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When to stop septic shock resuscitation: clues from a dynamic perfusion monitoring

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Abstract

Background: The decision of when to stop septic shock resuscitation is a critical but yet a relatively unexplored aspect of care. This is especially relevant since the risks of over-resuscitation with fluid overload or inotropes have been highlighted in recent years. A recent guideline has proposed normalization of central venous oxygen saturation and/or lactate as therapeutic end-points, assuming that these variables are equivalent or interchangeable. However, since the physiological determinants of both are totally different, it is legitimate to challenge the rationale of this proposal. We designed this study to gain more insights into the most appropriate resuscitation goal from a dynamic point of view. Our objective was to compare the normalization rates of these and other potential perfusion-related targets in a cohort of septic shock survivors.

Methods: We designed a prospective, observational clinical study. One hundred and four septic shock patients with hyperlactatemia were included and followed until hospital discharge. The 84 hospital-survivors were kept for final analysis. A multimodal perfusion assessment was performed at baseline, 2, 6, and 24 h of ICU treatment.

Results: Some variables such as central venous oxygen saturation, central venous-arterial pCO_2 gradient, and capillary refill time were already normal in more than 70% of survivors at 6 h. Lactate presented a much slower normalization rate decreasing significantly at 6 h compared to that of baseline (4.0 [3.0 to 4.9] vs. 2.7 [2.2 to 3.9] mmol/L; $p < 0.01$) but with only 52% of patients achieving normality at 24 h. Sublingual microcirculatory variables exhibited the slowest recovery rate with persistent derangements still present in almost 80% of patients at 24 h.

Conclusions: Perfusion-related variables exhibit very different normalization rates in septic shock survivors, most of them exhibiting a biphasic response with an initial rapid improvement, followed by a much slower trend thereafter. This fact should be taken into account to determine the most appropriate criteria to stop resuscitation opportunely and avoid the risk of over-resuscitation.

Keywords: Septic shock; Perfusion; Resuscitation; Lactate; Microcirculation

Background

Several clinical studies have demonstrated that persistent impairment of perfusion-related physiological variables is associated with increased mortality in septic shock patients [1-3]. Therefore, current guidelines recommend normalization of relevant physiologic variables such as lactate and/or central venous oxygen saturation ($ScvO_2$) as resuscitation goals, basically through oxygen transport (DO_2) optimization [4,5]. In addition, peripheral perfusion, central venous-arterial pCO_2 gradient ($P(cv\text{-}a)CO_2$), and microcirculatory abnormalities have also been linked to morbidity or mortality and suggested as potential complementary targets [6-8].

However, the issue of when to stop resuscitation has become more relevant in recent years as the risks of over-resuscitation have also been increasingly highlighted. In fact, pursuing complete normalization of all potential perfusion-related goals with repeated attempts to increase DO_2 could eventually result in severe adverse effects such as fluid overload, pulmonary edema, intra-abdominal

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hypertension, cardiac arrhythmias, and myocardial ischemia, thus possibly increasing morbidity and mortality [9-11].

From a physiological point of view, the problem is far more complex. For instance, it is not known if all perfusion-related variables are equally sensitive to DO_2 optimization [12], a factor that could critically influence their specific normalization rates. Besides, parameters traditionally considered as reflecting tissue perfusion like lactate are also mechanistically determined by non-flow dependent or mixed mechanisms [13]. This may result in a wide variability on individual recovery time courses after optimization of DO_2 depending on the predominant pathogenic mechanism. The practical aspect is that if a more likely flow-dependent parameter is selected as a goal (such as $P(cv\text{-}a)CO_2$ or $ScvO_2$), it may normalize earlier than a less flow-dependent one such as lactate. In other words, from a theoretical point of view, the resuscitation length could vary dramatically depending on these considerations leading eventually to the risk of over-resuscitation if the selected goal exhibits an intrinsic slow normalization rate.

To address this subject, we designed a prospective study to evaluate the specific normalization rates of several perfusion-related variables in a cohort of consecutive septic shock patients subjected to protocolized resuscitation and multimodal perfusion assessment. We *a priori* decided to include only ultimately hospital-surviving patients for analysis to provide a relevance perspective to persistent abnormalities after initial resuscitation.

Methods

Setting

We conducted a prospective observational study from July 2011 to November 2012 in a mixed 16-bed ICU at our university hospital. The institutional review board of our university approved this study and waived the need of an informed consent because of the observational nature of the study (Comité de Etica en Investigación, Facultad de Medicina, Pontificia Universidad Católica de Chile; approval number 11-113).

Patient selection

We included all consecutive adult patients admitted to the ICU with septic shock diagnosis according to the 2001 consensus definition [14], with a basal arterial lactate >2 mmol/L and full commitment for resuscitation.

Protocol and measurements

Patients were studied for the first 24 h following initiation of ICU-based resuscitation and were followed until death or hospital discharge. Clinical and demographic data and severity scores [15,16] were collected for each patient at baseline (at inclusion = 0 h).

The following measurements as part of a multimodal perfusion assessment were obtained at baseline and at 2, 6, and 24 h after starting ICU resuscitation:

1. Macro-hemodynamic variables: mean arterial pressure (MAP), heart rate, norepinephrine (NE) or vasoactive drug doses, central venous pressure (CVP), pulse pressure variation (%), and pulmonary artery catheter-derived values (when in place). Fluid administration was also registered at each predefined time-point.
2. Metabolic-related perfusion variables: $ScvO_2$, arterial lactate and $P(cv\text{-}a)CO_2$.
3. Peripheral perfusion was assessed with the capillary refill time (CRT) (normal values ≤4.0 s) [17].

