

Figure 1. Study flow diagram. HYPE: parent study, the hypotension prediction trial.

Unadjusted outcomes	Standard haemodynamic care during surgery (*n*=26)	HPI-guided haemodynamic care during surgery (*n*=28)	Estimated median difference (95% CI)	*p*-value
POH event (%)	20 (76.9)	17 (60.7)		0.323
POH events per patient	11 [2, 30]	4 [0, 13]	–3 (–15, 1)	0.221
TWA	0.23 [0.01, 1.11]	0.07 [0.0, 1.10]	–0.03 (–0.31, 0.04)	0.295
AUT	227.2 [8.5, 697.3]	26.3 [0.0, 952.4]	–8.5 (–233.3, 30.3)	0.374
Duration of POH (min)	70.3 [3.8, 174.7]	11.0 [0.0, 190.1]	–8.0 (–69.0, 10.3)	0.333
% time spent in POH	7.08 [0.39, 27.11]	2.35 [0.0, 23.11]	–2.33 (–10.31, 0.41)	0.222

Table 2. Primary and secondary outcomes. Difference in the time-weighted average (TWA) of postoperative hypotension (POH) between standard haemodynamic care subjects and Hypotension Prediction Index (HPI)-guided haemodynamic care subjects during surgery (primary objective), and in area under threshold (AUT) of POH, time spend in POH, and percentage of observed time spent in POH (secondary objectives). Continuous data are given as median [IQR] unless otherwise specified. IQR, inter-quartile range; CI, confidence interval

Secondary outcomes

POH occurred in 37/54 subjects (68%), with an average of 14 individual hypotensive events per subjects. The AUT of POH, incidence of POH, total time spent in hypotension, and the percentage of observed time spent in hypotension were similar between HPI-guided and standard care during surgery (Table 2). After adjusting for severe postoperative complications, POH occurred in 33/50 subjects (66%), with an average of 13 hypotensive events per subjects. Subjects with HPI-guided haemodynamic care had four postoperative hypotensive events less than subjects receiving standard care during surgery (95% CI, –20.0 to –0.01; *P*=0.05). Subjects in the control group spent 8.75% of the observation time with hypotension, compared with 0.88% in the HPI-guided haemodynamic care group (adjusted median difference: –4.94%; 95% CI, –11.67 to –0.01; *P*=0.046). The median duration of POH was 70.3 min in the control group, compared with 7.3 min in patients with HPI-guided haemodynamic care during surgery (adjusted median difference: –22.6; 95% CI, –84.3 to 0.0; *P*=0.068; Table 3).

The number of subjects remaining in PACU declined over time, with mean TWA of POH between the two groups overlapping after 12 h (Figure 2). The adjusted estimated median difference in TWA of POH was –0.119 (95% CI, –0.503 to 0.0; *P*=0.058) during the first 12 postoperative hours and 0.01 (95% CI, –0.007 to 0.366; *P*=0.293) during the second 12 h (Figure 3).

Outcomes stratified by severe postoperative complication				
	Standard haemodynamic care during surgery (*n*=25)	**HPI-guided haemodynamic care during surgery (*n*=25)**	**Estimated median difference (95% CI)**	***P*-value**
Patients with a POH event (%)	19 (76.0)	14 (56.0)		0.232
Incidence of POH per patient	13 [2, 30]	2 [0, 9]	–4 (–20, 0)	0.050
TWA of POH	0.21 [0.0, 0.83]	0.02 [0.0, 0.34]	–0.12 (–0.33, 0.0)	0.112
AUT POH	219.8 [17.5, 732.3]	13.0 [0.0, 284.6]	–38.7 (–303.0, 0.0)	0.087
Time spent in POH (min)	70.3 [6.6, 197.4]	7.3 [0.0, 72.2]	–22.6 (–84.3, 0.0)	0.068
% time spent in POH	8.7 [0.7, 25.7]	0.9 [0.0, 6.7]	–4.9 (–11.7, –0.01)	**0.046**

Table 3. Primary and secondary objectives, adjusted for effect modification of severe postoperative complications using stratification. Difference in TWA of POH between patients with standard haemodynamic care and HPI-guided haemodynamic care during surgery (primary objective), and in AUT of POH, time spent in POH, and percentage of observed time spent in POH (secondary objectives). Continuous data are given as median [IQR] unless otherwise specified. Bold values denote statistical significance at the $p < 0.05$ level. POH, postoperative hypotension; TWA, time-weighted average; AUT, area under threshold; IQR, inter-quartile range; CI, confidence interval

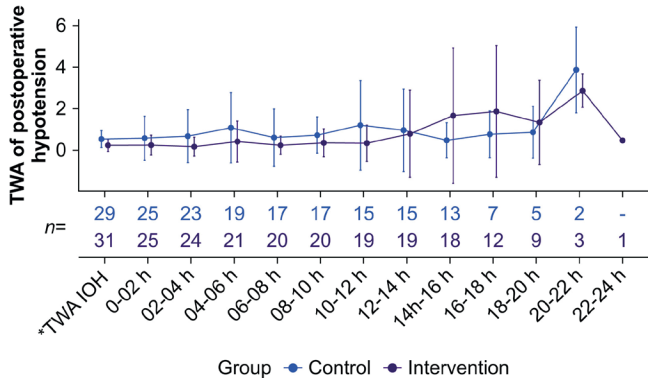

Figure 2. Time-weighted average (TWA) of postoperative hypotension during PACU stay. Under each time frame, the number of subjects not yet discharged to a general ward is plotted. Data presented as mean (standard deviation). IOH, intraoperative hypotension.

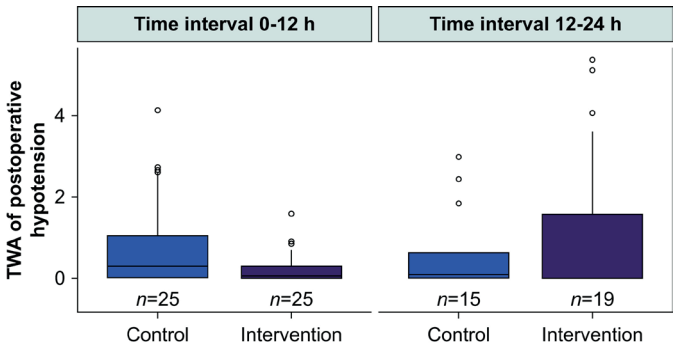

Figure 3. Difference in time-weighted average (TWA) of postoperative hypotension (POH), divided in 12 h intervals. During the first 12 h, the adjusted estimated median difference in TWA of POH was −0.119 (*P*=0.058, Wilcoxon rank-sum test). During the second 12 h, the adjusted estimated median difference in TWA of POH was 0.01 (*P*=0.293, Wilcoxon rank-sum test).

DISCUSSION

This sub-study of the HYPE trial analysed the effect of an intraoperative algorithm supporting haemodynamic treatment on the severity of POH. Intraoperative HPI-guided haemodynamic care did reduce IOH,[12] but did not lower the TWA of POH. However, patients without a severe postoperative complication showed less time spent in hypotension in the PACU, when HPI-guided haemodynamic care was used during surgery. The incidence of hypotensive events, total AUT, and duration of hypotension was comparable after surgery.

The effect of reducing the severity of IOH on the depth and duration of POH has never been studied before. Visual inspection of the change in TWA of POH indicated a decline over time. During the first 12 postoperative hours, the difference in POH was

similar to the findings in the parent HYPE trial. This emphasises the possible association between the intraoperative usage of HPI-guided haemodynamic care and the severity of POH. Increased depth, duration of IOH, or both may result in increased hypoxia-induced cell damage.[19, 20, 21]More cell damage might jeopardise the systemic regulation of blood flow, potentially leading to prolonged and therapy-resistant IOH and an increased likelihood of POH. Roshanov and colleagues[1] showed that reducing exposure to factors (e.g. preoperative medication) that may promote IOH reduced the severity of POH. After randomisation, these factors were likely to be distributed equally between groups in our trial.

The incidence of POH (66%) was high in our sample. We expect the high incidence to be partly explained by our definition and measuring method, as arterial BP was measured continuously. Hypotension was defined as MAP <65 mm Hg for longer than 1 min. The four patients with a severe postoperative complication had a 2.852 median TWA of POH and were responsible for 30% of the total TWA of POH. As these patients all had a confirmed bleeding complication requiring surgical intervention, the increased depth and duration of POH was most likely caused by hypovolaemic shock.[22] Roshanov and colleagues[1] found a much lower incidence of POH (19.5%). They defined a hypotensive event as 'having a systolic blood pressure less than 90 mm Hg for any duration for which an intervention was initiated'. We counted events regardless of the initiation of an intervention. Moreover, our selected sample had a high *a priori* risk of POH, mainly consisting of patients undergoing major abdominal surgery for cancer with numerous comorbidities, multiple preoperative medication, and longer duration of surgery. This higher *a priori* risk is illustrated when our cohort is compared with the one used by van Lier and colleagues,[8] who reported a 24.6% incidence of POH in a more heterogeneous mix of patients, using the MAP <65 mm Hg threshold. A consensus regarding an optimal postoperative BP threshold is needed to foster a more uniform treatment approach and to facilitate comparisons of study findings.[23]

Continuous monitoring of BP and other haemodynamic variables allows for optimising postoperative haemodynamic care,[24] although treatment is still reactive. Several factors influence the management of a postoperative hypotensive event, including practice variation of the attending nurse and physician. Studying and implementing ways to reduce this variation may reduce POH. Furthermore, as the parent HYPE trial showed that prediction of IOH is possible, machine learning might also prove effective in the prediction of POH.[12]

The analysed intervention in the parent study was a combination of HPI as an early warning system with a haemodynamic guidance protocol, before the occurrence of hypotension. To more precisely evaluate the impact of HPI, it would be interesting to compare the effect of this combined intervention with a group where an early warning is given when hypotension occurs, using the same haemodynamic guidance protocol.

Our study has several limitations. The loss to follow-up of six patients reduced the power of the study. All results show associations in the same direction, with 95% CIs including, rather than overlapping, the neutral value of 0. However, the true between-group difference is smaller than the *a priori* estimated minimum clinically relevant difference. Although the small sample size increases the likelihood of confounding and effect modifying variables, patients were analysed in their randomly allocated trial arm, increasing the probability of equal distribution of both measured and unmeasured confounding variables. The AUT of hypotension was divided by the total observed time. Therefore, differences in observation time between patients could not influence results. Some confounding by indication could still have occurred. Patients with hypotension will be transferred to a general ward later. Consequently, patients with more frequent or severe hypotension will be measured longer, increasing their individual effect on hypotension in their group.

In summary, HPI-guided haemodynamic care during surgery did not reduce the TWA of POH. Despite the absence of positive findings, our results remain clinically relevant, because the total percentage of time spent in hypotension after surgery was lower when HPI-guided haemodynamic care was used. Future studies with large sample sizes are required to validate these results.

Authors' contributions

Conception: JMM, MW, MWH, BFG, APV, DPV, RVI.
Design of study: JS, MW, JMM, MWH, BFG, APV, DPV, RVI.
Data collection: JS, MW, LH.
Data management: JS, MW, BJPS.
Data interpretation: JS, MWH, BFG, APV, DPV, RVI, BJPS.
Statistical analysis: JS, JMM.
Writing of the manuscript: JS.
Critical review of the manuscript: MW, JMM, LH, MWH, BFG, BJPS, APV, DPV, RVI.
All authors approved this final version of the manuscript to be published and are accountable for all aspects of the work.

Declarations of interest

The Department of Anaesthesiology of the Amsterdam UMC, location 'AMC' received financial support for this project from Edwards Lifesciences. DPV, APV, MW, RVI, and BFG received consultancy fees from Edwards Lifesciences. The Hypotension Prediction Index algorithm is proprietary to Edwards Lifesciences LLC. None of the investigators of the Amsterdam UMC have any form of (in)direct ownership in the algorithm, software or hardware of Edwards, and/or subject of this study. Also, no rights or claims to rights exist that might lead to financial gains for any of the authors or the Amsterdam UMC as an institution. BFG and DPV received consultancy fees and research grants from Philips outside the submitted word. MWH is executive section editor Pharmacology with *Anesthesia & Analgesia*. He received consultancy fees from Eurocept BV and speakers' fees from Eurocept and CSL Behring. JS, JMM, BJPS, and LH declare that they have no conflict of interest.

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Edward Lifesciences (for the parent HYPE trial). Edwards Lifesciences, the manufacturer of the Hypotension Prediction Index, provided funding of the trial after design of the trial by the investigators. The HYPE trial and its substudies are investigator initiated and the investigators will remain owner of all data and rights to publication. Edwards Lifesciences was not involved in design and conduct of the study, collection, management, analysis, interpretation of the data, preparation and review of this manuscript. Also, Edwards Lifesciences did not have to approve the manuscript; and had no decision to submit the manuscript for publication.

REFERENCES

1. Roshanov PS, Rochwerg B, Patel A, et al. Withholding versus continuing angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers before noncardiac surgery: an analysis of the vascular events in noncardiac surgery patients cohort evaluation prospective cohort. Anesthesiology 2017; 126: 16e27
2. Lienhart A, Auroy Y, Pequignot F, et al. Survey of anesthesia-related mortality in France. Anesthesiology 2006; 105: 1087e97
3. Monk TG, Bronsert MR, Henderson WG, et al. Association between intraoperative hypotension and hypertension and 30-day postoperative mortality in noncardiac surgery. Anesthesiology 2015; 123: 307e19
4. Monk TG, Saini V, Weldon BC, Sigl JC. Anesthetic management and one-year mortality after noncardiac surgery. Anesth Analg 2005; 100: 4e10
5. Sun LY, Wijeysundera DN, Tait GA, Beattie WS. Association of intraoperative hypotension with acute kidney injury after elective noncardiac surgery. Anesthesiology 2015; 123: 515e23
6. Walsh M, Devereaux PJ, Garg AX, et al. Relationship between intraoperative mean arterial pressure and clinical outcomes after noncardiac surgery: toward an empirical definition of hypotension. Anesthesiology 2013; 119: 507e15
7. Bijker JB, van Klei WA, Vergouwe Y, et al. Intraoperative hypotension and 1-year mortality after noncardiac surgery. Anesthesiology 2009; 111: 1217e26
8. van Lier F, Wesdorp F, Liem VGB, et al. Association between postoperative mean arterial blood pressure and myocardial injury after noncardiac surgery. Br J Anaesth 2018; 120: 77e83
9. Khanna A, Mao GM, Liu L, et al. Hypotension increases acute kidney injury, myocardial injury and mortality in surgical critical care. Crit Care Med 2018; 46: 71
10. Sessler DI, Khanna AK. Perioperative myocardial injury and the contribution of hypotension. Intensive Care Med 2018; 44: 811e22
11. Hatib F, Jian ZP, Buddi S, et al. Machine-learning algorithm to predict hypotension based on high-fidelity arterial pressure waveform analysis. Anesthesiology 2018; 129: 663e74
12. Wijnberge M, Geerts BF, Hol L, et al. Effect of a machine learning-derived early warning system for intraoperative hypotension vs standard care on depth and duration of intraoperative hypotension during elective noncardiac surgery: the HYPE randomized clinical trial. JAMA 2020; 323: 1052-60
13. Wijnberge M, Schenk J, Terwindt LE, et al. The use of a machine-learning algorithm that predicts hypotension during surgery in combination with personalized treatment guidance: study protocol for a randomized clinical trial. Trials 2019; 20: 582
14. Wesselink EM, Kappen TH, Torn HM, Slooter AJC, van Klei WA. Intraoperative hypotension and the risk of postoperative adverse outcomes: a systematic review. Br J Anaesth 2018; 121: 706e21
15. Salmasi V, Maheshwari K, Yang D, et al. Relationship between intraoperative hypotension, defined by either reduction from baseline or absolute thresholds, and acute kidney and myocardial injury after noncardiac surgery a retrospective cohort analysis. Anesthesiology 2017; 126: 47e65
16. Dindo D, Demartines N, Clavien PA. Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. Ann Surg 2004; 240: 205e13
17. Castor EDC. Castor electronic data capture 2019. Available from: https://castoredc.com. [Accessed 28 August 2019]
18. R Core Team. R: a language and environment for statistical computing. Vienna, Austria: R Foundation for Statistical Computing; 2018
19. Barber AE, Shires GT. Cell damage after shock. New Horiz 1996; 4: 161e7

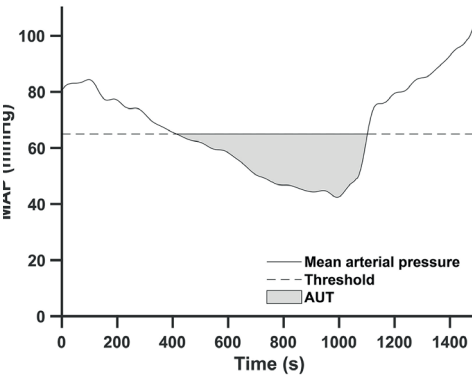
20. Vincent JL, De Backer D. Circulatory shock. New Engl J Med 2013; 369: 1726e34
21. De Backer D, Orbegozo Cortes D, Donadello K, Vincent JL. Pathophysiology of microcirculatory dysfunction and the pathogenesis of septic shock. Virulence 2014; 5: 73e9
22. Tuchschmidt JA, Mecher CE. Predictors of outcome from critical illness. Shock and cardiopulmonary resuscitation. Crit Care Clin 1994; 10: 179e95
23. Bijker JB, van Klei WA, Kappen TH, van Wolfswinkel L, Moons KG, Kalkman CJ. Incidence of intraoperative hypotension as a function of the chosen definition: literature definitions applied to a retrospective cohort using automated data collection. Anesthesiology 2007; 107: 213e20
24. Truijen J, van Lieshout JJ, Wesselink WA, Westerhof BE. Noninvasive continuous hemodynamic monitoring. J Clin Monit Comput 2012; 26: 267e78 Handl

LEGENDS SUPPLEMENTAL MATERIAL

Supplementary Figure S1.

Supplementary Table S1. Postoperative characteristics, measured until discharge to a normal care ward. Continuous data are given as median [IQR] unless otherwise specified.

SUPPLEMENTARY FIGURE S1.



AUT: area under the threshold. MAP: mean arterial pressure.

SUPPLEMENTARY TABLE S1.

Postoperative characteristics			
	Non-exposed to HPI n = 26	Exposed to HPI n = 28	*p*-value
Stayed overnight (%)	16 (61.5)	22 (78.6)	0.284
Severe complication (%)	1 (3.8)	3 (10.7)	0.658
Total observation time in minutes	843 [266, 941]	888 [542, 1106]	0.232
Norepinephrine administered (%)	8 (30.8)	9 (32.1)	1.000
Cumulative dose in mcg	1543 [931, 2746]	1903 [1192, 3111]	0.700
Fluid bolus administered (%)	7 (26.9)	9 (32.1)	0.903
Cumulative amount in ml	500 [375, 750]	500 [500, 1000]	0.304
Cumulative fluids administered at midnight	1275 [900, 1800]	1175 [865, 1678]	0.920
Fluidbalance 6 hours after surgery	624 [150, 910]	150 [-132, 631]	0.074
Fluidbalance at midnight	1335 [840, 2050]	1929 [800, 2272]	0.442
Urine output at midnight	690 [450, 800]	600 [430, 785]	0.420
Fluidbalance at midnight first day	500 [151, 1572]	335 [-623, 1460]	0.295

Postoperative characteristics, measured until discharge to a normal care ward. Continuous data are given as median [IQR] unless otherwise specified.

9

The Effect of Intermittent versus Continuous Non-Invasive Blood Pressure Monitoring on the Detection of Intraoperative Hypotension, a Sub-Study

Marije Wijnberge
Björn van der Ster
Alexander P.J. Vlaar
Markus W. Hollmann
Bart F. Geerts
Denise P. Veelo

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ABSTRACT

Intraoperative hypotension is associated with postoperative complications. However, in the majority of surgical patients, blood pressure (BP) is measured intermittently with a non-invasive cuff around the upper arm (NIBP-arm). We hypothesized that NIBP-arm, compared with a non-invasive continuous alternative, would result in missed events and in delayed recognition of hypotensive events. This was a sub-study of a previously published cohort study in adult patients undergoing surgery. The detection of hypotension (mean arterial pressure below 65 mmHg) was compared using two non-invasive methods; intermittent oscillometric NIBP-arm versus continuous NIBP measured with a finger cuff (cNIBP-finger) (Nexfin, Edwards Lifesciences). cNIBP-finger was used as the reference standard. Out of 350 patients, 268 patients (77%) had one or more hypotensive events during surgery. Out of the 286 patients, 72 (27%) had one or more missed hypotensive events. The majority of hypotensive events (92%) were detected with NIBP-arm, but were recognized at a median of 1.2 (0.6–2.2) minutes later. Intermittent BP monitoring resulted in missed hypotensive events and the hypotensive events that were detected were recognized with a delay. This study highlights the advantage of continuous monitoring. Future studies are needed to understand the effect on patient outcomes.

Keywords

hemodynamics, perioperative, anesthesiology, surgery

INTRODUCTION

An association between intraoperative hypotension and postoperative renal insufficiency, myocardial injury and increased mortality in non-cardiac surgical patients has been reported in numerous cohort studies.[1-4] Randomized clinical trials showed that maintaining an optimal blood pressure (BP) during surgery reduced the risk of postoperative organ dysfunction.[5,6] In 2019, the Perioperative Quality Initiative consensus statement concluded that anesthesiologists should aim to maintain a mean arterial pressure (MAP) above 60–70 mmHg during surgery.[7]

Intraoperatively, BP can be monitored continuously or intermittently. The current standard for continuous BP monitoring is invasively via cannulation of the radial artery. Placement of an arterial cannula poses a small risk of developing nerve damage, infection, thrombus formation or a pseudoaneurysm.[8-10] A finger BP cuff employing volume clamp technology allows for non-invasive continuous measurement of BP during surgery (cNIBP-finger).[11] MAP values measured by cNIBP-finger have shown to be comparable to invasive arterial BP.[12-14]

In the vast majority of surgical patients, however, BP is monitored intermittently using an oscillometric method with a non-invasive cuff around the upper arm (NIBP-arm).[15] On average, NIBP-arm is measured every 2–5 min which could potentially lead to a delay in recognition or missed hypotensive events. As intraoperative hypotension occurs frequently and even short durations of intraoperative hypotension may be harmful, wider implementation of continuous monitoring could be of benefit.[2,16,17] A recent randomized controlled trial has shown that continuous versus intermittent monitoring halved the time-weighted average (TWA) of intraoperative hypotension.[18] That study compared two non-invasive BP monitoring techniques, similar to the present study. No studies have yet assessed the delay time between recognition with NIBP-arm versus cNIBP-finger.

