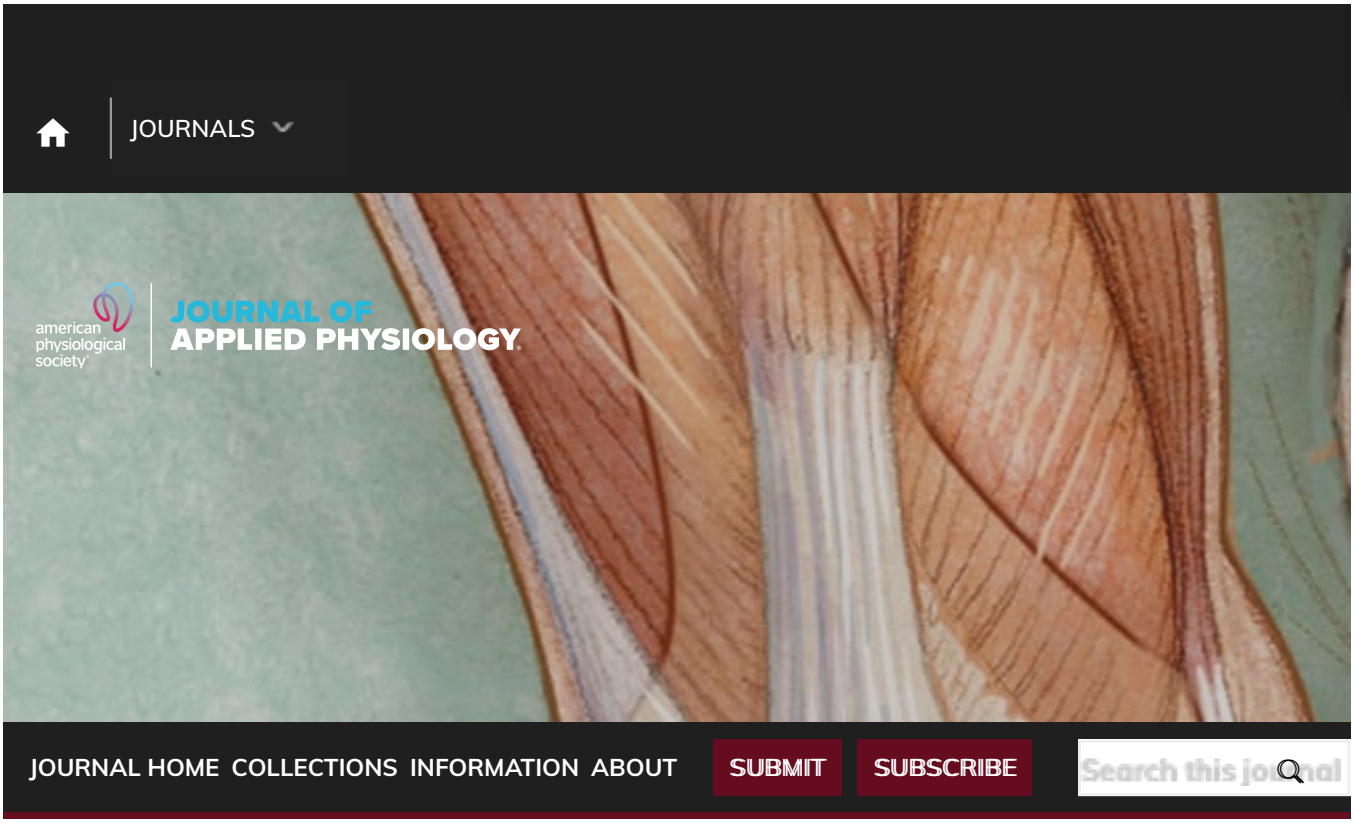

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Research Article

Defining human mean circulatory filling pressure in the Intensive Care Unit

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Abstract

Introduction:Potentially, mean circulatory filling pressure (Pmcf) could aid hemodynamic management in patients admitted to the intensive care unit (ICU). However, data regarding the normal range for Pmcf do not exist challenging its clinical use. We aimed to define the range for Pmcf for ICU patients and also calculated in what percentage of cases equilibrium between arterial blood pressure (ABP) and central venous pressure (CVP) was reached. In patients in which no equilibrium was reached, we corrected for arterial to venous compliance differences. Finally, we studied the influence of patient characteristics on Pmcf. We hypothesized fluid balance, the use of vasoactive

