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Physical examination, central venous pressure, and chest radiography for the prediction of transpulmonary thermodilution–derived hemodynamic parameters in critically ill patients: A prospective trial☆

Bernd Saugel MD[a,*], Stephan Ringmaier MD[a], Konstantin Holzapfel MD[b], Tibor Schuster PhD[c], Veit Phillip MD[a], Roland M Schmid MD[a], Wolfgang Huber MD[a]

[a]*II. Medizinische Klinik und Poliklinik, Klinikum rechts der Isar der Technischen Universität München, Ismaninger Strasse 22, D-81675 München, Germany*
[b]*Institut für Röntgendiagnostik, Klinikum rechts der Isar der Technischen Universität München, Ismaninger Strasse 22, D-81675 München, Germany*
[c]*Institut für Medizinische Statistik und Epidemiologie, Klinikum rechts der Isar der Technischen Universität München, Ismaninger Strasse 22, D-81675 München, Germany*

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Abstract

Purpose: Physical examination, assessment of central venous pressure (CVP) and chest radiography are diagnostic tools for estimation of volume status in intensive care unit (ICU) patients. Passive leg raising (PLR) is a test to estimate fluid responsiveness. Transpulmonary thermodilution (TPTD) is established for measurement of cardiac index (CI), global end-diastolic volume index (GEDVI), and extravascular lung water index (EVLWI). This study compares the estimation of volume status using physical examination, CVP, chest radiography, PLR, and TPTD.

Materials and Methods: This study was a prospective trial. Seventy-one patients in a medical ICU were studied. Interventions were as follows: physical examination by 2 independent examiners. CVP was measured. TPTD was performed. In 2 patient subgroups PLR and chest radiography was performed. Comparison of clinical and x-ray-based estimation of volume status, CVP, PLR, and TPTD variables was performed.

Results: Estimation of volume status based on physical examination showed a poor interobserver agreement between the examiners. There was no significant correlation between physical examination–based estimation of volume status and CVP or TPTD-derived GEDVI. There was no significant correlation between CVP and GEDVI, EVLWI or CI. PLR did not indicate fluid responsiveness. Radiographically estimated and TPTD-GEDVI/EVLWI values were significantly different.

Conclusions: In ICU patients, assessment of volume status remains difficult. Physical examination, CVP, and portable radiography do not correlate with TPTD assessment of volume status, preload, or pulmonary hydration.

☆ Conflict of interest: Wolfgang Huber is member of the Medical Advisory Board of Pulsion Medical Systems AG. All other authors have no conflict of interest to declare.

* Corresponding author. Tel.: +49 89 4140 2267.
E-mail address: bcs.muc@gmx.de (B. Saugel).

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1. Introduction

Early optimization of intravascular volume status is of central importance in the treatment of critically ill patients [1].

To estimate volume status physical examination, assessment of central venous pressure (CVP) and chest radiography are primary diagnostic tools.

However, physical examination procedures like inspection of the jugular veins (intravascular space), examination of the lower extremities for edema (interstitium), and clinical examination for ascites or pleural effusions ("third space") show poor specificity and sensitivity regarding the early estimation of a patient's intravascular and pulmonary volume status [2-4].

Besides physical examination procedures, simple functional tests can be performed in a clinical setting to estimate a patient's volume status:

For testing fluid responsiveness in critically ill patients, the passive leg raising (PLR) maneuver can be performed as an endogenous volume challenge [5]. Performing the PLR test increases cardiac preload because venous blood is shifted from the lower extremities to the intrathoracic compartment.

In a clinical setting, simple and ubiquitously available tools such as measurement of CVP and chest radiography are often the next diagnostic approach to volume assessment.

Since the majority of intensive care unit (ICU) patients is equipped with a central venous catheter, assessment of CVP is usually easily feasible in these patients. However, the predictive capabilities of CVP regarding cardiac preload and fluid responsiveness are limited [6].

The chest roentgenogram using portable chest radiography is a frequently used method for assessment of cardiac filling and pulmonary hydration in ICU patients [7].

