Early Lactate-Guided Therapy in Intensive Care Unit Patients

A Multicenter, Open-Label, Randomized Controlled Trial

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***Rationale*: It is unknown whether lactate monitoring aimed to decrease levels during initial treatment in critically ill patients improves outcome.**

***Objectives*: To assess the effect of lactate monitoring and resuscitation directed at decreasing lactate levels in intensive care unit (ICU) patients admitted with a lactate level of greater than or equal to 3.0 mEq/L.**

***Methods*: Patients were randomly allocated to two groups. In the lactate group, treatment was guided by lactate levels with the objective to decrease lactate by 20% or more per 2 hours for the initial 8 hours of ICU stay. In the control group, the treatment team had no knowledge of lactate levels (except for the admission value) during this period. The primary outcome measure was hospital mortality.**

***Measurements and Main Results*: The lactate group received more fluids and vasodilators. However, there were no significant differences in lactate levels between the groups. In the intention-to-treat population (348 patients), hospital mortality in the control group was 43.5% (77/177) compared with 33.9% (58/171) in the lactate group ($P = 0.067$). When adjusted for predefined risk factors, hospital mortality was lower in the lactate group (hazard ratio, 0.61; 95% confidence interval, 0.43–0.87; $P = 0.006$). In the lactate group, Sequential Organ Failure Assessment scores were lower between 9 and 72 hours, inotropes could be stopped earlier, and patients could be weaned from mechanical ventilation and discharged from the ICU earlier.**

***Conclusions*: In patients with hyperlactatemia on ICU admission, lactate-guided therapy significantly reduced hospital mortality when adjusting for predefined risk factors. As this was consistent with important secondary endpoints, this study suggests that initial lactate monitoring has clinical benefit.**

Clinical trial registered with www.clinicaltrials.gov (NCT00270673).

Keywords: lactate; shock; central venous oxygenation; early goal directed therapy; oxygen delivery

AT A GLANCE COMMENTARY

Scientific Knowledge on the Subject

Increased blood lactate levels have been associated with significant morbidity and mortality. Nevertheless, it is unknown whether monitoring of lactate aimed to decrease levels during initial treatment in critically ill patients improves outcome.

What This Study Adds to the Field

In patients with hyperlactatemia on ICU admission, lactate monitoring followed by targeted treatment significantly reduced ICU length of stay. In addition, ICU and hospital mortality were reduced when adjusting for predefined risk factors. This study suggests that initial treatment aimed at reducing lactate levels has clinical benefit.

Increased blood lactate levels have been associated with significant morbidity and mortality ever since their first description in 1843 by Scherer (1). Many studies have emphasized the prognostic importance of either a single lactate level (2) or limited lactate reduction during treatment (3–5). Interestingly, the prognostic value of lactate levels seems to be independent from the underlying critical illness (6) or the presence of shock or organ failure (7).

Despite this strong and already long-lasting predictive power of lactate levels, little evidence exists on what interventions would benefit patients with increased lactate levels or a failure to reduce lactate (8). Earlier studies have shown that improving lactate metabolism by the administration of dichloroacetate decreases lactate levels but does not result in improved outcome in critically ill patients (9, 10). This could indicate that the detrimental outcome associated with increased lactate levels or delayed reduction is more likely related to the underlying cause than to the hyperlactatemia itself.

Both experimental (11) and clinical studies (12, 13) have emphasized tissue hypoxia, characterized by supply-dependent oxygen consumption, as a cause of increased lactate levels. These findings would support therapy aimed at improving the balance between the demand for oxygen by the tissues and the delivery of oxygen to the tissues, by increasing oxygen delivery and/or decreasing oxygen demand, in patients with increased lactate levels or a failure to reduce lactate. However, as other processes, not related to anaerobic metabolism, can also result in increased blood lactate levels (14, 15), the efficacy of the latter approach could be limited. In the literature, the efficacy of

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therapy aimed at decreasing lactate levels is only indirectly supported by observational studies (16–18) and studies evaluating goal-directed therapy aimed at optimizing oxygen delivery (19, 20). The landmark study in the latter respect by Rivers and colleagues showed that early goal-directed therapy, aimed at improving hemodynamics and oxygen delivery improved outcome in patients with severe sepsis and increased lactate levels (19). Only one randomized controlled single-center study has specifically studied the effects of a resuscitation strategy aimed at normalizing lactate levels (21). Although this study showed a decrease in morbidity associated with this therapeutic approach, the findings cannot easily be extrapolated to the general intensive care population, as only postcardiac surgery patients were included.

Therefore, the primary objective of this multicenter study was to test whether patients with elevated lactate levels (≥ 3.0 mEq/L) on intensive care unit (ICU) admission would benefit from serial lactate monitoring, aimed to reduce these levels by 20% per 2 hours, when compared with patients in whom serial lactate monitoring was not available. Secondary objectives were the effects of lactate monitoring on the development of organ failure; the duration of mechanical ventilation; the use of inotropes, vasopressors, and renal replacement therapy; and the length of ICU stay.

Some of the results of this study have been previously reported in the form of an abstract (22).

METHODS

Study Population

Patients were recruited from four Dutch mixed ICUs (one university hospital and three university-affiliated hospitals) between February 2006 and March 2008. All consecutive patients with a blood lactate level at or above 3.0 mEq/L on ICU admission were eligible for inclusion. We excluded patients with liver failure (prothrombin time > 15 s or international normalized ratio equal to or greater than 1.5 and any hepatic encephalopathy [23]), after liver surgery, age less than 18 years, a contraindication for central venous catheterization, epileptic seizures (grand mal, shortly before or during admission), an evident aerobic cause of hyperlactatemia (at the discretion of the treating physician), or a do-not-resuscitate status.

Study Design

This was a multicenter, open-label randomized controlled study, conducted under supervision of an independent Data Safety Monitoring Board (DSMB). The ethics committees of all participating centers approved the study protocol. Because of the emergency nature and severity of disease in the target population, patients were enrolled under deferred consent: study procedures were temporarily allowed