medication, being on mechanical ventilation and the level of positive end-expiratory pressure would be positively associated with Pmcf. Methods:We retrospectively studied a cohort of 311 patients that had cardiac arrest in ICU whilst having active recording of ABP and CVP one minute after death. Results:Median Pmcf was 15 mmHg (IQR 12-18). ABP and CVP reached an equilibrium state in 52% of the cases. Correction for arterial to venous compliances differences resulted in a maximum alteration of 1.3 mmHg in Pmcf. Fluid balance over the last 24 hours, the use of vasoactive medication and being on mechanical ventilation were associated with a higher Pmcf. Conclusion:Median Pmcf was 15 mmHg (IQR 12-18). When ABP remained higher than CVP, correction for arterial to venous compliance differences did not result in a clinically relevant alteration of Pmcf. Pmcf was affected by factors known to alter vasomotor tone and effective circulating blood volume.

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Title: Defining human mean circulatory filling pressure in the Intensive Care Unit

Running title: Mean circulatory filling pressure (Pmcf) in the Intensive Care Unit.

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Abstract

Introduction: Potentially, mean circulatory filling pressure (Pmcf) could aid hemodynamic management in patients admitted to the intensive care unit (ICU). However, data regarding the normal range for Pmcf do not exist challenging its clinical use. We aimed to define the range for Pmcf for ICU patients and also calculated in what percentage of cases equilibrium between arterial blood pressure (ABP) and central venous pressure (CVP) was reached. In patients in which no equilibrium was reached, we corrected for arterial to venous compliance differences. Finally, we studied the influence of patient characteristics on Pmcf. We hypothesized fluid balance, the use of vasoactive medication, being on mechanical ventilation and the level of positive end-expiratory pressure would be positively associated with Pmcf.

Methods: We retrospectively studied a cohort of 311 patients that had cardiac arrest in ICU whilst having active recording of ABP and CVP one minute after death.

Results: Median Pmcf was 15 mmHg (IQR 12-18). ABP and CVP reached an equilibrium state in 52% of the cases. Correction for arterial to venous compliances differences resulted in a maximum alteration of 1.3 mmHg in Pmcf. Fluid balance over the last 24 hours, the use of vasoactive medication and being on mechanical ventilation were associated with a higher Pmcf.

Conclusion: Median Pmcf was 15 mmHg (IQR 12-18). When ABP remained higher than CVP, correction for arterial to venous compliance differences did not result in a clinically relevant alteration of Pmcf. Pmcf was affected by factors known to alter vasomotor tone and effective circulating blood volume.

Key words: hemodynamics, critical care, physiology, arterial pressure, venous pressure

New and Noteworthy: In a cohort of 311 ICU patients, median Pmcf measured after cardiac arrest was 15 mmHg (IQR 12-18). In 48% of cases ABP remained higher than CVP but correction for arterial to venous compliance differences did not result in clinically relevant alterations of Pmcf. Fluid balance, use of vasopressors or inotropes and being on mechanical ventilation were associated with a higher Pmcf.

Introduction

Mean circulatory filling pressure (Pmcf) is of clinical interest because it provides information on intravascular effective circulatory blood volume or stressed volume (Vs) and circulatory vascular compliance (Csys). (2, 5-7, 19, 20, 36, 37) Potentially, Pmcf could be used to guide hemodynamic treatment in patients admitted to the Intensive Care Unit (ICU). (12, 18)

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

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

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

We describe Pmcf in ICU patients one-minute following cardiac arrest. Our main objective was to define the range for Pmcf for patients admitted to the ICU. Secondly, we determined the percentage of patients for which an equilibrium of ABP and CVP was reached within one minute after cardiac arrest. In patients in whom no equilibrium was reached, we determined the impact of correcting for a CCP to CVP gap. Lastly, we determined the influence of patient characteristics and clinical conditions on Pmcf. We hypothesized fluid balance, being on mechanical ventilation, the level of positive end-expiratory pressure (PEEP) and use of vasoactive medication (vasopressors or inotropes) to be associated with a higher Pmcf. The effect of gender, age, ICU length of stay, hospital length of stay, APACHE IV score and APACHE IV admission diagnosis were studied in an exploratory fashion.

