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REVIEW

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Estimating mean circulatory filling pressure in clinical practice: a systematic review comparing three bedside methods in the critically ill

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Abstract

The bedside hemodynamic assessment of the critically ill remains challenging since blood volume, arterial–venous interaction and compliance are not measured directly. Mean circulatory filling pressure (P_{mcf}) is the blood pressure throughout the vascular system at zero flow. Animal studies have shown P_{mcf} provides information on vascular compliance, volume responsiveness and enables the calculation of stressed volume. It is now possible to measure P_{mcf} at the bedside. We performed a systematic review of the current P_{mcf} measurement techniques and compared their clinical applicability, precision, accuracy and limitations. A comprehensive search strategy was performed in PubMed, Embase and the Cochrane databases. Studies measuring P_{mcf} in heart-beating patients at the bedside were included. Data were extracted from the articles into predefined forms. Quality assessment was based on the Newcastle–Ottawa Scale for cohort studies. A total of 17 prospective cohort studies were included. Three techniques were described: P_{mcf} hold, based on inspiratory hold-derived venous return curves, P_{mcf} arm, based on arterial and venous pressure equilibration in the arm as a model for the entire circulation, and P_{mcf} analogue, based on a Guytonian mathematical model of the circulation. The included studies show P_{mcf} to accurately follow intravascular fluid administration and vascular compliance following drug-induced hemodynamic changes. Bedside P_{mcf} measures allow for more direct assessment of circulating blood volume, venous return and compliance. However, studies are needed to determine normative P_{mcf} values and their expected changes to therapies if they are to be used to guide clinical practice.

Keywords: Blood pressure, Venous pressure, Blood volume, Intensive care, Critical care, Hemodynamics

Background

It is difficult to determine the cause for hemodynamic instability in patients and to predict the best treatments. Currently, cardiovascular resuscitation options are triggered by arterial pressure and cardiac output (CO) measures, focusing on the oxygen delivery side of the circulation. However, the primary determinants of CO reside on the venous side. Veins are 30–50 times more compliant than arteries and contain approximately 75% of the total blood volume [1–5]. Mean circulatory filling pressure (P_{mcf}) provides vital information on this "forgotten venous side of the circulation" [6].

In 1894, P_{mcf} was defined as the equilibrium pressure throughout the circulation during circulatory arrest [7]. In the 1950s, Guyton and colleagues described a linear relationship between venous return (V_R) and right atrial pressure (P_{ra}), described as: $V_R = (P_{mcf} - P_{ra})/(\text{RVR})$ [8, 9]. RVR is resistance to V_R and defines the slope of the V_R curve. This linearity has been confirmed in intact circulations in animal studies and is not affected by hypo- or hypervolemia [10–15]. V_R curves enable to determine the equilibrium point of the circulation, which

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is the intersection between the CO and V_R curve. Central venous pressure (CVP) is a surrogate of P_{ra} used in clinical practice. CVP at zero flow equals P_{mcf} (Fig. 1).

Vascular volume requires a minimal volume before its distending pressure becomes positive. The amount of blood not causing pressure on the vessels is called unstressed volume (V_u) and reflects intravascular volume present with P_{mcf} of zero. Stressed volume (V_s) is the additional blood causing a distending pressure on the vascular walls and reflects the effective circulating volume. V_u and V_s together define the total blood volume. V_s is approximately 25% of the total blood volume [3–5]. V_s and vascular compliance (Csys) define P_{mcf} [16]. An increase in V_s increases P_{mcf}, and an increase in Csys decreases P_{mcf}. Fluid loading should increase P_{mcf}, but V_R only increases if the pressure gradient for V_R (i.e., P_{mcf} CVP) increases, RVR decreases, or both. Since in the steady state $V_R = CO$, knowing the determinants of V_R is relevant to understanding cardiovascular state.

Recently, methods have emerged to enable clinicians to estimate P_{mcf} at the bedside. Our objectives for this review were to describe the techniques and to highlight their clinical applicability, precision, accuracy and limitations in critically ill patients.

Materials and methods

Publication selection

This review was performed according to PRISMA guidelines [17] (Additional file 1) and methodology outlined in the Cochrane Handbook for systematic reviews [18]. No study protocol was published. A PubMed, Embase and Cochrane Library database search was performed with help of a clinical librarian with no restriction on publication date. The search was performed up to May 18, 2017. The search strategy combined the following concepts: (1) "mean systemic filling pressure" or "mean circulatory filling pressure" or "static filling pressure" and (2) "intensive care" or "critical care" or "perioperative" or "intraoperative" (Additional file 1). Titles, abstracts and full-texts were independently screened by two reviewers for relevance (MW and DPS), and discrepancies were resolved by a third reviewer (BFG). The references of the selected articles were examined for additional eligible articles. Studies were included when available in English and full-text, described prospective studies in which P_{mcf} estimation methods were examined in heart-beating ICU patients and contained a description of their clinical applicability, precision and accuracy or limitations.

