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## RESEARCH ARTICLE

# Defining human mean circulatory filling pressure in the intensive care unit

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<sup>1</sup>Department of Anesthesiology, Amsterdam University Medical Center, Academic Medical Center, Amsterdam, The Netherlands; <sup>2</sup>Department of Intensive Care, Amsterdam University Medical Center, Academic Medical Center, Amsterdam, The Netherlands; <sup>3</sup>Laboratory of Experimental Intensive Care and Anesthesiology, Amsterdam University Medical Center, Academic Medical Center, Amsterdam, The Netherlands; <sup>4</sup>Department of Intensive Care Medicine, Leiden University Medical Center, Leiden, The Netherlands; and <sup>5</sup>Department of Critical Care Medicine, University of Pittsburgh, Pittsburgh, Pennsylvania

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**Wijnberge M, Schuurmans J, de Wilde RB, Kerstens MK, Vlaar AP, Hollmann MW, Veelo DP, Pinsky MR, Jansen JR, Geerts BF.** Defining human mean circulatory filling pressure in the intensive care unit. *J Appl Physiol* 129: 311–316, 2020. First published July 2, 2020; doi:10.1152/jappphysiol.00298.2020.—Potentially, mean circulatory filling pressure (Pmcf) could aid hemodynamic management in patients admitted to the intensive care unit (ICU). However, data regarding the normal range for Pmcf do not exist challenging its clinical use. We aimed to define the range for Pmcf for ICU patients and also calculated in what percentage of cases equilibrium between arterial blood pressure (ABP) and central venous pressure (CVP) was reached. In patients in whom no equilibrium was reached, we corrected for arterial-to-venous compliance differences. Finally, we studied the influence of patient characteristics on Pmcf. We hypothesized fluid balance, the use of vasoactive medication, being on mechanical ventilation, and the level of positive end-expiratory pressure would be positively associated with Pmcf. We retrospectively studied a cohort of 311 patients that had cardiac arrest in ICU while having active recording of ABP and CVP 1 min after death. Median Pmcf was 15 mmHg [interquartile range (IQR) 12–18]. ABP and CVP reached an equilibrium state in 52% of the cases. Correction for arterial-to-venous compliances differences resulted in a maximum alteration of 1.3 mmHg in Pmcf. Fluid balance over the last 24 h, the use of vasoactive medication, and being on mechanical ventilation were associated with a higher Pmcf. Median Pmcf was 15 mmHg (IQR 12–18). When ABP remained higher than CVP, correction for arterial-to-venous compliance differences did not result in a clinically relevant alteration of Pmcf. Pmcf was affected by factors known to alter vasomotor tone and effective circulating blood volume.

**NEW & NOTEWORTHY** In a cohort of 311 intensive care unit (ICU) patients, median mean circulatory filling pressure (Pmcf) measured after cardiac arrest was 15 mmHg (interquartile range 12–18). In 48% of cases, arterial blood pressure remained higher than central venous pressure, but correction for arterial-to-venous compliance differences did not result in clinically relevant alterations of Pmcf. Fluid balance, use of vasopressors or inotropes, and being on mechanical ventilation were associated with a higher Pmcf.

arterial pressure; critical care; hemodynamics; physiology; venous pressure

## INTRODUCTION

Mean circulatory filling pressure (Pmcf) is of clinical interest because it provides information on intravascular effective circulatory blood volume or stressed volume (Vs) and circulatory vascular compliance (C<sub>sys</sub>) (2, 5–7, 19, 20, 36, 37). Potentially, Pmcf could be used to guide hemodynamic treatment in patients admitted to the intensive care unit (ICU) (12, 18).

Pmcf can be estimated by several techniques. The inspiratory hold method (Pmcf-hold) is most commonly used to determine Pmcf in patients in whom the heart is beating (33). However, Pmcf-hold data for different patient populations are lacking. Absence of a range of Pmcf values in ICU patients hampers the clinical use of Pmcf.

The “gold standard” Pmcf is determined during a no-flow state vascular equilibrium pressure where arterial pressure (ABP) equals central venous pressure (CVP) (1, 12, 30, 32). This Pmcf value can be determined in deceased patients shortly after cardiac arrest.

