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Definition and incidence of hypotension in intensive care unit patients, an international survey of the European Society of Intensive Care Medicine



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ABSTRACT

Introduction: Although hypotension in ICU patients is associated with adverse outcome, currently used definitions are unknown and no universally accepted definition exists.

Methods: We conducted an international, peer-reviewed survey among ICU physicians and nurses to provide insight in currently used definitions, estimations of incidence, and duration of hypotension.

Results: Out of 1394 respondents (1055 physicians (76%) and 339 nurses (24%)), 1207 (82%) completed the questionnaire. In all patient categories, hypotension definitions were predominantly based on an absolute MAP of 65 mmHg, except for the neuro(trauma) category (75 mmHg, $p < 0.001$), without differences between answers from physicians and nurses. Hypotension incidence was estimated at 55%, and time per day spent in hypotension at 15%, both with nurses reporting higher percentages than physicians (estimated mean difference 5%, $p = 0.01$; and 4%, $p < 0.001$).

Conclusions: An absolute MAP threshold of 65 mmHg is most frequently used to define hypotension in ICU patients. In neuro(trauma) patients a higher threshold was reported. The majority of ICU patients are estimated to endure hypotension during their ICU admission for a considerable amount of time, with nurses reporting a higher estimated incidence and time spent in hypotension than physicians.

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1. Introduction

Hypotension is frequently encountered in Intensive Care Unit (ICU) patients and may be defined by alterations in systolic blood pressure (SBP), mean arterial pressure (MAP) and/or diastolic blood pressure (DBP). Reported incidences of hypotension in the ICU are dependent on the definition used, and range from 23% to 72% [1–4]. Most frequently occurring causes for hypotension are hypovolemic, distributive and

cardiogenic shock with previously reported incidences of 62.2%, 16.7% and 15.5%, respectively [5].

Both depth and duration of hypotensive events affect the association of hypotension with morbidity and mortality [2,6–10]. This association has been reported in various ICU patient groups. However, strengths of associations between studies vary, with differences among studied outcomes, studied patient groups and the definition used to define hypotension [2,4,7,10–17].

A systematic review reported up to 140 different definitions of hypotension in intraoperative studies [18]. A comprehensive overview of definitions used in the ICU is not available, but those commonly reported are based on an absolute SBP or MAP threshold, or a percentage change in SBP or MAP from baseline [19–21]. A recent survey among

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European critical care providers reported no consensus on the blood pressure target for critically ill trauma patients [22]. Currently, no universally adopted definition for the depth and/or duration of a hypotensive event in the ICU exists. As a consequence, data on incidence and severity of hypotension are difficult to compare, hampering progress in this field of hemodynamic management in intensive care medicine.

The aim of this worldwide survey among ICU physicians and nurses was to assess currently used hypotension definitions, its variation among patient categories and estimations of hypotension incidence. Furthermore, responses of physicians and nurses regarding the definition and incidence of hypotension were compared.

2. Methods

This international open survey was peer-reviewed and endorsed by the European Society of Intensive Care Medicine (ESICM) and received in-principle support of the World Federation of Intensive and Critical Care. The questionnaire was available on the ESICM website and was distributed among their members in their newsletter. Furthermore, national societies for Intensive Care physicians and nurses were contacted and asked to distribute the questionnaire among their members, with a maximum of two reminders. A list of distributing societies is available in Supplemental Appendix A. Questionnaire distribution was at the discretion of the society, either via email, newsletter or social media. The online questionnaire (listed in Supplemental Appendix B) was available from November 20, 2019 until April 1, 2020.

2.1. Ethical considerations

Institutional approval was obtained from the medical ethical committee of Amsterdam UMC (W19_292). Participation was anonymous, voluntary and none of the presented results can be traced to an individual. No incentive was offered for participating. Upon start of the questionnaire, the respondents agreed on analyses and publication of their provided answers.

2.2. Survey development

This survey was developed to provide insight in the opinion of ICU physicians and nurses, regarding two aspects of hypotension in ICU patients: 1) definitions and incidence and 2) management and outcome. Since both aspects are closely related and would be studied within the same target population, we opted for a combined questionnaire of the two sections, thereby minimizing the burden for participants.

