

Lactate Monitoring in Critically Ill Patients

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Lactate Monitoring in Critically Ill Patients

Lactaat monitoring bij ernstig zieke patienten

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INTRODUCTION AND OUTLINE OF THE THESIS

CHAPTER 1

Based on:

- **Why measure lactate on the ICU?**

Neth J Crit Care 2006 Dec;10(6):624-26

- **Don't take vitals, take a lactate**

Intensive Care Med. 2007 Nov;33(11):1863-5

- **How do I use venous saturations?**

Neth J Crit Care 2007;11 (3):141-144

- **Controversies in goal-directed therapy: venous saturations and lactate**

Controversies in Intensive Care Medicine.

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CASE PRESENTATION

The resident internal medicine called from the Emergency Department (ED). “Can you please come and see my patient, I think he is becoming septic and needs admission to the intensive care”. In the ED we found a confused older patient with an oxygen mask who was clearly dyspnoeic, the urinary catheter was filled with a dark brown fluid, the collecting bag was empty. The resident reported that he admitted the patient 4 hours earlier as he suspected pneumonia. On admission the patient was hypoxic but this clearly improved with the supplemental oxygen. The resident was still waiting for all the laboratory results and the chest X-ray. However, now that the patient had developed hypotension he thought the patient was clearly at risk and intensive care admission was required. When we asked why he had not called us earlier, he replied that he intended to admit the patient to the general ward as he was haemodynamically stable and oxygenation had improved on supplemental oxygen so intensive care admission was not required. When reviewing the blood sample that was drawn 30 min following presentation, besides hypoxaemia, an increased lactate level of 4.6 mmol/l was present. The resident pointed out that hyperlactataemia in sepsis is not related to tissue hypoxia but rather is a marker of increased aerobic metabolism. Therefore he thought there was no need to react to this hyperlactataemia.

In this case presentation the presence of hyperlactataemia did not result in treatment consequences. When having read this thesis the reader should be able to indicate whether the resident was right or wrong in this decision.

AIM OF THE THESIS

The general aim of this thesis is to evaluate the clinical value of blood lactate monitoring by assessing various aspects of lactate monitoring, including aetiology, the prognostic value and the impact on clinical outcome when incorporating lactate measurement

in a treatment algorithm at the bedside. As the process of obtaining informed consent for participation in research is challenging in intensive care patients due to the emergency nature of critical illness, the secondary aim of this thesis is to evaluate consent procedures in emergency critical care research.

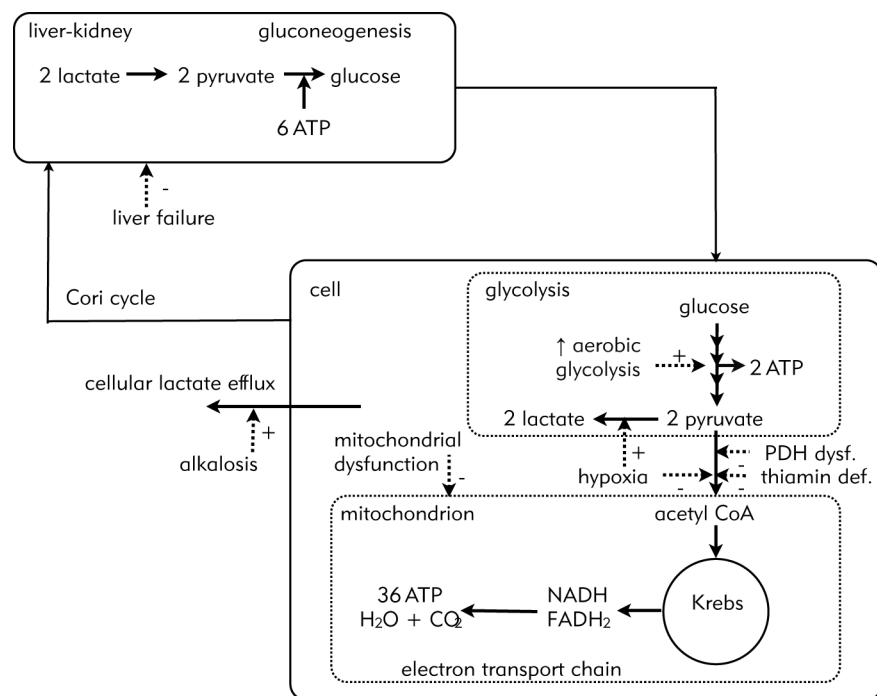
OUTLINE OF THE THESIS

First, a summary of the history of lactate measurement is presented: although lactic acid was first found and described in sour milk by the Swedish chemist Karl Wilhelm Scheele (1742–1786) in 1780 (1), we aimed to honor the forgotten observations of the German physician–chemist Johann Joseph Scherer who first demonstrated the presence of lactate in human blood in shock in 1843 (**chapter 2**).

Since then, hyperlactataemia in intensive care medicine has been regarded mainly as a sign of tissue hypoxia (2). However, as lactate is a normal end product of carbohydrate metabolism, other processes, unrelated to tissue hypoxia, may also cause lactate levels to rise (3). Therefore, the exact aetiology of hyperlactataemia needs to be examined at the bedside to be able to properly interpret the results, which requires sufficient understanding of lactate metabolism (figure 1).

Despite our extensive knowledge on lactate metabolism, the use of blood lactate monitoring still remains controversial. This is reflected by its variable clinical use in different hospitals worldwide: some routinely measure it whereas others hardly do so. Because the clinical benefit of blood lactate monitoring in critically ill patients has never been subjected to rigorous clinical evaluation, we performed a systematic health technology assessment (**chapter 3**). Using this format, we reviewed the technological aspects of lactate monitoring and the clinical impact on healthcare workers confidence, decision-making, patient outcomes and the associated benefits and costs of its application in real clinical practice.

Figure 1. Lactate metabolism



Lactate metabolism: the process of glycolysis, Krebs cycle, electron transport chain and gluconeogenesis. Dotted arrows depict the point of action of the various mechanisms of hyperlactataemia: - inhibitory effect, + excitatory effect. Definitions of abbreviations: ATP= adenosin triphosphate, NADH= nicotinamide adenine dinucleotide, FADH₂= flavin adenosine dinucleotide, PDH= pyruvate dehydrogenase, dysf = dysfunction, def = deficiency.

At least one thing is clear throughout the history of critical care: critically ill patients with increased blood lactate levels generally have significantly increased risk of morbidity and mortality, and the early identification and rapid treatment of these patients is widely acknowledged as a vital step towards improving survival (4). However, many issues remain to be elucidated. As in clinical practice treatment is frequently started before the first lactate level has been measured (e.g. oxygen, fluids), the prognostic value of lactate in the very early stage of critical illness, where no treatment has taken place (e.g. in pre-hospital care), is unknown. We therefore investigated the value of lactate measurements when performed by paramedic ambulance staff in the earliest possible stage (chapter 4).

Another unresolved question is whether the predictive value of blood lactate levels equally applies to different groups of critically ill patients. Therefore, we investigated if the ICU admission diagnosis has any relevance for the prognostic value of lactate (chapter 5).

Finally, although lactate is clearly related to mortality, it is not yet established why patients with hyperlactataemia have a worse outcome. As multiple organ failure is the leading cause of death in ICU patients, we investigated the association between blood lactate levels and organ failure as expressed by the SOFA (sequential organ failure assessment) score and its various sub scores (chapter 6).

Despite all these considerations the most important question still remains unanswered: will the use of lactate as an endpoint of resuscitation in goal-directed therapy actually improve patient outcome? Therefore, we conducted a randomized controlled multi-centre trial, in which critically ill patients were randomly allocated to either lactate monitoring (lactate group) or no lactate monitoring (control group) during the first eight hours of ICU stay (chapter 7). The results of this study should have important implications, not only for the use of lactate as a clinical monitor, but also for the initial goal-directed therapy of ICU patients in general.

Furthermore, during the enrolment process of this clinical trial that used deferred consent, the situation arose that no deferred consent could be obtained from patients who died very early after start of the study. In chapter 8 we discuss whether data of these patients should be used or not? In chapter 9 we illustrate the impact of this ethical dilemma with data of our randomized controlled trial. Finally, in order to solve this matter for future research in an ethically valid and practically feasible way, we designed a flow chart for the conduct of emergency critical care research (chapter 10).

BACKGROUND INFORMATION ON OXYGEN TRANSPORT

Before investigating goal-directed therapy (**chapter 7**), some basic principles related to oxygen transport require clarification.

Global O₂ transport can be described using the following formulas:

$$DO_2 = CO \times CaO_2$$

$$VO_2 = CO \times (CaO_2 - CvO_2)$$

$$CvO_2 = CaO_2 - VO_2/CO$$

$$O_2ER = VO_2 / DO_2 = (SaO_2 - SvO_2) / SaO_2$$

DO₂ = oxygen delivery (ml/min)

VO₂ = oxygen consumption (ml/min)

CO = cardiac output

Hb = haemoglobin

SaO₂ = arterial oxygen saturation

SvO₂ = mixed venous oxygen saturation

CaO₂ = arterial oxygen content = (1.36 x Hb x SaO₂) + (0.0031 x PaO₂)

CvO₂ = mixed venous oxygen content = (1.36 X Hb X SvO₂) + (0.0031 X PvO₂)

PaO₂ = arterial partial pressure of oxygen

PvO₂ = mixed venous partial pressure of oxygen

O₂ER = oxygen extraction ratio

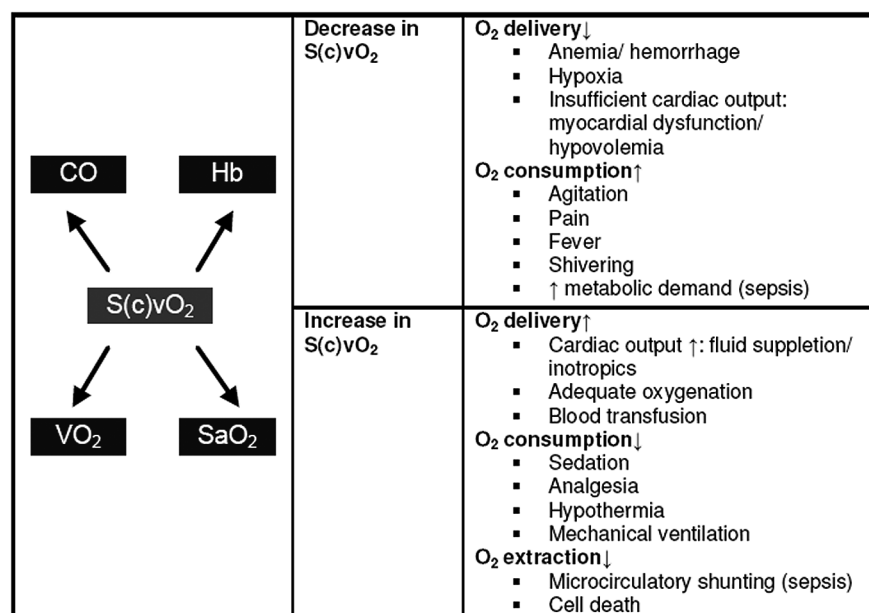
When haemoglobin levels and arterial oxygen saturation remain unchanged and given the fact that the freely dissolved oxygen can be neglected (multiplier of 0.0031), SvO₂ is directly proportional to changes in the ratio of VO₂ to CO. SvO₂ thus reflects the relationship between whole-body O₂ consumption and cardiac output.

With help of the oxygen transport formulas, multiple causes of SvO₂ changes can be described. VO₂ and the components of DO₂ (CO, Hb and SaO₂) interfere as is shown in figure 2. Note that drops in SvO₂ are not only caused by decreases in DO₂. Elevated oxygen consumption due to fever (5), pain, agitation (6) and increased metabolic activity in sepsis (7), are very common in the ICU. In the first hours after major surgery, significant reductions in ScvO₂ were observed and these were not related to lower DO₂, stressing the importance of post-operative increased oxygen consumption for ScvO₂ (8).

The human body cannot spontaneously increase SaO₂ or hemoglobin level (at least not immediately). Increased VO₂ is thus compensated by increased CO or by elevated oxygen extraction in the peripheral tissues. An increase of CO would be the organism's first choice to maintain VO₂. When O₂ need is not fulfilled by an adequate rise in CO, however, increased O₂ extraction ensues, decreasing the SvO₂ value. Importantly, also in healthy individuals, SvO₂ decreases during heavy exercise despite a marked increase in CO. Adaptation may play an important role, as healthy individuals may exhibit tissue hypoxia when ScvO₂ values drop to 30 – 40% for a relatively short time, whereas patients with severe chronic heart failure may live constantly in this low range without developing tissue hypoxia (9). However, these patients can increase their VO₂ only to a limited degree, as cardiac output cannot be raised and oxygen extraction is close to its limits. In hyperdynamic septic shock, patients seldom exhibit SvO₂ levels less than 65%. However, it is a misperception that septic patients always have normal or high venous saturations. In the early (hypovolemic) course of severe sepsis and septic shock, venous saturations may well be below 50% (4).

A normal or high SvO_2 or $ScvO_2$ (>70%) may indicate a well-balanced oxygen supply for the body's need. Unfortunately, normal or high values do not guarantee adequate tissue oxygenation. Only if tissue is still capable of extracting oxygen, $S(c)vO_2$ can be reduced. In case of microcirculatory and mitochondrial dysfunction in sepsis (10) or local necrosis (e.g. limb or bowel ischaemia), venous return may have high O_2 content despite persistent cellular hypoxia. Venous hyperoxia (>80%) was found to be indicative of a defect in systemic oxygen utilization after prolonged cardiac arrest (11).

Figure 2. Multiple factors influencing $S(c)vO_2$



SvO_2 versus $ScvO_2$

The use of central ($ScvO_2$) rather than mixed (SvO_2) venous saturation has attracted attention of ICU clinicians. Central venous catheters are routinely inserted for central venous pressure recording and the infusion of vasoactive drugs or parenteral nutrition and consequently, $ScvO_2$ measurement does not involve extra risks. Moreover, it is less time-consuming compared with SvO_2 measurement.

The central venous catheter sampling-site usually resides in the superior vena cava. Blood from the inferior vena cava (e.g. effluent from intra- abdominal organs) is therefore mainly neglected and $ScvO_2$ thus represents upper body oxygen balance. Venous O_2 saturations differ among several organ systems since different organs extract different amounts of O_2 (12). In healthy conditions, SvO_2 exceeds $ScvO_2$ by about 2–3% (7). However, this difference changes under conditions of circulatory shock. In shock, $ScvO_2$ exceeds SvO_2 by about 5% (13, 14). During redistribution in low- flow shock states, splanchnic, mesenteric and renal blood flow decrease, resulting in an increase in O_2 extraction in these regions and a subsequent decrease in inferior vena cava saturation. In hyperdynamic septic shock, increased regional splanchnic metabolic rate rather than reduced perfusion, leads to lower SO_2 in lower body venous return (7). Contrary to blood flow to the abdominal organs, cerebral flow is maintained over some period in shock, resulting in a delayed or absent drop of $ScvO_2$ compared with SvO_2 .

Another possible explanation of a lower level of SvO_2 in comparison with $ScvO_2$ is the mixing of atrial blood with blood emanating from the coronary sinus. Although coronary sinus flow may only be a fraction of total blood flow, the effluent from the coronary sinus has a very low SO_2 (15). In shock, coronary blood flow is increased as a consequence of coronary vasodilatation while oxygen extraction of the myocardium remains high (16), thereby reducing SvO_2 in comparison with $ScvO_2$.

The difference between $ScvO_2$ and SvO_2 is not equal in different ranges of cardiac output. A reversed correlation of the magnitude of the $ScvO_2 - SvO_2$ difference to CI and DO_2 has been found (13, 17). Again, distribution of blood flow in low- flow conditions away from renal, splanchnic and mesenteric areas towards the brain and myocardium is likely to explain this phenomenon.

Due to the lack of numerical equivalence, some authors have concluded that $ScvO_2$ cannot be used as a surrogate for SvO_2 in the clinical setting (13, 14, 18, 19). Biases (mean of the differences) between the two sample sites ranged from 1% (17) to 7% (20) but

more importantly, 95% confidence intervals of these biases were often clinically unacceptable (13, 14, 18, 21). In a study with a mean bias of -5% and a 95% confidence interval of 5% to -16% (14), a ScvO₂ measurement of 74% would correspond to an SvO₂ of 69% with an uncertainty of the estimate ranging from 58 to 79%. It thus demonstrates a great variability between individual absolute values and such variability would possibly urge the clinician to inappropriate actions; especially when the ScvO₂ value is around the normal limit of 70%.

Others stated that ScvO₂ could indeed be used as a substitute for SvO₂. They emphasized that from a clinical point of view, ScvO₂ needs to be interpreted over time and changes in ScvO₂ would be able to parallel changes in SvO₂ across a wide range of hemodynamic conditions (20-22). In addition, the approximately 5% numerical difference between SvO₂ and ScvO₂ values is found to be consistent, yet less important when addressing severe cases of oxygen imbalance (23). A low ScvO₂ – the range in which Rivers' goal directed therapy was beneficial (4) – would result in even lower SvO₂ values. Thus, irrespective of whether ScvO₂ equals SvO₂, the presence of a low ScvO₂ level is associated with adverse outcome, and correcting this value could improve this. Insertion of a pulmonary artery catheter can be time-consuming (24), whereas a central venous catheter can be introduced faster or is already inserted prior to ICU admission (in the operation theatre or emergency department). Therefore, the lack of accuracy of ScvO₂- measurement could be compensated by positive outcome-effects of an earlier start of ScvO₂- based therapy (25).

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HISTORY OF BLOOD LACTATE MEASUREMENT

CHAPTER 2

The first demonstration of lactic acid in human blood in shock by Johann Joseph Scherer (1814-1869) in January 1843

Intensive Care Med 2007 Nov;33(11): 1967-71

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ABSTRACT

Lactic acid was first found and described in sour milk by Karl Wilhelm Scheele (1742–1786) in 1780. The German physician–chemist Johann Joseph Scherer (1841–1869) demonstrated the occurrence of lactic acid in human blood under pathological conditions in 1843 and 1851. In this article we honour the forgotten observations by Scherer and describe the influence of Scherer’s finding on further research on lactic acid at the end of the 19th century. We conclude that Scherer’s 1843 case reports should be cited as the first description of lactic acid in human blood after death and also as the first demonstration of lactic acid as a pathological finding in septic and haemorrhagic shock. Carl Folwarczny was, in 1858, the first to demonstrate lactic acid in blood in a living patient.

INTRODUCTION

Lactic acid was first found and described in sour milk by the Swedish chemist Karl Wilhelm Scheele (1742–1786) in 1780 [1]. The Swedish chemist Jöns Jakob Berzelius (1779–1848) found lactic acid in fluid extracted from meat in 1808 [2, 3], and the German chemist Justus von Liebig (1803–1873), who established the world’s first school of chemistry at Giessen, proved that lactic acid was always present in muscular tissue of dead organisms [4]. In 1859, Emil Heinrich du Bois-Reymond (1818–1896) published several articles on the influence of lactic acid on muscle contraction [5–9]. Araki and Zillessen found that if they interrupted oxygen supply to muscles in mammals and birds, lactic acid was formed and increased [10–14]. This was the first demonstration of the relationship between tissue hypoxia and the formation of lactate. The occurrence of increased lactic acid in blood (hyperlactataemia) nowadays reflects severe illness, in which the increased blood lactate levels may result from both anaerobic and aerobic production or from a decreased clearance.

It was the German physician–chemist Johann Joseph Scherer who first demonstrated the occurrence of lactic acid in human blood under pathological conditions after death in 1843 and 1851 [15, 17], and Carl Folwarczny in 1858 who first demonstrated lactic acid in blood of a living patient. In this article we wish to honour Scherer’s forgotten observations and describe the influence of his finding on further research on lactic acid at the end of the 19th century.

BIOGRAPHY OF JOHANN JOSEPH SCHERER

Born on 18 March 1814 in Aschaffenburg, Germany, Scherer studied medicine, chemistry, geology and mineralogy at the university of Würzburg between 1833 and 1836. He obtained his PhD in medicine and surgery in 1838 with a thesis entitled “*Versuche über die Wirkung einiger Gifte auf verschiedene Thierclassen*” (Experiments on the action of some poisons on several classes of animals). He practiced medicine in Wipfeld, but inspired by the chemist Ernst

von Bibra (1806–1878) he completed his studies in chemistry at the University of Munich between 1838–1840 [18]. In 1840 he was employed at the laboratory of Justus Liebig at Giessen, and became professor at the medical faculty in 1842, professor of organic chemistry in 1847, and later professor of general, anorganic and pharmaceutical chemistry. His work especially concerned quantitative

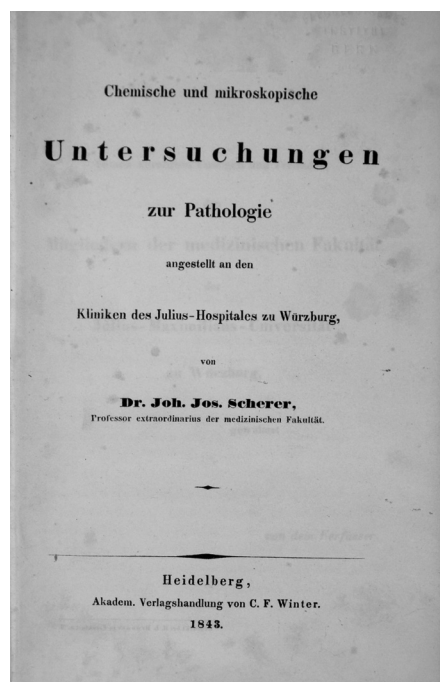


Fig. 1 Title page of Scherer's 1843 book

research on blood and urine in pathological conditions. In 1843 he published his book 'Chemische und Mikroskopische Untersuchungen zur Pathologie angestellt an den Kliniken des Julius-Hospitals zu Würzburg' (Chemical and microscopic investigations of pathology carried out at the Julius Clinic at Würzburg) [15] (Fig. 1), in which he described 72 case reports, giving details on clinical course, diagnosis, and results obtained during autopsy and analysis of body fluids. Scherer died on 17 February 1869 [18].

THE 1843 CASES

In one chapter in his 1843 book entitled 'Untersuchungen von krankhaften Stoffen bei der im Winter 1842–1843 in Würzburg und der Umgegend herrschenden Puerperal-Fieber-Epidemie' (Investigations of pathological substances obtained during the epidemic of puerperal fever which occurred in the winter of 1842–1843 in and around Würzburg) Scherer described the cases of seven young women who all died peripartum.

One of the women, the 23-year-old primipara Eva Rumpel, gave birth to a healthy child on 9 January 1843. The same night she developed a painfully swollen abdomen and became ill, feverish, and sweaty, with rapid pulse and severe thirst. The initiated treatment was bloodletting and clystering. The next evening she deteriorated, became delirious, with anxious breathing, a tense abdomen, cold extremities and rapid pulse, finally losing consciousness. Again, bloodletting followed. At 4:30 a.m., 36 h after the onset of the first symptoms, she died. During autopsy, severe purulent endometritis, vaginal pus, pulmonary oedema, and shock liver and shock spleen were found. The blood that was obtained directly from the heart was chemically analyzed, in which lactic acid was found. Most likely this unfortunate woman had died from a fulminant septic shock caused by group A haemolytic streptococci (*Streptococcus pyogenes*). Scherer diagnosed this case as perimetritis with secondary peritonitis.

Another patient, the 28-year-old, 7 months pregnant (second pregnancy) Margaretha Glück, was, after being icteric, nauseous, vomiting and complaining about epigastric pain for 8 days, admitted to the lying-in birth clinic on 6 February 1843. Four days later she was transferred to the hospital with severe nosebleeds and generalized exanthema or purpura. In the evening she suffered from severe gastric bleeding and epistaxis, showing rapid pulse, cold extremities and dizziness. The next morning, she was transferred back to the birth clinic, where she gave birth to a premature child (30 weeks) and suffered from a severe post-partum fluxus. She was again transferred to the hospital with the following symptoms: cold clammy skin, tachycardia, severe lochia and persistent exanthema or purpura, but without signs of an acute abdomen. During the night of February 11, she became aphasic and restless, followed by chills and profound sweating. On the morning of February 13, she further deteriorated and bilirubinuria was detected. The next day she was comatose, finally developed rattling breathing and convulsions. Death occurred during the following night. Autopsy revealed a small intracerebral haematoma, normal lungs without pulmonary oedema, ascites and an anaemic, foul smelling uterus filled with purulent and decayed tissue and pus. Blood was also obtained directly

from the heart during autopsy and lactic acid was found. In this case we could think of a haemorrhagic shock and cerebral haemorrhage due to clotting disorders possibly resulting from either acute fatty liver of pregnancy/ HELLP syndrome, idiopathic thrombocytopenic purpura, thrombotic microangiopathy (TTP/HUS) or DIC. The case was most likely complicated by a sepsis (endometritis). Scherer himself diagnosed this case as septic endometritis.

In the conclusions of his 1843 book, Scherer attached high importance to the fact that he found lactic acid in cases of puerperal fever, which he had not found before in healthy persons. He held the opinion that lactic acid was formed in blood during bodily deterioration in severe diseases like puerperal fever. Lactic acid was thus described for the first time in human blood and was demonstrated for the first time as a symptom of septic and haemorrhagic shock.

In the same period a junior obstetrician in Vienna, Ignaz Philipp Semmelweis (1818–1865), discovered in 1847 that physicians carried infectious particles on their hands from the mortuary to the obstetrical clinic, causing puerperal fever and puerperal sepsis, and he introduced a successful method for its prevention. Louis Pasteur (1822–1894) found in 1879 that infection with streptococci was the most important cause of puerperal fever [16].

THE 1851 ARTICLE

Scherer worked closely with the famous pathologist Rudolf Virchow (1821–1902) on several projects (Fig. 2). In 1851 Virchow performed an autopsy on a patient who had died from leukaemia and offered Scherer blood from this patient for analysis. The results of this analysis were published the same year in the *‘Verhandlungen der Physikalisch-Medicinischen Gesellschaft in Würzburg’* [17]. Virchow and Scherer had previously studied the spleens of patients who died from leukaemia, and were curious if they could find the same results in the blood. Scherer reached the conclusion that: the blood of this patient contains: *“Ameisensäure, Essigsäure und Milchsäure,*

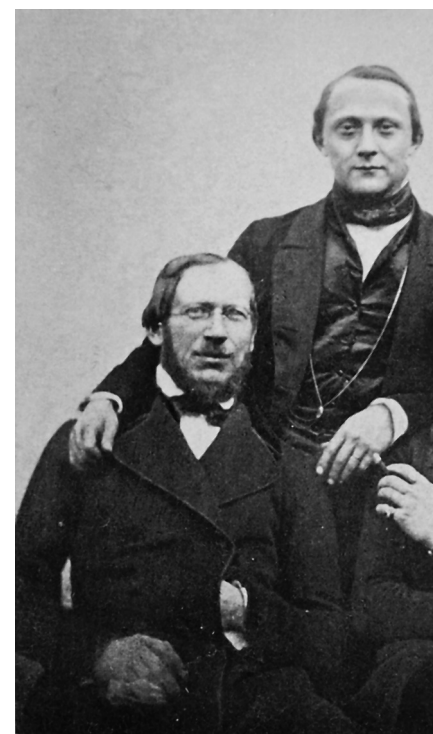


Fig. 2 Johann Joseph Scherer (left) and Rudolf Virchow (right) in 1849

die gleichfalls von mir schon früher als in der Milzflüssigkeit vorkommend bezeichnet wurden“ (Formic acid, acetic acid, and lactic acid, as also found by me previously in fluids from the spleen).

FURTHER RESEARCH

Scherer’s observations inspired others to conduct further research, primarily in patients with leukaemia [19–22], but also in patients with other conditions and diseases and in animal experiments with dogs and rabbits [23]. While Scherer found lactic acid in blood obtained after

death during autopsy, Mosler and Körner [19] mention an observation made by Carl Folwarczny, published in the *Allgemeinen Wiener Medicinischen Zeitung* in 1858, where blood was withdrawn from a leukaemia patient during life, analyzed according to Scherer’s method, and found positive for lactic acid. In addition, Carl Folwarczny described in 1863 in his *‘Handbuch der Physiologischen Chemie’* [24] that lactic acid can be found in the blood of patients with leukaemia, septicaemia (pyaemia) and in conditions leading to septicaemia like puerperal fever, the latter probably after Scherer’s observations. In an extensive article, the Berliner physician Georg Salomon [25], who had serious doubts that the occurrence of lactic acid in blood was mostly related to leukaemia, proved in 1878 that lactic acid was also present in the blood of patients who were suffering and died from other diseases. He studied blood obtained during autopsy from cadavers, but also blood from patients obtained by bloodletting or cupping, and in some cases he compared the

blood before and after death. He was able to demonstrate lactic acid in the blood of patients suffering from leukaemia, (pernicious) anaemia, congestive heart failure, chronic obstructive pulmonary disease, pleuritis, pericarditis, pneumonia and several solid malignant tumours.

Gaglio [26] is often erroneously mentioned as the first author to find lactic acid in blood [27–29]. He was able to demonstrate lactic acid in fresh arterial blood withdrawn from dogs and rabbits after blood-letting. Berlinerblau [30] confirmed these observations in mammalian and venous human blood. Both Gaglio and Berlinerblau, however, neglected previous research, as indignantly described by Salomon in 1888 [*“Ich erlaube mir, den Inhalt meiner Arbeiten, die von Gaglio nur ganz flüchtig, von Berlinerblau gar nicht berührt sind, in Kürze zu reproducieren”* (I take the liberty of summarizing the contents of my work, which was mentioned only briefly by Gaglio and not at all by Berlinerblau)] [31].

The Japanese chemist Trasaburo Araki showed that the amount of lactic acid in exhausted muscle results from muscle activation [11]. Irisawa [32], inspired by the results obtained by Salomon and Gaglio, obtained fresh blood of 11 dying patients with serious conditions. In six cases he found hyperlactataemia, in four cases normal values. He speculated on the aetiology of hyperlactataemia, the most plausible cause being the severe hypoxia during the dying process. In an experiment in which he made a dog anaemic for several days, he found a rise in lactic acid levels during the time leading up to death.

In Cambridge (UK), Walter Morley Fletcher (1873–1933) and Frederick Gowland Hopkins (1861–1947) worked together on the metabolic changes occurring in muscular contractions and rigor mortis under anaerobic conditions, and found that lactate was the product of carbohydrate metabolism [33]. Their classic 1907 paper demonstrated rigorously that muscle contraction is accompanied by the anaerobic formation of lactic acid, which is removed aerobically, at a rate depending on the level of exposure to oxygen [34]. Poul Astrup and John Severingshaus mentioned Scherer’s 1851 article

as first demonstration of lactic acid in blood, but overlooked the 1843 cases and Folwarczny’s work [35]. In conclusion, Scherer’s 1843 case reports [15] should be cited as the first description of lactic acid in human blood and also as the first demonstration of lactic acid as a pathological finding in septic and haemorrhagic shock. Folwarczny, in 1858, was the first to demonstrate lactic acid in blood in a living patient.

Acknowledgements

We would like to thank Mrs Helga Seifert, librarian, Pathologisches Institut der Universität Würzburg Bibliothek, Würzburg, Germany, for providing copies of Scherer’s 1851 paper and Gaglio’s 1888 article.