Regarding invasive and more advanced hemodynamic monitoring techniques, transpulmonary thermodilution (TPTD) and pulse contour analysis are increasingly used for the measurement of cardiac index (CI) and the assessment of cardiac preload, fluid responsiveness and pulmonary fluid status [8,9]. Using these monitoring systems, in patients with sinus rhythm and controlled ventilation the dynamic cardiac preload variable stroke volume variation (SVV) can help to predict intravascular volume status and volume responsiveness [8]. In patients not fulfilling this prerequisites, volumetric parameters such as global end-diastolic volume index (GEDVI) are established for the assessment of cardiac preload [8]. In addition, pulse contour analysis provides an index of myocardial left ventricular contractility (dPmax; ie, greatest left ventricular pressure velocity increase) [10]. In addition to the assessment of cardiac preload and potential volume responsiveness, the TPTD technique provides the variable extravascular lung water index (EVLWI) for the assessment of pulmonary hydration [9,11].

However, the use of TPTD for hemodynamic monitoring causes additional costs, requires an arterial catheter, and is therefore predominantly restricted to the ICU.

The aim of our study was to evaluate physical examination procedures, measurement of CVP, and chest radiography with regard to intravascular and pulmonary volume status compared with the assessment of hemodynamic variables using TPTD.

2. Materials and methods

2.1. Patients

Between March 2005 and January 2007, we prospectively studied 71 critically ill patients admitted to the general ICU of a German university hospital (Klinikum rechts der Isar, Technical University Munich) who were monitored using TPTD. The study was approved by the local ethics committee. Patients were included immediately after admission to the ICU or in the course of their ICU stay as soon as the inclusion criteria where fulfilled (eg, installment of the TPTD-device).

2.2. Physical examination

Each of the 71 patients underwent 2 independent structured and standardized physical examinations. One examination was performed by the study investigator (physical examination 1). The study investigator was not working in the ICU during the period of the study, and he was blinded to the patients' diagnoses, medical history, laboratory results, and hemodynamic monitoring parameters. The clinical examination was performed and categorized as follows.

- Inspection of the tongue: dry, normal, moist, engorged sublingual veins.
- Inspection of the veins on the back of the patient's hand after arm elevation above heart level: do the veins collapse? Yes or no.
- Inspection of the external jugular vein in inspiration and head-up tilt position: external jugular vein distension? No distension, mild, moderate, high-grade distension.
- Auscultation of the lungs regarding moist rales: bubbling rales: yes or no. Small clicking rales: yes or no. Localization of the rales: superior, (middle), inferior lobe.
- Percussion and auscultation of the chest regarding presence of pleural effusions: no pleural effusions, right-sided, left-sided, both sides. Localization of pleural effusions: superior, (middle), inferior lobe.
- Inspection and palpation of the abdomen: presence of ascites? No ascites; mild, moderate, or severe ascites.
- Inspection and palpation of the lower legs: presence of lower leg edema? No edema; mild, moderate, or severe edema.
- Inspection and examination of the skin turgor: normal; mild, moderate, or severe decreased skin turgor.
- Final global estimation of intravascular volume status considering all above mentioned examinations on a

scale of 1 to 9 (1 means massive hypovolemic volume status, 9 means massive fluid overload).

The same standardized physical examination was performed by a physician working in the ICU who knew only the patients' diagnoses, medical history, and laboratory results but no hemodynamic monitoring parameters (physical examination 2).

2.3. Measurement of CVP

CVP was recorded throughout the respiratory cycle and measured at end-expiration.

2.4. TPTD measurements

For TPTD we used a 5-French thermistor-tipped arterial line (Pulsiocath; Pulsion Medical Systems AG, Munich Germany) that was inserted in the abdominal aorta through the femoral artery and connected to a hemodynamic monitor (PiCCO-Plus; Pulsion Medical Systems AG). TPTD was performed within 30 minutes after physical examination. Based on TPTD following injection of 15 mL cold saline 0.9% via a central venous catheter, CI, systemic vascular resistance index (SVRI), GEDVI, and EVLWI were determined [8,12]. Each TPTD measurement represents the mean of 3 consecutive thermodilution measurements. Global end-diastolic volume (GEDV) was indexed to the body surface area, and extravascular lung water (EVLW) was indexed to the predicted body weight.