Our primary objective was to determine whether use of intermittent (NIBP-arm) compared with continuous (cNIBP-finger) BP monitoring results in missed hypotensive events. This is not a validation study; we purely studied the effect of continuous monitoring. Our second objective was to assess the delay time between continuous and intermittent BP monitoring in the recognition of hypotensive events. We hypothesize that intermittent BP monitoring would result in missed hypotensive events and would result in delayed recognition of hypotensive events. In an exploratory manner, we assessed the effect of NIBP-arm sample interval on the number of missed events and delay time.

METHODS

The present study describes a sub-study from a prior published prospective cohort study.[15] The study is written according to the Strobe guidelines for cohort studies.[19-20] The local medical ethical committee of the Amsterdam University Medical Centers (UMC), location AMC, provided a waiver for the study (W15_080#15.0094, 11 March 2015). The trial was registered at clinicaltrials.gov with registration number NCT03533205. Data were collected in two phases, between April and October 2015 and between May and December 2016. Adult patients (>18 years of age) undergoing surgery were included. During surgery, BP was monitored as per standard care and additionally with cNIBP-finger. Standard care could entail either invasive BP monitoring with cannulation of the radial artery or with oscillometric NIBP-arm monitoring. Subjects were excluded when technical problems or strong local vasoconstriction (i.e., cold fingers) prevented cNIBP-finger measurements.

For this sub-study, those patients receiving NIBP-arm as standard care (opposed to invasive arterial BP monitoring) and experiencing at least one hypotensive event during surgery were selected (see Supplementary Figure S1).

Study measurements

Prior to induction, a cNIBP finger cuff (Nexfin, Edwards Lifesciences Corp., Irvine, CA, USA) was connected to the patient and the heart reference sensor was zeroed at heart level. The Nexfin measured non-invasive finger BP continuously using the volume clamp method. The cuff pressure varied dynamically to keep the volume of the finger arteries under the cuff constant throughout the cardiac cycle.[11,21] The finger BP was reconstructed based on the brachial BP waveform using a physiological transfer function developed employing a large clinical database.[22-23] Care givers were blinded to the Nexfin monitor in order to prevent guidance of clinical practice based on those data.

NIBP-arm was measured with a BP cuff around the upper arm (Comfort Check™ Long, Salter Labs, Arvin, CA, USA). The NIBP-arm cuff was inflated intermittently and the interval was chosen by the treating anesthesiologist. cNIBP-finger was connected contralateral from NIBP-arm to allow continuous monitoring. Per institutional practice, BP was treated when MAP dropped below 65 mmHg.

Data collection

cNIBP-finger data were extracted from the Nexfin device and NIBP-arm data were extracted from the electronical medical records system (EPIC version 2016, EPIC Systems Corporation, Verona, WI, USA and Metavision 5.46.38, iMDsoft, Tel Aviv, Israel). Patient data were collected and de-identified.

Sample size

No sample size analysis was performed as data for the present sub-study were derived from an earlier published prospective cohort study and no inferential statistics were performed.[15] The results from this sub-study analysis are presented using descriptive statistics only.

Data analysis

For the analysis of this study, cNIBP-finger arterial waveform data after the start of surgery (surgical incision) were included. Nexfin samples blood pressure at 200 Hz. Data was extracted from the device after internal online beat-detection was completed. Values for MAP were averaged for every 20 s. Data points during a period of poor or noisy signal quality were excluded from further analyses.[15]

Hypotension was defined as a cNIBP-finger MAP below 65 mmHg for at least one minute.[7] cNIBP-finger MAP was used as reference standard. cNIBP-finger-determined hypotension was presented as total number of hypotensive events, number of hypotensive events per patient, absolute time spent in hypotension, percentage of time spent in hypotension during surgery, the area under the threshold and the time-weighted average in hypotension. The TWA of hypotension is measured by calculating the area under the threshold (AUT) divided by the total duration of surgery: time-weighted average = (depth of hypotension in millimeters of mercury below a MAP of 65 mmHg × time in minutes spent below a MAP of 65 mmHg)/total duration of the operation in minutes.[24-25]

NIBP-arm intermittent data points were interpolated to allow time synchronization between cNIBP-finger and NIBP-arm (Supplementary Figure S2). All patients were visually checked for time synchronization, independently by two authors (BS and MW).

Primary endpoint: missed hypotensive events were calculated as cNIBP-finger hypotensive events (MAP below 65 mmHg for more than one minute) not recognized by NIBP-arm. A missed hypotensive event based on >5 mmHg offset between cNIBP-finger and NIBP-arm was not counted as a true missed event.

Because NIBP-arm provides intermittent data, one NIBP-arm data point of a MAP below 65 mmHg was sufficient to count as a recognized event. For the missed hypotensive events, the lowest cNIBP-finger MAP value reached and the average cNIBP-finger MAP for the hypotensive events were reported. The average cNIBP-finger MAP was calculated by adding all blood pressure values during the hypotensive event divided by the number of data points. For example, for a hypotensive event with MAP 62, 60, 56, 54, 60, 64 mmHg, the average MAP would be 59 mmHg (all values/6) and the lowest MAP would be 54 mmHg.

Secondary endpoint: the time from recognition of a hypotensive event with cNIBP-finger to recognition with NIBP-arm was presented as the delay in detection time.

Exploratively, the missed events and delay times per NIBP-arm sample interval subgroup were reported. The NIBP-arm sample interval was the sample interval (e.g., 1, 2, 3, 4, 5 or more minutes) most frequently chosen during surgery. As subgroups had different numbers of patients, the missed events per subgroup had to be corrected to allow for comparison. We presented the number of missed hypotensive events as a percentage of the number of patients per subgroup.

Data analyses were performed with MATLAB and SPSS. Continuous data were presented as median with interquartile range (IQR), or mean with standard deviation (SD) when normally distributed. Categorical data were given as frequencies with percentages.

RESULTS

Study population

In the database consisting of 507 patients, a median of 2.3% of the data [IQR 0.6–9.7], which had poor signal quality, was removed. For this sub-study, 404 out of 507 patients receiving NIBP-arm as standard care (and the blinded cNIBP-finger monitoring for study purposes) were selected.[15] The other 103 excluded patients were monitored employing invasive blood pressure monitoring. Out of those 404 patients, 54 had unavailable electronical medical records for NIBP-arm data. Out of the remaining 350 patients, 268 patients (77%) had at least one hypotensive event (cNIBP-finger) during surgery and were included in our analyses. In 24 patients, missed events were based on an offset of >5 mmHg between cNIPB-finger and NIBP-arm and those events were not counted as true missed events.

The median age was 56 years (IQR 43–66) and 54% of the patients were female. The study group was heterogenous in terms of types of surgeries. The majority of anesthesiologists set the NIBP-arm interval at 3 min (43%), followed by 2 min (28%) and 5 min (20%) (see Table 1 and Supplementary Figure S3).

Primary endpoint

In 268 patients, 1006 total hypotensive events were recognized with cNIBP-finger, whereas 80 (8%) of these events were missed by NIBP-arm (see Table 2). The 80 missed events were distributed over 72 patients; in other words, 72 out of the 286 patients (27%) had one or more hypotensive event(s). Sixty-five patients had one missed hypotensive event, six patients had two missed hypotensive event and one patient had three missed hypotensive events (see Supplementary Figure S4). The median lowest MAP for the missed hypotensive events was 59.7 mmHg (IQR 57.0–61.4) and the median average MAP for the missed hypotensive events was 61.9 mmHg (IQR 60.2–63.0).

Characteristics	n = 268 patients
Age	56.0 (43.3-66.0)
Male	123 (46%)
Female	145 (54%)
Height (in cm)	173.0 (166.3-181.0)
Weight (in kg)	75.0 (65.0-88.8)
BMI	24.8 (22.6 – 22.8)
ASA	
I	105 (39.2%)
II	126 (47.0%)
III	37 (13.8%)
IV	0 (0%)
Length of data-collection (in hours)	2.2 (1.4 – 3.2)
Type of surgery:	
Gynaecological	46 (17.2%)
Abdominal	50 (18.7%)
Urological	34 (12.7%)
Vascular	12 (4.5%)
Pulmonary	2 (0.7%)
Trauma and orthopaedic	18 (6.8%)
Ophtalmic	44 (16.4%)
Ear, nose, and throat	37 (13.8%)
Oral and maxillofacial	10 (3.7%)
Plastic	9 (3.4%)
Neuro	6 (2.2%)
NIBP-arm interval (in minutes)	
1	1 (0.4%)
2	75 (28.0%)
3	114 (42.5%)
4	18 (6.7%)
5	54 (20.1%)
>5minutes	6 (2.3%)

Table 1. Baseline data of included patients
Categorical data are presented as counts with percentage. Continuous data are presented as median with interquartile range. Length of data-collection is calculated as measurement duration of cNIBP-finger. BMI = body mass index; ASA = American Society of Anesthesiologists.

Secondary endpoint

The median delay time between the cNIBP-finger and NIBP-arm was 1.2 min (0.6–2.2).

Exploratory analyses

The fraction of missed events, corrected for the number of patients per group, did increase with increasing sample intervals up to five minutes, but paradoxically showed a decrease at a sample interval of five minutes or higher (see Table 3). The delay times increased slightly as the NIBP-arm sample interval increased (see Figure 1). To illustrate, in patients with a NIBP-arm sample interval of two minutes, NIBP-arm detected hypotension a median of 1.0 min (0.5–2.3) later compared with cNIBP-finger. In patients with a NIBP-arm sample interval of five minutes, the median delay time was 1.4 min (0.9–2.5).

	n = 268 patients
Total hypotensive events[a]	1006
Number of hypotensive events per patient[a]	3 (IQR 2-5)
Time in hypotension[a] (minutes)	13.5 (4.8 - 31.25)
% time during surgery in hypotension[a]	11.6 (4.1 - 27.4)
AUC hypotension[a]	81.9 (28.2 – 205.6)
TWA hypotension[a]	0.6 (0.2-1.6)
Total number of missed hypotensive events, NIBP-arm versus cNIBP-finger[b]	80 (8%)
Average BP for missed events[c] (mmHg)	61.9 (60.2 – 63.0)
Lowest missed BP[c] (mmHg)	59.7 (57.0 - 61.4)
Delay in detection time (minutes), NIBP-arm versus cNIBP-finger[d]	1.2 (0.6-2.2)

Table 2. Hypotensive events detected with cNIBP-finger versus NIBP-arm
[a]Continuous blood pressure monitoring was used as the reference standard (cNIBP-finger). [b]Missed hypotensive events were calculated as events detected by cNIBP-finger but not detected by intermittent NIBP-arm monitoring. [c]Number of patients with one of more missed hypotensive events was 72. [d]Delay in detection time was calculated from the onset of hypotension detected by cNIBP-finger to the first detection of the hypotensive events with NIBP-arm. BP= blood pressure.

	Median delay time (in minutes)	Number of patients	Total number of missed events	% missed
1 min	-*	1	0	0%
2 min	1.0 (0.5 – 2.3)	75	13	17%
3 min	1.3 (0.8 - 2.0)	114	42	36%
4 min	1.4 (0.9 – 2.3)	18	7	39%
5 min	1.4 (0.9 – 2.5)	54	17	32%
>5min	- *	6	1	17%

Table 3. Exploratory analyses. Missed events and delay times per NIBP-arm subgroup
*Not calculated due to small sample sizes. Min= minutes.

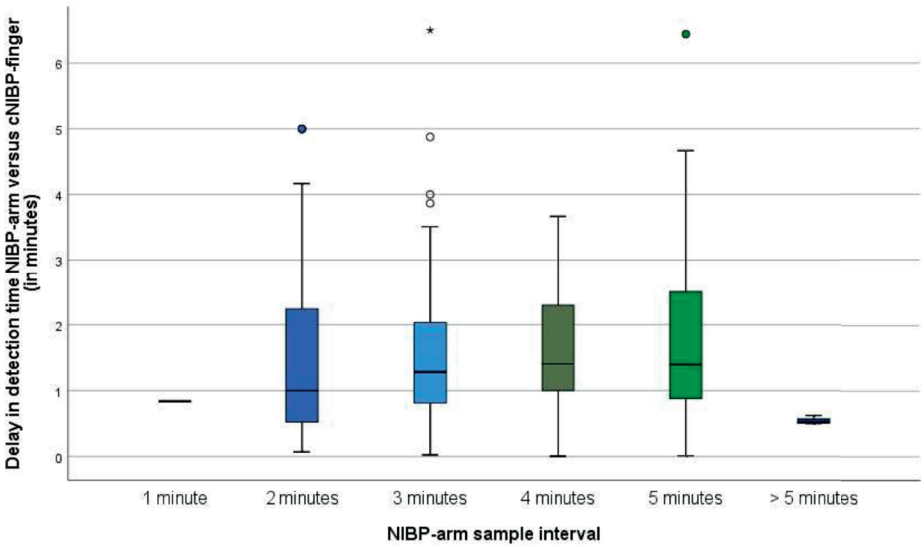

Figure 1. Boxplots demonstrating median delay time per NIBP-arm sample interval. NIBP-arm sample interval was the sample interval the patient experienced the majority of surgical time. To illustrate, if a patient had a duration of surgery of 120 minutes and 10 minutes were sampled at an interval of 2 minutes and the remaining 110 minutes were sampled at an interval of 3 minutes, we listed this as a sample interval of 3 minutes. The round dots represent outliers within the presented scale. The asterisk represents an outlier outside of the presented scale, it represents a 9.7 minutes delay in detection time.

DISCUSSION

Intraoperatively, intermittent BP monitoring resulted in one or more missed hypotensive events in 27% of the patients. The majority of hypotensive events were detected with intermittent BP monitoring; however, hypotensive events were recognized with a median delay time exceeding one minute. The majority of anesthesiologists measure NIBP-arm every two, three or five minutes. Notably, it is not common to measure NIBP-arm every four minutes.

As expected, the delay time between recognition of a hypotensive event increased when the sample interval increased. Paradoxically, more missed hypotensive events were recognized in patients where NIBP-arm was measured every three minutes compared with those with a five-minute sample interval. Selection bias might be the underlying cause of this finding, as for hemodynamically more stable patients the measurement interval is more often set at 5 min. Moreover, the small subgroups in these exploratory analyses might also explain this observation.

This study adds to previous work demonstrating that continuous BP monitoring reduces intraoperative hypotension.[18,26,27] However, our work is different from previous studies as we report missed events and delay time. The hypotensive events that were detected by cNIBP-finger but missed with NIBP-arm occurred between two NIBP-arm

measurements. The lowest median MAP during these missed events was 60 mmHg, which is not considered a very important drop in blood pressure. It makes sense that the missed hypotensive events that resolved before the next NIBP-arm measurement do not represent severe hypotensive events. More severe hypotensive events would present as a delay in detection time as the underlying pathophysiological cause leading to the hypotension would still be present and the hypotension would not resolve spontaneously. However, a brief moment of hypotension between two NIBP-arm measurements could easily be iatrogenic, for example caused by a short drop in venous return because of compression by the surgeon. In addition, it is possible that treatments were administered between two NIBP-arm measurements. Because of the nature of this cohort study, the causes of the short missed hypotensive events remain speculative. In the majority of cases, hypotension was recognized with intermittent monitoring (NIBP-arm), but with a median delay time of 1.2 min. This is an important outcome. Earlier recognition with continuous monitoring enables earlier treatment. One could argue that missing one minute of hypotension is of limited clinical relevance; however, patients often experience more than one episode of hypotension intraoperatively, and thus delay times add up. In the present study we demonstrated a median of three (IQR 2–5) hypotensive events per patient. Additionally, previous studies have suggested even short periods of hypotension to be hazardous.[2]

The continuous non-invasive device we used in this study has substantial costs. It requires an extra monitor system in the operating room and, contrary to NIBP-arm, a new finger BP cuff is required for every patient.[28] A study based on Monte Carlo simulations concludes that prevention of hypotension in a hospital with an annual volume of 10.000 non-cardiac surgical patients is associated with mean cost reductions ranging from 1.2 to 4.6 million American dollars per year. The authors calculated that the estimated mean marginal cost reduction per surgical patient linked to acute kidney injury (AKI) and myocardial injury after non-cardiac surgery (MINS) was around 272 dollars.[29] The costs of non-invasive continuous BP monitoring devices are variable. Not all patients develop intraoperative hypotension. In our study sample, 268 out of 350 patients (77%) had at least one hypotensive event. In these patients, non-invasive continuous monitoring resulted in more hypotensive events being recognized, and earlier detection of these events. Future studies should assess the cost-effectiveness of continuous non-invasive BP monitoring.

This study has some limitations. First, to answer our study question we had to use two different methods to measure BP: the current oscillometric standard (NIBP-arm) and a continuous alternative (NIBP-finger) which utilizes the arterial pressure waveform.[21,30] Although previous studies have demonstrated that—at the group level—cNIBP-finger can be interchangeably used as an alternative for NIBP-arm,[12-14] at the patient level, an offset of >5 mmHg (the validity criterion proposed by the Association for the Advancement of

Medical Instrumentation) between the two devices can exist.[31] We predefined the study to exclude those offset events. Including these events would have resulted in additional missed events.

Second, cNIBP-finger was connected contralaterally from NIBP-arm to allow continuous monitoring. A previous study demonstrated no relevant cNIBP measurement differences between contralateral side measurements.[32]

Third, the 8% missed events in the present study were in between two intermittent BP measurements. As this was not an intervention trial, we do not know if these hypotensive events resolved with or without treatment. The median minimal missed MAP during those missed episodes was 60 mmHg, which is generally considered mild hypotension. However, evidence that intraoperative hypotension is hazardous is increasing and not detecting those hypotensive events in patients could lead to a false sense of safety.[33]

Fourth, we took the cNIBP-finger as the reference standard in this study, and we calculated hypotension endpoints (such as TWA) for the continuous BP monitoring only. Since NIBP-arm measurements are intermittent we were not able to reliably calculate a true TWA for NIBP-arm. An additional disadvantage of the NIBP-arm is that is does not provide an arterial waveform and thus does not allow for pulse wave analysis. Pulse wave analysis can provide hemodynamic variables such as cardiac output (CO) and stroke volume variation (SVV) to assess the underlying cause of hypotension.[25]

Fifth, in this study a hypotensive event was defined as a MAP below 65 mmHg for more than one minute in line with our previous studies.[15,24,25] This is important to keep in mind, as the definition of hypotension determines the number of missed events. For example, if one would define hypotension as any data point below a MAP of 65, the number of missed events would be substantially higher.

Six, the current study is a sub-study of a previously published paper.[15] As such, no sample size analysis and no inferential statistics were performed. The results from this sub-study analysis are presented using descriptive statistics only.

Seven, although the literature regarding the hazardousness of intraoperative hypotension is increasing, evidence is mostly based on associations reported in cohort studies. Randomized clinical trials demonstrating a causal effect between hypotension and worse postoperative outcome are sparse.[5,6] Future trials should aim to assess the impact of prevention of hypotension on postoperative outcomes.

Conclusions

In this single-center intraoperative cohort study, intermittent BP monitoring resulted in one or more missed events in 72 out of 268 patients. The majority of hypotensive events (92%) were detected with intermittent BP monitoring but were recognized at a median of 1.2 min later. As even short durations of hypotension could be hazardous, continuous

monitoring might be preferred. Future studies are needed to determine the effect of continuous BP monitoring on patient outcomes and to assess cost-efficiency.

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Author contributions
Conceptualization, M.W., B.v.d.S. and D.P.V.; methodology, M.W., B.v.d.S. and D.P.V.; software, M.W. and B.v.d.S.; validation, M.W. and B.v.d.S.; formal analysis, M.W. and B.v.d.S.; investigation, M.W. and B.v.d.S.; resources, M.W., B.v.d.S. and D.P.V.; data curation, M.W. and B.v.d.S.; writing—original draft preparation, M.W.; writing—review and editing, B.v.d.S., D.P.V., M.W.H., B.F.G. and A.P.J.V.; visualization, M.W. and B.v.d.S.; supervision, M.W.H., D.P.V., A.P.J.V. and B.F.G.; project administration, M.W.; funding acquisition, B.F.G. and D.P.V. All authors have read and agreed to the published version of the manuscript.

Institutional review board statement
The study was conducted in accordance with the Declaration of Helsinki. Ethical review and approval were waived for this study by the local medical ethical committee of the Amsterdam University Medical Centers, location AMC (W15_080#15.0094, 11 March 2015) due to the non-interventional design of the study. The trial was registered at clinicaltrials.gov with registration number NCT03533205.

Informed consent statement
Informed consent was obtained from all subjects involved in the study.

Data availability statement
Study data is anonymized and securely stored at the Amsterdam UMC.