Pmcf at equilibrium, defined as ABP equals CVP, is not reached in all cases. No-flow ABP greater than no-flow CVP can occur if arterioles collapse when arterial pressure decreases. This no-flow ABP is usually referred to as the critical closing pressure (CCP) (16, 32). The presence of an ABP to CVP gap is hypothesized to be caused by a self-regulating vascular mechanism, or ‘vascular waterfall’; which functions to keep arterial pressure slightly elevated potentially sustaining blood flow to vital organs (16). In the presence of an ABP (CCP)-to-CVP gap, Pmcf can be calculated using the correction formula  $Pmcf = CVP + 1/c * (CCP - CVP)$ , where  $1/c$  is the arterial-to-venous compliance ratio (15).

We describe Pmcf in ICU patients 1 min following cardiac arrest. Our main objective was to define the range for Pmcf for patients admitted to the ICU. Second, we determined the percentage of patients for which an equilibrium of ABP and CVP was reached within 1 min after cardiac arrest. In patients in whom no equilibrium was reached, we determined the impact of correcting for a CCP-to-CVP gap. Last, we determined the influence of patient characteristics and clinical conditions on Pmcf. We hypothesized fluid balance, being on mechanical ventilation, the level of positive end-expiratory pressure (PEEP), and use of vasoactive medication (vasopres-

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sors or inotropes) to be associated with a higher Pmcf. The effect of gender, age, ICU length of stay, hospital length of stay, Acute Physiology and Chronic Health Evaluation scoring system (APACHE IV) score, and APACHE IV admission diagnosis were studied in an exploratory fashion.

## METHODS

**Study design and ethics.** This was a retrospective observational study. The study protocol was assessed by the Medical Ethics Committee of the Leiden University Medical Center (LUMC). A waiver to perform the study was obtained (P15.144/NV/nv; 2 September 2015).

**Patient population and data acquisition.** All adult patients that died in the LUMC ICU between 2007 and 2015 while having continuous ABP and CVP monitoring at the time of cardiac arrest were included for data acquisition. ABP was measured via an arterial catheter (Arrow 20–22G, Arrow International Inc., Reading, PA) in the radial artery or femoral artery, and CVP was measured via a central venous catheter (Vygon MultCath 3, Vygon GmbH, Aachen, Germany) in the internal jugular vein. Hewlett Packard blood pressure modules were used (M1006B, Boeblingen, Germany), and both arterial and venous pressure monitors were zeroed to the patient's phlebostatic point.

A data query employing the patient digital management system (Metavision, PDMS, IMDSOFT version 5.0, Needham, MA) was performed to collect data. ABP and CVP measurements were extracted 1 min after cardiac arrest. Cardiac arrest was defined by a flat line on the monitor. Data were reviewed for validity by two researchers (M. Wijnberge and M. K. Kerstens).

Patients were included for data analysis if both ABP and CVP measurements were present 1 min after cardiac arrest. Patient data were excluded if no CVP recordings were present or CVP values were reported as less than  $-1$  mmHg. Patient data were also excluded when CVP was higher than ABP since accuracy of the measured pressures in these cases can be questioned. Patients on mechanical-assist devices were excluded.

For our second objective, we determined the percentage of patients in which equilibrium of ABP and CVP after cardiac arrest was reached. Equilibrium pressure was defined as a difference between ABP and CVP of  $<2$  mmHg. The 2 mmHg cut-off was decided upon the taking into account of the accuracy of the disposable pressure transducers and the pressure modules (connected to the bedside patient monitor) (9). The group in which no equilibrium pressure was reached (ABP-to-CVP gap of  $>2$  mmHg) was described as the CCP group. In this CCP group, Pmcf was calculated using the formula:  $Pmcf = CVP \times 1/c * (CCP - CVP)$ , where  $1/c$  is the arterial-to-venous compliance ratio. Pmcf was calculated for three different  $c$  values ( $c = 16, 30, \text{ and } 60$ ) since the reported arterial-to-venous compliance ratio varies (12, 13, 21, 25, 35).

For our third objective, the influence of patient characteristics and clinical conditions on Pmcf was determined. Before the start of the study, we hypothesized that fluid balance, use of vasopressors or inotropes, mechanical ventilation of the lungs, and the level of PEEP to be associated with a higher Pmcf value. Fluid balance was analyzed over the last 24 h and for the cumulative total during the ICU stay. Vasoactive medication was defined as noradrenaline, adrenaline, dopamine, and dobutamine. Exploratory studies were the effect of patient characteristics such as gender and age, ICU length of stay, hospital length of stay, APACHE IV score, and APACHE IV admission diagnosis.