2.5. Hemodynamic parameters and assumed reference values used in the study

Reference values of hemodynamic parameters were used according to the recommendations of the manufacturer of the device:

CI (reference value, 3.0-5.0 L/min per m^2)
CVP (reference value, 4-9 mm Hg)
EVLWI (reference value, ≤7 mL/kg)
GEDVI (reference value, 680-800 mL/m^2)
Left ventricular pressure velocity increase (dPmax; assumed reference value, 1200-2000 mm Hg/s; reference values not provided by the manufacturer of the device)
SVRI (reference value, 1700-2400 dyn ∗ s ∗ cm^{-5} ∗ m^2).

2.6. PLR test

Following TPTD, in a subgroup of 30 patients, the PLR test was performed by elevating the patient's legs from the supine position for 15 minutes. Before PLR as well as 1, 3, 5, 10, and 15 minutes after the start of the PLR test, hemodynamic and pulse contour analysis parameters were recorded as follows: mean arterial pressure (MAP), heart rate (HR), pulse contour CI, SVRI, and dPmax. According to the study protocol, contraindications for PLR (eg, acute respiratory insufficiency, threat of aspiration, cardiac shock, intracerebral hemorrhage, and increased intracerebral pressure) were excluded before performing the test.

2.7. Chest x-ray

In a subgroup of 48 patients, chest radiography was performed for clinical indications unrelated to the study using portable radiography. All chest roentgenograms were read by the same experienced radiologist not knowing the patients' medical history or diagnoses. The radiologist was aware of the definitions and reference values of EVLWI and GEDVI. Following a structured and standardized protocol, the radiologist judged the extent of pleural effusions, pulmonary edema, as well as dilatation of the heart and estimated EVLWI, GEDVI, and intravascular volume status on a scale of 1 to 9 (1 meaning massive hypovolemic volume status, 9 meaning massive fluid overload).

2.8. End points

The primary end point was the prognostic capability of clinically estimated GEDVI, CVP, and radiographic estimation of GEDVI compared with TPTD-derived GEDVI in terms of sensitivity and specificity based on clinically established cutoff values.

The secondary end point was the prognostic capability of clinically estimated EVLWI and radiographic estimation of EVLWI compared with TPTD-derived EVLWI.

2.9. Statistical analysis

Data analysis was performed using SPSS software for Windows (version 17.0; SPSS Inc, Chicago, Ill). Central tendency and variability of measurements were described by mean ± SD. Nonparametric comparison of quantitative data was performed using the Mann-Whitney *U* test and the Kruskal-Wallis test, respectively. Bivariate relationship of measurements was quantified using Spearman correlation coefficient rho (*r*). Agreement of different examiners was quantified and assessed using κ coefficient. All tests were conducted 2-sided, and statistical significance was considered for $P < .05$. No adjustment of α error level was considered for multiple tests performed.

3. Results

3.1. Patients and patients' characteristics

Seventy-one critically ill ICU patients were enrolled in this study, and physical examination and measurements of CVP and TPTD were performed (study group). In a subgroup of 30 patients, additionally, PLR was performed (subgroup 1). For

clinical indications, a subgroup of 48 patients underwent chest radiography (subgroup 2). For ethical and safety reasons, PLR and chest x-ray were only performed for clinical indications unrelated to the study and not in all patients. Basic demographic and cardiopulmonary data are depicted in Table 1. The reasons for ICU admission in the study group were cirrhosis of the liver (32%), sepsis (23%), pancreatitis (19%), pneumonia (12%), and other reasons (14%).

