Value and determinants of the mean systemic filling pressure in critically ill patients

Running title: Mean systemic filling pressure in critically ill patients

Xavier Repessé¹, M.D., Cyril Charron¹, M.D., Julia Fink¹, M.D., Alain Beauchet⁴, M.D.,
Florian Deleu¹, M.D., Michel Slama⁵, M.D., Ph.D., FACCp, Guillaume Belliard¹, M.D.,
Antoine Vieillard-Baron¹,²,³, M.D., Ph.D.

Author information

¹ Assistance Publique-Hôpitaux de Paris, University Hospital Ambroise Paré, Intensive Care
Unit, Section Thorax-Vascular Disease-Abdomen-Metabolism, 92100 Boulogne-Billancourt,
France

² University of Versailles Saint-Quentin en Yvelines, Faculty of Medicine Paris Ile-de-France
Ouest, 78280 Saint-Quentin en Yvelines, France

³ INSERM U-1018, CESP, Team 5 (EpReC, Renal and Cardiovascular Epidemiology),
UVSQ, 94807 Villejuif, France

⁴ Assistance Publique-Hôpitaux de Paris, University Hospital Ambroise Paré, Department of
Biostatistics and Clinical Research Unit, 92100 Boulogne-Billancourt, France

⁵ Intensive Care Unit, University Hospital of Amiens, 80000 Amiens, France

Address for correspondence and reprint requests

Prof. Antoine Vieillard-Baron,
Intensive Care Unit, Section Thorax-Vascular Disease-Abdomen-Metabolism,
University Hospital Ambroise Paré, 9, avenue Charles-de-Gaulle 92100 Boulogne-Billancourt
Email: antoine.vieillard-baron@apr.aphp.fr, Phone: +33149095603 Fax: +33149095892

Key words: mean systemic filling pressure, hemodynamics, venous return
Abstract

Mean systemic filling pressure (Pmsf) is a major determinant of venous return. Its value is unknown in critically ill patients (ICU). Our objectives were to report Pmsf in critically ill patients and to look for its clinical determinants, if any. We performed a prospective study in 202 patients who died in the ICU with a central venous and/or arterial catheter. One minute after the heart stopped beating, intravascular pressures were recorded in the supine position after ventilator disconnection. Parameters at admission, during the ICU stay and at the time of death were prospectively collected. One-minute Pmsf was 12.8 ± 5.6 mmHg. It did not differ according to gender, severity score, diagnosis at admission, fluid balance, need for and duration of mechanical ventilation, or length of stay. Nor was there any difference according to suspected cause of death, classified as shock (cardiogenic, septic, and hemorrhagic) and non-shock, although a large variability of values was observed. The presence of norepinephrine at the time of death (102 patients) was associated with a higher one-minute Pmsf (14 ± 6 versus 11.4 ± 4.5 mmHg), whereas the decision to forgo life-sustaining therapy (34 patients) was associated with a lower one-minute Pmsf (10.9 ± 3.8 versus 13.1 ± 5.3 mmHg). In a multiple regression analysis, norepinephrine (beta 2.67, p = 0.0004) and age (beta -0.061, p = 0.022) were associated with one-minute Pmsf. One-minute Pmsf appeared highly variable without any difference according to the kind of shock and fluid balance, but was higher with norepinephrine.
New and Noteworthy

This study reports the value and the determinants of the mean systemic filling pressure (Pmsf) in a cohort of 202 patients died in intensive care unit. The Pmsf measured one minute after the cardiac arrest was 12.8 mmHg and its major determinant was norepinephrine infusion.
**Introduction**