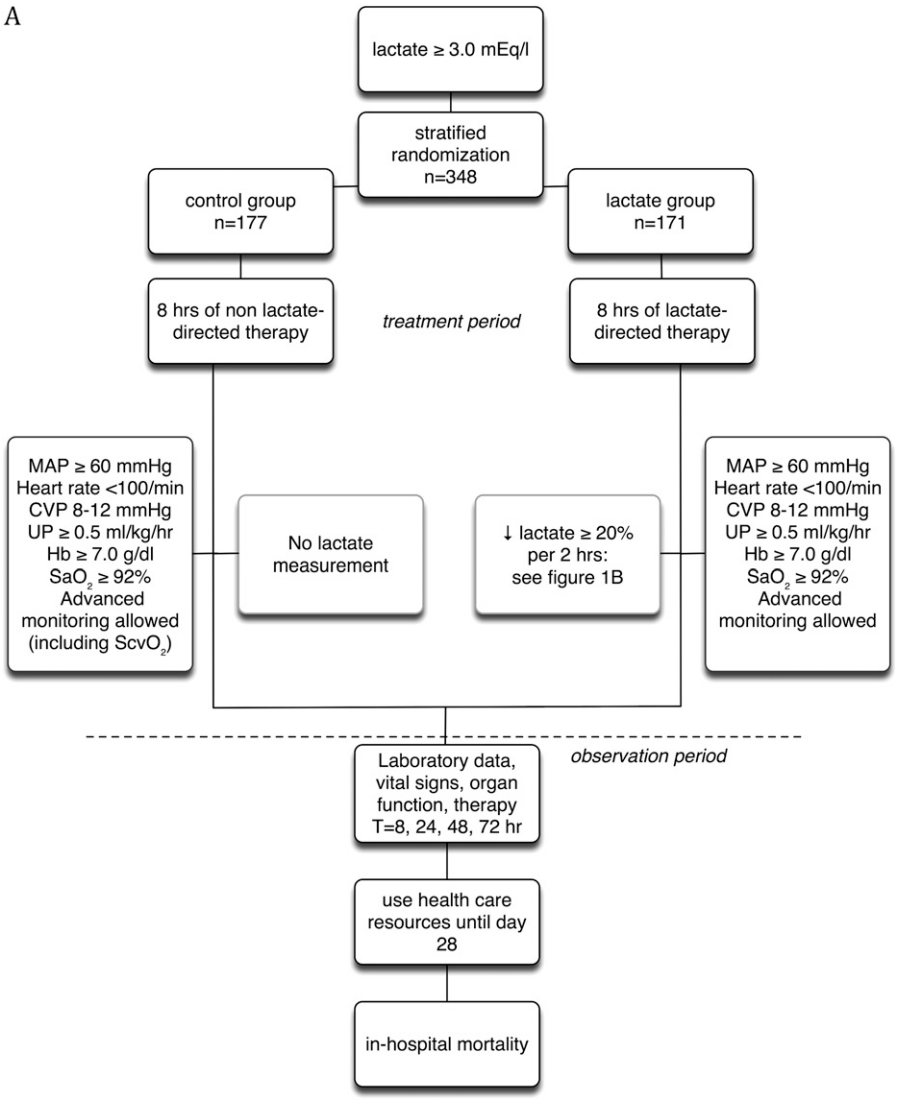


Figure 1. (*A*) Treatment algorithm, control group and lactate group. The goal for central venous pressure (CVP) was 12 to 15 mm Hg in mechanically ventilated patients. Besides the static CVP goals, CVP was used as a dynamic safety limit during fluid challenges (27). Both crystalloids and colloids could be used at the discretion of the clinician. Albumin was not a standard resuscitation fluid in the participating centers. The goal for hemoglobin was 10 g/dl in patients with cardiac ischemia. (Hemoglobin [Hb] 7.0 g/dl = 4.3 mmol/L, 10 g/dl = 6.2 mmol/L). (*B*) Additional treatment algorithm, lactate group. If the lactate level became less than or equal to 2.0 mEq/L, a further decrease was no longer required. Fluid responsiveness was assessed by a fluid challenge of 200 ml crystalloids or colloids. The goal was an increase in blood pressure, Scv_{O_2}, or stroke volume, or a decrease in heart rate. CVP was used as a dynamic safety limit (27): if CVP increased less than or equal to 2 mm Hg, fluid administration was continued; if CVP increased more than 2 and less than or equal to 5 mm Hg, the fluid challenge was repeated after waiting for 10 minutes; if CVP increased greater than or equal to 5 mm Hg, fluid administration was stopped. Before administration of vasodilators, fluid responsiveness was assessed and fluids were infused if necessary. The recommended dose for nitroglycerin was 2 mg in 1/2 hour followed by 2 mg per hour. Hb 7.0 g/dl = 4.3 mmol/L, 10 g/dl = 6.2 mmol/L. MAP = mean arterial pressure; NTG = nitroglycerin; RBCs = red blood cell transfusions; Sa_{O2} = arterial oxygen saturation; Scv_{O_2} = central venous oxygen saturation; T = time; UP = urine production.

without consent and, as soon as possible, written consent from the patient or legal representative was obtained. The Dutch central committee on research involving human subjects approved the use of all data if the research procedures were finished or if the patient had died before consent could be obtained (24).

The start of the study was defined as the time of the first available lactate level immediately after ICU admission. For the next 8 hours (treatment period), patients were randomly allocated to either treatment aimed to decrease lactate levels by at least 20% per 2 hours or to standard therapy, wherein the treatment team was blinded for the results of lactate level measurements (except for the admission value). Thereafter, patients were followed up until discharge from the hospital or death, whichever came first (observation period). The randomization, using a block size of eight, was stratified according to participating center and the presence or absence of sepsis as defined by standard criteria (25). Randomization was done with the use of opaque, sealed envelopes. The statistician of the DSMB generated the random allocation sequence with the use of a computer program. Physicians enrolled the patients and opened the envelope with the lowest available registration number within the appropriate stratum. By immediately filling out name and date on the randomization form the connection between the patient and the outcome of the randomization was safeguarded. Physicians were unaware of the randomization block size.

Treatment assignment was not recorded in the medical chart or electronic patient data monitoring system and clinicians on general wards, who cared for the patients after ICU discharge, were not aware of the treatment assignment.

Treatment

Patients were treated according to their randomization group by qualified intensivists available 7 × 24 hours in a closed-format setting. In both groups the treating clinicians, and not the (principle) investigator(s), were primarily responsible for the treatment of the included patients. Duration of the 8-hour treatment period was based on the study of Polonen and colleagues (21). Thereafter, both groups received standard treatment, during which lactate levels could be obtained in all patients at the discretion of the treating physician.

In the control group, hemodynamic support was aimed at standard resuscitation endpoints, adapted from recently published guidelines (26) (Figure 1A): heart rate less than 100 beats/min, mean arterial pressure (MAP) at or above 60 mm Hg, central venous pressure (CVP) 8–12 mm Hg (12–15 in mechanically ventilated patients) with the use of CVP as a dynamic safety limit during fluid challenges (27), urinary output more than 0.5 ml/kg/h, arterial oxygen saturation (Sa_{O_2}) at or above 92%, and hemoglobin level at or above 7.0 g/dl (≥10.0 g/dl in case of cardiac ischemia) (28). The use of central venous oxygen saturation (Scv_{O_2}) and clinical assessment of peripheral perfusion (e.g., by touching the skin or measuring capillary refill time [29]) was allowed at the discretion of the attending clinician. Most important, in the control group lactate levels were not available for the treatment team and patient during the treatment period.

In the lactate group, blood lactate levels were measured every 2 hours. The therapeutic endpoints were identical to those in the control group (Figure 1A). However, in addition, the therapeutic interventions had to result in a decrease in the lactate level of at least 20% every 2 hours (cut-off level based on findings of two studies [3, 30]). This endpoint was to be achieved by a resuscitation strategy as outlined in Figure 1B. Scv_{O_2} was measured continuously with a fiberoptic probe (CeVOX; Pulsion Medical Systems AG, Munich, Germany), which was inserted through a lumen of the central venous catheter. The central venous oxygenation parameter was used to balance oxygen delivery with demand as suggested by Pinsky and Vincent (31). This probe was removed at the end of the treatment period. When Scv_{O_2} was at or above 70%, but lactate levels did not decrease by at least 20% during

