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Monitoring, management, and outcome of hypotension in Intensive Care Unit patients, an international survey of the European Society of Intensive Care Medicine

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ABSTRACT

Introduction: Hypotension in the ICU is common, yet management is challenging and variable. Insight in management by ICU physicians and nurses may improve patient care and guide future hypotension treatment trials and guidelines.
Methods: We conducted an international survey among ICU personnel to provide insight in monitoring, management, and perceived consequences of hypotension.
Results: Out of 1464 respondents, 1197 (81.7%) were included (928 physicians (77.5%) and 269 nurses (22.5%)). The majority indicated that hypotension is underdiagnosed (55.4%) and largely preventable (58.8%). Nurses are primarily in charge of monitoring changes in blood pressure, physicians are in charge of hypotension treatment. Balanced crystalloids, dobutamine, norepinephrine, and Trendelenburg position were the most frequently reported fluid, inotrope, vasopressor, and positional maneuver used to treat hypotension. Reported complications believed to be related to hypotension were AKI and myocardial injury. Most ICUs do not have a specific hypotension treatment guideline or protocol (70.6%), but the majority would like to have one in the future (58.1%).
Conclusions: Both physicians and nurses report that hypotension in ICU patients is underdiagnosed, preventable, and believe that hypotension influences morbidity. Hypotension management is generally not protocolized, but the majority of respondents would like to have a specific hypotension management protocol.

1. Introduction

Hypotension in patients admitted to the Intensive Care Unit (ICU) is common with an incidence ranging from 47% to 72% [1-7], and is often one of the presenting symptoms of underlying distributive, cardiogenic, hypovolemic, or obstructive shock. Treatment of hypotensive events is traditionally directed towards improvement of preload, contractility, and/or afterload. Due to the heterogeneity of its causes and presentation, management of hypotension can be challenging and multifactorial. Current treatment strategies often include fluid resuscitation, inotropes, and/or vasopressors, but fluid type and medication preferences are still debated [8-14].

In ICU patients with distributive shock, hypotension is associated with acute kidney injury (AKI) [3-5], myocardial infarction [5], and mortality [3-6]. The strength of these associations increases with

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incremental severity and duration of hypotension [3-6]. Hypotension has also been identified as a risk factor for AKI in the general ICU population [2], but studies on other potential complications related to hypotension in this diverse population are scarce. Insight in the opinion of ICU physicians and nurses regarding monitoring, preferred management, and perceived consequences of hypotensive events, could improve patient care, facilitate uniformity in future trials, and aid in conceptualization of guidelines.

In this questionnaire among critical care personnel, we surveyed current practice of monitoring and management of hypotension in ICU patients and assessed their opinion regarding the influence of hypotension on outcome.

2. Methods

This worldwide, open, and peer-reviewed survey was endorsed by the European Society of Intensive Care Medicine (ESICM) and received in-principle support of the World Federation of Intensive and Critical Care (WFICC). National critical care and anesthesiology societies for physicians and nurses were contacted and asked to distribute the questionnaire among their members, with a maximum of two reminders. Distribution of the questionnaire was either via email, newsletter, or social media. A list of distributing societies is available in Supplementary material 1. The online questionnaire (Supplementary material 2) was available from November 20, 2019 until April 1, 2020.

2.1. Ethical considerations

The local medical ethical committee of the Amsterdam UMC (W19_292) approved this anonymous and voluntary survey. Respondents gave consent for analyses and publication of their provided answers upon start of the questionnaire. No incentive was offered for participation.

2.2. Survey development

The objective of this survey was to provide insight in the opinion of ICU physicians and nurses regarding two aspects of hypotension; 1) definitions and incidence and 2) monitoring, management, and outcome. We combined these topics in a single questionnaire with two sections to minimize the burden for respondents, since both topics are closely related and would be studied in the same target population. This study reports on the findings of the second section. The results of the first section have been reported previously [15].

A focus group ($n = 8$) consisting of physicians, nurses, epidemiologists, and a methodologist at the Amsterdam UMC, developed the questionnaire according to the guide of the Association for Medical Education in Europe (AMEE) [16]. A non-systematic review of the literature on hypotension in ICU patients was conducted prior to developing the questionnaire, to explore relevant topics. The questionnaire was built in SurveyMonkey Platinum (SurveyMonkey Inc., San Mateo, CA, USA). Expert validation was performed through a panel of Dutch intensivists and anesthesiologists ($n = 11$). Finally, a pilot test was conducted among 9 physicians and 9 nurses working in the ICU of the Amsterdam UMC, location AMC, to test face and content validity (following the COnsensus-based Standards for the selection of health status Measurement INstruments (COSMIN) criteria) [17].

