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Resolution and outcome of acute circulatory failure does not correlate with hemodynamics

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Abstract

Introduction Hemodynamic goals in the treatment of acute circulatory failure (ACF) are controversial. In critical care, organ failures can be assessed using Sequential Organ Failure Assessment and its refinement, total maximal Sequential Organ Failure Assessment (TMS). We studied the associations between resolution of ACF and hemodynamics in the early (<24 hours) phase of intensive care unit care and their relation to TMS and mortality.

Patients and methods Eighty-three patients with ACF (defined as arterial lactate >2 mmol/l and/or base deficit >4) who had pulmonary artery catheters and stayed for longer than 24 hours in the intensive care unit were included. Hemodynamics, oxygen transport, vasoactive drugs and TMS scores were recorded. Normalisation of hyperlactatemia and metabolic acidosis in less than 24 hours after admission was defined as a positive response to hemodynamic resuscitation.

Results Fifty-two patients responded to resuscitation. Nonresponders had higher mortality than responders (52% versus 33%, $P=0.044$). Hospital mortality was highest (63%) among nonresponders who received vasoactive drugs. The TMS scores of nonresponders (median [interquartile range], 12 [9–16]) were higher than the scores of responders (10 [7–12], $P=0.019$). Late accumulation of TMS scores was associated with increasing mortality, and if the TMS score increase occurred >5 days after admission then the mortality was 77%. Responders had higher mean arterial pressure at 24 hours, but it was no different between survivors and nonsurvivors. No other hemodynamic and oxygen transport variables were associated with the success of resuscitation or with mortality.

Conclusions Except for the mean arterial pressure at 24 hours, invasively derived hemodynamic and oxygen transport variables are not associated with the response to resuscitation or with mortality. Positive response to resuscitation in ACF is associated with less severe organ failures as judged by TMS scores. Late accumulation of the TMS score predicts poor outcome.

Keywords acidosis, blood circulation, hemodynamics, lactic acid, multiple organ failure

Introduction

Multiple organ failure (MOF) remains the main problem in intensive care because of increased morbidity, mortality and resource use [1]. MOF can develop due to multiple causes, such as infection, trauma or surgery, which may lead to activation of various endogenous cascades causing cellular dysfunction and death [2,3]. Surviving patients in several studies have had higher cardiac index and oxygen delivery than

ACF = acute circulatory failure; ICU = intensive care unit; MOF = multiple organ failure; SOFA = Sequential Organ Failure Assessment; TMS = total maximal Sequential Organ Failure Assessment.

patients who died. This led to the rationale of supranormal oxygen delivery, and indeed surgical and trauma patients had better outcome if oxygen delivery was augmented by giving fluids and inotropes [4,5]. This treatment does not uniformly improve outcome, however, and aggressive efforts to increase oxygen delivery may even increase mortality [6–10]. Most trials testing the effect of augmented oxygen delivery on outcome have used the cardiac index, oxygen delivery or mixed venous oxygen saturation as goals for hemodynamic support [8,11]. However, the use of routine invasive monitoring has recently been questioned [12]. A meta-analysis of 21 randomised controlled trials revealed that when critically ill patients are treated early before organ failure develops, and optimal goals and differences in oxygen transport can be achieved, the mortality can be reduced [13].

Acute circulatory failure (ACF) can be defined in several ways. The definition can be based on biochemical markers, hemodynamic measurements, end-organ dysfunction or on combinations of these. Biochemical markers of impaired tissue perfusion are useful because they relate more to consequences of hypoperfusion than to underlying hemodynamic patterns, which can vary considerably in different groups of patients. In critically ill patients, arterial blood lactate concentration and base deficit can reflect the severity of hypoperfusion and they correlate with outcome [14–17]. Therefore, by improving tissue perfusion, as reflected by a disappearance of hyperlactatemia and metabolic acidosis, one may assume to improve patient outcome. However, the lactate elevation is not always caused by hypoxia resulting from insufficient tissue perfusion [18,19] and it can also be confounded by factors not related to tissue perfusion [20].

Prolonged organ system failure is associated with poor prognosis [21]. Attempts to characterise the severity of organ failures and to predict patient outcome has lead to the generation of numerous scoring systems, but none of them has gained general acceptance [22]. Recently, calculation of the total maximal Sequential Organ Failure Assessment (TMS) score has been proposed as a refinement of Sequential Organ Failure Assessment (SOFA) classification [23], and it was shown to be applicable for outcome prediction [24,25].