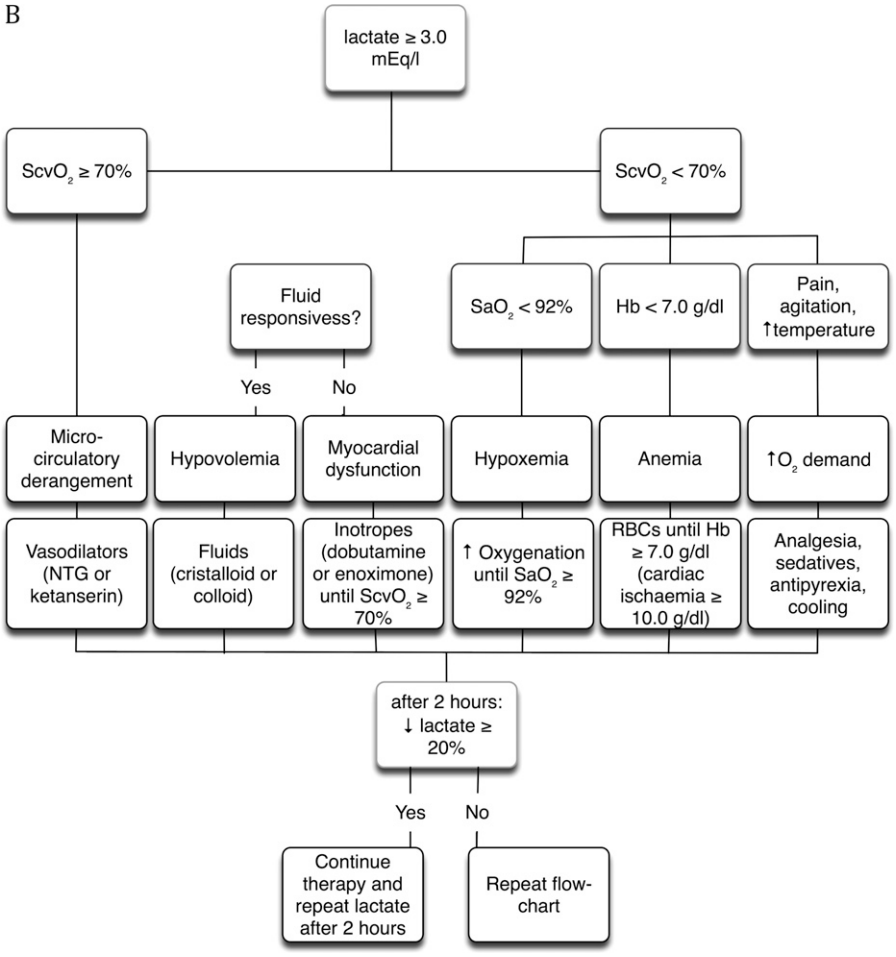


Figure 1. (continued).

a 2-hour time interval, vasodilator therapy was started with the goal to improve microvascular perfusion (32) (Figure 1B). Before the start of a vasodilator, fluid responsiveness was assessed and fluids were administered when needed.

Data Collection

Biochemical and clinical variables required for calculation of Acute Physiology and Chronic Health Evaluation (APACHE) II and Sequential Organ Failure Assessment (SOFA) scores were collected at 0, 8, 24, 48, and 72 hours after the start of the study. APACHE II and SOFA scores were calculated in a way to record baseline information and to assess outcome after an 8-hour intervention (19). Blood lactate levels, CVP, heart rate, MAP, and urine output were recorded at 0, 2, 4, 6, 8, 24, 48, and 72 hours. Scv_{O_2} levels were only recorded during the treatment period. Lactate levels were measured in arterial blood (but capillary or venous blood was also allowed) using the hospital's central laboratory, a blood gas analyzer (ABL 700; Radiometer, Copenhagen, Denmark), or a hand-held lactate analyzer (Accutrend; Roche Diagnostics, Mannheim, Germany) (33). In the lactate group, lactate levels were measured on site to facilitate immediate lactate-guided treatment. In the control group, blood samples for lactate measurements were sent to the laboratory where they were coded and measured but not reported to the treatment team and not recorded in the patient records. All samples were transported and analyzed immediately to prevent erroneous lactate elevation by *in vitro* glycolysis. The use of fluids, inotropes, vasopressors, vasodilators, and blood products was recorded every 2 hours during the treatment period and subsequently from 9 to 24, 25 to 48, and 49 to 72 hours. The use of additional therapy and therapeutic interventions (e.g., antibiotics, corticosteroids, surgery) was recorded from 0 to 8, 9 to 24, 25 to 48, and 49 to 72 hours. When patients were discharged before 72 hours, vital signs, laboratory values, and administered therapy were no longer recorded. The duration of mechanical ventilation (invasive and noninvasive), renal replacement therapy (all techniques), and vasopressor and inotrope use were registered until 28 days after start of the study. Survival was captured until hospital discharge.

All sites were monitored for data quality by a team consisting of the principal investigator (T.C.J.) and three research nurses (W.M., W.intV., C.B.).

Statistical Analysis

In-hospital mortality was the primary endpoint. Secondary predefined endpoints were ICU and 28-day mortality, resuscitation endpoints, administered treatment, APACHE II and SOFA scores, duration of mechanical ventilation, use of renal replacement therapy, use of vasopressors and inotropes, and length of ICU stay.

Based on a retrospective observational pilot study (n = 931, unpublished data) that we performed before this study, we estimated an in-hospital mortality rate for the control group of 42%. To detect a 15% absolute reduction in hospital mortality, similar to the study by Rivers and colleagues (19), with a two-sided α of 0.05, a power of 80%, and to allow for a 20-patient dropout, we calculated that a sample size of 350 patients was required.

An interim analysis was performed by the DSMB after the enrollment of 175 patients. Based on an α-spending function halfway between the O'Brien and Fleming and the Pocock boundary shapes, the α used in the interim analysis was set at 0.013, resulting in an α of 0.043 to be used at the end of the study. Based on the results of the interim analysis, the DSMB recommended the continuation of the study, as the predefined criteria for superiority or futility were not met.

The results were analyzed according to an intention-to-treat principle. Differences in hospital mortality and in ICU mortality were tested using the log-rank and chi-square test. Day 28 mortality was estimated by the Kaplan-Meier method. Differences in mortality rates were also tested using multivariate Cox proportional hazards analysis, stratified by center and presence or absence of sepsis. Adjustments were made for the following predefined covariables: age, sex, baseline APACHE II score, and baseline SOFA score. Mixed models were estimated to quantify differences in vital signs, laboratory variables, and APACHE II and SOFA scores during the treatment period, at 8 hours after start of the study, and during the observation period. The effect on time to ICU discharge, time to weaning from mechanical ventilation, time to cessation of vasopressors and inotropes, and dura-

TABLE 1. BASELINE CHARACTERISTICS OF THE PATIENTS

Variable	Control Group (*N = 177*)	Lactate Group (*N = 171*)
Age, yr	62 ± 18	62 ± 15
Male sex, n (%)	109 (62)	112 (66)
Median time from arrival at hospital to randomization, h (interquartile range)	8 (1–79)	5 (1–65)
ICU admission within 6 h from hospital admission, n (%)	87 (49)	90 (53)
Median time from ICU admission to randomization, h (interquartile range)	0.5 (0.1–1.0)	0.6 (0.2–1.3)
APACHE II score	22.7 ± 9.1	23.6 ± 8.6
SOFA score	8.8 ± 4.3	9.1 ± 3.7
Diagnostic category, (% of patients in the randomization group)		
Sepsis category	67 (38)	68 (40)
Severe sepsis	39 (22)	30 (18)
Septic shock	28 (16)	38 (22)
Nonsepsis category	110 (62)	103 (60)
Neurologic	19 (11)	18 (11)
Cardiac arrest	24 (14)	24 (14)
Other nonsepsis	67 (38)	61 (36)
Hospital, n (% of patients in the randomization group)		
Hospital I	98 (55)	98 (57)
Hospital II	27 (15)	25 (15)
Hospital III	15 (8)	14 (8)
Hospital IV	37 (21)	34 (20)
Referring department, n (% of patients in the randomization group)		
Operation theater (acute surgery)	55 (31)	38 (22)
Operation theater (elective surgery)	21 (12)	21 (12)
Ward or emergency department	95 (54)	103 (60)
Other ICU	6 (3)	9 (5)
Treated with metformin	7 (4)	8 (5)
Treated with antiretroviral therapy	0 (0)	2 (1)
Median blood lactate level, mEq/L (interquartile range)	4.5 (3.5–6.2)	4.5 (3.6–6.1)
Central venous oxygen saturation, %	—	73 ± 11

Definition of abbreviations: APACHE = Acute Physiology and Chronic Health Evaluation; ICU = intensive care unit; SOFA = Sequential Organ Failure Assessment. Values are means ± SD unless otherwise specified.