3.2. TPTD results

In the study group, the mean GEDVI was 806 ± 182 mL/m^2 (minimum, 361 mL/m^2; maximum, 1460 mL/m^2; GEDVI, <680 mL/m^2 in 19 [27%] patients; GEDVI, 680-800 mL/m^2: 15 [21%]; GEDVI, >800 mL/m^2: 37 [52%]). Values measured for EVLWI ranged from 3 to 21 mL/kg, with a mean of 9.3 ± 4.0 mL/kg. Mean CI in these 71 patients was 4.1 ± 1.4 L/min per m^2 (minimum, 1.6 L/min per m^2; maximum, 7.0 L/min per m^2). Because only 8 patients (11%) fulfilled the criteria for the use of dynamic variables of preload (ie, sinus rhythm and controlled ventilation), dynamic variables of preload are not presented in the article.

3.3. Physical examination

Comparing the 2 examiners' global estimations of intravascular volume status as values on the scale of 1 to 9 without any categorization and determination of the interobserver correlation revealed a weak but significant correlation ($r = 0.29$, $P < .01$).

After categorization of the examiners' estimations (1-3: hypovolemic volume status, 4-6: normal volume status, 7-9: hypervolemic volume status), there was an agreement in estimation in 52% of patients. In 3% of the patients, physical examination resulted in a diametrically opposed estimation. Interobserver agreement showed a poor and not significant κ value ($\kappa = 0.093$, $P > .05$). The accuracy and prognostic capabilities of physical examination regarding estimation of fluid status compared with the TPTD-derived preload parameter GEDVI are shown in Table 2. Comparing the agreement of the results of the single examination procedures according to the physical examination protocol, the agreement of the 2 examinations was around 50% (estimation of pleural effusions: agreement in 39%, diametrically opposed estimation in 20%; estimation of lower leg edema: 47%/0%; inspection of the external jugular vein: 46%/0%; estimation of skin turgor: 52%/2%; estimation of ascites: 52%/5%; inspection of the veins on the back of the hand: 54%/46%; inspection of the tongue: 59%/10%; auscultation of the lungs regarding moist rales: 70%/3%).

There was no significant correlation between the examination-based estimation of volume status and TPTD-derived GEDVI or CVP (both examinations, $P > .05$).

The prognostic capabilities of different physical examination procedures for prediction of intravascular volume status and pulmonary hydration are depicted in Table 3.

Regarding the presence and degree of pleural effusions, the physical examination results and radiographic results agreed in only 44% (physical examination 1) and 36% (physical examination 2) of cases.

Table 1 Patients' demographic and cardiopulmonary characteristics

	Study group (n = 71)	Subgroup 1, PLR (n = 30)	Subgroup 2, chest x-ray (n = 48)
Age (y)	62 ± 15	63 ± 14	63 ± 16
Sex			
Male	48 (68%)	19 (63%)	34 (71%)
Female	23 (32%)	11 (37%)	14 (29%)
APACHE II	22.8 ± 9.0	24.2 ± 8.0	23.6 ± 9.3
HR (beat/min)	93 ± 24	89 ± 20	94 ± 26
MAP (mm Hg)	79 ± 16	75 ± 16	76 ± 17
Serum creatinine (mg/dL)	2.3 ± 1.9	1.9 ± 1.2	2.4 ± 1.8
SR, n (%)	36 (51)	18 (60)	18 (38)
Controlled ventilation, n (%)	24 (34)	8 (27)	20 (42)
SR + controlled ventilation, n (%)	8 (11)	4 (13)	6 (13)
PEEP >5 mbar, n (%)	36 (51)	15 (50)	(26) 54
Catecholamine therapy, n (%)	34 (48)		
Central venous oxygenation saturation (%)	76 ± 10	78 ± 10	75 ± 11
GEDVI (mL/m^2)	806 ± 182	814 ± 215	809 ± 182
EVLWI (mL/kg)	9.3 ± 4.0	9.0 ± 3.7	9.7 ± 4.0
CI (L/min per m^2)	4.1 ± 1.4	4.3 ± 1.5	4.0 ± 1.3

APACHE II indicates Acute Physiology and Chronic Health Evaluation II score; SR, sinus rhythm.

