## Adverse effects of infusion therapy in anesthesia and intensive care

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Chapter 1

# GENERAL INTRODUCTION AND OUTLINE OF THIS THESIS

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# Background

Oxygen is vital for humans to preserve aerobic metabolism at a mitochondrial level. Maintaining the delivery of oxygen to body tissues is one of the primary treatment goals during anesthesia and in intensive care. One can express delivery of oxygen ($DO_2$) to the tissues on a macro circulatory level as the cardiac output (CO) multiplied by the arterial oxygen content ($CaO_2$). In a formula, we can express delivery of oxygen as follows;

$$DO_2 = CO \times CaO_2$$

or

$$DO_2 = CO \times ((1.31 \times Hb \times SaO_2 \times 0.01) + (0.0225 \times PaO_2))$$

where Hb is the hemoglobin level in gram per deciliter, $SaO_2$ the arterial hemoglobin saturation in percent, and $PaO_2$ the arterial partial pressure of oxygen in kilopascals.

Tissue hypoxia, imbalance of oxygen delivery and consumption of the tissues, will result in a change from aerobic to anaerobic cellular respiration. This anaerobic state can only continue for a limited time. Ultimately, tissue hypoxia will result in cell death. Therefore, anesthesiologists and intensivists focus on optimizing oxygen delivery of their patients.

In clinical practice, the majority of infusion therapies to optimize $DO_2$ include blood transfusion, to increase hemoglobin levels, and fluid administration, to optimize CO. However, both treatments have adverse effects. Complications of blood transfusion include but are not limited to transfusion-associated circulatory overload (TACO), transfusion-related acute lung injury (TRALI), allergic reactions, and transfusion-transmitted infections. Currently, pathophysiologic understanding of TACO, one of the major contributors to transfusion-related morbidity and mortality, is lacking. Furthermore, excessive perioperative fluid administration is associated with increased mortality and morbidity. Therefore, care givers should only prescribe fluid therapy when the expected advantages outweigh the risk of adverse effects.

In this thesis we investigate different aspects of adverse effects of infusion therapy of both transfusion and infusion products in the operating room, intensive care and on the ward. In this chapter we introduce these different aspects.

### Blood transfusion

Annually, physicians prescribe 650.000 transfusion products in the Netherlands. [1] Although studies describe a decline in prescriptions, [2] still 400.000 units of red blood cells (RBCs),

250.000 platelet units and up to 2000 units of plasma are transfused each year. 350.000 volunteers donate blood in a total of 750.000 donations a year. The Dutch blood supply chain Sanquin ensures the availability of high quality and safe transfusion products, as preparation of these products is a complicated process. In short, Sanquin takes 500 ml of whole blood in a single donation. [3] Centrifugation separates the different components; erythrocytes, plasma and buffy coat, consisting of most of the white blood cells and platelets. Filtration separates the white blood cells from the platelets and erythrocytes. The plasma products are pooled, solvent detergent treated and prion filtered to reduce the risk of transfusion-related acute lung injury and transmission of viruses and prions. The particular transfusion products are stored until a patient requires a transfusion.



**Erythrocytes**

Erythrocytes are flexible biconcave hemoglobin-containing cells produced by the bone marrow. Hemoglobin enables erythrocytes to transport oxygen from the lungs to cells anywhere in the body by blood circulation. Patients with a low hemoglobin level have a reduced oxygen-carrying capacity. A transfusion of erythrocytes, or RBCs, is indicated when oxygen consumption of the tissues supersedes oxygen delivery, and hemoglobin transport capacity limits oxygen delivery to the tissue. However, RBCs transfusion carries risks that may, at times, not outweigh the benefit of increasing hemoglobin level.