TABLE 2. BLOOD LACTATE LEVELS

Hours after Start of Therapy	Lactate Level (mEq/L)		*P* Value
	Control Group	Lactate Group	
Baseline (0 h)	4.7 (3.9–5.5)	4.6 (3.9–5.4)	0.75
8	2.7 (2.3–3.2)	2.6 (2.2–3.1)	0.59
0–8	3.3 (2.8–3.9)	3.2 (2.7–3.8)	0.80
9–72	1.7 (1.4–2.0)	1.6 (1.3–1.9)	0.17

The adjusted mean values (95% confidence interval) were obtained from mixed model analysis. Lactate levels are expressed as geometric means. *P* values were calculated after logarithmic transformation of lactate levels.

tion of renal replacement therapy was assessed by cumulative hazard estimates and adjusted Cox proportional hazard analysis, censoring for early deaths (34).

Because of possible heterogeneity between septic and nonseptic hyperlactatemia and its subsequent treatment, prespecified subgroup analyses were performed in these two groups of patients and in further subsets of severe sepsis, septic shock, neurologic, cardiac arrest, and other nonsepsis patients.

RESULTS

Patient enrollment is shown in Figure E1 of the online supplement. The intention-to-treat population consisted of 348 patients; 177 patients were randomized to the control group and 171 to the lactate group. In 18 patients a major protocol violation occurred (Table E1). These patients remained in the intention-to-treat population. Table 1 shows the baseline characteristics of the patients in the intention-to-treat population. Sixteen patients died during the 8-hour treatment period (10 control patients vs. 6 patients in the lactate group). From 8 to 72 hours after study entry another 52 patients died (27 control patients vs. 25 patients in the lactate group) and 79 patients were discharged from the ICU to the ward (38 control patients vs. 41 patients in the lactate group). At 72 hours after study entry, 201 patients were still admitted to the ICU (102 control patients and 99 patients in the lactate group).

Therapeutic Endpoints

The proportion of patients who reached the conventional resuscitation goals that were applicable to both randomization groups was equal in both groups at any time point (except for heart rate at 6 h, which was more often met in the control group) (Table E2). However, despite that the goal of a decrease in lactate level of 20% or more per 2 hours was only used in the lactate group, this goal was also equally met in both randomization groups.

TABLE 3. FLUIDS AND VASOACTIVE MEDICATION USE DURING THE INITIAL TREATMENT PHASE AND UP TO 72 HOURS

Treatment	Control Group	Lactate Group	*P* Value
Fluids, ml*			
0–8 h†	2,194 ± 1,669	2,697 ± 1,965	0.011
9–72 h‡	10,043 ± 6,141	8,515 ± 4,987	0.055
Red blood cell transfusion, ml			
0–8 h†	196 ± 495	322 ± 1037	0.15
9–72 h‡	345 ± 667	423 ± 1300	0.59
Any inotropic agent, %§			
0–8 h†	32.9	40.1	0.17
9–72 h‖	44.2	35.2	0.12
Any vasodilator, %¶			
0–8 h†	20.2	42.5	<0.001
9–72 h‖	27.1	43.2	0.005
Any vasopressor, %**			
0–8 h†	63.6	69.5	0.25
9–72 h‖	63.7	71.4	0.16

Definition of abbreviation: ICU = intensive care unit.

P values as calculated by two-sample Student *t* test or the chi-square test, as appropriate.

* Sum of crystalloid and colloid fluids.

† Values are shown for all patients.

‡ Cumulative values (± SD) are shown for patients who were still admitted to the ICU after 72 h.

§ Dobutamine, enoximone, or epinephrine.

‖ Proportions are shown for patients who stayed for more than 8 h in the ICU.

¶ Nitroglycerin or ketanserin.

** Norepinephrine, dopamine, or phenylephrine.

During the treatment period and the subsequent observation period, mean values of lactate were similar (Table 2). pH, base excess, bicarbonate, MAP, heart rate, CVP, and hemoglobin were similar in both groups as well (Table E3).

Administered Therapy

During the treatment period, patients in the lactate group received significantly more fluids than control group patients (Table 3). In addition, more patients in the lactate group received vasodilator therapy (Table 3, Table E4). Patients in both groups received similar quantities of red blood cell transfusion. Similar proportions of patients in both groups required the use of vasopressors and inotropes.

Similar proportions of patients in the control and lactate group received mechanical ventilation (86% vs. 84%, $P = 0.76$, including 2% vs. 2% noninvasive ventilation), antibiotics (67% vs. 61%, $P = 0.27$), corticosteroids (45% vs. 40%, $P = 0.38$), additional surgery after ICU admission (9 vs. 6%, $P = 0.36$), analgesics (fentanyl or morphine; 58% vs. 50%, $P = 0.13$), sedatives (midazolam, lorazepam, or propofol; 71% vs. 71%,

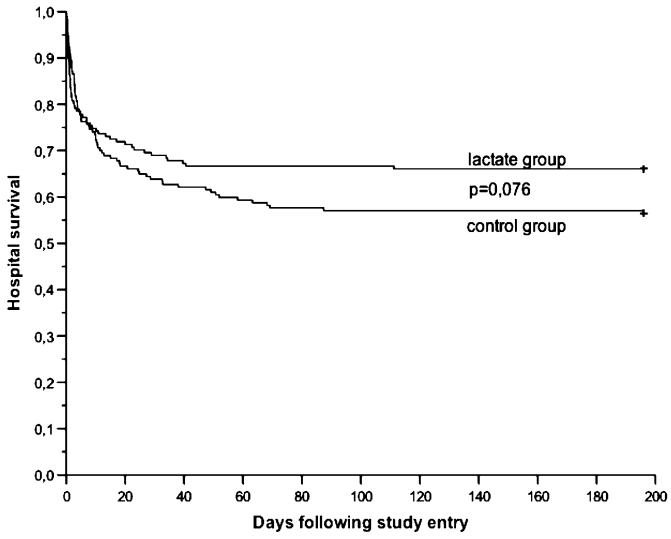
TABLE 4. MORTALITY

Variable	Control Group (*n* = 177)	Lactate Group (*n* = 171)	Relative Risk (95% CI)	*P* Value
Unadjusted analysis, % (n)*				
In-hospital mortality	43.5 (77/177)	33.9 (58/171)	0.78 (0.60–1.02)	0.067
28-d mortality	35.6 (63/177)	30.4 (52/171)	0.85 (0.63–1.16)	0.30
ICU mortality	34.5 (61/177)	28.7 (49/171)	0.83 (0.61–1.14)	0.24
Adjusted analysis, hazard ratio (95% CI)†				
In-hospital mortality		0.61 (0.43–0.87)		0.006
28-d mortality		0.75 (0.52–1.09)		0.134
ICU mortality		0.66 (0.45–0.98)		0.037

Definition of abbreviations: APACHE = Acute Physiology and Chronic Health Evaluation; CI = confidence interval; ICU = intensive care unit; SOFA = Sequential Organ Failure Assessment.