Mean systemic filling pressure (Pmsf) represents the pressure generated by the elastic recoil in the systemic circulation during a no-flow state (9). It is considered a key hemodynamic parameter because of its crucial role as the upstream pressure of systemic venous return (1, 7). It is considered that physiological understanding of venous return may help intensivists to improve management of critically ill patients (6, 17). Applying Guyton’s approach, to increase venous return means decreasing central venous pressure (the backward pressure) or increasing Pmsf. However, despite its key property, Pmsf has never become a routinely accessible hemodynamic parameter in critically ill patients and there is no incontrovertible study of the expected value of Pmsf in the intensive care unit (ICU). This is due to the complexity of this parameter and the difficulty in practice of extrapolating Pmsf in heart-beating patients. Pmsf has only been measured in humans during electrophysiological explorations inducing cardiac arrest (22). Numerous methods based on heart-lung interactions in ventilated heart-beating animals were initially proposed for indirect determination of Pmsf by plotting the venous return curve (3, 7, 24), and the same indirect method was also proposed in ventilated patients in the ICU (13, 14).

Our main objective was to measure Pmsf in a large cohort of critically ill patients, following expected death. Our hypothesis was that the value would be lower than values previously reported using the extrapolation method in heart-beating patients. The secondary goal was to find clinical factors associated with Pmsf, if any.

**Material and methods**

**Study design**

This observational prospective study was conducted in a 12-bed ICU in the University Hospital Ambroise Paré, Boulogne-Billancourt, France. All patients who died, and in whom
an arterial catheter and/or a central venous catheter had been previously inserted for care, were included. The study protocol was approved by the Comité de Protection des Personnes Nord-Ouest II. A French legal expert also confirmed that the study was in accordance with French law, providing that the integrity of the body was preserved, which was the case since we only measured pressure using a previously inserted catheter.

In practice, the experienced intensivist in charge of recording pressures was at the bedside just before the expected death. After the heart stopped beating, he recalibrated the pressure transducer using the monitor, as usually recommended, disconnected the patient from the ventilator and then recorded the equilibrium pressure in the arterial and/or central venous lines after one minute (Figure 1). The recorded pressure was then called the “one-minute Pmsf”. Measurements were done with the patient in a strictly supine position before interruption of catecholamine infusion, if any, catheter removal and extubation. The same 2 intensivists (XR, GB) performed all the evaluations.

Arterial blood pressure was monitored via a 20-Ga, 8 cm arterial catheter (Arterial Catheterization Set, Arrow, Reading, USA) in the radial artery or via an 18-Ga, 23 cm catheter in the femoral artery. Venous blood pressure was measured via a previously inserted central venous catheter (Multi-Lumen Central Venous Catheterization Set, Arrow, Reading, USA) in the internal jugular, subclavian or femoral vein. The pressure transducers (Pressure Monitoring Set, TruWave, Edwards Lifesciences, Irvine, USA) were calibrated with the monitor (IntelliVue MP 70, Philips Healthcare, Best, Netherlands). Both arterial and venous blood pressures were referenced to the intersection of the anterior axillary line and the fifth intercostal space, as recommended (15).

Data collection

The following data were collected following admission: age, gender, cause of admission to the ICU, simplified acute physiology score (SAPS) II (12), and organ
dysfunction, assessed using the sequential organ failure assessment (SOFA) score (28). The cause of death was also reported, as were mechanical ventilation at the time of death, duration of mechanical ventilation and length of stay in the ICU. Cause of death was prospectively classified by the intensivist in charge of the patient as shock (separated into cardiogenic, septic or hemorrhagic) or non-shock (severe brain injury, refractory hypoxemia, decision to forgo life-sustaining therapy). This classification was retrospectively checked by 2 other experienced intensivists blinded to the one-minute Pmsf value, using the patient’s charts.

For each patient, we prospectively reported the presence of norepinephrine at the time of death, as well as the fluid balance. In our unit, fluid balance is routinely and prospectively recorded each day by nurses, using our electronic monitoring system. Fluid balance is calculated during the length of stay as the difference between entries defined as all infusions, and the outputs defined as the diuresis plus gastric aspiration and drain leakages. Fluid balance is expressed in mL.