The combined questionnaire was developed by a focus group ($n = 8$) consisting of physicians, nurses, epidemiologists and a methodologist at Amsterdam UMC, according to the guide of the Association for Medical Education in Europe (AMEE) [23]. Items were created following a non-systematic review of the literature on hypotension in ICU patients. The questionnaire was built in SurveyMonkey Platinum (SurveyMonkey Inc., San Mateo, CA, USA). An expert panel ($n = 11$) of Dutch anaesthesiologists and intensivists evaluated the questionnaire. Finally, the survey was pretested for face and content validity, including relevance and readability, by 9 physicians and 9 nurses working in the ICU of Amsterdam UMC. Aiken's Content Validity Coefficient V was calculated to quantify content validity, and eleven questions were adjusted based on the results of the preliminary evaluation and the face and content validity pretest [24]. Development of the questionnaire followed the Consensus-based Standards for the selection of health status Measurement Instruments (COSMIN) criteria [25].

The questionnaire contained 129 questions, with the number of questions per respondent varying between 42 and 69 due to skip logic. It was possible to review and edit every question until submission. Respondents' demographics (including occupation and area of training) and the type and size of their ICU were collected in questions 1–10. The first section of the questionnaire entailed questions on: the definition of

hypotension in general and various ICU patient categories (questions 11 to 87); the definition of post-induction hypotension (questions 88 to 98); the minimum duration to define a hypotensive event (questions 99 and 100), and the incidence of hypotension (questions 101 to 103). The second section of the questionnaire included questions on the opinion on associated outcomes and management of hypotension (questions 104 to 129). A flowchart visualising and explaining possible pathways through the questionnaire is available in Supplemental Appendix C. This study reports on the findings of the first section of the questionnaire.

2.3. Target population

To obtain a balanced and reliable overview of the current views on definitions and incidence of hypotension in ICU patients, we were interested in the opinions of both ICU physicians and nurses. Therefore, the target population was a convenience sample of physicians and nurses working in any type of ICU, worldwide. Intensivists, ICU trainees, and specialists (non-intensivist) practising ICU are referred to as physicians; Critical Care Nurses, Nurse Practitioners and Physician Assistants are referred to as nurses. Respondents were asked to answer questions from the perspective of standard practice in their ICU. To facilitate comparison between physicians and nurses a minimum sample size, regardless of question category, given a theoretical population size of $> 10,000$, was calculated at 740 valid responses (370 per group), with a 0.05 two-sided significance level [26].

2.4. Statistical analyses

Data were downloaded from the Survey Monkey server as a csv file and subsequently stored as an Excel file (Microsoft Corp, Redmond, WA, USA). Responses were considered valid if both the demographic questions and at least one question of the first section were answered. Open-ended questions answered in non-English languages were censored for analyses. Any missing data was not imputed.

Continuous data are presented as mean with standard deviation (SD), or median with Interquartile Range (IQR) when appropriate. Normality of data distribution was assessed visually using boxplots, histograms and Q-Q plots, and statistically using the Shapiro-Wilk normality test. 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. Analyses were performed using R, version 3.5.1. (R Core Team, Vienna, Austria) [27].

While developing the survey, physicians and nurses were identified as two main subgroups, allowing analyses of differences based on occupation. The potential effect of confounding differences between groups were analysed using (multivariate) linear and logistic regression techniques when appropriate. The results are reported according to the Checklist for Reporting Results of Internet *E*-Surveys (CHERRIES) guideline [28].

3. Results

3.1. Survey respondents

A total of 1464 respondents started the questionnaire. From these, 49 were excluded for only answering demographic questions, and 21 were excluded for reporting an occupation other than ICU physician or nurse. Out of the 1394 respondents included for analyses, 1207 (82.4%) completed the questionnaire (see Supplemental Appendix C), with a significantly higher completion rate among physicians when compared to nurses (88.6% vs 80.2%, $p < 0.001$).

Table 1
Baseline characteristics.