* Chi-square test.

† Cox proportional hazard analysis with adjustment for age, sex, APACHE II score (modified; at baseline) and SOFA score (modified; at baseline), and stratified for center and sepsis group, as predefined in the study protocol.



Number at risk:											
Control	177	118	110	105	102	101	101	101	101	101	100
Lactate	171	122	115	114	114	114	113	113	113	113	113

Figure 2. Kaplan-Meier survival curve. Survival was followed up until hospital discharge. The longest duration of hospital stay was 196 days.

$P = 0.91$), therapeutic hypothermia (10% vs. 6%, $P = 0.20$), and a percutaneous coronary intervention (1% vs. 1%, $P = 0.96$).

During the observation period, more patients assigned to the lactate group received vasodilators when compared with the control group (Table 3). During the observation period a trend toward less use of fluids was observed in the lactate group when compared with control group.

Mortality

In the control group 43.5% (77/177) of the patients did not survive to hospital discharge, whereas in the lactate group 33.9% (58/171) died during their hospital stay ($P = 0.067$, Table 4, Figure 2). When adjusted for the predefined risk factors at baseline, the treatment protocol to decrease lactate levels resulted in a significant reduction in the risk of hospital death (hazard ratio [HR], 0.61; confidence interval [CI], 0.43–0.87; Table 4, Table E5).

Organ Failure, Inotropes, Vasopressors, Renal Replacement Therapy, and Length of Stay

Patients assigned to the lactate group had reduced organ failure (SOFA score) in the observation period (Table 5). Patients in the lactate group were faster weaned from mechanical ventilation (HR, 0.72; 95% CI, 0.54–0.98; Figure 3A) and inotropes (HR, 0.65; 95% CI, 0.42–1.00; Figure 3B) than patients in the control group. More importantly, patients in the lactate group could be discharged from the ICU earlier (HR, 0.65; 95% CI, 0.50–0.85; Figure 4).

There were no significant differences in the time to stop vasopressors (HR, 0.84; 95% CI, 0.61–1.15; Figure 3C) or renal replacement therapy (HR, 0.56; 95% CI, 0.22–1.43; Figure 3D) between both groups.

Subgroup and Exploratory Analyses

Prespecified and *post hoc* specified subgroup analyses are shown in Figure 5. In addition, two *post hoc* exploratory analyses were performed to investigate the difference in statistical significance between the unadjusted and the adjusted primary outcome. First, when adding interaction terms for age and APACHE II score to the predefined multivariable model for hospital mortality, effect modification could not be demonstrated (age × randomization group [$P = 0.74$] and APACHE II score × randomization group [$P = 0.85$]). Second, when excluding six patients with missing data on covariates (APACHE II and SOFA scores at 0 h), effect size and P value remained similar (data not shown).

DISCUSSION

In this multicenter, open-label randomized controlled study, lactate monitoring during the first 8 hours of ICU admission, aimed at reducing lactate levels by at least 20% per 2 hours, significantly reduced ICU length of stay and also ICU and hospital mortality when adjusting for predefined and commonly accepted risk factors.

There was a discrepancy in statistical significance between the adjusted and unadjusted analysis of the study's primary outcome measure. This could not be explained by different data sets being used due to missing data or by a heterogeneous effect of the randomization therapy in some end of the spectrum of age or APACHE II score. Instead, this difference might prob-

TABLE 5. DISEASE SEVERITY AND ORGAN FAILURE

Hours after Start of Therapy	Control Group	Lactate Group	*P* Value
APACHE II score			
Baseline (0 h)	15.6 (14.4–16.8)	16.3 (15.1–17.5)	0.28
8	13.4 (12.2–14.7)	13.0 (11.8–14.3)	0.52
0–8	14.5 (13.4–15.7)	14.7 (13.5–15.8)	0.78
9–72	10.5 (9.3–11.6)	9.9 (8.7–11.0)	0.17
SOFA score			
Baseline (0 h)	6.4 (5.6–7.1)	6.4 (5.6–7.1)	0.89
8	7.2 (6.5–7.9)	6.9 (6.2–7.6)	0.27
0–8	6.8 (6.0–7.5)	6.8 (6.0–7.5)	0.58
9–72	7.0 (6.3–7.7)	6.4 (5.7–7.2)	0.009

Definition of abbreviations: APACHE = Acute Physiology and Chronic Health Evaluation; CI = confidence interval; SOFA = Sequential Organ Failure Assessment.

The adjusted mean values (95% CI) were obtained from mixed model analysis. APACHE II and SOFA scores were calculated at the various time points (0, 8, 24, 48, and 72 h after study entry).