**Statistical analyses.** Descriptive statistics were used for objectives one and two. Continuous data were presented as median with range and/or IQR or mean with SD when normally distributed (assessed by inspection of the histogram). Categorical data were given as frequencies with percentages.

Inferential statistics were used for our third objective. Linear regression analyses were used to assess the effect of fluid balance, vasoactive medication (vasopressors or inotropes), being on mechan-

ical ventilation, and the level of PEEP on Pmcf. For these analyses, a probability value of  $P < 0.05$  was considered statistically significant. The effect of gender and age, ICU length of stay, hospital length of stay, APACHE IV score, and APACHE IV admission were studied in an exploratory fashion. First scatterplots were made to visually assess the correlations; subsequently, univariate analyses were performed. Categorical variables (e.g., APACHE IV admission diagnosis) were transformed into dummy variables.

All analyses were performed using IBM SPSS Statistics, version 23.0.

## RESULTS

The data query resulted in data on 1,341 patients; 907 patients were excluded for having no CVP measurement, and 90 patients were excluded for not having an ABP measurement 1 min after cardiac arrest (Fig. 1). Exclusion of evidently false ABP or CVP (extremely high or low), exclusion of one patient being below 18 yr of age, and exclusion of four patients on mechanical circulatory assist devices resulted in 311 patients for final analysis.

**Baseline characteristics.** Table 1 shows the baseline characteristics. The median age of included patients was 67 yr, and 64% were men. The primary reason for ICU admission was cardiovascular pathology (31%). Median Pmcf for all patients was 15 mmHg (IQR 12–18).

**Proportion of patients for which equilibrium between ABP and CVP was reached.** In 162 patients (52%), an equilibrium pressure was reached 1 min after cardiac arrest. In the remaining 149 patients, (48%) ABP remained higher than CVP. In this CCP group, the median difference between ABP and CVP was 8 mmHg (IQR 5–13). Median Pmcf in the CCP group was lower compared with the equilibrium (non-CCP) group (13 mmHg, IQR 9–18 vs. 16 mmHg IQR 14–18). In the CCP group, fewer vasopressors and inotropes were used and fewer patients were on mechanical ventilation (Table 1). Correction for arterial-to-venous compliance differences with  $c$  values of 16, 30, and 60, respectively, resulted in a 1.3, 1.1, and 0.9 mmHg difference (Table 2).

**Pmcf related to patient characteristics.** Table 3 demonstrates median Pmcf per Apache IV admission diagnosis. Patients who underwent cardiac surgery had the highest median Pmcf (17 mmHg, IQR 14–21) compared with the other subgroups. Univariate regression analysis (Table 4) revealed fluid balance within the last 24 h, use of vasoactive medication

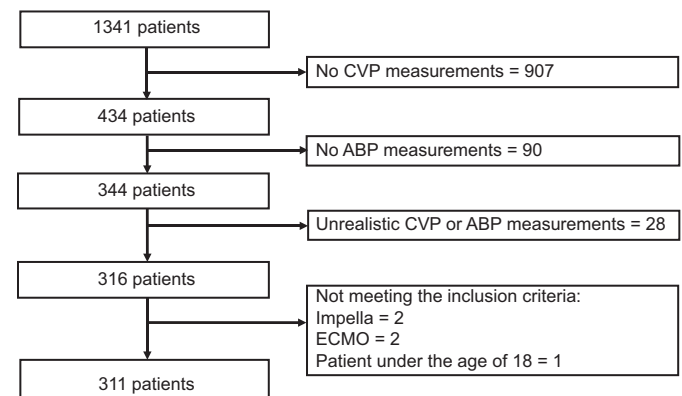


Fig. 1. Flowchart of patient exclusion. CVP, central venous pressure; ABP, arterial blood pressure; ECMO, extracorporeal membrane oxygenation.