	Total n = 1394	Physician n = 1055	Nurse n = 339	p value
Age, mean (SD)	42.6 (10.3)	43.4 (10.1)	40.2 (10.8)	<0.001
Male, n (%)	813 (58.3)	715 (67.8)	98 (28.9)	<0.001
Primary area of training, n (%)				
Anesthesiology		615 (61.3)		
Internal Medicine		192 (19.1)		
Cardiology		29 (2.9)		
Neurology		24 (2.4)		
Pulmonology		23 (2.3)		
Surgery		22 (2.2)		
Other		98 (9.8)		
Years of experience, n (%)				0.001
<2	110 (7.9)	71 (6.7)	39 (11.5)	
2–5	325 (23.3)	232 (22.0)	93 (27.4)	
6–10	290 (20.8)	239 (22.7)	51 (15.0)	
11–20	371 (26.6)	286 (27.1)	85 (25.1)	
>20	298 (21.4)	227 (21.5)	71 (20.9)	
Employed in, n (%)				<0.001
Europe	773 (55.5)	623 (59.1)	150 (44.2)	
Asia	298 (21.4)	280 (26.6)	18 (5.3)	
North America	229 (16.4)	79 (7.5)	150 (44.2)	
South America	47 (3.4)	36 (3.4)	11 (3.2)	
Oceania	26 (1.9)	19 (1.8)	7 (2.1)	
Africa	20 (1.4)	17 (1.6)	3 (0.9)	
Hospital type, n (%)				<0.001
University (academic) hospital	605 (43.4)	490 (46.4)	115 (33.9)	
Non-university public hospital	372 (26.7)	243 (23.0)	129 (38.1)	
University affiliated hospital	207 (14.8)	160 (15.2)	47 (13.9)	
Private hospital	188 (13.5)	146 (13.8)	42 (12.4)	
Other	22 (1.6)	16 (1.5)	6 (1.8)	
ICU type, n (%)				0.001
Mixed	977 (70.1)	745 (70.6)	232 (68.4)	
Surgical/Trauma	121 (8.7)	97 (9.2)	24 (7.1)	
Cardiac	110 (7.9)	74 (7.0)	36 (10.6)	
Neurological	64 (4.6)	40 (3.8)	24 (7.1)	
Post-Anesthesia Care Unit	54 (3.9)	50 (4.7)	4 (1.2)	
Other	68 (4.9)	49 (4.6)	19 (5.6)	
ICU beds, n (%)				0.047
≤10	407 (29.2)	320 (30.3)	87 (25.7)	
11–15	335 (24.0)	264 (25.0)	71 (20.9)	
16–20	250 (17.9)	182 (17.3)	68 (20.1)	
>20	402 (28.8)	289 (27.4)	113 (33.3)	

Table 2
Reported thresholds used to define hypotension in a general patient, regardless of patient category.

Questions 11–21 Is there a threshold to define hypotension in a general patient?	n (%)	median [IQR], mmHg or %
Yes	993 (71.2)	
SBP: absolute threshold	162	90 [85–90]
SBP: % change threshold	47	–25 [–30 to –20]
MAP: absolute threshold	611	65 [65–65]
MAP: % change threshold	149	–25 [–25 to –20]
No	352 (25.3)	
I don't know	49 (3.5)	

Table 1 shows baseline characteristics of the respondents. Physicians were more strongly represented than nurses (75.7% vs 24.3%, $p < 0.001$). A heat map showing respondent frequencies for all countries is available in Fig. 1. Overall, most respondents were European (55.5%), and were working at a university (academic) hospital (43.4%). With 70.1%, respondents from ICUs with a mixed patient population were most common. The total bed count per ICU was evenly distributed among respondents. Statistically significant differences between physicians and nurses were found for all demographic questions.

3.2. Reported hypotension thresholds

Overall, 993 respondents (71.2%) stated that a certain threshold to define hypotension is used in their ICU for a general patient, regardless of diagnosis or background. 298 respondents (21.4%) reported that hypotension thresholds vary between patient categories, and 90 (6.5%) stated that there is no threshold used in their ICU. Absence of a definition was more commonly reported by males (73.7% vs 57.3% $p = 0.003$), and participants employed in Europe, without a difference between physicians and nurses. Furthermore, 13 participants (0.9%) were not aware of any threshold used in their ICU.