**Adverse events**

Blood transfusion is associated with numerous complications. Transfusion-related adverse events include TACO, TRALI, hemolytic transfusion reaction, allergic reactions, and transfusion-transmitted bacterial and viral infections. Since the 1990's, national hemovigilance systems opened to improve patient safety through surveillance of adverse events. Recognition of adverse events led to the identification of TRALI as a significant cause of transfusion-related morbidity, resulting in research on risk factors, pathogenesis, and prevention of TRALI. [8] After the introduction of multiple mitigation strategies, including solvent/detergent treatment of pooled plasma and male-only plasma, the incidence of TRALI has dropped significantly. [9,10] Currently, TACO is the leading severe transfusion-related adverse event, [11-13] with an incidence of 1-6 % in transfused patients. [14-17]

**Transfusion-associated circulatory overload (TACO)**

TACO is marked by the formation of pulmonary edema after transfusion, resulting in respiratory distress. [18] Traditionally, TACO is regarded as a circulatory volume overload due to the transfusion product. Circulatory overload will increase hydrostatic pulmonary

pressure, resulting in pulmonary edema. Yet, fever is reported in one-third of TACO cases, [19] and leukoreduction of RBCs decreased the incidence of TACO. [20] Therefore, it has been suggested pro-inflammatory mediators may play a role in TACO pathogenesis. However, there is a lack of trials providing insights into the TACO pathogenesis. Furthermore, it is hard to differ TACO from conventional circulatory overload resulting in cardiogenic pulmonary edema. There is a need for studies on the formation of pulmonary edema after the transfusion of blood products, giving mechanistic insights into TACO pathogenesis and differentiation from conventional circulatory overload.

### Diagnosis

The diagnosis of TACO is made at the bedside, based on a combination of symptoms. These symptoms are supported by evidence of pulmonary edema and circulatory overload. The recognition of changes in vital signs is crucial for TACO diagnosis. [21] However, no clear diagnostic criteria have been defined. In a revised surveillance definition, the International Society of Blood Transfusion, the International Haemovigilance Network, and AABB defined TACO as a syndrome combining various general symptoms. Within 12 hours after transfusion, these symptoms should include acute or worsening respiratory distress or evidence of pulmonary edema, and a total of three or more criteria of the latter and the following; development of cardiovascular system changes not explained by the patient's underlying medical condition, evidence of fluid overload, or supportive result of a relevant biomarker. [22] These nonspecific symptoms are also used in anesthesia and ICU patients, who commonly present with a number of these criteria. Since the symptoms are nonspecific, a clinical TACO diagnosis is challenging. It is crucial to understand with which criteria care providers make a diagnosis, as this can help in identification of knowledge gaps, early recognition of TACO and initiation of therapy.

### Risk factors

Identification of risk factors is important, to identify those patients where the risks for TACO outweighs the benefit of a transfusion. Furthermore, risk factors can help to form a hypothesis for TACO pathogenesis. Surveillance studies identified heart failure, kidney disease and beta-blocker use as risk factors for TACO in a surgical, medical Intensive Care Unit (ICU), and hospital wide population. [16,23-25] Furthermore, several investigations with limited sample size, have found the infusion rate, [16] number of transfused products, [16,24] and plasma transfusion to be product-specific risk factors. [16,23,26] However, there is conflicting evidence with respect to plasma transfusion being an independent risk factor for the development of TACO. [25] Patients with a limited reserve to compensate for the

additional volume load associated with a transfusion are at risk. However, it remains to be determined how pulmonary edema after transfusion (after a limited volume of the equivalent of two coffee) is different from conventional circulatory overload without a blood transfusion.