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**HEALTH
TECHNOLOGY
ASSESSMENT OF
BLOOD LACTATE
MONITORING**

CHAPTER 3

Blood lactate monitoring in critically ill patients: A systematic Health Technology Assessment

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ABSTRACT

Objective: Blood lactate monitoring has been implemented widely but its clinical value in critically ill patients has never been evaluated properly. To decide whether the use of blood lactate monitoring in critical care practice is appropriate, we performed a systematic Health Technology Assessment.

Data sources: Pubmed, other databases and citation review

Study selection: We searched for lactate combined with critically ill patients as the target patient population. Two reviewers independently selected studies based on relevance for the following questions: *I) perform well in a laboratory setting? II) provide information in a number of clinical situations? III) relate to metabolic acidosis? IV) increase workers confidence? V) alter therapeutic decisions? VI) result in benefit to patients? VII) result in similar benefits in your own setting? VIII) result in benefits which are worth the extra costs?*

Data synthesis: We concluded that blood lactate measurement in critically ill patients: I) is accurate in terms of measurement technique but adequate understanding of the (an)aerobic etiology is required for its correct interpretation, II) provides not only diagnostic but also important prognostic information III) should be directly measured instead of estimated from other acid-base variables IV) has an unknown effect on healthcare workers confidence, V) can alter therapeutic decisions, VI) could potentially improve patient outcome when combined with a treatment algorithm to optimize oxygen delivery, but this has only indirectly been shown, VII) is likely to have similar benefits in critical care settings worldwide, VIII) has an unknown cost-effectiveness.

Conclusions: the use of blood lactate monitoring certainly has a place in risk-stratification in critically ill patients, but it is unknown whether the routine use of lactate as a resuscitation endpoint improves outcome. This warrants randomized controlled studies on the efficacy of lactate-directed therapy.

INTRODUCTION

Measurement of lactate in human blood was first described by Scherer in 1843 when he described a lethal case of fulminant septic shock due to puerperal fever in a young woman (1). Blood lactate monitoring is frequently performed in critically ill patients, usually aiming to detect tissue hypoxia (2). However, other processes not related to tissue hypoxia and subsequent anaerobic metabolism can also result in increased blood lactate levels (3), complicating clinical interpretation and therapy in cases of raised lactate levels. The use of blood lactate monitoring remains controversial which is reflected by its variable clinical use in different hospitals worldwide: some routinely measure it whereas others hardly do so. Because the clinical benefit of blood lactate monitoring in critically ill patients has never been subjected to rigorous clinical evaluation, the question remains: should we routinely monitor lactate in the critically ill and if so, when should we measure it, what would be the therapeutic consequences and would this improve patient outcome? In order to address these controversies, we performed a systematic Health Technology Assessment (HTA) (4-6) which includes eight key questions (6) (table 1).

Table 1. Eight-question format for performing a systematic Health Technology Assessment

I.	Does lactate measurement perform well in a laboratory setting
II.	Does lactate monitoring provide important information in a number of clinical situations?
III.	Is there a relationship between lactate levels and metabolic acidosis?
IV.	Does lactate monitoring increase workers confidence?
V.	Does lactate measurement alter therapeutic decisions?
VI.	Does lactate monitoring result in benefit to the patients?
VII.	Can you expect a similar benefit in your own setting?
VIII.	Are the expected benefits worth the extra costs?

Adapted from Keenan et al. (6).

METHODS

Data sources

Pubmed and other databases of English and non-English language literature (up to April 2008): the Cochrane CENTRAL Register of Controlled Trials, Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews of Effects, the Health Technology Assessment Database and NHS Economic Evaluation Database. Information on ongoing clinical trials was derived from the US National Institutes of Health Web site (<http://www.clinicaltrials.gov>).

Study selection

We performed a systematic search for lactate (Medical Subject Heading (MeSH) *terms lactic acid or lactic acidosis*), in combination with critically ill patients as the target patient population (MeSH *terms intensive care units, critical care, critical illness, hospital emergency service, emergency medicine or postoperative care*). References of retrieved literature were manually reviewed for additional relevant material.

Out of the retrieved information, two reviewers (TJ and JvB) independently selected studies to be included in this health technology assessment on the basis of relevance for answering the eight key questions. Disagreements were resolved by consensus. General exclusion criteria were: no original research, case reports and articles describing D-lactate or lactate concentration in other fluids than whole blood or plasma.

For each key question (table 1), separate inclusion criteria were defined:

Question I

To evaluate how accurate lactate measurement is in ideal controlled conditions, we first included studies that evaluated the accuracy of the measurement itself by comparison with a gold standard (arterial blood as reference site and central hospital laboratory as reference technique) and that used the Bland-Altman method for assessing agreement (7).

To evaluate the diagnostic performance of lactate measurement we subsequently included studies that investigated the anaerobic and/or aerobic etiology of hyperlactatemia. Because the etiology is complex and we could not find consensus definitions of gold standards for comparison we didn't define specific methodological or statistical requirements.

Question II

In this step we focussed on the use of lactate as a prognostic tool. Because mortality is the most important and least subjective endpoint, we restricted inclusion to studies that used mortality as the primary endpoint and that provided sufficient information to construct 2x2 contingency tables or area under the receiver operating characteristic curve (AUROC).

Question III

We included studies on the association between blood lactate levels and other acid-base variables. Due to space limitations we did not include studies on the prognostic value of these acid-base variables.

Question IV

We included studies evaluating the effect of blood lactate monitoring on healthcare workers confidence.

Question V

We included studies that evaluated alterations in treatment following implementation of blood lactate monitoring protocols. We also included professional guidelines providing recommendations on blood lactate monitoring in critically ill patients.

Question VI

We included studies that combined the measurement of lactate levels with a treatment algorithm in order to provide benefit to the patient. Most studies focused on oxygen delivery (DO₂) therapy, which we classified in increasing order of importance:

1. Observational cohort studies following implementation of a lactate-guided DO₂ therapy algorithm.
2. Randomized controlled studies evaluating goal-directed DO₂ therapy that were not specifically lactate-guided, but that used lactate levels as a primary or secondary endpoint
3. Randomized controlled studies evaluating goal-directed DO₂ therapy that included a lactate-guided group and a non lactate-guided group.

For question VI, studies evaluating pre- and intra-operative interventions were excluded to increase homogeneity.

Question VII

In order to estimate whether you could experience the same benefits in your own ED or ICU, you need to know whether the demographics of your patient population are comparable, whether you have an equally educated and organized team and whether you have similar access to facilities and equipment. For this question we were not able to define specific criteria. Instead, we subjectively assessed external validity of the studies selected in step I to VI.

Question VIII

We included studies evaluating costs or cost-effectiveness of blood lactate monitoring.

RESULTS

The results of the search and selection process are described in figure 1.

I. Does it perform well in the laboratory?**Accuracy of lactate measurement:**

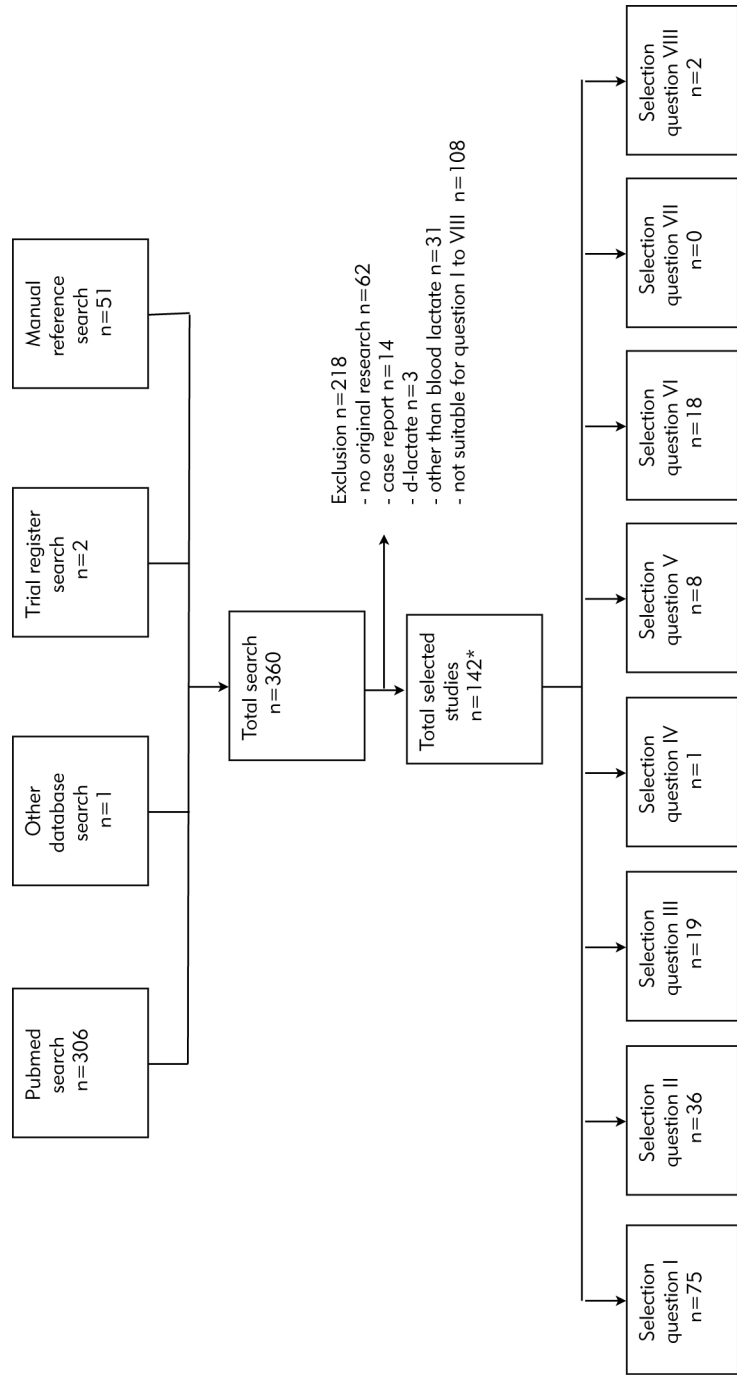
Device: Using the hospital's standard laboratory as the reference method, the selected studies generally reported small biases with clinically acceptable limits of agreement for point-of-care blood gas analyzers (Nova Stat Profile 7,10, ultra[®], Nova Biomedical, Waltham, Mass., USA (8-10), Chiron Diagnostics[®], 865 series, Fernwald, Germany/ Medfield, USA (11-14) and Radiometer ABL 725, Radiometer Medical A/S, Bronshoj, Denmark (15)) and hand-held devices (Accusport/trend[®], Roche Diagnostics, Mannheim, Germany (9-11, 16), i-STAT CG4+, East Windsor, NJ, USA (15) and Lactate Pro, ARKRAY, Kyoto, Japan (17)). Lactate plus (Nova Biomedical, Waltham, MA, USA) produced higher lactate values than the reference method (15, 17).

Compartment: Although some described slightly higher peripheral venous (18) or capillary levels (11), most investigators found satisfactory agreement comparing capillary (16, 19, 20), venous (21) or central/ mixed venous (22-24) levels with arterial levels as reference.

Sample handling: Ongoing in-vitro glycolysis was reported to occur after blood sampling, resulting in erroneous elevation of lactate levels (25), particularly in case of leucocytosis or high hematocrit (26). Analysis within 15 minutes or storage <4°C were suggested for avoiding this.

Exogenous factors: Infusion of Ringer's lactate didn't hamper accuracy (27), provided that blood was drawn from a catheter that was adequately cleared from Ringer's lactate (28). Another study showed that the most commonly used critical care drugs neither affected the

Figure 1. Search and selection process



* Sum of selected studies of question I to VIII is not equal to 142 because selected studies could be included in more than one question.

accuracy (29). Finally, renal replacement therapy eliminated only negligible amounts of lactate and consequently did not interfere with lactate monitoring (30). However, lactate-containing buffer solutions were able to induce transient hyperlactatemia (31-33).

Etiology of hyperlactatemia: *Anaerobic hyperlactatemia*

Systemic oxygen imbalance: Traditionally, hyperlactatemia is associated with tissue hypoxia. The causal relationship has been confirmed by experimental (34-36) and clinical (2) studies: when reducing the components of systemic DO_2 until oxygen demand could no longer be met, and oxygen consumption was limited by DO_2 , this coincided with a sharp increase in lactate levels.

Several other observations also pointed to an anaerobic origin of hyperlactatemia in critically ill patients. Hemodynamically unstable patients with septic or cardiogenic shock had increased lactate/pyruvate ratio's (37) and decreased arterial ketone body ratio's (i.e. ratio between acetoacetate to β -hydroxybutyrate: proposed to reflect mitochondrial redox state), suggesting anaerobic production (37, 38). In the early phase of septic shock, hyperlactatemia was accompanied by oxygen supply dependency (39). Rivers and colleagues demonstrated that hyperlactatemia in severe sepsis or septic shock prior to resuscitation coincided with a low central venous oxygen saturation ($ScvO_2$) and that increases in DO_2 were associated with reductions in lactate (40). Similarly, low skin temperature, cardiac output and mixed venous oxygen saturation (SvO_2) were associated with higher lactate levels (41).

Regional/microcirculatory oxygen imbalance: No critical level of DO_2 or SvO_2 could be associated with hyperlactatemia which could represent regional differences in oxygen delivery and demand (42). Furthermore, improving capillary perfusion was correlated with a reduction in lactate levels in patients with septic shock, independent of changes in systemic haemodynamic variables (43). The latter observation illustrates the hypothesis that, in the absence of low *systemic* DO_2 relative to *systemic* metabolic demand, microcirculatory processes hampering oxygen utilization at the tissue level may raise lactate levels.

Aerobic hyperlactatemia

Selected studies demonstrated that other mechanisms than tissue hypoxia can also account for hyperlactatemia. We found the following aerobic mechanisms:

- Increased aerobic glycolysis, resulting in amounts of pyruvate that exceed the pyruvate dehydrogenase capacity. Such enhanced glycolysis can be triggered by cytokine-mediated uptake of glucose (44, 45) or catecholamine-stimulated increased Na-K-pump activity (46-51), which was supported by a study of Levy et al. in septic shock patients, where antagonizing the Na-K-pump completely stopped muscle lactate overproduction (3).
- Mitochondrial dysfunction (52-54).
- Impaired activity of pyruvate dehydrogenase (PDH), essential for the conversion of pyruvate into acetyl co-enzyme A. This enzyme is inhibited in septic conditions (55, 56) and increasing its activity with dichloroacetate significantly reduces blood lactate levels (57). Thiamin deficiency (beri-beri's disease) inhibits PDH activity and can cause hyperlactatemia (58).
- Liver dysfunction (59-62) and liver surgery (63). Reduced lactate clearance was also reported following cardiac surgery (64) and in sepsis (65, 66), where it was shown to predict poor outcome (67).
- Not the splanchnic area (68), but the lung can be an important source of lactate, both in pulmonary (61, 69) and extra-pulmonary (70) disease, probably reflecting metabolic adaptations in response to inflammatory mediators rather than tissue hypoxia (71).
- Alkalosis (72), because an H⁺-linked carrier mechanism is involved in the transport of lactate across the cell membrane that increases cellular lactate efflux during alkalosis.

- Several drugs and intoxications: Nucleosidic reverse transcriptase inhibitors used for the treatment of HIV (by inducing mitochondrial cytopathy) (73-75), epinephrine (by increased glycogenolysis, glycolysis and stimulation of the Na-K-pump) (76, 77), metformin (particularly in the presence of renal insufficiency), although a Cochrane review found no evidence that metformin is associated with increased lactate levels if prescribed under study conditions (78). Intoxications with methanol, cyanide (by inhibition of oxidative phosphorylation) (79) or ethylene-glycol (by artifactual reaction of lactate electrodes) (80) also significantly elevated lactate levels.

II. Does it provide important information in a number of clinical situations?

We selected studies on the prognostic value of hyperlactatemia in many different critical care conditions (table 2 (ED) and 3 (ICU)). In the ED setting, AUROC for mortality varied from 0.67 (81) to 0.98 (82), which indicates moderate to excellent prognostic accuracy. In the ICU setting, AUROC varied from 0.53 (83) and 0.58 (84) to 0.86 (85), which indicates poor to good prognostic performance.

To answer the question whether a hyperlactatemic patient will die, which is what clinicians want to know when individually assessing patients, the positive predictive value or post-test probability is important. In some of our selected studies, positive predictive values for death in case of abnormal lactate levels (>2.0-2.5 mmol/l) were very low (4-15% (81, 86, 87)). However, comparison of the pre-test probability (which is the study population mortality rate) with the post-test probability determines the value that lactate can add in risk-stratification: from our selected studies it becomes clear that lactate generally increased the ability to predict non-survival, both in the ED and in ICU setting.

None of the studies took into account that the real pre-test probability not only depends on the mortality rate, but also on the clinicians'

Table 2. Prognostic value of blood lactate levels in the ED

Study	N (mortality)	Population	Timing	Cut-off value	Cut-off a priori	Sens (95% CI)	Spec (95%CI)	+LR	-LR	PPV (95%CI)	NPV (95%CI)	AUROC (95%CI)
Infection/sepsis												
Shapiro (81)	1278 (8% ²)	Patients with suspected infection	ED admission	2.5	Yes	59% (50-68)	71% (69-74)	2.0	0.5	15% (12-19)	95% (94-96)	0.67
				4.0		36% (27-46)	92% (90-93)	4.5	0.7	28% (21-37)	94% (93-95)	
Howell (87)* #	1287 (6% ³)	Patients with suspected infection	ED admission	2.5	Yes	37% (26-49)	73% (71-76)	1.4	0.9	8% (5-11)	95% (94-96)	0.72
				4.0		38% (27-50)	94% (92-95)	6.3	0.7	27% (19-37)	96% (95-97)	
Treziack (88)	1177 (19% ¹)	Patients with infection (60% ED, 22% ICU, 18% non-ICU ward)	In .60% of patients during ED stay (exact timing not available)	2.0	Yes	45% (39-52)	74% (71-77)	1.7	0.7	29% (24-34)	85% (83-88)	-
				4.0		19% (15-23)	93% (91-94)	2.6	0.9	38% (29-48)	83% (81-85)	0.56 (0.53-0.59)
Nguyen (123)	111 (42% ¹)	Patients with severe sepsis or septic shock	First 6 hrs of ED stay	10% decrease in 6 hrs	Yes	45% (30-60)	84% (73-92)	2.8	0.7	68% (49-83)	68% (56-78)	-
Trauma												
Pal (86)	5995 (3% ¹)	Trauma patients	Trauma service admission	2.0	Yes	85% (79-90)	38% (37-39)	1.4	0.4	4% (3-5)	99% (98-99)	0.72
Dunne (124)	15179 (5% ¹)	Trauma patients	Trauma center admission	6.0	Not clear	-	-	-	-	23%	98%	-
Kaplan (82)	282 (23% ²)	Major vascular injury patients	ED admission	5.0	Not clear	98% (92-100)	-	-	-	-	-	0.98 (0.96-0.99)
Cardiac arrest												
Kliegel (125)	394 (51% ⁴)	Post cardiac arrest patients (surviving > 48 hrs)	ED admission 24 hrs later 48 hrs later	2.0	Yes	-	-	-	-	-	-	-
						40% (33-47)	68% (61-75)	1.3	0.9	-	56% (47-64)	52% (46-59)
						31% (25-38)	86% (80-91)	2.2	0.8	-	70% (59-79)	55% (49-60)
Heterogeneous												
Sankoff (126)	176 (11% ³)	Heterogeneous patients with SIRS	ED admission	-	-	-	-	-	-	-	-	0.78 (0.66-0.90)

- = not available * = 3 months inclusion overlap with (81), # sens, spec, LR, PPV, NPV calculated from estimates from figure 1 = in-hospital mortality 2 = ICU mortality 3 = 28 (or 30)-day mortality 4 = 6 month mortality 5 = 24-hour mortality 6 = unspecified mortality sens = sensitivity, spec = specificity, +LR = positive likelihood ratio, -LR = negative likelihood ratio, PPV = positive predictive value, NPV = negative predictive value, AUROC = area under the receiver operating characteristic curve, CRT = capillary refill time SIRS = systemic inflammatory response syndrome

Table 3. Prognostic value of blood lactate levels in the ICU

Study	N (mortality)	Population	Timing	Cut-off value	Cut-off a priori	Sens (95% CI)	Spec (95%CI)	+LR	-LR	PPV (95%CI)	NPV (95%CI)	AUROC (95%CI)
Infection/sepsis												
Friedman (127)	35 (46% ²)	ICU patients with severe sepsis	Timing start study not clear 24 hrs after start study	2.0	Yes	81% (54-96)	47% (24-71)	1.5	0.4	57% (34-77)	75% (43-99)	-
						69% (41-89)	84% (60-97)	4.3	0.4	79% (49-95)	76% (53-92)	-
Tamion (128)	44 (30% ³)	ICU patients with septic shock	ICU admission	4.5	No	62% (32-86)	68% (49-83)	1.9	0.6	44% (22-69)	81% (61-93)	-
Dondorp (103)	268 (17% ⁴)	ICU patients with severe malaria	ICU admission	-	-	-	-	-	-	-	-	0.66 (0.56-0.76)
Trauma/ surgery												
Meregalli (84)	44 (16% ¹)	Hemodynamically stable surgical ICU patients	ICU admission (T0) and 24 and 48 hrs later	-	-	-	-	-	-	-	-	T0: 0.58
Singhai (129)	30 (50% ³)	Patients with ruptured abdominal aortic aneurysm	Post operative ICU admission	4.0	No	87% (60-98)	80% (52-96)	4.3	0.2	81% (54-96)	86% (57-98)	-
Maillet (130)	325 (5% ²)	Post cardiac surgery patients	ICU admission During ICU stay	3.0	Yes	69% (38-88)	81% (77-86)	3.6	0.4	15% (7-28)	98% (96-100)	0.84 (0.73-0.95)
						62%	75%	2.5	0.5	-	-	0.72 (0.57-0.88)
Abramson (131)	76 (33% ⁶)	Multiple trauma patients	24 hrs after ICU admission 48 hrs after ICU admission	2.0	Yes	100% (86-100)	53% (38-67)	2.1	0.0	51% (36-66)	100% (87-100)	-
						76% (55-91)	94% (84-99)	12.7	0.3	86% (65-97)	89% (77-96)	-
Martin (92)	1298 (18% ¹)	Trauma and emergency surgery patients	ICU admission	2.2	Yes	84% (78-88)	34% (32-37)	1.3	0.5	22% (19-25)	91% (87-93)	0.70 (0.67-0.74)
Blow (111)	79 (10% ⁶)	Major trauma patients, hemodynamically stable	ICU admission 24 hrs later	2.5	Yes	100% (63-100)	30% (19-42)	1.4	0.0	14% (6-25)	100% (84-100)	-
						100% (63-100)	92% (83-97)	12.5	0.0	57% (29-82)	100% (94-100)	-

Clardige (113) [^]	364 (3%)	Major trauma patients	ICU admission 24 hrs later	2.5	Yes	92% (64-100) 54% (25-81)	33% (28-39) 86% (82-89)	1.4 3.9	0.2 0.5	5% (3-8) 12% (5-24)	99% (95-100) 98% (96-99)	-
Wahl (132)	169 (11% ⁶)	Postoperative ICU patients	ICU admission	-	-	-	-	-	-	-	-	0.79
Murillo-Cabezas (133)	210 (14% ²)	Hemodynamically stable patients with moderate or severe head injury	During first 48 hrs ICU stay	2.2	Yes	53% (34-72)	56% (49-63)	1.2	0.8	17% (10-26)	88% (80-93)	-

Liver disease

Bernal (134)	93 (39% ⁶), 85 at T12,	Paracetamol induced acute liver failure (initial sample)	± ICU admission ± 12 hrs later	3.5	No	86% (71-95)	91% (81-97)	9.8	0.2	86% (71-95)	91% (81-97)	-
				3.0	-	82% (65-93)	96% (87-100)	20.5	0.2	93% (77-99)	89% (78-96)	-
Watanabe(85)	99 (21% ⁶), 85 at T12	Paracetamol induced acute liver failure (validation sample)	± ICU admission ± 12 hrs later	3.5	Yes	67% (43-85)	95% (87-99)	13.4	0.3	78% (52-94)	91% (83-96)	-
				3.0	-	76% (53-92)	97% (89-100)	25.3	0.2	89% (65-99)	93% (83-98)	-
Funk (135)	181 (50% ²)	Post liver resection patients	ICU admission	-	-	-	-	-	-	-	-	0.86
Kruse (136)	38 (68% ¹)	ICU patients with liver cirrhosis	ICU admission	8.9	No	36% (26-46)	99% (94-100)	36.0	0.6	97% (84-100)	61% (53-69)	0.81 (0.75-0.87)
				2.2	No	80% (59-93)	62% (32-86)	2.1	0.3	80% (59-93)	62% (32-86)	-
			Maximum value during ICU stay	7.0		52% (31-72)	100% (75-100)	∞	0.5	100% (75-100)	52% (31-72)	-

Heterogeneous

Smith (137)	T0: 148 (35% ³) T24: 131 (31% ³)	Heterogeneous ICU patients	ICU admission (T0) and 24 hrs later	T0: 1.5	No	69% (54-81)	77% (68-85)	3.0	0.4	61% (48-74)	82% (73-90)	0.78
				T24: 1.0	-	68% (52-82)	83% (74-90)	4.0	0.4	65% (49-79)	85% (76-92)	-
Suistomaa (138)	98 (13% ¹)	Heterogeneous emergency ICU patients	ICU admission during first 24 hrs (12 measurements)	2.0	Yes	69% (39-91)	73% (63-83)	2.7	0.4	29% (14-48)	94% (85-98)	-
					-	77% (46-95)	55% (44-66)	1.7	0.4	21% (10-35)	94% (83-99)	-

Freire (139)	319 (25% ¹)	Medical ICU patients	During first 24 hrs of ICU stay	2.0	Yes	77% (66-86)	53% (46-59)	1.6	0.4	35% (28-52)	88% (81-92)	-
				8.0	-	30% (21-42)	97% (94-99)	10.0	0.7	77% (59-90)	81% (76-85)	0.65 (0.52-0.78)
Cusack (140)	100 (31% ³)	Heterogeneous ICU patients	ICU admission	-	-	-	-	-	-	-	-	0.66 (0.59-0.73)
					-	-	-	-	-	-	-	-
Rocktaeschel (95)	300 (28% ¹)	Heterogeneous ICU patients	ICU admission	-	-	-	-	-	-	-	-	-
					-	-	-	-	-	-	-	-
Marik (83)	45 (50% ¹)	ICU patients requiring PAC	PAC insertion	-	-	-	-	-	-	-	-	-
					-	-	-	-	-	-	-	-
Maynard (141)	60 (33% ²)	Heterogeneous ICU patients	Any of 3 timepoints (ICU admission, 12 or 24 hrs later)	2.0	Yes	75% (51-91)	55% (38-71)	1.7	0.5	45% (28-64)	81% (62-94)	-
					Yes	-	-	-	-	-	-	-
Dubin (142)	935 (11% ³)	Heterogeneous ICU patients	ICU admission	2.4	Yes	-	-	-	-	-	-	-
					No	62% (39-84)	88% (71-98)	5.2	0.4	80% (52-96)	77% (59-90)	-
Aduen (8)	46 (41% ⁶)	Hypotensive ICU/ED patients (76% ICU)	During ICU/ED stay	4.0	No	29% (17-42)	96% (93-98)	7.3	0.7	57% (37-76)	88% (84-91)	-
					-	-	-	-	-	-	-	-
Levy (143)	95 (44% ³)	Heterogeneous ICU patients	ICU admission	-	-	-	-	-	-	-	-	-
				2.5	No	72% (55-84)	73% (60-85)	2.7	0.4	68% (52-81)	77% (63-87)	0.74

Others

Sasaki (144)	41 (44% ¹)	ICU patients with RRT	At onset RRT	3.5	No	83% (59-96)	91% (72-99)	9.2	0.2	88% (64-99)	88% (68-97)	-
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Children

Hatherill (145)	705 (10% ³) 50 (64% ²), from cohort of 705	PICU children Hyperlactatemic (>2.0) PICU children	PICU admission PICU admission 24 hrs later	2.0	Yes	46% (34-58)	97% (96-98)	15.3	0.6	64% (49-77)	94% (92-96)	-
					No	-	-	-	-	-	-	-
Hatherill (146)	99 (9% ²)	Post- cardiac surgery children	PICU admission	6.0	No	78% (40-97)	83% (74-90)	4.6	0.3	32% (14-55)	97% (91-100)	-
					Yes	70% (60-90)	89% (65-99)	7.1	0.2	93% (76-99)	70% (47-87)	0.86 (0.73-0.99)

Hatherill (147)	46 (35%) ²	PICU patients with hypotension or CRT	PICU admission	5.0	No	75% (49-93)	63% (44-80)	2.0	0.4	52% (31-73)	83% (61-95)	0.83 (0.71-0.95)
	38 (21%) ²		24 hrs later			25% (3-65)	83% (65-94)	1.5	0.9	29% (4-71)	81% (63-93)	-
Garcia Sanz (148)	500 (7%) ²	Heterogeneous PICU patients	PICU admission	2.0	Yes	65% (46-79)	71% (66-75)	2.2	0.5	16% (9-21)	97% (94-98)	0.76 (0.67-0.85)
				3.7	No	56% (38-72)	91% (88-94)	6.2	0.5	33% (21-46)	96% (94-98)	
				5.0	Not clear	47% (30-65)	94% (92-96)	7.8	0.6	41% (24-55)	96% (94-97)	
				7.0	Not clear	32% (19-51)	98% (96-99)	16	0.7	52% (31-73)	95% (93-97)	
Balasubramanyan (91)	66 (29%) ²	Heterogeneous PICU patients	Not clear	5.0	Not clear	37% (16-62)	87% (74-95)	2.8	0.7	54% (25-81)	77% (64-88)	0.63
Shime (157)	141 (8%) ²	Post cardiac surgery children	PICU admission	3.0	Not clear	64% (31-89)	87% (80-92)	4.9	0.4	29% (13-51)	97% (91-99)	-
				4.0	clear	36% (11-69)	93% (87-96)	5.1	0.7	31% (9-61)	94% (89-98)	
Koliski (149)	75 (24%) ⁶	Heterogeneous PICU patients	PICU admission	2.0	Yes	83% (59-96)	39% (26-52)	1.4	0.4	30% (18-44)	88% (69-98)	-
				2.8	No	71% (47-90)	63% (49-76)	1.9	0.5	38% (22-56)	88% (74-96)	0.68
				1.3	No	64%	61%	1.6	0.6			0.62
Gotay-Cruz (150)	10 (20%) ⁶	Heterogeneous PICU patients	Peak during PICU stay	3.0	No	56%	97%	18.7	0.5			0.81
				2.5	Yes	100% (16-100)	63% (24-92)	2.7	0.0	40% (5-85)	100% (48-100)	-
Cheung (151)	85 (16%) ¹	Infants post congenital heart surgery	PICU admission	7.0	No	92% (66-100)	69% (57-79)	3.0	0.1	33% (21-55)	98% (89-100)	-
					Yes	40% (16-68)	97% (88-100)	13.3	0.6	75% (35-97)	86% (76-94)	-
Cheung (152)	74 (20%) ²	Neonates treated with ECMO	NICU admission	25	Yes	53% (27-79)	100% (94-100)	∞	0.5	100% (63-100)	89% (79-96)	-
				15	No	60% (15-95)	83% (72-90)	3.5	0.5	18% (4-43)	97% (90-100)	0.71 (0.44-0.98)
Durward (101)	85 (6%) ²	Post cardiac surgery children	PICU admission	2.0	Yes	60%	94%	9.6		60%	94%	
				3.0	No	60%	83% (72-90)	3.5	0.5	18% (4-43)	97% (90-100)	0.80 (0.56-1.00)
			24 hrs later	2.0	Yes	60% (15-95)	83% (72-90)	3.5	0.5	18% (4-43)	97% (90-100)	

- = not available [^] = 6 months inclusion overlap with (11), # sens, spec, LR, PPV, NPV calculated from estimates from figure 1 = in-hospital mortality 2 = ICU mortality 3 = 28 (or 30)-day mortality 4 = 6 month mortality 5 = 24 hour mortality 6 = unspecified mortality 6 = unspecified mortality sens = sensitivity, spec = specificity, +LR = positive likelihood ratio, -LR = negative likelihood ratio, PPV = positive predictive value, NPV = negative predictive value, AUROC = area under the receiver operating characteristic curve, CRT = capillary refill time, RRT = renal replacement therapy, PAC = pulmonary artery catheter, ∞ = infinite, PICU = pediatric intensive care unit, CRT = capillary refill time, ECMO = extracorporeal membrane oxygenation

ability to estimate risk using all other available clinical parameters. Some authors therefore called for a future study that captures clinicians' estimates for probability of death prior to lactate measurement, in order to evaluate the capacity to influence clinical practice decisions (88).