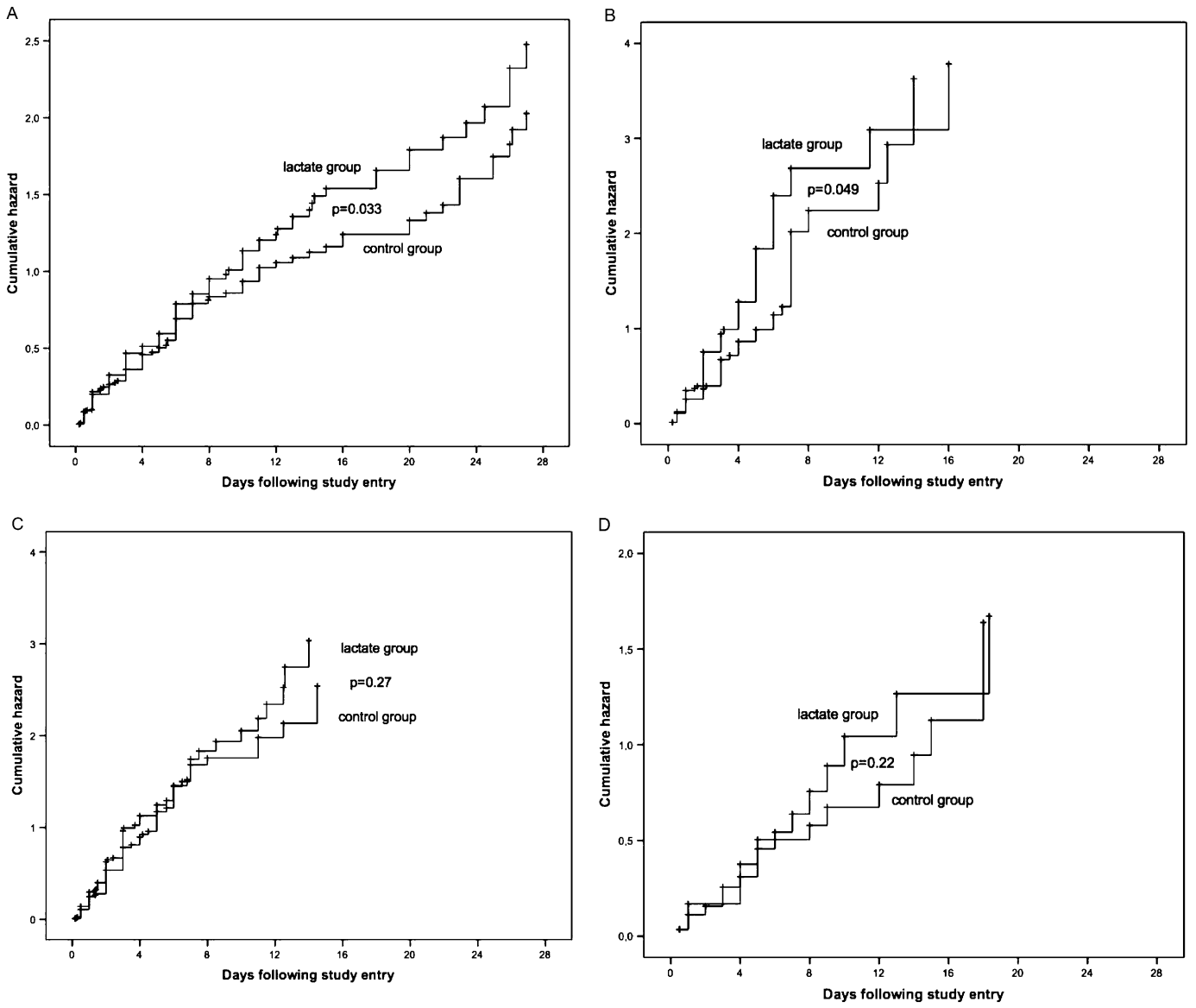


Figure 3. Time to weaning from (*A*) mechanical ventilation, (*B*) inotropes, and (*C*) vasopressors, and (*D*) the use of renal replacement therapy. Assessed by cumulative hazard estimates and Cox proportional hazard analysis, with censoring for early deaths.

ably be explained by a clearer estimation of the actual effect when adjusting for risk factors that are well-known predictors of mortality: such predefined covariate adjustment makes treatment effect estimation more individualized and reduces noise in the analysis. In our study, which was originally powered to detect a 15% mortality difference, it thereby improved the statistical power (i.e., the ability to identify a smaller treatment effect when it really exists) (35). In addition, the observed 9.6% absolute reduction in hospital mortality was consistent with substantial improvement in important clinical outcomes, including reduced short-term organ failure, earlier weaning from the ventilator, and subsequent earlier discharge from the ICU.

Monitoring itself cannot improve outcome; therefore, the therapeutic plan associated with the monitor is equally important. As for all studies investigating efficacy of a treatment algorithm, the effect in this study is the result of the combination of all individual treatment goals and therapy components. The main differences in therapy between the two groups in the treatment period were the administration of more fluids and the increased use of vasodilators in patients assigned to the lactate group. Although goal-directed fluid resuscitation is widely recommended (36–38), the use of vasodilators in critically ill patients is controversial (39). Nevertheless, some studies have suggested beneficial effects of vasodilator therapy in critically ill patients. For instance, in fluid-resuscitated patients with septic shock, administration of nitroglycerin reversed microcirculatory shutdown and shunting (32). In severe heart failure and cardiogenic shock, nitroglycerin has been shown to improve microcirculatory perfusion (40, 41). Finally, Buwalda and Ince described positive effects on tissue perfusion and oxygen extraction in addition to microcirculatory recruitment (42).

Surprisingly, the treatment algorithm of the lactate group did not result in faster reduction of lactate when compared with control group therapy, despite a more aggressive resuscitation in the lactate group. In fact, this observation might actually argue against lactate as a target of hemodynamic therapy. It suggests that hyperlactatemia does not sufficiently reflect tissue hypoperfusion and emphasizes its complicated etiology in critical illness (14, 15). On the other hand, our study underscored the function of lactate as a warning signal. In the control group

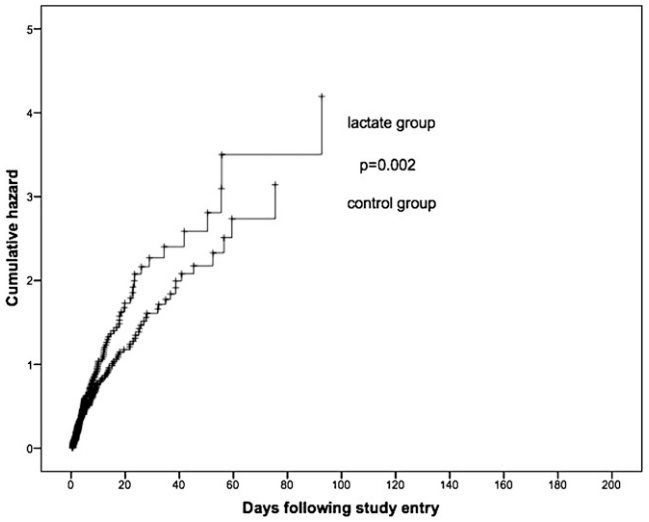


Figure 4. Time to discharge from the intensive care unit. Assessed by cumulative hazard estimates and Cox proportional hazard analysis, with censoring for early deaths.

the treating clinicians might not have been sufficiently warned that their patients did not improve or even deteriorated in the presence of stable hemodynamic parameters and conventional resuscitation. Also, in the lactate group the availability of lactate levels might have resulted in restricted treatment in selected patients when lactate levels had already decreased sufficiently. In this way, lactate-guided resuscitation potentially made treatment tailor-made to the individual patient.

The early goal-directed therapy study by Rivers and colleagues reported reduced mortality in the treatment group (19). However, as their study was exclusively done in the emergency department of a single hospital, growing concerns arose about the applicability of this strategy in other settings and other patient groups (43, 44). The Rivers study was situated in the emergency department where resuscitation was initiated earlier in a population with generally higher lactate levels and lower CVP and Scv_{O_2} values (45). This probably explains the difference in resuscitation intensity (i.e., difference in fluid administration) between the two studies. Nevertheless, similar to the Rivers study, therapy guided by repeated lactate measurements in our study resulted in an increased use of fluids during the treatment period, whereas during the subsequent observation period a trend toward decreased use of fluids was found when compared with the control group. Our study therefore confirms the early goal-directed therapy study results (19), underscoring the importance of adequate resuscitation as long as lactate levels remain elevated, even after ICU admission after early stabilization in the emergency department. In addition, our study extends the concept of early goal-directed therapy to other patient groups, as only about 40% of the patients enrolled in the current study had severe sepsis or septic shock.

The treatment effect seemed consistent throughout almost all predefined subgroups, although it might arguably be more pronounced in septic than in nonseptic patients and in severe septic than in septic shock patients. The only predefined subgroup in which mortality did not seem to be lower in the lactate group was the neurological subgroup (i.e., patients with traumatic brain injury, neurovascular conditions, or neuro-oncological conditions). In this particular group of patients, vasodilatation therapy might possibly interfere with optimal targeting of cerebral perfusion. Finally, analogous to previous studies on hemodynamic optimization in high-risk patients (46), the treatment effect seemed larger when patients were admitted to the ICU early before the development of organ failure. However, although subgroup analysis might provide valuable exploratory information and facilitate hypothesis generation, care has to be taken in the interpretation given its well-known limitations, including limited statistical power (47).