### Perioperative infusion therapy

Perioperative infusion therapy is necessary to prevent hypovolemia due to bleeding and is used to optimize CO. Hypovolemia may result in tissue hypoxia by a diminished $DO_2$ due to a decrease in CO. Perioperative hypovolemia is mainly associated with kidney failure. Correction of hypovolemia depicts a risk of excessive fluid administration leading to hypervolemia. Hypervolemia has adverse effects such as pulmonary and tissue edema. Perioperative excessive fluid administration is associated with adverse outcome including respiratory insufficiency and renal injury. The field investigating the perioperative fluid management is broad. In this thesis, we will focus on strategies to prevent hypervolemia in the perioperative period. We will focus on of the association of fluid therapy on the ward and patient outcome, and a novel method of non-invasive CO monitoring to guide fluid therapy, which can have impact in environments without quick access to invasive monitoring. It remains challenging for care providers to assess the actual volume status of their patient, illustrated by the variability of infusion therapy in clinical practice. [27]

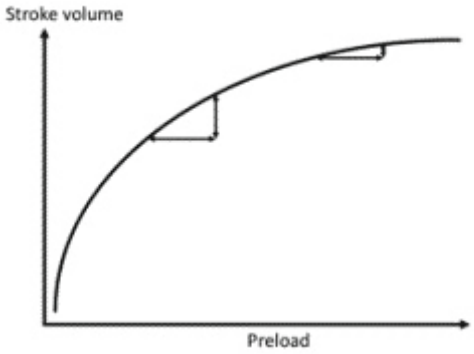
### Ward fluid therapy

Although surgical patients spent most of their time during a hospital admittance in the ward, there is limited data for fluid administration on the ward and its relation to patient outcome. Currently, there are multiple challenges at the ward for patient tailored fluid administration. Vital signs are measured 3 times a day, nurses and doctors have a round once a day, and in 75% of the hospitals no protocols for fluid therapy are present. There is a need for studies investigating the association between perioperative fluid administration and outcome.

### Cardiac output optimization

Besides prevention of hypovolemia, practitioners administer fluids to optimize CO. CO is expressed as the stroke volume (SV) multiplied by the heart rate. SV depends on preload, contractility and afterload of the heart. The relation between the preload and SV is expressed in the Frank-Starling curve (figure 1).

Figure 1. Frank-Starling curve




In this figure, two hypothetical patients are treated with a fluid challenge. A fixed amount of fluid in time is administered to increase preload, and thereby SV. Administration of a fluid challenge to a patient on the steep left part of the curve will lead to a modest increase in SV. In contrast, the same fluid challenge and increase in preload to a patient on the right horizontal part of the curve has minimal effect on SV. Merely, half of OR and ICU patients will demonstrate a significant increase in CO after a fluid challenge, indicating that they are on the horizontal part of the curve.

**Cardiac output measurement**

An accurate and precise CO monitoring method is essential to identify patients with a low CO. CO optimization is recommended for the high-risk surgical population. [30,31] Current CO monitoring devices are invasive, difficult to use, operator-dependent, non-continuous, or expensive. The more recently developed non-invasive finger cuff methods seem less accurate, [32] and CO measurements are not comparable to those employing more invasive methods. [33] Common carotid artery (CCA) blood flow measurement by ultrasound has been suggested as a novel method to estimate CO. [34-36] A non-invasive, easy-to-use CO monitoring device that is accurate and precise would be a helpful tool to optimize CO, in environments where more invasive CO monitoring techniques are contra-indicated, or not directly available.

## Outline of this thesis

The obvious relation between infusion therapy and adverse outcomes is the starting point of this thesis. In this thesis we investigated a selection of adverse events following transfusion and infusion therapy during anesthesia and intensive care. The aims of this thesis were first, to investigate the current clinical perspective on TACO, TACO diagnosing and reporting, and risk factors for TACO, in comparison to patients with fluid overload in the absence of a transfusion, to form a hypothesis regarding the pathophysiology of TACO and to provide insights as to for which patients the risk of TACO outweighs the potential benefit of a transfusion. Second, to investigate colloid osmotic pressure of transfusion products and the effect of red blood cells transfusion in comparison to saline infusion on pulmonary edema formation as possible mechanisms for TACO. Third, to investigate a restrictive fluid regimen on the ward and a novel non-invasive CO measurement as potential ways to optimize infusion therapy in the perioperative period.