Conflicts of interest
The funders had no role in the design of the study; in the collection, analyses, or interpretation of data; in the writing of the manuscript, or in the decision to publish the results. Bart Geerts and Denise Veelo received consultancy fees and research grants from Philips and Edwards Lifesciences outside of the submitted work. Alexander Vlaar

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REFERENCES

1. Hallqvist L., Granath F., Huldt E., Bell M. Intraoperative hypotension is associated with acute kidney injury in noncardiac surgery: An observational study. *Eur. J. Anaesthesiol.* 2018;35:273–279. doi: 10.1097/EJA.0000000000000735.
2. Salmasi V., Maheshwari K., Yang D., Mascha E.J., Singh A., Sessler D.I., Kurz A. Relationship between Intraoperative Hypotension, Defined by Either Reduction from Baseline or Absolute Thresholds, and Acute Kidney and Myocardial Injury after Noncardiac Surgery. *Anesthesiology.* 2017;126:47–65. doi: 10.1097/ALN.0000000000001432.
3. Xu L., Yu C., Jiang J., Zheng H., Yao S., Pei L., Sun L., Xue F., Huang Y. Major adverse cardiac events in elderly patients with coronary artery disease undergoing noncardiac surgery: A multicenter prospective study in China. *Arch. Gerontol. Geriatr.* 2015;61:503–509. doi: 10.1016/j.archger.2015.07.006.
4. Monk T.G., Bronsert M.R., Henderson W.G., Mangione M.P., Sum-Ping S.T., Bentt D.R., Nguyen J.D., Richman J.S., Meguid R.A., Hammermeister K.E. Association between Intraoperative Hypotension and Hypertension and 30-day Postoperative Mortality in Noncardiac Surgery. *Anesthesiology.* 2015;123:307–319. doi: 10.1097/ALN.0000000000000756.
5. Futier E., Lefrant J.Y., Guinot P.G., Godet T., Lorne E., Cuvillon P., Bertran S., Leone M., Pastene B., Piriou V., et al. Effect of Individualized vs Standard Blood Pressure Management Strategies on Postoperative Organ Dysfunction Among High-Risk Patients Undergoing Major Surgery: A Randomized Clinical Trial. *JAMA.* 2017;318:1346–1357. doi: 10.1001/jama.2017.14172.
6. Wu X., Jiang Z., Ying J., Han Y., Chen Z. Optimal blood pressure decreases acute kidney injury after gastrointestinal surgery in elderly hypertensive patients: A randomized study: Optimal blood pressure reduces acute kidney injury. *J. Clin. Anesth.* 2017;43:77–83. doi: 10.1016/j.jclinane.2017.09.004.
7. Sessler D.I., Bloomstone J.A., Aronson S., Berry C., Gan T.J., Kellum J.A., Plumb J., Mythen M.G., Grocott M.P.W., Edwards M.R., et al. Perioperative Quality Initiative consensus statement on intraoperative blood pressure, risk and outcomes for elective surgery. *Br. J. Anaesth.* 2019;122:563–574. doi: 10.1016/j.bja.2019.01.013.
8. Nuttall G., Burckhardt J., Hadley A., Kane S., Kor D., Marienau M.S., Schroeder D.R., Handlogten K., Wilson G., Oliver W.C. Surgical and Patient Risk Factors for Severe Arterial Line Complications in Adults. *Anesthesiology.* 2016;124:590–597. doi: 10.1097/ALN.0000000000000967.
9. Scheer B., Perel A., Pfeiffer U.J. Clinical review: Complications and risk factors of peripheral arterial catheters used for haemodynamic monitoring in anaesthesia and intensive care medicine. *Crit. Care.* 2002;6:199–204. doi: 10.1186/cc1489.
10. Cousins T.R., O'Donnell J.M. Arterial cannulation: A critical review. *AANA J.* 2004;72:267–271.
11. Bogert L.W., van Lieshout J.J. Non-invasive pulsatile arterial pressure and stroke volume changes from the human finger. *Exp. Physiol.* 2005;90:437–446. doi: 10.1113/expphysiol.2005.030262.
12. Martina J.R., Westerhof B.E., van Goudoever J., de Beaumont E.M., Truijen J., Kim Y.S., Immink R.V., Jobsis D.A., Hollmann M.W., Lahpor J.R., et al. Noninvasive continuous arterial blood pressure monitoring with Nexfin(R) *Anesthesiology.* 2012;116:1092–1103. doi: 10.1097/ALN.0b013e31824f94ed.
13. Vos J.J., Poterman M., Mooyaart E.A., Weening M., Struys M.M., Scheeren T.W., Kalmar A.F. Comparison of continuous non-invasive finger arterial pressure monitoring with conventional intermittent automated arm arterial pressure measurement in patients under general anaesthesia. *Br. J. Anaesth.* 2014;113:67–74. doi: 10.1093/bja/aeu091.

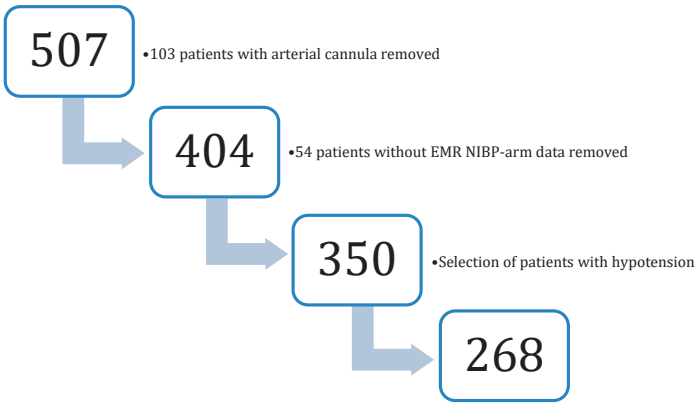
14. Heusdens J.F., Lof S., Pennekamp C.W., Specken-Welleweerd J.C., de Borst G.J., van Klei W.A., van Wolfswinkel L., Immink R.V. Validation of non-invasive arterial pressure monitoring during carotid endarterectomy. *Br. J. Anaesth.* 2016;117:316–323. doi: 10.1093/bja/aew268.
15. Wijnberge M., van der Ster B.J.P., Geerts B.F., de Beer F., Beurskens C., Emal D., Hollmann M.W., Vlaar A.P.J., Veelo D.P. Clinical performance of a machine-learning algorithm to predict intra-operative hypotension with noninvasive arterial pressure waveforms: A cohort study. *Eur. J. Anaesthesiol.* 2021;38:609–615. doi: 10.1097/EJA.0000000000001521.
16. Stapelfeldt W.H., Yuan H., Dryden J.K., Strehl K.E., Cywinski J.B., Ehrenfeld J.M., Bromley P. The SLUScore: A Novel Method for Detecting Hazardous Hypotension in Adult Patients Undergoing Noncardiac Surgical Procedures. *Anesth. Analg.* 2017;124:1135–1152. doi: 10.1213/ANE.0000000000001797.
17. Davies S.J., Vistisen S.T., Jian Z., Hatib F., Scheeren T.W.L. Ability of an Arterial Waveform Analysis-Derived Hypotension Prediction Index to Predict Future Hypotensive Events in Surgical Patients. *Anesth. Analg.* 2019;130:352–359. doi: 10.1213/ANE.0000000000004121.
18. Maheshwari K., Khanna S., Bajracharya G.R., Makarova N., Riter Q., Raza S., Cywinski J.B., Argalious M., Kurz A., Sessler D.I. A Randomized Trial of Continuous Noninvasive Blood Pressure Monitoring During Noncardiac Surgery. *Anesth. Analg.* 2018;127:424–431. doi: 10.1213/ANE.0000000000003482.
19. Von Elm E., Altman D.G., Egger M., Pocock S.J., Gøtzsche P.C., Vandenbroucke J.P. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: Guidelines for reporting observational studies. *Lancet.* 2007;370:1453–1457. doi: 10.1016/S0140-6736(07)61602-X.
20. Cuschieri S. The STROBE guidelines. *Saudi J. Anaesth.* 2019;13:S31–S34. doi: 10.4103/sja.SJA_543_18.
21. Saugel B., Kouz K., Scheeren T.W.L., Greiwe G., Hoppe P., Romagnoli S., de Backer D. Cardiac output estimation using pulse wave analysis-physiology, algorithms, and technologies: A narrative review. *Br. J. Anaesth.* 2021;126:67–76. doi: 10.1016/j.bja.2020.09.049.
22. Gizdulich P., Prentza A., Wesseling K.H. Models of brachial to finger pulse wave distortion and pressure decrement. *Cardiovasc. Res.* 1997;33:698–705. doi: 10.1016/S0008-6363(97)00003-5.
23. Guelen I., Westerhof B.E., van der Sar G.L., van Montfrans G.A., Kiemeneij F., Wesseling K.H., Bos W.J. Validation of brachial artery pressure reconstruction from finger arterial pressure. *J. Hypertens.* 2008;26:1321–1327. doi: 10.1097/HJH.0b013e3282fe1d28.
24. Wijnberge M., Geerts B.F., Hol L., Lemmers N., Mulder M.P., Berge P., Schenk J., Terwindt L.E., Hollmann M.W., Vlaar A.P., et al. Effect of a Machine Learning-Derived Early Warning System for Intraoperative Hypotension vs Standard Care on Depth and Duration of Intraoperative Hypotension During Elective Noncardiac Surgery: The HYPE Randomized Clinical Trial. *JAMA.* 2020;323:1052–1060. doi: 10.1001/jama.2020.0592.
25. Wijnberge M., Schenk J., Terwindt L.E., Mulder M.P., Hollmann M.W., Vlaar A.P., Veelo D.P., Geerts B.F. The use of a machine-learning algorithm that predicts hypotension during surgery in combination with personalized treatment guidance: Study protocol for a randomized clinical trial. *Trials.* 2019;20:582. doi: 10.1186/s13063-019-3637-4
26. Meidert A.S., Nold J.S., Hornung R., Paulus A.C., Zwissler B., Czerner S. The impact of continuous non-invasive arterial blood pressure monitoring on blood pressure stability during general anaesthesia in orthopaedic patients: A randomised trial. *Eur. J. Anaesthesiol.* 2017;34:716–722. doi: 10.1097/EJA.0000000000000690.

27. Benes J., Simanova A., Tovarnicka T., Sevcikova S., Kletecka J., Zatloukal J., Pradl R., Chytra I., Kasal E. Continuous non-invasive monitoring improves blood pressure stability in upright position: Randomized controlled trial. *J. Clin. Monit. Comput.* 2015;29:11–17. doi: 10.1007/s10877-014-9586-2.
28. Gellert G., Bramlage P. Use of the ClearSight(R) System for Continuous Noninvasive Hemodynamic Monitoring during Heart Valve Interventions: Review of the Literature and Single-Site Experience. *Heart Surg. Forum.* 2018;21:E476–E483. doi: 10.1532/hsf.2177.
29. Keuffel E.L., Rizzo J., Stevens M., Gunnarsson C., Maheshwari K. Hospital costs associated with intraoperative hypotension among non-cardiac surgical patients in the US: A simulation model. *J. Med. Econ.* 2019;22:645–651. doi: 10.1080/13696998.2019.1591147.
30. Booth J. A short history of blood pressure measurement. *Proc. R. Soc. Med.* 1977;70:793–799. doi: 10.1177/003591577707001112.
31. Association for the Advancement of Medical Instrumentation; Arlington, VA, USA: American National Standard for Non-Invasive Sphygmomanometers—Part 2: Clinical Validation of Automated Measurement Type.
32. Van der Ven W.H., Kleinsteuber S.P.C., Terwindt L.E., Schenk J., van der Ster B.J.P., Vlaar A.P.J., Hollmann M.W., Veelo D.P., Immink R.V. Ipsilateral and contralateral validation of continuous noninvasive finger blood pressure: Does side matter? *Br. J. Anaesth.* 2021;127:e149–e151. doi: 10.1016/j.bja.2021.07.032.
33. Wijnberge M., Schenk J., Bulle E., Vlaar A.P., Maheshwari K., Hollmann M.W., Binnekade J.M., Geerts B.F., Veelo D.P. Association of intraoperative hypotension with postoperative morbidity and mortality: Systematic review and meta-analysis. *BJS Open.* 2021;5:33609377. doi: 10.1093/bjsopen/zraa018.

LEGENDS SUPPLEMENTAL MATERIAL

Supplemental Figure 1. Flowchart patient selection
Supplemental Figure 2. Example time-matching patients
Supplemental Figure 3. NIBP-arm sample interval
Supplemental Figure 4. Number of missed hypotensive events per patient

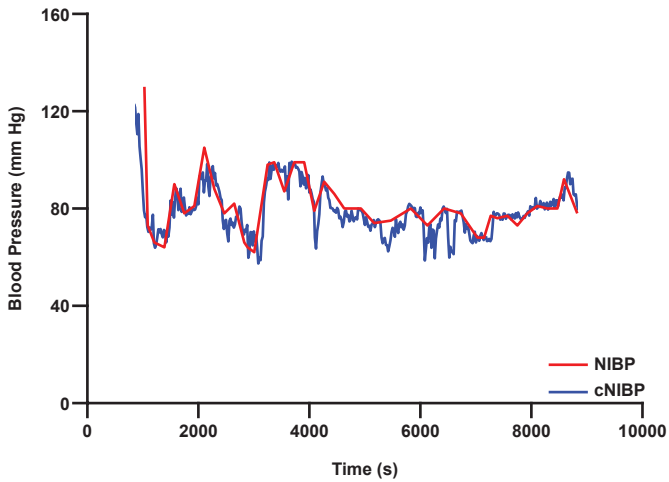
SUPPLEMENTAL FIGURE 1



Flowchart selection patients. The original study had 507 patients[1], first step was selection of patients with non-invasive blood pressure monitoring. Second step was removal of patients with missing NIBP-arm data. Third step was selection of patients with at least one cNIBP-finger hypotensive event. Hypotension defined as a MAP < 65 mmHg for at least one minute.

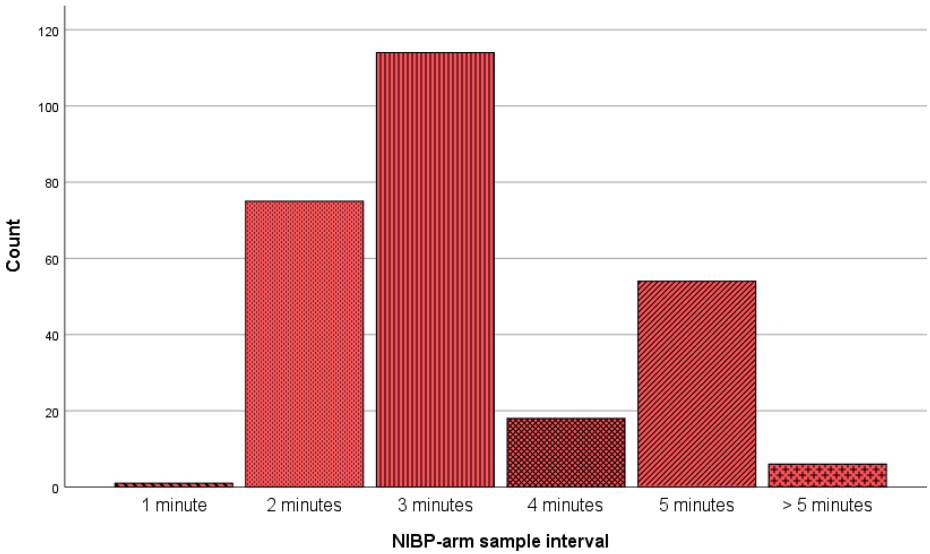
1= Wijnberge M, van der Ster BJP, Geerts BF, et al. Clinical performance of a machine-learning algorithm to predict intra-operative hypotension with non-invasive arterial pressure waveforms: A cohort study. *European journal of anaesthesiology.* 2021;38(6):609-615.

SUPPLEMENTAL FIGURE 2



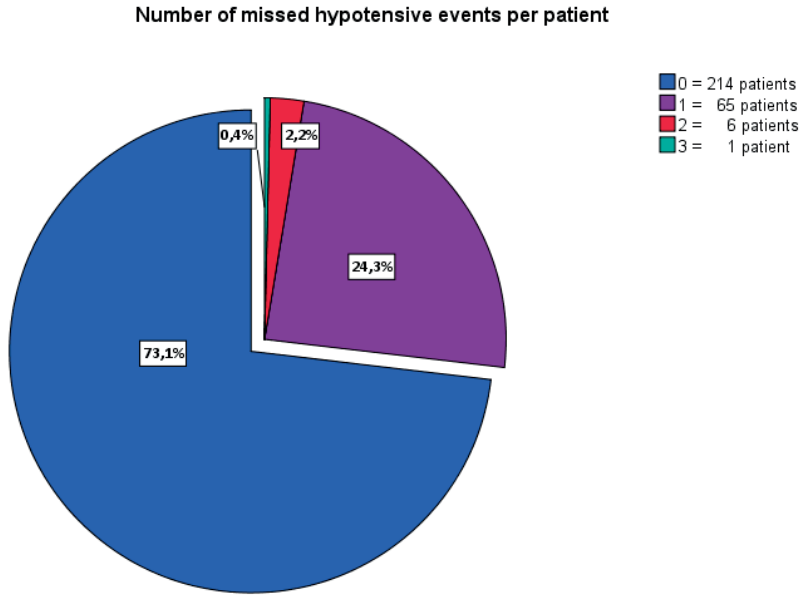
Example of time synchronization continuous (cNIBP-finger) and intermittent (NIBP-arm) blood pressure monitoring. Blue line = cNIBP-finger. Red line = NIBP-arm.

SUPPLEMENTAL FIGURE 3



Number of patients per NIBP-arm sample interval. The majority of anesthesiologists set the NIBP-arm interval the majority of the anesthesia time at 3 minutes (n=114, 43%), followed by 2 minutes (n=75, 28%) and 5 minutes (n=54, 20%).

SUPPLEMENTAL FIGURE 4



Number of missed events per patient

Θάλασσα πλατιά
σ' αγαπώ γιατί μου
μοιάζεις
θάλασσα βαθιά
μια στιγμή δεν ησυχάζεις
λες κι έχεις καρδιά
τη δικιά μου την μικρούλα
την καρδιά

Oh wide sea
I love you because you
look like me
Oh deep sea
you don't calm down not
even for a moment
as if you have a heart
my own tiny heart

Thalassa Platia
Hatzidakis

Daphne Psaltaki

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10

Clinical performance of a machine learning algorithm to predict intraoperative hypotension with non-invasive arterial pressure waveforms: an observational study

Marije Wijnberge
Björn van der Ster
Bart F. Geerts
Friso de Beer
Charlotte Beurskens
Dina Emal
Markus W. Hollmann
Alexander P.J. Vlaar
Denise P. Veelo

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SUMMARY

Background

Intraoperative hypotension is associated with adverse postoperative outcomes. A machine-learning-derived algorithm developed to predict hypotension based on arterial blood pressure (ABP) waveforms has shown to significantly reduce intraoperative hypotension. The algorithm calculates the likelihood of hypotension to occur in the following minutes, expressed as a Hypotension Prediction Index (HPI) with ranges from 0-100. Currently, HPI is only available for patients monitored with invasive ABP which is restricted to high-risk surgeries and populations. In this study the performance of HPI, employing non-invasive continuous ABP measurements, is assessed.

Objectives

The first aim was to compare the performance of the HPI algorithm, using non-invasive versus invasive ABP measurements, at a mathematically optimal HPI alarm threshold (Youden index).

The second aim was to assess the performance of the algorithm using a HPI alarm threshold of 85 which is currently used in clinical trials. Hypotension was defined as a mean arterial pressure (MAP) below 65 mmHg for at least one minute. The predictive performance of the algorithm at different HPI alarm thresholds (75 and 95) was studied exploratory.

Design

Observational cohort study

Setting

Tertiary academic medical centre

Patients

507 adult patients undergoing general surgery

Results

The performance of the algorithm with invasive and non-invasive ABP input was similar. A HPI alarm threshold of 85 showed a median time from alarm to hypotension of 2.7 minutes (IQR 1.0 – 7.0) with a sensitivity of 92.7 (95%CI 91.2-94.3), specificity of 87.6 (95%CI 86.2-89.0), positive predictive value of 79.9 (95%CI 77.7-82.1) and negative predictive value of 95.8 (95%CI 94.9-96.7). A HPI alarm threshold of 75 provided a lower positive predictive value but a prolonged time from prediction to actual hypotension.

Conclusions

This study demonstrated that the algorithm can be used employing continuous non-invasive ABP waveforms. This opens up the potential to predict and prevent hypotension in a larger patient population.

Trial registration

Clinical trials registration number NCT03533205.

INTRODUCTION

Intraoperative hypotension is a clinically challenging problem; it occurs frequently and is associated with postoperative morbidity and mortality.[1-5] Current treatment of intraoperative hypotension is mostly reactive, as early haemodynamic instability is typically preceded by subtle changes of physiological variables that are difficult to discern.[6,7]

An algorithm aimed to help solve this problem was developed by using machine learning to interpret the arterial waveform. This algorithm, named the Hypotension Prediction Index (HPI), provides the anaesthesiologist with a number between 0-100 that corresponds to the likelihood of hypotension to occur in the following minutes. HPI was validated with good sensitivity and specificity in patients receiving invasive arterial blood pressure (ABP) monitoring [8,9] and its use has been shown to significantly reduce intraoperative hypotension.[10,11]

Since invasive ABP monitoring is mainly restricted to high-risk surgeries and populations [12-15], we set out to validate HPI, employing continuously, non-invasively measured ABP using the volume clamp technology (cNIBP).[16] To compare performance of HPI using invasive versus non-invasive ABP input, the same performance assessment methodology as described previously was used.[8] We hypothesised that the sensitivity and specificity using non-invasive ABP measurements would be above 80 but lower compared with those employing invasive ABP input.

All previous validation studies of the algorithm employed the mathematical optimal HPI alarm threshold calculated using the Youden Index [8,9,17] The hypotensive event was taken as starting point and next it was determined whether HPI crossed the threshold going backwards in time. However, the Youden Index does not take the positive and negative prediction into account and in previous validation studies the HPI Youden Index ranged between 30 and 40, resulting in hypotensive events in only 41-44% of the cases.[9,17] Also, in clinical practise the HPI alarm, rather than hypotension, is a more natural starting point for further evaluation. To overcome these limitations, for our second objective we used the clinically more relevant HPI threshold of 85 currently used in clinical trials.[10,11,18,19] Crossing the HPI alarm threshold was our starting point and we searched forward in time for hypotension. For exploratory purposes the clinical analysis was repeated with various HPI alarm thresholds.

MATERIAL AND METHODS

Study design and participants

This prospective validation study was performed according to STROBE and STARD guidelines.[20,21] Because of the non-interventional design of the study, a waiver was provided (W15_080#15.0094, March 11, 2015) by the local medical ethical committee, Amsterdam UMC, University of Amsterdam. The clinical trials registration number is NCT03533205. Data were collected in two phases, between April and October 2015 and between May and December 2016 in the Amsterdam UMC, University of Amsterdam, The Netherlands. In these two periods, adult patients (>18 years of age) undergoing mixed general surgery were consecutively included in the study. Because of the limited number of available cNIBP devices, we were not able to include all eligible patients. Preference was given to patients undergoing non-cardiac surgery and to patients undergoing surgeries with a planned duration of more than two hours because those patients could provide a sufficient amount of high quality data. Subjects were only excluded in case of technical problems or when strong local vasoconstriction (i.e., cold fingers) prevented cNIBP measurements.

Data collection

Prior to induction of anaesthesia, a cNIBP finger cuff (Nexfin, Edwards Lifesciences Corp, Irvine, CA) was connected to a finger of the patient and the heart reference sensor was zeroed at heart level. The Nexfin monitor measured the finger ABP using the volume clamp method with the Physiocal set point method. The cuff pressure varied dynamically to keep the volume of the finger arteries under the cuff constant throughout the cardiac cycle.[16,22] Nexfin reconstructs the finger ABP to the brachial ABP waveform using a physiological transfer function developed on a large clinical database.[23,24] The cNIBP MAP has shown to agree well with invasive (arterial line) MAP measurements.[25,26] In these studies the mean differences between MAP values. were less than the mean 5 mmHg with a standard deviation of 8 mmHg criterion proposed by the Association for the Advancement of Medical Instrumentation.[27]

During surgery, ABP was monitored according to standard care, which could entail either invasive ABP measurement with a radial arterial catheter (20-gauge arterial catheter) or NIBP-arm, measured intermittently with a ABP cuff around the upper arm (Comfort Check™ Long, Salter Labs). When possible, the cNIBP finger cuff was connected contralateral from the NIBP-arm cuff in order to have continuous data collection with the Nexfin device. The HPI algorithm was not available on the Nexfin monitors and was thus not used to guide treatment in this study. According to institutional practice, ABP was treated when MAP dropped below 65 mmHg.

The continuous non-invasive ABP waveform data were downloaded from the Nexfin device. Patient and treatment data (EPIC version 2016, PDMS Metavision 5.46.38) were collected and de-identified.