III. Is there a relationship between lactate levels and metabolic acidosis?

The level of lactate may be estimated from other acid base variables. However, there was no clinically important relationship between lactate and pH or base excess (89-94), although one study showed that base excess could predict hyperlactatemia (95). Accuracy of the anion gap for screening for hyperlactatemia was generally poor (96-99), but this varied to reasonably accurate (95). Other studies showed that lactate was only responsible for a minor percentage of metabolic acidosis in critically ill patients (93, 100-103). Furthermore, lactate or non-lactate etiologies of metabolic acidosis are associated with different mortality rates (89, 104). Therefore, although hyperlactatemia has often been associated with the presence of a metabolic acidosis (lactic acidosis), this relationship appeared not straightforward at all. Because the conversion of pyruvate to lactate does not directly result in production of H⁺ ions, it was hypothesized that only if the H⁺ ions generated during the hydrolysis of adenosine triphosphate cannot be recycled in the mitochondria, i.e. in anaerobic conditions, acidosis coincides with hyperlactatemia (105). Following this hypothesis, it has been argued that the presence of metabolic acidosis can be used to distinguish aerobic from anaerobic hyperlactatemia (106).

The weak correlation between hyperlactatemia and metabolic acidosis has also been explained from another point of view. In Stewart's acid-base classification three independent variables control pH: strong ion difference (SID), pCO₂ and the sum of the weak acids and proteins in plasma (107). An increased lactate level reduces SID, which has an acidifying effect. However, in the Stew-

art's model, this does not necessarily result in acidosis because other simultaneous alterations in SID, changes in the amount of weak acids and proteins, or changes in $p\text{CO}_2$ can all influence pH (93, 100).

IV. Does it increase healthcare worker confidence?

Information provided by a parameter may lead to increased confidence among health care providers. Although questionable if no other clinical endpoint (mortality, morbidity, costs) is improved, increased confidence might be an important goal when decisions are made in conditions of uncertainty in critical care. For instance, in a trial on peri-operative pulse oximetry, the rate of complications was not reduced, but 80% of the anesthesiologists felt more secure when using a pulse oximeter (108). It seems likely that lactate determinations could increase worker confidence because rapidly available and definite endpoints of resuscitation are scarce. An observation that the nursing team expressed a positive attitude towards implementation of a hemodynamic protocol that included frequent lactate measurements, indirectly supports this (109). However, we were not able to find a study that specifically evaluated the effect on healthcare workers confidence.

V. Are therapeutic decisions altered as a result of blood lactate levels?

In studies on treatment alterations following implementation of lactate monitoring, hyperlactatemia was interpreted as a result of anaerobic conditions due to systemic oxygen imbalance and this was a trigger to increase oxygen delivery or decrease oxygen demand (110-113). This included administration of fluids, inotropic agents, red blood cell transfusion, mechanical ventilation, paralytic agents, sedatives and analgetics. In the only randomized controlled study in which measurement of lactate was compared with not

measuring lactate, more fluids and inotropes were administered in the lactate group (114).

We also selected professional guidelines: the Surviving Sepsis Campaign recommends the use of lactate as a trigger for early goal-directed therapy (≥ 4 mmol/l) (115). The Clinical Practice Guideline concerning trauma resuscitation recommends lactate as a resuscitation endpoint but acknowledged that evidence of improved survival of such strategy has not been shown (116). Finally, the International Consensus Conference (ICC) 2006 on hemodynamic monitoring and management of patients in shock also stresses the lack of clinical trials investigating the clinical value of incorporating lactate in a treatment protocol (117).

VI. Does application of blood lactate monitoring result in benefit to patients?

As monitoring itself will not change outcome, an integrated treatment algorithm has to provide the benefit to patients. This has to be aimed at the conditions leading to hyperlactatemia rather than at reduction of lactate levels alone. For instance, improving pyruvate metabolism by administration of dichloroacetate decreased lactate levels (57) but this was not associated with a clinical benefit. Another study showed that bicarbonate therapy didn't improve hemodynamic variables in patients with lactic acidosis (118). These observations indicate that the detrimental outcome associated with hyperlactatemia is more likely to be determined by the underlying cause than by the hyperlactatemia itself.

We selected four observational studies evaluating implementation of a lactate-guided DO_2 therapy algorithm (table 4A). Lactate levels decreased significantly during lactate-guided therapy (110, 111, 113), which coincided with an increase in ScvO_2 in one study (110). Patients who responded with normalization of lactate had lower mortality than those who remained hyperlactatemic (111, 113). One observational study made a comparison with an historical

Table 4A. Observational cohort studies following implementation of a lactate-guided DO₂ therapy algorithm

Study	N	Patients	Timing	Goals of therapy	Provided therapy	Primary endpoint	Lactate on entry:	Lactate after therapy:	Outcome
Rady (110)	36	Heterogeneous critically ill ED patients	During ED stay (6±3 hrs)	Lactate < 2.0 and ScvO ₂ ≥65%	22% MV and paralysis, 6% RBC's, 97% fluids, 75% vasoactive agents	Lactate and ScvO ₂	4.6±3.8	2.6±2.5, (p<0.05 vs entry)	↓ lactate and ↑ ScvO ₂ (52±18% to 65±13%, p<0.05) after DO ₂ therapy
Blow (111)	79	Hemodynamically stable major trauma patients	First 24 hrs of ICU stay	Lactate < 2.5	Fluids, RBC's, dopa, dobu (amounts not recorded)	In-hospital mortality	58/79 (73%) lactate >2.4	14/79 (18%) lactate >2.4 after 24 hrs (p<0.05 vs entry)	↓ mortality in normo- vs hyperlactatemia after 24 hrs: 0/65 (0%) vs 6/14 (43%), p<0.05
Claridge (113)	364	Major trauma patients	First 24 hrs of ICU stay	Lactate < 2.5	Fluids, RBC's, dopa, dobu (amounts not recorded)	Infectious complications	246/364 (68%) lactate >2.4	57/364 (16%) lactate >2.4 after 24 hrs (p<0.05 vs entry)	↑ infection rate late (>12 hrs) vs early (<12 hrs) normalization lactate: OR 5.3 (95% CI 3.1-9.3)
Rossi (112)	710 (+ 1656 historical controls)	Children after congenital heart surgery	Early hrs of ICU stay	Lactate < 2.2 or decrease > 0.5/hr vs no lactate in control group	Any method to ↑ DO ₂ or ↓ VO ₂ (type/amount not recorded)	In-hospital mortality	Not available	Not available	↓ mortality on comparison with historical control group: 13/710 (2%) vs 61/1656 (4%), p=0.02

Lactate = mean blood lactate level (mmol/l), CI = cardiac index (l/min/m²), DO₂I = oxygen delivery index (ml/min/m²), VO₂I = oxygen consumption index (ml/min/m²). ED = emergency department, MV = mechanical ventilation, RBCs = red blood cells, ICU = intensive care unit

control group and found lower mortality following implementation of a lactate-guided DO₂ therapy algorithm (112).

We selected nine randomized controlled studies that evaluated goal-directed DO₂ therapy, which was not specifically lactate-guided, but that used lactate levels as a primary or secondary endpoint (table 4B). Out of the five studies that showed a positive outcome (40, 119-122), three studies reported a decrease of lactate in the intervention group compared with the control group (40, 120, 122).

However, we found only one completed randomized controlled study evaluating goal-directed DO₂ therapy that included a lactate-guided and a non lactate-guided group (table 4C). This study in a post cardiac-surgery population showed a reduction in length of stay in the lactate-guided group (114). Two studies are currently ongoing.

VII. Can you expect a similar benefit in your own setting?

To answer this question the external validity of the previously selected studies needs to be determined. Given that lactate measurement is generally considered as easy and accurate, that it is commonly available worldwide and given that evidence on the prognostic value of hyperlactatemia has been very consistent and applies to many different populations, it is clear that lactate can be used as a prognostic marker in your own setting. However, the value of lactate as a therapeutic tool remains unclear.

VIII. Are the expected benefits worth the costs?

A hand-held lactate device, such as accutrend®, costs around € 200 and a test strip costs € 2. The price of a blood gas analyzer is around € 30 000 and total costs per sample are € 2 (10). In a German study, total costs were lowest with €1 per measurement using

Table 4B. Randomized controlled studies evaluating goal-directed DO2 therapy that were not specifically lactate-guided, but that used lactate levels as a primary or secondary endpoint

Study	N (intervention vs control)	Patients	Timing	Goals of therapy (differences intervention vs control)	Provided therapy (significant differences intervention vs control)	Primary endpoint	Lactate on entry: (intervention vs control)	Lactate after therapy: (intervention vs control)	Outcome: (intervention vs control)
Tuschmidt (153)	51 (26 vs 25)	Septic shock patients	72 hrs in the ICU	CI \geq 6 vs CI \geq 3	\uparrow dose dobu (30 \pm 1 vs 12 \pm 1 μ g/kg/min)	In-hospital mortality	4.7 \pm 0.1 vs 5.1 \pm 0.6, p>0.05	After 72 hrs: 3.8 \pm 0.6 vs 4.5 \pm 0.8, p>0.05	Equal mortality: 13/26 (50%) vs 18/25 (72%), p=0.14
Hayes (154)	100 (50 vs 50)	Heterogeneous ICU patients	During ICI stay	CI \geq 4.5, DO2I \geq 600 and VO2I \geq 170 vs CI \geq 2.8	\uparrow max dose dobu: (25 vs 10 μ g/kg/min), \uparrow max dose nor: (1.2 vs 0.23 μ g/kg/min)	In-hospital mortality	2.2 (median, IQR 1.8-3.5) vs 2.1 (1.5-3.3), p=0.69	After 48 hrs: 1.7 (median, IQR 1.2-2.5) vs 1.5 (1.1-2.1), p=0.20	\uparrow mortality: 27/50 (54%) vs 17/50 (34%), p=0.04
Durham (155)	58 (27 vs 31)	Heterogeneous ICU patients (most trauma)	During indication PAC	DO2I \geq 600 or VO2I \geq 150 vs CI > 2.5	Not available	Mortality	5.3 \pm 2.3 vs 5.8 \pm 2.9, p=0.53	After 24 hrs: 2.1 \pm 1.3 vs 2.4 \pm 2.0, p=0.52	Equal mortality: 3/27 (11%) vs 3/31 (10%), p=0.85
Ueno (120)	34 (16 vs 18)	Partial hepatectomy patients	First 24 post-operative hours in ICU	CI \geq 4.5, DO2I \geq 600 or VO2I \geq 170 vs CI \geq 2.8-4.0	\uparrow dobu (69 vs 0%), \uparrow fluids 12-24 hrs (43 \pm 19 vs 32 \pm 6 ml/kg)	Not clear	3.2 \pm 1.0 vs 3.3 \pm 0.8, p>0.05 (from figure)	After 12 hrs: 2.0 \pm 0.7 vs 2.9 \pm 0.8, p<0.05 After 24 hrs: 1.1 \pm 0.2 vs 2.0 \pm 0.3, p<0.05 (from figure)	\downarrow postoperative hyperbilirubinemia: 0/16 (0%) vs 3/18 (17%), p<0.05 Equal mortality: 0/16 (0%) vs 2/18 (11%), p>0.05
Yu (119)	105 (64 vs 41)	Surgical ICU patients (age 50-75 and >75 yrs)	During indication PAC	DO2I \geq 600 vs DO2I \geq 450-550	\uparrow inotropes in 50-75 yrs (91 vs 52%), \uparrow inotropes in >75 yrs (95 vs 56%)	Mortality	\bullet 50-75yrs: 2.5 \pm 1.7 vs 2.2 \pm 1.4, p=0.44 \bullet >75 yrs: 3.4 \pm 2.3 vs 3.7 \pm 2.8, p=0.76	After 24 hrs: \bullet 50-75yrs: 1.8 \pm 1.0 vs 1.5 \pm 0.9, p=0.36 \bullet >75 yrs: 2.1 \pm 0.1 vs 2.3 \pm 1.7, p=0.56	\downarrow mortality (age 50-75 yrs): 9/43 (21%) vs 12/23 (52%), p=0.01 Equal mortality (>75 yrs): 12/21 (57%) vs 11/18 (61%), p>0.99
Alia (156)	63 (31 vs 32)	Severe sepsis/septic shock	96 hrs in the ICU	DO2I \geq 600 vs DO2I \geq 330	\uparrow dobu (71 vs 34%)	ICU mortality	2.6 (median, IQR 1.4-3.9) vs 1.8 (1.1-3.5), p=0.11	Average during 96 hrs: 2.0 (median, IQR 1.6-3.1) vs 2.0 (1.3-3.7), p=0.18	Equal mortality: 23/31 (74%) vs 21/32 (66%), p=0.46
Rivers (40)	263 (130/133)	ED patients with severe sepsis or septic shock	First 6 hrs of ED stay	ScvO2 \geq 70% vs no ScvO2	\uparrow fluids (5.0 \pm 3.0 vs 3.5 \pm 2.4 l) \uparrow RBC's (64 vs 19%), \uparrow dobu (14 vs 1%)	In-hospital mortality	7.7 \pm 4.7 vs 6.9 \pm 4.5, p=0.17	4.3 \pm 4.2 vs 4.9 \pm 4.7, p=0.01	\downarrow in-hospital mortality: 38/130 (47%) vs 59/133 (31%), p=0.009
Pearse (121)	122 (62 vs 60)	High risk general surgery patients	First 8 hours in the ICU	DO2I \geq 600 vs CVP goals	\uparrow colloids (1.9 \pm 0.9 vs 1.2 \pm 0.9 l), \uparrow dopexamine (89% vs 2%)	Post-operative complications	Change during 8 hrs: -0.6 \pm 1.1, p=0.11	Change during 8 hrs: -0.3 \pm 0.8 vs -0.6 \pm 1.1, p=0.11	\downarrow complications: 27/62 (44%) vs 41/60 (68%), p=0.003
Chytra (122)	162 (80/82)	Multiple-trauma patients (no TBI)	First 12 hrs in the ICU	Oesophageal doppler goals vs CVP 12-15	\uparrow colloids (1.7 \pm 0.4 vs 0.7 \pm 0.3 l), \downarrow nor (23 vs 40%)	Lactate after 12 and 24 hrs	4.2 \pm 1.0 vs 3.9 \pm 0.9, p=0.08	\bullet 2.9 \pm 0.5 vs 3.2 \pm 0.5, p<0.001 (12 hrs) \bullet 2.0 \pm 0.4 vs 2.4 \pm 0.6, p<0.001 (24 hrs)	\downarrow infectious complications: 15/80 (19%) vs 28/82 (34%), p=0.032

Lactate = mean blood lactate level (mmol/l), CI = cardiac index (l/min/m²), DO2I = oxygen delivery index (ml/min/m²), VO2I = oxygen consumption index (ml/min/m²), CVP=central venous pressure, RBC=red blood cell transfusion, PAC=pulmonary artery catheter, nor=norepinephrine, dobu=dobutamine, dopa=dopamine, TBI=traumatic brain injury
Studies evaluating pre-operative or per-operative DO2 optimization were excluded

Table 4C. Randomized controlled studies on goal-directed DO₂ therapy comparing a lactate-guided group and a non lactate-guided group

Study	N (intervention vs control)	Patients	Timing	Goals of therapy (intervention vs control)	Provided therapy (significant differences intervention vs control)	Primary endpoint	Lactate on entry: (intervention vs control)	Lactate after therapy: (intervention vs control)	Outcome: (intervention vs control)
Polonen et al. (114)	393 (196 vs 197)	Post- cardiac surgery patients	First 8 hrs of ICU stay	Lactate \leq 2.0 and SvO ₂ > 70% vs no lactate/ no ScvO ₂	\uparrow crystalloids (2.3 \pm 1.5 vs 2.0 \pm 1.2 l), \uparrow colloids (0.9 \pm 0.4 vs 0.8 \pm 0.4), \uparrow inotropes after 6 (38 vs 20%) and 8 (41 vs 20%) hours, \downarrow vasopressors after 0 (8 vs 15%), 2 (8 vs 15%), 6 (3 vs 10%) and 8 (5 vs 10%) hrs	Hospital length of stay	-	-	\downarrow hospital stay: 6 (IQR 5-7) vs 7 (IQR 5-8) days
Jansen et al. * ongoing	Target: n=350 (2x 175)	Heterogeneous ICU patients with lactate \geq 3.0	First 8 hours of ICU stay	Decrease in lactate \geq 20% in two hrs vs no lactate	-	In-hospital mortality	-	-	-
Shapiro et al. # ongoing	Target: n=300	ED patients with severe sepsis or septic shock	First 6 hours of ED stay	Decrease in lactate > 10% in six hrs vs ScvO ₂ \geq 70%	-	In-hospital mortality	-	-	-

* <http://clinicaltrials.gov/ct2/show/NCT00270673>

<http://clinicaltrials.gov/ct2/show/NCT00372502>

the hand-held device, followed by € 2 using the blood gas analyzer (Chiron 865 series®) and € 5 when using the central hospital's laboratory (11). In the Netherlands, external budget costs per measurement are € 12. We didn't find a study on the cost-effectiveness of lactate monitoring. Although costs of lactate measurement itself are relatively low, costs of subsequent therapeutic consequences and use of health care resources are unknown.

DISCUSSION

We found that lactate performs well in the laboratory: the measurement itself is accurate and clinicians at the bedside can trust the numerical value of lactate levels they collect. However, sufficient understanding of anaerobic and aerobic mechanisms of production and clearance is essential for the correct interpretation of hyperlactemia. Although the prognostic accuracy of lactate varied considerably, lactate generally increased the ability to predict non-survival, both in the ED and ICU. The consistency of this finding means that lactate certainly has a place in the risk-stratification of critically ill patients. Because of the weak correlation between hyperlactatemia and metabolic acidosis, lactate should be directly measured instead of estimated from other acid-base variables. Furthermore, lactic or non-lactic metabolic acidoses are associated with different mortality.

Concerning the clinical impact of lactate monitoring, it seems likely that it can increase healthcare workers confidence, although we were not able to find studies on this topic. Lactate monitoring has the potential to alter therapeutic decisions as hyperlactatemia in critically ill patients is often interpreted as a result of systemic oxygen imbalance, triggering goal-directed DO₂ therapy. Indirect evidence supports the therapeutic benefit of lactate monitoring. However, there is a lack of clinical trials investigating the clinical value of lactate-directed therapy; the only single-center clinical trial advocating its efficacy was performed in post-cardiac surgery patients and this cannot easily be extrapolated to other critical care populations.

In addition, although costs of lactate measurement itself are relatively low, cost-effectiveness of lactate measurements is unknown.

Strengths of our study include the systematic search and selection strategy and the eight-question format that provides a complete and clinically relevant assessment of the real value of lactate monitoring. Our study also has limitations. We didn't perform a methodological quality assessment of the selected studies. The variety of study designs was too large for a single methodological quality score. We neither performed a meta-analysis, which would have been valuable when evaluating prognostic accuracy or efficacy of lactate-directed therapy. However, the studies were far too heterogeneous (large variations in patient categories, mortality rates, lactate cutoff values and timing of measurements or interventions). Last, the results of this study obviously need to be interpreted in the light of the search and selection criteria, and we might have missed information.

CONCLUSION

Based on the results of this systematic health technology assessment, blood lactate monitoring is recommended in critical care settings as the ED and ICU because it clearly has a place in the risk-stratification of critically ill patients. However, it is unknown whether the routine use of lactate as a resuscitation endpoint improves outcome. This warrants randomized controlled studies on the efficacy of lactate-directed therapy.

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Conflict of interest

The authors report no conflict of interest

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**OBSERVATIONAL
STUDIES ON THE
PROGNOSTIC
VALUE OF BLOOD
LACTATE LEVELS**

CHAPTER 4

The prognostic value of blood lactate levels relative to that of vital signs in the pre-hospital setting: a pilot study

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ABSTRACT

Introduction: A limitation of pre-hospital monitoring is that vital signs often do not change until a patient is in a critical stage. Blood lactate levels are suggested as a more sensitive parameter to evaluate a patient's condition. The aim of this pilot study was to find presumptive evidence for a relation between pre-hospital lactate levels and in-hospital mortality, corrected for vital sign abnormalities.

Methods: In this prospective observational study (n = 124), patients who required urgent ambulance dispatching and had a systolic blood pressure below 100 mmHg, a respiratory rate less than 10 or more than 29 breaths/minute, or a Glasgow Coma Scale (GCS) below 14 were enrolled. Nurses from Emergency Medical Services measured capillary or venous lactate levels using a hand-held device on arrival at the scene (T1) and just before or on arrival at the emergency department (T2). The primary outcome measured was in-hospital mortality.

Results: The average (standard deviation) time from T1 to T2 was 27 (10) minutes. Non-survivors (n = 32, 26%) had significantly higher lactate levels than survivors at T1 (5.3 vs 3.7 mmol/L) and at T2 (5.4 vs 3.2 mmol/L). Mortality was significantly higher in patients with lactate levels of 3.5 mmol/L or higher compared with those with lactate levels below 3.5 mmol/L (T1: 41 vs 12% and T2: 47 vs 15%). Also in the absence of hypotension, mortality was higher in those with higher lactate levels. In a multivariable Cox proportional hazard analysis including systolic blood pressure, heart rate, GCS (all at T1) and delta lactate level (from T1 to T2), only delta lactate level (hazard ratio (HR) = 0.20, 95% confidence interval (CI) = 0.05 to 0.76, p = 0.018) and GCS (HR = 0.93, 95% CI = 0.88 to 0.99, p = 0.022) were significant independent predictors of in-hospital mortality.

Conclusions: In a cohort of patients that required urgent ambulance dispatching, pre-hospital blood lactate levels were associated with in-hospital mortality and provided prognostic information superior to that provided by the patient's vital signs. There is potential for

early detection of occult shock and pre-hospital resuscitation guided by lactate measurement. However, external validation is required before widespread implementation of lactate measurement in the out-of-hospital setting.

INTRODUCTION

An important limitation of patient monitoring in the pre-hospital phase is that the standard vital signs such as heart rate and blood pressure often do not change until a patient reaches a critical stage [1-3]. Pain and anxiety, contributing to increased sympathetic tone, influence these vital signs and render them insensitive for monitoring the adequacy of tissue perfusion [4]. Many patients who appear to be haemodynamically stable based on normal vital signs have increased blood lactate levels ('occult hypoperfusion' or 'compensated shock') [1, 5]; as a result, lactate levels are often considered to be better resuscitation endpoints than standard vital signs [6].

Lactate levels are commonly used to stratify risk and to assess adequacy of resuscitation in the intensive care unit (ICU) [7, 8] and in the emergency department (ED) [9-11], but are not currently used in the pre-hospital setting [12]. As it is possible to measure blood lactate levels on-site using a fast and accurate hand-held analyser on capillary or venous blood [13, 14], lactate monitoring can be transferred from the hospital to the pre-hospital setting. The aim of this pilot study was to find presumptive evidence for a relation between pre-hospital lactate levels and patient outcome. We hypothesised that pre-hospital blood lactate measurements would enable the prediction of in-hospital mortality and that this prognostic value would be independent of commonly available standard vital parameters.

MATERIALS AND METHODS

Study design

This was a prospective observational cohort study.

Setting

A Dutch Emergency Medical Service (EMS), referring to three university-affiliated hospitals, dispatched ambulances that were staffed by certified EMS nurses with two years of postgraduate training in a critical care setting (ICU, cardiac care unit, anaesthesiology or ED) and one year of training in EMS-specific procedures.

Selection of participants

A convenience sample of patients were enrolled who required urgent ambulance dispatching and had a systolic blood pressure below 100 mmHg, respiratory rate of less than 10 or more than 29 breaths/minute or a Glasgow Coma Scale (GCS) of less than 14 on arrival of the ambulance. Exclusion criteria were the unavailability of a first lactate measurement or epileptic seizures, in which case hyperlactataemia is prognostically less sensitive [15]. The study was approved by the Medical Ethics Committee, which waived the need for obtaining informed consent.

Interventions

Pre-hospital treatment was provided by EMS nurses according to Dutch national ambulance protocols (Landelijk Protocol Ambulancezorg (LPA)). These protocols are in accordance with the pre-hospital and advanced trauma life support guidelines of the National Asso-

ciation of Emergency Medical Technicians, based on the Advanced Trauma Life Support standard of the American College of Surgeons. During the study period from June 1997 to November 1998, LPA version 4 (1996 to 1999) was used. When compared with the current version 7 (2007 to 2010), most protocols were similar.

Methods of measurements and data collection

The first lactate measurement (T1) was performed by EMS nurses as soon as possible after arrival at the scene (before any pre-hospital treatment); the second measurement (T2) was obtained just before or on arrival at the ED (after pre-hospital treatment). The lactate level was measured in venous or capillary blood immediately after blood was drawn (at T1 or T2) using a point-of-care handheld lactate analyser (Accutrend, Roche Diagnostics, Mannheim, Germany). This is a small, battery-powered, reflectance photometer with a turnaround time of 60 seconds that uses chemistry test strips on which a drop of blood is applied. Hospital physicians were not informed about the lactate levels collected by the EMS nurses. Other obtained data at both T1 and T2 included heart rate, diastolic and systolic blood pressures, peripheral oxygen saturation obtained by pulse oxymeter (SpO₂) and GCS. SpO₂ was regarded as a binary variable, which was defined as abnormal if it was lower than 92% or if the pulse oxymeter signal could not be retrieved because of inadequate peripheral perfusion (n = 25). If heart rate and blood pressure readings could not be obtained because of cardiac arrest at T1 (asystole or ventricular fibrillation, n = 11), we considered these values as 0 (this was only done at T1, not at T2).

Outcome measures

The primary outcome measured was in-hospital mortality.

Primary data analysis

Because lactate levels were not normally distributed, they were logarithmically transformed before analysis. To evaluate the prognostic accuracy of the lactate levels, receiver operating characteristic (ROC) curves for in-hospital mortality were constructed and area under the ROC curves (AUROC) were calculated. Using ROC-curve analysis, we defined appropriate cut-off values (which are not available for the pre-hospital setting) and calculated sensitivity, specificity, positive predictive values (PPV) and negative predictive values (NPV). In order to identify patients who were likely to die, the test had to be sensitive while remaining specific [16] and had to have an acceptable PPV [17]. Mortality rates of patients with high or low lactate levels were compared using a chi squared test or Fisher's exact test if necessary, based on sample size.

In order to identify independent predictors of in-hospital death, adjusted for standard variables available in the pre-hospital setting, a multivariable Cox proportional hazards (PH) model was constructed. The variables systolic blood pressure, heart rate, GCS and the change in lactate level from T1 to T2 were simultaneously entered in this model (the number of variables was restricted to four to reduce the possibility of overfitting). A backward elimination method was used, in which each step removed the variable with the highest p-value above 0.10 according to the likelihood ratio test. Interaction between all variables was not tested because of the risk of overfitting. The PH assumption was confirmed by entering variable-by-time interaction terms one by one, with time on the log scale. By choosing Cox PH instead of logistic regression analysis, we took account of the time of death, rather than just dead (yes or no) in the analysis. Statistical analyses were performed using SPSS version 11.0.1/12.0.1 (SPSS, Inc., Chicago, IL, USA).

RESULTS

Characteristics of study subjects

We enrolled 135 patients. Three patients were excluded because of a missing first lactate measurement and eight patients had epileptic seizures. The baseline characteristics of the remaining 124 patients are described in Table 1. The mean (standard deviation) time at the scene from arrival to departure of the ambulance was 16 (8) minutes. Mean duration of the subsequent transfer to the ED was 11 (6)

Table 1. Baseline characteristics

	Total: n = 124	Non-survivors: n = 32	Survivors: n = 92
Age (years, \pm SD)	62 \pm 19	68 \pm 14 *	59 \pm 20 *
Sex (n, % male)	73 (59%)	22 (69%)	51 (55%)
Intensive care unit admission (n, %)	57 (46%)	15 (47%)	42 (46%)
Length of stay in hospital (days, \pm SD)	13 \pm 21	3 \pm 6 *	17 \pm 23 *
Time arrival ambulance to ED (minutes, \pm SD)	27 \pm 9	29 \pm 10	26 \pm 10
Ambulance diagnosis (n, %):			
- cardiac arrest	12 (10%)	8 (25%) *	4 (4%) *
- myocardial infarction	17 (14%)	2 (6%)	15 (16%)
- other cardiological disorders	8 (6%)	1 (3%)	7 (8%)
- sepsis	8 (6%)	4 (13%)	4 (4%)
- haemorrhage	10 (8%)	3 (9%)	7 (8%)
- neurological disorder	19 (15%)	9 (28%) *	10 (11%) *
- trauma without severe traumatic brain injury	18 (15%)	2 (6%)	16 (17%)
- trauma with severe traumatic brain injury	2(2%)	1 (3%)	1 (1%)
- attempted suicide	4 (3%)	0 (0%)	4 (4%)
- others	26 (21%)	2 (6%) *	24 (26%) *

Continuous data are presented as mean \pm standard deviation (SD). Binary data are presented as n (percentage of total, non-survivors or survivors). * $p < 0.05$. ED = emergency department.

minutes. The total time from arrival at the scene to arrival in the ED was 27 (10) minutes.

Before pre-hospital treatment (T1)

Of the 124 patients who were included in the study on arrival of the ambulance at the scene, 92 survived and 32 died. Compared with the survivors, the non-survivors had a lower systolic blood pressure, lower GCS, more often an abnormal SpO₂ and an older age (Table 2). Heart rates were not significantly different. Lactate levels were higher in the non-survivors (Figure 1).