In a subgroup of patients who arrived within the first 2 h of onset of septic shock and were already in mechanical ventilation, we performed also the following microcirculatory and micro-oxygenation assessments:

1. Thenar muscle oxygen saturation (StO_2) was measured by a tissue spectrometer (InSpectra Model 650, Hutchinson Technology, Minneapolis, MN, USA) [18]. A value ≥75% was considered as normal for this protocol. A vascular occlusion test (VOT) was performed as described elsewhere [19]. During the reperfusion phase of the VOT, the recovery slope of the StO_2 signal was registered and calculated with a software (InSpectra V3-03, Hutchinson Technology, MN, USA) and expressed in percentage per second (values >3.5%/s were considered as normal for this study based on our own data in healthy volunteers (data not shown)).
2. Microcirculatory-derived variables: sublingual microcirculation was assessed with sidestream dark field video microscopy imaging (Microscan® for NTSC, MicroVision Medical, Amsterdam, the Netherlands). Image acquisition and analysis were performed following recent recommendations of a consensus conference [20]. A trained independent investigator performed image analysis in all cases, and these data were not disclosed to the attending physicians or considered for management. Parameters considered for this study were proportion of perfused vessels (PPV; values ≥90% were considered as normal); perfused vessel density (PVD; values ≥14 n/mm were considered as normal); and microcirculatory flow index (MFI; values ≥2.5 were considered as normal).

All patients were managed according to a local algorithm [21] aimed at macrohemodynamic stabilization and improvement of hypoperfusion abnormalities (both

$ScvO_2$ and lactate) during the first 24 h following implementation of adequate maneuvers for source control. The main strategy to improve oxygen transport/oxygen consumption unbalance was preload optimization. For this purpose, the algorithm included early fluid loading, followed by NE as needed to maintain a MAP >65 mmHg. Further fluid resuscitation was guided by dynamic predictors (pulse pressure variation) in patients under mechanical ventilation, except in patients with atrial fibrillation [22]. To assess pulse pressure variation in patients with acute respiratory distress syndrome, we transiently increased tidal volume to 8 mL/kg. A pulmonary artery catheter was placed in patients with high NE requirements (>0.3 mcg/kg/min) or past medical history of cardiac disease. In patients with atrial fibrillation and with a pulmonary artery catheter in place, volume administration was guided by a Starling curve approach in which progressive fluid boluses were administered until reaching a plateau in cardiac index. In patients with spontaneous breathing, fluid resuscitation was guided by central venous pressure criteria as suggested by current guidelines [4]. Dobutamine was restricted to patients with cardiac index <2.2 L/min/m^2 in whom attending physicians had ruled-out hypovolemia as the cause of persistent hypoperfusion. Arterial hemoglobin oxygen saturation was maintained at >90%, and hemoglobin concentrations at 8 g/dl or higher to optimize arterial oxygen content. Mechanical ventilation settings were adjusted according to current recommendations [4]. Intra-abdominal pressure was monitored and treated according to recent recommendations [23].

Statistical analysis

Categorical data were analyzed with chi-square or Fisher's exact test when appropriate. Repeated measures were analyzed with Friedman test with Bonferroni post-hoc correction. All data are presented as medians and 25 to 75 interquartile ranges. We performed trend estimations of different perfusion and microcirculatory variables computing the average ranks for each variable using Pearson's correlation coefficient as described by Cuzick [24]. We also performed a normalization procedure for lactate, P(cv-a)CO_2, and CRT values to rescaling them in order to allow comparison of these parameters' relative changes in specific time periods. For each variable, the highest normal value was taken, and each individual value was divided by it. Hence, medians and interquartile ranges were plotted. Fractional polynomials analyses were done to model realistic fitting curves for each parameter trend. All reported p values are two-sided, with a significant alpha level at 5%. SPSS 17 (SPSS Inc., Chicago, IL, USA) and Stata 12 (StataCorp LP, College Station, TX, USA) statistical packages were used for analyses.

Results

One hundred and four patients were admitted with a diagnosis of septic shock during the 18-month period, with a hospital mortality of 19% ($N = 20$).

Within this group, 84 were discharged alive from the hospital and constitute our definitive study group. Thus, data regarding non-survivors were not considered for final analysis and are only provided in Additional file 1: Table S1. Basal demographic, clinical, and physiological data and severity scores of the whole population and the 84 survivors are provided in Table 1. The main septic sources were abdominal ($n = 45$), pulmonary ($n = 23$), urinary tract ($n = 8$), and others, including soft tissue and catheter sources ($n = 8$). Sixteen patients were admitted directly from the operating room.

Patients received 1,750 [640 to 2,400] mL of crystalloids in the pre-ICU setting after meeting septic shock criteria. The rate of fluid administration tended to decrease over time during ICU resuscitation. A total of 1,150 [600 to 1,600] mL of crystalloids were administered during the first 2 h, 980 [510 to 1,410] mL from 3 to 6 h, and 1,020 [290 to 2,400] mL from 7 to 24 h of ICU-based resuscitation. A pulmonary artery catheter was placed in 38 patients. Basal cardiac index and pulmonary arterial occlusion pressure were 3.1 [2.5 to 3.9] L/min/m^2 and 17 [12 to 23] mmHg, respectively. Dobutamine was used in ten patients. Basal and 24-h intra-abdominal pressures were 13 [9 to 17] and 13 [8 to 15] mmHg, respectively.

By definition, all patients started ICU-based resuscitation with an abnormal lactate as compared to only 8, 31, 32, and 39 patients with abnormal $ScvO_2$, StO_2, P(cv-a)CO_2, and CRT values, respectively. Medians values for individual macrohemodynamic and perfusion variables at different time-points in patients with abnormal values at baseline are shown in Table 2. Lactate decreased significantly from 0 to 6 h (4.0 [3.0 to 4.9] vs. 2.7 [2.2 to 3.9] mmol/L; $p < 0.01$).