Sample size analysis

The sample size calculation showed that 492 patients were needed to show 80% sensitivity of the HPI algorithm's ability to predict hypotensive events at a significance level of 0.05, with an assumed prevalence of at least one hypotensive event per patient of 50%.

Data analyses

For the analyses of this study, only cNIBP waveform data after the start of surgery (incision) were included and the cNIBP measurement was continued until the end of anaesthesia. The HPI algorithm as developed for invasive ABP was applied to the non-invasive ABP waveform data for the calculation of HPI which included pre-processing, artefact rejection and calculation of waveform features.[8] All further data analyses were performed after computing 20 second period averages of MAP and HPI which is similar to previous validation analyses.[8,9,17] The 20 second period averages are also similar to the current display of HPI on monitors. For both objectives, a hypotensive event was defined as a cNIBP MAP < 65 mmHg for at least one minute.

Hypotension was characterised by the total number of hypotensive events, the total duration of hypotension in minutes per patient, the percentage of time spent with hypotension during surgery and by the time-weighted average of hypotension during surgery. The time-weighted average combines the duration and severity (minimal MAP reached) of hypotension, corrected for the total time of surgery.[10]

Our first objective was to compare the performance of the HPI algorithm with continuous non-invasive (cNIBP) versus invasively determined ABP. As invasive ABP comparator the results as published previously by Hatib et al, were used [8]. To be able to compare the results the exact same methodology was followed [28]. The first analysis assessed whether hypotensive events were correctly predicted by the algorithm. This was done by taking hypotensive events as starting point, and looking back in time over a certain window. For time windows -5, -10 and -15 minutes the receiver operating curves (ROC) curves were constructed and the area under the ROC-curve (AUC) was calculated. Similar to the study by Hatib et al., sensitivity, specificity, positive predictive value and negative predictive value (NPV) were determined at the mathematically optimal Youden Index HPI alarm threshold. At this HPI alarm index sensitivity and specificity are equally weighed and their difference is at its minimum and the sum of sensitivity and specificity and its maximum.[28] The Youden Index was used as a cut-off value, meaning that any HPI

below the Youden Index was considered a negative prediction (no alarm) and any HPI above the Youden Index was considered a positive prediction (alarm).

During the development of the HPI algorithm, hypotension was defined as a MAP below 65 mmHg and non-hypotension as a MAP above 75 mmHg. Similar to the analyses by Hatib et al. all MAP values between 65-75 mmHg were excluded from the first analysis.[8]

The method as described for our first objective is similar to previous validation studies [8,9,17]; first the mathematical optimal HPI alarm threshold using the Youden Index was calculated and then the performance at this specific HPI alarm threshold was calculated. In this method, hypotension was the starting point. Next it was determined whether HPI crossed this mathematical optimal threshold going backwards in time. As stated before, the mathematically optimal HPI threshold according to Youden means that the sensitivity and specificity are equally weighted meaning their difference is at its minimum and the sum of sensitivity and specificity were maximal. [28] However, the Youden Index does not take the positive and negative prediction into account. We considered this method to be suboptimal with regard to its clinical relevance for two reasons: First, the mathematical optimal HPI Youden Index alarm thresholds in previous validation studies ranged between 30 and 40, five minutes before a hypotensive event. [8,9,17] This, however, resulted in hypotensive events in only 41-44% of the cases.[9,17] Initiating treatment at this mathematically optimal HPI Youden Index could result in overtreatment. Second, in clinical practise the HPI alarm, rather than hypotension, is the starting point.

Therefore, our second, and main, objective was to perform a validation analysis from a clinical point of view, a forward analysis, with a HPI alarm threshold of 85. This means that any HPI value for more than one minute below 85 was considered a negative prediction and any HPI value above 85 for more than one minute, was considered a positive prediction. If, within a one-minute window, the HPI was above 85 we considered this as an alarm. From the start of this alarm, hypotension (< 65 mmHg) was checked for over the next 20 minutes window of MAP. The time between the alarm and the onset of hypotension was stored. If the HPI did not raise above 85, we considered this a negative prediction. Every 20 minutes timeframe could count as either a true positive, false positive, true negative or false negative prediction. To make sure that each alarm and each hypotensive event was counted only once in the analysis, the window was shifted forward 20 minutes in time following a true positive, false positive or a false negative detection. Non-hypotensive events were counted as one event for every 20 minutes (three for an hour, six for 2 hours and so on). The time from HPI alarm to event, sensitivity, specificity, positive predictive value and NPV were determined. Employing this forward method determination of a ROC is not feasible.

In the paper by Hatib et al., describing the development of the HPI algorithm and the validation using invasive ABP, MAP values between 65-75 mmHg were excluded from

the analyses.[8] In clinical practice, however, the HPI algorithm will also be used in this range, therefore for this second analysis we decided to include MAP values between 65-75 mmHg.

Validation of the HPI algorithm is disturbed by haemodynamic interventions, e.g. administration of vasopressors (in our hospital the most used vasopressors are ephedrine, phenylephrine and norepinephrine) or fluids. In current practice, most vasopressors are used in a reactive way, after the hypotensive events have occurred. However, in some cases physicians might have used vasopressors to prevent hypotension. This could result in a valid prediction falsely labelled as 'false positive'. Since fast changes in MAP are most likely related to drug administration, we defined haemodynamic interventions as a baseline MAP < 70 mmHg and either 1) a delta increase in MAP of 5 mmHg in 20 seconds or 2) an 8 mmHg increase in MAP in a two-minute period. This definition of interventions is based on previous publications.[9,17] Segments with a detected haemodynamic intervention were not used for further analyses. Lack of accuracy of our Patient data monitoring system (PDMS) in our hospital and mostly retrospective registration of haemodynamic interventions for hypotensive episodes made us employ this methodology.

Post-hoc we determined the lowest MAP reached after a false positive alarm to assess the MAP range in which the HPI algorithm became false positive.

Exploratory, the HPI alarm threshold was altered (75-95 range) to assess the effect of a lower and higher HPI alarm setting on the performance of the algorithm.

All data processing and statistical analyses were done with MATLAB and Statistics Toolbox Release 2014a (The MathWorks, Inc., Natick, MA). Continuous data were presented as median with interquartile range (IQR), or mean with standard deviation when normally distributed. Categorical data were given as frequencies with percentages.

RESULTS

Patient characteristics

We included 568 adult patients that underwent anaesthesia, 61 patients were excluded because of technical problems with the Nexfin device or inability to measure ABP at the finger, leaving 507 patients for analyses. Patient characteristics of our cohort are presented in Table 1. In 404 (80%) patients, ABP was monitored with NIBP-arm, in the remaining 103 (20%) ABP was monitored via an arterial line in the radial artery. Per patient, a median of 2.3% of data [IQR 0.6 - 9.7] with poor signal quality was removed.

In 376 (74.1%) patients, at least one hypotensive event occurred during surgery. The total number of hypotensive events was 2,236 (Table 2).

Baseline data	
Total number of patients	507
Age	54.7 (±5.3)
Male	226 (45%)
Height (in cm)	173 (±10.2)
Weight (in kg)	78.2 (±16.7)
BMI	25.9 (±4.9)
ASA	
I	177 (34.9%)
II	244 (48.1%)
III	84 (16.6%)
IV	2 (0.4%)
Length of surgery (in hours)	2.3 [1.4 -3.5]
Type of surgery:	
Gynaecological	91 (17.9%)
Abdominal	133 (26.3%)
Urological	55 (10.8%)
Vascular	19 (3.7%)
Cardiopulmonary	15 (3.0%)
Trauma and orthopedic	33 (6.5%)
Ophtalmic	61 (12.2%)
Ear, nose, and throat	49 (9.7%)
Oral and maxillofacial	61 (3.2%)
Plastic	18 (3.6%)
Neurological	16 (3.2%)
Blood pressure measurement via arterial line	103 (20%)
Non-invasive arterial blood pressure measurement	404 (80%)
Surgery>two hours	303 (60%)
Number of patients with at least one event	389 (77%)

Table 1. Baseline data of included patients
Categorical data are presented as counts with percentage. Continuous data are presented as mean with standard deviation. BMI = body mass index; ASA = American Society of Anesthesiologists.

Data for all 507 patients	
Total hypotensive events	2,236
Total duration of hypotension per patient (in minutes)	8.3 [0.0 – 25.8]
Total duration of hypotension (% of case time)	6.1 [0.0 – 19.0]
Area under MAP 65 mmHg threshold (in mmHg x minute)	43.0 [0.0 – 154.7]
Time weighted average MAP 65 mmHg threshold (in mmHg)	0.3 [0.0 – 1.2]

Table 2. Duration of hypotension
All data is represented as median with interquartile range []. MAP = mean arterial pressure. Time weighted average = area under MAP 65 mmHg threshold divided by the surgical case time (per individual patient).

Objective 1: Comparison of the HPI algorithm with invasive versus non-invasive arterial pressure waveforms, using the mathematical optimal Youden index HPI alarm threshold.

The performance of the algorithm with non-invasive ABP resulted in AUC's of 0.93, 0.91 and 0.90 at five, ten and 15 minutes prior to the hypotensive event (Appendix Figure 1). The performance of the algorithm was similar for invasive compared to non-invasive ABP input (Table 3).

HPI alarm threshold	Time to event	AUC	Sens	Spec	PPV	NPV
HPI in combination with invasive blood pressure measurements (Hatib et al)						
>39	5	0.95 (0.93-0.96)	86.8 (83.6-89.9)	88.5 (84.9-92.0)	93.2 (91.0-95.3)	78.6 (74.3-82.9)
>37	10	0.92 (0.90-0.94)	84.2 (79.6-88.8)	84.3 (80.2-88.4)	83.6 (79.4-87.8)	84.8 (80.8-88.8)
>36	15	0.91 (0.89-0.94)	83.6 (78.2-89.0)	83.3 (78.9-87.8)	74.0 (67.9-80.1)	90.0 (86.5-93.4)
HPI in combination with non-invasive blood pressure measurements (this study)						
>34	5	0.93 (0.92-0.94)	86.6 (84.1-89.2)	85.5 (83.3-87.6)	88.2 (85.7-90.7)	83.6 (80.5-86.7)
>32	10	0.91 (0.90-0.92)	83.7 (80.1-87.4)	83.4 (78.4-88.4)	78.9 (75.0-82.8)	87.4 (84.5-90.2)
>31	15	0.90 (0.89-0.91)	81.7 (77.1-86.3)	82.3 (73.5-91.1)	70.3 (65.3-75.4)	89.7 (87.0-92.4)

Table 3. Objective 1: Comparison of the performance of the algorithm with invasive versus non-invasive BP input. Performance of the algorithm presented in area under the ROC curve (AUC), sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV). All presented with 95%CI.

Objective 2: Performance of the algorithm using the clinical HPI alarm threshold of 85

The second analysis, mimicking the use of the algorithm in clinical practice demonstrated, that the median time from HPI alarm, at 85 HPI alarm threshold, to a hypotensive event was 2.7 minutes (IQR 1.0 – 7.0). With a sensitivity of 92.7 (95%CI 91.2-94.3), a specificity of 87.6 (95%CI 86.2-89.0), a positive predictive value of 79.9 (95%CI 77.7-82.1) and a NPV of 95.8 (95%CI 94.9-96.7) (Table 4). The post-hoc analysis revealed the false positives to be in the MAP range of 65-75 mmHg (Figure 1).

Exploratory analyses:

The performance of the algorithm at a HPI alarm threshold of 75 showed an increased median time to hypotension of 3.0 minutes (IQR 1.0-7.7) at the cost of a lower positive predictive value of 75.3 (CI 73.0-77.6). At an HPI alarm threshold of 95 the time until

hypotension was shortened to 1.3 minutes (IQR 0.7-4.3) with a positive predictive value of 90.4 (CI 88.6-92.2) (Supplemental Table 1).

	Hypotension	No hypotension
HPI > 85	1,017 (a)	256 (b)
HPI <85	80 (c)	1,806 (d)

Sensitivity	Specificity	PPV	NPV
92.7 (91.2-94.3)	87.6 (86.2-89.0)	79.9 (77.7-82.1)	95.8 (94.9-96.7)

Table 4. Objective 2: Clinically relevant analysis with HPI alarm threshold of 85.
Two by two table. a True positives. b. False positives c. false negatives. d. true negatives. Sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) in % with 95% CI ().

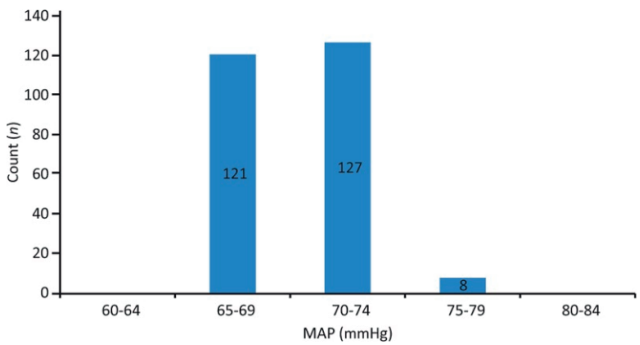

Figure 1. Objective 2: mean arterial pressure values corresponding with false positives.

DISCUSSION

The aim of this study was to evaluate the performance of a machine learning derived algorithm to predict intraoperative hypotension, using non-invasive ABP waveform data. The main findings of this study were: 1) the HPI algorithm performs similarly on invasive and non-invasive ABP data. This enables prediction and potentially prevention of hypotension in a much larger patient population for which hypotension and complications occur but arterial lines are less frequently used. 2). At the clinically relevant HPI alarm threshold of 85 the median time from HPI alarm to hypotension was 2.7 minutes (IQR 1.0 - 7.0) with a high negative predictive value but a lower positive predictive value meaning that the algorithm nearly never missed hypotension but was regularly false positive in the MAP 65-75 mmHg zone. Exploratory analyses demonstrated that modifying the HPI alarm threshold (75-85-95) altered the time from alarm to event and positive predictive value balance, i.e. increasing the HPI alarm threshold

to 95 increased the positive predictive value but lowered the time from HPI alarm to hypotension.

Our study builds on the work of Hatib et al., Davies et al. and Maheswari et al. [8,9,17] Hatib et al. and Davies et al. validated HPI in combination with invasive ABP monitoring.[8,9] Hatib et al. found, at a HPI threshold of 37, 10 minutes before hypotension a sensitivity of 84.2, a specificity of 84.3, a positive predictive value of 83.6 and a negative predictive value of 84.8 (Table 3). Only 20% of patients in our academic centre receive invasive monitoring during surgery (table 1). Arterial cannulation imposes a small risk of nerve damage, infection or pseudoaneurysm and is therefore currently restricted to be used in specific surgical cases only.[12] Therefore, validation of HPI in the context of non-invasive ABP measurements is relevant. Using the mathematical optimal HPI alarm threshold (Youden Index), the performance of the HPI algorithm with non-invasive ABP was only slightly worse compared to the performance with invasive ABP input. As the HPI algorithm is developed employing invasively measured ABP, the most likely factor explaining this difference in performance is the indirect measurement method of the cNIBP-finger. Compared to the invasive reference, the non-invasive method has a larger likelihood of measurement errors, which trickles down to the transformation from the finger ABP to the brachial ABP and ultimately to the performance of the HPI algorithm to predict intraoperative hypotension. This is in line with the results reported by Maheshwari et al. [17]

For our second objective, we assessed the performance of the algorithm from a clinical perspective, using the HPI alarm threshold of 85. The algorithm predicts hypotension with a median time from alarm to hypotension of 2.7 minutes with an interquartile range from one to seven minutes.

Our analysis revealed, that the algorithm predicts hypotension with high sensitivity (92.7). HPI was false negative once every twelve hypotensive events, meaning that, when using this algorithm, perioperative hypotensive events are rarely missed. Worth mentioning, that this also included cases where the HPI was above the 85 alarm threshold shortly (i.e. 20 seconds) before the hypotensive event.

The specificity was adequate (87.6%), illustrating that in the absence of hypotension, the HPI was below 85 for most of the time. During surgery the duration of non-hypotension far exceeds the duration of hypotension. This could lead to unjustified inflation of the true negatives. We aimed to tackle this problem by dividing surgeries in 20 minutes time-frames, such that every 20 minutes could only count for one true positive, false positive, true negative or false negative.

The NPV was high (95.8%), reflecting that the likelihood of experiencing hypotension in the following minutes should be low when the HPI is below 85. The positive predictive value value was 80%, illustrating that the HPI was falsely positive every one out of five alarms. This can be annoying, might facilitate alarm fatigue and carries the risk of

overtreatment. In our post-hoc analyses we found almost all false positives (figure 1) to have corresponding MAP values in the range of 65-75 mmHg. It is debatable whether treatment in this ABP range is harmful. [29] In this study HPI was blinded and we did not study how to manage possible false positive alarms. Our advice based on a recently published clinical trial evaluating efficacy of HPI, is to when in doubt, wait at least one minute and assess the secondary screen for treatable underlying causes. If HPI drops this probably was a false positive alarm. If HPI remains high, our current advice is to start treatment.[10]

The results from our second objective represent the anaesthetist experience using the algorithm in the operating theatre. Our exploratory analyses with different HPI alarm thresholds demonstrate that the higher the HPI alarm threshold the higher the positive predictive value but the shorter the time to event (Supplemental Table 1). This is in line with previous studies. [9] With a HPI alarm threshold above 85 the median time to hypotension in our dataset was less than three minutes, which is ample time to prepare for the appropriate intervention to be taken. To create more time from HPI alarm to hypotension, the HPI alarm threshold could be lowered at the cost of potential overtreatment (a lower positive predictive value). Lowering false positive alarms would require to increase the HPI alarm threshold, however, at the expense of a shortened time to hypotension and thus less time to prepare for the appropriate intervention.

Our study has several limitations. The use of real-time predictive algorithms in clinical practice is new and a there is not yet a universally accepted way to validate these continuous predictive algorithms. As a result, different validation studies are not one-on-one comparable. Comparing methodology of different validation studies before comparing the results is crucial. [30]

Second, interventions based on HPI interact with the cause-effect relationship the algorithm wants to quantify. As the cause of the (potential) hypotensive event is taken away, hypotension might not occur and this might incorrectly be deemed as a false positive alarm. Therefore, we corrected for employed haemodynamic interventions. This methodology was the best available but has obvious limitations.

Third, the time to hypotension is not fixed in the machine learning model but rather depends on the individual patient. In our database, the median time from HPI alarm to hypotension was less than three minutes and in previous studies with a HPI alarm threshold of 85 this was reported to be between four and six minutes. [9,17] The average time to hypotension seems to depend on the patient population. Based on the time from HPI alarm to hypotension, different HPI thresholds might be optimal for different patient populations. Generally, in surgical patients, the time to event is expected to be shorter due to rapid haemodynamic changes whereas in the Intensive Care Unit, haemodynamic changes are usually more gradual and the time to event is expected to be longer.

Fourth, we analysed the ability of the machine learning model to detect intraoperative hypotension after surgical incision. We did not analyse the period from induction to surgical incision.

Fifth, this study demonstrates good performance of HPI in combination with non-invasive continuous ABP monitoring. Future studies should aim to assess whether prediction of hypotension in these low-medium risk patients will result in reduction of hypotension, leads to less postoperative complications and will be cost-effective.

CONCLUSIONS

We demonstrated that an algorithm to predict intraoperative hypotension developed on invasive ABP input was able to predict impending intraoperative hypotension with similar sensitivity and specificity when non-invasive ABP data are employed. This finding enables prediction and potentially prevention of hypotension in a much larger patient population. The clinical analyses demonstrated the algorithm to predict hypotension shortly before a hypotensive event, it rarely missed hypotension but regularly led to false positive alarms for MAP between 65-75 mmHg. Altering the HPI alarm thresholds influences the balance between positive predictive value and the time from alarm to hypotension. Future studies should assess the clinical impact of the predicting of hypotension.

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4. Presentation: preliminary data for this study were presented as a poster presentation at the Annual Amsterdam Cardiovascular Sciences Symposium, July 5th 2018

REFERENCES

1. Futier E, Lefrant JY, Guinot PG, et al. Effect of Individualized vs Standard Blood Pressure Management Strategies on Postoperative Organ Dysfunction Among High-Risk Patients Undergoing Major Surgery: A Randomized Clinical Trial. *JAMA.* 2017.
2. Salmasi V, Maheshwari K, Yang D, et al. Relationship between Intraoperative Hypotension, Defined by Either Reduction from Baseline or Absolute Thresholds, and Acute Kidney and Myocardial Injury after Noncardiac Surgery. *Anesthesiology.* 2017;126(1):47-65.
3. Monk TG, Bronsert MR, Henderson WG, et al. Association between Intraoperative Hypotension and Hypertension and 30-day Postoperative Mortality in Noncardiac Surgery. *Anesthesiology.* 2015;123(2):307-319.
4. Ahuja S, Mascha EJ, Yang D, et al. Associations of Intraoperative Radial Arterial Systolic, Diastolic, Mean, and Pulse Pressures with Myocardial and Acute Kidney Injury after Noncardiac Surgery: A Retrospective Cohort Analysis. *Anesthesiology.* 2020;132(2):291-306.
5. Gregory A, Stapelfeldt WH, Khanna AK, et al. Intraoperative Hypotension Is Associated With Adverse Clinical Outcomes After Noncardiac Surgery. *Anesth Analg.* 2020.
6. Pinsky MR. Complexity modeling: identify instability early. *Crit Care Med.* 2010;38(10 Suppl):S649-655.
7. Holder AL, Clermont G. Using what you get: dynamic physiologic signatures of critical illness. *Critical care clinics.* 2015;31(1):133-164.
8. Hatib F, Jian Z, Buddi S, et al. Machine-learning Algorithm to Predict Hypotension Based on High-fidelity Arterial Pressure Waveform Analysis. *Anesthesiology.* 2018;129(4):663-674.
9. Davies SJ, Vistisen ST, Jian Z, Hatib F, Scheeren TWL. Ability of an Arterial Waveform Analysis-Derived Hypotension Prediction Index to Predict Future Hypotensive Events in Surgical Patients. *Anesthesia and analgesia.* 2019.
10. Wijnberge M, Geerts BF, Hol L, et al. Effect of a Machine Learning-Derived Early Warning System for Intraoperative Hypotension vs Standard Care on Depth and Duration of Intraoperative Hypotension During Elective Noncardiac Surgery: The HYPE Randomized Clinical Trial. *Jama.* 2020.
11. Schneck E, Schulte D, Habig L, et al. Hypotension Prediction Index based protocolized haemodynamic management reduces the incidence and duration of intraoperative hypotension in primary total hip arthroplasty: a single centre feasibility randomised blinded prospective interventional trial. *Journal of clinical monitoring and computing.* 2019.
12. Nuttall G, Burckhardt J, Hadley A, et al. Surgical and Patient Risk Factors for Severe Arterial Line Complications in Adults. *Anesthesiology.* 2016;124(3):590-597.
13. Brzezinski M, Luisetti T, London MJ. Radial artery cannulation: a comprehensive review of recent anatomic and physiologic investigations. *Anesth Analg.* 2009;109(6):1763-1781.
14. Scheer B, Perel A, Pfeiffer UJ. Clinical review: complications and risk factors of peripheral arterial catheters used for haemodynamic monitoring in anaesthesia and intensive care medicine. *Critical care (London, England).* 2002;6(3):199-204.
15. Cousins TR, O'Donnell JM. Arterial cannulation: a critical review. *AANA journal.* 2004;72(4):267-271.
16. Perel AS, J.J. Totally non-invasive continuous cardiac output measurement with the Nexfin *Annual Update in Intensive Care and Emergency Medicine.* 2011(2011:434-42).

