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: $V_R = (P_{mcf} - P_{ra})/(RVR)$ [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
is the intersection between the CO and $V_R$ curve. Central venous pressure (CVP) is a surrogate of $P_mcf$ 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]. $V_u$ and vascular compliance ($C_{sys}$) define $P_mcf$ [16]. An increase in $V_s$ increases $P_mcf$ and an increase in $C_{sys}$ decreases $P_mcf$. Fluid loading should increase $P_mcf$, but $V_R$ only increases if the pressure gradient for $V_R$ (i.e., $P_mcf \times CVP$) 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.

**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 3 CABG 6 AVR 1 MVP + TVP 7 CABG 64 (11) 9 (90%) 64 (10) 10 (83%) | Not described |       |                               |
| Keller et al. [23]  | $P_{mcf}$ hold | 9  | Postoperative cardiac surgery 3 CABG 6 AVR 64 (10) 10 (83%) Not described 6 (11) 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 | Postoperative cardiac surgery 3 CABG 6 AVR 64 (11) 9 (90%) | 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 | Postsurgical gastrointestinal 16 esophageal resection 1 pancreaticoduodenectomy 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 | 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 | Not described |       |                               |
| Ceccconi et al. [48] | $P_{mcf}$ analogue | 39 | 22 Cardiac surgery 8 Shock 8 CABG + valve replacement 8 Valve replacement 5 Bentall’s procedure 6 Shock 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 | Initial period at ICU (not further defined) |       |                               |
Table 1 (continued)

| References   | Method      | N  | Patient population (all adult ICU patients) | Age  | Male           | Timeframe Pmcf measurement |
|--------------|-------------|----|---------------------------------------------|------|----------------|---------------------------|
| Maas et al. [16] | Pmcf hold   | 11 | Postoperative cardiac surgery               | 64   | 9 (82%)        | Within 2 h after ICU admission |
|              | Pmcf arm    | 11 | 9 CABG                                      |      |                |                           |
|              | Pmcf analogue | 11 | 2 AVR                                       |      |                |                           |
| Maas et al. [30] | Pmcf arm    | 15 | Postoperative cardiac surgery               | 64 (11)|              | Within 1 h after ICU admission |
|              | Pmcf hold   | 12 | 9 CABG                                      |      |                |                           |

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.

Pmcf hold

Technique description

Pmcf 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 cmH2O 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 \( P_{vent} 30 \) cmH2O) 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 (\( \text{FiO}_2 = 90\% \) 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                               | –                           | –         |
| 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     | 32.1 (7.1)        | 28.1 (11.1)                     | < 0.001   | 500 mL saline in 10 min                      | –                           | –         |
| Geerts et al. [43]   | $P_{mcf}$, arm | 24 | Cardiac surgery    | Supine            | 22.4 (7.7)        | –                               | –         | –                                             | –                           | –         |
| Aya et al. [41]      | $P_{mcf}$, arm | 20 | Cardiac surgery    | Supine            | 23.0              | –                               | –         | –                                             | –                           | –         |
| Aya et al. [42]      | $P_{mcf}$, arm | 80 | Cardiac surgery    | Supine            | 23.0              | –                               | –         | –                                             | –                           | –         |
| Parkin et al. [49]   | $P_{mcf}$, analogue | 10 | CVVH               | Not described     | 20.9 (5.1)        | 28.1 (10.9)                     | < 0.001   | Mean 252 (8.4) mL                            | –                           | –         |
| Ceccconi et al. [48] | $P_{mcf}$, analogue | 39 | Heterogenous       | Not described     | 21.0 (4.9)        | 30.9 (5.0)                      | < 0.001   | 52.5% crystalloid                             | –                           | –         |
| Gupta et al. [20]    | $P_{mcf}$, analogue | 61 | Cardiac surgery    | Supine            | 19.4 (3.7)        | 29.4 (10.3)                     | 0.02      | –                                             | –                           | –         |
| Aya et al. [51]      | $P_{mcf}$, analogue | 26 | Heterogenous       | Not described     | 19.4 (3.7)        | 29.4 (10.3)                     | 0.03      | –                                             | –                           | –         |
| 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     |
| Maas et al. [30]     | $P_{mcf}$, arm  | 15 | Cardiac surgery    | Supine            | 14.7 (2.7)        | 19.2 (1.1)                      | < 0.001   | 15.4 (2.1)                                   | 10.9 (2.0)                 | < 0.001   |

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
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 $C_{sys}$ 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 euvoicemic 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.

### 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                      |                              |            |             |            |
| $P_{mcf}$ hold (in mmHg)    | Range 0.10–1.40    |     | Range 0.08–1.15              |                              | 0.003      |             |            |
| Maas et al. [25]            | 16 Baseline 1      |     | NE increase of 0.04 (0.02)   | 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                |            |             |            |
| $P_{mcf}$ 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%                  | $< 0.001$                    |            |             |            |
| $P_{mcf}$ hold (in mmHg)    | 20.8 (3.5)         |     | 23.1 (4.0)                   |                             |            |             |            |

$NE$ 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
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 $P_{mcf}$ arm 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 = $a$xCVP + $b$MAP + $c$CO [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].
|                         | $P_{mcf}$ hold | $P_{mcf}$ arm | $P_{mcf}$ analogue |
|-------------------------|----------------|---------------|--------------------|
| **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 | Continuous and accurate CO, MAP and CVP measurements needed |
|                         | Restricted to patients without a contraindication for inspiratory holds (such as COPD with bullae) | Not suitable in cardiac arrhythmia | Not suitable in cardiac arrhythmia |
|                         | Continuous and accurate CO and CVP measurements needed |                               |                                |
|                         | Not suitable in cardiac arrhythmia |                               |                                |
| **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. $< \text{hypoxia-induced vasodilatation}$ | $P_{mcf}$ analogue can be transformed to $P_{mcf}$ hold values (constant error) |
|                         | Mechanical ventilation may overestimate $P_{mcf}$ | 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: Barotrauma from inspiratory holds | No complications reported in published studies. In theory: | No complications reported in published studies. In theory: |
|                         |                               | 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)

| $P_{mcf}$ | CO | $P_{mcf}$ | $P_{mcf}$ |
|-----------|----|-----------|-----------|
| hold      | $CVP/RVR$ | arm       | analogue  |
| $\text{Severe hemodynamic instability induced by}$ | $P_{mcf}$ | $P_{a} = P_{v}$ | $P_{mcf} = axCVP + bxMAP + cxCO$ |
| inspiratory holds |  |  |  |
| 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; FiO2: 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; $P_{na}$: 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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