When analyzing the time-trend changes of lactate, P(cv-a)CO_2, and CRT values, a biphasic curve could be drawn (Figure 1) where a rapid decrease in every variable during the first 6 h was followed by a slower decay thereafter.

Medians values for microcirculatory variables and the percentage of normalization for lactate, P(cv-a)CO_2, CRT, and microcirculatory variables at different time-points for the subgroup of patients arriving within the first 2 h of septic shock are shown in Table 3 and Figure 2, respectively. In these patients, lactate levels dropped to normal in 52% of the patients at 24 h. During follow-up of the 40 remaining patients with persistent hyperlactatemia at 24 h, 24 normalized lactate at 48 h, ten at 72 h, and six up to the seventh day. In contrast, microcirculatory variables remained abnormal in the majority of the patients, even at

Table 1 General characteristics of the study population

Parameters	Total patients	Survivors without MC	Survivors with MC	*p* value between survivors
Number	104	53	31	
Age (years)	66 [56 to 75]	63 [52 to 71]	67 [56 to 76]	0.4
Male/female (%)	45/55	47/53	39/61	0.3
APACHE II	23 [19 to 26]	23 [18 to 27]	24 [19 to 27]	0.5
Basal SOFA	10 [8 to 13]	10 [8 to 13]	10 [8 to 13]	0.9
24 h SOFA	10 [7 to 12]	10 [7 to 12]	11 [10 to 13]	0.6
Length of hospital stay (days)	23 [15 to 35]	24 [16 to 36]	24 [15 to 43]	0.8
Length of ICU stay (days)	11 [7 to 17]	11 [7 to 25]	10 [7 to 16]	0.5
MV duration (days)	8 [5 to 15]	9 [5 to 15]	8 [5 to 14]	0.4
Basal NE requirements (mcg/kg/min)	0.11 [0.03 to 0.30]	0.10 [0.04 to 0.28]	0.16 [0.03 to 0.34]	0.4
Basal lactate (mmol/L)	4.0 [3.0 to 4.9]	4.2 [3.0 to 5.3]	4.0 [2.8 to 4.9]	0.9

Values are expressed as median [interquartile range] or percentage. MC, microcirculatory assessment; APACHE II, acute physiology and chronic health evaluation II; SOFA, sequential organ failure assessment; ICU, intensive care unit; MV, mechanical ventilation; NE, norepinephrine.

24 h (Figure 2). No difference in SOFA scores (9 [7 to 11] vs. 11 [8 to 15]; $p = 0.2$) or NE requirements (0.01 [0 to 0.04] vs. 0.17 [0 to 0.24]; $p = 0.16$) was observed between patients that had normalized lactate or not at 24 h.

Discussion

Perfusion-related variables exhibit markedly different normalization rates in septic shock survivors, most of them exhibiting a biphasic response with an initial rapid improvement, followed by a much slower trend thereafter. This fact should be taken into account to determine the most appropriate criteria to stop resuscitation opportunely and avoid the risk of over-resuscitation.

Central venous oxygen saturation, P(cv-a) CO_2, and CRT values were already normal in the majority of patients at ICU admission after some previous volume loading, and it appears that these variables are particularly responsive to DO_2 increasing maneuvers. In a previous study, $ScvO_2$, increased from 49% to 77% in septic shock patients subjected to early aggressive DO_2 optimization [3]. The sensitivity of $ScvO_2$ to pre-ICU fluid loading probably explains the almost negligible incidence of low $ScvO_2$ values in the ICU setting [25,26]. CRT may also improve rapidly after fluid resuscitation, and we found that normality of CRT values increased from 46% to 70% after 2 h of resuscitation. Changes in $ScvO_2$, P(cv-a) CO_2, and CRT appeared to become slower after 6 h, eventually representing the influence of non-flow dependent mechanisms on the remaining abnormalities [6,27,28].

The case of hyperlactatemia is paradigmatic. Although tissue hypoperfusion has been traditionally considered

Table 2 Evolution of different perfusion and hemodynamic parameters in a cohort of 84 hospital survivors

Perfusion parameters	Number of patients with altered baseline values	Baseline	2 h	6 h	24 h	*p* value[a]
Lactate (mmol/L)	84	4.0 [3.0 to 4.9]	3.4 [2.4 to 4.2]	2.8 [2.0 to 3.8]	1.8 [1.4 to 2.5]	<0.001
P(cv-a)CO_2 (mmHg)	34	8 [7 to 9]	6 [5 to 8]	5 [3 to 7]	4 [3 to 6]	<0.001
CRT (s)	43	6 [5 to 8]	4 [3 to 5]	3 [2 to 6]	2 [2 to 4]	0.001
$ScvO_2$ (%)	8	62 [58 to 67]	65 [60 to 69]	71 [70 to 74]	74 [70 to 79]	0.001
Hemodynamic parameters	**Number of patients assessed**	**Baseline**	**2 h**	**6 h**	**24 h**	***p* value[a]**
CI (L/min/m^2)	38	3.1 [2.5 to 3.9]	3.5 [2.9 to 4.6]	3.2 [2.6 to 3.8]	2.8 [2.4 to 4.1]	NS
Pulse pressure variation (%)	63	6 [3 to 8]	5 [2 to 8]	6 [2 to 8]	5 [4 to 9]	NS
CVP (mmHg)	84	13 [9 to 17]	14 [10 to 16]	14 [10 to 16]	14 [11 to 17]	NS
MAP (mm Hg)	84	73 [67 to 79]	71 [68 to 74]	71 [68 to 74]	72 [70 to 77]	NS
NE dose (mcg/kg/min)	84	0.11 [0.04 to 0.3]	0.18 [0.06 to 0.31]	0.17 [0.07 to 0.35]	0.05 [0 to 0.23]	NS
IAP (mmHg)	72	12 [9 to 15]	11 [9 to 13]	12 [9 to 12]	11 [8 to 14]	NS

Values are expressed as median [interquartile range]. [a]Comparison within group of variables was made with non-parametric trend. p(cv-a)CO_2, central venous to arterial pCO_2 gradient; CRT, capillary refill time; $ScvO_2$, central venous oxygen saturation; CI, cardiac index; CVP, central venous pressure; MAP, mean arterial pressure; NE, norepinephrine; IAP, intra-abdominal pressure.