Clinical research reported in this thesis has been performed at the department of Anesthesiology and Intensive Care of the Amsterdam UMC, location AMC , Amsterdam, The Netherlands. Pre-clinical studies were performed at the Laboratory of Intensive Care and Anesthesiology of the Amsterdam UMC, location AMC, Amsterdam, at the laboratory for Clinical Chemistry and Hematology, University Medical Centre, Utrecht, and the laboratory of Sanquin Blood Bank, Amsterdam, The Netherlands

**Part I** of this thesis focusses on transfusion-associated circulatory overload.

**Chapter 2** systematically reviews the recent literature on advances in pathophysiological understanding, risk factors, diagnostic modalities and therapeutic interventions of transfusion-associated circulatory overload.

In **chapter 3**, we performed a survey among professionals involved in blood transfusion to investigate the practice of diagnosing and reporting transfusion-associated circulatory overload in the Netherlands.

In **chapter 4**, we retrospectively investigated the incidence, risk factors and outcome of transfusion-associated circulatory overload in intensive care patients, in comparison to patients with fluid overload in the absence of a transfusion.

**Chapter 5** describes the colloid osmotic pressure of current and future transfusion products and its relation to possible mechanisms of transfusion-associated circulatory overload.

In **chapter 6,** we investigated in a randomized crossover trial the effect of autologous red blood cells transfusion and saline on pulmonary capillary wedge pressure and pulmonary edema.

**Part II** of this thesis explores potential ways to optimize perioperative infusion therapy.

**Chapter 7** systematically reviews the effects of a restrictive fluid strategy in postoperative surgical patients on the ward. We performed a meta-analysis to investigate whether postoperative restrictive fluid administration is associated with patient outcome.

**Chapter 8** describes the results of a diagnostic accuracy study on the performance of cardiac output estimation by non-invasive carotid artery ultrasound measurements compared to transpulmonary thermodilution derived cardiac output.

**Chapter 9** discusses the results the studies focusing on transfusion-associated circulatory overload and potential strategies to improve perioperative fluid management and provides future perspectives.