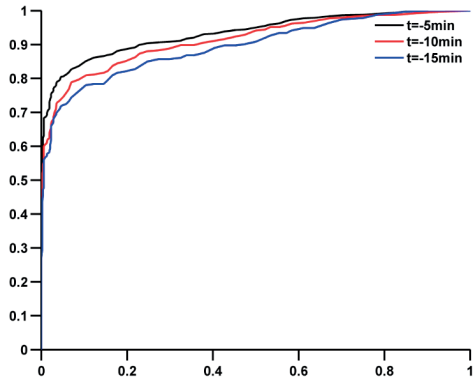
17. Maheshwari K, Buddi S, Jian Z, et al. Performance of the Hypotension Prediction Index with non-invasive arterial pressure waveforms in non-cardiac surgical patients. *Journal of clinical monitoring and computing.* 2020.
18. Wijnberge M, Schenk J, Terwindt LE, et al. The use of a machine-learning algorithm that predicts hypotension during surgery in combination with personalized treatment guidance: study protocol for a randomized clinical trial. *Trials.* 2019;20(1):582.
19. Maheshwari K, Shimada T, Fang J, et al. Hypotension Prediction Index software for management of hypotension during moderate- to high-risk noncardiac surgery: protocol for a randomized trial. *Trials.* 2019;20(1):255.
20. von Elm E, Altman DG, Egger M, et al. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. *Lancet.* 2007;370(9596):1453-1457.
21. Cohen JF, Korevaar DA, Altman DG, et al. STARD 2015 guidelines for reporting diagnostic accuracy studies: explanation and elaboration. *BMJ open.* 2016;6(11):e012799.
22. Bogert LW, van Lieshout JJ. Non-invasive pulsatile arterial pressure and stroke volume changes from the human finger. *Experimental physiology.* 2005;90(4):437-446.
23. Gizdulich P, Prentza A, Wesseling KH. Models of brachial to finger pulse wave distortion and pressure decrement. *Cardiovascular research.* 1997;33(3):698-705.
24. Guelen I, Westerhof BE, van der Sar GL, et al. Validation of brachial artery pressure reconstruction from finger arterial pressure. *Journal of hypertension.* 2008;26(7):1321-1327.
25. Martina JR, Westerhof BE, van Goudoever J, et al. Noninvasive continuous arterial blood pressure monitoring with Nexfin(R). *Anesthesiology.* 2012;116(5):1092-1103.
26. Heusdens JF, Lof S, Pennekamp CW, et al. Validation of non-invasive arterial pressure monitoring during carotid endarterectomy. *British journal of anaesthesia.* 2016;117(3):316-323.
27. Association for the Advancement of Medical Instrumentation. American national standard for non-invasive sphygmomanometers—Part 2: clinical validation of automated measurement type. ISO 81060-2. Arlington VA. In.
28. Youden WJ. Index for rating diagnostic tests. *Cancer.* 1950;3(1):32-35.
29. Sessler DI, Bloomstone JA, Aronson S, et al. Perioperative Quality Initiative consensus statement on intraoperative blood pressure, risk and outcomes for elective surgery. *British journal of anaesthesia.* 2019;122(5):563-574.
30. Topol EJ. Welcoming new guidelines for AI clinical research. *Nat Med.* 2020;26(9):1318-1320.

SUPPLEMENTAL MATERIAL

Supplemental Figure 1. Objective 1: Receiver operating characteristic curve illustrating the performance of Hypotension Prediction Index with the Youden Index threshold to predict hypotension at the one, three, five, ten, and 15 minutes before the actual event is to occur.

Supplemental Table 1. Exploratory analyses, performance of the algorithm with various HPI alarm thresholds.

SUPPLEMENTAL FIGURE 1. OBJECTIVE 1: ROC WITH YOUDEN INDEX 5, 10 AND 15 MINUTES PRIOR TO HYPOTENSION

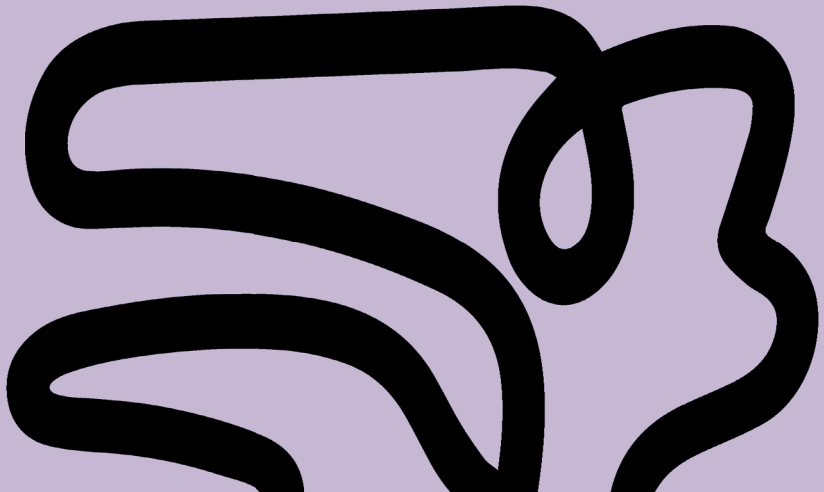


Objective 1. Receiver operating characteristic curve illustrating the performance of Hypotension Prediction Index with the Youden Index threshold to predict hypotension at the five, ten, and 15 minutes before the actual event is to occur.

SUPPLEMENTAL TABLE 1. EXPLORATORY ANALYSES, PERFORMANCE OF THE ALGORITHM WITH VARIOUS HPI ALARM THRESHOLDS.

	Sensitivity	Specificity	PPV	NPV	Median time till hypotension (min)
HPI alarm threshold 75	94.9 (93.6-96.2)	82.9 (81.3-84.6)	75.3(73.0-77.6)	96.7 (95.9-97.6)	3.00 (1.00 – 7.67)
HPI alarm threshold 85	**92.7 (91.2-94.2)**	**87.6 (86.2-89.0)**	**79.9 (77.7-82.1)**	**95.7 (94.8-96.7)**	**2.67 (1.00 – 7.00)**
HPI alarm threshold 95	90.6 (88.8-92.5)	95.8 (95.8-95.8)	90.4 (88.6-92.2)	95.8 (95.1-96.7)	1.33 (0.67 – 4.33)

Objective 2. Clinical analyses with different HPI alarm thresholds, presented with 95% confidence intervals. PPV = positive predictive value



11

One of the first validations of an artificial intelligence algorithm for clinical use: The impact on intraoperative hypotension prediction and clinical decision-making

Ward H. van der Ven
Denise Veelo
Marije Wijnberge
Bjorn J. van der Ster
Alexander P. Vlaar
Bart F. Geerts

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ABSTRACT

This review describes the steps and conclusions from the development and validation of an artificial intelligence algorithm (the Hypotension Prediction Index), one of the first machine learning predictive algorithms used in the operating room environment. The algorithm has been demonstrated to reduce intraoperative hypotension in two randomized controlled trials via real-time prediction of upcoming hypotensive events prompting anesthesiologists to act earlier, more often, and differently in managing impending hypotension. However, the algorithm entails no dynamic learning process that evolves from use in clinical patient care, meaning the algorithm is fixed, and furthermore provides no insight into the decisional process that leads to an early warning for intraoperative hypotension, which makes the algorithm a ”black box.” Many other artificial intelligence machine learning algorithms have these same disadvantages. Clinical validation of such algorithms is relatively new and requires more standardization, as guidelines are lacking or only now start to be drafted. Before adaptation in clinical practice, impact of artificial intelligence algorithms on clinical behavior, outcomes and economic advantages should be studied too.

HIGHLIGHTS

Topic: Hypotension during surgery is common and has repeatedly been associated with postoperative morbidity and mortality.

Purpose: Timely recognition of hypotensive events might be provided by machine learning algorithms and may lead to early treatment and prevention of these events. State-of-the-Art: The Hypotension Prediction Index is a commercially available machine learning algorithm that can be used for real-time prediction of upcoming hypotensive events.

Knowledge Gaps: Validation and implementation of machine learning algorithms in clinical medicine are relatively new and this process requires more standardization, as guidelines are lacking.

Technology Gaps: The Hypotension Prediction Index entails no dynamic learning process that evolves from use in clinical patient care, meaning the algorithm is fixed, and furthermore provides no insight in the decisional process that leads to an early warning for intraoperative hypotension, which makes the algorithm a "black box"; it shares these disadvantages with many other machine learning algorithms.

Future Directions: Validation of machine learning algorithms in medicine should go beyond the current state of external validation, mere mathematic proof of performance in retrospective data sets, but should include clinical behavior, outcome, and economic study. Future research with machine learning algorithms such as the Hypotension Prediction Index should focus on perioperative hemodynamic improvement with regard to reduction of post-operative morbidity and mortality.

INTRODUCTION

Interest in the application of artificial intelligence (AI) in medicine has been growing recently. AI is a field within computer science that aims to allow machines (ie, computers) to take over cognitive tasks from humans. In medicine, this would mean dealing with the increasing amount of patient data available to aid with menial tasks, but also to aid in diagnoses, predictions of events, drug discovery, personalization of treatment, and decision support in general.[1] The concept of AI, first discussed in 1955, was described as "the science and engineering of making intelligent machines, especially intelligent computer programs."[2] Machine learning (ML), a subfield of AI, is based on the aspect

that a computer can be trained on specific input data and is able to apply obtained knowledge from that data to newly presented data without being explicitly programmed to do so.[3] First attempts to use algorithms as an aid in anesthesiology practice date back to the 1950s, where maintenance of general anesthesia was controlled in an electroencephalographic activity-guided closed-loop setting.[4, 5, 6] Despite receiving broad interest and additional research underlining the potential of these automated systems,[7,8] they were never implemented in routine care. After several cycles that ended with so-called "AI winters," AI received renewed attention in medicine recently, resulting in many ML algorithms, for instance for the prediction of major complications and in-hospital mortality after surgery.[9,10] Furthermore, opportunities for AI to optimize patients' perioperative hemodynamic status were recognized, primarily focusing on the prediction of hypotension.[11-15] Some of the interest in AI is attributable to the increase in computer power and data storage capacities worldwide, which makes it more feasible to perform AI. However, because studies on clinical efficacy of AI algorithms are scarce, we see that the statistical and scientific methodology of evaluating clinical impact and safety of AI applications is still evolving.[1]

AIM

In this narrative review, we describe the steps from development to clinical implementation of the Hypotension Prediction Index (HPI) as one of the first ML-derived predictive algorithms used in the operating room environment. The potential value of the HPI in clinical use is to provide real-time information to the treating anesthesiologist, enabling proactive treatment of upcoming hypotensive events. We discuss the development and validation process, strengths, limitations, and potential clinical utility of the HPI. We end by making suggestions for future research.

RELEVANCE

Hypotension during surgery occurs frequently and incidence varies considerably depending on the chosen definition.[16] When defined as a mean arterial pressure (MAP) <65 mm Hg, it occurs in 71% of patients under general anesthesia[17] Cohort studies demonstrated that intraoperative hypotension is associated with increased morbidity and mortality.[18-21] Recently the first randomized controlled trial (RCT) investigating, the effect of personalized blood pressure control during general anesthesia was done.[22] The authors reported significantly reduced postoperative organ dysfunction in the intervention group where blood pressure was maintained within the 10% range

of the resting (awake) blood pressure,[22] thereby going beyond the mere associative findings in retrospective studies with this prospective trial. As a consequence, the MAP of patients under general anesthesia is now advised to be maintained in the range of 60 to 70 mm Hg, as was presented in a recent consensus statement.[23] Current treatment for hypotension, however, still remains reactive, meaning that it is acted on when it occurs, by administering fluids or vasoactive drugs. Ideally, hypotensive events may be prevented by proactive treatment based on the predictive abilities of a ML algorithm.

DEVELOPMENTAL PROCESS OF THE HPI

In an attempt to reduce hypotensive events using ML, Hatib et al[11] developed the HPI, which identifies possible hypotensive events in the next 5 to 15 minutes.[11] The HPI is a supervised ML algorithm, meaning it was trained to classify labeled outputs to predict a desired or undesired event.[24,25] Supervised ML algorithms are trained on a labeled data set (ie, the training set), after which its predictive accuracy is tested on new data (ie, the test set). Events were binary labeled as hypotensive (MAP <65 mm Hg) or non-hypotensive (MAP >75 mm Hg). The HPI produces a number ranging from 0 (ie, no hypotension expected) to 100 (ie, certain hypotensive event), where 85 is advised as the threshold at which to begin treatment. The numbers are based on blood pressure waveform analysis of signals obtained via an arterial cannula with a commercially available FloTrac IQ pressure transducer (Edwards Lifesciences, Irvine, CA, USA).

The algorithm (see the Figure for the different steps in the development) was trained on data of 1,334 surgical and intensive care patients, incorporating 545,959 minutes of arterial waveform recordings and 25,461 episodes of hypotension. From these data, 3,022 individual features were retrieved, for instance pulse pressure, cardiac output, and stroke volume variation, to more abstract features such as “the area under the pressure waveform greater than the beat mean pressure.” Next, these features were engineered by combining all known features like heart rate (HR) up to the second degree (like HR^2, HR^{-1} or MAP/HR^2) that may provide better predictive capabilities than individual features alone. Resulting in more than 2.6 million features, the 23 features with the best predictive results were selected using logistic regression.[11,24] This process, extracting the key features, is referred to as *feature selection*. The extracted features were subsequently entered into the learning algorithm, together with labeled hypotensive and non-hypotensive events. Hypotensive events were selected if they lasted more than 1 minute and if data were available from 5, 10, and 15 minutes before the event. Non-hypotensive events had to be 20 minutes apart from any hypotensive event and last at a minimum of 30 minutes. Finally, the training data were split in several subsets to optimize the algorithm by cross-validating it on the complementary subset of the data.

VALIDATION PROCESS

Regulatory evaluation standards (eg, Conformité Européenne for the European Union and the Food and Drug Administration for the United States) to allow clinical use of AI tools are undergoing frequent changes as they try to keep up with technologic development. Because regulatory approval does not necessarily equate to a safe and efficacious tool ready for patient use, we are also awaiting the creation of consensus guidelines that specifically look at the process of validation of AI-based tools. Also, the manner in which to report this validation research must be drafted.[26] In a recent meeting abstract,[27] upcoming reporting guidelines for the validation of AI tools were presented and are expected to be published soon.

INTERNAL AND EXTERNAL VALIDATION

The HPI algorithm underwent internal validation in 350 cases that were randomly selected from the initial dataset. Afterward, it was externally validated in 204 cases of intensive care patients, ultimately leading to a highly accurate algorithm with an area under the receiver operating characteristic curve (AUC) ranging from 0.95, 0.95 and 0.97 for 15, 10, and 5 minutes before a hypotensive event, respectively.[11] Although the algorithm was developed according to current guidelines,[28] it was unclear whether obtained results were generalizable to other data sets from different institutions or patient groups (ie, robustness).

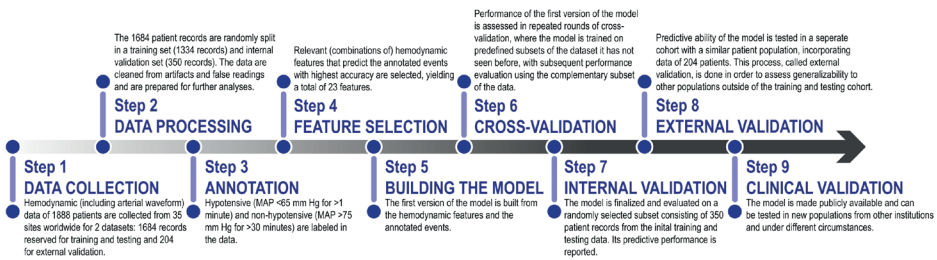

Figure 1. Steps in the development and validation of the Hypotension Prediction Index from data collection to clinical validation. MAP, mean arterial pressure.

CLINICAL VALIDATION

For additional clinical validation, it is important to recognize that the user determines the alarm threshold and defines what counts as hypotension, because the HPI produces a continuous number from 0 to 100. This data dichotomization allows for binary

classification of performance assessment. However, because most data are retrieved as time series, unique events cannot be observed as separate independent events and thus may bias the performance metrics. Retrospective analysis requires one to decide whether to apply forward or backward analyses for performance of the algorithm. Basically, meaning whether to use the alarm or the hypotensive event as the defining metric for classification success.

Clinical HPI performance was tested in 4 studies: 2 retrospective trials and 2 RCTs. In a retrospective analysis validating the performance of the HPI in 255 patients undergoing major surgery, similar accuracy was obtained for the prediction of hypotension within 5, 10, or 15 minutes before their occurrence (AUCs 0.93, 0.90, and 0.88, respectively).[29] In a small retrospective study of 23 patients undergoing vascular or cardiac surgery, performance of the HPI was less, with an AUC of 0.77 for the prediction of hypotension 5 to 7 minutes before the event.[30] This may be attributable to routine MAP targets between 66 and 70 mm Hg, resulting in higher HPI values without the occurrence of a hypotensive event.

The first prospective study, an RCT of patients scheduled for hip arthroplasty, compared 25 patients treated with goal-directed hemodynamic therapy, including administration of colloids and/or vasopressors, to 24 patients receiving routine care. Significant reduction of time spent in hypotension was observed in the intervention group (0% vs 6% of total anesthetic time, $P < .001$). The appropriate interventions, in accordance with the treatment protocol, were performed on 77,8% of the HPI alarms. Most likely as a result of the treatment protocol, the intervention group received fewer crystalloids and more colloids. Noticeably, a lower HPI threshold of 80 was used, according to the authors to enable early intervention.[31]

Recently, our group conducted a similar pilot RCT in a heterogeneous surgical population. A total of 68 patients were assigned to an HPI-guided treatment protocol or to standard care.[32] The HPI-guided protocol, which was consulted with HPI values >85, included treatment advice based on hemodynamic variables signaling problems in preload, afterload, or contractility. In the intervention group, less time spent in hypotension (2.8% vs 10.3% of total surgical time, $P < .001$) was observed, without an observed difference in administered fluids or vasopressors. Compliance with the protocol was high, with an overall 81% of HPI alarms being treated according to the proposed intervention in the treatment protocol. Fluid boluses were used more frequently in the intervention group than in the control group (16% vs 6%, $P < .001$). On the contrary, phenylephrine (24% vs 19%, $P = .04$) and ephedrine (14% vs 6%, $P < .001$) were used more often in the control group. These differences in treatment choices demonstrate a shift toward more frequent but smaller interventions and to the more frequent administration of fluids in the intervention group, without any effect on totally administered fluids and vasopressors overall.

RESULTS

As one of the first publicly available and clinically validated AI applications, the HPI is capable of predicting hypotension. Moreover, AI has demonstrated its value in reducing intraoperative hypotension in two RCTs, using it as a real-time decision aid in the operating room.

Although these results are promising, we learned that the HPI has several limitations:

The HPI has been developed from records of non-cardiac surgical and intensive care patients, but validation of the algorithm was only performed in non-cardiac surgical cases,[11] thereby possibly reducing generalizability to cardiac surgical and intensive care patient cohorts.

The HPI is powered on static values, namely MAP <65 mm Hg (hypotensive) and MAP >75 mm Hg (non-hypotensive), thereby leaving a "gray zone in between, which is sensitive to ambiguity.[11] Treatment based on MAP values in this gray zone may lead to overtreatment, as these were not incorporated in the algorithm.

When MAP targets other than 65 mm Hg are desired, the HPI is not suitable to use in these patients. This excludes patients with uncontrolled preoperative hypertension who may require a higher MAP target during general anesthesia.[33]

No indication of the underlying cause of hypotension is offered by the HPI. When the HPI rises, clinicians must still determine whether the (impending) hypotensive event is attributable to a problem in preload, contractility, or afterload. In both reported RCTs, a treatment protocol was used to suggest appropriate treatment, and both had moderate-to-good adherence to the protocol, which may explain the achieved effect.

The HPI cannot predict hypotension attributable to surgical manipulation, for instance during vascular clamping or compression of the vena cava.[11] It is therefore unable to replace medical care provided by a physician, but should be regarded as a tool to prevent or reduce time in hypotension.

In the RCTs discussed, HPI thresholds of 80 and 85 were chosen. These thresholds are arbitrary; higher thresholds result in higher positive predictive values (ie, if the HPI exceeds the threshold, a hypotensive event is likely to occur) and less overtreatment, but with the risk that other hypotensive events may be missed. Lower thresholds may benefit the patient, as more potential hypotensive events are prevented, and there are no data available that (slight) overtreatment will harm the patient.

The HPI provides no insight in the decision-making process, thereby impeding any feedback for the treating anesthesiologist from previous cases. This is an often-mentioned pitfall of ML algorithms, referred to as the "black box of ML."[1,3,34,35]

The HPI entails no dynamic learning process that evolves from use in clinical patient care, meaning the algorithm is fixed and will not improve on newly offered cases.

Most important, despite the reported reduction in intraoperative hypotension in these small RCTs, effects on clinical and financial outcomes (length of stay, morbidity, mortality, and cost-effectiveness) remain unclear. The HPI would not be of additional clinical use if it does not improve patient outcome.[36] Results of larger multicenter RCTs are warranted and should entail the effect of HPI-guided treatment in the perioperative period on postoperative morbidity and mortality.

In general, as more AI applications reach clinical practice, we would strongly advocate obliging manufacturers to go beyond the current de-factor standard of external dataset testing and study the impact on clinical behavior, outcomes and economic advantages too prior to adaption.

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Conflict of interest/Disclosure

Dr. Veelo reports having received personal fees and other from Edwards Lifesciences outside the submitted work as well as consultancy fees and research grants from Philips and Hemologic. Dr. Wijnberge reports having received consultancy fees from Edwards Lifesciences outside the submitted work. Dr. Vlaar reports having received grants from Edwards Lifesciences and Philips and personal fees from AKPA and InflaRx. Dr. Geerts reports having received grants from Edwards Lifesciences outside the submitted work and consultancy fees and research grants from Philips. The other authors have no related conflicts of interest to declare.