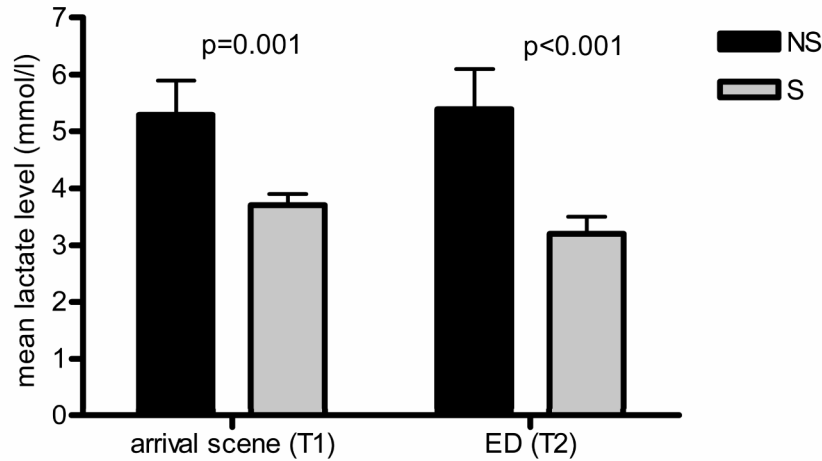
Table 2. Vital signs in survivors (S) and non-survivors (NS) on arrival of the ambulance on the scene (T1) and just before or on arrival at the emergency department (T2)

	T1		T2	
	NS	S	NS	S
Heart rate (beats/minute, \pm SD)	75 \pm 51	89 \pm 30	90 \pm 40	90 \pm 22
Systolic arterial pressure (mmHg, \pm SD)	101 \pm 66 *	126 \pm 41 *	132 \pm 43	136 \pm 28
Mean arterial pressure (mmHg, \pm SD)	86 \pm 56 *	108 \pm 35 *	113 \pm 36	117 \pm 23
SpO ₂ < 92% or no signal (n, %)	23 (72%) *	34 (37%) *	12 (43%)	22 (28%)
GCS (\pm SD)	8 \pm 6 *	13 \pm 4 *	9 \pm 6 *	13 \pm 4 *

Continuous data are presented as mean \pm standard deviation (SD). Binary data are presented as n (percentage non-survivors or survivors). Number of patients: T1 n = 124 (32 NS and 92 S), T2 n = 106 (28 NS and 88 S). * $p < 0.05$. SpO₂ = peripheral oxygen saturation, GCS = Glasgow Coma Scale.

At T1, the AUROC of lactate for in-hospital death was 0.69 (95% confidence interval (CI) = 0.58 to 0.80, $p = 0.001$). We established a lactate level of 3.5 mmol/L as the best cut-off point for T1. A lactate level of 3.5 mmol/L or more was 75% sensitive (95% CI = 60 to 90%) and 63% specific (95% CI = 53 to 73%) for prediction of death, with a PPV of 41% (95% CI = 29 to 54%) and a NPV of 88%

Figure 1. Mean lactate levels in survivors (S) and non-survivors (NS) upon arrival of the ambulance at the scene (T1) and just before/on arrival at the emergency department (T2)



Arrow bar represents standard error. Number of patients at T1: n = 124 and at T2: n = 106.

(95% CI = 80 to 96%). Mortality in patients with a high lactate level was 41% (95% CI = 29 to 54%), compared with 12% (95% CI = 4 to 20%) for those with a lower level (Figure 2). Patients with high lactate levels also had lower systolic blood pressures (100 vs 137 mmHg, $p < 0.001$), lower GCS (10 vs 14, $p < 0.001$), more often an abnormal SpO₂ (74 vs 21%, $p < 0.001$) and were more often admitted to the ICU (57 vs 36%, $p = 0.022$).

At T1, 33 patients had a systolic blood pressure below 100 mmHg. To adjust for the presence of a systolic blood pressure below 100 mmHg [18], a stratified analysis was performed, which showed that lactate was still significantly associated with mortality (Figure 3).

After pre-hospital treatment (T2)

Follow-up lactate measurements were available for 106 patients. Of these patients, 78 survived and 28 died in the hospital. Compared with the survivors, the non-survivors had a lower GCS (9 vs 13,

Figure 2. Patient survival according to lactate levels below or above the cut-off threshold of 3.5 mmol/L

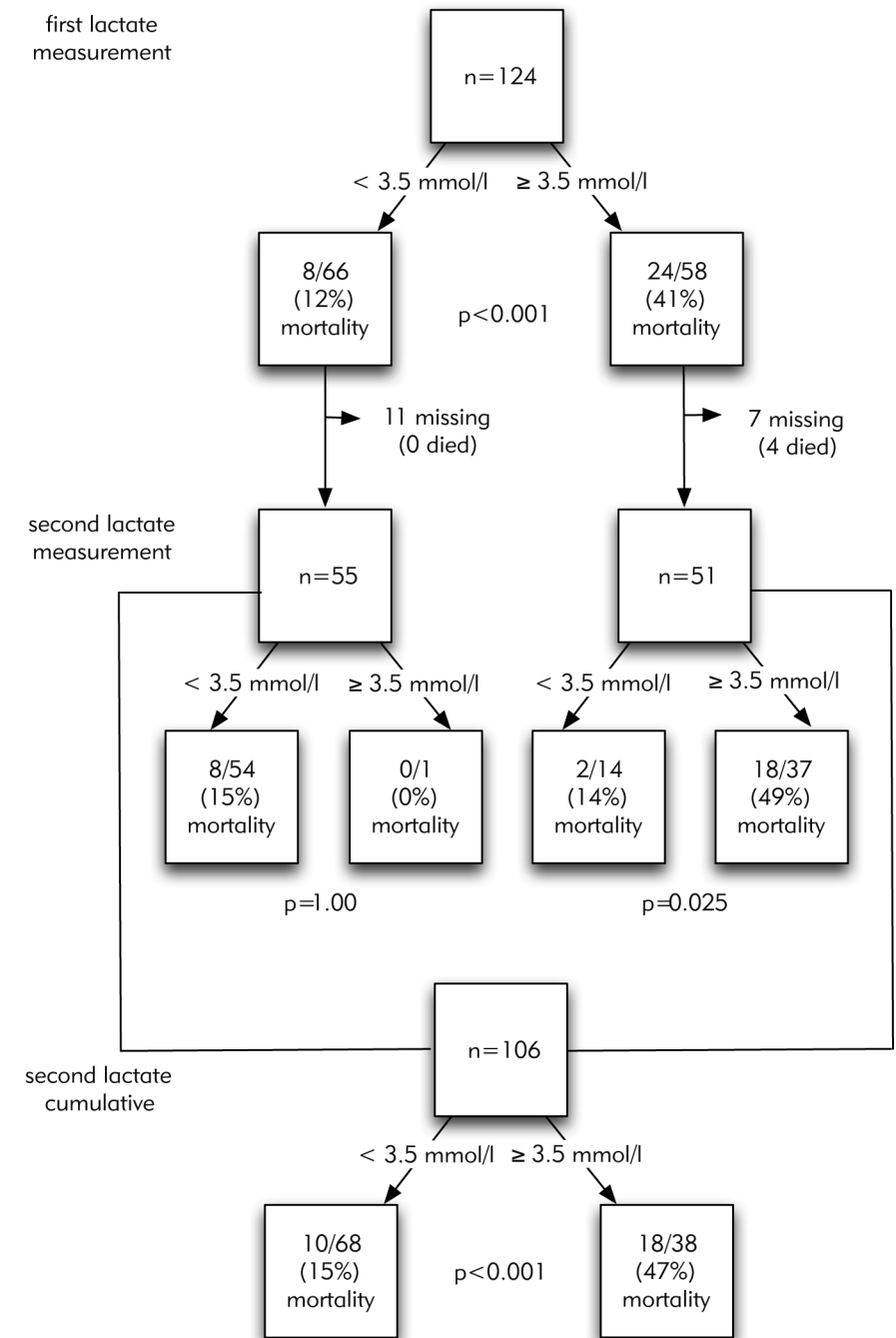
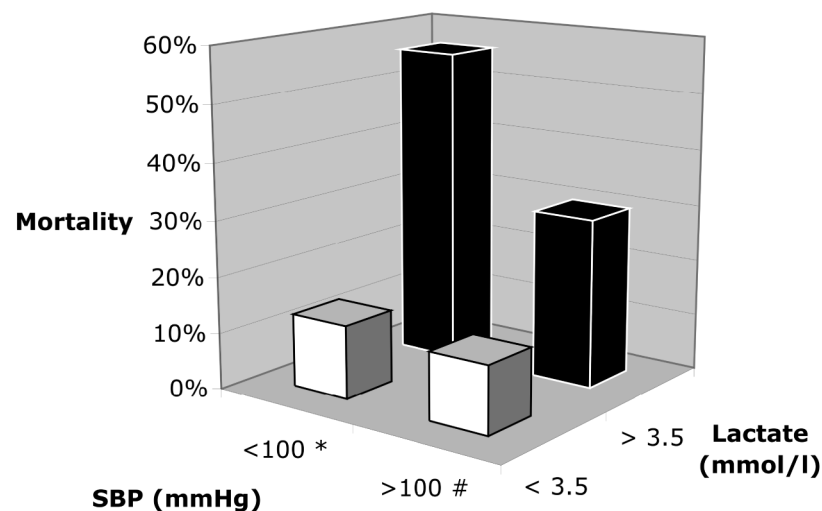


Figure 3. In-hospital mortality stratified by systolic blood pressure and blood lactate level measured at arrival of the ambulance at the scene (T1).



* $p = 0.046$ # $p = 0.032$ Number of patients per group: low systolic blood pressure (SBP)/low lactate $n = 8$, low SBP/high lactate $n = 25$, high SBP/low lactate $n = 58$, high SBP/high lactate $n = 33$.

$p < 0.001$) and a higher lactate level (Figure 2). Systolic blood pressure, heart rate and SpO_2 did not significantly differ between the two groups.

At T2, the AUROC was 0.72 (95% CI = 0.60 to 0.84, $p = 0.001$). Here, 3.5 mmol/L was again considered as the most appropriate cut-off point with a sensitivity for death of 64% (95% CI = 47 to 82%), specificity of 74% (95% CI = 65 to 84%), PPV of 47% (95% CI = 31 to 63%) and a NPV of 85% (95% CI = 77 to 94%). In the high lactate group, 47% (95% CI = 31 to 63%) of the patients died, while only 15% (95% CI = 6 to 23%) of those with a lower lactate level died (Figure 2). Additionally, patients in the high lactate group had a lower systolic blood pressure (125 vs 140 mmHg, $p = 0.017$), lower GCS (10 vs 13, $p = 0.002$), more often an abnormal SpO_2 (50 vs 22%, $p = 0.003$) and were more often admitted to the ICU (71 vs 35%, $p < 0.001$).

Eleven patients had a systolic blood pressure below 100 mmHg at T2. In the other patients with a systolic blood pressure of 100 mmHg

or above ($n = 95$), mortality rates remained significantly higher in those with high (47%, 14 out of 30) versus low lactate levels (15%, 10 out of 65, $p = 0.001$).

When examining the evolution of lactate during the pre-hospital phase, the lactate level, on average, increased 0.1 mmol/L in non-survivors, whereas in survivors it decreased 0.6 mmol/L ($p = 0.044$). This evolution of lactate from T1 to T2 had prognostic significance even after the effect of the other parameters (systolic blood pressure, heart rate and GCS) had been taken into account in the multivariable Cox PH model. Of the variables, only the change in lactate level and the GCS were independently associated with in-hospital mortality (Table 3). The hazard of death decreased by 80% (95%

Table 3. Multivariable Cox proportional hazards model for the identification of independent variables associated with in-hospital death

Variable	Start model			Final model		
	HR	95% CI	p value	HR	95% CI	p value
$\Delta \ln(\text{lactate})$ T1 to T2*	0.20	0.05 to 0.79	0.022	0.20	0.05 to 0.76	0.018
SBP T1 per mmHg	1.00	0.99 to 1.01	0.56	Not in model		0.87
Heart rate T1 per beat/minute	1.01	0.99 to 1.02	0.47	Not in model		0.66
GCS T1 per unit	0.93	0.87 to 0.99	0.034	0.93	0.88 to 0.99	0.022

The variables were simultaneously entered in the model (start model). A backward elimination method was used to construct the final model.

* $\Delta \ln(\text{lactate})$ T1 to T2: for every 63% decrease ($100 \times (1 - (1/e)) = 63\%$) of the lactate level at T2 relative to the level at T1, the hazard of death decreased by 80% ($100 (1 - HR)$) in the final model (95% CI = 24 to 95%). $e = 2.71828$, GCS = Glasgow Coma Scale, HR = hazard ratio, \ln = natural logarithm, SBP = systolic blood pressure, T1 = on arrival of the ambulance on the scene, T2 = just before or on arrival at the emergency department.

CI = 24 to 95%) for every 63% decrease of the lactate level at T2 relative to the level at T1 (i.e. a larger decrease in lactate during pre-hospital treatment was associated with decreased mortality). Although a model with six instead of four entered variables is a possible overfit, adding age and SpO_2 to the start model resulted in a final model in which delta lactate remained independently associ-

ated with in-hospital mortality (with equal hazard ratio, 95% CI and p value, data not shown).

Subgroup of patients without cardiac arrest

To test the hypothesis that blood lactate levels remained predictive for outcome in a population that is not obviously in circulatory shock, we repeated the analyses in the subgroup of patients without cardiac arrest. In addition, this would correct for possible negation of the association of tachycardia with mortality because of the coding of heart rate as 0 in cases of cardiac arrest.

Twelve patients had cardiac arrest at T1. Four patients died out-of-hospital (before T2). Of the eight patients with return of spontaneous circulation at T2, four died during hospital admission and four survived. In the subgroup excluding the 12 patients with cardiac arrest ($n = 112$, in-hospital mortality 21%), lactate level remained a prognostic marker for in-hospital death. The AUROC was 0.66 (95% CI = 0.52 to 0.80, $p = 0.015$) at T1 and 0.69 (95% CI = 0.55 to 0.82, $p = 0.007$) at T2. A lactate level of 3.5 mmol/L remained the most appropriate cut-off value at both time points. Using this value at T1, mortality was 35% (95% CI = 21 to 49%) in the group with high lactate levels compared with 12% (95% CI = 4 to 20%) in the group with low lactate levels ($p = 0.005$). At T2, this was 43% (95% CI = 26 to 61%) compared with 15% (95% CI = 11 to 19%) ($p = 0.002$). In the final model of multivariable Cox PH analysis performed in the non-cardiac arrest patients, the effect of the change in lactate levels from T1 to T2 remained equally strong with a hazard ratio of 0.22 (95% CI = 0.04 to 1.11), but it was not statistically significant ($p = 0.067$).

DISCUSSION

Our results show that in a cohort of patients that required urgent ambulance dispatching, pre-hospital blood lactate levels were associated with in-hospital mortality. In addition, lactate was more sensitive in identifying patients at risk of death than the conventional vital parameters such as systolic blood pressure and heart rate.

The mortality rate of 41% for patients with a first lactate level of 3.5 mmol/L or more indicates that a high-risk population could be identified immediately on arrival of the ambulance at the scene. This was clinically relevant because a simple procedure such as measurement of lactate levels increased the ability to predict death from 26% (pre-test probability or study population mortality) to 41% at T1 and 47% at T2 (post-test probability or PPV). Furthermore, the NPV of 88% demonstrated that low lactate levels identified patients with a low risk of dying. Our study found that a cut-off value of 3.5 mmol/L for the out-of-hospital setting is close to 4.0 mmol/L, which was found to have prognostic significance in the ED [7, 9, 19]. The prognostic accuracy of pre-hospital lactate levels for predicting in-hospital death, as expressed by AUROC, sensitivity and specificity, was comparable with values found in the ED and ICU setting [5, 7, 9, 19]. Aside from the prognostic information obtained from single lactate measurements, our data also emphasised the value of serial measurements in which the response to administered pre-hospital therapy could be monitored [10, 20].

Importantly, the prognostic value of lactate was independent of vital signs. In particular, the association between hyperlactataemia and mortality was not confounded by simultaneous hypotension. Our observation that lactate was a more sensitive marker is in line with earlier studies in the ED or ICU describing the phenomenon of occult hypoperfusion [1, 5, 11, 20-23]. Apparently, compensated shock in which there are signs of tissue hypoperfusion despite the presence of stable vital signs is equally important in the pre-hospital setting. Insufficient oxygen delivery might have been an important cause of hyperlactataemia in our patients, particularly in the earliest phase of disease presentation as was the case in our study [24-

26]. In addition, increased aerobic metabolism [27] and reduced clearance [28] might have also contributed to the increased blood lactate levels early in critical illness when blood pressure and heart rate were not yet affected [12].

The use of blood lactate measurement in EMS might have clinical potential: as a triage tool and as a trigger for optimisation of oxygen delivery [29-33] where the pre-hospital setting provides the earliest possible timing, which is regarded as crucial to avoid irreversible damage [34-36].

This study has several limitations. First, an important limitation is that the data were collected in 1997 and 1998. Due to practical reasons, these data have not been analysed and published until now. Although substantial time has elapsed, we believe that our data are still useful as differences between ambulance protocols of the study period (LPA version 4) in comparison with the current guidelines (LPA version 7) are minimal. Also, even if changes in pre-hospital treatment over the past few years would have affected the pre-hospital evolution of lactate, we still assume that the intrinsic association between a certain lactate course and its related impact on outcome remains unaltered. Furthermore, the impact of in-hospital care on mortality was limited because the average time to in-hospital death was only three days. Nonetheless, progress over the years in in-hospital care in the fields of emergency medicine and critical care medicine may affect the rate of in-hospital mortality.

Second, in this pilot study, we chose to include patients based on abnormal vital signs rather than including all patients for whom ambulances were dispatched. This allowed establishing associations between lactate levels, abnormalities in vital signs and outcome without needing to enroll a very large cohort of patients. However, this resulted in a relatively high mortality rate (26%), limiting the ability of the result to be generalised to other out-of-hospital settings. Also, stratified analyses of more homogeneous groups, such as trauma or medical patients, were not possible.

Last, the chosen entry criteria are compensatory mechanisms for hypoperfusion and may have confounded the potential to discover hyperlactataemia in haemodynamically stable patients. By adjusting for vital parameters in multivariable analysis and by excluding cardiac arrest patients, who are in apparent shock, we tried to correct for this.

CONCLUSIONS

The present data show that pre-hospital blood lactate levels predicted in-hospital mortality in a population that required urgent ambulance dispatching, and that these measurements provided prognostic information over and above common vital signs. In the early pre-hospital phase, measuring lactate level was a more sensitive way of identifying a population at risk than measuring systolic blood pressure and heart rate. Its use in EMS has the potential for earlier detection of occult shock, optimisation of triage decisions and earlier start of goal-directed therapy. However, external validation in larger cohorts of consecutive patients for which ambulances are dispatched is required before widespread implementation of lactate level measurement in the out-of-hospital setting.

Key messages

- Pre-hospital blood lactate levels were associated with in-hospital mortality.
- A blood lactate level of 3.5 mmol/L was the best cut-off value in the pre-hospital phase to discriminate survivors from non-survivors.
- The prognostic value of pre-hospital blood lactate level was superior to that of heart rate and systolic blood pressure.
- The use of blood lactate measurement in EMS might have potential for triage decisions, earlier detection of occult shock and earlier start of goal-directed therapy.

Abbreviations

AUROC = area under the ROC curve, CI = confidence interval, ED = emergency department, EMS = Emergency Medical Services, GCS = Glasgow Coma Scale, ICU = intensive care unit, LPA = Landelijk Protocol Ambulancezorg (Dutch ambulance protocols), NPV = negative predictive value, PH = proportional hazards, PPV = positive predictive value, ROC = receiver operating characteristic, SD = standard deviation, SpO₂ = peripheral oxygen saturation obtained by pulseoxymeter, T1 = on arrival of the ambulance at the scene, T2 = just before or on arrival at the emergency department.

Competing interests

The authors have no conflicts of interest. The study was supported by Roche Diagnostics (Mannheim, Germany), which provided the Accutrend hand-held lactate analysers.

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CHAPTER 5

Prognostic value of blood lactate levels: does the clinical diagnosis at admission matter?

J Trauma 2009;66(2):377-385

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ABSTRACT

Background: Hyperlactatemia and its reduction following admission in the ICU have been related to survival. Because it is unknown whether this equally applies to different groups of critically ill patients, we compared the prognostic value of repeated lactate levels (a) in septic patients versus patients with hemorrhage or other conditions generally associated with low-oxygen-transport (LT) (b) in hemodynamically stable versus unstable patients.

Methods: In this prospective observational two-center study (n=394 patients), blood lactate levels at admission to the ICU (Lac T0) and the reduction of lactate levels from T=0 to T=12 hours (Δ Lac T0-12) and from T=12 to T=24 hours (Δ Lac T12-24), were related to in-hospital mortality.

Results: Reduction of lactate was associated with a lower mortality only in the sepsis group (Δ Lac T0-12: hazard ratio (HR) 0.34, $p=0.004$ and Δ Lac T12-24: HR 0.24, $p=0.003$), but not in the LT group (Δ Lac T0-12; HR 0.78, $p=0.52$ and Δ Lac T12-24; HR 1.30, $p=0.61$). The prognostic values of Lac T0, Δ Lac T0-12 and Δ Lac T12-24 were similar in hemodynamically stable and unstable patients ($p=0.43$).

Conclusions: Regardless of the hemodynamic status, lactate reduction during the first 24 hours of ICU stay is associated with improved outcome only in septic patients, but not in patients with hemorrhage or other conditions generally associated with low-oxygen-transport. We hypothesize that in this particular group a reduction in lactate is not associated with improved outcome due to irreversible damage at ICU admission.

INTRODUCTION

Blood lactate levels are often determined in critically ill patients, because repeated measurements identify those patients who are at risk for multiple organ failure and death [1-3]. In these patients, hyperlactatemia is thought to be predominantly caused by impaired organ perfusion. Although this condition is often associated with hemodynamic instability, hyperlactatemia can also occur during stable hemodynamic conditions, in which case it is considered to be due to occult hypoperfusion [4-6]. Treatment aims at correction of tissue perfusion, resulting in decreased lactate levels and improved patient outcome [7].

With this purpose, monitoring of lactate levels is used in a very broad range of patients, including trauma as well as sepsis patients [8, 9]. The generalized use of lactate in critically ill patients has given rise to a universal concept that a high lactate level is bad and that a decrease in lactate levels is good, despite considerable differences in underlying disease (e.g. hemorrhage versus sepsis) and hemodynamic status within the patient population. In fact, it is unknown whether these factors, which can be clinically evaluated at admission, influence the risk of death associated with initial lactate levels and their course during therapy. Therefore it was our objective to compare the prognostic value of repeated lactate levels following ICU admission in different categories of patients: (a) in septic patients versus patients with hemorrhage and other conditions generally associated with low-oxygen-transport and (b) in hemodynamically stable versus unstable patients.

MATERIALS AND METHODS

Study design and patients

In this prospective observational two-center study we enrolled all consecutive unscheduled patients admitted to the general ICU of two Dutch university-affiliated hospitals from May 2000 to April

2002. In patients who were readmitted during the study period only data of the first admission were used. This study was approved by the Medical Ethical Committees of both hospitals and informed consent was waived.

Patient classification

In order to categorize patients according to their disease on admission to the ICU, we used pre-specified admission diagnoses derived from the APACHE III scoring system [10]. In this way, patients were classified as SEPSIS (all conditions associated with infectious disease), LT (hemorrhage and other conditions generally associated with low-oxygen-transport: low cardiac output, hemoglobin level or oxygen saturation) or OTHERS. The SEPSIS group comprised the following admission diagnoses: bacterial/viral pneumonia, aspiration pneumonia, meningitis/encephalitis, sepsis, septic shock, intestinal perforation and cholecystitis/cholangitis. The LT group comprised the following admission diagnoses: trauma with or without traumatic brain injury, gastro-intestinal bleeding, ruptured aortic aneurysm, cardiogenic shock, congestive heart failure, arrhythmia, acute myocardial infarction, pulmonary embolism with circulatory failure and cardiac arrest. Patients who could not be classified as either SEPSIS or LT, were classified as OTHERS because we were not able to determine whether these patients should be regarded as either SEPSIS or LT according to their disease on admission. As a result, the OTHERS group of admission diagnoses became very heterogeneous, including patients with completely different mechanisms of hyperlactatemia (e.g. liver failure). Therefore, we focused on the SEPSIS and LT groups in the first analysis.

In a second analysis, patients were classified as hemodynamically stable (HD stable) or hemodynamically unstable (HD unstable), which was defined as a mean arterial pressure (MAP) < 60 mmHg and/or the requirement of catecholamines (dopamine \geq 3 mcg/kg/min, dobutamine any dose, norepinephrine any dose or epinephrine any dose) during the first 24 hours following ICU admission.

Data collection

For each patient base-line characteristics were recorded, including APACHE III [10] (for admission diagnosis), APACHE II [11] (for disease severity) and hospital and ICU length of stay and mortality. Predicted hospital death rate was calculated as $e^{-3.517+(APACHE\ II)*0.146}/(1+e^{-3.517+(APACHE\ II)*0.146})$ [11]. Blood lactate levels were collected at the time of ICU admission (Lac_{T_0}) and after 12 and 24 hours following admission. The reduction in lactate was calculated from 0 to 12 hours (ΔLac_{T_0-12}) and from 12 to 24 hours ($\Delta Lac_{T_{12-24}}$). For lactate measurement, arterial blood samples were drawn from an arterial catheter and analyzed in the central hospital laboratory. Renal, respiratory and circulatory organ function were assessed on the basis of serum creatinine levels (creat), requirement of mechanical ventilation (MV) and a MAP < 60 mmHg/ requirement of catecholamines (\downarrow MAP/catechol).

Treatment

Normalization of blood lactate levels was a treatment target in both hospitals. This was primarily done by increasing DO_2 (fluids guided by fluid challenges, dobutamine or other inotropic agents, red blood cell transfusion, mechanical ventilation/ optimization of oxygenation) and/or decreasing VO_2 (e.g. analgesia/sedation).

Statistical analysis

Since blood lactate levels were not normally distributed, they were logarithmically transformed before analysis. To compare lactate levels of survivors and non-survivors, the Student's t-test was used. Mortality rates of patients with hyperlactatemia (\geq 2.5 mmol/l [5, 7, 12]) were compared with those of patients with normal levels by using χ^2 testing or Fisher's exact test if necessary, based on sample size. To evaluate the prognostic values of lactate levels at $T=0$,

T=12 and T=24, receiver-operating-characteristic (ROC)-curves for in-hospital death (primary outcome measure) were constructed with corresponding area-under-the-ROC values (AUROC).

In order to evaluate whether the prognostic values of lactate at admission (Lac_{T0}) and of the reduction over time (ΔLac_{T0-12} and ΔLac_{T12-24}) were dependent of admission diagnosis (SEPSIS or LT) or hemodynamic status (HD_{stable} or $HD_{instable}$), multivariable Cox proportional hazards models were constructed. These models excluded patients who died within 24 hours and those with missing lactate levels. Two multivariable analyses were constructed: (a) for the comparison between SEPSIS and LT and (b) for the comparison between HD_{stable} and $HD_{instable}$ patients:

- (a) The following variables were entered in the model: Lac_{T0} , ΔLac_{T0-12} , ΔLac_{T12-24} and diagnosis (SEPSIS or LT) and subsequently, interaction terms were added ($diagnosis \cdot Lac_{T0}$, $diagnosis \cdot \Delta Lac_{T0-12}$ and $diagnosis \cdot \Delta Lac_{T12-24}$). For this analysis, patients classified as OTHERS were excluded.
- (b) The following variables were entered in the model: Lac_{T0} , ΔLac_{T0-12} , ΔLac_{T12-24} and HD status (HD_{stable} or $HD_{instable}$) and again, interaction terms were added ($HD\ status \cdot Lac_{T0}$, $HD\ status \cdot \Delta Lac_{T0-12}$ and $HD\ status \cdot \Delta Lac_{T12-24}$).

To correct for the hemodynamic status within the SEPSIS vs. LT comparison, an additional subgroup analysis was performed:

- (c) The following variables were entered in this model: Lac_{T0} , ΔLac_{T0-12} , ΔLac_{T12-24} , diagnosis, HD status, $diagnosis \cdot Lac_{T0}$, $diagnosis \cdot \Delta Lac_{T0-12}$ and $diagnosis \cdot \Delta Lac_{T12-24}$. Subsequently, additional interaction terms were added: $HD\ status \cdot diagnosis$, $HD\ status \cdot Lac_{T0}$, $HD\ status \cdot \Delta Lac_{T0-12}$, $HD\ status \cdot \Delta Lac_{T12-24}$, $diagnosis \cdot Lac_{T0} \cdot HD\ status$, $diagnosis \cdot \Delta Lac_{T0-12} \cdot HD\ status$ and $diagnosis \cdot \Delta Lac_{T12-24} \cdot HD\ status$.

Values are provided as mean \pm standard error of the mean (SE) (with exception of the baseline characteristics where the values

represent mean \pm standard deviation (SD)). Statistical analyses were performed using SPSS version 11.0.1/12.0.1 (SPSS, Inc., Chicago, IL, USA).

RESULTS

Patient characteristics

421 patients were enrolled during the study period, of which 27 patients were excluded because data were recorded during re-admissions. The flow chart of patient enrollment is shown in figure 1. Table 1 provides an overview of the distribution of admission diagnoses in the SEPSIS, LT and OTHERS groups. Table 2 describes the baseline characteristics and clinical variables of the total population and more specifically for the SEPSIS and LT groups and the HD_{stable} and $HD_{instable}$ groups.

Figure 1. Flow-chart of enrolled patients.

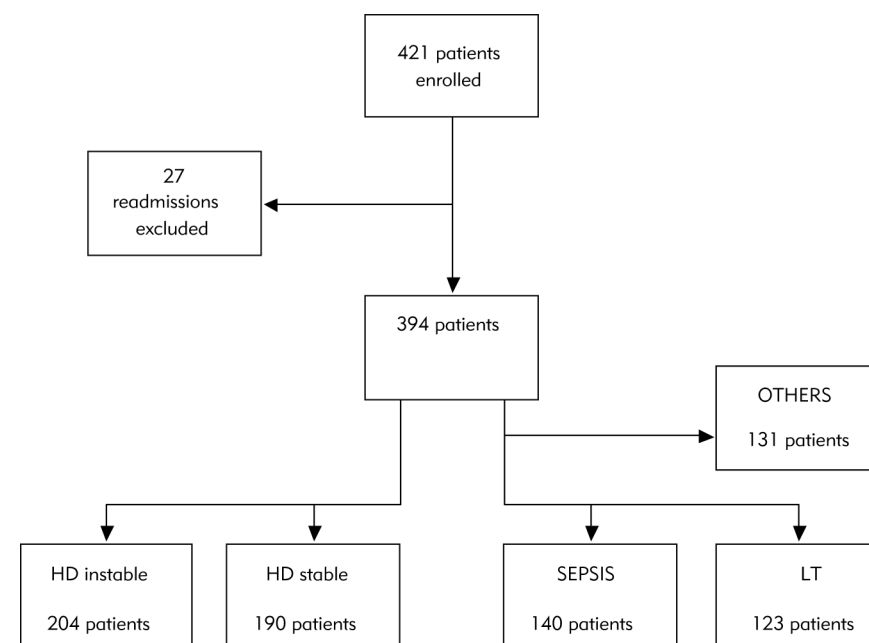


Table 1. The groups classified on the basis of APACHE III admission diagnoses.