The questionnaire consisted of 129 questions in total, but the number of questions per respondent varied between 42 and 69 due to skip logic. All answers could be reviewed and edited until final submission. Respondents' demographics (including occupation and area of training) and the type and size of their ICU were collected in questions 1 to 10. The first section of the questionnaire (questions 11 to 103) focused on the definition and incidence of hypotension in ICU patients and has been reported separately [15]. The second section of the questionnaire (questions 104 to 129) included questions on organ perfusion and function (questions 104 to 106), monitoring and treatment of hypotension (questions 107 to 110), necessary variables to treat hypotension (questions 111 to 114), treatment preferences and perceived outcome of hypotension (questions 115 to 124), and on hypotension treatment protocols (questions 125 to 129). A flowchart of the questionnaire is presented in Supplementary material 3.

2.3. Target population

Physicians and nurses working in any type of ICU worldwide were the target population. Intensivists, ICU trainees, and specialists (non-intensivist) practicing ICU are referred to as physicians; Critical Care Nurses, Nurse Practitioners and Physician Assistants are referred to as nurses. Respondents were instructed to answer questions from the perspective of standard practice in their ICU. Given a theoretical population size of >10,000, a minimum sample size regardless of question category was calculated at 740 valid responses, with a 0.05 two sided significance level [18].

2.4. Statistical analyses

Data were downloaded as a csv file and subsequently stored as an Excel file (Microsoft Corp, Redmond, WA, USA). Responses were included in the analyses if both the demographic questions and at least one question of the second section of the questionnaire were answered. Exclusion criteria included occupation other than ICU physician or nurse and open-ended questions answered in non-English. Missing data were not imputed.

Continuous data are presented as mean with standard deviation (SD), or median with interquartile range (IQR), when appropriate. Normality of distribution was visually assessed using boxplots, histograms, and Q-Q plots, and statistically using the Shapiro-Wilk normality test. Differences between continuous data were analysed with the Student's *t*-test. Categorical data were expressed as frequencies with percentages. Differences between categorical data were analysed with the Fisher's exact test. For each of the analyses, a p-value <0.05 was considered statistically significant. Analyses were performed using RStudio, version 3.5.1 (R Core Team, Vienna, Austria) [19]. Graphs were made with RStudio and GraphPad Prism (GraphPad Software, San Diego, CA, USA).

While developing the survey, physicians and nurses were identified as two main subgroups, allowing analyses of differences based on occupation. Furthermore, answers from physicians and nurses were compared based on geographical location, stratified by continent. The results are reported according to the Checklist for Reporting Results of Internet E-Surveys (CHERRIES) guideline [20].

3. Results

3.1. Survey respondents

In total, 1197 of 1464 respondents (81.8%) were included in the analyses. Reasons for excluding the remaining 267 respondents were: occupation other than ICU physician or nurse ($n = 21$), answered demographic questions only ($n = 49$), or did not answer any questions from the second section of the questionnaire ($n = 197$). The last question of the survey was answered by 1023 respondents, which translates to a completion rate of 85.5% (1023/1197). The number of respondents answering each question are provided in Supplementary material 3. The majority of respondents were physicians (77.5% vs 22.5% nurses, $p < 0.001$), European (55.1%), and male (60.0%). Main areas of primary training of physicians were anesthesiology (61.7%) and internal medicine (19.7%). Statistical differences between physicians and nurses were found for all demographic questions, as shown in Table 1.

Table 1
Baseline characteristics.

	Total	Physician	Nurse	*p*-value
	$n = 1197$	$n = 928$	$n = 269$	
Age, mean (SD)	43 (10.1)	43.7 (9.8)	40.5 (10.8)	< 0.001
Male, *n* (%)	718 (60.0)	633 (68.2)	85 (31.6)	< 0.001
Primary area of training, *n* (%)				
Anesthesiology		545 (61.7)		
Internal medicine		174 (19.7)		
Cardiology		25 (2.8)		
Neurology		21 (2.4)		
Pulmonology		20 (2.3)		
Surgery		17 (1.9)		
Other		81 (9.2)		
Years of experience, *n* (%)				0.002
< 2	81 (6.8)	52 (5.6)	29 (10.8)	
2–5	279 (23.3)	207 (22.3)	72 (26.8)	
6–10	247 (20.6)	208 (22.4)	39 (14.5)	
11–20	329 (27.5)	258 (27.8)	71 (26.4)	
> 20	261 (21.8)	203 (21.9)	58 (21.6)	
Employed in, *n* (%)				< 0.001
Europe	659 (55.1)	545 (58.8)	114 (42.4)	
Asia	262 (21.9)	249 (26.9)	13 (4.8)	
North America	195 (16.3)	69 (7.4)	126 (46.8)	
South America	41 (3.4)	32 (3.5)	9 (3.3)	
Oceania	21 (1.8)	16 (1.7)	5 (1.9)	
Africa	18 (1.5)	16 (1.7)	2 (0.7)	
Hospital type, *n* (%)				< 0.001
University (academic) hospital	528 (44.1)	437 (47.1)	91 (33.8)	
Non-university public hospital	307 (25.6)	209 (22.5)	98 (36.4)	
University affiliated hospital	181 (15.1)	141 (15.2)	40 (14.9)	
Private hospital	164 (13.7)	128 (13.8)	36 (13.4)	
Other	17 (1.4)	13 (1.4)	4 (1.5)	
ICU type, *n* (%)				0.007
Mixed	845 (70.6)	661 (71.2)	184 (68.4)	
Surgical/trauma	102 (8.5)	82 (8.8)	20 (7.4)	
Cardiac	98 (8.2)	66 (7.1)	32 (11.9)	
Neurological	53 (4.4)	35 (3.8)	18 (6.7)	
Post-Anesthesia Care Unit	47 (3.9)	43 (4.6)	4 (1.5)	
Other	52 (4.3)	41 (4.4)	11 (4.1)	
ICU beds, *n* (%)				0.041
≤ 10	348 (29.1)	282 (30.4)	66 (24.5)	
11–15	291 (24.3)	234 (25.2)	57 (21.2)	
16–20	217 (18.1)	159 (17.1)	58 (21.6)	
> 20	341 (28.5)	253 (27.3)	88 (32.7)	