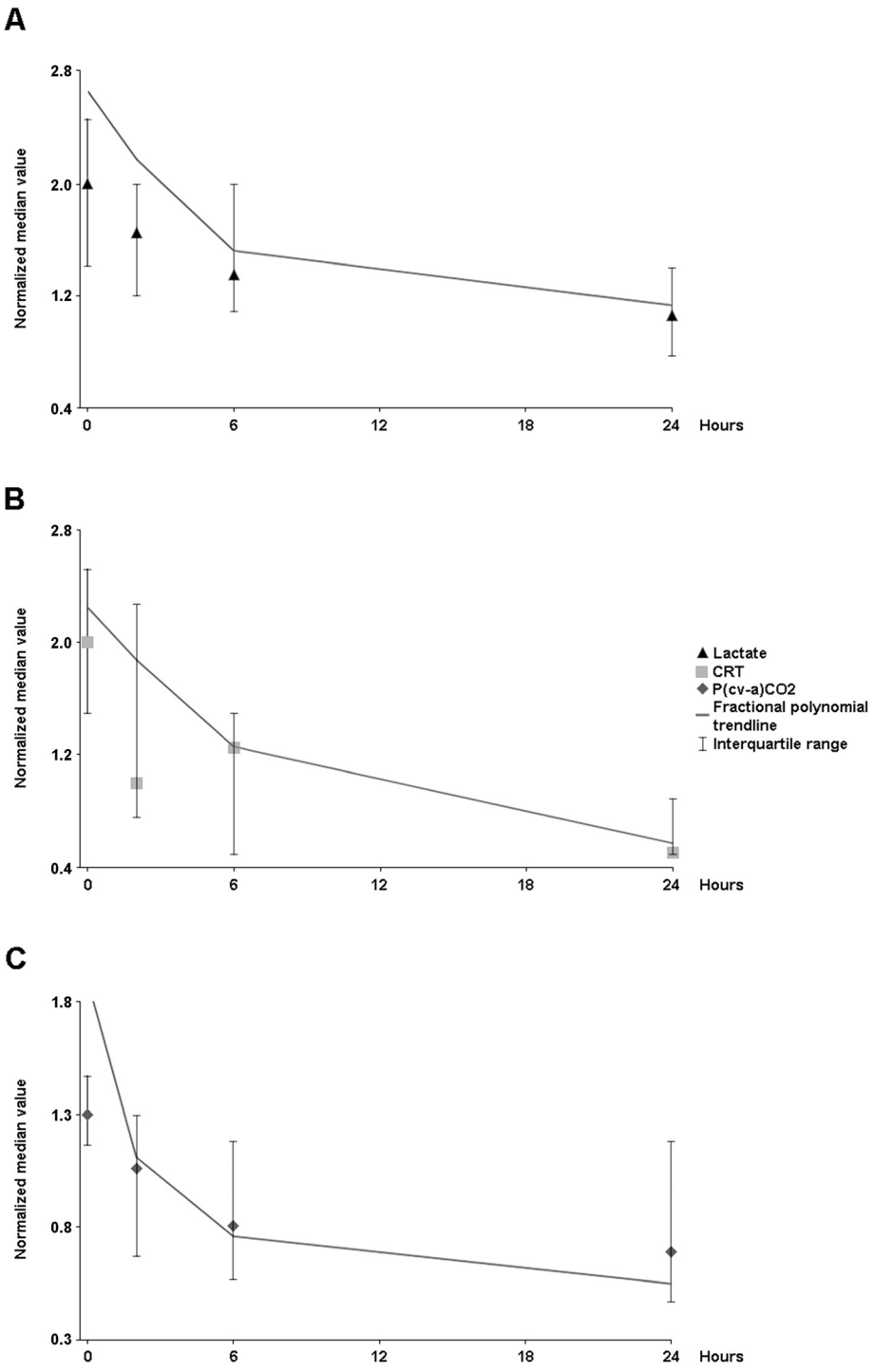

Figure 1 Time-trend changes for selected perfusion parameters after normalization showing a biphasic recovery trend (see statistical analysis): A, ***lactate;*** **B,** ***capillary refill time (CRT);*** **C,** ***central venous-arterial*** pCO_2 ***gradient (P(cv-a)*** CO_2**).**

the most common cause of hyperlactatemia, there is increasing evidence for concomitant non-hypoxic and thus, non-flow dependent mechanisms [28,29] that may influence the time course of lactate recovery rate. The distinction between these two scenarios (flow-responsive vs. non-flow dependent hyperlactatemia) should strongly impact the therapeutic approach [13].

As an example, treatment of the latter with sustained efforts aimed at increasing DO_2 could lead to detrimental effects of excessive fluids or inotropes. In our study,

Table 3 Evolution of microcirculatory parameters in a cohort of 31 hospital survivors

Perfusion parameters	Number of patients with altered baseline values	Baseline	2 h	6 h	24 h	*p* value[a]
PPV (%)	30	69 [62 to 75]	70 [68 to 78]	71 [67 to 79]	77 [68 to 83]	0.04
MFI (score)	28	1.9 [1.5 to 2.2]	2.0 [1.6 to 2.2]	2.1 [1.8 to 2.3]	2.2 [2.0 to 2.5]	0.003
StO_2 (%)	8	72 [65 to 74]	73.5 [71 to 76]	75.5 [69 to 84]	77 [68 to 85]	NS
StO_2 recovery slope (%/s)	23	1.72 [0.6 to 2.0]	1.76 [0.7 to 2.7]	1.70 [1.2 to 2.8]	2.0 [1.6 to 3.1]	0.055