Some methodological aspects are important, particularly regarding the open-label protocol design of this study (48, 49). First, as blinding of the treatment team in a study like this is impossible, this imposes a risk of bias. However, none of the monitored cointerventions were significantly different between the two groups. Also, the treatment team was practically blinded to treatment assignment after the initial 8-hour period and at discharge to the general ward. Second, the therapy endpoints in the control group have been acknowledged by international guidelines. These endpoints were as often met in the control group as in the lactate group, suggesting no undertreatment in the control group. Additionally, the control group mortality was comparable with the mortality in the pilot study, conducted immediately before the start of the study. However, given that Scv_{O_2} monitoring was mandatory in the lactate group and facultative in the control group, we cannot exclude the possi-

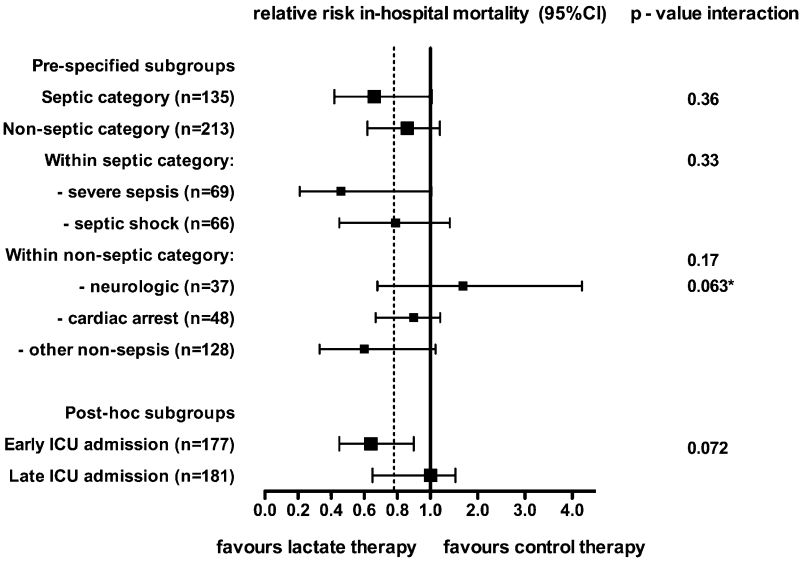


Figure 5. Prespecified and *post hoc* subgroup analyses. Early intensive care unit (ICU) admission = less than 6 hours after hospital admission. Late ICU admission = more than 6 hours after ICU admission. *P* value for interaction according to Breslow-Day test of homogeneity. **P* value between neurologic and other nonsepsis. CI = confidence interval.

bility that this had an impact on the observed outcome difference. Third, an important limitation of the study design is that the observed differences in treatment between the two groups provide only suggestive, and not conclusive, support for a mechanism that is responsible for the clinical outcome benefit. In addition, as the treatment mechanism is determined by the sum of its multiple resuscitation endpoints and treatments, this limits the interpretation of the individual interventions used in the algorithm. For instance, given the debate on the best method to assess fluid responsiveness and adequate endpoints of fluid resuscitation (50, 51), we have chosen a dynamic approach using central venous pressure (27), as it was practically most suitable in a multicenter environment within the earliest hours of ICU admission. In addition, this would probably resemble usual care in many ICUs worldwide (52), enlarging external generalizability of the results.

In summary, in ICU patients with a lactate level at or above 3.0 mEq/L on admission, early monitoring of lactate levels with the added target to reduce levels by 20% per 2 hours on top of currently recommended resuscitation guidelines significantly reduced ICU length of stay. ICU and hospital mortality were significantly reduced when adjusting for predefined risk factors, and as this was consistent with important secondary endpoints, the results of this study suggest that initial lactate monitoring has clinical benefit.

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References

1. Kompanje EJ, Jansen TC, van der Hoven B, Bakker J. The first demonstration of lactic acid in human blood in shock by Johann Joseph Scherer (1814–1869) in January 1843. *Intensive Care Med* 2007;33:1967–1971.
2. Aduen J, Bernstein WK, Khastgir T, Miller J, Kerzner R, Bhatiani A, Lustgarten J, Bassin AS, Davison L, Chernow B. The use and clinical importance of a substrate-specific electrode for rapid determination of blood lactate concentrations. *JAMA* 1994;272:1678–1685.
3. Nguyen HB, Rivers EP, Knoblich BP, Jacobsen G, Muzzin A, Ressler JA, Tomlanovich MC. Early lactate clearance is associated with improved outcome in severe sepsis and septic shock. *Crit Care Med* 2004;32:1637–1642.
4. Arnold RC, Shapiro NI, Jones AE, Schorr C, Pope J, Casner E, Parrillo JE, Dellinger RP, Trzeciak S. Multicenter study of early lactate clearance as a determinant of survival in patients with presumed sepsis. *Shock* 2009;32:35–39.
5. Bakker J, Gris P, Coffernils M, Kahn RJ, Vincent JL. Serial blood lactate levels can predict the development of multiple organ failure following septic shock. *Am J Surg* 1996;171:221–226.
6. Bakker J. Lactate: may I have your votes please? *Intensive Care Med* 2001;27:6–11.
7. Mikkelsen ME, Miltiades AN, Gaieski DF, Goyal M, Fuchs BD, Shah CV, Bellamy SL, Christie JD. Serum lactate is associated with mortality in severe sepsis independent of organ failure and shock. *Crit Care Med* 2009;37:1670–1677.
8. Jansen TC, van Bommel J, Bakker J. Blood lactate monitoring in critically ill patients: a systematic health technology assessment. *Crit Care Med* 2009;37:2827–2839.
9. Stacpoole PW, Wright EC, Baumgartner TG, Bersin RM, Buchalter S, Curry SH, Duncan CA, Harman EM, Henderson GN, Jenkinson S, *et al.* A controlled clinical trial of dichloroacetate for treatment of lactic acidosis in adults. The dichloroacetate-lactic acidosis study group. *N Engl J Med* 1992;327:1564–1569.
10. Stacpoole PW, Harman EM, Curry SH, Baumgartner TG, Misbin RI. Treatment of lactic acidosis with dichloroacetate. *N Engl J Med* 1983; 309:390–396.
11. Cain SM. Oxygen delivery and uptake in dogs during anemic and hypoxic hypoxia. *J Appl Physiol* 1977;42:228–234.
12. Friedman G, De Backer D, Shahla M, Vincent JL. Oxygen supply dependency can characterize septic shock. *Intensive Care Med* 1998; 24:118–123.
13. Ronco JJ, Fenwick JC, Tweeddale MG, Wiggs BR, Phang PT, Cooper DJ, Cunningham KF, Russell JA, Walley KR. Identification of the critical oxygen delivery for anaerobic metabolism in critically ill septic and nonseptic humans. *JAMA* 1993;270:1724–1730.
14. Levy B, Gibot S, Franck P, Cravoisy A, Bollaert PE. Relation between muscle Na+K+ ATPase activity and raised lactate concentrations in septic shock: a prospective study. *Lancet* 2005;365:871–875.
15. Levraut J, Ciebiera JP, Chave S, Rabary O, Jambou P, Carles M, Grimaud D. Mild hyperlactatemia in stable septic patients is due to impaired lactate clearance rather than overproduction. *Am J Respir Crit Care Med* 1998;157:1021–1026.
16. Blow O, Magliore L, Claridge JA, Butler K, Young JS. The golden hour and the silver day: detection and correction of occult hypoperfusion within 24 hours improves outcome from major trauma. *J Trauma* 1999;47:964–969.
17. Claridge JA, Crabtree TD, Pelletier SJ, Butler K, Sawyer RG, Young JS. Persistent occult hypoperfusion is associated with a significant increase in infection rate and mortality in major trauma patients. *J Trauma* 2000;48:8–14.
18. Rossi AF, Khan DM, Hannan R, Bolivar J, Zaidenweber M, Burke R. Goal-directed medical therapy and point-of-care testing improve outcomes after congenital heart surgery. *Intensive Care Med* 2005; 31:98–104.
19. Rivers E, Nguyen B, Havstad S, Ressler J, Muzzin A, Knoblich B, Peterson E, Tomlanovich M. Early goal-directed therapy in the treatment of severe sepsis and septic shock. *N Engl J Med* 2001;345: 1368–1377.
20. Chytra I, Pradl R, Bosman R, Pelnar P, Kasal E, Zidkova A. Esophageal Doppler-guided fluid management decreases blood lactate levels in multiple-trauma patients: a randomized controlled trial. *Crit Care* 2007;11:R24.
21. Polonen P, Ruokonen E, Hippelainen M, Poyhonen M, Takala J. A prospective, randomized study of goal-oriented hemodynamic therapy in cardiac surgical patients. *Anesth Analg* 2000;90:1052–1059.
22. Jansen TC, Van Bommel J, Schoonderbeek FJ, Sleeswijk Visser SJ, Van der Klooster JM, Lima AP, Willemsen SP, Bakker J. Early lactate-directed therapy in critically ill patients: A randomized controlled multi-centre trial [abstract]. *Intensive Care Med* 2009; (September, Supplement 1)S213.
23. O'Grady JG, Schalm SW, Williams R. Acute liver failure: redefining the syndromes. *Lancet* 1993;342:273–275.
24. Jansen TC, Kompanje EJ, Bakker J. Deferred proxy consent in emergency critical care research: Ethically valid and practically feasible. *Crit Care Med* 2009;37:S65–S68.
25. Bone RC, Balk RA, Cerra FB, Dellinger RP, Fein AM, Knaus WA, Schein RM, Sibbald WJ. Definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. The ACCP/