**Chapter 10** is een Nederlandse samenvatting van de resultaten van deze thesis en een toekomstperspectief.

# References


1. Sanquin. Jaarverslag 2018.
2. Hoeven L, Koopman R, Koffijberg H, Roes K, Janssen M. Historical time trends in red blood cell usage in the Netherlands. International Journal of Clinical Transfusion Medicine 2016;**Volume 4**: 67-77.
3. Sanquin S. Bloedwijzer, 2019.
4. Carson JL, Guyatt G, Heddle NM, Grossman BJ, Cohn CS, Fung MK, Gernsheimer T, Holcomb JB, Kaplan LJ, Katz LM, Peterson N, Ramsey G, Rao SV, Roback JD, Shander A, Tobian AAR. Clinical Practice Guidelines From the AABB: Red Blood Cell Transfusion Thresholds and Storage. JAMA 2016;**316**: 2025-35.
5. Roffi M, Patrono C, Collet JP, Mueller C, Valgimigli M, Andreotti F, Bax JJ, Borger MA, Brotons C, Chew DP, Gencer B, Hasenfuss G, Kjeldsen K, Lancellotti P, Landmesser U, Mehilli J, Mukherjee D, Storey RF, Windecker S. 2015 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation: Task Force for the Management of Acute Coronary Syndromes in Patients Presenting without Persistent ST-Segment Elevation of the European Society of Cardiology (ESC). Eur Heart J 2016;**37**: 267-315.
6. Rossaint R, Bouillon B, Cerny V, Coats TJ, Duranteau J, Fernández-Mondéjar E, Filipescu D, Hunt BJ, Komadina R, Nardi G, Neugebauer EA, Ozier Y, Riddez L, Schultz A, Vincent JL, Spahn DR. The European guideline on management of major bleeding and coagulopathy following trauma: fourth edition. Crit Care 2016;**20**: 100.
7. Theusinger OM, Spahn DR, Ganter MT. Transfusion in trauma: why and how should we change our current practice? Curr Opin Anaesthesiol 2009;**22**: 305-12.
8. Vlaar APJ, Juffermans NP. Transfusion-related acute lung injury: a clinical review. The Lancet 2013;**382**: 984-94.
9. Vossoughi S, Gorlin J, Kessler DA, Hillyer CD, Van Buren NL, Jimenez A, Shaz BH. Ten years of TRALI mitigation: measuring our progress. Transfusion 2019;**59**: 2567-74.
10. Otrock ZK, Liu C, Grossman BJ. Transfusion-related acute lung injury risk mitigation: an update. Vox Sang 2017;**112**: 694-703.
11. TRIP Rapport 2018 Hemovigulantie. Available at https://www.tripnet.nl/wp-content/uploads/2020/01/Trip.HEMO_uitgebreid-2018_versie-def.met-links.pdf. Accessed 13 november 2020.
12. Annual SHOT report 2019 summary. Available at https://www.shotuk.org/wp-content/uploads/myimages/2019-SHOT-Summary.pdf. Accessed 13 november 2020.
13. Fatalities reported to FDA following blood collection and transfusion. Annual summary for fiscal year 2018. Available at: https://www.fda.gov/media/136907/download. Accessed 13 november 2020.
14. Popovsky MA, Audet AM, Andrzejewski C, Jr. Transfusion-associated circulatory overload in orthopedic surgery patients: a multi-institutional study. Immunohematology 1996;**12**: 87-9.
15. Roubinian NH, Hendrickson JE, Triulzi DJ, Gottschall JL, Chowdhury D, Kor DJ, Looney MR, Matthay MA, Kleinman SH, Brambilla D, Murphy EL. Incidence and clinical characteristics of transfusion-associated circulatory overload using an active surveillance algorithm. Vox Sang 2017;**112**: 56-63.
16. Li G, Rachmale S, Kojicic M, Shahjehan K, Malinchoc M, Kor DJ, Gajic O. Incidence and transfusion risk factors for transfusion-associated circulatory overload among medical intensive care unit patients. Transfusion 2011;**51**: 338-43.
17. Leanne C, Qing J, Hemang Y, Arun S, Gregory AW, Sean PM, Jyotishman P, Darrell RS, Mark HE, Daryl JK. Characterizing the Epidemiology of Perioperative Transfusion-associated Circulatory Overload. Anesthesiology;**122**: 21.
18. Andrzejewski C, Jr., Casey MA, Popovsky MA. How we view and approach transfusion-associated circulatory overload: pathogenesis, diagnosis, management, mitigation, and prevention. Transfusion 2013;**53**: 3037-47.
19. Parmar N, Pendergrast J, Lieberman L, Lin Y, Callum J, Cserti-Gazdewich C. The association of fever with transfusion-associated circulatory overload. Vox Sang 2017;**112**: 70-8.