In the present study, we evaluate the impact of rapid resolution of ACF (as indicated by disappearance of hyperlactatemia and metabolic acidosis) on the development of organ failures (as assessed by the TMS score) and on death. We also study the associations between hemodynamics, the resolution of shock and the development of organ failures. Finally, we study the evolution of organ failures and its association with mortality in these critically ill patients.

Patients and methods

The Ethics Committee of the Kuopio University Hospital approved this study. Informed consent was waived because all data were analysed retrospectively and no research-related interventions were carried out. Emergency admittances because of ACF and of patients who had pulmonary artery catheters were identified from our clinical information management system (Clinisoft; Datex-Ohmeda, Helsinki, Finland) and from patient records for a period of 1 year (between 1 August 1998 and 31 July 1999).

Only patients with an intensive care unit (ICU) length of stay longer than 24 hours were included. ACF was defined as a presence of metabolic acidosis (base deficit >4) and/or hyperlactatemia (arterial lactate >2 mmol/l) during the first 24 hours of ICU care. Open heart surgery patients, neurosurgical patients, patients younger than the age of 15, patients treated in referring ICUs for longer than 12 hours and patients with intoxications were excluded. For nine patients with multiple admissions, the last admission was selected. Treatment was withdrawn very soon after admission in two cases because of extremely poor prognosis, and these patients were also excluded. One patient was excluded because of technical problems with the database. From 210 screened patients, 83 fulfilled all inclusion criteria. Treatment of ACF was defined as successful and patients defined as responders if both metabolic acidosis and hyperlactatemia were not present 24 hours after admission. If hyperlactatemia and/or metabolic acidosis were still present at this time point, patients were defined as nonresponders. If laboratory values for base deficit and/or lactate concentrations were not available at exactly the 24-hour time point, a linear trend of adjacent values was assumed and the value at 24 hours was estimated. Patients were treated according to the clinical practise of the unit without having consistent targets for hemodynamic variables.

The hemodynamic and treatment profiles of each patient were studied by reconstructing identical sets of trend curves as in the original clinical situation using the clinical information management system. The trend curves consisted of all hemodynamic data, urine output, Glasgow Coma Scale value, blood gas values, arterial lactate concentrations, pulse oximetry readings and vasoactive drug infusions. The infusion rates of vasoactive drugs were recorded if they were necessary for the SOFA scoring. A combination of drugs could be administered either simultaneously or in sequence. Dobutamine and dopamine were the inotropes used most often. Other sympathomimetic drugs used were norepinephrine and epinephrine. Sodium nitroprusside or nitroglycerin was used for vasodilatation.

Continuously measured variables were stored in the database as 2-min median values, and other variables were stored as often as they were measured. The pulmonary artery occlusion pressure, the cardiac output, the urine output and the Glasgow coma scale value were measured hourly by nurses. The oxygen delivery index was calculated using the formula: $DO_2I = 1.34 \times [\text{hemoglobin}] \times SaO_2 \times \text{cardiac index}$. We also recorded the amounts of fluids and red blood cells infused

Table 1

Demographic data of the patients

Number of patients	83
Mean (range) age (years)	63.7 (15–89)
Male/female	54/29
Acute Physiologic and Chronic Health Evaluation II score, median (interquartile range)	23 (19–27)
Length of intensive care unit stay (days)	
Mean (range)	5.7 (1.0–45.5)
Median (interquartile range)	2.6 (1.6–6.6)
Admission causes	
Cardiac	12
Respiratory	8
Infection	37
Trauma or surgery	12
Cardiac arrest	9
Other causes	5

during the first 24 hours of ICU care. Laboratory tests were taken when clinically indicated. ICU admission causes were divided into six diagnostic categories: cardiovascular, respiratory, infection, trauma, cardiac arrest and others. Sepsis was defined according to the Consensus conference recommendation [26] and, in each case, either the positive microbial culture or the obvious source of infection was identified.