SCCM consensus conference committee. American College of Chest Physicians/Society of Critical Care Medicine. *Chest* 1992;101: 1644–1655.
26. Dellinger RP, Carlet JM, Masur H, Gerlach H, Calandra T, Cohen J, Gea-Banacloche J, Keh D, Marshall JC, Parker MM, *et al.* Surviving sepsis campaign guidelines for management of severe sepsis and septic shock. *Crit Care Med* 2004;32:858–873.
27. Vincent JL, Weil MH. Fluid challenge revisited. *Crit Care Med* 2006;34: 1333–1337.
28. Hebert PC, Wells G, Blajchman MA, Marshall J, Martin C, Pagliarello G, Tweeddale M, Schweitzer I, Yetisir E. A multicenter, randomized, controlled clinical trial of transfusion requirements in critical care. Transfusion requirements in critical care investigators, Canadian critical care trials group. *N Engl J Med* 1999;340:409–417.
29. Lima A, Jansen TC, van Bommel J, Ince C, Bakker J. The prognostic value of the subjective assessment of peripheral perfusion in critically ill patients. *Crit Care Med* 2009;37:934–938.
30. Vincent JL, Dufaye P, Berre J, Leeman M, Degaute JP, Kahn RJ. Serial lactate determinations during circulatory shock. *Crit Care Med* 1983; 11:449–451.
31. Pinsky MR, Vincent JL. Let us use the pulmonary artery catheter correctly and only when we need it. *Crit Care Med* 2005;33: 1119–1122.
32. Spronk PE, Ince C, Gardien MJ, Mathura KR, Oudemans-van Straaten HM, Zandstra DF. Nitroglycerin in septic shock after intravascular volume resuscitation. *Lancet* 2002;360:1395–1396.
33. Brinkert W, Rommes JH, Bakker J. Lactate measurements in critically ill patients with a hand-held analyser. *Intensive Care Med* 1999;25: 966–969.
34. Van den Berghe G, Wilmer A, Hermans G, Meersseman W, Wouters PJ, Milants I, Van Wijngaerden E, Bobbaers H, Bouillon R. Intensive insulin therapy in the medical ICU. *N Engl J Med* 2006;354:449–461.
35. Roozenbeek B, Maas AI, Lingsma HF, Butcher I, Lu J, Marmarou A, McHugh GS, Weir J, Murray GD, Steyerberg EW. Baseline characteristics and statistical power in randomized controlled trials: selection, prognostic targeting, or covariate adjustment? *Crit Care Med* 2009;37:2683–2690.
36. Tisherman SA, Barie P, Bokhari F, Bonadies J, Daley B, Diebel L, Eachempati SR, Kurek S, Luchette F, Carlos Puyana J, *et al.* Clinical practice guideline: endpoints of resuscitation. *J Trauma* 2004;57: 898–912.
37. Dellinger RP, Levy MM, Carlet JM, Bion J, Parker MM, Jaeschke R, Reinhart K, Angus DC, Brun-Buisson C, Beale R, *et al.* Surviving sepsis campaign: international guidelines for management of severe sepsis and septic shock: 2008. *Crit Care Med* 2008;36:296–327.
38. Antonelli M, Levy M, Andrews PJ, Chastre J, Hudson LD, Manthous C, Meduri GU, Moreno RP, Putensen C, Stewart T, *et al.* Hemodynamic monitoring in shock and implications for management. International consensus conference, Paris, France, 27–28 April 2006. *Intensive Care Med* 2007;33:575–590.
39. Preiser JC, De Backer D, Vincent JL. Nitroglycerin for septic shock. *Lancet* 2003;361:880.
40. den Uil CA, Caliskan K, Lagrand WK, van der Ent M, Jewbali LS, van Kuijk JP, Spronk PE, Simoons ML. Dose-dependent benefit of nitroglycerin on microcirculation of patients with severe heart failure. *Intensive Care Med* 2009;35:1893–1899.
41. den Uil CA, Lagrand WK, Spronk PE, van der Ent M, Jewbali LS, Brugts JJ, Ince C, Simoons ML. Low-dose nitroglycerin improves microcirculation in hospitalized patients with acute heart failure. *Eur J Heart Fail* 2009;11:386–390.
42. Buwalda M, Ince C. Opening the microcirculation: can vasodilators be useful in sepsis? *Intensive Care Med* 2002;28:1208–1217.
43. Perel A. Bench-to-bedside review: the initial hemodynamic resuscitation of the septic patient according to surviving sepsis campaign guidelines - does one size fit all? *Crit Care* 2008;12:223.
44. Bellomo R, Reade MC, Warrillow SJ. The pursuit of a high central venous oxygen saturation in sepsis: Growing concerns. *Crit Care* 2008;12:130.
45. van Beest PA, Hofstra JJ, Schultz MJ, Boerma EC, Spronk PE, Kuiper MA. The incidence of low venous oxygen saturation on admission to the intensive care unit: A multi-center observational study in the Netherlands. *Crit Care* 2008;12:R33.
46. Kern JW, Shoemaker WC. Meta-analysis of hemodynamic optimization in high-risk patients. *Crit Care Med* 2002;30:1686–1692.
47. Wang R, Lagakos SW, Ware JH, Hunter DJ, Drazen JM. Statistics in medicine–reporting of subgroup analyses in clinical trials. *N Engl J Med* 2007;357:2189–2194.
48. Delaney A, Angus DC, Bellomo R, Cameron P, Cooper DJ, Finfer S, Harrison DA, Huang DT, Myburgh JA, Peake SL, *et al.* Bench-to-bedside review: the evaluation of complex interventions in critical care. *Crit Care* 2008;12:210.
49. Chiche JD, Angus DC. Testing protocols in the intensive care unit: complex trials of complex interventions for complex patients. *JAMA* 2008;299:693–695.
50. Michard F, Boussat S, Chemla D, Anguel N, Mercat A, Lecarpentier Y, Richard C, Pinsky MR, Teboul JL. Relation between respiratory changes in arterial pulse pressure and fluid responsiveness in septic patients with acute circulatory failure. *Am J Respir Crit Care Med* 2000;162:134–138.
51. Marik PE, Baram M, Vahid B. Does central venous pressure predict fluid responsiveness? A systematic review of the literature and the tale of seven mares. *Chest* 2008;134:172–178.
52. Boldt J, Lenz M, Kumle B, Papsdorf M. Volume replacement strategies on intensive care units: results from a postal survey. *Intensive Care Med* 1998;24:147–151.