Table 2 Estimation of volume status using physical examination

	TPTD: hypovolemic intravascular volume status (GEDVI, <680 mL/m^2), n = 19		TPTD: normal intravascular volume status (GEDVI, 680-800 mL/m^2), n = 15		TPTD: hypervolemic intravascular volume status (GEDVI, >800 mL/m^2), n = 37	
	Examiner 1	Examiner 2	Examiner 1	Examiner 2	Examiner 1	Examiner 2
Accuracy (%)	18	33	18	33	18	33
Sensitivity (%)	5	17	60	67	8	26
Specificity (%)	87	84	25	44	74	76
PPV (%)	13	27	21	26	25	53
NPV (%)	71	73	70	82	42	50

Diagnostic accuracy, sensitivity, specificity, PPV, and NPV of physical examination regarding estimation of intravascular fluid status compared with the preload parameter GEDVI derived from TPTD.

3.4. Central venous pressure

Mean CVP was 12.2 ± 6.7 mm Hg (minimum, 1 mm Hg; maximum, 27 mm Hg) in the study group. There was no significant correlation between CVP and GEDVI, EVLWI or CI ($P > .05$).

Even after categorization of CVP (CVP 1-3 mm Hg: hypovolemic volume status, CVP 4-9 mm Hg: normal volume status, CVP > 10: hypervolemic volume status), CVP showed a poor diagnostic accuracy of only 46% for prediction of intravascular volume status. Sensitivity for prediction of hypovolemic volume status (GEDVI, <680 mL/m^2) was 15% with a specificity of 85% (positive predictive value [PPV], 28%; negative predictive value [NPV], 72%). For prediction of hypervolemia (GEDVI, >800 mL/m^2), CVP also showed poor predictive capabilities (sensitivity, 68%; specificity, 40%, PPV, 54%; NPV, 54%).

3.5. PLR maneuver

In 30 patients, PLR was performed for testing fluid responsiveness (subgroup 1). In 15 (50%) of these patients, TPTD revealed elevated GEDVI values (GEDVI, >800 mL/m^2) as an indicator of elevated cardiac preload (GEDVI, <680 mL/m^2 in 10 patients [33%]; GEDVI, 680-800 mL/m^2 in 5 patients [17%]). The changes of HR, MAP, pulse

Table 3 Physical examination procedures for prediction of volume status

Diagnostic accuracy, sensitivity, specificity, PPV, and NPV of physical examination procedures regarding prediction of a hypervolemic intravascular volume status (GEDVI, >800 mL/m^2) or increased pulmonary hydration (EVLWI, >7 mL/kg)

	Moist rales in pulmonary auscultation; EVLWI, >7 mL/kg (n = 43)		Lower leg edema; GEDVI, >800 mL/m^2 (n = 37)		External jugular vein distension; GEDVI, >800 mL/m^2 (n = 37)	
	Examiner 1	Examiner 2	Examiner 1	Examiner 2	Examiner 1	Examiner 2
Accuracy (%)	52	36	51	52	41	40
Sensitivity (%)	37	7	81	74	37	33
Specificity (%)	76	79	21	28	45	46
PPV (%)	70	25	52	53	39	35
NPV (%)	44	37	50	50	42	45

Diagnostic accuracy, sensitivity, specificity, PPV, and NPV of physical examination procedures regarding prediction of a hypovolemic intravascular volume status (GEDVI, <680 mL/m^2)

	Inspection of the tongue; GEDVI, <680 mL/m^2 (n = 19)		Inspection of the veins on the back of the hand; GEDVI, <680 mL/m^2 (n = 19)		Inspection/palpation of the abdomen, ascites? GEDVI, <680 mL/m^2 (n = 19)		Inspection of skin turgor; GEDVI, <680 mL/m^2 (n = 19)	
	Examiner 1	Examiner 2	Examiner 1	Examiner 2	Examiner 1	Examiner 2	Examiner 1	Examiner 2
Accuracy (%)	48	58	35	44	41	53	58	48
Sensitivity (%)	21	26	25	66	68	68	26	47
Specificity (%)	59	70	47	45	30	47	70	48
PPV (%)	17	26	14	31	27	34	26	26
NPV (%)	64	70	64	79	71	69	70	71