Numbers may not add up due to rounding. SD: standard deviation; ICU: Intensive Care Unit.

3.2. Hypotension monitoring

Most respondents stated that hypotensive events in ICU patients are underdiagnosed and largely preventable (55.4% and 58.8%, respectively), and that they feel comfortable in treating hypotension autonomously (70.9%). The majority of respondents stated that nurses are (75.4%) and should be (73.0%) in charge of monitoring changes in blood pressure. When asked who are, and should be in charge of treatment of hypotension, physicians were mentioned most frequently (80.9% and 80.4%, respectively). Furthermore, the majority (63.2%) indicated that hypotension management should be improved in their ICU.

3.3. Hypotension management

Respondents were asked which hemodynamic, physical examination, laboratory, and mechanical ventilation variables are minimally required to guide treatment of hypotension. Multiple choice, multiple answer questions were used for these questions, as detailed in Fig. 1. Most commonly reported hemodynamic variables included urine production (60.5%) and fluid balance (52.5%). Heart rate (72.4%) and capillary refill time (62.7%) were the most commonly used variables obtained from physical examination. The most frequently reported laboratory values included lactate level (74.8%) and arterial blood gas sample (61.6%). Within the mechanical ventilation variables, positive end-expiratory pressure (PEEP) (70.5%) was most frequently named. There were no statistical differences found when comparing the answers of physicians and nurses.

We asked respondents which fluid type, inotrope, vasopressor, and positional maneuver they predominantly use in their ICU for treatment of hypotension (Fig. 2). Most frequently selected treatment options per category were: balanced crystalloids (73.0%), dobutamine (56.2%), norepinephrine (96.4%), and Trendelenburg position (48.9%). Almost a third of the respondents indicated not using positional maneuvers to treat hypotension (31.5%).

3.4. Potential consequences of hypotension

Overall, 86.9% of respondents considered hypotension to affect organ perfusion and 74.6% to affect organ function. Compared to physicians, nurses were more likely to agree with statements that hypotension affects organ perfusion (85.2 vs 92.9%, $p = 0.010$) and function (72.0% vs 83.5%, $p = 0.001$). There was no consensus on the statement whether the level of blood pressure decrease contributes more than the duration of a hypotensive event to poor outcome in ICU patients (36.7% disagree, 30.3% neutral, 33.0% agree). The majority of respondents reported that hypotension has significant or major influence on length of ICU stay, morbidity, and mortality in older (> 50 years) patients, but no or minor influence on morbidity and mortality in younger (< 50 years) patients (Fig. 3). Most frequent complications believed to be related to hypotension were AKI (91.0%), myocardial injury/infarction (51.3%), and gastro-intestinal ischemia (48.2%) (Fig. 4). In total, 41 respondents (3.4%) stated they did not relate any complication in their patients to hypotension, in the past six months.

3.5. Hypotension treatment protocol

Among respondents, 29.4% stated that a hypotension treatment guideline or protocol was available in their ICU. These protocols most frequently include a diagnostic algorithm for detection of the underlying cause (58.1%), administration of fluids (89.1%), administration of vasopressors (82.1%), administration of inotropes (58.8%), and positional maneuvers (40.2%). In the majority of these protocols (65.6%), nurses are authorised to start treatment of hypotensive events autonomously. Reasons for not allowing nurses to treat hypotension autonomously included "requires physicians expertise" (58.8%) and "insufficiently trained nurses" (27.5%). When respondents indicated that no protocol was available in their institution, most stated they would like (58.1%) or might like (29.0%) a specific hypotension treatment protocol in the future. A minority of respondents denied the need for a hypotension protocol (11.1%), without a statistically significant difference between physicians and nurses ($p = 0.232$).