Methods

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

Patient population and data acquisition: All adult patients that died in the LUMC ICU between 2007 and 2015 while having continuous ABP and CVP monitoring at the time of cardiac arrest were included for data acquisition. ABP was measured via an arterial catheter (Arrow, 20-22G Arrow International Inc, Reading PA, USA) in the radial artery or femoral artery and CVP was measured via a central venous catheter (Vygon MultCath 3, Vygon GmbH Aachen, Germany) in the internal jugular

vein. Hewlett and Packard blood pressure modules were used (M1006B, Boeblingen, Germany) and both arterial and venous pressure monitors were zeroed to the patient's phlebostatic point.

A data query employing the patient digital management system (Metavision, PDMS, IMDSoft vers 5.0, Needham, MA, USA) was performed to collect data. ABP and CVP measurements were extracted one minute after cardiac arrest. Cardiac arrest was defined by a flat line on the monitor. Data were reviewed for validity by two researchers (MW and MK).

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

For our second objective, we determined the percentage of patients in which equilibrium of ABP and CVP after cardiac arrest was reached. Equilibrium pressure was defined as a difference between ABP and CVP of less than 2 mmHg. The 2 mmHg cut-off was decided upon taking into account the accuracy of the disposable pressure transducers and the pressure modules (connected to the bedside patient monitor). (9) The group in which no equilibrium pressure was reached (ABP to CVP gap of more than 2 mmHg) was described as the CCP group. In this CCP group, Pmcf was calculated using the formula: Pmcf = CVP x 1/c*(CCP-CVP), where 1/c is the arterial to venous compliance ratio. Pmcf was calculated for three different c

values (c=16, 30 and 60) since the reported arterial to venous compliance ratio varies. (12, 13, 21, 25, 35)

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

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

Inferential statistics were used for our third objective. Linear regression analyses were used to assess the effect of fluid balance, vasoactive medication (vasopressors or inotropes), being on mechanical ventilation and the level of PEEP on Pmcf. For these analyses a probability value of $p<0.05$ was considered statistically significant. The effect of gender and age, ICU length of stay, hospital length of stay, APACHE IV score, APACHE IV admission were studied in an exploratory fashion. First scatterplots were made to visually assess the correlations; subsequently univariate analyses were performed. Categorical variables (e.g., APACHE IV admission diagnosis) were transformed into dummy variables.

All analyses were performed using IBM SPSS Statistics version 23.0.

Results

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

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

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

Pmcf related to patient characteristics: Table 3 demonstrates median Pmcf per Apache IV admission diagnosis. Patients who underwent cardiac surgery had the highest median Pmcf (17 mmHg, IQR 14-21) compared to the other subgroups. The univariate regression analysis (Table 4) revealed fluid balance within the last 24 hours, use of vasoactive medication (vasopressors or inotropes), mechanical ventilation to be associated with a higher Pmcf. Specifically, Pmcf was higher (16.4 mmHg +/- 5.8 versus 14.6 mmHg +/- 5.7) in patients on vasopressors or inotropes and in patients on mechanical ventilation (16.3 mmHg +/- 5.9 versus 14.1 mmHg +/- 5.4). The level of PEEP was not associated with a higher Pmcf value. The cumulative fluid balance was not associated with a higher Pmcf value. The exploratory analyses demonstrated admission diagnosis to be associated with Pmcf

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

Discussion

In this study we determined Pmcf one minute after cardiac arrest in a cohort of 311 ICU patients. Our main findings were: 1) Median Pmcf in this population was 15 mmHg (IQR 12-18); 2) ABP and CVP reached equilibrium within one minute after cardiac arrest in 52% of patients. In the remaining 48% of patients ABP was higher than CVP, indicating presence of a critical closing pressure. 3) Fluid balance over the

last 24 hours, use of vasopressors or inotropes and being on mechanical ventilation were associated with a higher Pmcf. Cardiac surgical patients had the highest Pmcf 17 mmHg (IQR 13-21) compared to the other subgroups.