Statistical analysis

Statistical calculations were performed by a statistician (AB) using SAS software v 9.3 (SAS Institute Inc, USA). Quantitative data were expressed as mean ± 1 standard deviation and qualitative data as frequency and percentage. A univariate analysis was performed to determine the factors associated with one-minute Pmsf among age, gender, cause of admission to the ICU, SAPS II, SOFA score, length of ICU stay, duration of mechanical ventilation, decision to forgo sustaining-life therapy, and also fluid balance, suspected cause of death, presence of norepinephrine and of mechanical ventilation at the time of death. Student’s t-test, the Kruskall-Wallis test or Pearson’s r correlation was used for comparisons as appropriate. A p value <0.05 was considered as statistically significant. Variables found to be associated with one-minute Pmsf with a p value < 0.20 were entered into a multiple regression analysis. Effect coding was used to include causes of admission in the analysis.
Regression coefficients with a 95% confidence interval (95% CI) were calculated for all independent significant predictors of one-minute Pmsf.

**Results**

Two-hundred and two patients were included. The main characteristics of the patients are listed in Table 1. Length of stay was 4.8 ± 6 days and duration of mechanical ventilation 3.8 ± 4.9 days. One hundred and two patients (50.5%) were receiving norepinephrine infusion at the time of death with a dose of 1.3 ± 1.2 µg.kg⁻¹.min⁻¹.

One hundred and fifty seven patients (78%) had both arterial and central venous catheters, whereas 8 patients (4%) had only a central venous catheter and 37 patients (18%) had only an arterial catheter. One-minute Pmsf was 12.8 ± 5.6 mmHg. No difference in one-minute Pmsf was observed in patients with a central venous catheter, an arterial catheter or both (p = 0.74). In all patients with both catheters, one-minute Pmsf represented the equilibrium pressure between the arterial and the central venous lines. There was no difference in one-minute Pmsf between the 109 patients who died in the first 48 hours (53.9% of the patients) and the 93 who died later (12.3 ± 5.6 and 13.3 ± 5.3 mmHg, respectively, p = 0.22).

In univariate analysis (Table 2), we found no significant difference in one-minute Pmsf according to age, gender, cause of admission, SAPS II, length of stay in the ICU, mechanical ventilation at the time of death or duration of mechanical ventilation. We also found no difference according to the suspected cause of death (Figure 2), classified as cardiogenic shock (50 patients, one-minute Pmsf 13.4 ± 6.2 mmHg), septic shock (88 patients, one-minute Pmsf 12.7 ± 5.5 mmHg), hemorrhagic shock (15 patients, one-minute Pmsf 11.6 ± 6 mmHg), or non-shock (49 patients, one-minute Pmsf 12.5 ± 4.5 mmHg). A significant difference was found for one-minute Pmsf in patients who did (n = 102 patients) or
who did not (n = 100 patients) receive norepinephrine infusion at the time of death (14 ± 6
versus 11.4 ± 4.5 mmHg, respectively), with a large overlap of individual values between
both groups (Figure 3, panel A). No difference was observed according to fluid balance
(Figure 3, panel B). In patients who finally died after a decision to forgo life-sustaining
therapy (n = 34 patients), one-minute Pmsf was significantly lower (10.9 ± 3.8 versus 13.1 ±
5.6 mmHg in the rest of the population). As compared to patients with septic shock, patients
who died from a cardiogenic shock had a lower length of stay in the ICU (5.5±7 versus
3.08±4.6 days respectively, p=0.03) and a lower fluid balance (5933±6607 versus 2218±3597
mL respectively, p=0.0007). They did not have any difference for age and decision to forgo
life-sustaining therapy (p=0.3 and 0.8, respectively). In multivariate analysis, only
norepinephrine infusion at the time of death and age were associated with one-minute Pmsf
(Table 3).