Group	Admission diagnosis	N	Percentage of subtotal	
SEPSIS group	Sepsis respiratory tract	64	46%	
	Sepsis urinary tract	9	6%	
	Abdominal sepsis	35	25%	
	Cholecystitis/ cholangitis	8	6%	
	Meningitis/ encephalitis	3	2%	
	Others	21	15%	
	Subtotal group			
	140	100%		
LT group	Trauma without traumatic brain injury	15	12%	
	Trauma with traumatic brain injury	13	11%	
	Ruptured abdominal aortic aneurysm	28	23%	
	Gastro-intestinal bleeding	35	29%	
	Arrhythmia	5	4%	
	Acute myocardial infarction	3	2%	
	Pulmonary embolism with circulatory failure	2	2%	
	Congestive heart failure	9	7%	
	Cardiogenic shock	4	3%	
	Cardiac arrest	9	7%	
	Subtotal group			
		123	100%	
	OTHERS group	Non-infectious respiratory disease (e.g. COPD)	19	15%
Liver failure		1	1%	
Pancreatitis		4	3%	
Intestinal obstruction (non-surgical)		2	2%	
GI surgery: obstruction		19	15%	
GI surgery: Inflammatory bowel disease		4	3%	
GI surgery: intestinal ischemia		3	2%	
SAH/ intracerebral hemorrhage/ CVA		9	7%	
Epileptic seizure		5	4%	
Metabolic disease (e.g. diabetic ketoacidosis)		8	6%	
Autointoxication		8	6%	
Hematological disorder		7	5%	
Renal insufficiency		13	10%	
Others		29	22%	
Subtotal group				
	131	100%		
Total		394		

GI surgery = gastro-intestinal surgery, SAH = subarachnoid hemorrhage

SEPSIS vs. LT

Sepsis compared with LT patients had a higher APACHE II score, longer length of ICU stay but an equal length of hospital stay and mortality (table 2). The proportion of patients with hyperlactatemia at admission was equal.

In the SEPSIS group, the mean lactate level was significantly higher in non-survivors than in survivors at T=12 and T=24, but not at admission (figure 2). In contrast, in the LT group, it was higher in non-survivors at admission and T=12, but not at T=24. When looking at patients with normal or elevated levels, a similar difference

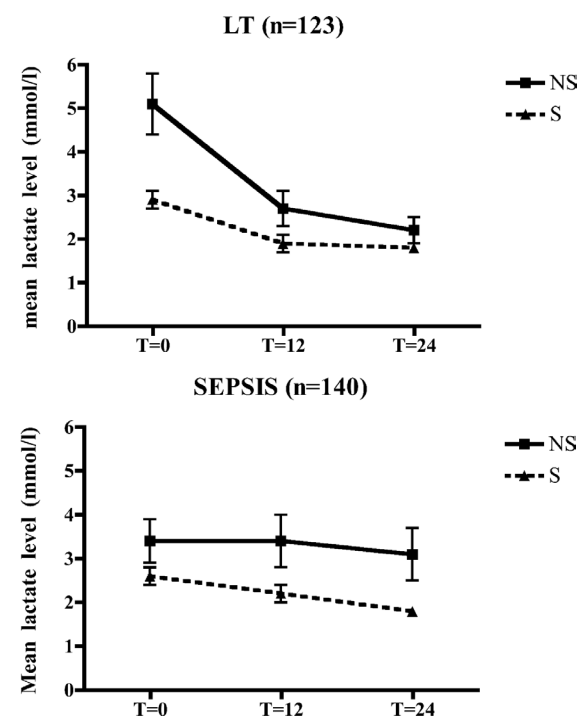


Figure 2. Mean lactate levels in survivors (S) and non-survivors (NS) in SEPSIS and LT groups. Error bars represent ± 1 standard error of the mean. * $p < 0.05$, ** $p < 0.01$ for comparison between survivors and non-survivors at the different time points (T=0, T=12 and T=24 hours).

between the SEPSIS and LT groups was found (figure 3a and 3b). In the SEPSIS group, mortality was not significantly higher in those with elevated levels at admission, but those with normalized levels after 24 hours did have a lower risk of dying. In the LT group, outcome was worse in patients with abnormal levels directly at admission, whereas after 24 hours, mortality in those with abnormal levels was not higher anymore than in those with levels in the normal range. In the subgroup of LT patients with initial

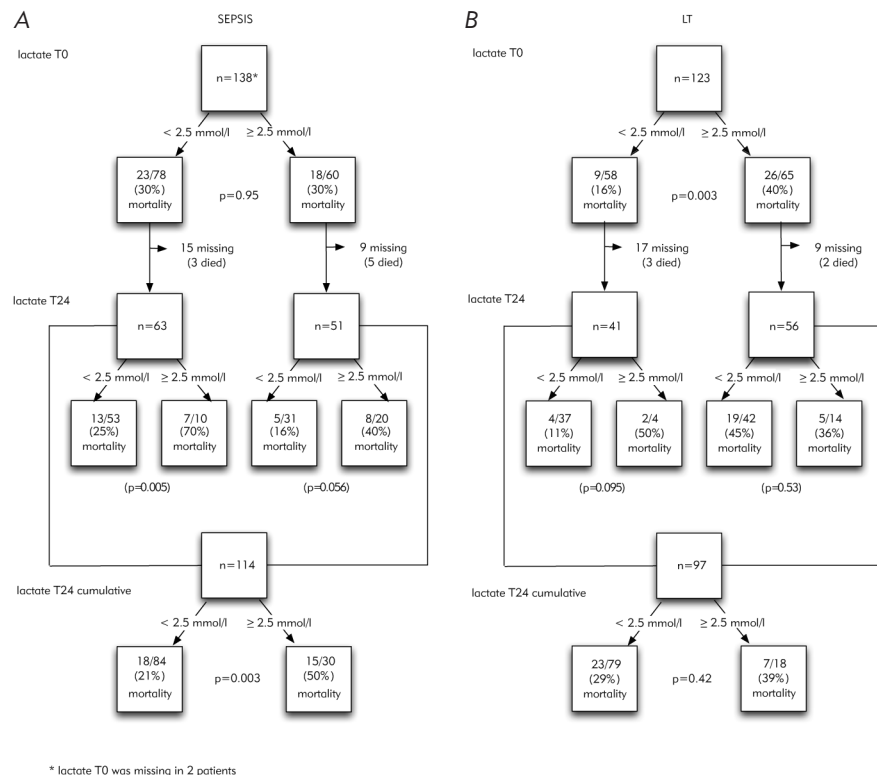
Table 2. Baseline characteristics and clinical variables of the total population and more specifically for the SEPSIS and LT groups and the HD_{stable} and HD_{instable} groups.

	TOTAL (n=394)	HD _{instable} (n=204)	HD _{stable} (n=190)	P-value HD _{instable} vs HD _{stable}	SEPSIS (n=140)	LT (n=123)	P-value SEPSIS vs LT
Age (yrs)	65± 16	69± 13	61± 18	<0.001	67± 14	65± 17	0.76
Sex: male/female (%)	56/44	54/46	58/42	0.48	56/44	66/34	0.10
In-hospital mortality (%)	27	31	22	0.041	30	29	0.89
Predicted hospital mortality (%)	29	39	24	0.001	36	26	0.09
ICU mortality (%)	16	22	10	0.001	16	19	0.62
Hospital LOS (days)	25± 26	28± 28	21± 22	0.005	28± 30	21± 18	0.13
ICU LOS (days)	7± 13	10± 16	5± 8	<0.001	10± 17	7± 11	0.004
Apache II	18± 8	21± 7	16± 7	<0.001	20± 7	17± 8	0.001
Hospital: I / II (%)	45/55	45/55	46/54	0.76	45/55	43/57	0.80
Referring department:				0.07			<0.001
ED (%)	34	29	38		24	42	
Ward (%)	45	48	41		59	33	
OT (%)	10	13	7		5	15	
Others (%)	11	10	13		11	10	
MV at admission (%)	52	66	37	<0.001	47	63	0.013
RRT first 24 hrs (%)	8	13	4	0.002	9	1	0.002
Surgery 7 days prior to ICU (%)	31	35	26	0.06	23	35	0.040

Lactate T= 0 (mmol/l)	3.2± 3.1	3.7± 3.5	2.5± 2.4	<0.001	2.9± 2.3	3.5± 3.1	0.10
Lactate T= 12 (mmol/l)	2.2± 2.1	2.5± 2.3	1.8± 1.7	<0.001	2.5± 2.6	2.2± 1.8	0.17
Lactate T= 24 (mmol/l)	2.0± 1.8	2.3± 2.2	1.6± 0.9	<0.001	2.2± 2.1	1.9± 1.2	0.26
Lactate ≥ 2.5 mmol/l T=0 (%)	169/391 (43%)	106/203 (52%)	63/188 (34%)	<0.001	60/138 (44%)	65/123 (53%)	0.13
Lactate ≥ 2.5 mmol/l T=12 (%)	93/362 (26%)	63/198 (32%)	30/164 (18%)	0.003	42/136 (31%)	29/110 (26%)	0.44
Lactate ≥ 2.5 mmol/l T=24 (%)	60/305 (20%)	48/176 (27%)	12/129 (9%)	<0.001	30/114 (26%)	18/97 (19%)	0.19
Heart rate T= 0 (beats/min)	100	103	97	0.015	106	97	0.001
Heart rate T= 12 (beats/min)	96	99	93	0.002	97	94	0.22
Heart rate T= 24 (beats/min)	96	97	94	0.21	97	94	0.35
MAP T= 0 (mmHg)	84	76	92	<0.001	79	85	0.022
MAP T= 12 (mmHg)	78	74	84	<0.001	75	79	0.022
MAP T= 24 (mmHg)	81	77	87	<0.001	79	82	0.34
Vasopressor/inotropics T=0 (%)	27	52	0	<0.001	30	29	0.89
Vasopressor/inotropics T=12(%)	39	76	0	<0.001	50	37	0.040
Vasopressor/inotropics T=24(%)	35	67	0	<0.001	46	32	0.020
pH at admission	7.36± 0.11	7.34± 0.11	7.38± 0.10	0.001	7.37± 0.09	7.35± 0.10	0.09
BE at admission (mmol/l)	-4.2± 5.9	-5.3± 5.9	-3.0± 5.7	<0.001	-3.9± 5.3	-4.4± 4.7	0.66

Values represent means ± standard deviation (SD). LOS=length of stay, APACHE II=Acute Physiology and Chronic Health Evaluation, Hospital I = Isala Clinics Zwolle, Hospital II=Gelre Hospitals Apeldoorn, ED=emergency department, OT=operation theatre, MV=mechanical ventilation, RRT=renal replacement therapy. BE=base excess, MAP=mean arterial pressure, vasopressor/inotropics = dopamine ≥ 3 mcg/kg/min, dobutamine any dose, norepinephrine any dose or epinephrine any dose. Student's t-test, Chi-square test, ANOVA or non-parametric Kruskal-Wallis were used when appropriate.

Figure 3. A) Mortality rates of SEPSIS patients with high (≥ 2.5 mmol/l) or normal (<2.5 mmol/l) blood lactate levels at admission or after 24 hours of ICU therapy. **B)** Mortality rates of LT patients with high (≥ 2.5 mmol/l) or normal (<2.5 mmol/l) blood lactate levels at admission or after 24 hours of ICU therapy.



hyperlactatemia who succeeded to normalize lactate during 24 hours of treatment, still 45% died compared to 36% in those who did not.

The accuracy to predict mortality also differed when focusing on the ROC curves. AUROC values increased from T=0 to T=24 in the SEPSIS group whereas they decreased in the LT group (figure 4).

Multivariable analysis confirmed the impact of admission diagnosis on the ability of lactate levels to predict outcome: the prognostic values of Lac_{T0} , ΔLac_{0-12} and ΔLac_{12-24} were significantly different between SEPSIS and LT ($p=0.043$ for the interaction term). In the SEPSIS-group reductions in lactate level were associated with

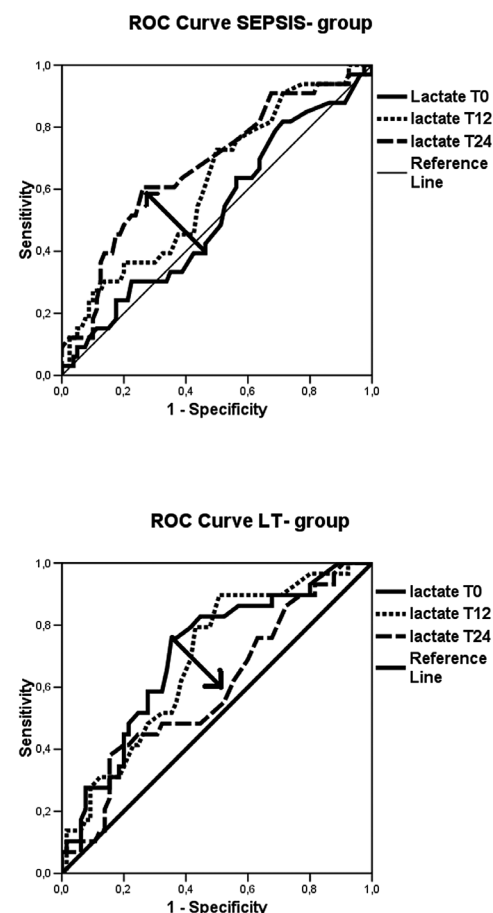


Figure 4. Receiver operating characteristic (ROC) curves of lactate levels at the different time points to predict in-hospital death. The arrows depict the progression of the prognostic value of lactate during the first 24 hours of ICU admission. The area-under-the-ROC value increased from T=0 to T=24 in the SEPSIS group (T=0 0.52, $p=0.73$; T=12 0.62, $p=0.049$; T=24 0.68, $p=0.004$) whereas it decreased in the LT group (T=0 0.71, $p=0.002$; T=12 0.69, $p=0.004$; T=24 0.59, $p=0.15$).

significantly lower mortality, whereas in the LT-group this was not the case (table 3).

To evaluate whether the LT group would be a valid comparison group for trauma patients only, we have separated out the 23% trauma patients and compared these to the entire LT group.

Although the results are not significant, as expected due to the low number of patients ($n=28$), they trended towards the same direction as in the LT group. Similar to the LT group, mortality seemed to be higher in trauma patients with an abnormal (27%, 4/15) versus a normal lactate on admission (15%, 2/13). Also in agreement with the LT group, mortality in trauma patients who normalized their lactate within 24 hours (35%, 6/17) didn't seem to be lower compared with those who failed to normalize lactate (0%, 0/5).

Administered catecholamines could possibly confound lactate levels and their prognostic values. However, epinephrine, mostly associated with increased production of lactate, was hardly used ($n=2$) and

Table 3. Cox proportional hazard model: hazard ratios (95% CI) for in-hospital death for the lactate level at ICU admission (Lac_{T0}) and the reduction from 0 to 12 hours (ΔLac_{T0-12}) and 12 to 24 hours (ΔLac_{T12-24}).

	Sepsis	Low-TO2
Lac_{T0}	2.72 (1.42-5.20) $p=0.003$	2.43 (1.14-5.16) $p=0.021$
ΔLac_{T0-12}	0.34 (0.16-0.71) $p=0.004$	0.78 (0.36-1.67) $p=0.52$
ΔLac_{T12-24}	0.24 (0.10-0.61) $p=0.003$	1.30 (0.48-3.49) $p=0.61$

Because of logarithmic transformation, interpretation of the hazard ratios is as follows: in the SEPSIS group, each decrement specified as a 10% increase of the 0 to 12 hours lactate ratio (ΔLac_{T0-12}) causes a -10% (-16 to -3%) change of the mortality hazard. Each 10% increase of ΔLac_{T12-24} causes a -13% (-20 to -5%) change. In the LT group, the corresponding (non-significant) changes in mortality are -2% (-9 to +5%) for ΔLac_{T0-12} and +3% (-7 to +13%) for ΔLac_{T12-24} . Each 10% reduction in Lac_{T0} causes a -10% (-16 to -4%) change of the mortality hazard in SEPSIS and -9% (-16 to -1%) in LT.

additional correction for catecholamine use in general (any infusion of norepinephrine, dopamine, dobutamine or epinephrine) did not affect the difference in prognostic value between the SEPSIS and LT groups ($p=0.13$ for the interaction term).

When looking at organ function, we found that in the LT group renal, respiratory and circulatory organ function were similar in non-survivors and survivors at $T=0$ (creat 122 vs 106, $p=0.26$; MV 71% vs 59%, $p=0.22$; \downarrow MAP/catechol 28% vs 37%, $p=0.39$). However, at $T=24$ LT non-survivors on average had more severe organ dysfunction (creat 141 vs 94, $p<0.001$; MV 70% vs 46%, $p=0.030$; \downarrow MAP/catechol 49% vs 25%, $p=0.017$).

On the other hand, in the SEPSIS group non-survivors had more severe renal and circulatory organ dysfunction at $T=0$ (creat 245 vs 154, $p=0.009$; MV 39% vs 50%, $p=0.27$; \downarrow MAP/catechol 55% vs 29%, $p=0.004$), whereas at $T=24$ organ function was comparable (creat 172 vs 140, $p=0.24$, MV 75.8% vs 62.2%, $p=0.200$, \downarrow MAP/catechol 55% vs 42%, $p=0.20$). The use of renal replacement therapy was similar at all times, both in the LT ($T=0$: 0 vs 0%, $T=24$: 3 vs 0%, $p=0.30$) and in the SEPSIS groups ($T=0$: 5 vs 1%, $p=0.21$, $T=24$: 9 vs 8%, $p=0.73$).

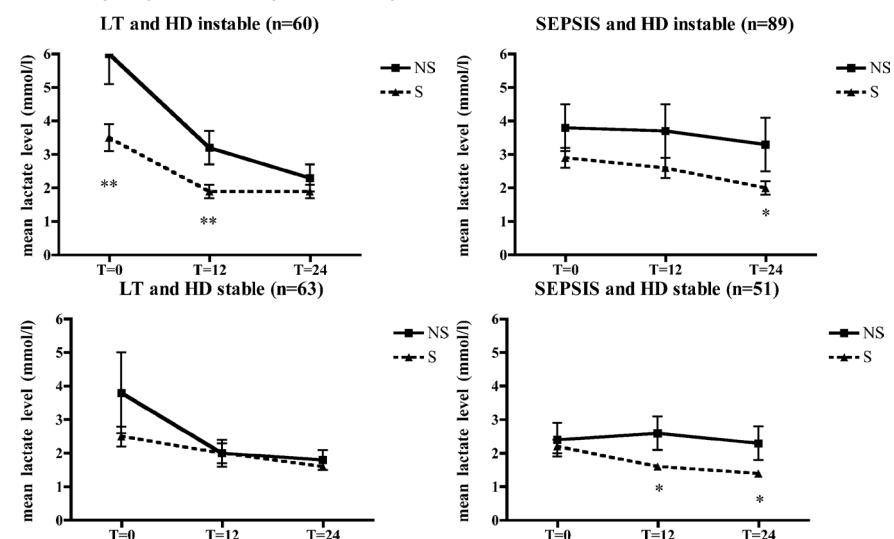
Hemodynamic status

Patients in the HD_{instable} group ($n=204$) had a higher APACHE II score, longer length of stay and a higher mortality than patients in the HD_{stable} group ($n=190$) (table 2). The proportion of patients with hyperlactatemia at admission was higher in HD_{instable} patients. Nevertheless, multivariable analysis showed that the prognostic value of Lac_{T0} , ΔLac_{0-12} and ΔLac_{12-24} was similar in HD_{instable} and HD_{stable} patients ($p=0.43$ for the interaction term).

Sepsis vs LT according to hemodynamic status

The effect of SEPSIS or LT on the relationship between serial lactate levels and outcome persisted after subdivision by hemodynamic status (Figure 5). This can be illustrated by the dichotomous analyses (table 4): both in the hemodynamically instable and stable patients of the SEPSIS group, mortality was equal in those with abnormal

Figure 5. Mean lactate levels in survivors (S) and non-survivors (NS) of the SEPSIS and LT groups according to hemodynamic status.



Error bars represent ± 1 standard error of the mean. * $p<0.05$, ** $p<0.01$ for comparison between survivors and non-survivors at the different time points ($T=0$, $T=12$ and $T=24$). Solid line = non-survivors. Dashed line = survivors.

Table 4. Mortality rates of SEPSIS and LT patients with normal and high blood lactate levels according to hemodynamic status.

		Hemodynamically instable			Hemodynamically stable		
		Lactate < 2.5	Lactate ≥ 2.5	p-value	Lactate < 2.5	Lactate ≥ 2.5	p-value
Sepsis	T=0	31% (13/42)	35% (16/46)	0.70	28% (10/36)	14% (2/14)	0.32
	T=24	24% (12/50)	46% (12/26)	0.049	18% (6/34)	75% (3/4)	0.035
LT	T=0	14% (3/22)	48% (18/38)	0.008	17% (6/36)	30% (8/27)	0.22
	T=24	38% (15/40)	39% (5/13)	0.95	21% (8/39)	40% (2/5)	0.32

and normal levels at admission, but after 24 hours, mortality became higher in patients with elevated levels. In the LT group, patients with high and normal levels after 24 hours had equal mortality rates, also irrespective of their hemodynamic status.

This could be confirmed in the Cox PH model, in which additional correction for hemodynamic status within the Sepsis-LT model did not change the found differences in prognostic value between SEPSIS and LT ($p=0.16$ for the interaction term). Similarly, when looking at ROC curve analysis, both in the hemodynamically instable and stable patients of the SEPSIS group, AUROC was lowest at admission and highest after 24 hours. In both hemodynamic subgroups of the LT group, AUROC was highest at admission and decreased over time (data not shown). Thus, the impact of admission diagnosis (SEPSIS or LT) on the prognostic value was really independent of the hemodynamic status.

DISCUSSION

This study shows that a reduction in lactate concentration during the first 24 hours following ICU admission is associated with improved outcome in septic patients, but not in patients presenting with hemorrhage or other conditions frequently associated with low-oxygen-transport.

Surprisingly, the lactate levels at admission, but not the reduction over time, predicted mortality in the LT group. This is illustrated by the high mortality (45%) in LT patients with initial hyperlactatemia despite the normalization of lactate levels during the first 24 hours. We hypothesize that the non-survivors, who had significantly higher admission lactate levels, experienced a more severe insult in the time before ICU admission that could have led to irreversible organ damage. During the first 24 hours in the ICU the conditions leading to increased lactate levels (e.g. tissue oxygen delivery-demand mismatch) could have been resolved, leading to a reduction in lactate levels, but not to a recovery of tissue damage [13]. As a result, only the lactate levels at admission and not after 24 hours were related to patient survival.

Such a phenomenon is probably best illustrated by the recovery from cardiac arrest, in which the extent of (neurological) organ damage determines prognosis [14], rather than the ability to reduce lactate levels in 24 hours following return of spontaneous circulation [15, 16]. Possibly a likewise mechanism is present in other low-oxygen-transport conditions such as trauma and hemorrhage. Following hemorrhage control and restoration of circulation, severe and irreversible organ damage might already have occurred despite a normalization of lactate levels at a later stage. This explanation is supported by our observation that the LT non-survivors developed more severe organ dysfunction after 24 hours, while the mean lactate concentration was equal to survivors at that time-point.

In the SEPSIS group we found opposite results. Lactate levels in the SEPSIS non-survivors remained elevated over 24 hours, which is in agreement with previous studies [3, 17]. Several explanations exist for the hyperlactatemia in this group of patients other than impaired tissue oxygen delivery [18, 19]. First, cytokine-mediated uptake of glucose [20] or catecholamine-stimulated increased Na-K-pump activity [21] might have increased aerobic glycolysis. Second, pyruvate dehydrogenase dysfunction may have limited the conversion of pyruvate to acetyl co-enzyme A [22, 23] and last, microcirculatory derangement [24, 25] or mitochondrial dysfunction [26] may have hampered oxygen utilization at the tissue level. Based on our re-

sults we can only conclude that if these processes can somehow be resolved within the first 24 hours of ICU admission, thereby leading to decreased lactate levels, patient survival in this group is improved.

The different time course of lactate levels in the SEPSIS and LT non-survivors could possibly be explained by differences in the etiology of hyperlactatemia, although mechanisms such as catecholamine stimulated Na-K-ATP-ase activation have been described in hemorrhage as well [27-29]. Another hypothesis could be that the SEPSIS patients suffered a less severe and more continuous insult from their disease compared to the LT patients. As a result organ damage and dysfunction might be more reversible and less related to patient survival. This is supported by our observation that the extent of organ dysfunction in SEPSIS survivors and non-survivors became similar after 24 hours (i.e. survivors had similar organ dysfunction but somehow this was reversible), whereas the exact opposite happened in LT patients. Reversal of organ dysfunction in septic patients has been suggested to be part of a protective regulatory process, which induces a temporary hypometabolic state resembling hibernation that may protect the cells from dying and allow the possibility of functional recovery [30].

With regard to the patients' hemodynamic status, we found that the prognostic value of hyperlactatemia was similar in hemodynamically stable and instable patients, also within the SEPSIS and LT groups. This means that, regardless of hemodynamics, reduction or normalization of lactate was not associated with improved outcome in LT patients. This finding might be in contradiction with previous studies in trauma patients with occult hypoperfusion [5, 7], in which a long time to normalization was associated with a higher mortality. Besides potential variation in time prior to ICU admission, this discrepancy could perhaps be explained by the higher mortality in our LT patients (29% versus 3-11% [5, 7]), possibly corresponding with more irreversible organ damage at admission.

Our study has several limitations. First, the group classification might have changed during the 24 hours. For instance, a trauma

patient with a hemorrhagic shock at admission could have developed ischemia-reperfusion damage or sepsis within 24 hours. However, for clinical relevance we were interested in the course of lactate concentration in different categories of patients who can be easily identified immediately at admission. Although this classification might have introduced some inaccuracy, it does resemble daily clinical practice where the prognosis needs to be estimated at the bedside as soon as patients are admitted. Second, we did not collect indices to examine anaerobic or aerobic etiology of hyperlactatemia (e.g. lactate to pyruvate ratio, liver function test, serum catecholamine concentration or microcirculation imaging). We felt that it was beyond the scope of this study to speculate on the exact causes of hyperlactatemia in our patients. Third, we did not register any form of advanced hemodynamic monitoring, such as cardiac output or SvO₂, nor measured oxygen transport. This might be considered a disadvantage because septic patients can be hypodynamic in the early phase [19] and trauma or aortic aneurysm surgery patients can be hyperdynamic in a later phase due to sepsis or ischaemia-reperfusion. However, as mentioned before we categorized our patients according to their admission diagnosis, prior to invasive monitoring. In this way we tried to make an early classification based on underlying disease rather than on hemodynamic profile. Last, although treating clinicians generally aimed at normalization of lactate levels by increasing DO₂ and reducing VO₂, we did not collect data on actual provided treatment. Different clinicians might have responded differently to patients with increased lactate levels, in ways we did not capture in our documentation. We don't know in which way this might have influenced the study results. However, because the same trained intensivists were primarily responsible for the treatment of both SEPSIS and LT patients, it seems unlikely that the difference between SEPSIS and LT is systematically biased by a difference in compliance with resuscitation protocols.

In conclusion, we found that lactate reduction during the first 24 hours of ICU stay is associated with improved outcome only in septic patients, but not in patients with hemorrhage or other conditions generally associated with low-oxygen-transport, regardless of the hemodynamic status. Therefore, lactate-directed therapy might not

be as beneficial in this particular group of patients, or should be started in an earlier phase in the emergency department.

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CHAPTER 6

The association between blood lactate levels, SOFA (sub)scores and 28-day mortality during early and late ICU stay: a retrospective observational study

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ABSTRACT

Objective: To evaluate whether the level and duration of increased blood lactate levels is associated with daily SOFA scores and organ subscores and to evaluate these associations during the early and late phase of ICU stay.

Design: Retrospective observational study

Setting: Mixed ICU of a university hospital

Patients: 134 heterogeneous ICU patients

Interventions: None

Measurements and main results: We calculated the area under the lactate-curve above 2.0 mmol/l (lactate_{AUC>2}). Daily SOFA scores were collected during the first 28 days of ICU stay to calculate initial (day 1), maximal, total and mean scores. Daily lactate_{AUC>2} were related to both daily SOFA scores and organ subscores using mixed model ANOVA. This was also done separately during the early (<2.75 days) and late (>2.75 days) phase of ICU stay.

Compared to normolactatemic patients (n=78), all median SOFA variables were higher in patients with hyperlactatemia (n=56)(initial SOFA: 9 (inter quartile range 4-12) vs 4 (2-7); max SOFA: 10 (5-13) vs 5 (2-9); total SOFA: 28 (10-70) vs 9 (3-41); mean SOFA: 7 (4-10) vs 4 (2-6), all p<0.001). The overall relationship between daily lactate_{AUC>2} and daily SOFA was an increase of 0.62 SOFA-points per 1 day·mmol/l of lactate_{AUC>2} (95% CI: 0.41-0.81, p<0.00001). During early ICU stay, the relationship between lactate_{AUC>2} and SOFA was 1.01 (95% CI: 0.53-1.50, p<0.0005), and during late ICU stay, this was reduced to 0.50 (95% CI: 0.28-0.72, p<0.0005). Respiratory (0.30, 0.22-0.38, p<0.001) and coagulation (0.13, 0.09-0.18, p<0.001) subscores were most strongly associated with lactate_{AUC>2}.

Conclusion: Blood lactate levels were strongly related to the SOFA score. This relationship was stronger during the early phase of ICU stay, which provides additional indirect support for early resuscitation to prevent organ failure. The results confirm that hyperlactatemia can be considered as a warning signal for organ failure

INTRODUCTION

Multiple organ failure (MOF), which can occur in many severe conditions including trauma (1), sepsis(2), burns (3) and severe acute pancreatitis (4), is an important cause of morbidity and mortality. Blood lactate levels have been associated with the occurrence of organ failure using lesser-known organ failure scales (1, 5, 6). However, the relationship between lactate levels and the well validated Sequential Organ Failure Assessment (SOFA) score (7-11) has not yet been studied. Although lactate as a biomarker and SOFA as an organ dysfunction scale have different functions, an association between the two might have clinical implications. Blood lactate measurement may act as a real-time marker for the severity of organ failure, whereas calculating the SOFA score takes 24 hours. Potentially, this might improve therapy by adapting resuscitation to serial lactate measurements, which might prevent organ failure and eventually improve clinical outcome.

Because the SOFA score comprises scores from six different organ systems, it is also possible to evaluate the association of lactate with separate organ systems. It is unknown to which extent the cardiovascular and other SOFA subscores are related to lactate levels.

The aim of our study was to evaluate whether the level and duration of increased blood lactate levels (represented by the area under the lactate-curve) is associated with daily SOFA scores and its separate organ subscores and to evaluate whether these associations are time-dependent (early versus late phase of ICU stay). We hypothesize that increased lactate levels will be associated with higher SOFA scores and that this association will be stronger in the early phase than in the late phase.

PATIENTS AND METHODS

Design

Retrospective observational study in the mixed ICU of a tertiary care university hospital.

Patients

Consecutive ICU patients with available lactate measurements who were admitted in January and February 2005 were eligible for study participation. Patients admitted with acute or chronic liver failure, defined as the presence of any kind of liver disease and a prothrombin time > 15 seconds, were excluded. The study was exempt from review and approval of the Local Ethics Committee by the Dutch Central Committee on research involving Human Subjects (CCMO), which waived the need for informed consent.

Data collection

Data from the first 28 days spent in the ICU were collected retrospectively from the electronic patient data monitoring system and hospital administration database. We collected demographic information, serial blood lactate levels and relevant variables for calculation of daily SOFA scores. The Glasgow Coma Scale collected in sedated patients was the assumed score without sedation. Mortality and length of stay were recorded. 28-day mortality was the primary outcome measure to evaluate survival.