4. Discussion

This is the first worldwide survey on the clinical practice of both critical care physicians and nurses regarding hypotension in adult ICU patients. The results provide insight in the current opinion on monitoring, preferred management, and perceived consequences of hypotension. The main findings are: 1) hypotension is considered an underdiagnosed problem, is perceived largely preventable and management should be improved in the ICUs of most respondents; 2) nurses are usually in charge of monitoring hypotensive events while physicians are mostly responsible for treating them; 3) variables minimally required to guide treatment of hypotensive events include urine production, fluid balance, heart rate, capillary refill time, lactate level, arterial blood gas values, and PEEP level; 4) most frequently used treatments include balanced crystalloids, dobutamine, norepinephrine, and the Trendelenburg maneuver; 5) hypotension is believed to influence length of stay, morbidity, and mortality in older patients (> 50 years);

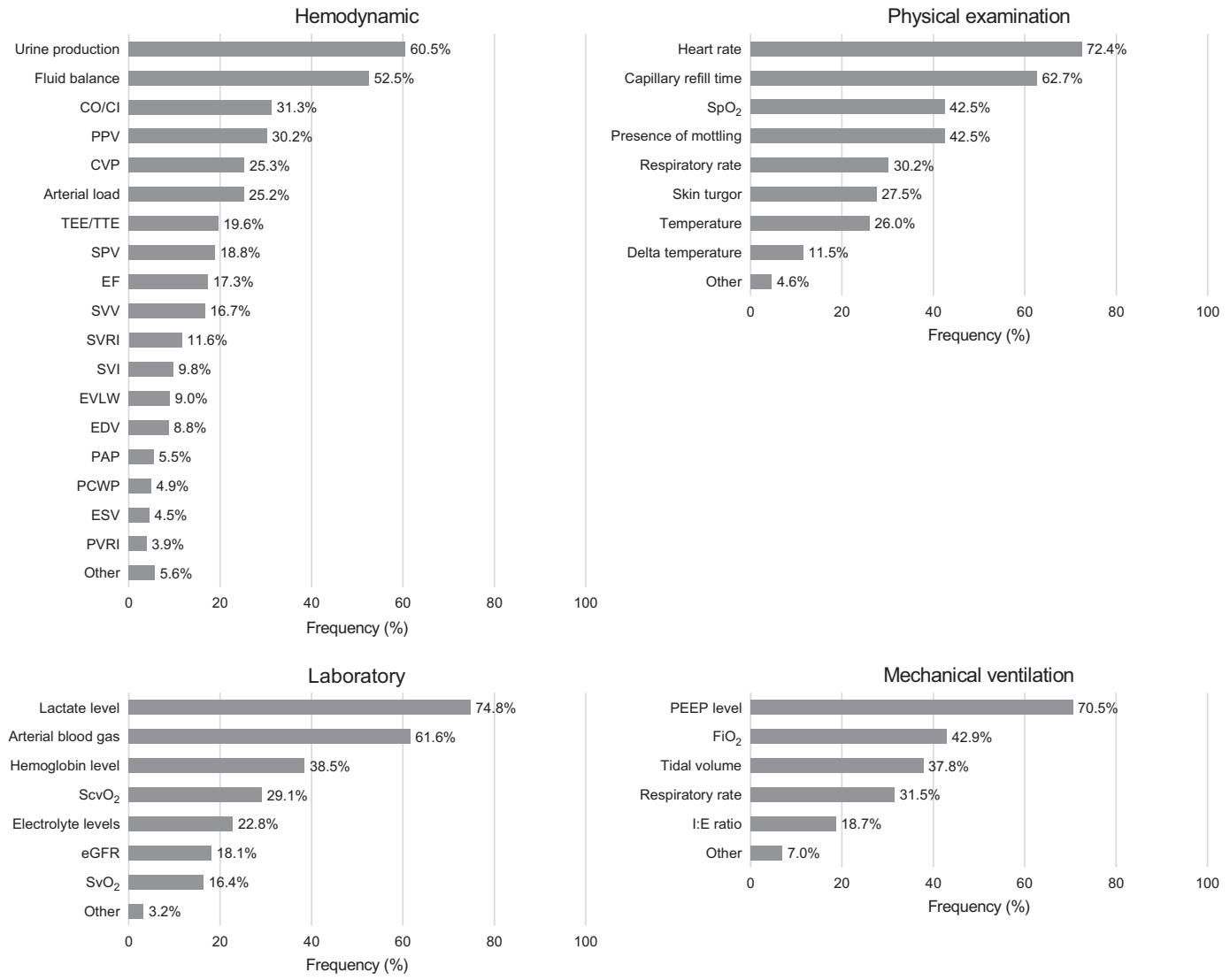

Fig. 1. Minimally required variables to guide treatment for hypotensive events in ICU patients.
ICU: Intensive Care Unit; CO/CI: cardiac output/cardiac index; PPV: pulse pressure variation; CVP: central venous pressure; TEE/TTE: parameters derived from transesophageal echocardiogram/transthoracic echocardiogram; SPV: systolic pressure variation; EF: ejection fraction; SVV: stroke volume variation; SVRI: systemic vascular resistance (index); SVI: stroke volume (index); extravascular lung water; EDV: end-diastolic volume; PAP: pulmonary arterial blood pressure; PCWP: pulmonary capillary wedge pressure; ESV: end-systolic volume; PVRI: pulmonary vascular resistance (index); SpO_2: peripheral oxygen saturation; $ScvO_2$: central venous oxygen saturation; eGFR: estimated glomerular filtration rate; SvO_2: mixed venous oxygen saturation; PEEP: positive end expiratory pressure; FiO_2: fraction of inspired oxygen; I:E ratio: inspiratory:expiratory ratio.

6) while most ICUs do not have a hypotension treatment guideline or protocol, 58.1% of respondents would like one in the future.