REFERENCES

1. Topol EJ. High-performance medicine: the convergence of human and artificial intelligence. Nat Med. 2019;25:44e56.
2. McCarthy J. What is artificial intelligence?. http://jmc.stanford.edu/articles/whatisai/whatisai.pdf; 2007. Accessed May 15, 2020.
3. Alexander JC, Joshi GP. Anesthesiology, automation, and artificial intelligence. Proc (Bayl Univ Med Cent). 2018;31:117e119.
4. Bickford RG. Automatic electroencephalographic control of general anesthesia. Electroencephalogr Clin Neurophysiol. 1950;2:93e96.
5. Bickford RG. Use of frequency discrimination in the automatic electroencephalographic control of anesthesia (servo-anesthesia). Electroencephalogr Clin Neurophysiol. 1951;3:83e86.
6. Bellville JW, Attura GM. Servo control of general anesthesia. Science. 1957;126: 827e830.
7. Brogi E, Cyr S, Kazan R, Giunta F, Hemmerling TM. Clinical performance and safety of closed-loop systems: a systematic review and meta-analysis of randomized controlled trials. Anesth Analg. 2017;124:446e455.
8. Pasin L, Nardelli P, Pintaudi M, et al. Closed-loop delivery systems versus manually controlled administration of total IV anesthesia: a meta-analysis of randomized clinical trials. Anesth Analg. 2017;124:456e464.
9. Lee CK, Hofer I, Gabel E, Baldi P, Cannesson M. Development and validation of a deep neural network model for prediction of postoperative in-hospital mortality. Anesthesiology. 2018;129:649e662.
10. Bihorac A, Ozrazgat-Baslanti T, Ebadi A, et al. MySurgeryRisk: Development and validation of a machine-learning risk algorithm for major complications and death after surgery. Ann Surg. 2019;269:652e662.
11. Hatib F, Jian Z, Buddi S, et al. Machine-learning algorithm to predict hypotension based on high-fidelity arterial pressure waveform analysis. Anesthesiology. 2018;129:663e674.
12. Kendale S, Kulkarni P, Rosenberg AD, Wang J. Supervised machine-learning predictive analytics for prediction of postinduction hypotension. Anesthesiology. 2018;129:675e688.
13. Jeong YS, Kang RA, Jung W, et al. Prediction of blood pressure after induction of anesthesia using deep learning: a feasibility study. Appl Sci. 2019;9:5135.
14. Kang AR, Lee J, Jung W, et al. Development of a prediction model for hypotension after induction of anesthesia using machine learning. PloS One. 2020;15: e0231172.
15. Lin CS, Chang CC, Chiu JS, et al. Application of an artificial neural network to predict postinduction hypotension during general anesthesia. Med Decis Making. 2011;31:308e314.
16. Bijker JB, van Klei WA, Kappen TH, van Wolfswinkel L, Moons KG, Kalkman CJ. Incidence of intraoperative hypotension as a function of the chosen definition: literature definitions applied to a retrospective cohort using automated data collection. Anesthesiology. 2007;107:213e220.
17. Maheshwari K, Turan A, Mao G, et al. The association of hypotension during non-cardiac surgery, before and after skin incision, with postoperative acute kidney injury: a retrospective cohort analysis. Anaesthesia. 2018;73:1223e1228.
18. Sessler DI, Meyhoff CS, Zimmerman NM, et al. Period-dependent associations between hypotension during and for four days after noncardiac surgery and a composite of myocardial infarction and death: a substudy of the POISE-2 trial. Anesthesiology. 2018;128:317e327.
19. Wesselink EM, Kappen TH, Torn HM, Slooter AJC, van Klei WA. Intraoperative hypotension and the risk of postoperative adverse outcomes: a systematic review. Br J Anaesth. 2018;121:706e721.

20. Salmasi V, Maheshwari K, Yang D, et al. Relationship between intraoperative hypotension, defined by either reduction from baseline or absolute thresholds, and acute kidney and myocardial injury after noncardiac surgery: a retrospective cohort analysis. Anesthesiology. 2017;126:47e65.
21. Mascha EJ, Yang D, Weiss S, Sessler DI. Intraoperative mean arterial pressure variability and 30-day mortality in patients having noncardiac surgery. Anesthesiology. 2015;123:79e91.
22. Futier E, Lefrant JY, Guinot PG, et al. Effect of individualized vs standard blood pressure management strategies on postoperative organ dysfunction among high-risk patients undergoing major surgery: a randomized clinical trial. JAMA. 2017;318:1346e1357.
23. Sessler DI, Bloomstone JA, Aronson S, et al. Perioperative quality initiative consensus statement on intraoperative blood pressure, risk and outcomes for elective surgery. Br J Anaesth. 2019;122:563e574.
24. Connor CW. Artificial intelligence and machine learning in anesthesiology. Anesthesiology. 2019;131:1346e1359.
25. Deo RC. Machine learning in medicine. Circulation. 2015;132:1920e1930.
26. CONSORT-AI, SPIRIT-AI Steering Group. Reporting guidelines for clinical trials evaluating artificial intelligence interventions are needed.Nat Med. 2019;25:1467e1468.
27. Liu X, Rivera SC, Faes L, Keane PA, Moher D, Calvert M, et al. CONSORT-AI and SPIRIT-AI: new reporting guidelines for clinical trials and trial protocols for artificial intelligence interventions. Invest Ophthalmol Vis Sci. 2020;61: 1617.
28. Luo W, Phung D, Tran T, et al. Guidelines for developing and reporting machine learning predictive models in biomedical research: a multidisciplinary view. J Med Internet Res. 2016;18:e323.
29. Davies SJ, Vistisen ST, Jian Z, Hatib F, Scheeren TWL. Ability of an arterial waveform analysis-derived hypotension prediction index to predict future hypotensive events in surgical patients. Anesth Analg. 2020;130:352e359.
30. Ranucci M, Barile L, Ambrogi F, Pistuddi V. Discrimination and calibration properties of the hypotension probability indicator during cardiac and vascular surgery. Minerva Anestesiol. 2019;85:724e730.
31. Schneck E, Schulte D, Habig L, et al. Hypotension Prediction Index based protocolized haemodynamic management reduces the incidence and duration of intraoperative hypotension in primary total hip arthroplasty: a single centre feasibility randomised blinded prospective interventional trial. J Clin Monit Comput. 2020;34:1149e1158.
32. Wijnberge M, Geerts BF, Hol L, et al. Effect of a machine learning-derived early warning system for intraoperative hypotension vs standard care on depth and duration of intraoperative hypotension during elective noncardiac surgery: The HYPE randomized clinical trial. JAMA. 2020;323:1052e1060.
33. Ackland GL, Brudney CS, Cecconi M, et al. Perioperative quality initiative consensus statement on the physiology of arterial blood pressure control in perioperative medicine. Br J Anaesth. 2019;122:542e551.
34. Gambus PL, Jaramillo S. Machine learning in anaesthesia: Reactive, proactive... predictive!. Br J Anaesth. 2019;123:401e403.
35. Castelvecchi D. Can we open the black box of AI? Nature. 2016;538:20e23. 36. Keane PA, Topol EJ. With an eye to AI and autonomous diagnosis. NPJ Digit Med. 2018;1:40.

12

Summary

In this thesis we aimed to improve haemodynamic assessment in perioperative patients, both in the intensive care unit (ICU) and in the operating theatre. The overarching aims of this thesis were: (1) to improve assessment of the haemodynamic status of patients admitted to the ICU by focusing on basic physiology and (2) to improve the haemodynamic status of patients in the operating theatre by predicting and ultimately preventing intraoperative hypotension.

Part I - Mean systemic filling pressure

In the first part of this thesis we focus on the patient admitted to the ICU. We primarily focus on Guyton's view on the circulation. In **Chapter 2** the current bedside methods to assess mean systemic filling pressure are described; $MSFP_{hold}$, $MSFP_{arm}$ and $MSFP_{analogue}$. $MSFP_{analogue}$ was lower compared to $MSFP_{arm}$ and $MSFP_{hold}$.

The systematic review highlighted one of the problems implementing MSFP in clinical care; the absence of normal values for different patient groups. In **Chapter 3** we analysed a cohort of patients who died in the ICU whilst having active recording of arterial and venous pressures. This cohort enabled to describe normal MCFP values for various patient groups and to study the influence of patient characteristics on MCFP. We found fluid balance, the use of vasoactive medication and being on mechanical ventilation to be associated with a higher MCFP. We found MCFP to behave as expected within the haemodynamic framework. Future studies are needed to determine cut-off values to allow for therapeutic interventions to be triggered, and to determine the value of this parameter in clinical practice.

In **Chapter 4** we aimed to implement $MSFP_{hold}$ in clinical practice. MSFP was able to track a 500 mL fluid bolus ($p<0.001$) and exploratory a difference was found in the response between crystalloids and colloids. In 16 out of the total of 20 patients (80%), stressed volume and vascular compliance could be determined. Although $MSFP_{hold}$ might provide valuable insights into the haemodynamic status of a patient, our initial enthusiasm was hampered as $MSFP_{hold}$ seems to be restricted to highly controlled research settings only. Less invasive techniques, such as $MSFP_{arm}$ or $MSFP_{analogue}$ might be more suitable alternatives for clinical use.

Part II - Hypotension

In the second part of this thesis we focus on the patient undergoing surgery. We primarily focus on the arterial side of the circulation.

In **Chapter 5** we reviewed the risk of postoperative morbidity associated with intraoperative hypotension. A total of 29 studies were included consisting of a total of 130 862 patients. Comparison of studies was complicated by the various definitions of hypotension used. Because overall heterogeneity was high, the robustness of the results was assessed with subgroup analyses, sensitivity analyses and a meta-regression.

Intraoperative hypotension (IOH) was associated with an increased risk of postoperative morbidity and mortality. This effect was most notable for cardiac events (Odds ratio 2.44, 1.52-3.93), acute kidney injury (OR 2.69, 1.31-5.55) and mortality (OR 1.94, 1.32-2.84).

In **Chapter 6** we described the study protocol for our randomised controlled trial (RCT). Currently, treatment of hypotension is reactive. In order to reduce hypotension, it would be beneficial to alter treatment behaviour from reactive to proactive. However, care providers are not always able to discern subtle changes in the arterial waveform and predict hypotension. Moreover, it is neither feasible nor desirable for an anaesthetist to solely focus on the haemodynamic status of a patient. A machine learning derived early warning system could be of help. In our study protocol, we explained why treatment above a hypotension prediction index of 85% might be warranted. To assess the underlying cause of the impending hypotension, we designed a flowchart, which can assist in making a per patient personalised treatment decision. Also, for a prediction system to be useful in clinical practice, treatment behaviour needs to change. For humans in general, but for medical staff in particular, change is challenging.

Chapter 7 described our RCT. We found that the early warning system in combination with our haemodynamic diagnostic guidance and treatment protocol significantly reduced the time weighted average (TWA) of hypotension (0.44 to 0.10 mmHg, p 0.001) without increasing the cumulative dose of vasoactive medication or fluids used. In this study, predicting hypotension obliged the treating anaesthetist to diagnose the underlying cause of the impending hypotension based on dynamic haemodynamic variables such as cardiac output, stroke volume variation, Eadyn and dp/dt. We found that after 81% of the alerts, treatment was started within the predefined two minutes. In 5% (20 alarms) the treatment was not according to the study treatment protocol and 14% of the alarms (53 alarms) were ignored by the treating anaesthetist.

In **Chapter 8** we exploratory assessed whether the beneficial effect found intraoperatively extended to the immediate post-operative phase. We hypothesised that preventing intraoperative hypotension might have a beneficial effect postoperatively. 68% of patients experienced postoperative hypotension. We found no significant difference in our primary endpoint, the TWA of postoperative hypotension (0.23 vs 0.07, p 0.30). No solid conclusions could be drawn as the loss to follow-up of six out of 60 patients (10%) reduced the power of the study. Future studies with large sample sizes are required to validate these results.

The majority of perioperative patients do not receive an arterial cannula for invasive blood pressure (BP) monitoring but BP is monitored intermittently with a BP cuff around the upper arm.

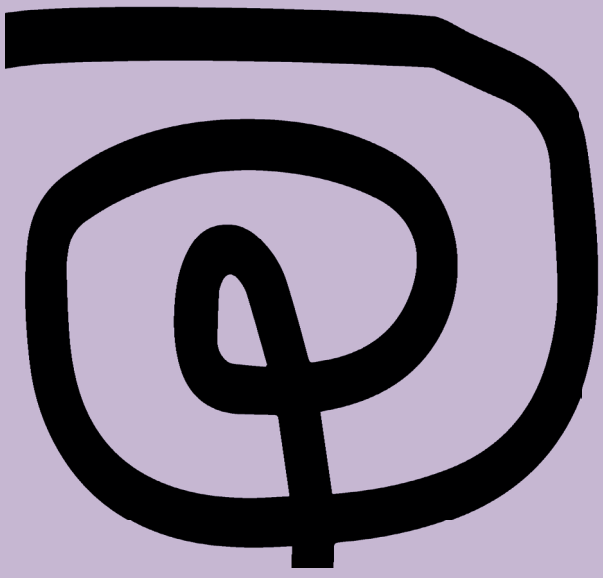
In **Chapter 9** we found that intermittent blood pressure monitoring resulted in missed hypotensive events and the hypotensive events that were detected, were recognised

with a median delay time of 1.2 (0.6-2.2) min. As even short periods of hypotension could be hazardous this study highlights the potential of continuous monitoring.

Chapter 10 describes the validation of the early warning system for hypotension on noninvasive continuous arterial finger blood pressure waveforms ($cNIBP_{finger}$). Our first aim was to compare the performance of the early warning system, using non-invasive versus invasive arterial blood pressure (ABP) measurements, at a mathematically optimal hypotension prediction index (HPI) alarm threshold (Youden index). This Youden Index method was chosen to enable comparison with previous validation studies and demonstrated that the performance of the early warning system with invasive and noninvasive ABP input was almost similar.

The second aim was to assess the performance of the algorithm using an HPI alarm threshold of 85 that is currently used in clinical trials. We used a forward analysis to mimic the use in clinical care. An HPI alarm threshold of 85 showed a median time from alarm to hypotension of 2.7 (IQR 1.0 to 7.0) min.

Chapter 11 describes our experience working with one of the first machine learning derived algorithms of its kind in anaesthesia and intensive care. The development, internal, external and clinical validation steps were described and we communicate our views on the limitations and discuss future directions.



13

Nederlandse samenvatting

Het doel van het onderzoek gepresenteerd in dit academisch proefschrift is om de hemodynamiek van patiënten te optimaliseren. Hemodynamiek ('bloedbewegingsleer') heeft als doel het aanvoeren van zuurstof naar de cellen in ons lichaam en het afvoeren van afvalproducten. Hemodynamiek omvat de gehele circulatie, dus het hart en de bloedvaten samen. In het eerste deel van dit proefschrift ligt de focus op het gebruik van basale fysiologie om de hemodynamische status van intensive care patiënten te verbeteren. In het tweede deel van dit proefschrift richten wij ons op het voorspellen en daarmee voorkomen van hypotensie (lage bloeddruk) in de operatiekamer.

Deel I - Mean systemic filling pressure

In het eerste deel van dit proefschrift richten we ons op de patiënt die opgenomen is op de intensive care. In **Hoofdstuk 2** beschrijven we de huidige methoden om mean systemic filling pressure (MSFP) in patiënten te bepalen. Om bloed vanuit het lichaam het hart in te krijgen moet de veneuze druk hoger zijn dan de druk in het rechter atrium (in het hart), deze 'upstream' bloeddruk wordt MSFP genoemd.

1. $MSFP_{hold}$; hierbij wordt er gebruik gemaakt van de hart-long interactie. Om $MSFP_{hold}$ te meten laten we de patiënt inademen en houden we deze ademteug een aantal seconden vast (inspiratory hold) met behulp van het beademingsapparaat. Hierbij wordt er gekeken naar de invloed van de inspiratory hold op de centraal veneuze druk en het hartminuut volume. Door het uitvoeren van meerdere inspiratory holds kun je hiermee MSFP bepalen. Deze methode kan enkel gebruikt worden in beademde en gesedeerde patiënten.
2. $MSFP_{arm}$; bij deze methode wordt de circulatie van de arm gebruikt als een model voor het gehele lichaam. Een manchet om de arm wordt razendsnel opgeblazen tot 50 mmHg boven de systolische bloeddruk ('de bovendruk') waarbij er geen bloed meer in en uit de arm kan stromen, de bloedstroom is daardoor nul. MSFP is gedefinieerd als de druk in de circulatie als er geen bloedstroom is.
3. $MSFP_{analogue}$; dit is de minst invasieve methode waarbij MSFP berekend wordt middels een formule gebaseerd op een model van de circulatie. De input variabelen voor de formule bestaan uit het hartminuut volume, de centraal veneuze druk en de bloeddruk.

In onze systematische review toonde $MSFP_{analogue}$ lagere waarden ten opzichte van $MSFP_{arm}$ en $MSFP_{hold}$. Dit komt waarschijnlijk doordat in de formule van $MSFP_{analogue}$ constanten zitten die voor acuut zieke patiënten mogelijk niet altijd correct zijn. Alle drie de methoden waren in staat een vochtbolus te volgen, oftewel, MSFP steeg na het toedienen van vocht.

Onze systematisch uitgevoerde review toonde aan dat er geen normaalwaarden voor MSFP beschreven zijn voor verschillende patiëntgroepen. Met die reden beschrijven wij in **Hoofdstuk 3** een cohort patiënten die overleden zijn op de intensive care, terwijl

de arteriële en veneuze bloeddruk via katheters in de bloedvaten werd gemonitord. MSFP normaalwaarden voor verschillende patiëntgroepen worden beschreven. Tevens hebben we de invloed van patiënt karakteristieken kunnen onderzoeken. Onze studie liet zien dat de vochtbalans, het gebruik van vasoactieve medicatie en beademd worden geassocieerd waren met een hogere MSFP. MSFP gedraagt zich zoals men volgens hemodynamische principes zou verwachten. We concludeerden dat meer studies nodig zijn om te bepalen hoe MSFP ingezet kan worden om de klinische praktijk te verbeteren.

In **Hoofdstuk 4** werd $MSFP_{hold}$ gemeten in 20 patiënten. MSFP steeg significant na het toedienen van 500 mL vloeistof. In 16 van de 20 patiënten (80%) konden wij het effectief circulerend volume (stressed volume) en de compliantie van de vaten bepalen. $MSFP_{hold}$ toonde aanvullende inzichten in de hemodynamische status van patiënten. Echter, we liepen ook tegen limitaties aan. Het meten van $MSFP_{hold}$ vraagt om een zeer gecontroleerde setting. De twee minder invasieve technieken; $MSFP_{arm}$ en $MSFP_{analogue}$ zijn mogelijk meer haalbare alternatieven voor de klinische praktijk.

Deel II - Hypotensie

In deel twee van dit academische proefschrift ligt de focus op de patiënt die een operatieve ingreep ondergaat. We richten ons hierbij primair op de arteriële (slagaderlijke) zijde van de circulatie.

In **Hoofdstuk 5** presenteren we een systematische review (een overzicht) van de associatie van intra-operatieve hypotensie (lage bloeddruk) met postoperatieve morbiditeit (ziekte) en mortaliteit (dood). Onze review bevat 29 studies waarbij in totaal 130 862 patiënten werden geïncludeerd. Het vergelijken van de studies werd bemoeilijkt doordat er in de studies verschillende definities van hypotensie werden gebruikt. Gezien de heterogeniteit tussen de studies hoog was, hebben we de robuustheid van de resultaten bevestigd middels subgroep analyses, sensitiviteit analyses en een meta-regressie. Intra-operatieve hypotensie was geassocieerd met een verhoogd risico op postoperatieve morbiditeit en mortaliteit. Dit risico was het hoogste voor cardiale events (Odds Ratio 2.44, 1.52-3.93), acute nierinsufficiëntie (Odds Ratio 2.69, 1.31-5.55) en mortaliteit (Odds Ratio 1.94, 1.32-2.84).

Hoofdstuk 6 beschrijft het studieprotocol voor onze gerandomiseerde studie (RCT). Momenteel is de behandeling van hypotensie reactief, dit houdt in dat tijdens een operatie een lage bloeddruk pas behandeld wordt als de bloeddruk daadwerkelijk laag is. Om hypotensie te reduceren zou je het liefst al behandelen voordat de hypotensie optreedt. Dit is echter niet gemakkelijk aangezien anesthesiologen hypotensie niet altijd kunnen voorspellen. Hypotensie wordt meestal voorafgegaan door zeer subtiele veranderingen in de invasieve arteriële bloeddruk (de golfvorm zichtbaar op een monitor) maar dit is niet altijd zichtbaar voor het menselijke oog. Een machine learning algoritme dat een waarschuwing geeft zou hierbij kunnen helpen. In ons studieprotocol wordt een

flowchart beschreven dat wij als studieteam hebben ontworpen. Dit flowchart helpt de behandelend anesthesioloog de onderliggende oorzaak van de voorspelde hypotensie te diagnosticeren. Op deze manier werken met een machine learning algoritme op de operatiekamer was nieuw en vroeg dus om een aanpassing in het behandelgedrag van het gehele medische team. Het medische team moest het behandelgedrag aanpassen van reactief naar proactief.

Hoofdstuk 7 beschrijft onze RCT. Onze resultaten lieten zien dat het gebruik van het machine learning algoritme in combinatie met het flowchart de 'time weighted average' (TWA) van intra-operatieve hypotensie significant verminderde (0.44 versus 0.10 mmHg, p-waarde 0.001). De TWA van hypotensie is een uitkomstmaat waarbij zowel de duur als de ernst (diepte) van de hypotensie meegenomen wordt. De gevonden reductie van intra-operatieve hypotensie resulteerde niet in significant meer gebruik van vasoactieve medicatie of vochttoediening. Deze studie verplichtte de anesthesioloog en de anesthesiemedewerker om de onderliggende oorzaak van de voorspelde hypotensie te diagnosticeren op basis van hemodynamische variabelen. De variabelen die we gebruiken in deze studie zijn onder andere cardiac output (hartminuut volume), slag volume, slag volume variatie, en informatie over de spanning in de vaten en de contractiliteit van het hart. Bij 81% van de voorspelde hypotensieve events werd er behandeld binnen de afgesproken 2 minuten. Bij 5% van de hypotensie voorspellingen was de behandeling niet volgens het behandel flowchart en 14% van de voorspellingen werden genegeerd door het behandelteam. Wereldwijd waren wij een van de eerste studiegroepen die hebben onderzocht of je met behulp van een machine learning algoritme hypotensie kan voorkomen.

