Journal of Zhejiang University-SCIENCE B (Biomedicine & Biotechnology)
ISSN 1673-1581 (Print); ISSN 1862-1783 (Online)
www.jzus.zju.edu.cn; www.springerlink.com
E-mail: jzus@zju.edu.cn

Mandatory criteria for the application of variability-based parameters of fluid responsiveness: a prospective study in different groups of ICU patients

Wolfgang HUBER[†‡1], Uli MAYR[1], Andreas UMGELTER[1], Michael FRANZEN[2], Wolfgang REINDL[3], Roland M. SCHMID[1], Florian ECKEL[4]

[1]*II. Medizinische Klinik und Poliklinik, Klinikum rechts der Isar der Technischen Universität München, Ismaninger Straße 22, D-81675 München, Germany*

[2]*Universitätsklinik für Innere Medizin I, Salzburger Landeskliniken, Universitätsklinikum Salzburg, Müllner Hauptstraße 48, A-5020 Salzburg, Austria*

[3]*II. Medizinische Klinik, Universitätsklinikum Mannheim, Theodor-Kutzer-Ufer 1-3, D-68167 Mannheim, Germany*

[4]*Klinik für Innere Medizin, RoMed Klinik Bad Aibling, Harthauser Straße 16, D-83043 Bad Aibling, Germany*

[†]E-mail: Wolfgang.Huber@tum.de

Received May 7, 2017; Revision accepted Nov. 20, 2017; Crosschecked June 6, 2018

Abstract: Background and objective: Stroke volume variation (SVV) has high sensitivity and specificity in predicting fluid responsiveness. However, sinus rhythm (SR) and controlled mechanical ventilation (CV) are mandatory for their application. Several studies suggest a limited applicability of SVV in intensive care unit (ICU) patients. We hypothesized that the applicability of SVV might be different over time and within certain subgroups of ICU patients. Therefore, we analysed the prevalence of SR and CV in ICU patients during the first 24 h of PiCCO-monitoring (primary endpoint) and during the total ICU stay. We also investigated the applicability of SVV in the subgroups of patients with sepsis, cirrhosis, and acute pancreatitis. Methods: The prevalence of SR and CV was documented immediately before 1241 thermodilution measurements in 88 patients. Results: In all measurements, SVV was applicable in about 24%. However, the applicability of SVV was time-dependent: the prevalence of both SR and CV was higher during the first 24 h compared to measurements thereafter (36.1% vs. 21.9%; P<0.001). Within different subgroups, the applicability during the first 24 h of monitoring ranged between 0% in acute pancreatitis, 25.5% in liver failure, and 48.9% in patients without pancreatitis, liver failure, pneumonia or sepsis. Conclusions: The applicability of SVV in a predominantly medical ICU is only about 25%–35%. The prevalence of both mandatory criteria decreases over time during the ICU stay. Furthermore, the applicability is particularly low in patients with acute pancreatitis and liver failure.

Key words: Hemodynamic monitoring; Preload; Fluid responsiveness; Stroke volume variation; Pulse pressure variation
https://doi.org/10.1631/jzus.B1700243 **CLC number:** R44

1 Introduction

Haemodynamic monitoring aims at optimized fluid support, vasomotor tonus, heart rate, contractility and pulmonary function (Huber et al., 2014; Sakka, 2015). The extent of changes in the arterial pressure curve induced by controlled mechanical ventilation (CV) such as stroke volume variation (SVV) and pulse pressure variation (PPV) is associated with the vascular fluid load (Perel, 1998; Michard, 2005; Preisman et al., 2005; Zhang et al., 2011). In patients with CV, SVV and PPV exceed critical thresholds in

‡ Corresponding author
ORCID: Wolfgang HUBER, https://orcid.org/0000-0001-9086-7908

the case of hypovolaemia (Reuter et al., 2002; Michard et al., 2007; Cannesson et al., 2009). Therefore, SVV and PPV have been established as predictors of fluid responsiveness (FR), in particular in the perioperative setting. A number of studies have demonstrated superior prediction of FR by the "dynamic indices" SVV and PPV compared to filling pressures and cardiac volumes derived from the echocardiography (e.g. left-ventricular end-diastolic volume index (LVEDVI)) or trans-pulmonary thermodilution (e.g. global end-diastolic volume index (GEDVI)) (Reuter et al., 2002; Huber et al., 2016b). Nevertheless, it has to be kept in mind that SVV and PPV are automatically derived changes in a regular arterial pressure curve induced by mechanical ventilation with a regular rate and tidal volume. Therefore, sinus rhythm (SR) and CV are mandatory for the application of dynamic indices. In addition to these "major criteria", a number of secondary criteria required for appropriate prediction of FR have been postulated (Cannesson et al., 2011; Mair et al., 2016). While their absence does not totally preclude the use of SVV and PPV, it seems to reduce the predictive capacities resulting in a "gray zone" of values not clearly associated to FR (Cannesson et al., 2011). Several recent studies suggest limited applicability of variability-based preload parameters in the general intensive care unit (ICU) setting (Cannesson et al., 2011; Maguire et al., 2011; Benes et al., 2014b; Mahjoub et al., 2014; Mair et al., 2016). However, some of these studies evaluated "virtual" applicability in ICU patients who were not at all under hemodynamic monitoring (Maguire et al., 2011; Benes et al., 2014b; Mahjoub et al., 2014).