The majority of our respondents indicated that hypotension is an underdiagnosed problem in ICU patients. Most patients however, receive continuous blood pressure monitoring during their ICU stay, which should enable timely recognition of hypotensive events. In a general ICU, physicians and nurses take care of multiple patients at the same time, which could potentially result in delayed or missed detection of hypotensive events. Furthermore, hypotension being underdiagnosed in ICU patients, may be the result of an underlying high incidence. General incidence rates are not available and are dependent on many factors, such as used definitions, reason for admission, and patients' medical history. Reported incidence of hypotension (defined as a mean arterial pressure (MAP) ≤ 65 mmHg) in septic and post-operative ICU patients is 47% and 61%, respectively [5,7]. In case of monitoring and treatment, most respondents reported that monitoring of changes in blood pressure is, and should be done, by nurses. Nurses spend more time with patients and are therefore more likely to observe changes in blood pressure first [21]. However, respondents stated that physicians are, and should be, in charge of treating hypotensive events. As a result, initiation of treatment likely depends on both the availability of the ICU physician and the effectiveness and timeliness of communication. Treatment of hypotensive events may therefore be delayed, whichis also reflected by the majority of respondents stating that hypotension is largely preventable and could be improved in their ICU. A delay in treatment could be resolved by implementing a nurse driven hypotension treatment protocol. The results of this survey in general show consensus on the opinion of physicians and nurses regarding hypotension management. In addition, most respondents expressed interest in a hypotension protocol and the majority of ICUs in which a hypotension treatment protocol is currently used allow nurses to initiate treatment for hypotensive events autonomously. However, most ICUs currently lack such a protocol. Potential barriers to development and implementation of a hypotension protocol were beyond the scope of this survey and have yet to be identified.