A threshold to define hypotension, regardless of diagnosis or background, was predominantly based on an absolute MAP value (61.5%), with a median threshold of 65 mmHg [IQR 65–65] (Table 2). If not based on an absolute MAP value, the threshold was based on an

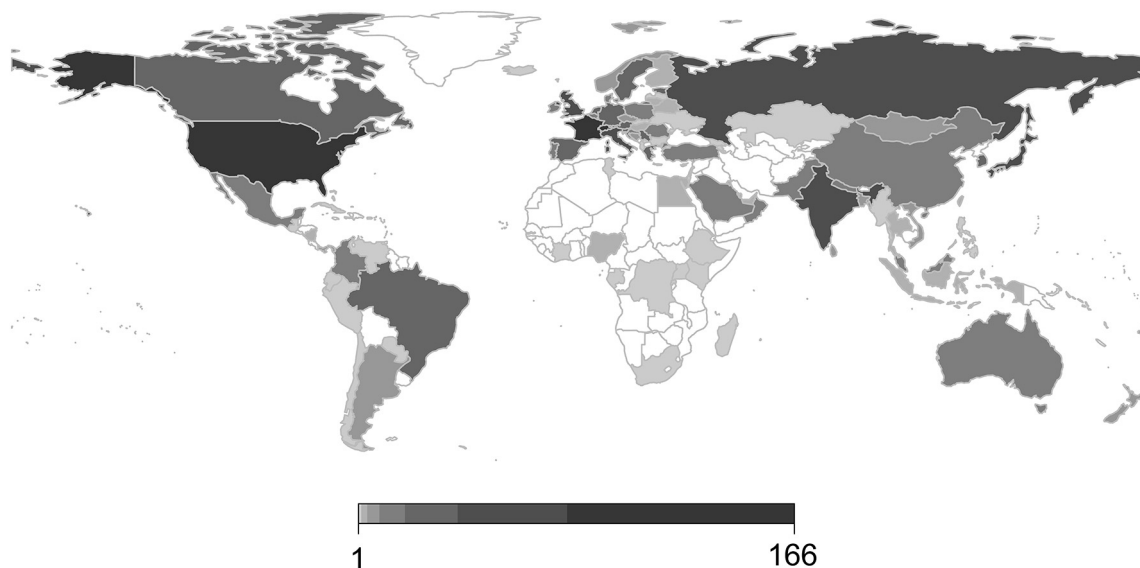


Fig. 1. Respondent frequencies for all countries.

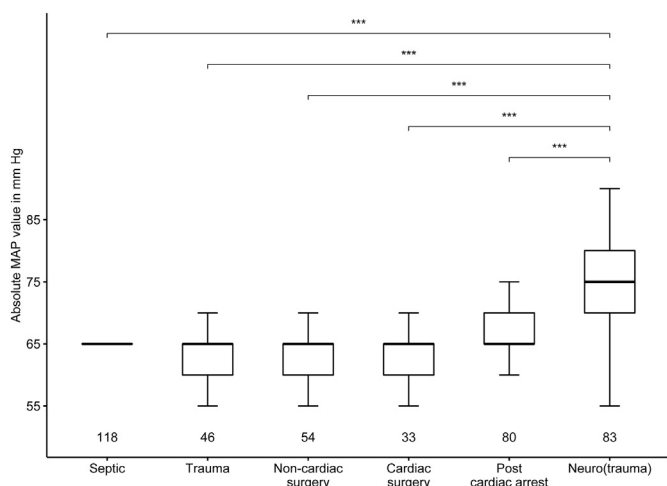


Fig. 2. Boxplots of absolute MAP thresholds in different patient categories. The number of respondents is depicted under each boxplot. The absolute MAP threshold in the neuro (trauma) category is statistically significantly higher in comparison to each of the other categories (Wilcoxon rank-sum, $p < 0.001$ (***)).

absolute SBP value (16.3%, median 90 mmHg, IQR 85–95) or on a percentage change of MAP from baseline (15%, median change 25%, IQR 20–30).