Table 4 Passive leg raising

	All patients of subgroup 1 (n = 30)	GEDVI, <680 mL/m^2 (n = 10)	GEDVI, 680-800 mL/m^2 (n = 5)	GEDVI, >800 mL/m^2 (n = 15)
HR	−0.9 ± 7.2	−2.9 ± 11.1	2.0 ± 3.4	−0.5 ± 3.9
MAP	4.7 ± 7.4*	6.0 ± 6.0*	6.7 ± 6.5	4.1 ± 7.2
PC-CI	−5.3 ± 10.1*	−4.7 ± 14.0	−1.8 ± 4.7	−6.9 ± 9.1
SVRI	9.8 ± 16.2*	8.4 ± 11.3*	8.5 ± 6.2*	13.4 ± 21.5
dPmax	−2.7 ± 11.5	2.9 ± 4.4	3.4 ± 3.7	−6.3 ± 13.4

Changes (in percent) of HR, pulse contour CI (PC-CI), SVRI, and dPmax after PLR for 15 minutes. Significant changes are indicated by an asterisk.

contour CI, SVRI, and dPmax after PLR for 15 minutes are shown in Table 4. Hemodynamic parameters recorded 1, 3, 5, and 10 minutes after the beginning of the PLR test were not significantly different from the parameters recorded after 15 minutes (end of PLR test).

3.6. Radiographic estimation of volume status (chest x-ray)

In 48 patients, a chest x-ray was performed for clinical indications (subgroup 2). Both GEDVI and EVLWI values estimated by the radiologist and TPTD-derived GEDVI and EVLWI were significantly different ($P < .01$; mean values: GEDVI TPTD 809 ± 182 mL/m^2, radiographic estimated GEDVI 913 ± 142 mL/m^2; EVLWI TPTD 9.7 ± 4.0 mL/kg, radiographic estimated EVLWI 7.5 ± 1.4 mL/kg). For the prediction of EVLWI greater than 7 mL/kg using radiographic estimation, diagnostic accuracy was 55% (sensitivity, 40%; specificity, 63%; PPV, 65%; and NPV, 38%) demonstrating low predictive capabilities of radiographic estimation regarding pulmonary hydration. Radiographic estimation for prediction of intravascular volume status showed a diagnostic accuracy of 44% with a sensitivity of 0%, specificity of 75%, PPV of 0%, and NPV of 73% for prediction of hypovolemia (GEDVI, <680 mL/m^2). Sensitivity for prediction of hypervolemia (GEDVI, >800 mL/m^2) was 68% (specificity, 40%; PPV, 59%; NPV, 50%).

4. Discussion

While concerning the importance of early optimization of intravascular volume status in critically ill ICU patients [1], we investigated the predictive capabilities of ubiquitously available clinical tools and simple procedures for the prediction of volume status compared with variables derived from an advanced hemodynamic monitoring system. Preload and pulmonary hydration variables were estimated using physical examination, CVP measurement, PLR, and chest radiography and were compared with TPTD parameters.

Physical examination in these critically ill patients performed by 2 different examiners showed poor interobserver correlation and agreement as well as poor predictive capabilities for the estimation of volume status (defined by the TPTD-derived GEDVI values). There was no correlation between the physical examination-based estimation of intravascular volume status and TPTD-derived GEDVI or CVP.

Despite the generally poor predictive capabilities of physical examination procedures, a hypovolemic volume status (defined as GEDVI <680 mL/m^2) could be excluded with an NPV of around 70% by both examiners.

Interestingly, the physical examination 2 performed by the physician working in the ICU who knew the patients' history and diagnoses did not show better results compared with the physical examination 1 performed by the investigator.

Closing conclusions about the value of clinical findings in the diagnosis of hypovolemia or congestion are difficult to make because very few studies have been conducted on this matter. However, so far, these few studies show—in accordance with our data—poor agreement between the clinical estimation of fluid status and modern hemodynamic monitoring measurements [2,13-15].