Table 1. Baseline characteristics

	n = 311	n = 162 (ABP = CVD)	n = 149 (ABP > CVD)
Pmcf, 1 min	100.0%	52.1%	47.9%
Men, n (%)	15 [12–18]	16 [14–18]	13 [9–18]
Age, yr	198 (63.7%)	99 (61.5%)	99 (66.4%)
Length, m	67 [59–75]	68 [60–75]	67 [57–75]
Weight, kg	1.74 ± 0.10	1.74 ± 0.09	1.75 ± 0.09
BMI	80 ± 17	80 ± 17	81 ± 17
ICU length of stay, days	26 ± 5	26 ± 5	26 ± 5
Hospital length of stay, days	3 [1–8]	2 [1–8]	3 [1–9]
Fluid balance 24 h before dying, mL	6 [2–16]	6 [2–17]	6 [2–16]
Vasoactive medication	3,949 [2,262–6,619]	4,022 [2,535–6,802]	3,846 [1,912–6,463]
Mechanical ventilation	137 (44.1%)	80 (49.7%)	57 (38.3%)
Underlying diagnosis (APACHE IV)	194 (62.4%)	110 (67.9%)	85 (56.4%)
Cardiosurgical	39 (12.5%)	26 (16.0%)	13 (8.7%)
Cardiovascular	96 (30.9%)	47 (29.0%)	49 (32.9%)
Sepsis	51 (16.4%)	29 (17.9%)	17 (11.4%)
Respiratory	46 (14.8%)	26 (16.0%)	25 (16.8%)
Neurology	17 (5.5%)	5 (3.1%)	12 (8.1%)
Gastrointestinal	53 (17.0%)	24 (14.8%)	29 (19.5%)
Hematology	9 (2.9%)	5 (3.1%)	4 (2.7%)

Continuous data are presented as median with interquartile range (I/) or mean with SD (±) when normally distributed. Categorical data are given as frequencies with percentages. Mean circulatory filling pressure (Pmcf) is shown in mmHg and represents the central venous pressure (CVP) 1 min after cardiac arrest at zero flow. ABP, arterial blood pressure at zero flow; BMI, body mass index; ICU, intensive care unit; APACHE, Acute Physiology and Chronic Health Evaluation scoring system.

(vasopressors or inotropes), and mechanical ventilation to be associated with a higher Pmcf. Specifically, Pmcf was higher ( $16.4 \pm 5.8$  vs.  $14.6 \pm 5.7$  mmHg) in patients on vasopressors or inotropes and in patients on mechanical ventilation ( $16.3 \pm 5.9$  vs.  $14.1 \pm 5.4$  mmHg). The level of PEEP was not associated with a higher Pmcf value. The cumulative fluid balance was not associated with a higher Pmcf value. Exploratory analyses demonstrated admission diagnosis to be associated with Pmcf.

Multivariate regression analysis (Table 5) revealed use of vasoactive medication, mechanical ventilation, and admission diagnosis to be associated with Pmcf. Fluid balance and mechanical ventilation showed high colinearity. Patients on mechanical ventilation had a significantly higher fluid balance. Therefore, only one of the two variables could be incorporated into the multivariate model. The best model was chosen.

## DISCUSSION

In this study, we determined Pmcf 1 min after cardiac arrest in a cohort of 311 ICU patients. Our main findings were the

Table 2. Pmcf in mmHg in the subset of patients reaching no equilibrium pressure (ABP &gt; CVP)

Subset ABP > CVP	n = 149
CVP	13.0 [9.0–18.0]
ABP	23.0 [17.0–30.0]
Difference	8.0 [5.0–13.0]
Pmcf for c = 16	14.3 [10.2–18.3]
Pmcf for c = 30	14.1 [9.8–18.1]
Pmcf for c = 60	13.9 [9.4–18.1]

Continuous data are presented as median with interquartile range (I/). The correction factors for critical closing pressure (Pmcf) = CVP + 1/c\*(CCP–CVP), where c is the arterial-to-venous compliance ratio (see text for details), ABP is arterial blood pressure at zero flow, CCP is critical closing pressure, CVP is central venous pressure at zero flow, ICU is intensive care unit, and Pmcf is mean circulatory filling pressure.

following: 1) median Pmcf in this population was 15 mmHg (IQR 12–18); 2) ABP and CVP reached equilibrium within 1 min after cardiac arrest in 52% of patients. In the remaining 48% of patients, ABP was higher than CVP, indicating the presence of a critical closing pressure. 3) Fluid balance over the last 24 h, use of vasopressors or inotropes and being on mechanical ventilation were associated with a higher Pmcf. Cardiac surgical patients had the highest Pmcf, 17 mmHg (IQR 13–21), compared with the other subgroups.