We hypothesized that some of these analyses might be prone to a bias, i.e. inclusion of patients who were without a real need for advanced monitoring. This might lead to an underestimation of the applicability of the dynamic indices. Furthermore, limited usefulness in heterogeneous ICU patients does not preclude substantial applicability in certain subgroups or at the onset of monitoring.

Therefore, we analysed the applicability of the dynamic indices of FR based on the fulfilling of major and minor criteria in patients of a medical ICU. The analyses were restricted to patients really equipped with the PiCCO device. To further reduce the risk of a bias, we focussed on the first measurement (primary endpoint) in each patient and also performed separate analyses in pre-defined subgroups of patients.

2 Materials and methods

2.1 Patients

Haemodynamic data of adult patients hospitalized in an eight-bed medical ICU with advanced hemodynamic monitoring irrespective of the study were documented for a prospectively maintained database. The analysis of these data was approved by the institutional review board (Technische Universität München, Ethikkommission, Germany; project number 3049/11). With regard to predominantly descriptive endpoints, the exploratory approach of the study and the estimated feasibility of recruitment, we aimed at the analysis of at least 1000 transpulmonary thermodilutions (TPTDs). Based on the prevalence of PiCCO monitoring in our eight-bed ICU within the last year before starting this study, we expected 10 patients per month with PiCCO monitoring and a mean of 10 TPTDs per patient. This resulted in an observation period of 10 months, in which all consecutive patients with PiCCO monitoring were analysed. There were no drop-outs, and the prevalence of the investigated criteria was exclusively documented at the time of measurement, which was performed irrespectively of the study.

Data analysed for this study have not been published previously, and there is no overlap with previous database analyses (Mair et al., 2016).

In our ICU, advanced hemodynamic monitoring is generally used in patients with shock refractory to 6 h of resuscitation, severe sepsis, acute respiratory distress syndrome (ARDS) (Villar et al., 2016), acute renal failure, hepatorenal syndrome, and severe acute pancreatitis.

2.2 Hemodynamic monitoring

For hemodynamic monitoring, the PiCCO-2 or PiCCO-plus-device (Pulsion Medical Systems SE, Feldkirchen, Germany) was used. TPTD and pulse contour analysis (PCA) were performed as described previously (Huber et al., 2008, 2016b; Hofkens et al., 2015). All patients had a 5-French catheter inserted in the femoral artery for arterial blood pressure monitoring. A central venous catheter (CVC) placed in the jugular or femoral vein (Arrow-Howes Multi-Lumen CVC AD-15703; Arrow-Howes; Morrisville, NC, USA) was used for bolus TPTD injection. TPTD measurements were recorded as sets consisting of three bolus injections of 15 ml of ice-cold saline.

2.3 Applicability criteria of SVV

Immediately before each routine TPTD, we documented whether the criteria of SR and CV were fulfilled. SR was defined as regular sinus rhythm with no arrhythmia or extra-systoles on the monitor screen. CV was defined as controlled mechanical ventilation in the absence of spontaneous breathing. SR and CV are major criteria for applicability of SVV (Mair et al., 2016). In addition, SVV outside the "gray zone" of 9%–13% was considered to be an additional minor criterion (Cannesson et al., 2011).

2.4 Endpoints

The prevalence of both SR and CV during the first three measurements within 24 h since baseline measurement of each patient was the primary endpoint. If more than three measurements were performed during the first 24 h, only the first three measurements were included in this analysis. The number was restricted to three measurements in order to avoid analysis of different numbers of measurements in different patients.

Secondary endpoints were the prevalence of SVV-values outside the "gray zone" of 9%–13%, in addition to SR and CV. Due to the particular interest in hemodynamic monitoring in defined clinical situations, subgroup analyses were performed for patients with sepsis as well as for patients with acute pancreatitis (Huber et al., 2008; Trepte et al., 2013; Sun et al., 2015; Yu et al., 2016) and liver failure (Umgelter et al., 2008; Umgelter and Schmid, 2009). Because of a potential overlap for patients with both sepsis and cirrhosis or pancreatitis, and also because of the difficulties in ruling out sepsis in acute pancreatitis and liver cirrhosis, we undertook two separate approaches. In the first approach, patients with cirrhosis or pancreatitis were classified as having cirrhosis or pancreatitis irrespective of the presence of sepsis (Table 1). With regard to the particular clinical interest in sepsis, we performed a second subgroup analysis restricted to the criterion sepsis (yes or no, irrespective of additional cirrhosis or pancreatitis; Table 1). Sepsis was defined according to international consensus (Rhodes et al., 2017).

2.5 Statistical analysis

All individual data were pooled for analysis. Categorical variables were expressed as number (valid percent). Mean and standard deviation (SD) were calculated for continuous variables. Analyses were performed regarding the first measurement of each patient, the first three measurements within the first 24 h and all measurements. The data for categorical variables were analysed using the *Z*-test for two population proportions, the chi-squared or the Fisher's exact test. The threshold for statistical significance was set to $P<0.05$. In a limited number of TPTD measurements, single variables were missing in the database. Therefore, statistical tests were calculated based on the measurements with valid data. All statistical tests were performed using PSPPIRE 0.8.5.