When respondents indicated that the threshold is dependent on patient category, it was also based on an absolute MAP value in the majority of cases (62.6%). The average reported value of absolute MAP thresholds per patient category is visualised in Fig. 2. The median absolute MAP threshold to define hypotension is 65 mmHg in all patient categories, with a statistically significant difference in the neuro(trauma) category (median 75 mmHg, IQR 70–80, $p < 0.001$), in comparison with each other category (Table 3 and Fig. 2). The averages for threshold definitions based on relative change in MAP, absolute SBP, and relative change in SBP are available in Table 3. Definitions based on DBP were not included in tables and figures, since they were only reported by 6 respondents (0.6%). A minimum duration to define a hypotensive event was reported by 29.6% of the respondents, with a median of 10 min [IQR 5–10]. No statistically significant differences in hypotension definitions or duration were found when comparing the answers of physicians and nurses.

A threshold to define hypotension after anesthesia induction, also known as post-induction hypotension, was reported by 40.2% of the respondents, which was predominantly based on an absolute MAP value (42.3%), with a median threshold of 65 mmHg [IQR 60–65]. A relative change in MAP value was used by 20.9% of the respondents, with a median change from baseline of 25% [IQR 20–25].

Table 3

Reported thresholds used to define hypotension, dependent on specific patient categories.

Patient category	Septic		Trauma		Postoperative non-cardiac		Postoperative cardiac		Post cardiac-arrest		Neuro(trauma)	
	n (%)	median [IQR], mmHg or %	n (%)	median [IQR], mmHg or %	n (%)	median [IQR], mmHg or %	n (%)	median [IQR], mmHg or %	n (%)	median [IQR], mmHg or %	n (%)	median [IQR], mmHg or %
Yes	206 (51.5)		88 (23.4)		102 (27.9)		53 (14.8)		108 (30.6)		107 (31.3)	
SBP: absolute threshold	22	90 [80–90]	23	88 [80–90]	19	90 [80–90]	7	90 [80–90]	15	90 [85–90]	18	100 [91–110]
SBP: -% change threshold	4	25 [20–29]	1	15 --	4	20 [20–25]	3	25 [23–25]	2	25 [20–32]	–	–
MAP: absolute threshold	119	65 [65–65]	45	65 [60–65]	53	65 [60–65]	34	65 [60–65]	81	65 [65–70]	81	75 [70–80]
MAP: -% change threshold	25	25 [20–29]	17	20 [20–25]	22	25 [20–30]	7	20 [18–23]	5	20 [18–21]	5	20 [16–20]
No	169 (42.2)		181 (48.1)		204 (55.7)		89 (24.9)		198 (56.1)		108 (31.6)	
Not treated in our ICU	6 (1.5)		80 (21.3)		35 (9.6)		196 (54.9)		20 (5.7)		107 (31.3)	
I don't know	19 (4.8)		27 (7.2)		25 (6.8)		19 (5.3)		27 (7.6)		20 (5.8)	

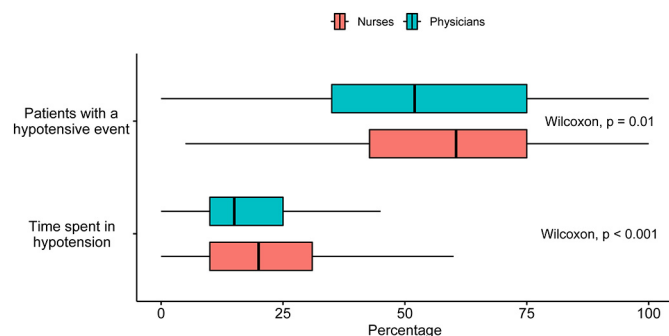


Fig. 3. Boxplots of the estimation of incidence and duration of hypotension. Nurses reported a higher estimated amount of patients with a hypotensive event when compared to physicians (5% estimated median difference, 95% CI = 1% - 7.5%, $p = 0.01$). Nurses also reported a higher estimation of total time spent in hypotension (4% estimated median difference, 95% CI = 0.1% - 5%, $p < 0.001$).