The first insights in human Pmcf measurements date from 1940, when cardiovascular physician-physiologist Isaac Starr measured Pmcf in deceased patients. (29, 30) The method in our study is similar to the method Starr used with one important distinction; our measurements were set at one minute after cardiac arrest, whereas in Starr his experiments the measurements were made within 30 minutes of death. (29, 30) Repessé et al. reported a mean Pmcf of 13 ± 6 mmHg in 202 ICU patients one minute after cardiac arrest. (23) In our study both ABP and CVP had to be present for patient inclusion whereas Repessé et al. extended inclusion to patients in which only one of the two pressures (ABP or CVP) was available. In that study, both ABP and CVP were present in 157 out of 202 patients. Strikingly, all 157 cases reached one-minute equilibrium whereas in our cohort only 52% of patients reached an equilibrium. Differences in the cohorts studied (e.g. medical versus surgical patients, differences in underlying pathology) and a possibly more conservative definition of equilibrium in our study might explain the diverging results. The latter is an assumption, since Repessé et al. did not give their definition of equilibrium. In our study we defined equilibrium as pressure differences between ABP and CVP smaller than or equal to 2 mmHg.

Median ABP (or CCP) to CVP pressure gap in patients who did not reach equilibrium was 8 mmHg. This closely resembles the pressure gap reported during ventricular fibrillation for pacemaker implantation. (13, 26) However, in that population duration of no-flow was not long enough for pressures to equilibrate. The persistence of a low

level of flow in the left carotid artery for up to four minutes has been described in pigs during ventricular fibrillation. (31) Waiting longer for the pressures to equilibrate in deceased patients poses the risk of confounding Pmcf measurements by vasodilation due to energetic loss of vasomotor tone or reflex vasoconstriction due to loss of vascular pulsatility. Measuring CVP at one minute after cardiac arrest currently represents the uniform standard for determination of Pmcf in deceased patients.

Maas et al. explain the existence of CCP as part of a self-regulating vascular mechanism referred to as the vascular waterfall. (16) Potentially, CCP could impede measurement of no-flow Pmcf, However, attempting to correct for arterial to venous compliance differences (1/16, 1/30 and 1/60) did not result in different Pmcf values. Existing literature on Pmcf measurements during induced cardiac arrest have reported similar findings, with most studies describing a negligible increase for Pmcf of 0.3-0.5 mmHg and 1.2 mmHg in animal and human studies respectively. (13, 14, 25, 35) This difference is within the 2 mmHg accuracy cut-off we used to define equilibrium pressure, and thus not considered to be clinically relevant. CVP is considered the main determinant of Pmcf in a no-flow state, suggesting that measuring no-flow CVP alone at one-minute after cardiac arrest is sufficient to determine Pmcf.

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

Influencing factors: We found that fluid balance within the last 24 hours, use of vasoactive medication, mechanical ventilation and admission diagnosis were

associated with Pmcf in the univariate regression analysis. Pmcf behaves in a predictable fashion in line with known physiologic mechanisms.

A higher Pmcf was found in patients with a more positive fluid balance over the last 24 hours. An increase in stressed volume (Vs) given a constant circulatory compliance (Csys) leads to a higher Pmcf (Pmcf = Csys x Vs). The univariate positive correlation found between fluid balance and Pmcf is consistent with existing literature. Guérin et al., also found an increase in Pmcf values after volume expansion. (11) An important note is that fluid overload does not equal a high Pmcf. Pmcf takes into account the intravascular volume status; a patient may have anasarca, be hypovolemic at the same time and thus have a low Pmcf. This probably explains why the cumulative fluid balance was not associated with Pmcf in the univariate analysis. In our multivariate analysis, fluid balance over the last 24 hours was no longer found to significantly associate with Pmcf. Fluid balance and mechanical ventilation showed high co-linearity. Patients receiving mechanical ventilation had a significantly higher fluid balance.