Values are expressed as median [interquartile range]. [a]Comparison within group of variables was made with non-parametric trend. PPV, proportion of perfused vessels; MFI, microcirculatory flow index; PVD, perfused vessel density; StO_2, tissue oxygen saturation.

lactate exhibited a significant decrease of almost 50% of basal median values during the first 6 h of resuscitation associated with a rapid normalization of other metabolic and peripheral perfusion parameters (Figure 1). However, further decrease in lactate was very slow since lactate of 48% of patients was normalized beyond the first ICU day. This behavior may raise a doubt whether these patients would have benefited from more volume loading. Nevertheless, as negative dynamic predictors or a plateau Starling curve discarded further fluid responsiveness, we had no objective evidence that persistent hyperlactatemia could be addressed to ongoing flow dependent mechanisms. Thus, it appears that lactate decrease can be characterized by a biphasic evolution: an early rapid response followed by a later slower recovery trend potentially explained by non-flow dependent mechanisms. Indeed, a recently published therapeutic algorithm focused lactate-driven resuscitation exclusively in the first 8 h of ICU management with a significant favorable impact on outcome [30].

In the present study, sublingual microcirculatory variables exhibited the slowest recovery rate. Moreover, since concomitant clinical and metabolic perfusion variables were already normal in the great majority of our patients, it appears as highly unlikely that persistent microcirculatory abnormalities may respond to additional fluids or DO_2 optimization maneuvers after 24 h of resuscitation. In fact, fluid loading after 48 h of sepsis failed to improve microcirculatory derangements in a recent report [31]. The time-course of microcirculatory recovery during septic shock resuscitation may also follow a biphasic pattern with an early apparently flow-responsive phase [32,33]. However, further improvements appear to be much slower with full recovery taking several days [8,34]. The recovery slope of StO_2 after a VOT maneuver was moderately abnormal in all patients, and like microcirculatory derangements, it

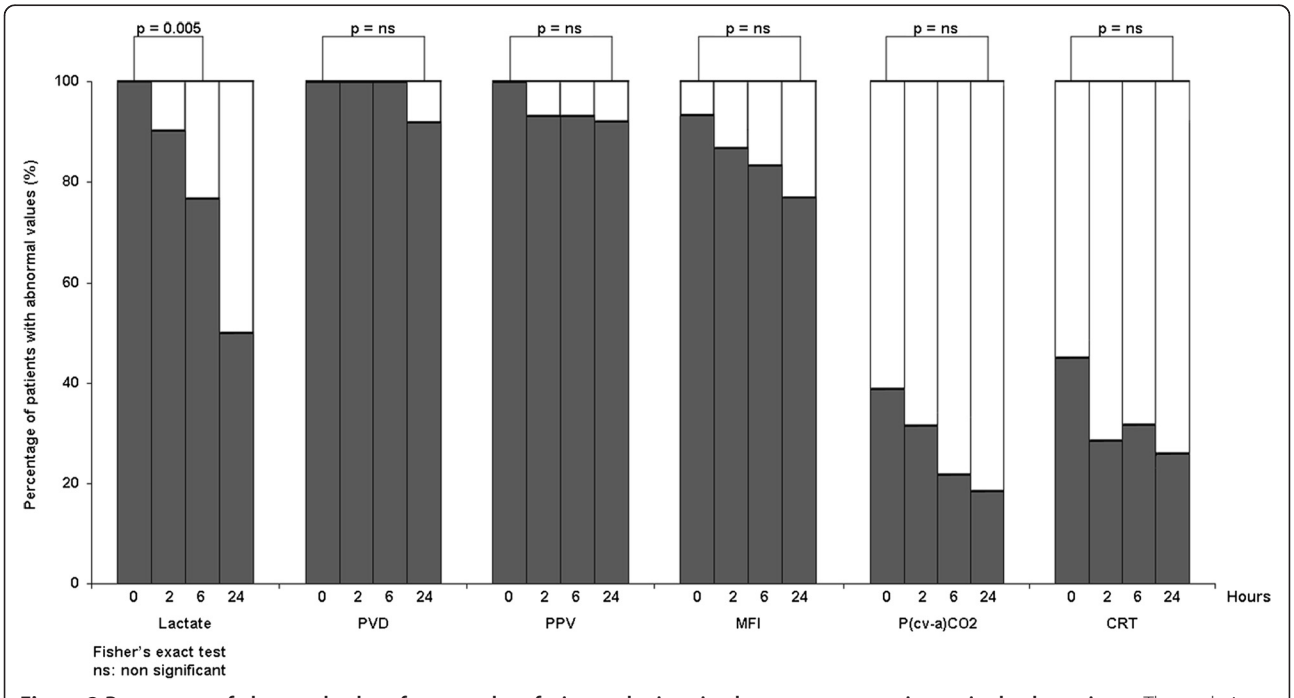

Figure 2 Percentage of abnormal values for several perfusion and microcirculatory parameters in septic shock survivors. The evolution of these parameters at different time-points during the first 24 h of intensive care unit-based resuscitation is presented. PVD, perfused vessel density; PPV, proportion of perfused vessels; MFI, microvascular flow index; P(cv-a)CO_2, central venous-arterial pCO_2 gradient; CRT, capillary refill time.

showed a very slow recovery trend without significant improvement at 24 h. Taken together, our current and previous data suggest that persistent microcirculatory abnormalities after 24 h of resuscitation may represent different pathogenic mechanisms not responsive to DO_2 increasing maneuvers.