Table 1 Reasons for ICU admissions and prevalence of sepsis

Item	Patient*
Reason for ICU admission[1]	
Pancreatitis	5 (6%)
Chronic or acute liver failure	22 (25%)
Sepsis and/or pneumonia without cirrhosis or pancreatitis	38 (43%)
Other	23 (26%)
Sepsis[2]	
No sepsis	60 (68%)
Sepsis	28 (32%)

* Data are expressed as number (percentage) of patients. [1] In this analysis, patients with pancreatitis or liver failure were classified as pancreatitis or liver failure irrespective of additional sepsis. [2] In this analysis, patients with sepsis were classified as sepsis irrespective of additional cirrhosis or pancreatitis

3 Results

3.1 Patients' characteristics

The characteristics of all 88 patients are shown in Table 2. One thousand two hundred and forty-one routine TPTD measurements in 88 patients were performed during the 10-month study period. The mean number of TPTD measurements per patient was 14.1 (SD 14.7, median 10.0) with a mean duration of 7.4 d (SD 9.5 d, median 3.7 d). The number of the first three measurements within the first 24 h after baseline measurement was 232. One hundred and six (45.7%) of these 232 measurements were done while the patient was on vasopressor therapy.

The prevalence of SR was 67/82 (81.7%), 179/216 (82.9%), and 985/1194 (82.5%) during first measurement, first three measurements within first

24 h, and all measurements, respectively. The corresponding rates of CV were 35/79 (44.3%), 95/215 (44.2%), and 374/1207 (31.0%), respectively.

3.2 Subgroup analyses

For further analysis, subgroups were defined by different diagnoses and sepsis as shown in Table 1. The prevalence of SR and CV in these subgroups during the first three measurements within 24 h is shown in Table 3.

3.3 Analyses based on the reason for ICU admission

3.3.1 Prevalence of SR

The prevalence of SR was higher in patients with pancreatitis and liver failure compared to the other reasons for admission: The prevalence of SR was significantly higher in patients with pancreatitis (15/15 (100%)) than in patients with sepsis and/or pneumonia (72/94 (76.6%); P=0.036), as well as in patients with liver failure (51/54 (94.4%)) compared to patients with sepsis and/or pneumonia (72/94 (76.6%); P=0.005) and other diagnoses (38/47 (80.9%); P=0.035). Furthermore, the prevalence of SR was significantly lower in patients with sepsis (50/68 (73.5%)) than in patients without sepsis (126/142 (88.7%); P=0.005).

3.3.2 Prevalence of CV

Patients with pancreatitis (0/15 (0.0%)) as well as liver failure (14/52 (26.9%)) were significantly less often on CV compared to the patients with sepsis and/or pneumonia (50/94 (53.2%)) as well as other diagnoses (28/48 (58.3%)) (all P-values 0.024 or less).

Table 2 Patients' characteristics

Parameter	Value*
Male	48 (55%)
Female	40 (45%)
Age (year)	60.9±16.7
Weight (kg)	73.7±21.8
Height (cm)	169.3±9.0
BMI (kg/m^2)	25.6±6.6
SAPS II score	38.3±17.0

There are 88 patients and 1241 TPTDs. * Values are expressed as number (percentage) of patients or mean±SD. BMI: body mass index; SAPS: simplified acute physiology score

Table 3 Prevalence of sinus rhythm (SR) and controlled mechanical ventilation (CV) during the first three measurements within the first 24 h in subgroups defined by different reasons for admission and prevalence of sepsis

Item	SR	CV
Reason for ICU admission		
Pancreatitis	15/15 (100.0%)	0/15 (0.0%)
Chronic or acute liver failure	51/54 (94.4%)	14/52 (26.9%)
Sepsis and/or pneumonia	72/94 (76.6%)	50/94 (53.2%)
Other	38/47 (80.9%)	28/48 (58.3%)
P value	0.010	<0.001
Sepsis		
No sepsis	126/142 (88.7%)	57/136 (41.9%)
Sepsis	50/68 (73.5%)	35/73 (47.9%)
P value	0.005	0.400

Values are expressed as SR or CV/total number (percentage) of patients

3.4 Analyses based on the time of measurement

During the first measurement, the prevalence of both SR and CV was 34.6%. In 46.2% of cases, the patients had SR, but did not have CV. In 10.3% of cases, the patients were under CV, but lacked SR. In 9.0% of cases, the patients had neither CV nor SR.

The prevalence of SR and CV and their combinations during the first measurement, the first three measurements of the first 24 h since baseline and all measurements is shown in Fig. 1.

Applicability of SVV defined by presence of both SR and CV was significantly higher during the first 24 h compared to the measurements thereafter (36.1% vs. 21.9%; P<0.001).

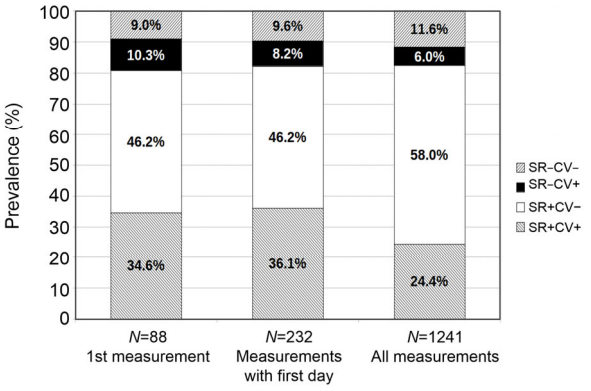

Fig. 1 Prevalence of sinus rhythm (SR), controlled mechanical ventilation (CV), and their combination during the first measurement, the first three measurements within the first 24 h since baseline, and all measurements in 88 patients

Analysis of several pre-defined subgroups demonstrated that the applicability of SVV was particularly poor in patients with acute pancreatitis (0/15 (0%)) compared to patients with liver failure (13/51 (25.5%); *P*=0.029), sepsis and/or pneumonia (36/89 (40.4%); *P*=0.002) and to patients with other diagnoses (23/47 (48.9%); *P*=0.0.001) (Fig. 2).