Vasopressors (e.g. norepinephrine) alter Pmcf by increasing Csys or by recruitment of unstressed volume. Unstressed volume (Vu) is the blood contained in the system at zero transmural pressure. Animal research has suggested that with increased sympathetic activity splanchnic resistance (a part of the circulation with a high proportion of unstressed volume) increased proportionally more than total vascular resistance. This results in blood flow redistribution away from larger unstressed vascular beds in the splanchnic region leading to an increase in Vs, and thereby increasing Pmcf without a change in total blood volume (Vs +Vu).(17, 24) Repesse et

al. also found the use of norepinephrine ($p<0.01$) to be associated with increased Pmcf. (23)

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

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

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

We report on the influence of the admission diagnosis. It may be that a fraction of the patients died from a cause different than their admission diagnosis. Unfortunately, we could not extract the cause of death from the patient files. However, the time from ICU admission till death was relatively short with a median of 3 days, therefore we think it is justifiable to use the admission diagnosis for these exploratory analyses.

This study has several limitations, all related to the retrospective design of the study. Most importantly, we were obliged to adhere to strict inclusion criteria in order to guarantee valid measurements. Prior to data collection we decided to only include patients when both ABP and CVP were present. As a result, we had to exclude 1030 out of 1341 patients limiting the size of our cohort and our results need to be confirmed in a larger study. However, we report on the biggest cohort available.

Conclusion

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

Disclosures

None of the authors have any conflict of interest, financial or otherwise, for any aspect of the submitted work