SOFA SCORES

SOFA scores were calculated every day that a patient was staying in the ICU during the observation period of maximal 28 days. To calculate the SOFA score, the worst value for each parameter in each 24-hour period was used. If variables that were required to calculate the SOFA score were missing, they were regarded as normal until the first real variable was available. For any missing value thereafter, the last known real value was used. The following SOFA-derived variables were used (8):

- 1.) Initial SOFA: the SOFA score on the first day of ICU admission (from time of admission to 24 hours following admission, e.g., from 16:00 to 16:00 hours the next day).
- 2.) Max SOFA: the highest daily SOFA score during the observation period (maximal 28 days following ICU admission).
- 3.) Total SOFA: the sum of all daily SOFA scores during the observation period
- 4.) Mean SOFA: the total SOFA score divided by the number of days spent on the ICU during the observation period

MOF was defined as a score of at least 3 on two or more different individual organs of the SOFA score on any day during the observation period (12).

Lactate

Lactate levels were measured in arterial blood using point-of-care blood gas analyzers (ABL 700, Radiometer Copenhagen, Denmark, upper normal limit 2.0 mmol/l). Lactate buffer solutions for renal replacement therapy and continuous epinephrine infusion were not used during the study period.

The area under the curve of lactate levels above the threshold of 2.0 mmol/l was calculated daily using the following formula:

$$\text{lactate}_{\text{AUC}>2} = (\sum ((\text{time 2} - \text{time 1}) \cdot 0.5 \cdot (\text{lactate level time 1} + \text{lactate level time 2}))) - (\sum ((\text{time 2} - \text{time 1}) \cdot 2.0 \text{ mmol/l})).$$

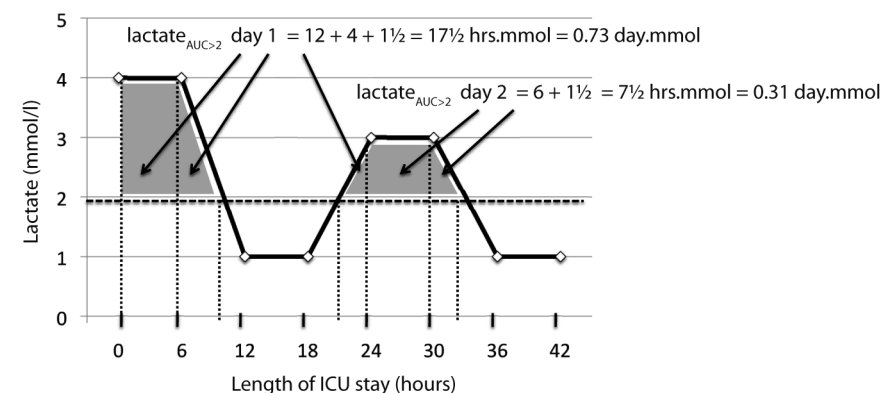
Time 1 = time of lactate level > 2.0 mmol/l or calculated time that the lactate-time curve between two subsequent lactate measurements crosses the threshold of 2.0 mmol/l

Time 2 = time of next lactate level > 2.0 mmol/l or next calculated time that the lactate-time curve crosses the threshold of 2.0 mmol/l

(Time periods between lactate measurements were calculated in minutes. Subsequently, lactate_{AUC>2} was converted into days·mmol/l)

Figure 1 clarifies the formula. Lactate_{AUC>2} was zero if lactate levels did not exceed the threshold of 2.0 mmol/l. Lactate_{AUC>2} was expressed as the value on the day of admission (initial lactate_{AUC>2}), the maximum of daily calculations of lactate_{AUC>2} (max lactate_{AUC>2}), the sum of all daily calculations (total lactate_{AUC>2}) and the mean of all daily calculations (mean lactate_{AUC>2}).

Figure 1. Example of calculation of the daily area under the curve of lactate levels above 2.0 mmol/l (lactate_{AUC>2})



Characteristic	Value: median (IQR)
Number of patients	134
Age (years)	61 (46-69)
Sex (male:female)	65%:35%
APACHE II	19 (14-25)
28-day mortality	22%
ICU mortality	16%
In-hospital mortality	31%
ICU LOS (days)	3 (1-8)
Hospital LOS (days)	14 (6-28)
Referring ward:	
- ED	34%
- Surgical ward/OT	34%
- Medical ward	15%
- Neurological ward	5%
- Other	13%
Admission diagnosis:	
- Sepsis/ severe sepsis/ septic shock*	36%
- Trauma	16%
- SAH/ intracerebral hemorrhage/ stroke/ neurosurgery	13%
- Ruptured aortic aneurysm	8%
- Oesophagectomy	7%
- Heart failure	4%
- Pulmonary embolus	3%
- Intoxication	3%
- Cardiac surgery	0%
- Others	10%
Vasopressor/ inotropic support day 1	34%
Lactate at admission (mmol/l)	1.3 (0.8-2.3)

Statistics

Values are described as medians with interquartile ranges (IQR). Kruskal-Wallis tests were performed to compare survivors and non-survivors and those with and without hyperlactatemia. To evaluate the prognostic value of SOFA and lactate_{AUC>2}, univariate Cox proportional hazards models were performed. Daily SOFA scores were related to daily lactate_{AUC>2} using mixed model ANOVA. In this way, between-patient and within-patient variations (e.g., within a single patient, the score on day 4 is correlated to the score on day 5, on day 6, etc.) of daily SOFA scores were taken into account. The day-to-day correlation of within-patients SOFA scores was assumed to have a first-order autore-

Table 1. Baseline and clinical characteristics
LOS=length of stay,
ED=emergency department, OT=operation theatre.
IQR=interquartile range.

*Sepsis, severe sepsis and septic shock classification as defined by (31).

gressive structure. The effects of daily values of lactate_{AUC>2} on daily SOFA were also estimated separately during the early and late phase of ICU stay; because consensus time definitions are unavailable, we arbitrarily defined the early phase of ICU stay as before the median length of ICU stay (= 2.75 days). Finally, the daily individual SOFA organ scores were related to daily lactate_{AUC>2}. $P < 0.05$ was considered statistically significant. Data were analysed using the SPSS/PC program (version 10.1.0/12.0.1, SPSS, Chicago, Ill, USA).

RESULTS

During the study period 205 patients were admitted to the ICU. 11 patients were excluded due to liver failure, and lactate was not measured within the first 24 hours of ICU admission in another 60 patients. The baseline and clinical characteristics of the remaining 134 patients are displayed in table 1. In total, 2627 lactate levels were available, which corresponded to an average of 3 measurements per patient per day. Median lactate at admission was 1.3 mmol/l (IQR 0.8-2.3), with a range between 0.5 and 19.0 mmol/l. Twenty-nine percent of the patients had hyperlactatemia

Table 2. SOFA and lactate in 28-day survivors and non-survivors

	Survivors (n=105)	Non-survivors (n=29)
Initial SOFA	5 (2-8)	9 (7-12)*
Max SOFA	5 (3-9)	9 (7-13)*
Total SOFA	13 (4-52)	26 (9-67)#
Mean SOFA	4 (2-6)	8 (6-11)*
Initial lactate _{auc>2}	0 (0-0.4)	0 (0-2.0)*
Max lactate _{auc>2}	0 (0-0.7)	0.5 (0-2.2)*
Total lactate _{auc>2}	0 (0-0.8)	0.5 (0-2.7)*
Mean lactate _{auc>2}	0 (0-0.2)	0.2 (0-1.0)*

Median values (interquartile range) of SOFA and area under the lactate-curve above 2.0 mmol/l (lactate_{AUC>2}) in 28-day survivors and non-survivors. Values are provided for the initial (day 1), maximal, total and mean variables of SOFA and lactate_{AUC>2}. * $p < 0.05$, # $p = 0.07$

(>2.0 mmol/l) at admission, 34% had hyperlactatemia within the first 24 hours and 42% at any time during their ICU stay.

SOFA and lactate in survivors and non-survivors

Generally, SOFA and lactate_{AUC>2} were higher in 28-day non-survivors than in survivors (table 2). Initial, max and mean (but not total) values of SOFA and lactate_{AUC>2} significantly predicted 28-day mortality (table 3).

Table 3. Hazard ratios of SOFA and lactate for prediction of 28-day mortality

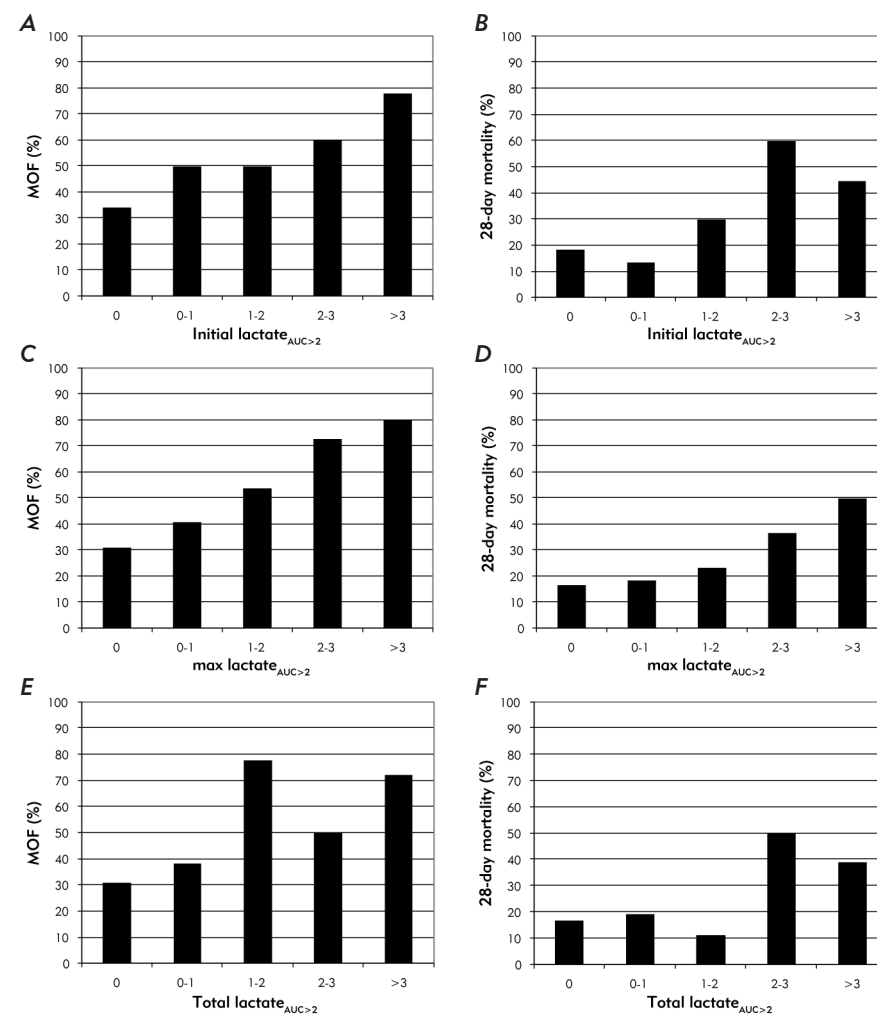
Variable	Hazard ratio	95% CI	P-value
Initial SOFA	1.14	1.05-1.24	0.002
Max SOFA	1.10	1.02-1.18	0.011
Total SOFA	1.00	0.99-1.00	0.70
Mean SOFA	1.24	1.13-1.24	<0.001
Initial lactate _{AUC>2}	1.39	1.19-1.63	0.001
Max lactate _{AUC>2}	1.33	1.14-1.55	0.002
Total lactate _{AUC>2}	1.07	0.99-1.17	0.14
Mean lactate _{AUC>2}	1.57	1.33-1.84	<0.001

Results of univariate Cox proportional hazard models. The hazard ratios of initial (day 1), maximal, total and mean SOFA and lactate_{AUC>2} for 28-day mortality are shown. For instance, this can be interpreted as a 57% increased hazard of death for every increase of 1 day·mmol/l in mean lactate_{AUC>2}.

Hyperlactatemia and SOFA

Generally, the risk of MOF or death increased when lactate levels were higher for a longer period (figure 2). In patients with hyperlactatemia (lactate_{AUC>2} >0, n=56) compared with normolactatemic patients (lactate_{AUC>2} =0, n=78), all SOFA-derived variables were significantly higher (figure 3).

Figure 2. Multiple organ failure (MOF) and 28-day mortality according to the initial (A and B), the maximal (C and D) and the total (E and F) daily area under the curve of lactate levels above 2.0 mmol/l.

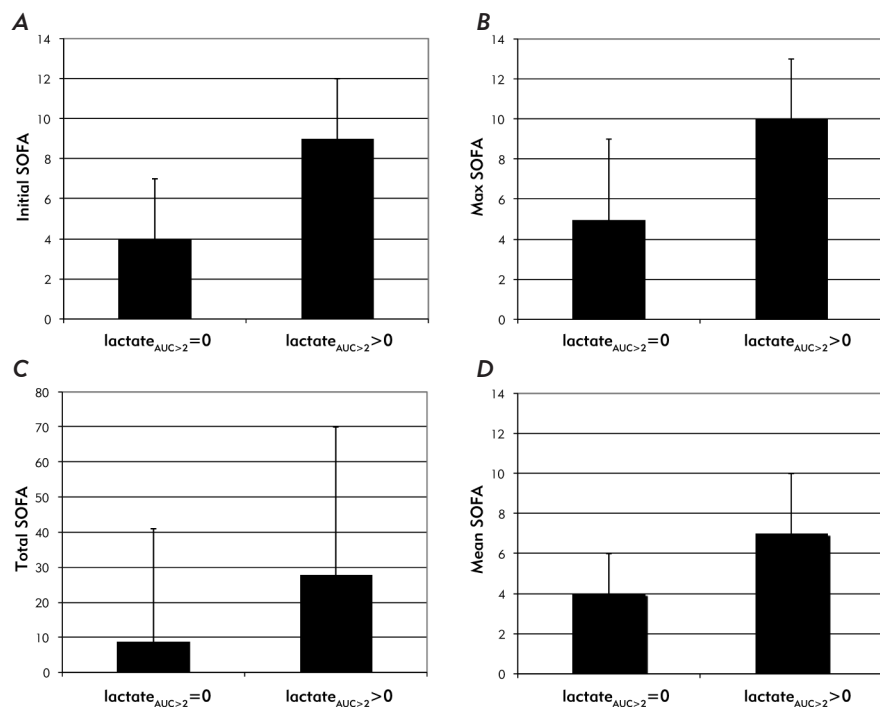


Number of patients: initial lactate_{AUC>2} (A and B) 0: n=88, 0-1: n=22, 1-2: n=10, 2-3: n=5, >3: n=9. Max lactate_{AUC>2} (C and D) 0: n=78, 0-1: n=22, 1-2: n=13, 2-3: n=11, >3: n=10. Total lactate_{AUC>2} (E and F) 0: n=78, 0-1: n=21, 1-2: n=9, 2-3: n=8, >3: n=18.

The daily lactate_{AUC>2} was significantly associated with the daily SOFA score.

The overall relationship between the two variables was an increase of 0.62 SOFA-points per 1 day·mmol/l of lactate_{AUC>2} (95% CI: 0.41-

Figure 3. Initial (A), maximal (B), total (C) and mean (D) SOFA for patients with hyperlactatemia ($\text{lactate}_{\text{AUC}>2} >0$, $n=56$) compared to the patients without ($\text{lactate}_{\text{AUC}>2} =0$, $n=78$).



Arrow bar represents the interquartile range.

0.81, $p < 0.00001$). During the early phase of ICU stay (before a median of 2.75 days), the relationship between $\text{lactate}_{\text{AUC}>2}$ and SOFA was 1.01 SOFA points per 1 day·mmol/l of $\text{lactate}_{\text{AUC}>2}$ (95% CI: 0.53-1.50, $p < 0.0005$). During the later ICU stay (>2.75 days), this was 0.50 SOFA points per 1 day·mmol/l of $\text{lactate}_{\text{AUC}>2}$ (95% CI: 0.28-0.72, $p < 0.0005$).

Hyperlactatemia and individual SOFA organ scores

Comparing patients with and without hyperlactatemia, the initial, max, total and mean scores of almost all individual organ systems were higher in patients with hyperlactatemia (table 4). However, lactate was only significantly associated with respiratory and coagu-

Table 4. SOFA organ subscores in normo- and hyperlactatemic patients

A		
Initial subscores	$\text{lactate}_{\text{AUC}>2} =0$	$\text{lactate}_{\text{AUC}>2} >0$
Initial SOFA _{respiratory}	2 (0-3)	2 (1-4)*
Initial SOFA _{coagulation}	0 (0-1)	1 (0-2)*
Initial SOFA _{cardiovascular}	1 (0-2)	1 (1-4)*
Initial SOFA _{CNS}	0 (0-2)	1 (0-4)
Initial SOFA _{renal}	0 (0-0)	0 (0-2)*
Initial SOFA _{liver}	0 (0-0)	0 (0-0)
B		
Max subscores	$\text{lactate}_{\text{AUC}>2} =0$	$\text{lactate}_{\text{AUC}>2} >0$
Max SOFA _{respiratory}	2 (0-3)	3 (2-4)*
Max SOFA _{coagulation}	0 (0-1)	1 (0-2)*
Max SOFA _{cardiovascular}	1 (0-3)	2 (1-4)*
Max SOFA _{CNS}	1 (0-3)	3 (0-4)*
Max SOFA _{renal}	0 (0-0)	0 (0-2)*
Max SOFA _{liver}	0 (0-0)	0 (0-1)*
C		
Total subscores	$\text{lactate}_{\text{AUC}>2} =0$	$\text{lactate}_{\text{AUC}>2} >0$
Total SOFA _{respiratory}	3.5 (0-17)	9.5 (3-23)*
Total SOFA _{coagulation}	0 (0-1)	2 (0-5)*
Total SOFA _{cardiovascular}	1.5 (0-6)	4 (1-13)*
Total SOFA _{CNS}	1 (0-8)	7.5 (0-28)*
Total SOFA _{renal}	0 (0-0)	0 (0-8)*
Total SOFA _{liver}	0 (0-0)	0 (0-2)*
D		
Mean subscores	$\text{lactate}_{\text{AUC}>2} =0$	$\text{lactate}_{\text{AUC}>2} >0$
Mean SOFA _{respiratory}	1.9 (0-2.3)	2.0 (1.3-2.6)*
Mean SOFA _{coagulation}	0 (0-0.5)	0.5 (0-1.1)*
Mean SOFA _{cardiovascular}	0.8 (0-1.1)	1.0 (0.5-2)*
Mean SOFA _{CNS}	0.5 (0-2)	1.1 (0-2.8)
Mean SOFA _{renal}	0 (0-0)	0 (0-2)*
Mean SOFA _{liver}	0 (0-0)	0 (0-0.3)*

Initial (A), maximal (B), total (C) and mean (D) values of the individual SOFA organ subscores for patients with hyperlactatemia ($\text{lactate}_{\text{AUC}>2} >0$, $n=56$) compared to the patients without ($\text{lactate}_{\text{AUC}>2} >0$, $n=78$), * = $p < 0.05$

Table 5. Relationship between lactate and SOFA organ subscores

	effect overall	p-value overall	effect early	p-value early	effect late	p-value late
SOFA _{respiratory}	0.30	<0.001	0.27	0.001	0.34	<0.001
SOFA _{coagulation}	0.13	<0.001	0.08	0.12	0.12	<0.001
SOFA _{cardiovascular}	0.09	0.053	0.22	0.033	0.03	0.60
SOFA _{CNS}	0.07	0.14	0.20	0.065	0.03	0.54
SOFA _{renal}	0.04	0.29	0.20	0.017	-0.03	0.95
SOFA _{liver}	0.02	0.21	0.02	0.61	0.04	0.80

Effects of an increase of 1 day·mmol/l in daily lactate_{AUC>2} on the daily different SOFA organ subscores. The effects are shown for overall ICU stay and then separated for the early (<2.75 days) and late (>2.75 days) phase of ICU stay. For instance, an increase in lactate concentration from 2.0 mmol/l to 3.0 mmol/l during a time period of a day was associated with a 0.30 increase in the respiratory SOFA score per day. This was 0.27 early in the ICU stay and 0.34 late in the ICU stay. Statistics: mixed model ANOVA.

lation systems during overall ICU admission when specifically looking at the effect of increases in lactate_{AUC>2} on different organs in mixed model analysis (table 5). In the early phase of ICU admission, increases in lactate levels were also associated with cardiovascular and renal dysfunction, but this association disappeared during the late phase.

DISCUSSION

We found a clear association between lactate and SOFA, which was stronger in the early phase of ICU admission as compared to the late phase. This provides additional indirect support for the importance of early resuscitation in the prevention of organ failure (13-17). Possibly, serial lactate measurements may guide the process of optimizing oxygen delivery in this early phase (<http://www.clinicaltrials.gov/ct/show/NCT00270673?order=1>).

When looking at the individual organ systems, the cardiovascular subscore was not strongly associated with lactate levels (table 5). This emphasizes the phenomenon of occult hypoperfusion in

which hypotension is not a necessary characteristic for the presence of raised blood lactate levels (18-20). In addition, many aerobic mechanisms of hyperlactatemia, not related to tissue hypoxia, have been described in critically ill patients (21). However, despite the weak overall association of the cardiovascular system with lactate, there was a significant and clinically relevant association in the early phase, but this later disappeared (table 5). Apparently, the link between the severity of the initial insult, cardiovascular collapse and a rise in lactate levels is stronger in the early phase.

Respiratory and coagulation subscores were most strongly associated with lactate (table 5). An increased SOFA_{respiratory} score often indicates the presence of acute lung injury or ARDS, which directly influences severity of disease and outcome (22). The lung has been described as an important source of lactate (23), probably reflecting metabolic adaptations in response to inflammatory mediators rather than actual tissue hypoxia (24). SOFA_{coagulation} is a more indirect marker of critical illness: a link exists from thrombocytopenia via disseminated intravascular coagulation to hyperlactatemia and unfavourable outcomes (25). Similar to the platelet count, lactate might possibly act as a general biomarker of critical illness (21, 26). Because liver dysfunction can lead to hyperlactatemia (27, 28), it was remarkable that the liver subscore was not related to lactate. Probably, the number of patients with liver dysfunction was too small for a statistically significant association because we excluded patients with acute or chronic liver failure and because liver failure is less prevalent compared to other organ failure in critically ill patients (1).

Finally, our data reconfirm the prognostic value of SOFA and lactate for mortality (18, 29, 30). Only total SOFA and total lactate_{AUC>2} did not predict 28-day mortality (table 3): it is difficult to establish a relationship between total values and survival in patients who died early because they could not accumulate many SOFA points or a high lactate_{AUC>2}, whereas they were the most severely ill (8).

Our study has limitations. First, although we focussed on individual organs by evaluating SOFA subscores, this observational study

does not allow speculation on the cause of the link between hyperlactatemia and organ dysfunction. Second, this was a retrospective observational study, which does not allow drawing of definitive conclusions; prospective validation of our findings is required. We did not conduct a prospective trial because this would interfere with an ongoing randomized controlled trial on the efficacy of early lactate-directed therapy (<http://www.clinicaltrials.gov/ct/show/NCT00270673?order=1>). Third, 60 patients were excluded due to unavailability of lactate within the first 24 hours.

The ICU consisted of three different units to which patients were randomly admitted. In 2 of 3 units, lactate measurement was automatically incorporated in routine blood gas analysis. In the other unit, lactate measurement was performed on clinical indication. 55 of 60 excluded patients without available lactate levels were admitted to the unit where lactate was measured on clinical indication. However, the random admission of patients to one of the units guaranteed that exclusion because of missing lactate levels took place in unselected patients. This prevented selection bias.

CONCLUSION

The present study shows that both the duration and level of hyperlactatemia estimate the risk of organ failure. This risk was greater early in the ICU stay, which provides additional indirect support for the concept of early-goal directed therapy. Of all individual SOFA organ systems, respiratory and coagulation subscores were most strongly associated with lactate. Further research is warranted to elucidate the contribution of individual organs in the etiology of hyperlactatemia and to study whether early blood lactate level-guided resuscitation can actually prevent organ dysfunction.

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**EFFICACY OF
GOAL-DIRECTED
THERAPY IN
THE ICU**

CHAPTER 7

Early lactate-guided therapy in ICU patients: a multicenter, open-label, randomized controlled trial

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ABSTRACT

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

Objective: To assess the effect of lactate monitoring and resuscitation directed at decreasing lactate levels in ICU patients admitted with a lactate level of ≥ 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 $\geq 20\%$ per two hours for the initial eight 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%CI 0.43-0.87, $p=0.006$). In the lactate group, SOFA scores were lower between 9 and 72 hours, inotropes could be stopped earlier, patients could be weaned from mechanical ventilation and discharged from the ICU earlier.

Conclusions: In patients with hyperlactatemia on ICU admission, lactate monitoring 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.

Trial registration: ClinicalTrials.gov NCT00270673

INTRODUCTION

Increased blood lactate levels have been associated with significant morbidity and mortality ever since its 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 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 et al. 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 post-cardiac 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 ICU admission would benefit from serial lactate monitoring, aimed to reduce these levels by 20% per two hours, when compared to 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 finally 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 upon ICU admission were eligible for inclusion. We excluded patients with liver failure (prothrombin time >15 seconds or INR equal or higher than 1.5 and any hepatic encephalopathy (23)), following liver surgery, age < 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 multi-center, 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 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).

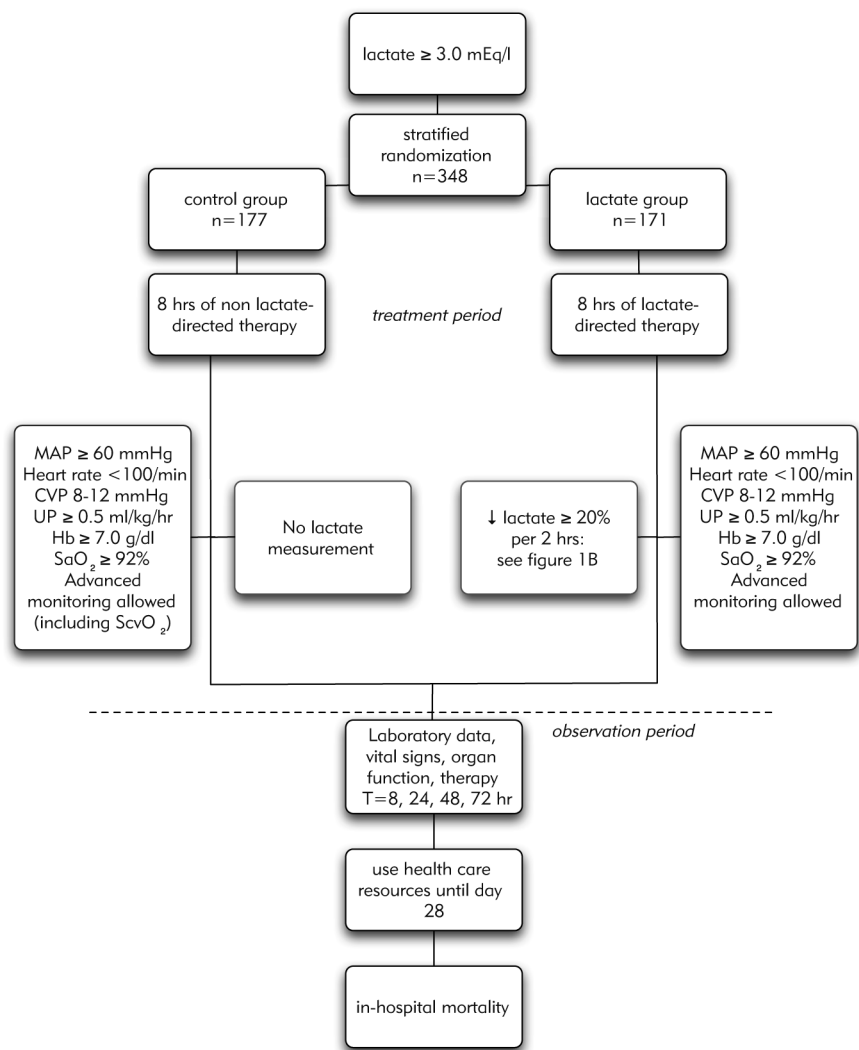
The start of the study was defined as the time of the first available lactate level immediately following ICU admission. For the next eight hours (treatment period), patients were randomly allocated to either treatment aimed to decrease lactate levels by at least 20% per two hours or to standard therapy where 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 following ICU discharge, were not aware of the treatment assignment.

Treatment

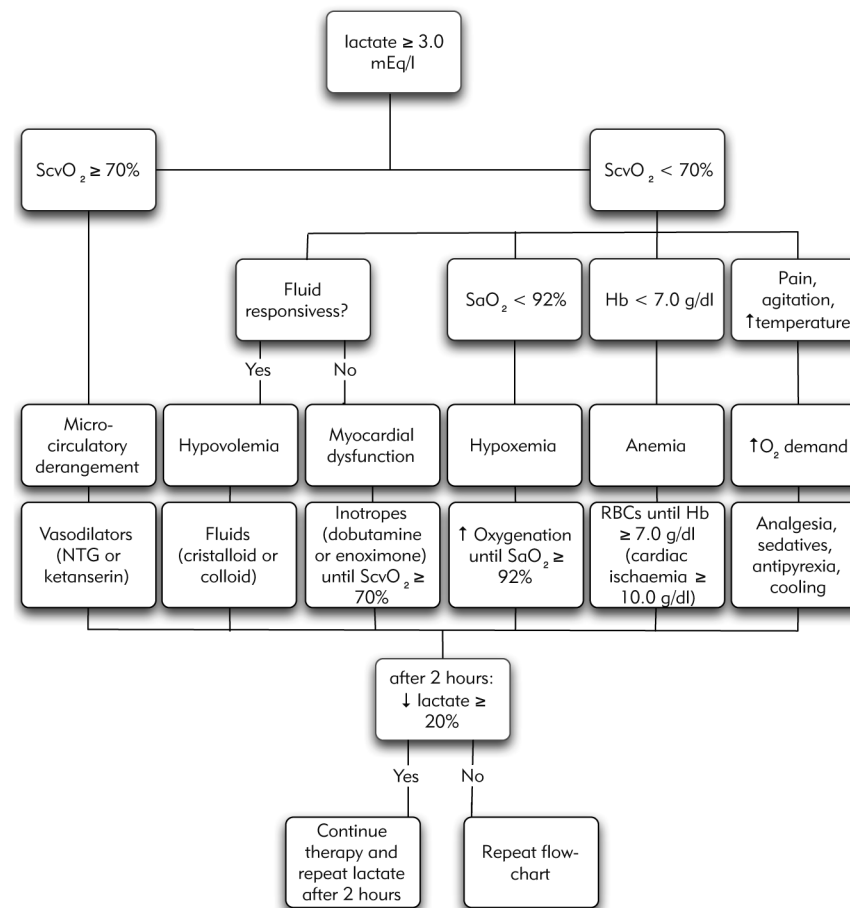
Patients were treated according to their randomization group by qualified intensivists available 7x24h in a closed format setting.