By contrast, there was no significant difference in the applicability of SVV between patients with (22/68 (32.4%)) and without (50/134 (37.3%); *P*=0.48) sepsis (Fig. 3).

SVV was within the "gray zone" of 9%–13% in 27.6% of all measurements in patients with both SR and CV. This results in a final rate of 19.0% of all measurements of patients fulfilling both major and minor applicability criteria (Table 4).

4 Discussion

4.1 Our data in the context of previous findings

There is increasing evidence that guidance of fluid support using SVV or PPV may improve outcome, in particular in the peri-operative setting (Benes et al., 2014a). Furthermore, the usefulness to guide therapy based on algorithms has been shown in animal studies in specific diseases such as acute pancreatitis (Trepte et al., 2013). However, the applicability of some of these data in clinical routine has been questioned because of the different setting of an animal experiment compared to clinical reality (Huber et al., 2015).

Several studies reported on the limited applicability of SVV and PPV in the ICU setting (Maguire

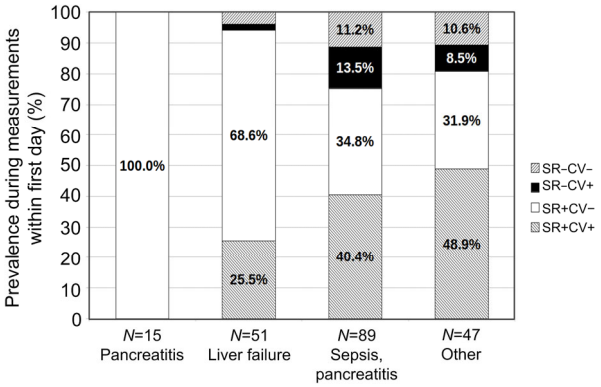

Fig. 2 Distribution of sinus rhythm (SR), controlled mechanical ventilation (CV), and their combination during the first three measurements within the first 24 h since baseline in subgroups of patients with different diagnoses
Patients with pancreatitis or liver failure were classified as pancreatitis or liver failure irrespective of an additional sepsis

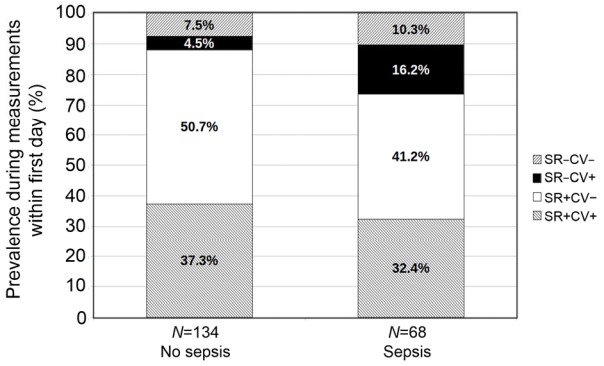

Fig. 3 Distribution of sinus rhythm (SR), controlled mechanical ventilation (CV), and their combination during the first three measurements within the first 24 h since baseline in patients with and without sepsis
Patients with sepsis were classified as sepsis irrespective of the underlying disease

Table 4 Prevalence of both sinus rhythm (SR) and controlled mechanical ventilation (CV)

Item	Number of measurements	Major criteria SR+ and CV+	SVV 9%–13% among measurements with SR+ and CV+	Major and minor criteria fulfilled
1st measurement	88	27/78 (34.6%)	9/27 (33.3%)	18/68 (26.5%)
1st day	232	75/208 (36.1%)	18/72 (25.0%)	54/182 (29.7%)
All measurements	1241	287/1176 (24.4%)	75/272 (27.6%)	197/1035 (19.0%)
Subgroups (1st day)				
Pancreatitis	15	0/15 (0.0%)	5/15 (33.3%)	0/14 (0.0%)
Liver failure	59	13/51 (25.5%)	3/13 (23.1%)	10/47 (21.3%)
Sepsis and/or pneumonia	100	36/89 (40.4%)	9/35 (25.7%)	26/79 (32.9%)
Other	51	23/47 (48.9%)	6/22 (27.3%)	16/40 (40.0%)
No sepsis	151	50/134 (37.3%)	14/49 (28.6%)	35/119 (29.4%)
Sepsis	74	22/68 (32.4%)	4/21 (19.0%)	17/61 (27.9%)

Major applicability criteria (column 3), portion of measurements fulfilling both major criteria and SVV within the gray zone (column 4) and prevalence of both major and minor criteria (both SR and CV) and SVV outside the gray zone (column 5) in various subgroups. 1st day: first three measurements within the first 24 h

et al., 2011; Benes et al., 2014b; Mahjoub et al., 2014; Mair et al., 2016). However, most of these studies analysed overall applicability of these parameters in the ICU which does not preclude their usefulness in certain subgroups or at specific time-points of the ICU stay.

Therefore, this study focussed on the applicability of SVV in patients with and without sepsis, acute pancreatitis or liver failure as well as on the applicability soon after admission.

In general, the finding of a limited applicability of SVV in about 24% of all measurements in our study is in line with the results of several previous studies (Maguire et al., 2011; Benes et al., 2014b; Mahjoub et al., 2014; Mair et al., 2016). Interestingly, our study demonstrated a time dependency of the applicability of SVV irrespective of the reason for ICU admission.