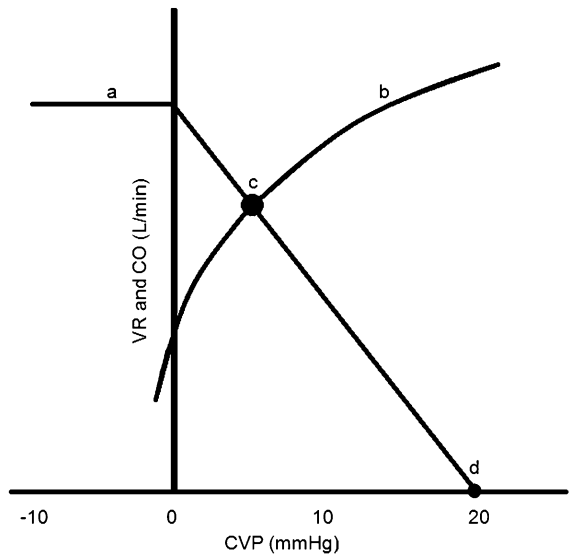

Fig. 1 The venous return curve (*a*) combined with the cardiac output curve (*b*). The intersection of these two curves (*c*) is the working point of the circulation. The central venous pressure when venous return equals zero is the P_{mcf} (*d*). The slope of the V_R is determined by the resistance to venous return

Data extraction and analysis

Data were extracted into predefined forms. No additional analyses were performed. Critical appraisal was based on the Newcastle–Ottawa Scale for cohort studies [19] to assess the quality of non-randomized studies at study level. A modified version of the scale was used since only five out of nine questions were applicable, resulting in a possible highest score of five stars (Additional file 1).

Results

Study selection and characteristics

The initial search identified 369 articles, of which 300 were excluded after screening title and abstract. A total of 53 articles were excluded based on full-text. Two relevant articles were found by citation tracking. Consequently, 17 prospective cohort studies estimating P_{mcf} in heart-beating ICU patients were included (Additional file 1). Three different bedside measurement techniques were found. Eight studies estimated P_{mcf} applying inspiratory hold maneuvers (P_{mcf} hold), three studies during a circulatory stop-flow in the arm (P_{mcf} arm) and four studies using a mathematical algorithm (P_{mcf} analogue). Two studies compared multiple techniques.

Eleven studies were performed in postoperative cardiac surgery patients (Table 1). All patients were hemodynamically stable without alteration in vasopressor use or fluid therapy during the study protocol. All patients were sedated and mechanically ventilated. In one study, spontaneous breathing efforts were observed [20]. The number of included patients ranged from nine to 80. In all studies, CVP was measured via a catheter in the right internal jugular vein. CO measurement techniques differed between studies (Additional file 1).

Table 1 Baseline characteristics for included studies

References	Method	*N*	Patient population (all adult ICU patients)	Age	Male	Timeframe P_{mcf} measurement
Maas et al. [21]	P_{mcf} hold	12	Postoperative cardiac surgery 10 CABG 2 AVR	64 (10)	10 (83%)	Not described
Keller et al. [23]	P_{mcf} hold	9	Postoperative cardiac surgery 3 CABG 6 AVR	Median 61 IQR 55–75	4 (44%)	Not described
Maas et al. [22]	P_{mcf} hold	10	Postoperative cardiac surgery 2 AVR 1 MVP + TVP 7 CABG	64 (11)	9 (90%)	Within 1 h after ICU admission
Persichini et al. [27]	P_{mcf} hold	16	Septic shock	67 (16)	8 (50%)	Not described
Maas et al. [25]	P_{mcf} hold	16	Postoperative cardiac surgery 1 MVP 15 CABG	64 (11)	Not described	Within 1 h after ICU admission
Guerin et al. [28]	P_{mcf} hold	30	Shock	65 (12)	21 (70%)	Not described
De Wit et al. [24]	P_{mcf} hold	17	Postsurgical gastrointestinal 16 esophageal resection 1 pancreaticoduodenectomy	62 (9)	14 (82%)	Not mentioned
Helmerhorst et al. [26]	P_{mcf} hold	22	Postoperative cardiac surgery 22 CABG	63 (59–66)	17 (85%)	1 h after ICU admission
Geerts et al. [43]	P_{mcf} arm	24	Postoperative cardiac surgery 17 CABG 7 CABG plus valve repair	64 (10)	19 (79%)	Within 2 h after ICU admission
Aya et al. [41]	P_{mcf} arm	20	Postoperative cardiac surgery 13 CABG 4 AVR 4 MVR	63 (11)	17 (85%)	Initial period at ICU (not further defined)
Aya et al. [42]	P_{mcf} arm	80	Postoperative cardiac surgery 36 CABG 27 AVR + CABG 12 MVR + CABG 5 Other	70 Range 52–80	62 (78%)	Initial period at ICU (not further defined)
Parkin et al. [49]	P_{mcf} analogue	10	Multi-organ failing patients receiving CVVH for acute renal failure	65 Range 24–77	7 (70%)	Not described
Cecconi et al. [48]	P_{mcf} analogue	39	22 Cardiac surgery 8 Shock 6 Non-cardiac surgery 3 Other	68 (12)	26 (67%)	Not described
Gupta et al. [20]	P_{mcf} analogue	61	Postoperative cardiac surgery 40 CABG 8 CABG + valve replacement 8 Valve replacement 5 Bentall's procedure 7 DDD pacing	63 (11)	46 (75%)	Within 6 h after ICU admission
Aya et al. [51]	P_{mcf} analogue	26	Postoperative fluid challenge 7 Cardiac surgery	68 Range 53–80	16 (62%)	Initial period at ICU (not further defined)