3.3. Estimating hypotension incidence

On average, the median estimated percentage of patients exposed to one or more hypotensive events during their ICU stay was 55% [IQR 39–75]. Nurses reported a higher percentage compared to physicians (5% estimated median difference, 95% CI = 1% - 7.5%, $p = 0.01$, Fig. 3). In a multivariate regression correcting for the baseline difference in both type of ICU and years of experience, nurses still reported an estimated 4.0% higher incidence of hypotension ($p = 0.019$). Notably, regardless of occupational background, a significantly lower estimated incidence of hypotension was reported in Neurological ($-9.8%$, $p = 0.017$) and PACU ($-11.5%$, $p = 0.007$) ICU types. The median percentage of time per day a patient spends in a hypotensive state was estimated at 15% [IQR 10–27], again with nurses reporting a higher percentage (4% estimated median difference, 95% CI = 0.1% - 5%, $p < 0.001$, Fig. 3). After adjusting for the difference in ICU type and years of experience, the estimated percentage of time spent in hypotension reported by nurses remained higher (estimated difference 4.6%, $p < 0.001$). Moreover, regardless of occupation, a higher estimation of percentage of time spent in hypotension was reported by participants employed in a mixed (5.8% increase, $p = 0.002$) or ‘other’ ICU type (10.1% increase, $p < 0.001$).

4. Discussion

This world-wide, multidisciplinary survey among ICU physicians and nurses provides important insight in used definitions and estimated incidence of hypotension in critically ill patients. The major findings of this survey are: 1) the majority of ICU physicians and nurses use a

fixed definition for all patients in their ICU, regardless of diagnosis or background, which was predominantly based on an absolute MAP threshold of 65 mmHg; 2) when respondents indicated they apply a variable threshold to define hypotension dependent on patient category, still an absolute MAP threshold of 65 mmHg was used most frequently, except for patients suffering from neuro-trauma or non-traumatic intracranial pressure (ICP) elevation and 3) hypotension is frequently occurring in the ICU. ICU physicians and nurses estimated that 55% of patients are exposed to hypotension during their ICU stay, during on average 15% of the admitted time per patient.

Our survey shows that ICU physicians and nurses use a fixed threshold of MAP 65 mmHg to define hypotension in general critically ill patients. This is in line with the consensus statement of the task force of the ESICM [29]. However, international guidelines recommending a target blood pressure for a critically ill patient in general, do not exist. Furthermore, our results indicate that ICU physicians and nurses primarily use a MAP target of 65 mmHg for distinct patient categories too, except for neuro(trauma) patients. However, international guidelines recommend varying blood pressure targets depending on the underlying condition, albeit mostly based on moderate to weak evidence. The Surviving Sepsis Campaign recommends a target MAP ≥ 65 mmHg for the initial treatment of septic patients [30], which is also primarily reported by the respondents of this survey. This threshold is based on RCTs in critically ill septic patients, showing that higher (75–85 mmHg) versus lower (60–70 mmHg) MAP targets did not reduce mortality [31,32]. For trauma patients, no general blood pressure target is defined, but during active bleeding a MAP of 50–60 mmHg, or SBP of 80–90 mmHg is advised [33,34]. No blood pressure target exists for non-cardiac postoperative patients admitted to the ICU. Outside the ICU, a SBP of at least 90 mmHg or a MAP of 60–70 mmHg is recommended by the Perioperative Quality Initiative [35]. A SBP of 90–140 mmHg or MAP of 60–90 mmHg is advised for postoperative cardiac patients, but these may be higher depending on comorbidities [36,37]. For patients after cardiac arrest, The American Heart Association recommends maintaining SBP > 90 mmHg and MAP > 65 mmHg [38], since higher blood pressure targets were associated with good neurological outcome [39]. The Brain Trauma Foundation recommends SBP targets > 100 mmHg for patients aged 50–69 years old, and > 110 mmHg for patients 15–49 or ≥ 70 years old after traumatic brain injury [40]. European guidelines advice maintaining MAP ≥ 80 mmHg in these patients [34]. Higher blood pressure targets in neuro(trauma) patients may be explained by the recommendation to maintain a cerebral perfusion pressure (MAP minus ICP) between 60 and 70 mmHg [40]. The recommendation of a higher blood pressure target in the latter patient population is reflected by the results of our survey, reporting a significantly higher MAP threshold to define hypotension for these patients. Nevertheless, the other advised thresholds from international guidelines do not appear to be consequently implemented in routine care, since a single hypotension threshold (MAP 65 mmHg) was predominantly reported, regardless of diagnosis or background. This threshold might be used to limit variance in clinical practice, as a MAP of 65 mmHg is within limits of most guidelines mentioned above. Notably, less than half of the respondents reported using a definition for post-induction hypotension, despite its association with mortality after emergency airway management [41]. When reported, the threshold was primarily based on a MAP value of 65 mmHg, although in literature SBP thresholds are used more often [42]. With pooled incidence of post-induction hypotension estimated at 11% [42], it may arguably be a less familiar or perhaps underreported phenomenon and therefore lacks a universal definition.