The prevalence of both SR and CV was significantly higher during the first 24 h compared to the measurements thereafter (36.1% vs. 21.9%; $P<0.001$). Although the applicability on the 1st day after admission might still be considered as low, in these patients fulfilling both major criteria at least on admission might be important with regard to the concept of "individually optimized hemodynamic therapy" (IOHT) (Goepfert et al., 2013). This approach is based on the superiority of SVV to other parameters of preload and FR such as global end-diastolic volume index (GEDVI) and central venous pressure (CVP). Assuming a high intra-individual association of SVV and GEDVI, fluid therapy aims to achieve an SVV $\leq$10% as long as the patient with SR is under CV. The corresponding GEDVI is documented and used as an individual goal of preload later during the ICU stay, when the patient is not any longer under CV. Consequently, in about 36% of our patients an initial measurement of SVV could have been used for "calibration" of GEDVI.

The prevalence of SR did not substantially change over time (80.8% in the 1st measurement, 82.4% in all measurements). By contrast, the prevalence of CV was markedly higher during the 1st measurement compared to the totality of measurements (44.8% vs. 30.6%).

The increase of patients without CV (from 46.2% to 58.0% for the patients with SR) over time is in line with a successful weaning from CV. The resulting decrease in applicability was not weighed out by a small proportion of patients changing from atrial fibrillation (potentially induced by the initial, severe disease) to SR.

Our study showed that the applicability of SVV was significantly different in several subgroups with a range from 0% in patients with acute pancreatitis up to nearly 50% in patients without pancreatitis, liver failure, pneumonia, or sepsis. This emphasizes that neither the data of usefulness of the dynamic indices in the OR nor the findings of low applicability in ICU can be generalized. A rapidly increasing number of haemodynamic parameters and devices available suggest a more specific "personalized" haemodynamic monitoring for different entities and settings. A recent experimental animal study nicely demonstrated an improved outcome in pigs with acute pancreatitis under CV when using an SVV-guided resuscitation algorithm compared to the controls with resuscitation according to CVP (Trepte et al., 2013). Nevertheless, the generalizability of this study has been questioned for the supposedly low applicability of SVV in a clinical setting with a low early prevalence of CV (Huber et al., 2015). These concerns are supported by our finding that despite a 100% rate of SR the dynamic indices were not applicable in any of the first three measurements within 24 h, since none of the patients was under CV. Although a certain number of patients might require CV during later stages of acute pancreatitis, parameters of TPTD such as GEDVI (Huber et al., 2016a) and extravascular lung water index (EVLWI) (Zhang et al., 2012; Huber et al., 2014) might be more useful in early management of acute pancreatitis. This is supported by several clinical studies (Huber et al., 2008; Sun et al., 2015; Yu et al., 2016).

Next to the patients with acute pancreatitis, patients with liver failure had the lowest percentage of early applicability of SVV and PPV: in only 25.5% of the first three measurements, the patients had SR and were under CV. Similarly to acute pancreatitis, patients had SR during nearly all measurements (94.4%), but in only 26.9% of cases were the patients under CV. Necessarily, one can question the use of (semi)-invasive monitoring early in these groups of patients. On the other hand, haemodynamic management during liver failure is particularly difficult and early mortality is high in complications such as hepato-renal syndrome, spontaneous bacterial peritonitis,

alcoholic steatohepatitis and variceal bleeding (Umgelter et al., 2008, 2009; Wendon et al., 2011; Saugel et al., 2012; Moreau et al., 2013; Huber et al., 2017). Several studies suggested the usefulness of early haemodynamic monitoring based on TPTD in these complications of liver cirrhosis (Umgelter et al., 2008; Saugel et al., 2012; Al-Chalabi et al., 2013; Phillip et al., 2014).

In addition to SR and CV ("major criteria for the applicability of SVV"), further minor limitations have been described (Mair et al., 2016). Furthermore, a recent study demonstrated limited predictive capabilities of FR for SVV and/or PPV, if the values were in the "gray zone" between 9% and 13% (Cannesson et al., 2011).

SVV was within the "gray zone" of 9%–13% in 27.6% of all measurements in patients with both SR and CV. Restricting the applicability of SVV to measurements with SR and CV (24.4%) as well as with values outside the gray zone would result in a final rate of 19.0% fulfilling all three applicability criteria (SR, CV, outside gray zone; Table 4).

Further "minor" limitations for the use of SVV and PPV include tidal volumes below 8 ml/kg predicted bodyweight (de Backer et al., 2009; Lakhal et al., 2011; Biais et al., 2014), a driving pressure <20 cmH_2O (1 cmH_2O=98.06 Pa) (Muller et al., 2010; Lakhal et al., 2011; Biais et al., 2014), a compliance ≤30 ml/cmH_2O (Monnet et al., 2012), open chest surgery (Reuter et al., 2005; de Waal et al., 2009), increased abdominal pressure (Duperret et al., 2007; Renner et al., 2009), a heart rate/respiratory rate ≤3.6 (de Backer et al., 2009), and PEEP values >10 cmH_2O (Maguire et al., 2011; Benes et al., 2014b). Strict application of six of these criteria in a multicentre study resulted in a very low overall applicability of only 2% (Mahjoub et al., 2014).

However, some of these criteria are still subject to debate. If these criteria are not fulfilled, the use of SVV or PPV is not completely precluded. However, the absence of minor criteria reduces the capacity of SVV and PPV to predict FR. As demonstrated by Biais et al. (2014), the absence of minor criteria results in an increased "gray zone". Nevertheless, these measurements cannot be classified as completely useless or unreliable, but should be interpreted more cautiously and in the context of other haemodynamic findings.