Figure 1A. Treatment algorithm control group and lactate group



The goal for CVP was 12-15 mmHg 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 7.0 g/dL = 4.3 mmol/L, 10 g/dL = 6.2 mmol/L)

Figure 1B. Additional treatment algorithm lactate group



If the lactate level became $\leq 2,0$ 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, ScvO₂ or stroke volume, or a decrease in heart rate. CVP was used as a dynamic safety limit (27): if CVP increased ≤ 2 mmHg, fluid administration was continued, if CVP increased > 2 and ≤ 5 mmHg, the fluid challenge was repeated after waiting for 10 minutes, if CVP increased ≥ 5 mmHg, 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. Hemoglobin 7.0 g/dL = 4.3 mmol/L, 10 g/dL = 6.2 mmol/L, NTG=nitroglycerine, RBCs= red blood cell transfusions

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 eight-hours treatment period was

based on the study of Polonen et al (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 b/min, mean arterial pressure (MAP) at or above 60 mmHg, central venous pressure (CVP) 8-12 mmHg (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.hr, arterial oxygen saturation (SaO₂) at or above 92% and hemoglobin level at or above 7.0 g/dL (at or above 10.0 g/dL in case of cardiac ischemia) (28). The use of central venous oxygen saturation (ScvO₂) 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 two 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 two 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. Central venous hemoglobin oxygen saturation (ScvO₂) 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 ScvO₂ was at or above 70%, but lactate levels did not decrease by at least 20% during a two-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 APACHE II and 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 following an eight-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. ScvO₂ 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 it was 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 two-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 non-invasive), renal replacement therapy (all techniques) and use of vasopressors and inotropes use was registered until 28 days following 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 (TJ) and three research nurses (WM, WintV, CB).

Statistical analysis

In-hospital mortality was the primary endpoint. Secondary pre-defined endpoints were ICU and day-28 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 prior to this study, we estimated an in-hospital mortality rate for the control group of 42%. In order to detect a 15% absolute reduction in hospital mortality, similar to the study by Rivers et al. (19), with a two-sided alpha 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 following the enrolment of 175 patients. Based on an alpha-spending function halfway between the O'Brien & Fleming and the Pocock boundary shapes, the alpha used in the interim analysis was set at 0.013, resulting in an alpha 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 pre-defined 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's proportional hazards analysis, stratified by center and presence or absence of sepsis. Adjustments were made for the following pre-defined co-variables: age, sex, baseline APACHE II and baseline SOFA-score. Mixed models were estimated to quantify differences in vital signs, laboratory variables, APACHE II and SOFA scores during the treatment period, at 8 hours following 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 ino-

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

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

Results

Patient enrolment is shown in figure E1 of the Online Data Supplement*. The intention-to-treat population consisted of 348 patients; 177 patients were randomized to the control group and 171 to lactate group. In 18 patients a major protocol violation occurred (table E1 Online Data Supplement). 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 eight-hour treatment period (10 control patients

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 – hours (interquartile range)	8 (1-79)	5 (1-65)
ICU admission within 6 hours from hospital admission - n (%)	87 (49%)	90 (53%)
Median time from ICU admission to randomization – hours (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

*The Online Data Supplement can be found at the end of this chapter

Diagnostic category – n (% of patients in the randomization group)		
- Sepsis category:	67 (38%)	68 (40%)
- Severe sepsis	- 39 (22%)	- 30 (18%)
- Septic shock	- 28 (16%)	- 38 (22%)
- Non-sepsis category:	110 (62%)	103 (60%)
- Neurologic	- 19 (11%)	- 18 (11%)
- Cardiac arrest	- 24 (14%)	- 24 (14%)
- Other non-sepsis	- 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 theatre (acute surgery)	55 (31%)	38 (22%)
- Operation theatre (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 anti-retroviral 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

Values are means ±SD unless otherwise specified.

vs. 6 patients in the lactate group). From eight to 72 hours following 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 following 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 that 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 hours, which was more often met in the control group)(table E2 Online Data Supplement). However, despite that the goal of a decrease in lactate level of $\geq 20\%$ per 2 hours was only used in the lactate group, this goal was also equally met in both randomization groups.

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 Online Data Supplement**).

Table 2. Blood lactate levels

Hours after start of therapy	Control group	Lactate group	P value
	Lactate level – mEq/l*		
Baseline (0 hours)	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% CI) were obtained from mixed model analysis. *Lactate levels are expressed as geometric means. P-values were calculated following logarithmic transformation of lactate levels.

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 Online Data Supplement). 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.

**The Online Data Supplement can be found at the end of this chapter

Similar proportions of patients in the control and lactate group received mechanical ventilation (86% vs. 84% $p=0.76$, including 2% vs. 2% non-invasive ventilation), antibiotics (67% vs. 61% $p=0.27$), corticosteroids (45% vs. 40% $p=0.38$), additional surgery following 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%, $p=0.91$), therapeutic hypothermia (10% vs 6%, $p=0.20$) and a percutaneous coronary intervention (1% vs. 1%, $p=0.96$).

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 hours [#]	2194 ± 1669	2697 ± 1965	0.011
9-72 hours [§]	10043 ± 6141	8515 ± 4987	0.055
Red blood cell transfusion, ml			
0-8 hours [#]	196 ± 495	322 ± 1037	0.15
9-72 hours [§]	345 ± 667	423 ± 1300	0.59
Any inotropic agent, %^{&}			
0-8 hours [#]	32.9	40.1	0.17
9-72 hours [±]	44.2	35.2	0.12
Any vasodilator, %[§]			
0-8 hours [#]	20.2	42.5	<0.001
9-72 hours [±]	27.1	43.2	0.005
Any vasopressor (%)[@]			
0-8 hours [#]	63.6	69.5	0.25
9-72 hours [±]	63.7	71.4	0.16

P-values as calculated by two-sample Student's t-test or the chi-square test, as appropriate.

[#] Values are shown for all patients

[§] Cumulative values (±SD) are shown for patients who were still admitted to the ICU after 72 hours

[±] Proportions are shown for patients who stayed for more than 8 hours in the ICU

[^] sum of crystalloid and colloid fluids

[&] dobutamine, enoximone or epinephrine

[§] nitroglycerine or ketanserin

[@] norepinephrine, dopamine or fenylephrine

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

MORTALITY

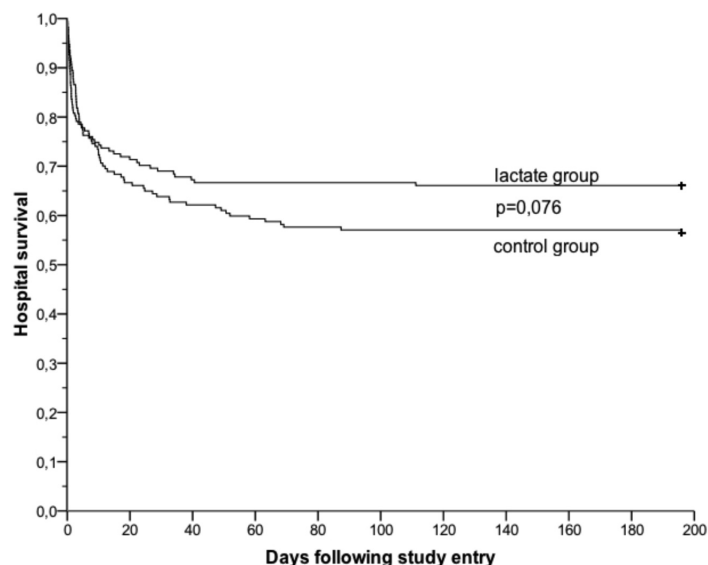
In the control group 43.5% (77/177) of the patients did not survive to hospital discharge whereas in the lactate group 33.9% (58/171) died during their hospital stay ($P=0.067$, table 4, figure 2). When adjusted for the predefined risk factors at baseline, the treatment protocol to decrease lactate levels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

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-day 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-day mortality		0.75 (0.52-1.09)		0.134
ICU-mortality		0.66 (0.45-0.98)		0.037

*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 centre and sepsis group, as predefined in the study protocol.

Figure 2. Kaplan Meier survival curve



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

Survival was followed-up until hospital discharge. The longest duration of hospital stay was 196 days.

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 (hazard ratio 0.72; 95% CI 0.54-0.98; figure 3a) and inotropes (hazard ratio 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 (hazard ratio 0.65; 95% CI 0.50-0.85; figure 4).

There were no significant differences in the time to stop vasopressors (hazard ratio 0.84; 95% CI 0.61-1.15; figure 3c) or renal re-

placement therapy (hazard ratio 0.56; 95% CI 0.22-1.43; figure 3d) between both groups.

Table 5. Disease severity and organ failure

Hours after start of therapy	Control group	Lactate group	P value
APACHE II score#			
Baseline (0 hours)	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 hours)	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

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 hours following study entry).

Subgroup and exploratory analyses

Pre-specified 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 pre-defined 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 T=0 hrs), effect size and p-value remained similar (data not shown).

Figure 3A. Time to weaning from mechanical ventilation

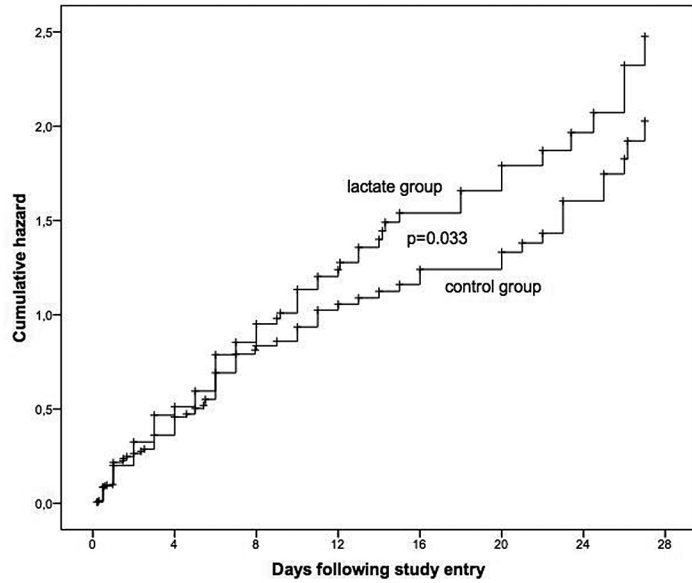


Figure 3C. Time to stop vasopressors

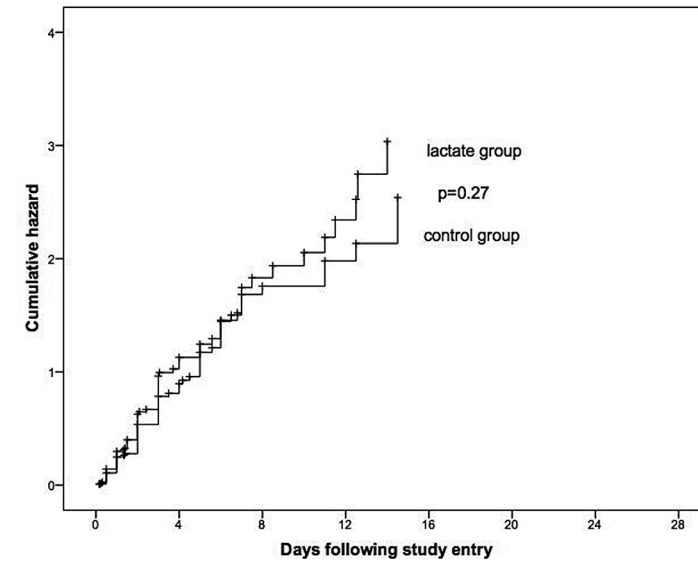


Figure 3B. Time to stop inotropes

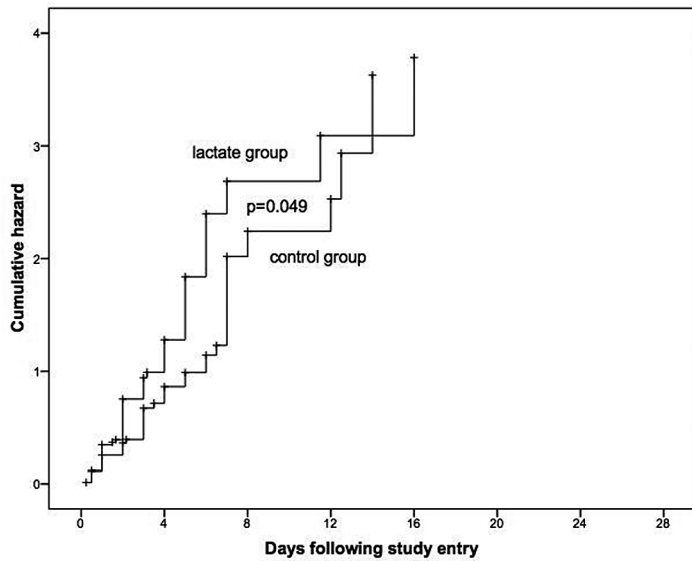
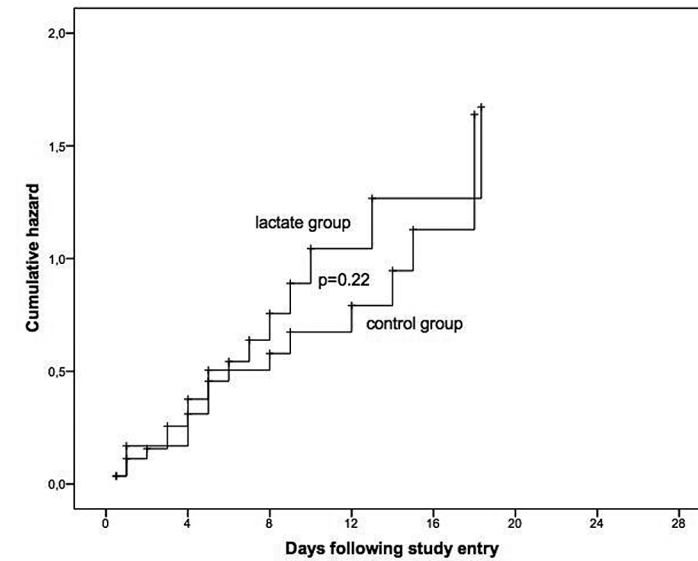
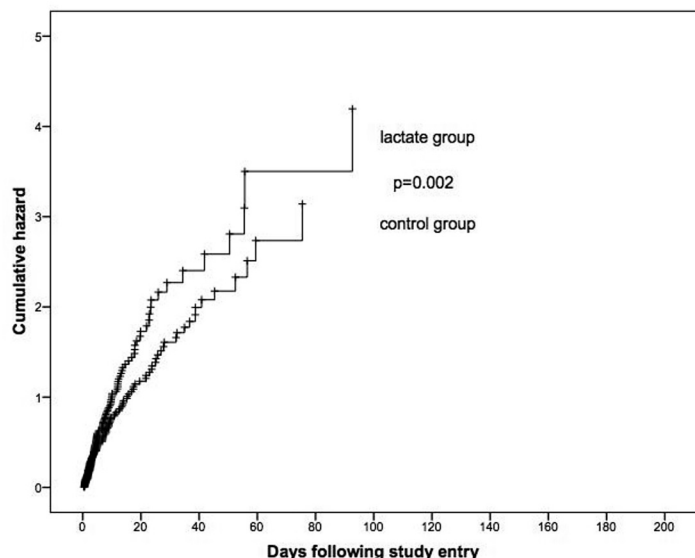


Figure 3D. Time to stop renal replacement therapy



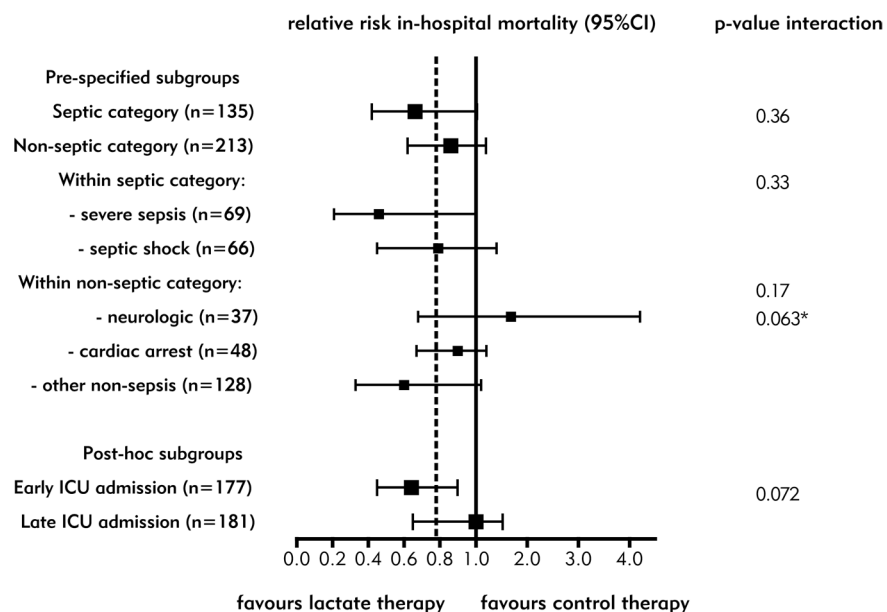
Assessed by cumulative hazard estimates and Cox's proportional hazard analysis, with censoring for early deaths.

Figure 4. Time to discharge from the ICU



Assessed by cumulative hazard estimates and Cox's proportional hazard analysis, with censoring for early deaths.

Figure 5. Pre-specified and post-hoc subgroup analyses.



Early ICU admission = < 6 hours following hospital admission. Late ICU admission = > 6 hours following ICU admission. P-value for interaction according to Breslow-Day test of homogeneity. * = p-value between neurologic and other non-sepsis.

DISCUSSION

In this multi-center, open-label randomized controlled study, lactate monitoring during the first eight hours of ICU admission, aimed at reducing lactate levels by at least 20% per two 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 probably 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. While 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, adminis-

tration of nitroglycerin reversed microcirculatory shutdown and shunting (40). In severe heart failure and cardiogenic shock nitroglycerine has been shown to improve microcirculatory perfusion (41, 42). Finally, Buwalda et al. described positive effects on tissue perfusion and oxygen extraction in addition to microcirculatory recruitment (43).

Surprisingly, the treatment algorithm of the lactate group did not result in faster reduction of lactate when compared to 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 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 et al. 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 on the applicability of this strategy in other settings and other patient groups (44, 45). 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 ScvO₂ values (46). 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 towards decreased use of fluids was found when compared to 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 following 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 pre-defined subgroups, although it might arguably be more pronounced in septic than in non-septic patients and in severe septic than in septic shock patients. The only pre-defined 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 (47), 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 (48).

Some methodological aspects are important, particularly regarding the open-label protocol design of this study (49, 50). 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 co-interventions were significantly different between the two groups. Also, the treatment team was practically blinded to treatment-assignment following the initial eight-hours 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 under-treatment in the control group. Additionally, the control group mortality was comparable with the mortality in the pilot study, conducted immediately prior to start of the study. However, given that ScvO₂ monitoring was mandatory in the lactate group and fac-

ultative in the control group, we cannot exclude the possibility 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 (51, 52), we have chosen a dynamic approach using central venous pressure (27) as it was practically most suitable in a multi-center environment within the earliest hours of ICU admission. In addition, this would probably resemble usual care in many ICUs worldwide (53) enlarging external generalizability of the results.

In summary, in ICU patients with a lactate level at or above 3.0 mEq/l upon admission, early monitoring of lactate levels with the added target to reduce levels by 20% per two 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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ONLINE DATA SUPPLEMENT

Table E1. Major protocol violations per patient

Patient	Group	Protocol violation
1	Control	Treated as lactate group
2	Lactate	Failure placement central venous catheter
3	Control	Wrong timing of measurements
4	Lactate	Treated as control group
5	Control	No measurements due to emergency surgery
6	Control	Missing study equipment (study forms)
7	Lactate	Missing study equipment (ScvO2 monitor)
8	Lactate	Missing study equipment (ScvO2 probe)
9	Lactate	Failure placement central venous catheter
10	Lactate	Failure protocol implementation (ward too busy)
11	Lactate	Failure protocol implementation (ward too busy)
12	Lactate	Missing study equipment (ScvO2 monitor)
13	Lactate	Failure protocol implementation (clinician unaware of study protocol)
14	Lactate	Failure placement central venous catheter
15	Lactate	Technical problems study equipment (ScvO2 probe)
16	Lactate	Failure placement central venous catheter
17	Lactate	Failure protocol implementation (refusal clinician to participate)
18	Lactate	Missing study equipment (reason unknown)

Table E2. Resuscitation endpoints during the treatment period (0-8 hours)

	Control group (N=177)	Lactate group (N=171)	P value
Mean arterial pressure \geq 60 mmHg			
- 0 hours	88%	87%	0.77
- 2 hours	93%	90%	0.36
- 4 hours	91%	93%	0.57
- 6 hours	95%	92%	0.27
- 8 hours	93%	91%	0.66

Heart rate \leq 100 beats/min			
- 0 hours	51%	46%	0.32
- 2 hours	51%	47%	0.47
- 4 hours	54%	50%	0.45
- 6 hours	60%	49%	0.045
- 8 hours	56%	51%	0.32
Central venous pressure \geq 8 mmHg			
- 0 hours	83%	80%	0.63
- 2 hours	82%	84%	0.65
- 4 hours	85%	88%	0.57
- 6 hours	86%	81%	0.30
- 8 hours	82%	83%	0.83
Urinary production \geq 0.5 ml/kg/hr			
- 0-8 hours	72%	76%	0.36
Hemoglobin level \geq 4.3 mEq/l			
- 0 hours	96%	95%	0.51
- 2 hours	94%	91%	0.55
- 4 hours	98%	92%	0.078
- 6 hours	94%	96%	0.57
- 8 hours	99%	98%	0.70
Δ lactate \geq 20% decrease			
- 0-2 hours	55%	53%	0.74
- 2-4 hours	38%	39%	0.86
- 4-6 hours	48%	40%	0.19
- 6-8 hours	47%	45%	0.71
Central venous oxygen saturation \geq 70%			
- 0 hours		60%	
- 2 hours		62%	
- 4 hours		65%	
- 6 hours		67%	
- 8 hours		74%	

Table E3. Metabolic parameters and hemodynamics

Hours after start of therapy	Control group	Lactate group	P value
pH			
Baseline (0 hours)	7.32 (7.27-7.36)	7.31 (7.26-7.36)	0.58
8	7.36 (7.31-7.41)	7.37 (7.32-7.41)	0.61
0-8	7.34 (7.29-7.39)	7.34 (7.29-7.39)	0.99
9-72	7.38 (7.33-7.43)	7.39 (7.34-7.43)	0.37
Base excess – mEq/l			
Baseline (0 hours)	-4.9 (-7.7- -2.8)	-5.5 (-8.3- -2.8)	0.27
8	-3.0 (-5.8- -0.2)	-3.5 (-6.3- -0.7)	0.40
0-8	-4.0 (-6.8- -1.1)	-4.5 (-7.3- -1.7)	0.27
9-72	-1.7 (-4.5-1.1)	-1.6 (-4.4-1.2)	0.79
Bicarbonate – mEq/l			
Baseline (0 hours)	20.1 (17.6-22.6)	19.8 (17.3-22.3)	0.57
8	21.4 (18.9-23.9)	21.3 (18.8-23.8)	0.79
0-8	20.8 (18.2-23.3)	20.5 (18.0-23.1)	0.63
9-72	22.9 (20.3-25.4)	22.9 (20.4-25.5)	0.90
Mean arterial pressure – mmHg			
Baseline (0 hours)	81 (76-87)	81 (75-86)	0.71
8	78 (73-84)	79 (74-84)	0.66
0-8	80 (75-86)	80 (74-86)	0.69
9-72	84 (79-90)	85 (79-90)	0.68
Heart rate – beats/minute			
Baseline (0 hours)	100 (95-104)	103 (98-108)	0.17
8	97 (92-102)	99 (94-104)	0.40
0-8	98 (94-103)	100 (95-105)	0.30
9-72	96 (91-100)	93 (89-98)	0.25
Central venous pressure – mmHg			
Baseline (0 hours)	13 (7-19)	13 (7-18)	0.72
8	12 (7-18)	12 (6-18)	0.71
0-8	12 (7-18)	13 (7-18)	0.90
9-72	12 (6-18)	11 (6-17)	0.30

Hemoglobin level – g/dl*			
Baseline (0 hours)	11.0 (10.2-11.6)	10.8 (10.2-11.4)	0.63
8	10.6 (10.0-11.4)	10.6 (10.0-11.4)	0.87
0-8	10.6 (10.0-11.4)	10.6 (9.8-11.4)	0.69
9-72	10.0 (9.3-10.8)	10.2 (9.3-10.8)	0.69

The adjusted mean values (95% CI) were obtained from mixed model analysis. &80% of the control group patients and 78% of the lactate group patients were mechanically ventilated at baseline. * to convert from g/dl to mmol/l: multiply by 0.6206

Table E4. Specified vasoactive medication use during the initial treatment phase and up to 72 hours

Treatment	Control group	Lactate group	P value
Inotropic agents			
- Dobutamine, % (mean dose)			
0-8 hours [#]	25.4% (6.7 µg/kg/min)	33.5% (5.6 µg/kg/min)	0.10
9-72 hours [‡]	27.8%	37.7%	0.076
- Enoximone, % (mean dose)			
0-8 hours [#]	8.1% (4.8 mg/hr)	9.0% (3.8 mg/hr)	0.77
9-72 hours [‡]	9.0%	11.6%	0.47
- Epinephrine, % (mean dose)			
0-8 hours [#]	1.7% (0.41 µg/kg/min)	0.6% (0.12 µg/kg/min)	0.62
9-72 hours [‡]	2.0%	0.0%	0.25
Vasodilators			
- Nitroglycerine, % (mean dose)			
0-8 hours [#]	14.5% (2.5 mg/hr)	31.7% (2.0 mg/hr)	<0.001
9-72 hours [‡]	18.1%	33.1%	0.004

- Ketanserin, % (mean dose)			
0-8 hours [#]	6.4% (2.5 mg/hr)	12.0% (3.3 mg/hr)	0.072
9-72 hours [‡]	11.1%	13.7%	0.51
Vasopressors			
- Norepinephrine, % (mean dose)			
0-8 hours [#]	50.3% (0.40 µg/kg/min)	62.3% (0.34 µg/kg/min)	0.026
9-72 hours [‡]	60.3%	67.6%	0.20
- Dopamine, % (mean dose)			
0-8 hours [#]	14.5% (5.4 µg/kg/min)*	10.8% (9.8 µg/kg/min)*	0.31
9-72 hours [‡]	15.9%	11.6%	0.30
- Fenylephrine, % (mean dose)			
0-8 hours [#]	7.5% (1.9 µg/kg/min)	4.8% (2.3 µg/kg/min)	0.30
9-72 hours [‡]	2.4%	1.4%	0.66

P-values as calculated by two-sample Student's t-test or the chi-square test, as appropriate.

Values are shown for all patients

‡ Proportions are shown for patients who stayed for more than 8 hours in the ICU

* = $p < 0.05$ for dose

Table E5. Cox's proportional hazard analysis

Model A. Univariate analyses using predefined variables						
	B	SE	Wald	Sig	Exp (B)	95% CI for Exp (B)
Lactate group	-0.308	0.175	3.121	0.077	0.735	Lower 0.522 Upper 1.034
Sex	0.142	0.183	0.600	0.438	1.152	0.805 1.649
Age	0.033	0.007	23.667	0.000	1.033	1.020 1.047
APACHE II at T 0h	0.113	0.011	100.405	0.000	1.119	1.095 1.144
SOFA at T 0h	0.158	0.025	40.089	0.000	1.172	1.116 1.231

Model B. Multivariable model: all predefined variables						
	B	SE	Wald	Sig	Exp (B)	95% CI for Exp (B)
Lactate group	-0.493	0.180	7.474	0.006	0.611	Lower 0.429 Upper 0.870
Sex	0.135	0.194	0.482	0.488	1.144	0.782 1.674
Age	0.023	0.007	12.429	0.000	1.023	1.010 1.037
APACHE II at T 0h	0.102	0.015	47.141	0.000	1.107	1.076 1.140
SOFA at T 0h	0.042	0.034	1.552	0.213	1.043	0.976 1.113

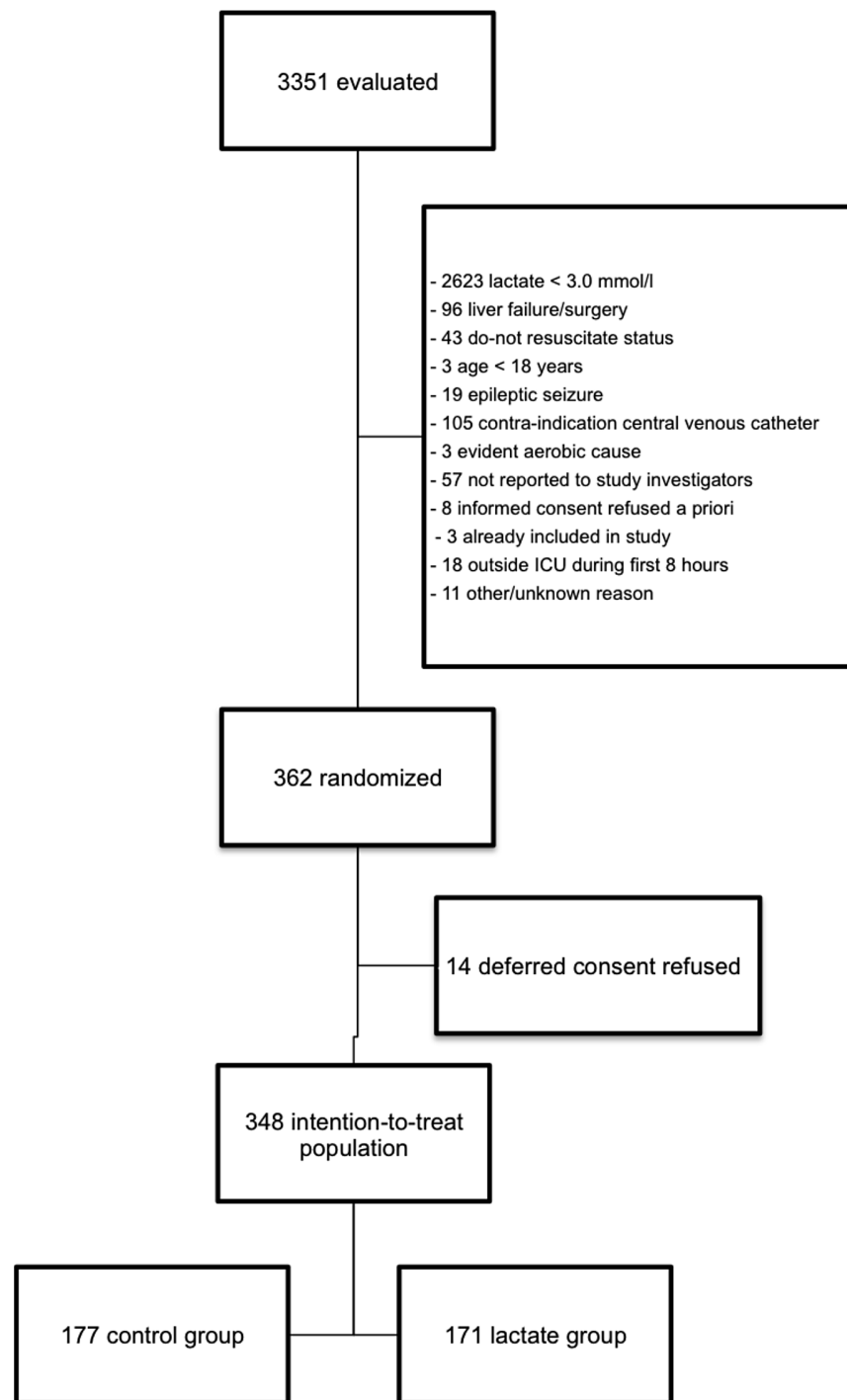
Model C. Multivariable model: excluding non-significant variables						
	B	SE	Wald	Sig	Exp (B)	95% CI for Exp (B)
Lactate group	-0.488	0.179	7.454	0.006	0.614	Lower 0.433 Upper 0.871
Age	0.023	0.007	11.736	0.001	1.023	1.010 1.036
APACHE II at T 0h	0.113	0.012	92.156	0.000	1.120	1.094 1.146

Model D. Exploratory multivariable model: only lactate group and age						
	B	SE	Wald	Sig	Exp (B)	95% CI for Exp (B)
Lactate group	-0.319	0.175	3.319	0.068	0.727	Lower 0.515 Upper 1.024
Age	0.033	0.007	23.817	0.000	1.033	1.020 1.047

Model E. Exploratory multivariable model: only lactate group and APACHE II						
	B	SE	Wald	Sig	Exp (B)	95% CI for Exp (B)
Lactate group	-0.513	0.178	8.322	0.004	0.599	Lower 0.423 Upper 0.848
APACHE II at T 0h	0.117	0.011	104.756	0.000	1.124	1.099 1.150

Model F. Exploratory multivariable model: only lactate group and SOFA						
	B	SE	Wald	Sig	Exp (B)	95% CI for Exp (B)
Lactate group	-0.448	0.178	6.357	0.012	0.639	Lower 0.451 Upper 0.905
SOFA at T 0h	0.167	0.025	43.168	0.000	1.182	1.125 1.243

Figure E1 Online Data Supplement.