Table 1 (continued)

References	Method	N	Patient population (all adult ICU patients)	Age	Male	Timeframe P_{mcf} measurement
			19 Non-cardiac surgery			
Maas et al. [16]	P_{mcf} hold	11	Postoperative cardiac surgery	64	9 (82%)	Within 2 h after ICU admission
	P_{mcf} arm	11	9 CABG	Range 50–80		
	P_{mcf} analogue	11	2 AVR			
Maas et al. [30]	P_{mcf} arm	15	Postoperative cardiac surgery	64 (11)	Not described	Within 1 h after ICU admission
	P_{mcf} hold	12	9 CABG			
			5 Valve			
			1 CABG + valve			

Age is presented as mean with standard deviation (SD) or median with range or interquartile range (IQR). Number of males per study is presented as counts with percentage

CABG coronary artery bypass, *MVR* mitral valve replacement, *MPV* mitral valve prolapse, *AVR* aortic valve replacement, *TVP* tricuspid valve prolapse, *CVVH* continuous veno-venous hemodiafiltration

P_{mcf} hold

Technique description

P_{mcf} hold is based on the linear relation between CVP and V_R ($P_{mcf} = (V_R - CVP)/RVR$). CVP is raised by performing a series of end-inspiratory hold maneuvers. In 2009, the method was first studied in humans [21]. Inspiratory hold maneuvers at 5, 15, 25 and 35 cmH_2O incremental ventilatory plateau pressures (P_{vent}) were performed, and CO was measured in the last 3 s of the 12 s inspiratory hold. They validated that after 7–10 s a steady state consists when $V_R = CO$. By plotting the CVP and CO values, a V_R curve is constructed and the zero-flow pressure (P_{mcf}) extrapolated. Seven studies [16, 21–26] estimated P_{mcf} hold using these four plateau pressures. Two studies [27, 28] used two points (P_{vent} 5 and 30 cmH_2O) at 15-s inspiratory and expiratory hold plateau phase. Between the P_{mcf} hold measurements, either 1-min pauses were used to re-establish the initial hemodynamic steady state [16, 21, 22, 24, 28], or the consecutive inspiratory hold was performed when CO had returned to baseline [23, 26, 27].

Clinical applicability

The average baseline P_{mcf} hold values found in the eight included studies range from 19 to 33 mmHg with a wide standard deviation (Tables 2, 3). Five studies [21–23, 26, 28] demonstrated fluid administration caused an increase in P_{mcf} hold, confirming that in humans, as in animals before [14, 15], P_{mcf} hold follows hemodynamic changes (Table 2). One of these studies found passive leg raising (PLR) to significantly increase P_{mcf} hold values [28]. RVR was not significantly affected by different volumetric conditions nor by PLR. V_s was calculated from P_{mcf} as a measure for effective circulating volume [22]. In one study, P_{mcf} was used to assess the hemodynamic effects of arterial hyperoxia ($FiO_2 = 90\%$ for 15 min) in ICU patients [26]. During this hyperoxia, left ventricular afterload increased and contractility remained similar; however, CO did not decrease. Both P_{mcf} and RVR increased significantly (Table 3), explaining why V_R (thus CO) remained unaltered.