The 27.6% prevalence of values within the gray zone was comparable to a prevalence of 98/413 (24%) patients in the study by Cannesson et al. (2011).

4.2 Practical implications

Our data confirm that in the ICU setting, the use of SVV and PPV is restricted to a small percentage of the measurements. Nevertheless, the applicability is higher soon after the admission and in certain subgroups. Despite a later loss of applicability, initial measurement of SVV or PPV might be useful with regard to IOHT by adjusting individual goals for GEDVI or CVP based on initial SVV measurement during appropriate conditions with CV and SR. However, feasibility and benefits of the IOHT remain to be proven outside the peri-operative setting.

In summary, dynamic indices are not suitable to replace other techniques of preload assessment including physical examination, echocardiography, TPTD and functional tests such as (mini) volume challenges in the ICU.

4.3 Strengths and weaknesses of the study

Several previous studies investigated "virtual applicability" of dynamic indices in patients who were frequently not under advanced haemodynamic monitoring or even lacked an arterial line in a substantial percentage (Maguire et al., 2011; Benes et al., 2014b; Mahjoub et al., 2014). By contrast, in our study, all patients were under advanced hemodynamic monitoring providing TPTD- and PCA-derived data.

Despite the heterogeneity of our patients and more than 1200 measurements, this study has the limitations of a single centre analysis with predominantly medical patients. Therefore, the results cannot be generalized to other populations, in particular not to the peri-operative setting.

Regarding the association of the absence of minor criteria with the "gray zone", we restricted our analysis of minor applicability criteria to the "gray zone" of 9%–13% and did not separately analyze the prevalence of single minor criteria.

Finally, the study was conducted with the focus on SVV, since only SVV was available for all measurements. Since the cut-offs for SVV and PPV are given in the same range, most of our findings regarding SVV might also apply to PPV, in particular the prevalence of SR and CV.

5 Conclusions

The applicability of SVV and PPV defined by the prevalence of both SR and CV in a predominantly medical ICU is only about 25%–35%. The prevalence of both mandatory criteria decreases over time during the ICU stay, in particular because of a decrease in the prevalence of CV. Furthermore, the applicability is particularly low in patients with acute pancreatitis and liver failure. Nevertheless, initial applicability of SVV and PPV might be useful with regard to the concept of IOHT.

Compliance with ethics guidelines

Wolfgang HUBER, Uli MAYR, Andreas UMGELTER, Michael FRANZEN, Wolfgang REINDL, Roland M. SCHMID, and Florian ECKEL declare that they have no conflict of interest.

All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2008 (5). The need for informed consent was waived due to the observational approach of the study.

References

Al-Chalabi A, Matevossian E, v Thaden AK, et al., 2013. Evaluation of the Hepa Wash® treatment in pigs with acute liver failure. *BMC Gastroenterol*, 13:83. https://doi.org/10.1186/1471-230X-13-83

Benes J, Giglio M, Brienza N, et al., 2014a. The effects of goal-directed fluid therapy based on dynamic parameters on post-surgical outcome: a meta-analysis of randomized controlled trials. *Crit Care*, 18(5):584. https://doi.org/10.1186/s13054-014-0584-z

Benes J, Zatloukal J, Kletecka J, et al., 2014b. Respiratory induced dynamic variations of stroke volume and its surrogates as predictors of fluid responsiveness: applicability in the early stages of specific critical states. *J Clin Monit Comput*, 28(3):225-231. https://doi.org/10.1007/s10877-013-9524-8

Biais M, Ehrmann S, Mari A, et al., 2014. Clinical relevance of pulse pressure variations for predicting fluid responsiveness in mechanically ventilated intensive care unit patients: the grey zone approach. *Crit Care*, 18(6):587. https://doi.org/10.1186/s13054-014-0587-9

Cannesson M, Vallet B, Michard F, 2009. Pulse pressure variation and stroke volume variation: from flying blind to flying right? *Br J Anaesth*, 103(6):896-899. https://doi.org/10.1093/bja/aep321

Cannesson M, le Manach Y, Hofer CK, et al., 2011. Assessing the diagnostic accuracy of pulse pressure variations for the prediction of fluid responsiveness: a "gray zone" approach. *Anesthesiology*, 115(2):231-241. https://doi.org/10.1097/ALN.0b013e318225b80a

de Backer D, Taccone FS, Holsten R, et al., 2009. Influence of respiratory rate on stroke volume variation in mechanically ventilated patients. *Anesthesiology*, 110(5):1092-1097. https://doi.org/10.1097/ALN.0b013e31819db2a1

de Waal EE, Rex S, Kruitwagen CL, et al., 2009. Dynamic preload indicators fail to predict fluid responsiveness in open-chest conditions. *Crit Care Med*, 37(2):510-515. https://doi.org/10.1097/CCM.0b013e3181958bf7

Duperret S, Lhuillier F, Piriou V, et al., 2007. Increased intra-abdominal pressure affects respiratory variations in arterial pressure in normovolaemic and hypovolaemic mechanically ventilated healthy pigs. *Intensive Care Med*, 33(1):163-171. https://doi.org/10.1007/s00134-006-0412-2

Goepfert MS, Richter HP, zu Eulenburg C, et al., 2013. Individually optimized hemodynamic therapy reduces complications and length of stay in the intensive care unit: a prospective, randomized controlled trial. *Anesthesiology*, 119(4):824-836. https://doi.org/10.1097/ALN.0b013e31829bd770