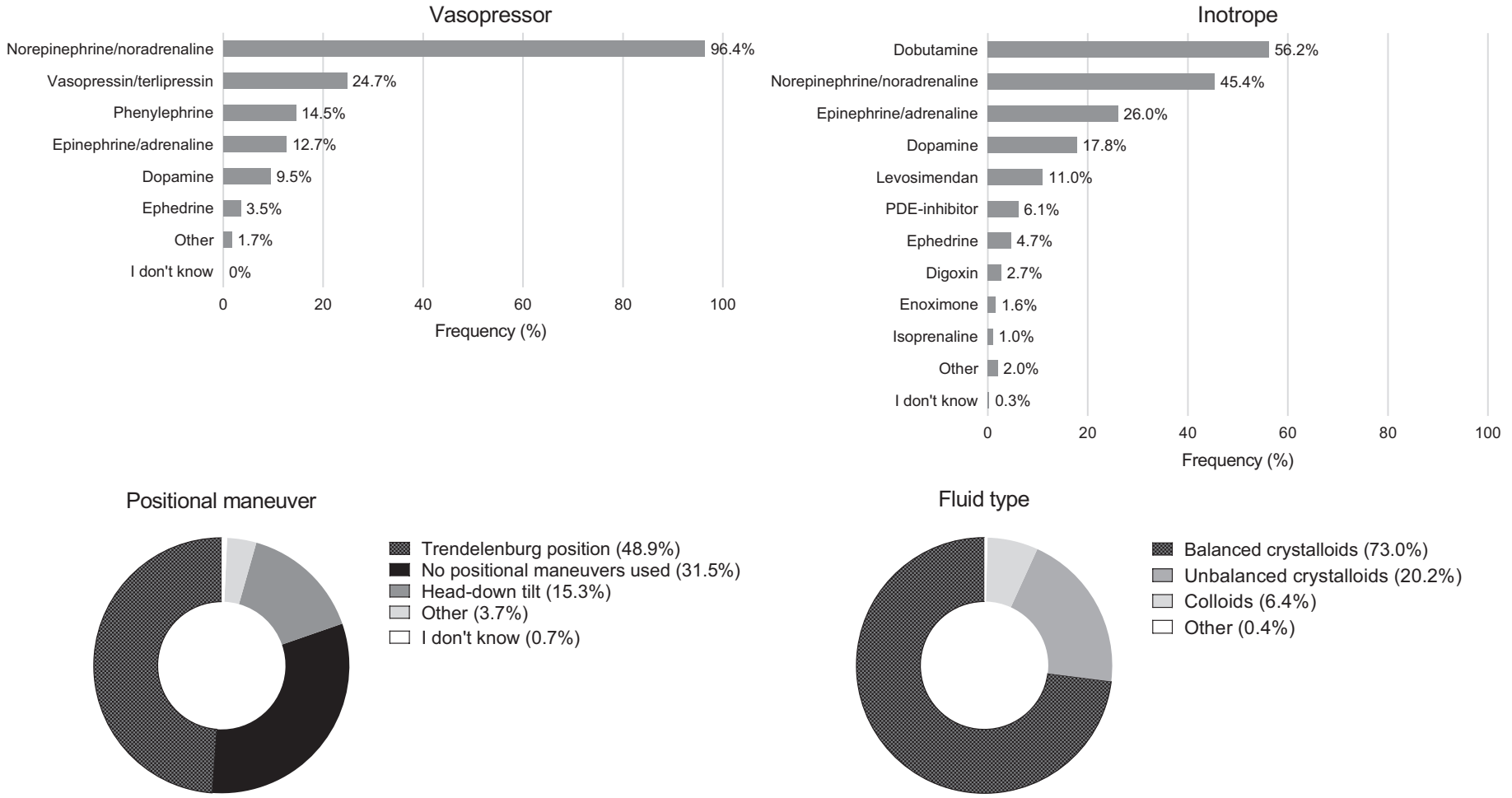

Fig. 2. Most frequently used interventions to treat hypotensive events in ICU patients.
Numbers may not add up due to rounding. ICU: Intensive Care Unit; PDE-inhibitor: phosphodiesterase inhibitor; balanced crystalloids (e.g. Ringer's lactate/acetate, Plasma-Lyte 148, Sterofundin); unbalanced crystalloids (e.g. saline); colloids (e.g. albumin, gelatin, hydroxy-ethyl starch).