Discussion

To the best of our knowledge, we report for the first time the value of Pmsf, called
here one-minute Pmsf because the pressure was measured one minute after the heart stopped
beating, in a large cohort of deceased patients in the ICU. Our measurement done one minute
following asystole may explain the higher value that we observed compared with Pmsf in
animal models, i.e. dogs and rats, where the value measured immediately after cessation of
heart pumping was between 6 and 10 mmHg (1, 8). Guyton et al. reported that within a few
seconds after the heart stopped beating, Pmsf was only about one-half the Pmsf value
measured 30 seconds or more later, because of a vasoconstrictor reflex following death (8). A
Pmsf lower than 10 mmHg was also reported in a model of conscious rats with preserved
vasomotor reflex (21, 29). Size difference (between animals and humans or among humans) is
probably not involved in the value of Pmsf since Guyton et al. reported that Pmsf was
identical regardless of the size of dogs (8) and Starr reported that Pmsf in dead persons was
approximately the same, i.e. 7.6 cmH₂O, as in dead dogs (23).

The only study that previously measured the value of Pmsf in humans was done in 82
patients in a completely different context of induced ventricular fibrillation for cardioverter-
defibrillator implantation (22). However, recording was done after only 20 seconds of
ventricular fibrillation, so that the equilibrium between arterial pressure (24.2 ± 5.3 mmHg)
and central venous pressure (11.0 ± 5.4 mmHg) was not achieved (22). In our study, arterial
and central venous pressures had reached equilibrium at the time of measurement in all cases
and no difference was found for one-minute Pmsf in the few patients with only an arterial or a
central venous catheter.

Our Pmsf value is lower than the estimated values for heart-beating patients in the ICU
calculated using an extrapolation method based on Guyton’s systemic venous return curve.
Maas et al. reported a Pmsf around 19 mmHg in 12 normovolemic patients in the supine
position after cardiac surgery (13). Cecconi et al. found comparable values in 39 post-surgical
patients (cardiac surgery in most cases) with very low doses of norepinephrine (2), using
another estimation method based on an algorithm previously described by Parkin and Leaning
(19). This approximation of Pmsf was 18 mmHg at baseline, increasing to 20 mmHg after a
250 mL fluid challenge (2). Finally, Persichini et al. found a value of 33 mmHg in 16 patients
with septic shock receiving 0.3 µg.kg⁻¹.min⁻¹ of norepinephrine (20). In our study, Pmsf was
13 ± 5.5 mmHg in patients with septic shock receiving a mean dose of norepinephrine of 1.3
µg.kg⁻¹.min⁻¹ at the time of death and did not differ from that of patients without septic shock.

Most of these techniques for evaluation of Pmsf in heart-beating patients are based on
heart-lung interactions. Using changes in right atrial pressure induced by tidal ventilation or
by different levels of positive end-expiratory pressure (PEEP), measurement of the
corresponding cardiac output could allow Guyton’s curve to be plotted using the linear
regression between cardiac output and right atrial pressure. Pmsf is then defined as the extrapolation of this linear regression to zero flow. However, three assumptions have to be made for accuracy. The first is that resistance to venous return is constant during mechanical ventilation; however, some great veins may collapse or dilate during tidal ventilation or after applying PEEP (4, 11, 25, 27). The second assumption is that venous return and cardiac output are similar; this is true providing that cardiac function does not change during mechanical ventilation, but the right ventricle may fail during tidal ventilation or increased PEEP (26). The third assumption is that Pmsf is not sensitive to changes in intra-thoracic pressure; however, Fessler et al. (5) and Jellinek et al. (10) reported that both right atrial pressure and Pmsf increase equally during increased PEEP or tidal ventilation. Altogether, this could suggest that Guyton’s curve may not be appropriate as a way of approximating the Pmsf in heart-beating patients. However, Maas et al. (14) reported no difference between the extrapolated value of Pmsf and the arm equilibrium pressure during an occlusion by cuff (14). This could suggest that extrapolated Pmsf represents another physiological parameter, albeit far away from Pmsf. A limitation of this speculative discussion is that the design of our study did not allow any objective comparison between the value measured after death, as we did, and the potential extrapolated value before death, which we did not. However, feasibility of such a comparison is questionable from a methodological and even ethical point of view.