Daily SOFA scores were calculated for the entire period of the ICU stay [23]. Missing laboratory values were interpolated if adjacent values were present. If more than one value was missing, they were not interpolated but scored as missing and given 0 points. This was necessary only for bilirubin. If more than one laboratory value was available for the same day, the worst value was chosen. To describe the severity of organ failure, the TMS score was calculated by summing the maximum scores of each of the six organ systems during the whole ICU period [27,28]. The theoretical maximum of the TMS score is thus 24. To describe the evolution of organ failure and its impact on outcome, we determined the time to peak TMS. This was defined as the ICU day when the TMS score reached its maximum.

Statistical methods

Between-group comparisons were performed with the Kruskal–Wallis and Mann–Whitney U tests. Proportions were tested in 2×2 tables with the McNemar test and in 2×3 tables with the chi-square test. Yates' correction was used if appropriate. Data are presented as the mean (95% confidence interval) or as the median (interquartile range) depending on the distribution of the data. Percentages were compared using the test of proportions. $P < 0.05$ was considered statistically significant. Statistical procedures were carried out using the SPSS 9.0 statistical package (SPSS Inc., Chicago, IL, USA).

Results

The clinical data of the patients are presented in Table 1. The ICU mortality was 33.7% and hospital mortality was 39.8%. Twenty out of 83 patients were operated on before admission or during the first day, and 64/83 patients were mechanically ventilated. Sepsis was identified in 20 out of 83 patients. Fifty-two patients (63%) responded to the treatment and the perfusion failure subsided during the first 24 hours, while 31 patients (37%) were nonresponders with a persisting circulatory failure (Table 2); there was no difference in Acute Physiologic and Chronic Health Evaluation II scores between these groups ($P = 0.1$). Vasoactive treatment was given to 63 patients: 48 patients received sympathomimetic drugs, either inotropes alone (27 patients), norepinephrine alone (12 patients) or their combination (9 patients). Vasodilators were given to 27 patients in order to reduce afterload; in 16 cases alone and in 11 cases with inotropic drugs. The hospital mortality of nonresponders was higher than that of responders (55% versus 33%, $P = 0.044$), and it was highest for nonresponders receiving vasoactive treatment (Table 2).

Table 2

Vasoactive treatment, total maximal Sequential Organ Failure Assessment (TMS) score and hospital mortality, and their association with outcome of the primary resuscitation

	n	Vasoactive treatment	*n*	Nonsurvivors	Mortality (%)	TMS score (interquartile range)
Responders	52	Yes	41	12	29	10 (7–12)
		No	11	5	45	8 (6–14)
Nonresponders	31	Yes	24	15	63[b]	13 (10–16)[a]
		No	7	1	14	8 (6–14)

[a]$P = 0.004$, compared to responders with vasoactive treatment.

[b]Significantly different from all other groups but 'responders-no vasoactives'.

Table 3

Hemodynamic parameters in responders and nonresponders of the resuscitation of acute circulatory failure

	Responders		Nonresponders	
Cardiac Index	Median	Interquartile range	Median	Interquartile range
Initial	3.3	2.3–3.8	2.8	2.1–4.5
Maximum	4.1	3.2–5.0	4.3	3.3–5.9
24 hours	3.2	2.5–4.2	3.3	2.5–4.6
Pulmonary arterial occlusion pressure[a]				
Initial	10	8–14	10	7–13
Maximum	11	8–13	10	9–13
24 hours	10	7–14	9	7–12
Oxygen delivery index				
Initial	424	303–564	410	316–590
Maximum	564	427–676	600	413–849
24 hours	439	343–548	442	335–666
Mean arterial pressure[a]				
Initial	72	60–81	66	58–85
Maximum	75	65–84	72	67–83
24 hours	76*	66–86	65	62–78

[a]Maximum measured at the maximal cardiac index.
*Responders compared with nonresponders, $P=0.005$ (Mann–Whitney U test).

The mean arterial pressure at 24 hours after admission was higher in responders than in nonresponders. The variables measured with a pulmonary artery catheter were not associated with the resolution of perfusion failure (Table 3). The oxygen delivery index did not differ between responders and nonresponders. Infusions of crystalloids and colloids were given in larger amounts to the nonresponders than to the responders, respectively (Table 4). TMS scores of the nonresponders (12 [9–16]) were higher than those of the responders (10 [7–12]) ($P=0.019$) (Fig. 1). The responders had lower daily SOFA scores on day 1 ($P=0.006$), on day 2 ($P<0.001$) and on day 3 ($P=0.001$) than the nonresponders, but not later on. Because the presence of perfusion failure defined as hyperlactatemia and/or base deficit was the main grouping factor in the present study, we tried to eliminate the contribution of circulatory failure to the TMS score. This was accomplished by calculating the TMS score without points of circulatory failure in order to assess the presence of remote organ dysfunction. TMS scores without circulatory failure were higher in nonresponders (9 [8–12]) than in responders (8 [6–10]) ($P=0.014$).