How can we conceptualize our results? The critical decision to stop resuscitation is complex and should probably be taken after a multimodal perfusion assessment has been performed. The normalization of some variables such as $ScvO_2$, lactate, or CRT is clearly a good signal, but eventually their normalization trend is more important than absolute values at certain periods. In practical terms, resuscitation would have been stopped at admission in 90% of these patients by using the single criterion of a normal $ScvO_2$ but only in 52% of patients at 24 h by using a normal lactate criterion. Our study was not designed to establish which criterion is better, but it does suggest that the length of septic shock resuscitation may vary dramatically depending on the selected perfusion goal and that the different potential targets are not equivalent or interchangeable as suggested by a recent guideline [4]. Since ours is only a hypothesis-generating study, these findings should be explored and confirmed in future studies, since as mentioned before an excess in resuscitation efforts may lead to severe side effects.

Finally, due to the complexity of the pathogenic mechanisms influencing each of the perfusion variables, and of their dynamic characteristics, it is clear that treatment of septic shock may also be guided by the presence of comorbidities, adequacy of source control, and the degree of systemic inflammation, among others.

We acknowledge several potential limitations of our study. This cohort exhibited a low mortality rate. Therefore, our findings may not be universally extrapolated. However, several recent studies report a mortality of around 20% in septic shock patients undergoing early resuscitation, especially when the main source is abdominal [35-37]. Second, the study period may be considered not long enough and the selected time points are arbitrary. Third, this is a single center study that limits its application to other settings and centers. Fourth, due to the design of this study, we cannot determine if changes in perfusion variables over time can be ascribed to the natural evolution of disease or to the effects of some specific treatment. Fifth, although our findings suggest that the length of the resuscitation process could vary dramatically according to the selected perfusion goal, we do not know if this effectively leads to over-resuscitation in some cases since our study was not designed to establish this point. Finally, since only surviving patients compose our cohort, we know that the main endpoint of any septic shock resuscitation strategy was successfully achieved. However, we do not know if additional resuscitation could have further reduced morbidity. Nevertheless, the lack of difference in 24-h SOFA scores or NE requirements between patients who normalized lactate vs. those who did not makes this possibility unlikely. Furthermore, as dynamic predictors of fluid responsiveness were persistently negative, there is no evidence that additional resuscitation could have benefited secondary outcomes, especially considering controversial data concerning other potential therapies such as dobutamine or nitroglycerine [38,39].

Conclusions

In conclusion, these results demonstrate that perfusion-related variables exhibit markedly different normalization rates in septic shock survivors, most of them showing a biphasic response with an initial rapid improvement, followed by a much slower trend thereafter. The length of septic shock resuscitation may vary dramatically depending on the selected perfusion goal. This fact should be taken into account to determine the most appropriate criteria to stop resuscitation opportunely and avoid the risk of over-resuscitation.

Additional file

Additional file 1: Table S1. Hemodynamic and perfusion-related parameters in 20 non-survivors.

Abbreviations

APACHE: Acute physiology and chronic health evaluation; CVP: central venous pressure; CRT: capillary refill time; DO_2: oxygen transport; IAP: intra-abdominal pressure; ICU: intensive care unit; MAP: mean arterial pressure; MFI: microcirculatory flow index; NE: norepinephrine; NIRS: near-infrared spectroscopy; $P(v\text{-}a)CO_2$: mixed venous to arterial pCO_2 gradient; PPV: proportion of perfused vessels; PVD: perfused vascular density; SOFA: Sequential Organ Failure Assessment; $ScvO_2$: central venous oxygen saturation; StO_2: tissue oxygen saturation; SvO_2: mixed venous oxygen saturation; VOT: vascular occlusion test.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

GH, CL, and AB conceived the study, participated in its design and coordination, and helped to draft the manuscript. JB, CI, GF, and GO conceived the study and helped to draft the manuscript. RC helped to draft the manuscript and performed statistical analyses. EK maintained the database, performed statistical analyses, and designed tables and figures. AF registered and analyzed microcirculatory images. CR recruited and followed up patients. TR recruited and followed up patients. All authors read and approved the final manuscript.

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Additional file 1: Table S1 Hemodynamic and perfusion-related parameters in 20 non-survivors

Parameter	0 h	2 h	6 h	24 h
Lactate (mmol/L)	3.0 [2.4-15.1]	2.9 [1.8-14.9]	3.1 [1.8-13.1]	2.7 [1.9-12.3]
NE dose (mcg/kg/min)	0.19 [0.07-0.52]	0.18 [0.07 -0.52]	0.25 [0.04 – 0.71]	0.45 [0.06 – 0.82]
P(cv-a)CO_2 (mmHg)	4 [2-6]	3 [1-4]	4 [1-20]	5 [0-11]
$ScvO_2$ (%)	77 [75-88]	82 [79-90]	82 [78-91]	81 [75-91]
CRT (s)	4 [2-6]	3 [2-6]	4 [2-5]	2 [2-2]

Values expressed as Median [interquartile range].
NE, norepinephrine; p(cv-a)CO_2, central venous to arterial pCO_2 gradient, $ScvO_2$, central venous oxygen saturation; CRT, capillary refill time.

THE ROLE OF LACTATE

AN INTERVIEW WITH PROFESSOR JAN BAKKER

Professor Jan Bakker is Professor of Medicine and Vice-chair of the Department of Intensive Care Adults at Erasmus Medical Centre in Rotterdam in the Netherlands. He is Visiting Professor at Columbia University - New York Presbyterian, U.S. and a Visiting Professor at the University Hospital Pontificia Catolica de Chile.

Can you explain the significance of lactate monitoring in critically ill patients and what it means in practice for the intensivist?

From the very first description in 1843 increased lactate has been associated with dying patients or patients that go on to develop morbidity like organ failure. The initial level, the trend, the time it takes to decrease to normal levels have all been associated with mortality and morbidity as long as intensive care medicine has existed. When Max Harry Weil did his first studies in the 1960s he found that between 4 and 5 was associated with 50% mortality. When we looked a few years ago, we found this level was associated with 45% mortality. Over the last 40-50 years nothing has changed in the relationship between lactate level and mortality.