In **Hoofdstuk 8** hebben we exploratief onderzocht of het voorkomen van intra-operatieve hypotensie (lage bloeddruk tijdens de operatie) ook resulteert in minder hypotensieve episodes direct postoperatief (na de operatie) op de post anesthesia care unit (PACU). De PACU wordt door patiënten ook wel de uitslaapkamer genoemd. Dit was een sub-studie van de HYPE trial gepresenteerd in hoofdstuk 7. Tijdens de PACU opname had 68% van de patiënten een of meer hypotensieve episodes. Onze resultaten toonden *postoperatief* geen verschil aan tussen patiënten waarbij intra-operatief wel of niet het machine learning algoritme was gebruikt. De TWA van hypotensie was gelijk tussen deze twee groepen (0.23 versus 0.07, p-waarde 0.30). Echter, een harde conclusie kan niet worden getrokken omdat de studie te weinig power heeft. De studie heeft power verloren aangezien 6 van de totaal 60 patiënten (10%) uitvielen. Toekomstige studies met grotere patiëntaantallen zijn nodig om onze resultaten te controleren.

In bovenstaande studies is invasief gemeten bloeddruk gebruikt, dit houdt in dat de bloeddruk continue gemeten werd middels een katheter in een arterie (slagader). Echter, in de meerderheid van de operatieve patiënten wordt de bloeddruk non-invasief en intermitterend gemeten middels een manchet (bloeddrukband) om de bovenarm.

Onze resultaten gepresenteerd in **Hoofdstuk 9** laten zien dat intermitterende bloeddruk meting resulteert in gemiste hypotensieve episodes. De hypotensieve episodes die niet werden gemist werden gemiddeld (mediaan) 1.2 minuten (interquartile range, IQR 0.6-2.2) later opgemerkt. Gezien korte periodes van hypotensie al geassocieerd zijn met een toename van postoperatieve morbiditeit, laat deze studie het potentieel zien van non-invasieve continue bloeddruk monitoring.

Hoofdstuk 10 beschrijft de validatie van het machine learning algoritme voor non-invasieve continue vingerbloeddrukmeting ($cNIBP_{finger}$). Ons eerste doel was om de performance van het algoritme met $cNIBP_{finger}$ te vergelijken met eerdere studies waarbij invasief gemeten bloeddruk als input data werd gebruikt. Om de performance te kunnen vergelijken, moesten we precies dezelfde methodiek gebruiken als in de eerder gepubliceerde studies. De performance van het machine learning algoritme in combinatie met $cNIBP_{finger}$ data was adequaat.

Ons tweede doel was om een klinische analyse uit te voeren. We gebruikten hiervoor een 'forward' analyse om zo dicht mogelijk bij het gebruik van het algoritme in de kliniek te komen. Onze resultaten lieten zien dat het algoritme goed voorspelde en dat de gemiddelde tijd (mediaan) van alarm naar hypotensie 2.7 minuten (IQR 1.0 - 7.0) was. Deze tijd is korter dan wat in eerdere studies beschreven is. Deze tijd is klinisch voldoende voor een anesthesioloog om de onderliggende oorzaak van de voorspelde hypotensie te diagnosticeren en om behandeling te starten.

Hoofdstuk 11 beschrijft onze ervaring met een van de eerste machine learning algoritmes om te gebruiken in de klinische zorg. We beschrijven de ontwikkeling, de interne, externe en klinische validatie stappen en beschrijven onze persoonlijke ervaring, limitaties en toekomstvisies. Toekomstig onderzoek zal moeten uitwijzen of het voorkomen van hypotensie ook daadwerkelijk resulteert in betere patiënt-gerelateerde uitkomsten.

Haren in de wind, in de zeilen, in de zee
Met de wind mee, deinen
Aan de horizon verdwijnen

Joeke Thewessem 2022

14

General discussion and future perspectives

Intensivists and Anaesthetists focus on maintaining normal physiology in the intensive care unit (ICU) and the operating theatre to prevent adverse outcomes. Optimising haemodynamics can be challenging as no holy grail marker exists. In this chapter, the results found in this thesis are put into a larger perspective.

Part I – Mean systemic filling pressure

What we knew before this thesis:

At the start of this thesis, MSFP was considered a hot topic at international ICU conferences. In this thesis, we build further on earlier performed research. Jansen et al. demonstrated it is possible to estimate mean systemic filling pressure (MSFP) and derived variables in clinical care.[1] To enable measurement in humans the invasively measured flow in the aorta was replaced with minimally invasive cardiac output (CO) measurement devices.[1] MSFP obtained with inspiratory holds ($MSFP_{hold}$) demonstrated to be a valid representation of mean circulatory filling pressure (MCFP) at zero blood flow ($MCFP_{stop\text{-}flow}$).[2] Thus, in this thesis, we perceived $MSFP_{hold}$ as an established reference method.

What this thesis adds:

All that glitters is not gold; although it is possible to estimate MSFP and derived variables in clinical care, the clinical value in its current form remains uncertain.

MSFP, stressed volume (Vs) and vascular compliance (Csys) may explain haemodynamic instability and help plan therapeutic interventions but MSFP cannot be directly measured in clinical practice. In the original study one $MSFP_{hold}$ measurement took 35-40 minutes as it consisted of seven inspiratory holds at different plateau levels, and the inspiratory hold manoeuvres were separated by five-minute intervals to re-establish the initial haemodynamic steady state.[1] Currently, an $MSFP_{hold}$ measurement takes around four to five minutes. For Vs or Csys determinations, a patient needs to be haemodynamically stable for a longer period of time ($MSFP_{hold}$ - fluid administration - $MSFP_{hold}$). It is questionable whether this requirement is realistic in the ICU as the patients who would benefit the most from Vs and Csys determination might not be haemodynamically stable to this extent.

In the original studies by Guyton, zero flow was caused by ventricular fibrillation, vagal stimulation or ligation of the pulmonary artery. Also, reflex activation was abolished by instituting total spinal anaesthesia.[3] $MSFP_{hold}$ enables measuring MSFP without ceasing blood flow, however it does require a level of sedation higher than usual in ICU patients. In our systemic review, we described two less invasive methods to estimate MSFP: $MSFP_{arm}$ and $MSFP_{analogue.}$ $MSFP_{arm}$ does require a level of sedation as the rapid inflation of the blood pressure cuff is unpleasant, and reflex mechanisms might kick in. $MSFP_{analogue}$ has the least requirements but suffers from greater inaccuracies as

the calculation uses standard arterial and venous compliances and resistances that might be false during acute disease states.

In this thesis $MSFP_{hold}$ was able to track changes in volume status. We found a significant difference in the response after a 100 cc crystalloid versus 100 cc colloid bolus. Indeed, Sondergaard et al. found the response after crystalloid administration widely variable in postoperative cardiac surgery patients.[4] As Vs and Csys assume the administered fluids to stay intravascular for the duration of the bolus we advise future studies in postoperative cardiac surgery patients to use colloids.

The research in this thesis highlights the potential of MSFP but also illustrates its limitations.

What we need to solve:

Through the years, Guyton's model of circulation has been debated, especially the relevance of MSFP in heart-beating patients.[5] The agreement between $MSFP_{hold}$ and $MCFP_{stop\text{-}flow}$ is also a topic of concern. To estimate MCFP in clinical practise we measure MSFP. Any method that attempts to estimate MSFP during ongoing circulation will be affected by potential volume shifts. PEEP itself influences the VR curve by downward displacement of the diaphragm, increasing intra-abdominal pressure and compression of the liver, and by squeezing of the lungs, resulting in an increase in stressed volume leading to an increase in MSFP.[6, 7] We considered a potential difference between $MCFP_{stop\text{-}flow}$ and $MSFP_{hold}$ as not relevant, based on the results found in the original study by Pinsky.[2] More recently, however, authors found that the agreement of $MSFP_{hold}$ and $MCFP_{stop\text{-}flow}$ (in an animal model) was dependent on volume state.[8, 9] Overestimation during euvolemia was suggested to be due to flow restorations seen -during the inspiratory hold- in the inferior vena cava, attributable to activation of vascular waterfalls in the splanchnic circulation.[8] This should be further explored.

In clinical care, the absolute values of MSFP - regardless of the method used - are likely to be less relevant than the tracking ability of MSFP. Up to date, no guidelines exist on how to use MSFP and the derived values in clinical care. We believe Vs to be a value of interest, however Vs and unstressed volume (Vu) can quickly inter-change by recruitment from the splanchnic circulation. In this thesis, we found that the qualitative changes in MSFP, Vs, compliance and the driving pressure of venous return are of interest physiologically but the quantitative values might be less useful. Although our initial enthusiasm was hampered, we should not throw the baby out with the bathwater. At this moment, we still lack a holy grail marker to optimise the haemodynamic status of patients admitted to the ICU. Most likely, we should not focus on one single marker, but rather find an optimal combination of many. Ideally, this will include macro – as well as microcirculation markers. Focus on the circulation as a whole, including the venous side, could prove beneficial.

MSFP is of interest for studies that investigate how the vascular system functions.[8,10,11] More research is needed before clinical decision-making on MSFP, Vs and Csys can commence. Future studies are needed to determine the value of this parameter in clinical practice and less invasive alternatives to determine MSFP should be further explored.

Part II – Hypotension

What we knew before this thesis:

Anaesthesia has a major impact on haemodynamics as most anaesthetic agents reduce sympathetic activity and suppress cardiovascular regulatory mechanisms.[12-17] In this thesis, hypotension is defined as a MAP below 65 mmHg. Maintaining this threshold is currently best practice perioperatively, in sepsis guidelines and in the ICU.[18-21]

There are a number of reasons for the focus on MAP. The morphology of the arterial waveform significantly changes depending on the location in the body, which highly alters systolic and diastolic pressure.[22,23] MAP on the other hand declines by only a small degree as the aortic pressure pulse travels away from the aorta and to the distributing arteries.[24] MAP has the benefit of being least sensitive to over- and underdamping of the blood pressure waveform.[25] Comparing invasive and non-invasive blood pressure devices, MAP is consistently the best corresponding value.[26]

Since most patient data are captured digitally, the opportunities to deploy machine learning are increasing rapidly.[27] Although incorporating machine learning in clinical care is promising, at the start of this thesis many physicians considered it a hype.

What this thesis adds:

We demonstrated that hypotension is associated with postoperative outcomes and that the risk of adverse outcome varied per organ. This organ-specific susceptibility seems plausible as within organs, significant heterogeneity in intra-organ blood flow occurs determined by altering resistance.[28] In recent years studies have tried to understand organ dependent flow, focussing on autoregulation.[29] The brain might be least susceptible to damage from low blood pressure, but large studies have shown that the association of myocardial injury and acute kidney injury starts at relatively high MAP thresholds.[30,31] It is important to acknowledge that in this thesis we did not study causal relationships; we report on associations.

We went beyond the hype;[27] the research in this thesis demonstrated that with the use of a machine learning derived algorithm in combination with a treatment flowchart, we were able to reduce the time weighted average (TWA) of hypotension during surgery without increasing the cumulative dose of vasoactive medication used. We demonstrated that anaesthesiologists are able to alter their treatment behaviour from reactive to proactive.

We showed that intermittent blood pressure monitoring results in delayed recognition of hypotensive events, highlighting the potential of continuous non-invasive blood pressure monitoring. Lastly, we demonstrated that the early warning system, designed for invasively obtained arterial waveforms, also works well with a non-invasive alternative.

What we need to solve:

Most studies report on an association between hypotension and outcome. Data from randomized clinical trials (RCT's) is sparse.[32, 33] This is understandable as it is currently not considered ethical to deliberately perform less (i.e. expose to hypotension) in one group. Working with predictive algorithms might solve this problem, comparing standard reactive care with proactive care.[34] For such a study to show a significant reduction on a clinically relevant endpoint a large sample size is required.

One size does not fit all; ICU microcirculation studies demonstrated that maintaining MAP above 65 mmHg improved organ perfusion,[35] but not for all patients, implicating that for some patients a higher threshold could be beneficial.[36] In other words, every patient – and depending on the target organ - may have a personal minimal MAP to be maintained during surgery.[24, 37] Also, MAP is not the only parameter to focus on. In an animal haemorrhage model, it was shown that treatment with phenylephrine alone did increase MAP but did not increase microcirculatory flow status.[38] Inappropriate fixation on blood pressure is not the goal, in this thesis we utilised it as a starting point with the aim to optimize tissue oxygen delivery.

In this thesis, hypotension prevention was personalized by diagnosing and treating the specific cause of the impeding hypotension (preload, afterload or contractility). Future studies focused on clinical endpoints should assess whether 'correct' treatment further improves outcomes compared to treating a number alone.

Machine learning has the additional benefit of providing new insights and could function as a stepping stone for new research. Unfortunately, the features of the early warning system (the machine learning derived algorithm) used in this thesis are not publicly available. An additional downside is that medical doctors might become sceptical, as the early warning system does not provide insight into the decisional process that leads to the alert. This is understandable, although - when placed in a larger perspective - perhaps a bit naive, as most doctors use algorithms they do not know the 'ingredients' of on a daily basis. Altogether, exchanging knowledge should be applauded.

In this thesis, the machine learning derived early warning system was used from surgical incision to end of surgery, meaning the post-induction phase was excluded. Post-induction hypotension is not surgery-related but purely patient- and anaesthesia-

related. As one third of hypotension occurs after induction and before incision, this time frame is of future interest.[39]

During anaesthesia, the patient is monitored intensively, namely, one healthcare professional per patient. Postoperatively, in the postoperative care unit (PACU) and in the ICU this is not the case. Both hypotension in the ICU and in the PACU are associated with outcomes.[31, 40-42] As haemodynamic changes in the PACU and the ICU are usually more gradual, as opposed to the rapid haemodynamic changes in the operating theatre, a prediction system could especially be of use.

Hampering widespread implementation of the early warning system are the substantial costs associated with both the obligatory monitor and sensor. The $cNIBP_{finger}$ device, also carriers significant costs.[43] Future studies should assess the effect on patient outcomes but also focus on the cost-effectiveness of continuous non-invasive BP monitoring and of the prevention of hypotension in general.[44]

Key findings of this thesis

In this thesis, we found MSFP to behave as expected within the haemodynamic framework. MSFP has proven beneficial in understanding the circulation. Although it is possible to estimate MSFP and derived variables in clinical care, the direct clinical benefit remains uncertain. MSFP is still in the research phase, and might not yet be fit for clinical use by physicians.

In this thesis, we demonstrated that the use of a machine learning derived algorithm in combination with a treatment flowchart reduced the time weighted average of hypotension during surgery by optimizing preload, afterload and contractility. Future research is needed to understand the effect on patient outcomes.

REFERENCES

1. Maas JJ, Geerts BF, Jansen JR. Evaluation of mean systemic filling pressure from pulse contour cardiac output and central venous pressure. *Journal of clinical monitoring and computing*. Jun 2011;25(3):193-201. doi:10.1007/s10877-011-9294-0
2. Pinsky MR. Instantaneous venous return curves in an intact canine preparation. *J Appl Physiol Respir Environ Exerc Physiol*. Mar 1984;56(3):765-71. doi:10.1152/jappl.1984.56.3.765
3. Guyton AC, Polizo D, Armstrong GG. Mean circulatory filling pressure measured immediately after cessation of heart pumping. *Am J Physiol*. Nov 1954;179(2):261-7. doi:10.1152/ajplegacy.1954.179.2.261
4. Sondergaard S, Larsson JS, Möller PW. The haemodynamic effects of crystalloid and colloid volume resuscitation on primary, derived and efficiency variables in post-CABG patients. *Intensive Care Med Exp*. Mar 4 2019;7(1):13. doi:10.1186/s40635-019-0224-7
5. Werner-Moller P, Berger D, Takala J. Letter to the Editor: Venous return and the physical connection between distribution of segmental pressures and volumes. *Am J Physiol Heart Circ Physiol*. Jan 1 2020;318(1):H203-h204. doi:10.1152/ajpheart.00698.2019
6. van den Berg PC, Jansen JR, Pinsky MR. Effect of positive pressure on venous return in volume-loaded cardiac surgical patients. *J Appl Physiol (1985)*. Mar 2002;92(3):1223-31. doi:10.1152/japplphysiol.00487.2001
7. Jellinek H, Krenn H, Oczenski W, Veit F, Schwarz S, Fitzgerald RD. Influence of positive airway pressure on the pressure gradient for venous return in humans. *J Appl Physiol (1985)*. Mar 2000;88(3):926-32. doi:10.1152/jappl.2000.88.3.926
8. Berger D, Moller PW, Weber A, et al. Effect of PEEP, blood volume, and inspiratory hold maneuvers on venous return. *Am J Physiol Heart Circ Physiol*. Sep 1 2016;311(3):H794-806. doi:10.1152/ajpheart.00931.2015
9. Werner-Moller P, Sondergaard S, Jakob SM, Takala J, Berger D. Effect of volume status on the estimation of mean systemic filling pressure. *J Appl Physiol (1985)*. Jun 1 2019;126(6):1503-1513. doi:10.1152/japplphysiol.00897.2018
10. Helmerhorst HJF, de Wilde RBP, Lee DH, et al. Hemodynamic effects of short-term hyperoxia after coronary artery bypass grafting. *Ann Intensive Care*. Dec 2017;7(1):20. doi:10.1186/s13613-017-0246-9
11. de Wit F, van Vliet AL, de Wilde RB, et al. The effect of propofol on haemodynamics: cardiac output, venous return, mean systemic filling pressure, and vascular resistances. *British journal of anaesthesia*. Jun 2016;116(6):784-9. doi:10.1093/bja/aew126
12. Aditianingsih D, Sukmono B, Agung TA, Kartolo WY, Adiwongso ES, Mochtar CA. Comparison of the Effects of Target-Controlled Infusion of Propofol and Sevoflurane as Maintenance of Anesthesia on Hemodynamic Profile in Kidney Transplantation. *Anesthesiol Res Pract*. 2019;2019:5629371. doi:10.1155/2019/5629371
13. Tanaka M, Nishikawa T. Arterial baroreflex function in humans anaesthetized with sevoflurane. *British journal of anaesthesia*. Mar 1999;82(3):350-4. doi:10.1093/bja/82.3.350
14. Ogawa Y, Iwasaki K, Shibata S, Kato J, Ogawa S, Oi Y. Different effects on circulatory control during volatile induction and maintenance of anesthesia and total intravenous anesthesia: autonomic nervous activity and arterial cardiac baroreflex function evaluated by blood pressure and heart rate variability analysis. *J Clin Anesth*. Mar 2006;18(2):87-95. doi:10.1016/j.jclinane.2005.06.004
15. Ebert TJ, Muzi M, Lopatka CW. Neurocirculatory responses to sevoflurane in humans. A comparison to desflurane. *Anesthesiology*. Jul 1995;83(1):88-95. doi:10.1097/00000542-199507000-00011

16. Bristow JD, Prys-Roberts C, Fisher A, Pickering TG, Sleight P. Effects of anesthesia on baroreflex control of heart rate in man. *Anesthesiology*. Nov 1969;31(5):422-8. doi:10.1097/00000542-196911000-00009
17. Carter JA, Clarke TN, Prys-Roberts C, Spelina KR. Restoration of baroreflex control of heart rate during recovery from anaesthesia. *British journal of anaesthesia*. Apr 1986;58(4):415-21. doi:10.1093/bja/58.4.415
18. Salmasi V, Maheshwari K, Yang D, et al. Relationship between Intraoperative Hypotension, Defined by Either Reduction from Baseline or Absolute Thresholds, and Acute Kidney and Myocardial Injury after Noncardiac Surgery. *Anesthesiology*. 2017-01-01 2017;126(1):47-65.
19. Sessler DI, Bloomstone JA, Aronson S, et al. Perioperative Quality Initiative consensus statement on intraoperative blood pressure, risk and outcomes for elective surgery. *British journal of anaesthesia*. May 2019;122(5):563-574. doi:10.1016/j.bja.2019.01.013
20. Evans L, Rhodes A, Alhazzani W, et al. Surviving Sepsis Campaign: International Guidelines for Management of Sepsis and Septic Shock 2021. *Crit Care Med*. Nov 1 2021;49(11):e1063-e1143. doi:10.1097/ccm.0000000000005337
21. Schenk J, van der Ven WH, Schuurmans J, et al. Definition and incidence of hypotension in intensive care unit patients, an international survey of the European Society of Intensive Care Medicine. *J Crit Care*. Oct 2021;65:142-148. doi:10.1016/j.jcrc.2021.05.023
22. Remington JW, Wood EH. Formation of peripheral pulse contour in man. *J Appl Physiol*. Nov 1956;9(3):433-42. doi:10.1152/jappl.1956.9.3.433
23. Hamilton WF, Dow P. An experimental study of the standing waves in the pulse propagated through the aorta. *American Journal of Physiology-Legacy Content*. 1938;125(1):48-59. doi:10.1152/ajplegacy.1938.125.1.48
24. Ackland GL, Brudney CS, Cecconi M, et al. Perioperative Quality Initiative consensus statement on the physiology of arterial blood pressure control in perioperative medicine. *British journal of anaesthesia*. May 2019;122(5):542-551. doi:10.1016/j.bja.2019.01.011
25. Saugel B, Kouz K, Meidert AS, Schulte-Uentrop L, Romagnoli S. How to measure blood pressure using an arterial catheter: a systematic 5-step approach. *Critical care (London, England)*. Apr 24 2020;24(1):172. doi:10.1186/s13054-020-02859-w
26. Ameloot K, Van De Vijver K, Van Regenmortel N, et al. Validation study of Nexfin® continuous non-invasive blood pressure monitoring in critically ill adult patients. *Minerva Anestesiol*. Dec 2014;80(12):1294-301.
27. Angus DC. Randomized Clinical Trials of Artificial Intelligence. *Jama*. Mar 17 2020;323(11):1043-1045. doi:10.1001/jama.2020.1039
28. Thiele RH, Durieux ME. Arterial waveform analysis for the anesthesiologist: past, present, and future concepts. *Anesthesia and analgesia*. Oct 2011;113(4):766-76. doi:10.1213/ANE.0b013e31822773ec
29. Just A. Mechanisms of renal blood flow autoregulation: dynamics and contributions. *Am J Physiol Regul Integr Comp Physiol*. Jan 2007;292(1):R1-17. doi:10.1152/ajpregu.00332.2006
30. Maheshwari K, Nathanson BH, Munson SH, et al. The relationship between ICU hypotension and in-hospital mortality and morbidity in septic patients. *Intensive Care Med*. 2018;44(6):857-867. doi:10.1007/s00134-018-5218-5
31. Khanna AK, Maheshwari K, Mao G, et al. Association Between Mean Arterial Pressure and Acute Kidney Injury and a Composite of Myocardial Injury and Mortality in Postoperative Critically Ill Patients: A Retrospective Cohort Analysis. *Crit Care Med*. Jul 2019;47(7):910-917. doi:10.1097/ccm.0000000000003763