The TMS scores of the nonsurvivors were higher (median, 13.0 [11–17]) than those of the survivors (8.0 [7–12]) ($P<0.001$). The hospital mortalities of patients with TMS score ≤ 5, with TMS score=6–10, with TMS score=11–15 and with TMS score >15 were 0%, 27%, 45% and 79%, respectively. The TMS score without circulatory failure of the nonsurvivors (10 [9–13]) was higher than that of the survivors (7 [6–9]) ($P<0.001$). The organ-specific components of the TMS score were analysed separately. The points of coagulation (2 [1–3] versus 3 [2–4], $P=0.02$), central nervous system (1 [0–2] versus 3 [3–4], $P<0.001$), renal (1 [0–2] versus 2 [2–3], $P=0.04$) and cardiovascular function (2 [1–3] versus 3 [3–4], $P=0.005$) were different between survivors and nonsurvivors, respectively. There were no differences in respiratory points and in liver points between survivors and nonsurvivors.

Mortality increased with time from admission to peak TMS (Fig. 2). When the time to peak TMS was less than 3 days the mortality was 28%, and when the time to peak TMS was 3–5 days the mortality was 47%. In patients with a time to peak TMS longer than 5 days, only three out of 13 patients were discharged alive from the hospital (mortality, 77%; $P=0.005$ for a difference in mortality between groups of time to

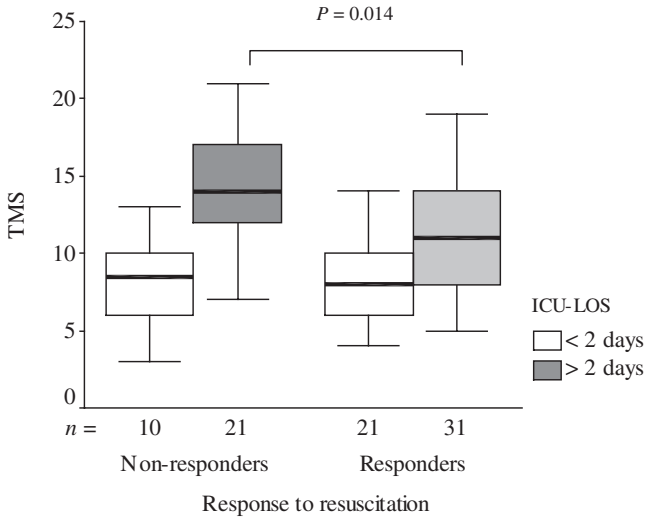
Table 4

Fluid therapy in responders and nonresponders of the early resuscitation and in hospital survivors and nonsurvivors, respectively

	Crystalloids	Colloids	Blood products (ml)
Resuscitation			
Responders	1489 (383–2992)	475 (202–950)	192 (0–963)
Nonresponders	3254 (1300–7096)	950 (475–1900)	350 (0–1650)
P value	0.006	0.001	Not significant
Outcome			
Survived	1502 ± 267–3084	475 ± 237–950	350 ± 0–700
Died	3000 ± 1284–5573	950 ± 475–1425	350 ± 0–1675
P value	0.009	0.008	Not significant

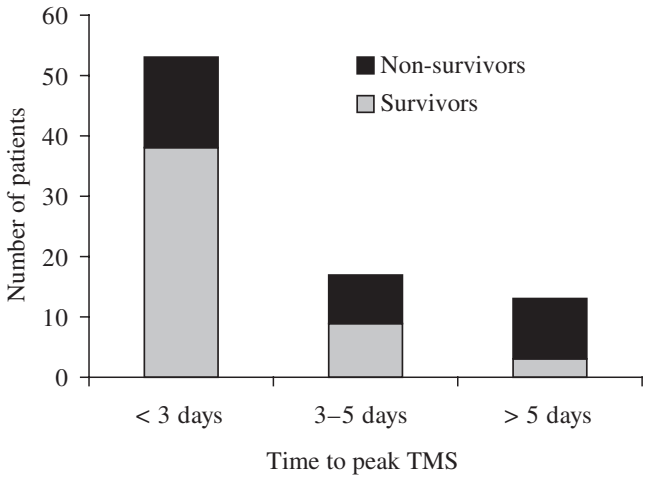
Values presented as median (interquartile range) or mean ± standard deviation. *P* values refer to the Mann–Whitney U test.