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Figure legend

Figure 1. Flowchart of patient exclusion

Figure 1. Flowchart of patient exclusion

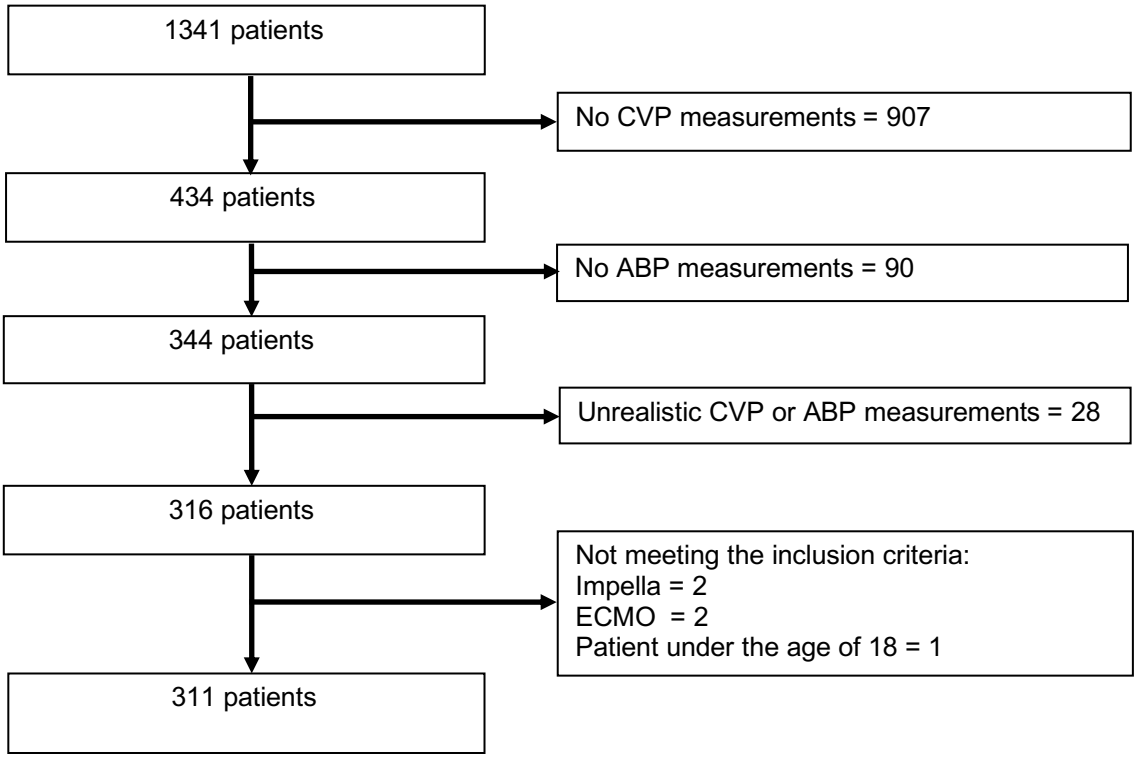

Figure 1. Flowchart of patient exclusion. ABP = arterial blood pressure. CVP= central venous pressure. ECMO = extracorporeal membrane oxygenation.

Table 1.

	n= 311	n=162 (ABP=CVD)	n=149 (ABP>CVD)
	100.0%	52.1 %	47.9 %
Pmcf (one minute)	15 [12-18]	16 [14-18]	13 [9-18]
Male (n, %)	198 (63.7%)	99 (61.5%)	99 (66.4%)
Age (years)	67 [59-75]	68 [60-75]	67 [57-75]
Length (meters)	1.74 +/- 0.10	1.74 +/- 0.09	1.75 +/- 0.09
Weight (kg)	80 +/- 17	80 +/- 17	81 +/- 17
BMI	26 +/- 5	26 +/- 5	26 +/- 5
ICU length of stay (days)	3 [1-8]	2 [1-8]	3 [1-9]
Hospital length of stay (days)	6 [2-16]	6 [2-17]	6 [2-16]
Fluid balance 24 hr before dying (in ml)	3949 [2262-6619]	4022 [2535-6802]	3846 [1912-6463]
Vasoactive medication	137 (44.1%)	80 (49.7%)	57 (38.3%)
Mechanical ventilation	194 (62.4%)	110 (67.9%)	85 (56.4%)
Underlying diagnosis (APACHE IV)			
-Cardiosurgical	39 (12.5%)	26 (16.0%)	13 (8.7%)
-Cardiovascular	96 (30.9%)	47 (29.0%)	49 (32.9%)
-Sepsis	51 (16.4%)	29 (17.9%)	17 (11.4%)
-Respiratory	46 (14.8%)	26 (16.0%)	25 (16.8%)
-Neurology	17 (5.5%)	5 (3.1%)	12 (8.1%)
-Gastro-intestinal	53 (17.0%)	24 (14.8%)	29 (19.5%)
-Hematology	9 (2.9%)	5 (3.1%)	4 (2.7%)

Table 1. Baseline characteristics. Pmcf in mmHg, the Pmcf represents the CVP one minute after cardiac arrest. Continuous data are presented median with interquartile range, or mean with standard deviation (+/-) when normally distributed. Categorical data are given as frequencies with percentages. ABP = arterial blood pressure at zero flow, BMI= body mass index, CVP = central venous pressure at zero flow, ICU = intensive care unit, Pmcf = mean circulatory filling pressure.

Table 2.

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

Table 2. Pmcf in mmHg in the subset of patients reaching no equilibrium pressure (ABP>CVP). The correction factors for critical closing pressure Pmcf = CVP + 1/c*(CCP-CVP) where c is the arterial to venous compliance ratio (see text for details). Continuous data are presented as median with interquartile range. ABP = arterial blood pressure at zero flow, CVP = central venous pressure at zero flow, ICU = intensive care unit, Pmcf = mean circulatory filling pressure.

Table 3.

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

Table 3. Pmcf (in mmHg) per Apache IV admission diagnosis presented in median with interquartile range. Pmcf = mean circulatory filling pressure.

Table 4.

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

Table 4. Univariate regression analysis. *= Statistical Baseline chosen based on largest group. Beta = unstandardized Beta. APACHE = Acute Physiology and Chronic Health Evaluation scoring system. ICU = Intensive Care Unit. PEEP = positive end-expiratory pressure.

Table 5.

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

Table 5. Multivariate regression analysis. APACHE = Acute Physiology and Chronic Health Evaluation scoring system. Beta = unstandardized Beta.