In our study, Pmsf was identical whatever the suspected cause of death, length of stay in the ICU, mechanical ventilation at the time of death, duration of mechanical ventilation and SAPS II. Similar results were also found in patients who died during the first 48 hours following admission. Although the average Pmsf was quite constant between groups, it varied greatly among patients, as shown in Figure 2. This is a potential reflection of the multivariate dynamics and complexity of Pmsf determination. But it could also be due to different response in terms of neutrally-mediated vasoconstriction among patients. Interestingly, Pmsf
was not statistically associated with fluid balance, neither expressed in mL nor in mL/kg of body weight (data not shown). Pmsf is directly related to the stressed volume, which is only a small part of the total blood volume. In 5 anesthetized patients undergoing cardiopulmonary bypass with hypothermic circulatory arrest, Magder et al. noted a stressed blood volume of about 30% of the total predicted blood volume (16). After a few days in the ICU, predicting the distribution between stressed and unstressed volume is quite impossible. As shown by Guyton et al., Pmsf rises immediately after volume expansion and then progressively falls and approaches the control value, suggesting some leakage from the vessel to the interstitial tissue in the case of excessive fluid, which ceases as Pmsf approaches the normal value (8).

Interestingly, despite a lower fluid balance, patients with cardiogenic shock had no different Pmsf as compared to patients with septic shock. Finally, Pmsf was statistically associated with the infusion of norepinephrine at the time of death. It has previously been shown by Guyton et al. that infusion of epinephrine significantly increases Pmsf to a plateau value around 16 mmHg (8). This has been confirmed experimentally by numerous authors who have shown in animals that norepinephrine and other α-adrenoreceptor agonists increase Pmsf (18, 21, 29).

The reason why we found a slight inverted relation between age and Pmsf is unclear but remains to be confirmed since only 19 patients of our cohort were less than 50 years old.

The fact that Pmsf appeared unexpectedly low in a few patients with cardiogenic shock deserves comment. Starr reported a high value, close to 20 cmH2O, in patients dying of heart disease (23). However, these patients had severe and prolonged congestive heart failure, which is far from the classic profile of cardiogenic shock in the ICU. In our cohort, most patients who died with a cardiogenic shock had an acute cardiac event since only 6/50 (12%) had a history of chronic congestive cardiomyopathy. More, fluid balance was strictly controlled with a much lower value than observed in patients with septic shock, as expected.
The main limitation of our study is that we investigated measurement of \( P_{msf} \) in deceased patients, which *per se* is a selected group of very severely ill patients. As a consequence, the impact of the value of \( P_{msf} \) on prognosis and treatment could not be evaluated. This approach is obviously not applicable in heart-beating patients, limiting the relevance of our findings for physiology and pathology in general. But our results may add to understanding of \( P_{msf} \) complexity. Another limitation is that for methodological reason, it was not possible to record central venous pressure (CVP) just before death. This did not allow us to study the driving pressure for the systemic venous return defined as \( P_{msf} - \text{CVP} \).

In conclusion, we report for the first time the value of \( P_{msf} \) in a large cohort of deceased patients in the ICU. \( P_{msf} \) measured after one minute following cardiac arrest was less than 13 mmHg on average. Average \( P_{msf} \) appeared quite constant regardless of the cause of death, kind of patient and fluid balance, although it varied greatly from one patient to another, reflecting the complexity of this physiological parameter. Only infusion of norepinephrine and age were statistically related to \( P_{msf} \). In the light of previously published studies in the field, our results indicate that \( P_{msf} \) is not easy to understand, leading us to wonder whether routine estimation of \( P_{msf} \), if accurate, is really useful as a guide to treatment. However, in view of our study’s limitations and design, no definitive conclusion can be drawn.

The authors declare that they have no conflicts of interest.
References


Figure legends

Figure 1: Illustration of measurement of one-minute Pmsf in a patient who died with central venous and arterial catheters. Note at the top and in the vignette the value of 10 mmHg recorded through the arterial (PA or AP) and venous (PVC or CVP) catheters and at the bottom the progressive equilibrium of central venous pressure (CVP) and arterial pressure. The dotted line represents the time when the heart stopped beating and the solid line one minute later when the measurement is done. Time line is noted in the X axis.