The first insights into human Pmcf measurements date from 1940, when cardiovascular physician-physiologist Isaac Starr measured Pmcf in deceased patients (29, 30). The method in our study is similar to the method Starr used with one important distinction; our measurements were set at 1 min after cardiac arrest, whereas in Starr his experiments the measurements were made within 30 min of death (29, 30). Repessé et al. (23) reported a mean Pmcf of  $13 \pm 6$  mmHg in 202 ICU patients 1 min after cardiac arrest. In our study, both ABP and CVP had to be present for patient inclusion whereas Repessé et al. extended inclusion to patients in which only one of the two pressures (ABP or CVP) was available. In that study, both ABP and CVP were present in 157 of 202 patients. Strikingly, all

Table 3. Pmcf (in mmHg) per APACHE IV admission diagnosis presented in median with interquartile range

APACHE IV admission diagnosis	n (%)	Pmcf
Cardiosurgical	39 (12.5%)	17 [14–21]
Cardiovascular	96 (30.9%)	14 [11–18]
Respiratory	51 (16.4%)	14 [12–17]
Sepsis	46 (14.8%)	14 [11–18]
Gastrointestinal	53 (17.0%)	16 [14–20]
Neurology	17 (5.5%)	13 [8–17]
Hematology	9 (2.9%)	16 [12–21]

Pmcf, mean circulatory filling pressure; Acute Physiology and Chronic Health Evaluation scoring system.

Table 4. *Univariate regression analysis*

	R <sup>2</sup>	Beta	95% CI	P Value
APACHE IV score	0.00	0.00	-0.17 to 0.02	0.96
Length	0.01	-4.44	-11.37 to 2.48	0.21
Weight	0.00	0.02	-0.21 to 0.05	0.39
BMI	0.01	0.09	-0.34 to 0.21	0.16
ICU length of stay	0.00	0.00	-0.00 to 0.00	0.81
Hospital length of stay	0.00	0.00	0.00 to 0.00	0.92
Age	0.01	-0.03	-0.08 to 0.02	0.18
Gender	0.00	0.08	-1.27 to 1.43	0.91
APACHE IV admission diagnosis				
Cardiovascular	Baseline*			
Cardiothoracic surgery		3.01	0.89 to 5.12	<b>&lt;0.01</b>
Gastrointestinal		2.02	0.11 to 3.92	<b>0.04</b>
Sepsis		-0.30	-2.30 to 1.69	0.77
Respiratory		-1.20	-3.13 to 0.73	0.22
Hematology		1.65	-2.23 to 5.53	0.40
Neurological		-2.14	-5.07 to 0.79	0.15
Fluid balance in L (24 h)	0.03	0.26	0.10 to 0.42	<b>&lt;0.01</b>
Cumulative fluid balance	0.01	0.00	0.00 to 0.00	0.15
Vasoactive medication	0.02	1.79	0.50 to 3.08	<b>&lt;0.01</b>
Mechanical ventilation	0.03	2.17	0.86 to 3.49	<b>&lt;0.01</b>
Level of PEEP	0.01	0.17	-0.04 to 0.37	0.11

Beta, unstandardized beta; CI, confidence interval; APACHE, Acute Physiology and Chronic Health Evaluation scoring system; ICU, intensive care unit; PEEP, positive end-expiratory pressure. \*Statistical baseline chosen based on largest group. Boldface values are statistically significant.

157 cases reached 1-min equilibrium whereas in our cohort only 52% of patients reached equilibrium. Differences in the cohorts studied (e.g., medical vs. surgical patients, differences in underlying pathology) and a possibly more conservative definition of equilibrium in our study might explain the diverging results. The latter is an assumption, since Repessé et al. did not give their definition of equilibrium. In our study, we defined equilibrium as pressure differences between ABP and CVP  $\leq 2$  mmHg.

The median ABP (or CCP)-to-CVP pressure gap in patients who did not reach equilibrium was 8 mmHg. This closely resembles the pressure gap reported during ventricular fibrillation for pacemaker implantation (13, 26). However, in that population duration of no-flow was not long enough for pressures to equilibrate. The persistence of a low level of flow in the left carotid artery for up to 4 min has been described in pigs during ventricular fibrillation (31). Waiting longer for the pressures to equilibrate in deceased patients poses the risk of confounding P<sub>mcf</sub> measurements by vasodilation due to energetic loss of vasomotor tone or reflex vasoconstriction due to loss of vascular pulsatility. Measuring CVP at 1 min after cardiac arrest currently represents the uniform standard for determination of P<sub>mcf</sub> in deceased patients.