CVP is an ubiquitously used parameter in ICUs to assess preload and volume status. In the present study, no significant correlation was observed between CVP and hemodynamic variables (GEDVI, EVLWI, CI) or physical examination results when using commonly used thresholds for CVP. CVP showed a poor diagnostic accuracy for the prediction of hypovolemia or fluid overload. In particular, the prediction of a hypovolemic intravascular volume status using CVP determination was not applicable according to our data (PPV, 28%). These results are in accordance with other studies showing that CVP is not able to predict cardiac preload or volume responsiveness in critically ill patients [6,16]. In ICU patients, several factors (like increased intra-abdominal pressure, mechanical ventilation with PEEP, pleural effusions) can contribute to an overestimation of CVP. Because CVP is not able to predict intravascular volume status and fluid responsiveness when using "traditional" threshold values, further studies investigating adjustment of CVP values (eg, by the development of correction formulas considering intra-abdominal pressure) in critically ill patients are needed.

A PLR maneuver was performed to test volume responsiveness reflected by an increase in CI after the

endogenous volume challenge. None of the patients in the present study increased their CI by 10% or more during the PLR test. Only 1 patient had an increase of CI of more than 5%. In fact, CI determined by pulse contour analysis significantly decreased and SVRI significantly increased independent from cardiac preload (ie, GEDVI values) before PLR. Because SVRI and MAP were highly significantly positively correlated ($P < .001$), whereas SVRI and pulse contour CI were significantly negatively correlated ($P < .05$), the increase in MAP during PLR may more likely be a result of the increased SVRI than of an increase of cardiac output. Assuming that dPmax is mainly determined by the interaction of CI and SVRI, the PLR-induced decrease in CI with an increase in SVRI may explain that there was no significant change in dPmax following PLR. The reason for the increase of SVRI during PLR still remains unclear. There are data indicating that both head-up tilt position and head-down tilt position (PLR) leads to an increase in SVRI probably induced by increased sympathicotonus [17,18]. However, that HR remained unchanged during PLR speaks against an increase in sympathicotonus [5]. Concerning changes in hemodynamic variables during PLR, there are few and inconsistent data: on the one hand, several studies revealed no changes in MAP and CI when performing PLR [19,20]. On the other hand, an increase in stroke volume and CI during PLR is postulated [21]. The biggest disadvantage of assessing fluid responsiveness by a fluid challenge is the administration of unnecessary volume in case the patient is a nonresponder. In our study population, PLR did not indicate reduced preload or fluid responsiveness. An explanation for the failure of PLR test regarding the prediction of fluid responsiveness in the study collective might be that PLR was performed by lifting the patient's lower limbs from the supine position and not by simultaneously lifting the lower limbs and transferring the upper part of the body from a semirecumbent position to a supine position. Moreover, there are data indicating that the PLR test cannot accurately predict fluid responsiveness in patients with increased intra-abdominal pressure [22,23]. Because the present study was conducted in patients in a medical/gastroenterologic ICU, the results of the PLR maneuver might in part be influenced by intra-abdominal hypertension.

According to our data, chest radiography was also not able to predict volume status. Regarding prediction of EVLWI and therefore estimation of pulmonary edema, the radiologist underestimated EVLWI values. EVLWI values estimated using chest x-ray and TPTD-derived EVLWI values were significantly different. Mechanical ventilation with PEEP (PEEP, > 5 mbar in 54% of patients in subgroup 2) can lead to an increased radiotransparency of the lungs and, therefore, to an underestimation of pulmonary edema [24]. Moreover, it has been shown that large pleural effusions can also have an impact on EVLWI determination using TPTD [25]. Therefore, thoracic ultrasound would have probably been a valuable additional diagnostic tool to exclude pleural effusions in combination with chest x-ray in these patients. The diagnostic accuracy of 55% regarding elevated EVLWI values (EVLWI, >7 mL/kg) is in accordance with previous described diagnostic accuracy of chest x-rays [26,27].