Pmsf: mean systemic filling pressure, HR: heart rate, SAP: systolic arterial pressure, MAP: mean arterial pressure, DAP: diastolic arterial pressure.

Figure 2: Box and whisker plot analysis of one-minute Pmsf in the overall population according to the classification of suspected cause of death. The central box represents the values from the lower to upper quartile (25 to 75 percentile). The middle line represents the median. The mean is at the center of the box.

Figure 3: Relation between one-minute Pmsf and norepinephrine (panel A) and fluid balance (panel B). Note in panel A the huge overlap of individual values in patients with or without norepinephrine infusion. As shown in panel B, no difference was observed according to fluid balance.
Table 1: Characteristics of the 202 patients.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male, n (%)</td>
<td>120 (59)</td>
</tr>
<tr>
<td>Age (y)</td>
<td>69 ± 14</td>
</tr>
<tr>
<td>SAPS II at admission</td>
<td>78 ± 18</td>
</tr>
<tr>
<td>MV, n (%)</td>
<td>163 (81)</td>
</tr>
<tr>
<td>SOFA at admission</td>
<td>11 ± 4</td>
</tr>
<tr>
<td>Underlying disease, n (%)</td>
<td></td>
</tr>
<tr>
<td>Preexisting heart disease</td>
<td>73 (36)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>35 (17)</td>
</tr>
<tr>
<td>Chronic kidney disease</td>
<td>29 (14)</td>
</tr>
<tr>
<td>COPD</td>
<td>24 (12)</td>
</tr>
<tr>
<td>CVD</td>
<td>29 (14)</td>
</tr>
<tr>
<td>Immunocompromised</td>
<td>32 (16)</td>
</tr>
</tbody>
</table>

Table 2: Factors associated with one-minute Pmsf in univariate analysis.

<table>
<thead>
<tr>
<th>Factor</th>
<th>p value</th>
</tr>
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<tbody>
<tr>
<td>Age</td>
<td>0.05</td>
</tr>
<tr>
<td>Gender</td>
<td>0.10</td>
</tr>
<tr>
<td>Cause of admission</td>
<td>0.20</td>
</tr>
<tr>
<td>SAPS II</td>
<td>0.97</td>
</tr>
<tr>
<td>MV at the time of death</td>
<td>0.21</td>
</tr>
<tr>
<td>Duration of MV</td>
<td>0.75</td>
</tr>
<tr>
<td>Length of stay</td>
<td>0.22</td>
</tr>
<tr>
<td>Fluid balance</td>
<td>0.98</td>
</tr>
<tr>
<td>Suspected cause of death</td>
<td>0.66</td>
</tr>
<tr>
<td>DFLST</td>
<td>0.009</td>
</tr>
<tr>
<td>Norepinephrine</td>
<td>0.001</td>
</tr>
</tbody>
</table>

SAPS II: simplified acute physiology score II, MV: mechanical ventilation, DFLST: decision to forgo life-sustaining therapy. Suspected cause of death was classified as refractory shock, classified as cardiogenic, septic or hemorrhagic, and non-refractory shock (refractory hypoxemia, severe brain injury, DFLST).

Factors with a p value < 0.20 were entered into a multiple regression analysis.
Table 3: Multiple regression analysis regarding factors associated with one-minute Pmsf.

<table>
<thead>
<tr>
<th></th>
<th>Multiple regression analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>p</td>
</tr>
<tr>
<td>Age (years)</td>
<td>0.022</td>
</tr>
<tr>
<td>NE (Yes/No)</td>
<td>0.0004</td>
</tr>
</tbody>
</table>

NE: norepinephrine, 95% CI: 95% confidence interval

Beta: coefficient of regression. A beta of 2.67 for norepinephrine means that infusion of norepinephrine at the time of death is associated with a mean increase in one-minute Pmsf of 2.67 mmHg. A beta of -0.061 for age means that one-minute Pmsf decreases by 0.061 mmHg per year as patient age increases.