Studies have used P_{mcf} hold to describe hemodynamic changes caused by propofol [24] and norepinephrine [25, 27] (Table 3). In septic shock patients, decreasing the dose of norepinephrine decreased both P_{mcf} and RVR [27]. Further, after increasing norepinephrine CO decreased in ten patients and CO increased in six patients [25]. In all patients, P_{mcf} and RVR increased, though the "balance" between the two values determined whether CO increased. One study showed an increase in propofol caused a decrease in V_s without a change in CO [24]. These studies show P_{mcf} behaves within the framework of hemodynamic reasoning and lends itself to being used as a less invasive method to assess drug-induced physiology. Since P_{mcf} exists at the intersection of arterial and venous flow, it enables to calculate the true arterial and venous resistance by calculating the critical closing pressure (P_{cc}). P_{cc} is the mean arterial pressure (MAP) to zero CO-intercept. Arterial resistance is calculated as $(MAP - P_{cc})/CO$ [22].

Precision and accuracy

The technique precision has not yet been assessed in humans. However, in an animal study the averaged coefficient of variation for repeated measurements of P_{mcf} hold was 6% [29]. Comparing the techniques' accuracy, no significant differences between P_{mcf} hold and P_{mcf} arm existed, whereas P_{mcf} analogue values were significantly lower [16, 30].

Table 2 Mean circulatory filling pressure during different volumetric state

Study	Method	N	Patient population	Baseline position	Baseline P_{mcf}	Hypervolemia (induced by fluid administration)	p value*	Amount of fluid administered to induce hypervolemia	Hypovolemia (induced by HUT)	p value†
Maas et al. [21]	P_{mcf} hold	12	Cardiac surgery	Supine	18.7 (4.5)	29.1 (5.2)	0.001	500 mL colloid in 15–20 min	14.5 (3.0)	0.005
Keller et al. [23]	P_{mcf} hold	9	Cardiac surgery	Semirecumbent	19.7	26.9	< 0.05	500 mL colloid	–	–
					IQR 17.0–22.6	IQR 18.4–31.0				
Maas et al. [22]	P_{mcf} hold	10	Cardiac surgery	Not described	18.7 (4.0)	26.4 (3.2)	< 0.001	500 mL colloid	–	–
Guerin et al. [28]	P_{mcf} hold	30	Shock	Semirecumbent	Responder: 25 (13)	32 (17)	< 0.01	500 mL saline in 10 min		
					Non-responders: 24 (10)	28 (12)	< 0.01			
Geerts et al. [43]	P_{mcf} arm	24	Cardiac surgery	Supine	Responders: 16.2 (6.3)	22.0 (7.6)	< 0.001	500 mL colloid	–	–
					Non-responders: 24.3 (8.2)	29.9 (9.1)	< 0.001			
Aya et al. [41]	P_{mcf} arm	20	Cardiac surgery	Supine	22.4 (7.7)	–	–	–	–	–
Aya et al. [42]	P_{mcf} arm	80	Cardiac surgery	Supine	23.0	–	–	–	–	–
					Range: 17.3–29.8					
Parkin et al. [49]	P_{mcf} analogue	10	CVVH	Not described	Target state = 15.9	–	–	CVVHD	–	–
Cecconi et al. [48]	P_{mcf} analogue	39	Heterogenous	Not described	Responders: 17.8 (5.1)	20.9 (5.1)	< 0.001	Mean 252 (8.9) mL	–	–
					Non-responders: 17.9 (5.1)	21.0 (4.9)	< 0.001	52.5% crystalloid		
								37.6% colloid		
								8.8% FFP & RBC		
Gupta et al. [20]	P_{mcf} analogue	61	Cardiac surgery	Supine	Responders: 17 (3.7)	19 (4.3)	0.02	Mean 264 (16) mL	–	–
					Non-responders: 17 (3.6)	19 (4.1)	0.03	50% saline. Other 50%: mix of FFP, platelets, albumin, packed RBC, return of pump blood		
Aya et al. [51]	P_{mcf} analogue	26	Heterogenous	Not described	Responders: 13.7 IQR: 10.9–16.9			250 mL crystalloid		
					Non-responders: 16.7 IQR: 10.5–18.9					
Maas et al. [16]	P_{mcf} hold	11	Cardiac surgery	Supine	19.7 (3.9)	28.3 (3.6)	< 0.001	500 mL colloid	16.2 (3.0)	0.001
	P_{mcf} arm				18.4 (3.7)	27.1 (4.0)	< 0.001		15.4 (3.1)	0.001
	P_{mcf} analogue				14.7 (2.7)	19.2 (1.1)	< 0.001		10.9 (2.0)	< 0.001
Maas et al. [30]	P_{mcf} arm	15	Cardiac surgery	Supine	21.0 (6.8)	27.7 (7.4)	< 0.001	500 mL colloid (10 steps of 50 mL)	–	–
	P_{mcf} hold#									