For intensivists, the question is firstly, if I have this problem of high or non-decreasing lactate, what should I do? Secondly, if I could change it will my patient benefit? There have been few studies addressing this topic. The Pölönen study showed that there was less morbidity when they chased lactate levels to remain normal or be normal as soon as possible (Pölönen 2000). Our multicentre study accepted that increased lactate is not a good sign, especially in the early phase (8 hours) of ICU admission (Jansen et al. 2010). In this phase there is more likely a haemodynamic cause of increased lactate, so low perfusion, low tissue saturation/perfusion, whatever you want to call it, there is a time window where optimisation of the circulation should lead to a decrease in lactate. We tested how to get adequate tissue oxygenation. I think it's the only study ever that incorporated oxygen demand and oxygen delivery into a resuscitation protocol. We said if you want to optimise tissue oxygenation and do something about the need for oxygen and the amount of oxygen going to the tissues, do this very aggressively for maximum 8 hours and then the goal should be to decrease lactate rapidly. What's a significant amount of lactate decrease? About 10% an hour. We measured every two hours. You've done all your stuff and everything seems ok, but your lactate is not coming down, then what? That's a question that's never been addressed in critical care. That could be microcirculatory dysfunction, maldistribution of blood flow in the tissue, so mandatory in the protocol was the use of a vasodilator. With this array of interventions, we showed a risk reduction in mortality by 20%, but to our surprise, there was no effect on lactate at all. In the control group they didn't know lactate for 8 hours, just the first level in order to randomise the patient. In the protocol group every two hours they got a signal, but the actual decrease in lactate was exactly the same. Without knowing the lactate level, it decreased to a similar amount in the control group, despite the fact that the absolute mortality was almost 20% higher [it was absolute 10% difference and relative 20% difference] in this group. The only explanation we could find was that if the lactate was in the very high levels (5-10), if you compare the groups there was about a 30% absolute difference in mortality.

We speculated that especially in this group of patients with very high lactate levels if you don't know the lactate when the patient comes in, then you have no clue what you're doing, because you don't get the signal that you are doing the right stuff, e.g. stop giving fluids or dobutamine. In the lactate group you have the signal that this is going the right way - it was 10 now it's 6, then it's 4, and the patient is improving. This signal was completely lacking in the control group, so we think that this contributed to the difference in mortality. In the post-hoc analysis, we found that the real decrease in lactate occurred in the first two hours of resuscitation not in the first eight hours. Also not studied yet is what the lactate that is not decreasing tells you.

In most patients, lactate is a marker of disease and adequacy of resuscitation, where we have doubt what the specific place is of the circulatory optimisation in lactate. We think there is absolutely a signal that your circulation is inadequate, but it's probably in the very first hours. We just submitted a study with Glenn Hernandez from Chile, where we looked at the bi-phasic change in lactate. I think there is a bi-phasal change, so that very early it drops dramatically, and then it trends down a little. We have an indication in the study we just finished that this indeed is present, but the interval of measurements was very large, so it's a bit difficult, so the first significant rapid drop is circulation, and the next is metabolism. This is optimisation of the balance between oxygen demand and oxygen delivery and the rest is marker of disease.
Lactate is not an easy parameter, it's a

mixed bag of signals. I always say to my residents, "Lactate means trouble." You have to go to the bedside and find out what the message is.

Do you think we have enough data from RCTs to answer the question you have posed on the routine use of lactate as a resuscitation endpoint?

I don't think there is convincing evidence that decreasing lactate levels should be a target of therapy in ICU patients. When lactate is decreasing, that is a good signal, but when lactate is not decreasing, whether you should then optimise or more aggressively treat the circulation I don't think there is enough evidence. Especially we lack evidence for when should we stop 'chasing the circulation' and look at lactate as a marker of metabolism, a marker of something wrong with the patient, but which won't be fixed by giving fluids or dobutamine or whatever. A recent dramatic case we had was a patient with severe septic shock, due to melioidosis, he was on ECMO (extracorporeal membrane oxygenation), and he had a lactate of 12 for three days. His circulation was optimal, as far as we could optimise his circulation, but due to the severe disease and the diffuse intervascular coagulation, his hypermetabolism, he had very high lactate levels, but it came down after three days. He made an uneventful recovery and went home, without any macro organ failure. He was on renal replacement therapy and he was off when he left the ICU. In that particular case it was a marker of disease at very high levels but couldn't have been fixed by circulatory management.

You have suggested that we need to define the correct context for use of fluids for brain injury, sepsis, haemorrhage etc. Could you expand on this?

There is an incredible amount of evidence that HES products have negative effects on a large proportion of ICU patients, in, for instance, renal function. We use a lot of HES products in our brain injury patients to lower intra-cranial pressure. In our study on a marker of kidney injury (de Geus et al. 2011) in almost 800 critically ill patients. there were around 30 patients with isolated brain injury, but none developed renal failure, despite our use of HES products.

Asking why we should use something where we have not shown that the patient will benefit is very valid. But crystalloids in brain oedema are risky. In the context in which you use these HES products, for example colloids are frequently used in surgery and they all improve outcome, maybe the signal is too weak in this population. If you have a huge outcome difference, then some harm is not bad. The context question is good, because basically we do not understand why HES products 'kill' your kidney. I could stop using it, but then let's research the adequate context, or the mechanism of harm in order to understand why we should not use HES products. It's important to know the possible side effects and before we introduce something new to do adequate studies on what's the mechanism of action and what's the safety issue. That's a day-to-day problem in the current ICU, because we have no definitive clues about the endpoint of resuscitation. Fluid unresponsiveness is a strange endpoint of resuscitation, because we are all fluid responsive. Fluid unresponsiveness by definition means the patient is fluid overload. What amount of stroke volume variation is safe, we don't know, we only know when you are not fluid responsive any more you are very unlikely to be hypovolemic. We don't know when it's going to harm you. What's a clinical problem that's going to be solved with fluids is one. If you have a clinical problem that's going to be solved, should you drive for fluid unresponsiveness? We don't know.