32. Futier E, Lefrant JY, Guinot PG, et al. Effect of Individualized vs Standard Blood Pressure Management Strategies on Postoperative Organ Dysfunction Among High-Risk Patients Undergoing Major Surgery: A Randomized Clinical Trial. *JAMA*. Oct 10 2017;318(14):1346-1357. doi:10.1001/jama.2017.14172
33. Wu X, Jiang Z, Ying J, Han Y, Chen Z. Optimal blood pressure decreases acute kidney injury after gastrointestinal surgery in elderly hypertensive patients: A randomized study: Optimal blood pressure reduces acute kidney injury. *J Clin Anesth*. Dec 2017;43:77-83. doi:10.1016/j.jclinane.2017.09.004
34. Wijnberge M, Schenk J, Terwindt LE, et al. The use of a machine-learning algorithm that predicts hypotension during surgery in combination with personalized treatment guidance: study protocol for a randomized clinical trial. *Trials*. Oct 11 2019;20(1):582. doi:10.1186/s13063-019-3637-4
35. Georger JF, Hamzaoui O, Chaari A, Maizel J, Richard C, Teboul JL. Restoring arterial pressure with norepinephrine improves muscle tissue oxygenation assessed by near-infrared spectroscopy in severely hypotensive septic patients. *Intensive Care Med*. Nov 2010;36(11):1882-9. doi:10.1007/s00134-010-2013-3
36. Thooft A, Favory R, Salgado DR, et al. Effects of changes in arterial pressure on organ perfusion during septic shock. *Critical care (London, England)*. 2011;15(5):R222. doi:10.1186/cc10462
37. Wesselink EM, Kappen TH, Torn HM, Slooter AJC, van Klei WA. Intraoperative hypotension and the risk of postoperative adverse outcomes: a systematic review. *British journal of anaesthesia*. Oct 2018;121(4):706-721. doi:10.1016/j.bja.2018.04.036
38. Davies SJ, Mythen M. Hemodynamic and Intestinal Microcirculatory Changes in a Phenylephrine Corrected Porcine Model of Hemorrhage. *Anesthesia and analgesia*. Oct 1 2021;133(4):1060-1069. doi:10.1213/ane.0000000000005388
39. Maheshwari K, Turan A, Mao G, et al. The association of hypotension during non-cardiac surgery, before and after skin incision, with postoperative acute kidney injury: a retrospective cohort analysis. *Anaesthesia*. Oct 2018;73(10):1223-1228. doi:10.1111/anae.14416
40. Smischney NJ, Shaw AD, Stapelfeldt WH, et al. Postoperative hypotension in patients discharged to the intensive care unit after non-cardiac surgery is associated with adverse clinical outcomes. *Critical care (London, England)*. Dec 7 2020;24(1):682. doi:10.1186/s13054-020-03412-5
41. van Lier F, Wesdorp F, Liem VGB, et al. Association between postoperative mean arterial blood pressure and myocardial injury after noncardiac surgery. *British journal of anaesthesia*. Jan 2018;120(1):77-83. doi:10.1016/j.bja.2017.11.002
42. Sessler DI, Khanna AK. Perioperative myocardial injury and the contribution of hypotension. *Intensive Care Med*. Jun 2018;44(6):811-822. doi:10.1007/s00134-018-5224-7
43. Gellert G, Bramlage P. Use of the ClearSight(R) System for Continuous Noninvasive Hemodynamic Monitoring during Heart Valve Interventions: Review of the Literature and Single-Site Experience. *The heart surgery forum*. Nov 14 2018;21(6):E476-e483. doi:10.1532/hsf.2177
44. Federici S, Bracalenti M, Meloni F, Luciano JV. World Health Organization disability assessment schedule 2.0: An international systematic review. *Disability and rehabilitation*. Nov 2017;39(23):2347-2380. doi:10.1080/09638288.2016.1223177

Appendices

List of Publications
PhD portfolio
Acknowledgments - Dankwoord
About the author

PUBLICATIONS

Wijnberge M, Parmar K, Kesse-Adu R, Howard J, Cohen AT, Hunt BJ. The utility of thromboelastography and thrombin generation in assessing the prothrombotic state of adults with sickle cell disease. *Thrombosis Research* 2017 (158):113-120

Wijnberge M, Daniels L, Cliteur V, Winkelhagen J.Unusual presentation of a late-onset recurrence of malignant peritoneal mesothelioma. *BMJ Case Reports* 2017(6)

Elbers LP, **Wijnberge M,** Meijers JC, Poland DC, Brandjes DP, Fliers E, Gerdes VE. Coagulation and fibrinolysis in hyperparathyroidism secondary to vitamin D deficiency. *Endocrine Connections* 2018 (2):325-333

Wijnberge M, Sindhunata DP, Pinsky MR, Vlaar AP, Ouweneel E, Jansen JR, Veelo DP, Geerts BF. Estimating mean circulatory filling pressure in clinical practise: a systemic review comparing three beside methods in the critically ill. *Annals of Intensive Care* 2018 (1):73

Kerstens M, **Wijnberge M**, Geerts BF, Vlaar AP, Veelo DP. Non-invasive cardiac output monitoring techniques in the ICU. *Netherlands Journal of Critical Care* 2018(3): 104-110

Wijnberge M, Schenk J, Terwindt LE, Mulder MP, Hollmann MW, Vlaar AP, Veelo DP, Geerts BF. The use of a machine-learning algorithm that predicts hypotension during surgery in combination with personalized treatment guidance: study protocol for a randomized clinical trial. *Trials* 2019 (1):582

Terwindt LE, Karlas AA, Eberl S, **Wijnberge M**, Driessen AH, Veelo DP, Geerts BF, Hollmann MW, Vlaar AP. Patient blood management in the cardiac surgical setting: an updated overview. *Transfusion and Apheresis Science* 2019 (4): 397-407

Wijnberge M, Geerts BF, Hol L, Lemmer N, Mulder MP, Berge P, Schenk J, Terwindt LE, Hollmann MW, Vlaar AP, Veelo DP. Effect of a machine learning-derived early warning system for intraoperative hypotension vs standard care on depth and duration of intraoperative hypotension during elective noncardiac surgery: the hype randomized clinical trial. *JAMA* 2020 (11):1052-1060

Wijnberge M, Schuurmans J, de Wilde RB, Kerstens MK, Vlaar AP, Hollmann MW, Veelo DP, Pinsky MR, Jansen JR, Geerts BF. Defining human mean circulatory filling pressure in the intensive care unit. *Journal of Applied Physiology* 2020 (2):311-316

Wijnberge M, Rellum SR, de Bruin S, Cecconi M, Oczkowski S, Vlaar AP. Erythropoiesis-stimulating agents as replacement therapy for blood transfusions in critically ill patients with anaemia: a systemic review with meta-analysis. *Transfusion Medicine* 2020 (6): 433-441

Vlaar AP, Oczkowski S, de Bruin S, **Wijnberge M**, Antonelli M, Aubron C, Aries P, Duranteau J, Juffermans NP, Meier J, Murphy GJ, Abbasciano R, Muller M, Shah H, Perner A, Rygaard S, Walsh TS, Guyatt G, Dionne JC, Cecconi M. Transfusion strategies in non-bleeding critically ill adults: a clinical practice guideline from the European Society of Intensive Care Medicine. *Intensive Care Medicine* 2020 (4): 673-696

Shah A, Oczkowski S, Aubron C, Vlaar AP, Dionne JC, ESICM Transfusion Task Force; de Bruin S, **Wijnberge M**, Antonelli M, Aries P, Duranteau J, Juffermans N, Meier J, Murphy G, Abbasciano R, Muller M, Rygard S, Perner A, Walsh G, Cecconi M. Transfusion in critical care: Past, present and future. *Transfusion Medicine* 2020 (6): 418-432

Vlaar AP, Oczkowski S, Murphy GJ, Perner A, Guyatt G, Dionne JC, Cecconi M, ESICM Transfusion Task Force; de Bruin S, **Wijnberge M**, Antonelli M, Aubron C, Aries P, Duranteau J, Juffermans N, Meier J, Abbasciano R, Muller M, Shah A, Rygaard S, Walsh T. Guidelines seek unbiased recommendations. *Intensive Care Medicine* 2020 (5):1056-1069.

Vlaar AP, Dionne JC, de Bruin S, **Wijnberge M**, Raasveld SJ, van Baarle FE, Antonelli M, Aubron C, Duranteau J, Juffermans NP, Meier J, Murphy GJ, Abbasciano R, Müller MC, Lance M, Nielsen ND, Schöchl H, Hunt BJ, Cecconi M, Oczkowski S. Transfusion strategies in bleeding critically ill adults: a clinical practice guideline from the European Society of Intensive Care Medicine. *Intensive Care Medicine* 2020 (4): 673-696

Wijnberge M, Schenk J, Bulle E, Vlaar AP, Maheshwari K, Hollmann MW, Binnekade JM, Geerts BF, Veelo DP. Association of intraoperative hypotension with postoperative morbidity and mortality: systemic review and meta-analysis. *BJS Open* 2021 (1)

Wijnberge M, van der Ster BJ, Geerts BF, de Beer F, Beurskens C, Emal D, Hollmann MW, Vlaar AP, Veelo DP. Clinical performance of a machine-learning algorithm to predict intra-operative hypotension with noninvasive arterial pressure waveforms: a cohort study. *European Journal of Anaesthesiology* 2021 (6): 609-615

Van der Ven WH, Terwindt LE, Risvanoglu N, le ELK, **Wijnberge M**, Veelo DP, Geerts BF, Vlaar AP, van der Ster BJ. Performance of a machine-learning algorithm to predict

hypotension in mechanically ventilated patients with COVID-19 admitted to the intensive care unit: a cohort study. *Journal of Clinical Monitoring and Computing* 2021

Van der Ven W, Veelo D, **Wijnberge M,** van der Ster BJ, Vlaar AP, Geerts BF. One of the first validations of an artificial intelligence algorithm for clinical use: The impact on intraoperative hypotension prediction and clinical decision-making. *Surgery* 2021 (6):1300-1303

Klanderman RB, **Wijnberge M,** Bosboom JJ, Roelofs JT, de Korte D, van Bruggen R, Hollmann MW, Vroom MB, Veelo DP, Juffermans NP, Geerts BF, Vlaar AP. Differential effects of speed and volume on transfusion-associated circulatory overload: a randomized study in rats. *Vox Sanguinis* 2021

Dionne JC, Oczkowski SJ, Hunt BJ, Antonelli M, **Wijnberge M,** Raasveld SJ, Vlaar AP; for ESICM Transfusion Taskforce and the GUIDE group. Tranexamic acid in gastrointestinal bleeding: a systematic review and meta-analysis. *Critical Care Medicine* 2021

De Bruin S, Eggermont D, van Bruggen R, de Korte D, Scheeren TW, Bakker J, Vlaar AP, Cardiovascular dynamics section and transfusion task force of the ESICM; Abbasciano R, Antonelli M, Aubron C, van Baarle F, Cecconi M, Dionne J, Duranteau J, Gyatt G, Hunt BJ, Juffermans N, Lance M, Meier J, Muller M, Murphy G, Nielsen N, Oczkowski S, Perner A, Raasveld J, Schochel H, **Wijnberge M.** Transfusion practice in the bleeding critically ill: an international online survey- The TRACE-2 survey. *Transfusion* 2021

Oczkowski S, Shah A, Aubron C, **Wijnberge M**, Vlaar AP; ESICM Transfusion Guideline Part 1 Task force, de Bruin S, Antonelli M, Aries P, Duranteu J, Juffermans N, Meier J, Murphy G, Abbasciano R, Muller M, Perner A, Rygaard S, Walsh T, Dionne J, Guyatt G, Cecconi M. Treating critically ill anemic patients with erythropoietin: less is more. *Intensive Care Medicine* 2021 (2):256-257

Schenk J, **Wijnberge M,** Maaskant JM, Hollmann MW, Hol L, Immink RV, Vlaar AP, van der Ster BJ, Geerts BF, Veelo FP. Effect of hypotension prediction index-guided intraoperative haemodynamic care on depth and duration of postoperative hypotension: a sub-study of the hypotension prediction trial. *BJA* 2021 (5):681-688

Wijnberge M, van der Ster B, Vlaar AP, Hollmann MW, Geerts BF, Veelo DP. The effect of intermittent versus continuous non-invasive blood pressure monitoring on the detection of intraoperative hypotension, a sub-study. *Journal of Clinical Medicine* 2022 (14):4083

De Bruin S, Peters AL, **Wijnberge M**, van Baarle FE, Abdelrahman AH, Vermeulen C, Beuger BM, Reisz JA, D'Alessandro A, Vlaar AP, de Korte D, van Bruggen R. Storage of red blood cells in alkaline PAGGGM improves metabolism but has no effect on recovery after transfusion. *Blood Advances* 2022 (13): 3899-3910

Bosboom JJ, Klanderman RB, Terwindt LE, Bulle EB, **Wijnberge M**, Eberl S, Driessen AH, Winkelman TA, Geerts BF, Veelo DP, Hollmann MW, Vlaar AP. Autologous red blood cell transfusion does not result in a more profound increase in pulmonary capillary wedge pressure compared to saline in critically ill patients: A randomized crossover trial. *Vox Sanguinis* 2022 (8): 1035-1042

Terwindt LE, Schuurmans J, van der Ster BJ, Wensing CA, Mulder MP, **Wijnberge M**, Cherpanath TG, Lagrand WK, Karlas AA, Verlinde MH, Hollmann MW, Geerts BF, Veelo DP, Vlaar AP. Incidence, severity and clinical factors associated with hypotension in patients admitted to an intensive care unit: a prospective observational study. *Journal of Clinical Medicine* 2022

Wijnberge M, Jansen JR, Pinsky MR, Klanderman RB, Terwindt LE, Bosboom JJ, Lemmers N, Vlaar AP, Veelo DP, Geerts BF Feasibility to estimate mean systemic filling pressure with inspiratory holds at the bedside. *Frontiers in Physiology* 2022

PHD PORTFOLIO

PhD student: Marije Wijnberge
PhD period: 2016-2022 (October 2016 – April 2019 fulltime researcher)
PhD supervisors: A.P.Vlaar, M.W.Hollmann, B.F.Geerts, D.P.Veelo

1. PhD training

	Year	ECTS
General courses		
Basic course on organization and regulation for clinical investigators (BROK)	2016	1.5
Good Clinical Practice	2016	1.0
Crash course basis chemistry, biochemistry and molecular	2017	0.4
Biology for MD's starting scientific research	2017	0.6
Clinical Epidemiology: Systematic reviews	2017	0.6
Clinical Epidemiology: Randomized Clinical Trials	2017	0.6
Practical Biostatistics	2017	1.1
Computing in R	2017	0.6
Data analysis in Matlab	2017	0.6
Advanced topics in Biostatistics	2018	1.1
Biosafety and Biosecurity	2018	0.4
Clinical Epidemiology: Evaluation of Medical Tests	2018	0.6
Clinical Epidemiology: Observational studies	2019	0.6
Scientific writing in English for publication	2019	1.5
Re-registration BROK	2020	0.5
Seminars, workshops and master classes		
Medical Business Masterclass	2017	0.4
Machine Learning, Stanford University, Coursera	2017	2.2
Presentations		
European Society of Anaesthesiology, Geneva, Swiss	2017	0.5
Big data symposium Intensive Care, Amsterdam	2018	0.5
Annual Amsterdam Cardiovascular Science	2018	0.5
symposium. Topic: hypotension prediction	2018	0.5
Annual Amsterdam Cardiovascular Science symposium. Topic: mean systemic filling pressure		
9t Rembrandt symposium		
European Society of Intensive Care Medicine, Paris,	2018	0.5
France	2018	0.5
Predictive Monitoring, Barcelona, Spain		
16e Wetenschapsdag, Nederlandse Vereniging voor	2019	0.5
Anesthesiologie, Utrecht, The Netherlands	2019	0.5
European Society of Intensive Care Medicine, Berlin,		
Germany. Topic: erythropoiesis stimulating agents	2019	0.5
European Society of Intensive Care Medicine, Berlin,		
Germany. Topic: hypotension prediction	2019	0.5
Society of Critical Care Medicine, Orlando, United		
States of America. Main stage	2020	0.5
Podcast for the European Society of Anaesthesiology		
and Intensive Care	2021	0.5
Discovery meeting Society of Critical Care Medicine,		
United States of America (online)	2022	0.5
Haemodynamics, Santander, Spain		
	2022	0.5

International conferences		
ISICEM, Brussels, Belgium	2017	0.5
ESA, Geneva, Swiss	2017	0.5
ESICM, Paris, France	2018	0.5
ESICM, Berlin, Germany	2019	0.5
SCCM, Orlando, United States of America	2020	0.5
ESICM, Paris, France	2022	0.5
Other		
Christmas coagulation symposium Anaesthesiology	2016	0.1
ACS symposia	2017	0.2
Sanquin research night	2017	0.1
Spinoza Lecture: building hearts	2017	0.1
Genootschap ter bevordering van natuur- genees- en heelkunde: artificial intelligence	2018	0.1

2. Teaching

	Year	ECTS
Lecturing		
Intensive Care Fellows, Amsterdam UMC	2017	0.2
Intensivists and Anaesthesiologists, Barcelona, Spain	2019	0.2
Intensivists and Anaesthesiologists, Santander, Spain	2022	0.2
Supervising		
Medical student, master thesis	2017	1.0
Medical student, master thesis	2017	1.0
Medical student, master thesis	2017	1.0
Medical student, master thesis	2018	1.0
Medical student, master thesis	2018	1.0
Medical student, extracurricular research	2018 - 2019	1.0
Medical student, extracurricular research	2018 - 2019	1.0
Medical student, extracurricular research	2019 - 2020	1.0
Technical Medicine student, master internship	2018	1.0
Technical Medicine student, master internship	2018	1.0
Technical Medicine student, master internship	2018	1.0
Technical Medicine student, master internship	2019	1.0
Technical Medicine student, master internship	2019	1.0
Other		
Various research meetings; Anaesthesiology, Intensive Care, LEICA and the Haemodynamics group	2016-2019	2.0

3. Parameters of Esteem

	Year
Grants	
Travel grant Amsterdam Infection and Immunity	2018
Awards and Prizes	
Amsterdam UMC Publication Award 2020 Second Prize	2021
Best publication award Nederlandse Vereniging voor Anesthesiologie	2022

DANKWOORD

Het onderzoek gepresenteerd in dit proefschrift was niet mogelijk geweest zonder de hulp van talloze mensen. Graag wil ik iedereen die heeft bijgedragen aan het tot stand komen van dit proefschrift onwijs bedanken.

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Prof. dr. Hollmann, Markus, ik bewonder je altijd kritische blik; een rood gearceerd artikel is een artikel dat goed is bekeken. Ook waardeer ik je streven om de experimentele wetenschappelijke anesthesiologie, en daaruit volgend de anesthesiologische zorg, continue naar een nog hoger niveau te tillen. De anesthesiologie is een droomvak, en zeker niet alleen een vakgebied van slaap en dromen.

Prof. dr. Vlaar, Alexander, met bewondering heb ik gezien hoe je in een record tempo een expert guideline op het gebied van bloedtransfusie opzet. Bedankt dat ik hier onderdeel van mocht zijn. Dank ook voor je immer positieve manier van superviseren. 'Top!' Gedurende mijn PhD ben je niet enkel hoogleraar geworden, maar ook nog eens hoofd van de intensive care. Onwijs gefeliciteerd.

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Dit proefschrift bevat niet enkel data uit Amsterdam. Samenwerken buiten de muren van het AMC was een van de meest waardevolle ervaringen van mijn PhD. Een roadtrip om te sparren met een professor in de statistiek, digitaal advies krijgen van 'the godfather of haemodynamics', of aan de keukentafel zitten bij een fysioloog die zijn eigen robots bouwt. Onwijs bedankt voor jullie welwillendheid om te helpen.

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Kiran Parmar, after working in your lab I was certain I wanted to continue in science before starting a clinical job. Thank you for your warm guidance.

Prof. dr. Beverley Hunt, thank you for being a role model. Your set of skills is truly unique, and I am glad they are recognized. Thank you for your guidance long after I left London.

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Samuel, jij maakt mijn leven mooier. Een levensgenietende surfer, werkend als expert in een academisch ziekenhuis. Beiden arts, maar gelukkig heb je maar globaal een idee van wat er in dit proefschrift staat. Samen de wereld over. Alegría.

Individually, we are a drop. Together, we are an ocean.
Ryunosuke Satoro.

ABOUT THE AUTHOR

Marije Wijnberge was born on Sunday, June 3rd 1990 in Landsmeer, the Netherlands. After ascertaining that the study of medicine would also entail performing scientific experiments, she started her medical training in 2009 at the University of Amsterdam.

Thanks to a junior internship in the cardiology department she became intrigued by physiology. In her second year she took part in a summer school in tropical medicine at the University of Yogjakarta. Here she studied Dengue haemorrhagic fever and her interest in the clotting system was born. Marije continued performing extra-curricular research throughout her bachelor and master studies. In 2015 she was granted the opportunity by prof. dr. Saskia Middeldorp, the Hendrik Muller Fund and the Bekker La Bastide Fund to do a scientific internship in London under the supervision of prof. dr. Beverley Hunt. In 2016 Marije obtained her medical degree with honours.

Over drinks with prof. dr. Alexander Vlaar and dr. Bart Geerts on a rooftop terrace in London, this PhD trajectory was born. During her PhD studies, Marije volunteered for Stichting Bootvluchteling.

After a period of being a fulltime PhD candidate Marije started combining clinical work with research. Under the supervision of dr. Marjolein Rentinck and prof. dr. Pieter Willem Kamphuisen she worked at the cardiology and internal medicine departments of the Tergooi Hospital. The shifts in the emergency room (SEH) and cardiac care unit (CCU) confirmed that her clinical interests would be optimally fuelled by pursuing a career in anaesthesiology and intensive care medicine.

At present, she is a specialty registrar in anaesthesiology (2020-2025) at the Amsterdam University Medical Centers, location AMC, under the supervision of prof. dr. Wolfgang Schlack and dr. Rogier Immink. In 2025 she will start her fellowship intensive care medicine under the supervision of dr. Marcella Müller.

ABOUT THE POEMS FOUND IN THIS THESIS

Science and art work well together. Some of my friends contributed to this book by writing a haiku or finding a poem that –to them- represents haemodynamics.

ABOUT THE COVER

This thesis design was born out of a collaboration between Pawan Anjana and Marije Wijnberge. The choice of paper for the cover represents basic science combined with a modern conceptual translation of the circulation.
The round structure at the left corner represents the heart. Please feel free to use your own imagination to unravel the circulation as a whole.

Marije Wijnberge