Data presented as mean with SD or median with interquartile range (IQR). P_{mcf} in mmHg. Hypovolemic state induced by head up tilt (HUT) to 30°. Responders = fluid responsiveness was defined by a 10% increase in CO

* *p* value, difference between baseline and hypervolemia induced by fluid administration

† *p* value, difference between baseline and hypovolemic state

Table 3 P_{mcf} and pharmacodynamics

References	Method	*n*	Situation A	Situation B	*p* value*	Situation C	*p* value#
Persichini et al. [27]		16	NE 0.30	NE 0.19			
			Range 0.10–1.40	Range 0.08–1.15			
	P_{mcf} hold (in mmHg)		33 (12)	26 (10)	0.003		
Maas et al. [25]		16	Baseline 1	NE increase of 0.04 (0.02)		Baseline 2	
			NE 0.04 (0.03)			NE 0.04 (0.03)	
	P_{mcf} hold (in mmHg)		21.4 (6.1)	27.6 (7.4)	< 0.001	22.0 (5.3)	
de Wit et al. [24]		17	Propofol low	Propofol medium		Propofol high	
			Cb 3.0 (0.90) µg/mL	Cb 4.5 (1.0) µg/mL		Cb 6.5 (1.2) µg/mL	
	P_{mcf} hold (in mmHg)		27.9 (5.4)	24.6 (4.9)	0.01	21.4 (4.2)	< 0.001
Helmerhorst et al. [26]		22	FiO_2 21–30%	FiO_2 90%			
	P_{mcf} hold (in mmHg)		20.8 (3.5)	23.1 (4.0)	< 0.001		

NE norepinephrine dose in µg/kg/min presented as mean with range or mean with standard deviation. P_{mcf} values are presented as mean with standard deviation. *Cb* target blood concentration of propofol in µg/mL. P_{mcf} hold values presented in mmHg. FiO_2 fractional oxygen concentration

* *p* value, *p* value for situation A compared to B

\# *p* value, *p* value for situation A compared to C

Limitations

The use of P_{mcf} hold is restricted to mechanically ventilated and sedated patients with a central venous catheter. The procedure of the inspiratory hold maneuvers is not yet automated and requires a direct link between monitor and ventilator, or advanced monitor analytics to detect the inspiratory holds and to perform the instantaneous CO calculations. Furthermore, it is not suitable during cardiac arrhythmia. This method is not suitable to measure rapid changes in hemodynamic status since it takes a couple of minutes to perform the multiple end-inspiratory (and end-expiratory) holds. Potentially, this technique is operator-dependent because a proper inspiratory plateau pressure is needed. CVP can be altered due to incorrect catheter placement. An absolute CO value is not necessary for P_{mcf} hold as the technique extrapolates to zero CO. If the trend measurements are accurate, the RVR slope might change, but the intersection P_{mcf} point remains constant. The latter holds only true for the P_{mcf} itself, the RVR is dependent of the slope of the curve. In clinical practice, a physician would use P_{mcf} together with RVR; therefore, for clinical use of the P_{mcf} an accurate CO value is needed.

Potentially, the inspiratory hold maneuver overestimates P_{mcf} by the blood translocation from the pulmonary into the systemic circulation [31–33]. However, the potential volume shifts relative to Csys suggest that this effect is minimal [10, 34]. During inspiratory hold maneuvers, arterial pressure decreases. If sustained, baroreflex-induced increased sympathetic tone may cause P_{mcf} to increase [35, 36]. Indeed one study performed in pigs found the P_{mcf} hold overestimating compared to a method using right atrial balloon occlusion in euvolemic conditions, in bleeding and hypervolemia; however, the values found between the two methods were similar [34]. Two clinical studies [16, 30] have shown P_{mcf} hold and P_{mcf} arm values not being significantly different, debating the former result found in pigs. Future studies in humans are needed. Moreover, all patients undergoing inspiratory holds are on neuro-humoral suppressive agents, probably dampening the baroreflex and other autonomic influences [37–39].