20. Blumberg N, Heal JM, Gettings KF, Phipps RP, Masel D, Refaai MA, Kirkley SA, Fialkow LB. An association between decreased cardiopulmonary complications (transfusion-related acute lung injury and transfusion-associated circulatory overload) and implementation of universal leukoreduction of blood transfusions. Transfusion 2010;**50**: 2738-44.
21. Andrzejewski C, Jr., Popovsky MA, Stec TC, Provencher J, O'Hearn L, Visintainer P, Steingrub J. Hemotherapy bedside biovigilance involving vital sign values and characteristics of patients with suspected transfusion reactions associated with fluid challenges: can some cases of transfusion-associated circulatory overload have proinflammatory aspects? Transfusion 2012;**52**: 2310-20.
22. Wiersum-Osselton JC, Whitaker B, Grey S, Land K, Perez G, Rajbhandary S, Andrzejewski C, Jr., Bolton-Maggs P, Lucero H, Renaudier P, Robillard P, Santos M, Schipperus M. Revised international surveillance case definition of transfusion-associated circulatory overload: a classification agreement validation study. Lancet Haematol 2019;**6**: e350-e8.
23. Clifford L, Jia Q, Subramanian A, Yadav H, Schroeder DR, Kor DJ. Risk Factors and Clinical Outcomes Associated with Perioperative Transfusion-associated Circulatory Overload. Anesthesiology 2017;**126**: 409-18.
24. Murphy EL, Kwaan N, Looney MR, Gajic O, Hubmayr RD, Gropper MA, Koenigsberg M, Wilson G, Matthay M, Bacchetti P, Toy P, Group TS. Risk factors and outcomes in transfusion-associated circulatory overload. Am J Med 2013;**126**: 357 e29-38.
25. Roubinian NH, Hendrickson JE, Triulzi DJ, Gottschall JL, Michalkiewicz M, Chowdhury D, Kor DJ, Looney MR, Matthay MA, Kleinman SH, Brambilla D, Murphy EL. Contemporary Risk Factors and Outcomes of Transfusion-Associated Circulatory Overload. Crit Care Med 2018.
26. Refaai MA, Goldstein JN, Lee ML, Durn BL, Milling TJ, Jr., Sarode R. Increased risk of volume overload with plasma compared with four-factor prothrombin complex concentrate for urgent vitamin K antagonist reversal. Transfusion;**55**: 2722-9.
27. Lilot M, Ehrenfeld JM, Lee C, Harrington B, Cannesson M, Rinehart J. Variability in practice and factors predictive of total crystalloid administration during abdominal surgery: retrospective two-centre analysis. Br J Anaesth 2015;**114**: 767-76.
28. Michard F, Teboul JL. Using heart-lung interactions to assess fluid responsiveness during mechanical ventilation. Crit Care 2000;**4**: 282-9.
29. Monnet X, Teboul JL. Assessment of volume responsiveness during mechanical ventilation: recent advances. Crit Care 2013;**17**: 217.
30. Vincent JL, Pelosi P, Pearse R, Payen D, Perel A, Hoeft A, Romagnoli S, Ranieri VM, Ichai C, Forget P, Della Rocca G, Rhodes A. Perioperative cardiovascular monitoring of high-risk patients: a consensus of 12. Crit Care 2015;**19**: 224.
31. Cecconi M, De Backer D, Antonelli M, Beale R, Bakker J, Hofer C, Jaeschke R, Mebazaa A, Pinsky MR, Teboul JL, Vincent JL, Rhodes A. Consensus on circulatory shock and hemodynamic monitoring. Task force of the European Society of Intensive Care Medicine. Intensive Care Med 2014;**40**: 1795-815.
32. Ameloot K, Palmers PJ, Malbrain ML. The accuracy of noninvasive cardiac output and pressure measurements with finger cuff: a concise review. Curr Opin Crit Care 2015;**21**: 232-9.
33. Saugel B, Hoppe P, Nicklas JY, Kouz K, Körner A, Hempel JC, Vos JJ, Schön G, Scheeren TWL. Continuous noninvasive pulse wave analysis using finger cuff technologies for arterial blood pressure and cardiac output monitoring in perioperative and intensive care medicine: a systematic review and meta-analysis. Br J Anaesth 2020;**125**: 25-37.
34. Weber U, Glassford NJ, Eastwood GM, Bellomo R, Hilton AK. A Pilot Assessment of Carotid and Brachial Artery Blood Flow Estimation Using Ultrasound Doppler in Cardiac Surgery Patients. J Cardiothorac Vasc Anesth 2016;**30**: 141-8.
35. Ma IWY, Caplin JD, Azad A, Wilson C, Fifer MA, Bagchi A, Liteplo AS, Noble VE. Correlation of carotid blood flow and corrected carotid flow time with invasive cardiac output measurements. Crit Ultrasound J 2017;**9**: 10.
36. Gassner M, Killu K, Bauman Z, Coba V, Rosso K, Blyden D. Feasibility of common carotid artery point of care ultrasound in cardiac output measurements compared to invasive methods. J Ultrasound 2015;**18**: 127-33.