Regarding the assumed reference values of EVLWI, we used the recommended thresholds for EVLWI provided by the manufacturer of the device (EVLWI reference range, <7 mL/kg, using indexation to predicted body weight). This reference value has been confirmed in a recent autopsy study comparing premortem EVLWI determined using TPTD with postmortem lung weight from 30 autopsies [11]. However, there are also recent data indicating that the use of higher upper thresholds for EVLWI might improve the predictive value of EVLWI regarding mortality, presence of ARDS, and the correlation of EVLWI with markers of lung injury severity [28].

Regarding radiographic estimation of cardiac preload based on chest x-ray using portable radiography, the radiologist overestimated GEDVI values. The radiologist was not able to detect intravascular hypovolemia. There was no significant correlation between radiographic estimation of fluid status and assessed volume status using TPTD.

Despite considerable advantages, assessment of volume status using advanced hemodynamic monitoring, the TPTD technique has some inherent limitations: the use of TPTD for hemodynamic monitoring causes additional costs, requires an arterial catheter, and is therefore restricted mainly to the ICU. TPTD should be performed for calibration after changes in preload, afterload, or aortic compliance (administration of fluids or catecholamines). TPTD–derived volumetric parameters can be influenced by valvulopathies [29]. In addition, cardiac preload obtained using TPTD might be misleading in patients with aortic aneurysms. To interpret preload conditions in greater detail, GEDVI might be seen in relation to left ventricular function [30]. Therefore, additionally performing echocardiography might be a promising approach for further investigations on determination of volume status in ICU patients.

Moreover, the thresholds for TPTD-derived GEDVI were defined by the manufacturer of the device in selected collectives of patients. Recent literature seems to indicate that predictive capabilities of GEDVI regarding cardiac preload can even be improved using a more diverse view of these thresholds. For instance, a recently published study in neurosurgery patients suggests that reference values of GEDVI may be age and sex dependent [31]. However, these data are not yet confirmed for medical ICU patients, and no binding correction algorithm regarding age or sex is established. Therefore, in the present study, a patient's intravascular volume status needed to be defined according to the existing and established GEDVI threshold values that are provided by the manufacturer of the device. Regarding determination of EVLWI, the presence of atelectasis and pulmonary hypoxic vasoconstriction can influence the accuracy of the measurement.

4.1. Limitations of the study

- In this study, we compared different physical examination procedures, determination of CVP, and chest x-ray to TPTD-derived variables regarding intravascular and pulmonary hydration. Although TPTD is established for assessment of CI, pulmonary hydration, preload, and volume responsiveness, the thresholds for TPTD-derived GEDVI were defined by the manufacturer of the device. Therefore, we can solely present and compare the results of the different methods for testing volume status without drawing conclusions on the superiority of a certain method and without assuming TPTD the superior criterion standard method.
- Testing fluid responsiveness performing a volume challenge test was not part of the study protocol in the presented trial. Further prospective trials including volume challenge tests are needed to learn more about the predictive capabilities of different methods regarding intravascular volume status.
- Echocardiography and thoracic ultrasound were not included in the study protocol in the present trial. Ultrasound might have been a valuable diagnostic tool to exclude pleural effusions in addition to chest x-ray. Additionally, performing echocardiography and thoracic ultrasound may be a intriguing approach for another prospective trial on assessment of volume status in critically ill patients.

5. Conclusion

In critically ill ICU patients, accurate assessment of intravascular volume status is difficult and challenging. Physical examination procedures, CVP determination, portable radiography, and TPTD do not correlate regarding estimation of intravascular volume status, cardiac preload, or pulmonary hydration. Regarding estimation of intravascular volume status in critically ill patients, the complex clinical situation with abnormal volume loading in different compartments (eg, leg edema, ascites, and intravascular volume depletion) can scarcely be assessed without additional monitoring parameters providing information in addition to MAP and CVP. Further prospective and interventional studies are needed to assess volume status in critically ill patients.

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