P_{mcf} arm

Technique description

As P_{mcf} is defined as the steady-state blood pressure during no-flow conditions, instantaneously P_{mcf} should mainly be similar for different vascular compartments even though each compartment may have different V_u and V_s [2, 40]. Four studies [16, 41–43] used the arm to estimate P_{mcf}. For arm occlusion, a rapid cuff inflator (inflates in 0.3 s) [16, 43] or a pneumatic tourniquet (inflates in 1.4 s) [41, 42] was inflated around the upper arm to 50 mmHg above systolic blood pressure. Arterial and venous pressures were measured via a radial artery catheter and a peripheral venous cannula in the forearm. When these two pressures equalize, P_{mcf} arm values are achieved. An initial study determined that a 25–30 s stop-flow time was adequate to achieve this equilibration [16]. Following this, in two studies P_{mcf} arm was measured as the average radial arterial pressure at 30 s after stop-flow [16, 43]. One study found the smallest difference between venous and arterial pressure after 60 s of stop-flow [41]. This discrepancy could be explained by different inflation time, i.e., induction of stop-flow.

Clinical applicability

The average baseline P_{mcf} arm values found in the included studies range from 16 to 24 mmHg (Table 2). P_{mcf} arm can be performed in spontaneously breathing subjects and requires only one measure. In two studies, P_{mcf} arm was assessed as a predictor of fluid loading responsiveness (FLR) [16, 43]. One study showed that a low P_{mcf} arm (< 22 mmHg) predicts FLR with 71% sensitivity and 88% specificity, where responders were defined when CO increased > 10% after 500 mL colloid administration [43]. Another study showed changes in circulating volume (500 mL colloid) are tracked well by changes in P_{mcf} arm [16]. Finally, one study indicated a minimum of 4 mL/kg fluid challenge was needed to define FLR [42].

Precision and accuracy

Repeated measurements of P_{mcf} arm showed no significant differences [41]. The coefficient of variation for a single measurement was 5%, which reduced to 3% after four measurements. Bland–Altman analysis showed a bias of -0.1 ± 1.68 mmHg for the first two measurements. The least significant change [44] for a single measurement was 14% (i.e., ± 3 mmHg for a P_{mcf} arm of 22 mmHg). One study observed a negligible bias of two P_{mcf} arm determinations at baseline position and after fluid expansion [16]. Two studies [16, 30] found no significant differences in P_{mcf} arm to P_{mcf} hold measures.

Limitations

Theoretically, a limitation of the technique is the influence of an auto regulatory hypoxia-induced response causing arterial vasodilation. The time of measuring P_{mcf} after arm occlusion should be enough for arterial and venous pressures to equilibrate, but before hypoxia-induced vasodilation causes an underestimation of P_{mcf} [45]. One study observed plateau pressures after 20–30 s and saw a further decrement after 35–40 s which indicates hypoxia-induced vasodilation [16]. Potentially, arm occlusion causes a small accumulation of blood volume because the venous outflow stops before the arterial inflow stops [16]. Though, this potential overestimation is negligible since the inflow is small compared to the total distal arm volume as long as cuff inflation is rapid. To note, P_{mcf} arm is only reliable when a stable plateau pressure is achieved [2].

In contrast to P_{mcf} hold, P_{mcf} arm measures can be made in non-sedated patients with cardiac arrhythmias. However, the possible influence of the rapid cuff inflator on reflex mechanisms needs to be studied. In septic patients, central and peripheral vasomotor tone might be altered differently [46]. Shortly after cardiac surgery differences between aortic and radial pressure can occur [47], still, the original validation studies were on postoperative cardiac surgery patients.

P_{mcf} analogue

Technique description

Based on a Guytonian model of the systemic circulation ($CO = V_R = (P_{mcf} - CVP)/RVR$), an analogue of P_{mcf} can be derived using a mathematical model: P_{mcf} analogue $= axCVP + bxMAP + cxCO$ [5, 20, 48, 49]. In this formula, a and b are dimensionless constants ($a + b = 1$). Assuming a veno-arterial compliance ratio of 24:1, $a = 0.96$ and $b = 0.04$; c resembles arteriovenous resistance and is based on a formula including age, height and weight [5, 48–50].

Clinical applicability

The average baseline P_{mcf} analogue values found in the included studies range from 14 to 18 mmHg (Table 2). One study compared fluid replacement based on target P_{mcf} analogue compared to conventional treatment in continuous veno-venous hemodiafiltration [49]. Fluid replacement based on target P_{mcf} analogue led to significantly less fluid administration with stable cardiovascular variables (CVP, MAP, CO) and no complications. So, P_{mcf} analogue measurement adequately follows intravascular volume status in patients. P_{mcf} analogue measurements are automatic making it an attractive alternative to P_{mcf} hold and P_{mcf} arm.