Figure 1



Total maximal Sequential Organ Failure Assessment (TMS) scores in relation to resuscitation outcome and in patients with intensive care unit length of stay (ICU-LOS) shorter or longer than 2 days, respectively. *P* value refers to the Mann–Whitney U test. Kruskal–Wallis test for a difference between groups, $P<0.001$.

Figure 2



The impact of the time to reach the peak total maximal Sequential Organ Failure Assessment (TMS) on the hospital mortality. $P=0.005$ for a difference in mortality between groups, chi square-test.

peak TMS). Daily SOFA scores of the nonsurvivors were higher than the scores of the survivors on day 1 ($P<0.001$), on day 2 ($P>0.001$) and on day 3 ($P=0.001$). Later on there was no difference in SOFA scores between survivors and nonsurvivors.

Discussion

We found that persisting tissue perfusion failure after treatment of 24 hours was associated with more severe MOF compared with resolved failure. However, the hemodynamic pattern, except for mean arterial pressure 24 hours after admission, did not differ between responders and nonresponders. The time from admission to peak TMS was associated with the overall prognosis, and a late peak TMS was associated with high mortality. The pattern of daily SOFA scores differed between responders and nonresponders as well as between survivors and nonsurvivors during the first 3 days of ICU care.

Increased blood lactate concentrations in hypovolemic and cardiogenic shock reflect anerobic metabolism due to hypoperfusion, but the interpretation of blood lactate concentrations in septic patients is more complicated. A number of studies have demonstrated that increased lactate concentration may result from cellular metabolic changes rather than from global hypoperfusion, and that increasing systemic oxygen delivery fails to normalise increased lactate concentrations in septic patients [29]. Dissociation of lactate production from oxygen transport has further been demonstrated in septic shock patients [30]. Lactate values of the survivors decreased but the value remained unchanged in nonsurvivors with catecholamine treatment in 24 hours. The oxygen transport pattern of the survivors did not differ from the nonsurvivors.

Increased oxygen delivery should be accompanied with increased oxygen consumption, and a failure to increase oxygen consumption with augmented oxygen delivery has been shown to be a sign of poor prognosis in sepsis patients [31]. Unfortunately, we have insufficient data on oxygen consumption measured with an independent method to analyse this in detail. In our study, 24% of patients were septic. The hemodynamics of septic patients did not differ from those without sepsis (data not presented). Increased lactate concentration and metabolic acidosis have been shown to be sensitive but unspecific clinical signs of general tissue perfusion failure despite the cause. Elevated arterial lactate without metabolic acidosis for longer than 6 hours in general ICU patients is associated with increased mortality [32]. Prolonged hyperlactatemia for longer than 24 hours is associated with increased mortality in trauma patients [14]. Prolonged lactic acidosis for longer than 24 hours is also associated with development of organ failures and MOF [15].

Our results support the finding that prolonged tissue perfusion failure, assessed by hyperlactatemia and metabolic acidosis, is associated with the development of more severe organ dysfunction and death. Except for mean arterial pressure, neither hemodynamic variables nor oxygen delivery differed between responders and nonresponders. Our results are in agreement with the study by Bernardin and colleagues [33] showing that mean arterial pressure and lactate level 24 hours after the onset of treatment for septic shock were the best early indicators of survival. Both an increased arterial lactate level and an increased carbon dioxide gap, assessed by gastric tonometry, at 24 hours after admission were recently shown to predict increased mortality in mechanically ventilated patients [34].

The nonresponders received more fluids than the responders in the resuscitation phase in the present study, and still both groups were treated to the same level of filling pressures. Other studies have shown that the amount of fluids and blood infused is a surrogate marker of the severity of illness and injury. More severe acute illness may also lead to increased capillary permeability and to increased fluid demand to reach the same increase in vascular volume. Seven nonresponders received only fluid resuscitation due to hypovolemia at admission. The mortality of these patients was low, suggesting that the prognosis of patients with prolonged hyperlactatemia caused by marked hypovolemia is good and does not necessitate vasoactive intervention.