Maas et al. (16) explain the existence of CCP as part of a self-regulating vascular mechanism referred to as the vascular waterfall. Potentially, CCP could impede measurement of

no-flow P<sub>mcf</sub>. However, attempting to correct for arterial-to-venous compliance differences (1/16, 1/30, and 1/60) did not result in different P<sub>mcf</sub> values. Existing literature on P<sub>mcf</sub> measurements during induced cardiac arrest have reported similar findings, with most studies describing a negligible increase for P<sub>mcf</sub> of 0.3–0.5 mmHg and 1.2 mmHg in animal and human studies, respectively (13, 14, 25, 35). This difference is within the 2 mmHg accuracy cut-off we used to define equilibrium pressure and thus not considered to be clinically relevant. CVP is considered the main determinant of P<sub>mcf</sub> in a no-flow state, suggesting that measuring no-flow CVP alone at 1 min after cardiac arrest is sufficient to determine P<sub>mcf</sub>.

Animal studies show a large variety in arterial-to-venous vascular compliance ratios, and in humans hypertension and comorbidity affect this ratio (21, 25, 27, 28). We therefore explored compliance correction using three physiological plausible potential ratios (16, 30, and 60).

*Influencing factors.* We found that fluid balance within the last 24 h, use of vasoactive medication, mechanical ventilation, and admission diagnosis were associated with P<sub>mcf</sub> in the univariate regression analysis. P<sub>mcf</sub> behaves in a predictable fashion in line with known physiological mechanisms.

A higher P<sub>mcf</sub> was found in patients with a more positive fluid balance over the last 24 h. An increase in stressed volume (V<sub>s</sub>) given a constant circulatory compliance (C<sub>sys</sub>) leads to a higher P<sub>mcf</sub> (P<sub>mcf</sub> = C<sub>sys</sub> × V<sub>s</sub>). The univariate positive correlation found between fluid balance and P<sub>mcf</sub> is consistent with existing literature. Guérin et al. (11) also found an increase in P<sub>mcf</sub> values after volume expansion. An important note is that fluid overload does not equal a high P<sub>mcf</sub>. P<sub>mcf</sub> takes into account the intravascular volume status; a patient may have anasarca, be hypovolemic at the same time, and thus have a low P<sub>mcf</sub>. This probably explains why the cumulative fluid balance was not associated with P<sub>mcf</sub> in the univariate analysis. In our multivariate analysis, fluid balance over the last 24 h was no longer found to significantly associate with P<sub>mcf</sub>.

Table 5. *Multivariate regression analysis*

	Beta	95% CI	P Value
Vasoactive medication	1.43	0.16–2.70	0.03
Mechanical ventilation	1.55	0.23–2.86	0.02
APACHE IV admission diagnosis			
Cardiothoracic surgery	2.90	0.97–4.83	<0.01
Gastrointestinal	2.25	0.55–3.93	<0.01

Beta, unstandardized beta; CI, confidence interval; APACHE, Acute Physiology and Chronic Health Evaluation scoring system.

Fluid balance and mechanical ventilation showed high colinearity. Patients receiving mechanical ventilation had a significantly higher fluid balance.

Vasopressors (e.g., norepinephrine) alter P<sub>mcf</sub> by increasing C<sub>sys</sub> or by recruitment of unstressed volume (V<sub>u</sub>). V<sub>u</sub> is the blood contained in the system at zero transmural pressure. Animal research has suggested that with increased sympathetic activity splanchnic resistance (a part of the circulation with a high proportion of V<sub>u</sub>) increased proportionally more than total vascular resistance. This results in blood flow redistribution away from larger unstressed vascular beds in the splanchnic region, leading to an increase in V<sub>s</sub> and thereby increasing P<sub>mcf</sub> without a change in total blood volume (V<sub>s</sub> + V<sub>u</sub>) (17, 24). Repesse et al. (23) also found the use of norepinephrine ( $P < 0.01$ ) to be associated with increased P<sub>mcf</sub>.