More recently, the P_{mcf} analogue dynamics, measured with the Navigator™ device (Applied Physiology, Pty Ltd, Australia), were observed [20, 48, 51]. Patients were defined as responders with an increase in stroke volume or CO > 10% after 250 mL fluid administration. P_{mcf} analogue increased after fluid administration; however, baseline P_{mcf} analogue did not differ between responders and non-responders [20, 45, 48] (Table 2). This is contrary to results of another study [43] using P_{mcf} arm, possibly due to different fluid volume (250 vs. 500 mL) [42]. Although the driving pressure for V_R (P_{mcf} CVP) was different between responders and non-responders, it showed low sensitivity (79%) and specificity (56%) to predict FLR [20, 48].

Precision and accuracy

Precision has not been assessed for P_{mcf} analogue (Table 4). Comparing measurement techniques revealed a lower P_{mcf} analogue value compared to P_{mcf} hold [16]. However, a significant regression of P_{mcf} analogue and P_{mcf} hold was observed enabling to adjust the P_{mcf} analogue value using calibration factor [5].

Table 4 Comparison of bedside P_{mcf} measurement techniques

	P_{mcf} hold $CO = (P_{mcf} - CVP)/RVR$	P_{mcf} arm $P_a = P_v$	P_{mcf} analogue $P_{mcf} = axCVP + bxMAP + cxCO$
Applicability to a broad patient population	−	±	±
	Restricted to fully sedated and mechanically ventilated patients	In theory applicable in all patients (sedated or awake) with an radial artery catheter	In theory applicable in all patients (sedated or awake)
	Restricted to patients without a contraindication for inspiratory holds (such as COPD with bullae)		Continuous and accurate CO, MAP and CVP measurements needed
	Continuous and accurate CO and CVP measurements needed		Not suitable in cardiac arrhythmia
	Not suitable in cardiac arrythmia		
Accuracy	+	+	−
	Values interchangeable with P_{mcf} arm	Values interchangeable with P_{mcf} hold	Values significantly lower than derived with P_{mcf} hold
	When sedated baroreflex probably of little influence	Dependent on time of measurement: > P_a and P_v equilibration. < hypoxia-induced vasodilatation	P_{mcf} analogue can be transformed to P_{mcf} hold values (constant error)
	Mechanical ventilation may overestimate P_{mcf} value	Possible influence rapid cuff inflator on reflex mechanism altering P_{mcf} value in non-sedated patients. This is not studied	Mathematical coupling and the equation is based on assumptions that may not be generalizable to all patient populations in ICU
Precision	?	+	?
	Not studied	No significant differences during repeated measurements. LSC for a single measurement is 14%	Not studied
Outcome operator independent	−	±	+
	Inspiratory holds	Timing of measurement	CVP transducer position and CO measurement technique
	CVP transducer position and CO measurement technique		
	Extrapolation of curve		
Responding time	−	+	+
	> 4 min	30–60 s	Fast, no exact times mentioned
Costs	−	+	+
	Theoretically no extra devices needed than standard present in ICU	Rapid Cuff Inflator (Hokanson E20, Bellevue, Washington, USA) = 3000 euro	Navigator™ (Applied Physiology, Pty Ltd, Sydney, Australia)
			Price unknown
Risk of complications	+	±	−
	No complications reported in published studies. In theory:	No complications reported in published studies. In theory:	No complications reported in published studies. In theory:
	Barotrauma from inspiratory holds	In sedated patients attention should be paid deflating the rapid cuff before hypoxemia-induced damage can occur	Complications associated with central venous catheters and CO measurement

Table 4 (continued)

	P_{mcf} hold $CO = (P_{mcf} - CVP)/RVR$	P_{mcf} arm $P_a = P_v$	P_{mcf} analogue $P_{mcf} = axCVP + bxMAP + cxCO$
	Severe hemodynamic instability induced by inspiratory holds	In awake patients local pain could be caused by inflating the rapid cuff inflator	
	Complications associated with central venous catheters and CO measurement		

CO cardiac output, *CVP* central venous pressure, *RVR* resistance to venous return, *MAP* mean arterial pressure, P_a arterial pressure, P_v venous pressure (the latter two measured in the arm)

Limitations

The mathematical model is based on CVP, MAP and CO measurements. As CVP values vary during ventilation, usually end-expiratory CVP-recordings can be used. Furthermore, CVP values depend on the position of the transducer. Accurate CO values are needed for this method. The limitation of P_{mcf} analogue is that the algorithm is based on a mathematical model with mathematical coupling between CO and P_{mcf} and fixed Csys and resistance parameters [5], therefore presumably not applicable for all patient populations or clinical conditions. We are unable to assess the availability of the Navigator™ for routine care.