Individualized blood pressure targets based on percentage change from baseline have shown beneficial effects on postoperative organ dysfunction in patients undergoing surgery [43]. Comparable evidence for critically ill patients is not available, presumably because of frequent absence of resting baseline blood pressure. This is reflected by the results of our survey, with approximately 15% of the reported hypotension thresholds being based on a percentage change from baseline.

Furthermore, baseline blood pressure is often determined in-hospital and poorly estimates true resting baseline blood pressure [44,45], which limits further use of relative hypotension thresholds in critically ill patients.

Besides depth, hypotension duration has shown to be independently associated with morbidity and mortality in ICU patients [2,8–10]. With 70%, most respondents stated that no minimum duration is used to define a hypotensive event, basing their definition solely on a blood pressure threshold. This suggests that most respondents consider any hypotension clinically relevant regardless of duration.

Respondents estimated that hypotension occurs in the majority (55%) of patients. Previous research reported incidence ranging from 47 to 72%, depending on patient category and threshold definition [1–4]. Compared to physicians, nurses reported statistically significantly higher estimates of both the incidence and amount of time spent in hypotension. Previous research showed that nurses spend over twice as much time in close proximity to ICU patients, and outperformed physicians in short-term outcome prediction [46–49]. Therefore, nurses might be more reliable in precisely estimating incidence and time spent in hypotension. Notably, there were significant differences in demographic characteristics between physicians and nurses, including hospital and ICU type, that were not corrected for.

4.1. Strengths and limitations

This questionnaire yielded global responses, resulting in a heterogeneous sample of ICU physicians and nurses, working in various types of ICUs and hospitals throughout the world. The multidisciplinary approach resulted in a representative sample for those professionals in charge of observing and treating hypotension. However, physicians were more strongly represented than nurses, potentially modifying the averages of estimations. Furthermore, baseline characteristics provided in Table 1 showed that, compared to physicians, nurses were more likely to be female, younger and less experienced. Since the completion rate was lower among nurses, these characteristics are also significantly different between participants with a complete or incomplete survey. We cannot conclude however, whether it was occupation, age or years of experience that had the most impact on completion rate.

Usage of the COSMIN criteria, AMEE guidelines and CHERRIES guidelines, strengthened the reliability and validity of the questionnaire. These guidelines advise the usage of an IP-blocking mechanism to prevent multiple entries by the same person, but we opted not to include this mechanism. It was anticipated that most of the target audience would fill out the questionnaire in a hospital with a common static IP-address, potentially limiting the response to one per hospital.

The survey design resulted in some specific limitations regarding the variability in answer options to define hypotension. For example, for some respondents hypotension thresholds may be dependent on individual patients' medical history, which was not a valid answer option. International guidelines recommend adjusting blood pressure targets individually based on pre-existing comorbidities, such as chronic arterial hypertension, without explicating precise adjustments [29,50]. Since we assessed commonly used hypotension definitions, respondents were not asked whether blood pressure targets were individually adjusted in their patients. However, respondents were able to deny using hypotension thresholds in all patient categories, as was done by 6.5%. Furthermore, some guidelines recommend thresholds within a certain range, which was not a valid answer option.

5. Conclusions

An absolute MAP of 65 mmHg is the most commonly used threshold to define hypotension in both general and specific ICU patient categories. A higher MAP threshold for hypotension in neuro(trauma) patients was reported, which is in line with current evidence and guidelines. The optimal blood pressure threshold for most patient categories however,

is still under debate. Regardless of the definition used, the majority of ICU patients are believed to endure hypotensive episodes during their ICU stay for a considerable amount of time per day, with nurses reporting a higher estimated incidence and duration than physicians.

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Declaration of Competing Interest

None.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.jcrrc.2021.05.023>.

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