Hofkens PJ, Verrijcken A, Merveille K, et al., 2015. Common pitfalls and tips and tricks to get the most out of your transpulmonary thermodilution device: results of a survey and state-of-the-art review. *Anaesthesiol Intensive Ther*, 47(2):89-116. https://doi.org/10.5603/AIT.a2014.0068

Huber W, Umgelter A, Reindl W, et al., 2008. Volume assessment in patients with necrotizing pancreatitis: a comparison of intrathoracic blood volume index, central venous pressure, and hematocrit, and their correlation to cardiac index and extravascular lung water index. *Crit Care Med*, 36(8):2348-2354. https://doi.org/10.1097/CCM.0b013e3181809928

Huber W, Höllthaler J, Schuster T, et al., 2014. Association between different indexations of extravascular lung water (EVLW) and PaO_2/FiO_2: a two-center study in 231 patients. *PLoS ONE*, 9(8):e103854. https://doi.org/10.1371/journal.pone.0103854

Huber W, Kemnitz V, Phillip V, et al., 2015. Outcome prediction, fluid resuscitation, pain management, and antibiotic prophylaxis in severe acute pancreatitis. *Intensive Care Med*, 41(11):2034-2035. https://doi.org/10.1007/s00134-015-4022-8

Huber W, Phillip V, Höllthaler J, et al., 2016a. Femoral indicator injection for transpulmonary thermodilution using the EV1000/VolumeView®: do the same criteria apply as for the PiCCO®? *J Zhejiang Univ-Sci B (Biomed & Biotechnol)*, 17(7):561-567. https://doi.org/10.1631/jzus.B1500244

Huber W, Fuchs S, Minning A, et al., 2016b. Transpulmonary thermodilution (TPTD) before, during and after sustained low efficiency dialysis (SLED). A prospective study on feasibility of TPTD and prediction of successful fluid removal. *PLoS ONE*, 11(4):e0153430. https://doi.org/10.1371/journal.pone.0153430

Huber W, Henschel B, Schmid R, et al., 2017. First clinical experience in 14 patients treated with ADVOS: a study on feasibility, safety and efficacy of a new type of albumin

dialysis. *BMC Gastroenterol*, 17(1):32. https://doi.org/10.1186/s12876-017-0569-x

Lakhal K, Ehrmann S, Benzekri-Lefèvre D, et al., 2011. Respiratory pulse pressure variation fails to predict fluid responsiveness in acute respiratory distress syndrome. *Crit Care*, 15(2):R85. https://doi.org/10.1186/cc10083

Maguire S, Rinehart J, Vakharia S, et al., 2011. Respiratory variation in pulse pressure and plethysmographic waveforms: intraoperative applicability in a North American academic center. *Anesth Analg*, 112(1):94-96. https://doi.org/10.1213/ANE.0b013e318200366b

Mahjoub Y, Lejeune V, Muller L, et al., 2014. Evaluation of pulse pressure variation validity criteria in critically ill patients: a prospective observational multicentre point-prevalence study. *Br J Anaesth*, 112(4):681-685. https://doi.org/10.1093/bja/aet442

Mair S, Tschirdewahn J, Götz S, et al., 2016. Applicability of stroke volume variation in patients of a general intensive care unit: a longitudinal observational study. *J Clin Monit Comput*, 31(6):1177-1187. https://doi.org/10.1007/s10877-016-9951-4

Michard F, 2005. Volume management using dynamic parameters: the good, the bad, and the ugly. *Chest*, 128(4): 1902-1903. https://doi.org/10.1378/chest.128.4.1902

Michard F, Lopes MR, Auler JO Jr, 2007. Pulse pressure variation: beyond the fluid management of patients with shock. *Crit Care*, 11(3):131. https://doi.org/10.1186/cc5905

Monnet X, Bleibtreu A, Ferré A, et al., 2012. Passive leg-raising and end-expiratory occlusion tests perform better than pulse pressure variation in patients with low respiratory system compliance. *Crit Care Med*, 40(1): 152-157. https://doi.org/10.1097/CCM.0b013e31822f08d7

Moreau R, Jalan R, Gines P, et al., 2013. Acute-on-chronic liver failure is a distinct syndrome that develops in patients with acute decompensation of cirrhosis. *Gastroenterology*, 144(7):1426-1437. https://doi.org/10.1053/j.gastro.2013.02.042

Muller L, Louart G, Bousquet PJ, et al., 2010. The influence of the airway driving pressure on pulsed pressure variation as a predictor of fluid responsiveness. *Intensive Care Med*, 36(3):496-503. https://doi.org/10.1007/s00134-009-1686-y

Perel A, 1998. Assessing fluid responsiveness by the systolic pressure variation in mechanically ventilated patients. Systolic pressure variation as a guide to fluid therapy in patients with sepsis-induced hypotension. *Anesthesiology*, 89(6):1309-1310. https://doi.org/10.1097/00000542-199812000-00005

Phillip V, Saugel B, Ernesti C, et al., 2014. Effects of paracentesis on hemodynamic parameters and respiratory function in critically ill patients. *BMC Gastroenterol*, 14(1):18. https://doi.org/10.1186/1471-230X-14-18

Preisman S, Kogan S, Berkenstadt H, et al., 2005. Predicting fluid responsiveness in patients undergoing cardiac surgery: functional haemodynamic parameters including the respiratory systolic variation test and static preload indicators. *Br J Anaesth*, 95(6):746-755. https://doi.org/10.1093/bja/aei262