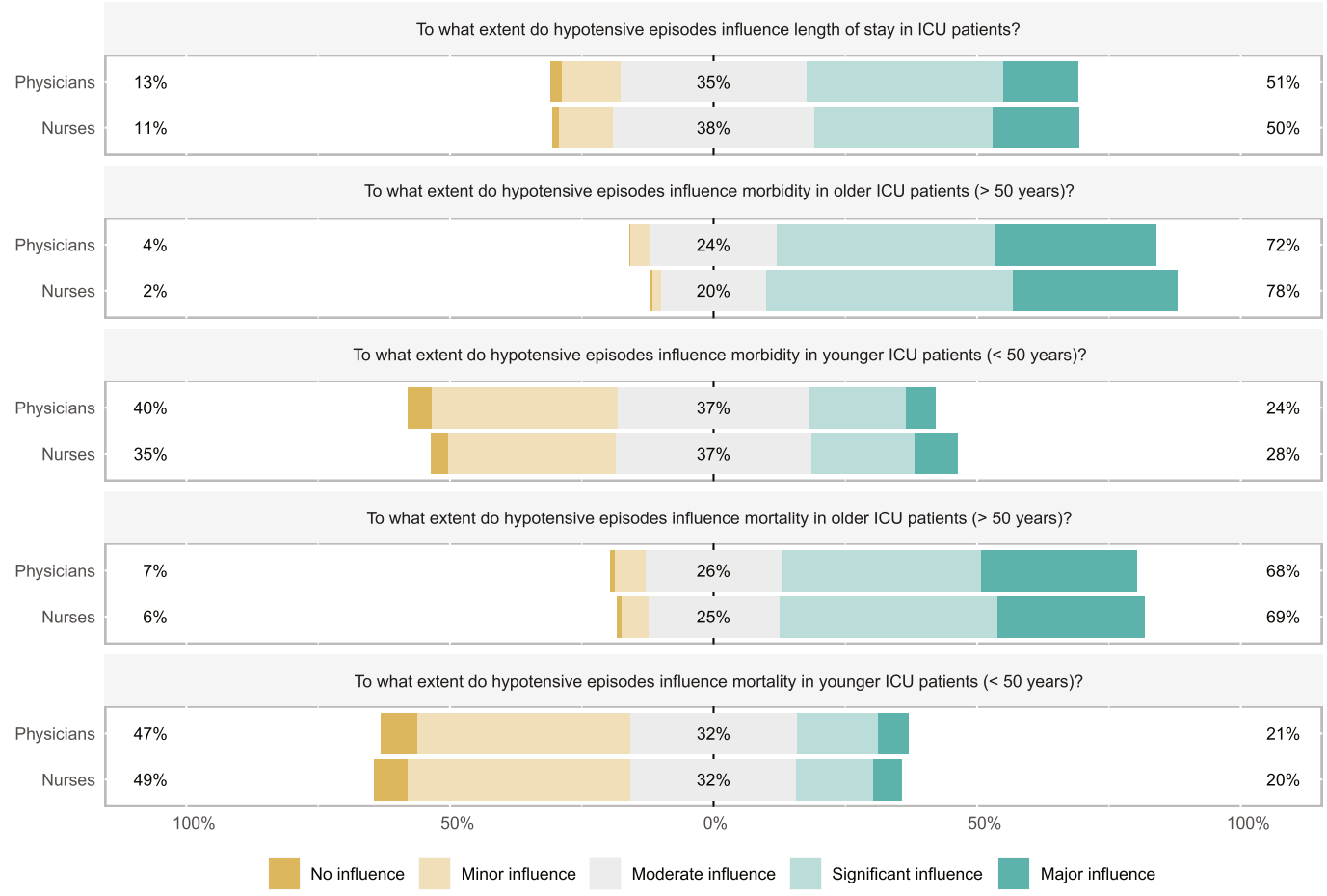

Fig. 3. 5-point Likert-scales showing perceived effects of hypotension in ICU patients by physicians and nurses.
Percentages shown on the left side of the figure indicate the combined percentages of "No influence" and "Minor influence", percentages in the middle represent "Moderate influence", and the percentages on the right side of the figure indicate the combined percentages of "Significant influence" and "Major influence". Numbers may not add up due to rounding. ICU: Intensive Care Unit.

With regard to treatment of hypotension, urine production, fluid balance, heart rate, capillary refill time, lactate level, arterial blood gas values, and PEEP level were reported to be minimally required to guide treatment. Monitoring of most of these variables mentioned is embedded in international guidelines and consensus statements for treatment of various ICU patient types [22-26]. Urine output, lactate level, and arterial blood gas values provide insight in the degree of tissue perfusion, fluid balance and capillary refill time provide an indication of the circulatory and fluid status of a patient, and PEEP level directly influences preload and thus cardiac output. Measurement of capillary refill time however, is the only variable not recommended by previously mentioned guidelines. Capillary refill time is an early available indicator of tissue perfusion, and is, when used as a dichotomous indicator (normal or prolonged), a reliable qualitative variable to identify septic shock patients at risk of morbidity [27], and may therefore be reported by our respondents.

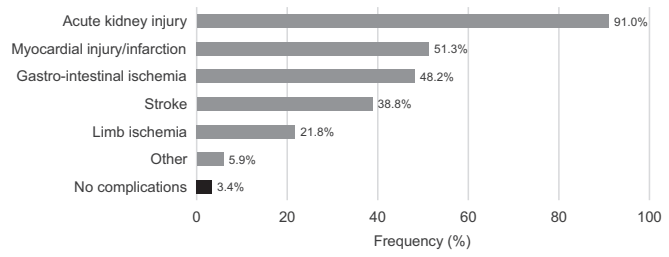

Fig. 4. Complications in ICU patients observed over the past six months and believed to be related to hypotension.
ICU: Intensive Care Unit; stroke: cerebrovascular accident or transient ischemic attack.

The majority of the respondents stated that norepinephrine is the most used vasopressor when treating hypotension. Norepinephrine can be safely used to maintain organ perfusion pressure, without a significant effect on coronary circulation [28]. Furthermore, its positive effects on contractility in critically ill patients have been shown [29], with the Surviving Sepsis Campaign consequently recommending norepinephrine as the vasopressor of first choice [24]. Dobutamine was reported as the most used inotrope, also in line with recommendations by the Surviving Sepsis Campaign [24] and with a recently published survey by Scheeren *et al.* [14]. It is the most used inotrope as treatment for heart failure, cardiogenic shock, and septic shock, and is usually combined with a vasopressor [30]. Balanced crystalloids were the most commonly reported choice of fluid type for resuscitation of hypotensive episodes. Compared to unbalanced crystalloids, using balanced crystalloids in critically ill patients has been associated with lower in-hospital mortality [31], and may be superior in fluid resuscitation in septic patients [32]. Compared to crystalloids, colloids were shown to be more effective for fluid resuscitation in ICU patients [33]. However, the use of colloids is associated with increased need for blood transfusion, renal replacement therapy, and mortality when compared to crystalloids [34,35]. As a result, the Surviving Sepsis Campaign recommends using