It has been shown that mortality of patients who can, as opposed to those who cannot, maintain a high level of oxygen delivery, self-generated or as a result of treatment, is lower [4,35]. We were unable to find any association between outcome and oxygen delivery. The results of a recent meta-analysis demonstrated that early optimisation of hemodynamics aiming to target goals reduced mortality in severely ill patients [13]. Rivers and colleagues [36] showed that septic shock patients treated to target values of central venous pressure, mean arterial pressure and mixed venous saturation with fluid loading and inotropes for at least 6 hours before ICU admission resulted in decreased hospital mortality. During ICU care, the protocol patients needed less fluids, blood and vasopressors. The treatment before ICU admission can thus influence both the treatment in the ICU and also the outcome. In our retrospective study, we could not demonstrate a beneficial effect of high oxygen delivery on the outcome. We demonstrated a correlation between mean arterial pressure and resuscitation response that is in accordance with the study by Rivers and colleagues. Our results demonstrate that early resolution of increased lactate concentration and acidosis is associated with less severe MOF and with reduced mortality, even though no differences in oxygen delivery could be found.

There are several alternatives for the definition of and grading of the severity of MOF [22]. For this study we used SOFA scoring [23]. The use of the daily SOFA score has been challenged, because daily evaluation can lead to underestimation of the cumulative failures [25]. In contrast to daily maximal SOFA scores, the calculation of the TMS score sums the maximal scores of all organ failures during the whole ICU stay independent of their time sequence. It thus quantifies the severity of organ failures and their combinations into one figure. The TMS score has been proved to be a fairly good discriminator between survivors and nonsurvivors [24].

Our results demonstrated that mortality was high if the TMS score at any time was greater than 15. On the contrary, if the time between admission and the time to the peak TMS score was longer than 5 days, mortality was also high. This suggests that circulatory failure leading to the development of severe multiple organ dysfunction with new organ systems involved, or amplification of the failures already present after treatment for 5 days, has a poor prognosis. Daily SOFA scores differed between survivors and nonsurvivors on ICU days 1–3. It is obvious that TMS scores and daily SOFA scores reflect different aspects of the same phenomenon. Some organ failures improve rapidly and are no longer counting towards the daily SOFA scores. However, all new or worsening organ failures add to the TMS score. In our study, TMS scores of both survivors and nonsurvivors were comparable with the multicenter study by Moreno and colleagues [25]. Also, the overall mortality in our patients with different TMS categories was comparable, even if only ICU mortality was reported in the study of Moreno and colleagues. In contrast to patients with cardiovascular and pulmonary diseases in the study by Janssens and colleagues [24], the TMS scores of survivors and nonsurvivors were remarkably lower. Our results are not biased with our definition of circulatory failure because the TMS without circulatory failure showed exactly the same result.

The present study has limitations. The study consisted of a retrospectively collected group of patients although the selection criteria were fixed *a priori*. The strength of the study is that the reconstruction of the hemodynamic profiles is precise, because all continuously measured variables are stored as 2-min median values in the computerised data management system. The patients we studied were selected from all consecutive admitted emergency patients who were treated in our ICU during a 1-year period. Hyperlactatemia can also result from confounding factors. Sympathomimetic medication can cause lactate elevations [20]. None of our patients had epinephrine infusion. None of the patients had proven severe liver failure but one patient had a pre-existing fat liver. One patient had a 4-hour dialysis and his metabolic acidosis was corrected during the first 24 hours of ICU care. Four patients had diabetes.

In conclusion, during the first 24 hours after admission, only the mean arterial pressure was associated with the resolution of acute tissue perfusion failure. The mean arterial pressure at 24 hours was higher in responders than in nonresponders. Successful resuscitation of tissue perfusion failure was associated with less severe MOF. The TMS score reflects well the development of MOF, and the time pattern of the TMS score is associated with overall mortality.

Key messages

- Except for mean arterial pressure at 24 hours, successful resuscitation of ACF is not associated with any invasively derived hemodynamic profile
- Successful resuscitation of ACF is associated with less severe organ failure as assessed by TMS scores and with lower mortality
- Late worsening of MOF as described by late TMS-score accumulation is associated with high mortality

Competing interests

None declared.

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