Renner J, Gruenewald M, Quaden R, et al., 2009. Influence of increased intra-abdominal pressure on fluid responsiveness predicted by pulse pressure variation and stroke volume variation in a porcine model. *Crit Care Med*, 37(2):650-658. https://doi.org/10.1097/CCM.0b013e3181959864

Reuter DA, Felbinger TW, Schmidt C, et al., 2002. Stroke volume variations for assessment of cardiac responsiveness to volume loading in mechanically ventilated patients after cardiac surgery. *Intensive Care Med*, 28(4): 392-398. https://doi.org/10.1007/s00134-002-1211-z

Reuter DA, Goepfert MS, Goresch T, et al., 2005. Assessing fluid responsiveness during open chest conditions. *Br J Anaesth*, 94(3):318-323. https://doi.org/10.1093/bja/aei043

Rhodes A, Evans LE, Alhazzani W, et al., 2017. Surviving sepsis campaign: international guidelines for management of sepsis and septic shock: 2016. *Intensive Care Med*, 43(3):304-377. https://doi.org/10.1007/s00134-017-4683-6

Sakka SG, 2015. Hemodynamic monitoring in the critically ill patient—current status and perspective. *Front Med (Lausanne)*, 2:44. https://doi.org/10.3389/fmed.2015.00044

Saugel B, Phillip V, Gaa J, et al., 2012. Advanced hemodynamic monitoring before and after transjugular intrahepatic portosystemic shunt: implications for selection of patients—a prospective study. *Radiology*, 262(1):343-352. https://doi.org/10.1148/radiol.11110043

Sun Y, Lu ZH, Zhang XS, et al., 2015. The effects of fluid resuscitation according to picco on the early stage of severe acute pancreatitis. *Pancreatology*, 15(5):497-502. https://doi.org/10.1016/j.pan.2015.06.006

Trepte CJ, Bachmann KA, Stork JH, et al., 2013. The impact of early goal-directed fluid management on survival in an experimental model of severe acute pancreatitis. *Intensive Care Med*, 39(4):717-726. https://doi.org/10.1007/s00134-012-2775-x

Umgelter A, Schmid RM, 2009. Terlipressin for hepatorenal syndrome—what is the role of plasma expansion and hemodynamic monitoring? *Z Gastroenterol*, 47(3):307-308 (in German). https://doi.org/10.1055/s-0028-1109113

Umgelter A, Reindl W, Wagner KS, et al., 2008. Effects of plasma expansion with albumin and paracentesis on haemodynamics and kidney function in critically ill cirrhotic patients with tense ascites and hepatorenal syndrome: a prospective uncontrolled trial. *Crit Care*, 12(1): R4. https://doi.org/10.1186/cc6765

Umgelter A, Reindl W, Miedaner M, et al., 2009. Failure of current antibiotic first-line regimens and mortality in

hospitalized patients with spontaneous bacterial peritonitis. *Infection*, 37(1):2-8. https://doi.org/10.1007/s15010-008-8060-9

Villar J, Pérez-Méndez L, Kacmarek RM, 2016. The berlin definition met our needs: no. *Intensive Care Med*, 42(5): 648-650. https://doi.org/10.1007/s00134-016-4242-6

Wendon J, Bernal W, Willars C, et al., 2011. Critical care and cirrhosis: outcome and benefit. *Curr Opin Crit Care*, 17(5):533-537. https://doi.org/10.1097/MCC.0b013e32834ab06f

Yu WQ, Zhang Y, Zhang SY, et al., 2016. Impact of misplaced subclavian vein catheter into jugular vein on transpulmonary thermodilution measurement variables. *J Zhejiang Univ-Sci B (Biomed & Biotechnol)*, 17(1):60-66. https://doi.org/10.1631/jzus.B1500167

Zhang Z, Lu B, Sheng X, et al., 2011. Accuracy of stroke volume variation in predicting fluid responsiveness: a systematic review and meta-analysis. *J Anesth*, 25(6): 904-916. https://doi.org/10.1007/s00540-011-1217-1

Zhang Z, Lu B, Ni H, 2012. Prognostic value of extravascular lung water index in critically ill patients: a systematic review of the literature. *J Crit Care*, 27(4):420.e1-420.e8. https://doi.org/10.1016/j.jcrc.2011.09.006

中文概要

题　目：不同患者群体容量反应性变量参数应用的强制性标准：重症监护病人窦性节律和控制呼吸流行情况的前瞻性研究

目　的：通过对危重病人在入院后 24 小时内和整个重症监护过程中窦性心律和控制呼吸情况的调查，分析每搏量变异在评估危重病人容量反应的适用性，并探究每搏量变异度在败血症、肝硬化和胰腺炎病人中的适用性。

创新点：通过探究窦性节律和控制呼吸情况评估每搏量变异度在重症监护病人临床上的适用性，弥补重症监护病人窦性节律和控制呼吸情况数据的空白。

方　法：在进行 1241 次热稀释法血流量测量前，对 88 位病人的窦性节律和控制呼吸情况进行调查。

结　论：每搏量变异度在主要的医疗重症监护病房中的适用性只约为 25%~35%。两项强制性指标的流行性在重症监护病房的情况随时间的延长而降低。此外，每搏量变异度在胰腺炎和肝功能衰竭患者中的适用性尤其低。

关键词：血液动力学检测；前负荷；容量反应性；每搏量变异度；脉压变异