Our study in Critical Care Medicine on sepsis vs tamponade, lowering cardiac output to the same amount in both models, then resuscitating the animals clearly showed you needed more fluids and a higher cardiac output to resuscitate the septic microcirculation. However, in a study we just submitted with Glenn Hernandez we showed that the microcirculation may not be an adequate endpoint of survival. Non-survivors to a large extent have abnormal microcirculation so I wonder about the endpoint. To what point should we resuscitate with fluids? In order to risk assess fluid responsiveness, what is hypovolaemia, I have no clue what hypovolaemia is. There's much more to gain, because that's what we do daily on our patients.

An important problem during the night in many ICUs: many patients are treated with fluid because their blood pressure drops when they sleep (I hope mine does when I sleep!), so probably that is normal physiology that doesn't require fluids. When do we need an increase in cardiac output brought about by fluids? We don't really know, we have no clear answers.

> *"Lactate is not an easy parameter, it's a mixed bag of signals"*

What do you see as challenges for critical care in the Netherlands?

The challenge will be to develop our specialty into a primary specialty like anesthesiology, internal medicine etc., and not be a subspecialty of anaesthesiology. That will be extremely hard, because everyone is fighting to keep their territory. Especially for anaesthesiology, it's a good variation of their daily routine to mix between OR and ICU. There are various reasons other then money to keep intensive care in the 'wrong' specialty. I don't think it will happen in the next 10 years in the Netherlands, although I would like it to.

Also, it's very difficult to translate research results from other countries into practice. We are very restrictive in the patients we admit, and there has to be a clear benefit for ICU admission. It's very different in the U.S. and the South of Europe and difficult to translate results. I would favour physiologic, mech-

anistic studies because that data is the same as in the Netherlands. Now we focus on fixing the patient more in a surgical type of way - you have a tumour, we get it out, you're fixed, you have hypotension, we give you volume and drugs, now it's fixed. When you turn it around to ask why the patient has hypotension, what is adequate blood pressure, go from there, then recovery is the result and not the goal. That's a completely new area of research.

What research are you working on currently?

I am still pursuing lactate, looking at where it's coming from, why is there lactate, why is it not coming down, what is the role of the liver, and the liver perfusion in lactate.

In ethics I'm interested in end-of-life care, futile/ disproportionate care, these difficult terms that are used interchangeably. The differences between the U.S. and Netherlands systems are clear. My U.S. colleagues are not allowed to do much without family consent. They have to keep patients alive when there is no chance of reasonable recovery. I'm interested in the financial and economic aspects. It's very difficult to study, to compare these two different moral/ ethical systems. My sense is that it costs an enormous amount of money. We argue about what an added Quality Adjusted Life Year (QALY) costs, but we never discuss what futility may cost. In the Netherlands the intensivist cannot be forced to continue care, if he thinks it's inappropriate. By law you have to stop treatment that doesn't make any sense. We are liable if we go on with treatment and the family changes their mind. That's to do with communication, informing (we do not ask for permission in the Netherlands!) the family to stop life support and continue to comfort care and explain what will happen. I would love to study something like that, but it's tricky.

> *"It's very difficult to translate research results from other countries into practice"*

You've written about the ethics of using data from patients who die before consent was given. Can you comment about this?

We convinced our ethics committee that if you're running a resuscitation study, you cannot allow patients or relatives to think for 24 hours whether to participate. They agreed we could start the study, then ask permission and, when the patient survives, ask again. We found that if the patient dies in the middle of the night, and the family left, it's difficult and maybe even unethical to contact them. We asked the committee about the data we had without consent, and the committee said we couldn't use it, as it's unethical. We explained that this would introduce bias, as the sickest patients die in the early hours of admission. If we remove the sickest patients from our study, we could end up in a negative study, when it should be positive. So we went to the national ethics committee, which took another approach. There is a file of data that you gathered ethically, as you had permission from the ethics committee. The data no longer belong to the patient, because he's dead. There is no law in the Netherlands to say these data automatically transfer to the relatives. The data is from the hospital. As long as you anonymise the data, you can do what you want with the data from that patient. Problem solved.

This interview will be in our Winter issue, which has a cover story on severe pulmonary infections. What do you see as the challenges of these?

In the Netherlands we have a debate with authorities and insurance companies over the use of extracorporeal membrane oxygenation (ECMO). It's extremely easy to use ECMO to solve the problem of oxygenation or hypercarbia or a combination. There are very scarce data that this is really good or should be a regular intervention in patients with pulmonary failure. If you are young, have H1N1 it works fine, because you know it's a transient disease and if there's not a lot of lung destruction then it's ok, but what about immune system diseases such as Lupus, Wegener's disease, necrotising diseases that destroy the lung, should they be on ECMO, if so, how long to try? We found that after 1-2 weeks, we doubted whether we should go on. Other centres go on for longer, a month to six weeks, then decide it hasn't worked. Should you go from ECMO to the waiting list for lung transplantation? We do it for patients with heart disease. Should we put in new lungs in a 26 year old with necrotising pneumoccal disease? The authorities are not interested to regulate, and would rather wait for guidelines from the national society. The insurance companies don't want to pay, saying there is no evidence. It's an expensive treatment, the incremental costs are significant. We found because you keep these lung patients alive much longer than before, they develop complications like fungi, candida infections in the lung that are very expensive to treat. It's a big question mark. Easy to do, so effective when you start, but you don't have a good endpoint, we don't have a good start point, so that's an open area of a new device looking for clear indications. ■

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