Discussion

We found three bedside techniques to measure P_{mcf}: P_{mcf} hold, P_{mcf} arm and P_{mcf} analogue. They were used to follow volumetric state and to study drug-induced hemodynamic changes in patients.

The interpretation of V_R curves and P_{mcf} in clinical practice is subject to debate [52–59]. The values found in heart-beating ICU patients are higher (14–33 mmHg) than in deceased ICU patients (12.8 ± 5.6 mmHg, mean ± sd), probably because of alteration of vasomotor tone after dying [53]. Furthermore, ICU patients often receive vasopressors which increase P_{mcf} and the study populations differed making it not one-to-one comparable. It is also speculated that the pressure described by Guyton is not measurable in heart-beating patients and the extrapolated pressure of the curve represents a different physiological parameter. Nevertheless, in two studies P_{mcf} arm was interchangeable with P_{mcf} hold [16–30]. Furthermore, although P_{mcf} values may differ, the CVP values do as well, which may account for a similar driving pressure for V_R. The reviewed studies illustrate the possible clinical benefits of using the bedside derived P_{mcf} values.

This review is limited since we were unable to pool the data because of the variety in used conditions and interventions. The 16 included studies were performed by only a few research groups with a limited amount of included patients. In most of the studies, each patient served as their own control since it is not clear what would be an appropriate outside control group.

Still, all studies testing the accuracy of P_{mcf} to follow intravascular changes and pharmacodynamics found significant results. Therefore, it is unlikely that a larger number of patients will show different outcomes. It is possible only positive studies were published, indicating publication bias. P_{mcf} values differ between the studies and have a wide range within studies (Table 2). Normal values for different patient populations need to be defined before P_{mcf} can be implemented into standard (ICU) care. The increase in P_{mcf} values after fluid administration depends on vascular redistribution, vasomotor tone and fluid loss into the interstitial space. Studies focusing on clinical decision-making based on P_{mcf}, driving pressure for V_R, V_s or Csys have not yet been performed. Study designs need to be created to see if using these measures improves outcomes. Also, no precision studies examining P_{mcf} hold or P_{mcf} analogue exist yet.

Conclusions

Presently, three bedside P_{mcf} measurement techniques are available. All require invasive hemodynamic monitoring. Though P_{mcf} measures allow for more direct assessment of circulating blood volume, V_R and Csys, studies are needed to determine cutoff values to allow P_{mcf} to trigger therapeutic interventions and to determine its value in clinical practice.

Abbreviations

CO: cardiac output; Csys: vascular compliance, CVP: central venous pressure; FiO_2: fractional oxygen concentration; FLR: fluid loading responsiveness; ICU: intensive care unit; MAP: mean arterial pressure; RVR: resistance for venous return.

List of symbols

P_{cc}: critical closing pressure; P_{mcf}: mean circulatory filling pressure; P_{ra}: right atrial pressure; V_R: venous return; V_s: stressed volume; V_u: unstressed volume.

Additional file

Additional file 1. I: Search in EMBASE, MEDLINE and Cochrane Library: Description of the used search terms per database. **II: Quality assessment according to a modified version of the Newcastle–Ottawa scale for cohort studies**: Including representativeness, ascertainment, demonstration, comparability and outcome. **III: PRISMA Flowchart**: Description of results of systematic literature search, reasons for excluding studies and the amount of included studies. **IV: Expanded baseline characteristics for included studies**: Authors, described P_{mcf} measurement method, patient population, exclusion criteria, age and sex of included patients, type of cardiac output measurement, used vasopressors, sedation and anesthesia techniques and timeframes of P_{mcf} measurements. **V: PRISMA 2009 Checklist**: an evidence-based minimum set of items for reporting in systematic reviews and meta-analysis.

Authors' contributions

All authors contributed to the manuscript. MW, DV and BG designed the study. MW performed a systematic search of the literature. MW and DS independently screened articles for relevance and subsequently performed data extraction into predefined forms. Quality assessment of the included articles was also independently performed by MW and DS. MW, DV, BG and MP wrote the manuscript. JJ, EO and AV critically reviewed and revised the manuscript. All authors read and approved the final manuscript.

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Competing interests
None of the authors have relevant conflict of interest present for any aspect of the submitted work. Denise Veelo performed consultancy work for Edwards Lifesciences, Hemologic and Merck outside the submitted work. Bart Geerts performed consultancy work for Edwards Lifesciences and Philips outside the submitted work. Michael Pinsky is a consultant for Cheetah Medical, Edwards Lifesciences, Exotstat Medical, LiDCO Ltd and Cyberonics outside the submitted work.

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