Mechanical ventilation increases P<sub>mcf</sub> by shifting blood from the pulmonary to the systemic circulation (13). Additionally, the increase in intrathoracic pressure by mechanical ventilation leads to an increase in CVP and a decrease in ABP. If sustained, both baroreflex-induced increased sympathetic tone and the reaction of fluid loading to a decrease in ABP may also increase P<sub>mcf</sub> (4, 22). We expected the level of PEEP to be also correlated with P<sub>mcf</sub>, since PEEP shifts the diaphragm in a more caudal position, increasing abdominal pressure, thereby increasing pressure in the splanchnic compartment, compressing the splanchnic vasculature, and consequently increasing V<sub>s</sub>, resulting in elevated P<sub>mcf</sub> (3). Furthermore, in clinical practice, decreases in cardiac output by increasing PEEP are often compensated for by fluid resuscitation. Surprisingly, in our univariate analysis the level of PEEP alone was not correlated with P<sub>mcf</sub>.

Rothe (24) stated “P<sub>mcf</sub> is a measure of the fullness of the circulation.” Both filling the container but also decreasing the cross-sectional area of the container increases fullness. Our study validates his statement and demonstrates that P<sub>mcf</sub> behaves in a fashion predictable from known physiological mechanisms. Currently, it is extremely difficult to determine the fullness of the vascular system, even in critically ill patients who regularly have invasive hemodynamic monitoring. The current hemodynamic variables do not provide a complete picture. P<sub>mcf</sub> might aid in guiding hemodynamic management in ICU patients. Clinical studies should determine whether integrating P<sub>mcf</sub> in clinical practice proves to be beneficial.

The exploratory analyses of the influence of the admission diagnosis demonstrated that cardiac surgical patients and gastrointestinal patients had a higher P<sub>mcf</sub>. Hypothetically, cardiac surgery patients have less decreased diastolic compliance, leading to an increased CVP for the same ventricular filling and requiring a higher driving pressure for venous return to sustain cardiac output. For blood to flow back from the periphery to the right atrium, there needs to be a pressure gradient such that P<sub>mcf</sub> exceeds CVP. Thus, if CVP is elevated, P<sub>mcf</sub> must be higher for blood to flow and for cardiac output to sustain (10). A considerable number of the gastrointestinal patients had hepatic failure (45%). Moreover, liver dysfunction and cardiac dysfunction often coexist, and they both result in renin-angiotensin-aldosterone system-driven fluid retention (8, 34).

We report on the influence of the admission diagnosis. It may be that a fraction of the patients died from a cause different than their admission diagnosis. Unfortunately, we could not extract the cause of death from the patient files.

However, the time from ICU admission till death was relatively short with a median of 3 days; therefore, we think it is justifiable to use the admission diagnosis for these exploratory analyses.

This study has several limitations, all related to the retrospective design of the study. Most importantly, we were obliged to adhere to strict inclusion criteria to guarantee valid measurements. Prior to data collection, we decided to only include patients when both ABP and CVP were present. As a result, we had to exclude 1,030 of 1,341 patients, limiting the size of our cohort, and our results need to be confirmed in a larger study. However, we report on the biggest cohort available.

**Conclusion.** Our database study is one of the first defining normal P<sub>mcf</sub> values. In a cohort of 311 patients who died in the ICU, we found that the median P<sub>mcf</sub> was 15 mmHg (IQR 12–18). CVP and ABP reached an equilibrium state in 52% of cases. In the remaining 48% of cases, the ABP remained higher than the CVP, illustrating the existence of a vascular waterfall. Correction for arterial-to-venous compliance differences, however, did not result in clinically relevant alterations of P<sub>mcf</sub> in those patients. Fluid balance over the last 24 h, use of vasopressors or inotropes, and being on mechanical ventilation were associated with a higher P<sub>mcf</sub>.

#### DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the authors.

#### AUTHOR CONTRIBUTIONS

J.R.J. and B.F.G. conceived and designed research; M.W., R.B.d.W., and M.K.K. performed experiments; M.W. and J.S. analyzed data; M.W., R.B.d.W., A.P.V., M.W.H., M.R.P., J.R.J., and B.F.G. interpreted results of experiments; M.W. prepared figures; M.W., J.S., M.W.H., and B.F.G. drafted manuscript; M.W., R.B.d.W., M.K.K., A.P.V., M.W.H., D.P.V., M.R.P., J.R.J., and B.F.G. edited and revised manuscript; M.W., J.S., R.B.d.W., M.K.K., A.P.V., M.W.H., D.P.V., M.R.P., J.R.J., and B.F.G. approved final version of manuscript.

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