crystalloids as the fluid of choice [24]. Furthermore, Trendelenburg position was the most commonly reported positional maneuver in treatment of hypotension. This position is associated with an increase in both cardiac output and MAP [36]. However, these effects have also been shown to be transient at most [37]. Our results suggest that it is still a much applied intervention. Even more surprising was the reported frequency of dopamine use. The use of dopamine in ICU patients has repeatedly been associated with an increase in morbidity and mortality [38,39]. Nevertheless, dopamine was still in the top five of most frequently used inotropes and vasopressors.

The results of this survey suggest awareness on the potential consequences of hypotension in ICU patients. Most frequently reported complications believed to be related to hypotension were AKI and myocardial injury, which is in line with associations described in literature. In patients with distributive shock, the incidence of AKI and myocardial injury was higher in patients with hypotension [4,5]. Similar associations have been described in trauma [40], post-cardiac arrest [1], post-operative [7,41], and general ICU patients [2]. Although physicians and nurses are familiar with the potential consequences, management of hypotensive events seems to remain challenging. The majority of respondents believed hypotension management should improve, but most respondents also stated that hypotension still is an underdiagnosed problem, which suggests an issue with timely recognition of (upcoming) events. Future blood pressure monitoring may be improved by prediction of impending hypotensive events using artificial intelligence algorithms [42], which are becoming increasingly available in critical care medicine and provide opportunities for future research and treatment.

4.1. Strengths and limitations

The strength of this survey is the large number of respondents from a variety of hospital types and countries of employment. In addition, both nurses and physicians participated in this survey which resulted in a heterogeneous sample of professionals in charge of monitoring and treating hypotension in ICUs worldwide.

To this date, validated guidelines or checklists for surveys are lacking. We therefore combined the COSMIN criteria, AMEE guidelines, and CHERRIES guidelines to ensure reliability and validity of the questionnaire. These guidelines recommend using an IP-blocking mechanism to prevent multiple entries from a single respondent. We expected most respondents to complete the questionnaire at work and some hospitals use a static IP-address. We therefore opted not to include an IP-blocking mechanism to allow more than one entry per hospital.

This survey has several limitations. First, the results of this survey are naturally at risk for nonresponse, agreement, and attrition bias. In the first section of this survey, 14% of respondents dropped out [15]. These respondents were therefore not included in the analyses of the second section. This may have influenced the generalisability of the sample. Second, as with all clinical practice surveys, we cannot rule out a discrepancy between reported hypotension management and actual clinical practice. Third, the exact response rate could not be determined since the number of ICU physicians and nurses that received the survey is unknown. Fourth, management of hypotension and its potential consequences may differ per ICU patient. In clinical practice, blood pressure targets can vary from patient to patient, for instance depending on medical history and/or reason for ICU admission. This survey does not take this variety in clinical practice in account, but merely provides an insight into the generally accepted opinion regarding hypotension in ICU patients. Fifth, although our study represents a heterogeneous sample of ICU personnel from various countries and ICU types, physicians, and first world countries were overrepresented in this survey. Multinomial logistic regression analyses to correct for geographic difference between physicians and nurse could not be performed due to insufficient subgroup sizes. The results of this survey thus should be interpreted cautiously.

5. Conclusions

This international survey provides insight in the opinion of ICU physicians and nurses regarding current monitoring, management, and perceived outcome of hypotension in ICU patients. Hypotension is believed to influence morbidity and mortality, especially in older patients. Current hypotension management often is not protocolized, but most ICU physicians and nurses would like having a hypotension management protocol in the future. The results of this survey could be of use when developing future hypotension management guidelines and trials.

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Declaration of Competing Interest

TWLS received research grants and honoraria from Edwards Lifesciences (Irvine, CA, USA) and Masimo Inc. (Irvine, CA, USA) for consulting and lecturing and from Pulsion Medical Systems SE (Feldkirchen, Germany) for lecturing (all payments made to institution).

DPV reported receipt of personal fees and other from Edwards Lifesciences (Irvine, CA, USA) as well as consultancy fees and research grants from Philips (Eindhoven, the Netherlands) and Hemologic (Amersfoort, the Netherlands).

APJV reported receipt of grants from Edwards Lifesciences (Irvine, CA, USA) and Philips (Eindhoven, the Netherlands).

WHV, JS, JS, SR, TGVC, WKL, PT, PWGE, PRT, JB, BFG, and FP declare that they have no conflicts of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jcrc.2021.10.008.

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