**ETHICAL
CONSIDERATIONS
RELATED TO
CONSENT IN
EMERGENCY
CRITICAL CARE
RESEARCH**

CHAPTER 8

Deferred Consent in Emergency Intensive Care Research: What if the patient dies early? Use the data or not?

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INTRODUCTION

Respect for individual autonomy, expressed in the concept of informed consent, is the basic ethical principle in research with humans.

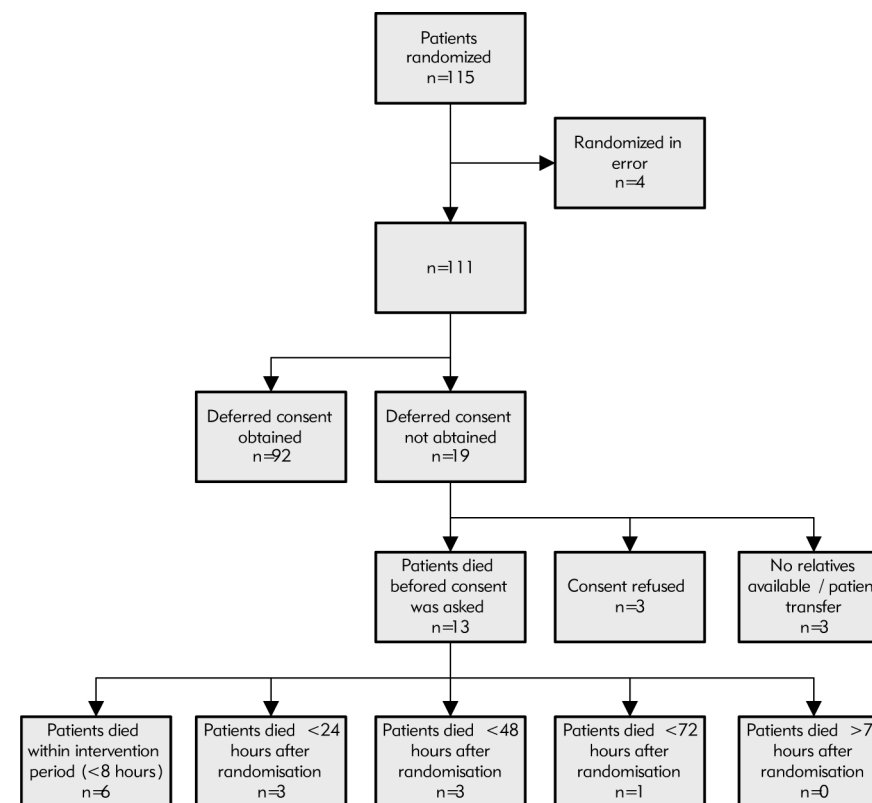
Many ICU patients are unable to give consent as a consequence of mental incapacity, and this can be further complicated in emergency situations, in which treatment needs to be initiated without delay. Various approaches are used as surrogate to subject consent: waiver of consent, consent by an independent physician and deferred consent (DC). DC involves randomization at the investigator's discretion according to criteria that have been explicit during ethical review of the protocol, followed by the request for patient's (deferred subject consent) or representative's (deferred proxy consent) informed consent in a later phase. Several emergency trials have used DC [1-4].

During the enrolment process in an ongoing Dutch multi-center randomized controlled trial using DC, the situation arose that no deferred (subject or proxy) consent was obtained from patients who died early after start of the study. Should data of these patients be used or not? In this article we analyze this practical and ethical problem.

THE "EARLY LACTATE-DIRECTED THERAPY ON THE ICU"- STUDY AS AN EXAMPLE

To evaluate the efficacy of early lactate-directed therapy, two of the authors (TCJ, JB) are currently conducting a multi-center trial. Patients eligible for inclusion are randomly allocated to either 8 hours of early lactate-directed therapy or control group therapy. Since early timing of goal-directed therapy is essential [7, 8], patients are randomized immediately after the first available lactate level, resulting in a very short inclusion time-window. The Ethics Committee approved the use of DC, referring to the Dutch revised "Medical Research in Human Subjects Act" [6]. Study procedures are temporarily undertaken without consent and, as soon as possible, written consent from the patient or legal representative is sought.

Figure 1. Flow-chart of the process of deferred consent in enrolled patients in the "Early Lactate-Directed Therapy on the ICU"-study (February-December 2006)



Until December 2006, we collected data from 115 patients (figure 1). In 11.7% (13/111), consent could not be obtained due to early death (< 72 hrs, before relatives could be approached). Given the predicted sample size of 350 patients, not using data of these patients would result in an additional requirement of 41 patients. In 2.7% (3/111), relatives could not be identified or contact was lost. In 2.7% (3/111), relatives refused consent and these patients were withdrawn from analysis. Median randomization-to-consent time was 1 day (n=92, IQR 0-3 days).

The Ethics Committee of the coordinating center was asked for a judgement on the use of already obtained data of patients who died before consent could be sought. Our proposal to use the data was rejected.

PREVIOUS EXPERIENCES ON PATIENTS WHO DIED BEFORE OBTAINED DC

Some emergency studies using DC have reported on the use of data from patients who died early. In the PAC-man trial using DC [2], consent was sought from patients who regained consciousness (deferred subject consent), whether or not relative's assent was obtained earlier. It was stated that "if the patient's died without regaining mental competency, the patient's data were included in the trial analysis" [9]. Fifty percent (249/500) of the patients died with obtained relative's assent (not consent) but without obtained subject DC. Nine percent (45/500) died with neither relative's assent nor subject DC. Data of these patients were included in the analysis. In another trial, 74% (220/300) of the patients were included under DC [1] and were asked consent as soon as possible. This was done only in survivors, suggesting that if patients died before regaining consciousness, data were used [10]. As overall 28-day mortality was high (58%), a substantial part of the data were probably analysed without consent. In another trial [4], diligent attempts to contact the relative were made and an independent physician was consulted before it was deemed necessary to waive consent. If attempts to

contact relatives continued to be unsuccessful, or if the patient died before relatives could be contacted, the IRB was notified and data were used. Summarizing, in these studies [1, 2, 4], data were used if the patient died before DC was obtained, and reasonable efforts were made to obtain permission from a patient representative.

ETHICAL CONSIDERATIONS

Guiding ethical principles for medical research are respect for patient autonomy, protection against discomfort, risk, harm and exploitation and the prospect of benefit. Taking our lactate-study as point of departure for analysis, some questions remain:

1. Why is DC necessary?

To optimally respect patient's autonomy, seeking consent before study participation is preferable. Principle One of the Nuremberg Code states that the primary consideration in research is the subject's voluntary consent, which is "absolutely essential" [11]. Unfortunately, in emergency ICU research this is often not possible, illustrated by the PAC-man trial in which only 2.6% of the patients could consent before starting the study [9]. Emergency research represents an exceptional situation, in which the mechanisms of the consent process may need to be modified, but the social contract between researcher and research subject must be respected in order to provide a safeguard against unethical research.

Despite the importance of the subject's voluntary consent or its various surrogate procedures, the question remains whether arguments in favour of not using data, are outweighed by the following arguments in favour of using data in such extraordinary case when patients die early and DC would have to be sought from bereaved proxies?

2. Is proxy consent valid in emergency situations?

Uncertainty exists whether a substituted judgement on what a patient would have decided would concur with the patient's preferences. Some have shown that most patients confirmed the judgement made earlier by the relatives [9]. However, surrogate decision-making for critical care research resulted in false-positive consent rates of 16-20% [12, 13]; a recent review showed overall inaccuracy of 32% [14].

The validity of proxy consent may be further reduced in emergency situations. Overwhelming emotions may decrease validity. Most proxies seem to make decisions based on what they hope will happen (benefit of therapy), not taking in consideration what is a real prospect (possible non-benefit and research-related burden) [15]. It is of ethical and fundamental concern that relatives cannot make balanced decisions in this period of uncertainty. If the risk exists that consent by relatives in emergency ICU situations reflects more a regime of bureaucracy (consent is required, we need a signature), rather than true ethical concern (by obtaining consent the relatives act in the patients interests) [16], then how can we value consent in the tragic situation in which the patient has died?

3. Do we harm the patients by using the obtained data?

Can we estimate how many patients or relatives would refuse the use of data obtained in acute situations without consent? In two studies evaluating emergency therapies [17, 18], waiver of consent was used with subsequent written notification. Survival hospital-discharge rates were 8% (43/538) and 17% (14/82). Only 0.4% (2/538) and 0% (0/82) were withdrawn at relatives request after written notification [19]. In the PAC-man trial 3.3% (6/181) of survivors refused consent [9]. In our lactate-study 2.7 % (3/111) of patients or relatives refused study participation after randomization. It seems that very few patients or relatives refuse consent for using already obtained data in emergency situations.

Do we harm patient's interests by using data without consent? The data in our lactate-study, consisting of regular data as survival, consumption of health care resources, laboratory values and haemodynamics data, are patient-identifiable only by the principal investigator. Given privacy-respecting handling of data and thorough confidentiality, patient's interests are not harmed by using the data.

4. Would we introduce selection bias by not using the data?

Patients who die early are the most severely ill (100% mortality) and excluding them could reduce external validity, jeopardize the balance between study arms and influence the effect of the intervention as this could be different in patients who die early compared with survivors or those who die later. The intention-to-treat principle, recommended in the ICH E9 [20], implies that the primary analysis should include all randomized subjects. Compliance with this principle would necessitate complete follow-up of all subjects for study outcomes. Not using study data of patients who died early would thus hamper the intention-to-treat principle.

Although the Registry of the Canadian Stroke Network used a different consent procedure than our study, it does show that important selection biases can be found if many patients died or left the hospital before they could be approached for consent [21]. The in-hospital mortality rate was much lower among enrolled patients (6.9%) than among those eligible for study participations but not enrolled (21.7%). Hence, study-patients were not representative anymore of typical stroke patients. Other studies showed that absolute requirements to obtain consent have led to selection biases in retrospective studies based on chart review [22, 23], and decreased enrolment in registries [24].

These concerns probably apply equally to the critical care/emergency medicine context, but additional data in this area would be

useful. After completion of our lactate-study, we plan to compare study results including or excluding data from patients who died before DC could be obtained. By doing this, the hypothesis posed in this article will be tested, that not using these data will introduce selection bias, make randomization arms asymmetrical and jeopardize trial results.

5. Do future patients benefit from the obtained data?

Clinical research plays an important role in obtaining knowledge for improvement of therapy, patient safety and progress in medicine. Future patients will benefit from critical care research results of today. If data, obtained in emergency ICU situations without consent, cannot be used, and selection bias is introduced, study results may be ruined and future patients be harmed. Degrading a study in this fashion also devalues the contribution made by subjects who do consent to take part in the study, which is an ethically undesirable consequence. While this premise cannot provide an argument for including data when research subjects expressly deny consent, it does make an ethically valid case for including data where such explicit denial of consent does not exist.

Notwithstanding this discussion, it should not be forgotten that the society's interests in medical progress may never overrule potential burden and risks for patients, as enshrined in the Nuremberg Code [26, 11].

6. What is the burden for the relatives?

Health care providers have a *prima facie* duty to relieve and prevent suffering (harm, burden) of patients, their relatives and society. Confronting relatives again with the event that their loved one died on the ICU can be seen as harm or burden. Indeed, concerning our

lactate-study, the local Ethics Committee acknowledged this psychological burden. If we can say that confronting bereaved relatives represents additional burden, which we have the duty to relieve or prevent, it seems morally correct to adopt policies that prevent seeking DC from proxy's after their relatives death. Extending the time period of seeking consent could theoretically reduce the burden. However, obtaining written consent a long time after the patient has died can be impractical (telephone consent is not allowed and it is questionable whether the agreeing relative will take effort to reply a request for written consent) and more importantly, actively approaching relatives for seeking consent in a "fatal medical research case" would still be a real burden for the relatives.

7. Is the individual's (or proxy's) decision about the privacy of their medical information binding?

The individual's decision (whether made by the individual him/herself or his/her proxy) is not absolutely binding. In certain situations it is permissible to use personal information even though the individual has not allowed it. This point is supported by principles in ethics and law: (i) Article 8 of the European Convention on Human Rights permits personal information to be used without consent (even if the individual expressly objects) if the processing is necessary and proportionate for "the protection of health". This is generally understood to include some medical research projects. Additionally (ii), the EU Data Protection Directive allows member states to adopt laws which allow personal data to be processed for scientific purposes without consent provided sufficient safeguards apply and last (iii), the UK Data Protection Act 1998 permits such processing if it is necessary and proportionate for the goals of medical research.

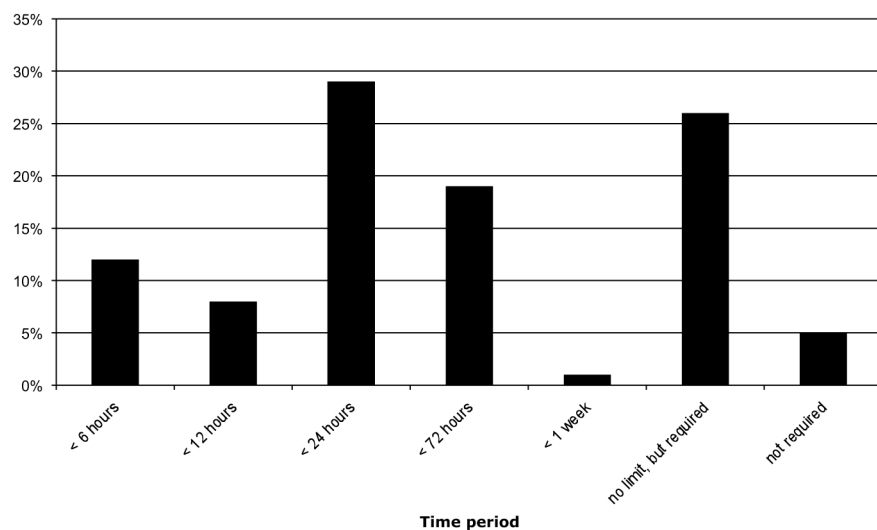
Although there is little case law, the courts would likely consider the following factors when deciding whether the twin principles of necessity and proportionality have been met include: the practicality of seeking consent (or proxy consent), the importance of answering the research question, alternative ways of answering this question, the

degree of anonymisation of the data, the practicality of discarding individuals' data, the implications of discarding the data (selection bias) and the degree of distress caused to the individual or proxy by ignoring their wishes.

8. Deferring consent: how long do circumstances continue to prevent the giving of consent?

In the lactate-trial, study procedures were allowed for as long circumstances continue to prevent the giving of consent [6]. The local Ethics Committee interprets such a circumstance as physical absence of the patient's relative arguing that, as soon as relatives arrive, this circumstance is not valid anymore and hence, consent should immediately be sought. Given that seeking proxy consent in emergency conditions is questionably valid (see consideration 2) and it is a burden for the relatives to consent for their dead relative (see consideration 6), it could be seen in a way that in fact the circumstance continues that prevents the giving of consent.

Figure 2. Survey among investigators active in the field of traumatic brain injury. Within which time period should proxy deferred consent be obtained or information provided? (n=77)



In order to prevent investigators' abuse of this ongoing circumstance, a time limit for seeking consent could be suggested. In a conducted survey among investigators active in the field of traumatic brain injury, opinions concerning the most appropriate time for requesting proxy DC, were investigated (figure 2). Peak preferences of time limits were "<24 hours" and "no limit". Accumulating the percentages, 68% (12+8+29+19) of the respondents believed that DC should be asked within 72 hours after starting the study. 32% (1+26+5) felt that the time limit should be longer than 72 hours (or even that consent was not at all required) [16].

COMPARISON WITH OTHER STATES IN THE EUROPEAN UNION

The United Kingdom has recently introduced legislative and regulatory provision for emergency research. In principle, these provisions allow for proxy and deferred consent, and are included in the Mental Capacity Act 2005 (<http://www.opsi.gov.uk/acts/acts2005/20050009.htm>) and an amendment (<http://www.opsi.gov.uk/si/si2006/20062984.htm>) to the UK Clinical Trials regulations.

Italian implementation of the European Clinical Trial Directive 2001/20/EC has enabled enrolment of incapacitated patients in clinical trials and DC is required according to the ethics committee's approval [27].

In the Austrian law, allowing proxy consent in case of mental incapacity, there is a special provision regarding "emergency" situations, in which inclusion of a patient can take place without proxy consent. The time period of the emergency is not considered as long as it takes to appoint a legal representative, but as long as the specific emergency is a medical emergency. Regains the patient the ability to consent, he/she is to inform without delay and to ask consent for further participation. Participation for such patients has to be with the prospect of a potential direct benefit, "which exceeds the risks".

Thus, the prospect of any kind of group benefit is not enough. If the presumed patient's will is known and documented, it has to be respected. Additionally, the public on the research site has to be informed about the clinical trial (e.g. by notice on a notice-board at the hospital or on a web-site).

The issue of whether data from patients who have died can be used without formal authorisation from patients or representatives is addressed in neither the Dutch, British, Italian and Austrian legislation. In the UK researchers have generally relied on interpretation of the provisions of the Data Protection Act 1998 ([http://ico-cms.amaze.co.uk/DocumentUploads/use and disclosure of health data.pdf](http://ico-cms.amaze.co.uk/DocumentUploads/use%20and%20disclosure%20of%20health%20data.pdf)) to legitimise such data use. The UK also allows the use of an independent physician's consent in restricted circumstances, which would indeed be very useful when judging whether or not sufficient care has been taken to seek consent otherwise (i.e. prior to death), before using data without relatives' agreement.

SYNTHESIS

Dutch regulatory bodies have indicated that if the patient has died shortly after randomization, and consent could not yet be obtained, this forms no reason to abandon the requirement to obtain DC to use the data.

It is our conviction that the obligation to obtain consent should be respected as thorough as possible. However, (i) the validity of proxy consent obtained during emergency situations can be ethically questioned; (ii) using data of patients who died and for whom DC was not yet obtained will not harm the patient or relatives (provided that appropriate confidentiality and privacy measures have been applied); (iii) not using data will probably introduce selection bias; (iv) using data will benefit future patients and society; (v) confronting bereaved relatives to obtain consent is an additional burden and (vi) an individual's decision about the privacy of their medical information is not absolutely binding. We therefore think that it is

inappropriate to enforce a strict rule that DC must be obtained from bereaved relatives of deceased patients.

Recommendations

In studies that use DC, data should be used if the patient dies before written (subject or proxy) consent can be sought. In order to prevent unauthorized use of this exception of the obligation to obtain consent, we however recommend a time limit for the exception of 72 hours (after start of study procedures). Only if a patient dies after this period and consent is not yet obtained, data should not be used. If national legislation (e.g. in the UK) allows the use of independent physician's consent, consent to use the data should be sought in this way. If not, as a sign of respect for patient autonomy, we plea for a written notification send to the patients' general practitioner and to relatives after the early mourning phase in cases where data are being used for study analyses despite the lack of DC [19]. Reports on all non-survivors without obtained consent should, in addition, be sent to the local Ethics Committees.

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CHAPTER 9

Inability to obtain deferred consent due to early death in emergency research: effect on validity of clinical trial results

Intensive Care Med; revision

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ABSTRACT

Purpose: To illustrate the impact on the validity of trial results when excluding patients from a randomized controlled trial in whom no deferred consent could be obtained after randomization because study procedures had already been finished.

Methods: The unadjusted and adjusted primary outcome measures of a recent randomized controlled multicentre study in the field of intensive care medicine were compared, including (n=348) or excluding (n=289) patients with missing deferred consent.

Results: Thirty-nine patients (11%) died early before the patient or his/her proxy could be approached and consent be obtained. In another 20 patients (6%), it was not possible to inform proxies and ask consent within the period of study procedures. A significant treatment effect ($p=0.006$) in the adjusted analysis became non-significant ($p=0.35$) when the patients with missing deferred consent were excluded.

Conclusions: The exclusion of patients without obtained deferred consent can reduce statistical power, introduce selection bias, make randomization asymmetrical, decrease external validity and can hereby jeopardize study results. This may have implications for emergency research in varying disciplines.

INTRODUCTION

Respect for individual autonomy, expressed in the concept of informed consent, is the basic ethical principle in research with humans. Many critically ill patients are unable to give consent as a consequence of mental incapacity, and this can be further complicated in emergency situations, in which treatment needs to be initiated without delay. Proxies are not always available in the first hours of hospital or intensive care admission or are too overwhelmed to understand the provided information to give valid consent. Deferred consent is an acceptable substitute in these emergency circumstances. [1] However, clinicians and investigators may encounter an important practical and ethical problem after enrolling patients under deferred consent: should the researcher use the study data if study procedures have already been finished before it was possible to inform the patient or his/her proxy and ask consent? This includes the situation in which the patient has died early.

The intention-to-treat principle implies that the primary analysis should include all subjects. Compliance with this principle would necessitate complete follow-up of all subjects for study outcomes. As patients who die early are the most severely ill, excluding them could reduce external validity, jeopardize the balance between study arms and influence the effect of the intervention. [1, 2]

In an earlier discussion paper we argued that deferred proxy consent is the preferable substitute for informed consent in emergency critical care research. In case of the situation when study procedures are finished or the patient dies before consent can be obtained, we recommend to use the study data that have already been obtained, provided sufficient privacy measures have been applied. Several arguments support this recommendation. First, using data of patients who died and for whom deferred consent was not yet obtained will not harm the patient or relatives. Second, confronting bereaved relatives to obtain consent after death of the patient is an additional burden. Third, using data will benefit future patients and society. Fourth, the Dutch

Central Committee on Research involving Human Subjects (CCMO) stated that the research has ended with the death of the patient and relatives do not have the legal right to give consent for the use of medical data after the patient has died. Finally and most importantly, not using the data will probably jeopardize validity of study results [2]

To support the latter argument, we compared the results of a recent randomized controlled multicentre study in the field of intensive care medicine [3], when including or excluding data from patients where study procedures were already finished before consent could be obtained. We hypothesize that not using these data will reduce internal and external validity.

METHODS

In the example study, patients with hyperlactatemia on intensive care admission were randomly allocated to either the lactate group or the control group. In the lactate group, resuscitation therapy was guided by blood lactate levels with the objective to decrease lactate levels by 20% or more per two hours, during the first eight hours of intensive care stay. In the control group the treatment team had no knowledge of lactate levels (except for the admission value). Because of the emergency nature and severity of disease in the target population, patients were enrolled under deferred (proxy) consent: study procedures were temporarily allowed without consent and, as soon as possible, written consent from the patient or legal representative was obtained. In-hospital mortality was the primary outcome measure. This primary outcome was compared between the two randomization groups using the chi-square test and using predefined multivariate Cox's proportional hazards analysis, stratified by centre and sepsis group, where adjustment was made for the following co-variables: age, sex, baseline APACHE II and baseline SOFA-score [4]. We compared the primary outcome measures in the study population with or without patients where study procedures were already finished before consent could be obtained.

RESULTS

The study-population consisted of 348 patients; 39 patients (11%) died early before the patient or his/her proxy could be approached and consent be obtained. In another 20 patients (6%), it was not possible to inform proxies and ask consent within the period of study procedures (no family available, non-Dutch speaking family, transfer to other hospital etc). Table 1 shows the baseline characteristics according to the obtained consent status. There were more patients with missing consent due to early death in the control group than in the lactate group (14.7% (26/177) vs. 7.6% (13/171), $p=0.042$). The number of patients in each group with missing consent due to other reasons (than early death) was equal (control group 6.8% (12/177) vs. lactate group 4.7% (8/171), $p=0.492$).

Table 1. Baseline characteristics according to consent status.

Variable	Obtained consent (N=289)	Missing consent (N=59)	P-value
Age – yr	61 ±17	66 ±17	0.042
Male sex – n (%)	177 (61%)	44 (75%)	0.053
Median time from arrival at hospital to randomization – hours (interquartile range)	8 (1-78)	3 (1-78)	0.90
ICU admission within 6 hours from hospital admission - n (%)	139 (48%)	38 (59%)	0.022
Median time from ICU admission to randomization – hours (interquartile range)	0.6 (0.2-1.3)	0.5 (0.2-0.8)	0.089
APACHE II score	22.3 ±8.7	27.5 ±8.7	<0.001
SOFA score	8.6 ±3.9	10.3 ±4.4	0.003
Diagnostic category – n (% of patients in the consent group)			
- Sepsis category:	113 (39%)	22 (37%)	0.020
- Severe sepsis	- 58 (20%)	- 11 (19%)	
- Septic shock	- 55 (19%)	- 11 (19%)	

- Non-sepsis category:	176 (61%)	37 (63%)	
- Neurologic	- 31 (11%)	- 6 (10%)	
- Cardiac arrest	- 32 (11%)	- 16 (27%)	
- Other non-sepsis	- 113 (39%)	- 15 (25%)	
Hospital – n (% of patients in the consent group)			
- Hospital I	159 (55%)	37 (63%)	0.15
- Hospital II	40 (14%)	12 (20%)	
- Hospital III	26 (9%)	3 (5%)	
- Hospital IV	64 (22%)	7 (12%)	
Referring department – n (% of patients in the consent group)			
- Operation theatre (acute surgery)	75 (26%)	18 (31%)	0.31
- Operation theatre (elective surgery)	39 (14%)	3 (5%)	
- Ward or emergency department	161 (56%)	36 (61%)	
- Other ICU	13 (5%)	2 (3%)	
Treated with metformin	12 (4%)	3 (5%)	0.75
Treated with anti-retroviral therapy	2 (1%)	0 (0%)	1.0
Median blood lactate level – mEq/l			
(interquartile range)	4.3 (3.5-5.8)	5.2 (3.8-8.0)	0.006
Central venous oxygen saturation - %	72 ± 12	74 ± 8	0.45

Values are means ±SD unless otherwise specified.

Table 2 shows the results of the unadjusted and adjusted primary outcome analyses. A significant treatment effect ($p=0.006$) in the adjusted analysis even became non-significant ($p=0.35$) when patients with missing deferred consent were excluded. In addition, when adding the variable “missing consent” to the multivariable Cox’s proportional hazards model the treatment effect of lactate-guided therapy was reduced from 0.006 to 0.063. When adding the variable “missing consent due to early death” the p-value was reduced to 0.210.

Table 2. Mortality with and without patients with missing deferred consent

	Control group	Lactate group	Relative risk (95%CI)	P Value
In-hospital mortality: unadjusted analysis - % (n)				
All patients (n=348)	43.5% (77/177)	33.9% (58/171)	0.78 (0.60-1.02)	0.067
Excluding early death (n=309)	33.8% (51/151)	28.5% (45/158)	0.84 (0.60-1.18)	0.32
Excluding all missing deferred consent (n=289)*	33.1% (46/139)	28.7% (43/150)	0.87 (0.61-1.22)	0.42
In-hospital mortality: adjusted analysis - hazard ratio (95% CI)				
All patients (n=348)		0.61 (0.43-0.87)		0.006
Excluding early death (n=309)		0.80 (0.53-1.21)		0.28
Excluding all missing deferred consent (n=289)		0.81 (0.53-1.25)		0.35

* P-value for interaction between consent status (missing or obtained consent) and treatment effect (Breslow-Day test of homogeneity): 0.59

When calculating interaction, we could not demonstrate a significant difference in the unadjusted treatment effect between those with and without missing consent.

DISCUSSION

As illustrated by the data, excluding patients in whom no deferred consent can be obtained after randomization may result in invalid study results. In our study a significant adjusted treatment effect became non-significant when excluding patients with missing deferred consent. This phenomenon can be ascribed to two different reasons. First, it is the effect of a lack of power due to the reduced sample size in combination with altered mortality rates. This can be

illustrated when calculating the actual power in the two populations. Based on an unadjusted absolute mortality reduction from 43.5% to 33.9% in the entire sample size of 348 patients, the calculated power was 45%. This was reduced to 12% when excluding all patients with missing deferred consent (sample size 289 patients, absolute mortality reduction from 33.1% to 28.7%). The second reason is the likely introduction of a selection bias. Furthermore, because patients with missing consent were more severely ill, this means that by excluding these patients, the study population will not be representative anymore for the actual population defined by the in- and exclusion criteria.

More patients in the control group had missing consent due to early death than in the lactate group (14.7% (26/177) vs. 7.6% (13/171), $p=0.042$). Besides that more patients have died in the control group due to the randomization treatment effect, this difference could possibly be explained by a more systematic search for consent in the lactate group because of the open-label design of the study. If the latter were really true than this would have resulted in an additional bias if these patients were excluded from the analysis.

In conclusion, the exclusion of patients with missing informed consent, because study procedures have already been finished before it was possible to obtain consent, is outweighed by the risk that this reduces statistical power, introduces selection bias, makes randomization asymmetrical, decreases external validity and so jeopardizes study results. In addition, very few patients or relatives refuse consent for the use of already obtained data in emergency situations [1, 3].

Therefore, not using data from patients in whom study procedures have been completed and deferred consent has not been obtained is unethical and, in addition, will be unjust to patients and proxies who have consented for using the data. These findings may have important implications for emergency research in disciplines varying from intensive care and emergency medicine to cardiology and (trauma) surgery.

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CHAPTER 10

Deferred proxy consent in emergency critical care research: Ethically valid and practically feasible

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ABSTRACT

Important ethical aspects apply to the process of obtaining consent in emergency critical care research: the incapacity of almost all patients for giving informed consent and the emergency and life threatening nature of the conditions involved, resulting in short therapeutic time frames. We argue that deferred proxy consent is the preferable substitute for informed patient consent in emergency critical care research. However, researchers can face two problems when using this consent procedure. First, can proxies give a valid judgment for consent or refusal in the acute phase of the life threatening illness of their relative and second, what should researchers do with already obtained data when study procedures are finished (e.g. because the patient has died) before proxies can be informed and consent be sought? We propose to approach the relatives with information about the trial and asking them for consent only if it is ethically valid to do so. The first psychological distress may prohibit a complete understanding of the information, which is necessary for a true and valid informed proxy consent. In addition, we recommend to use the study data if study procedures are finished before proxies can be informed and consent be sought, provided sufficient privacy measures have been applied.

INTRODUCTION

The need for medical research programs involving critically ill patients is real and profound. However, involving this patient category in observational or interventional trials raises ethical, juridical and practical concerns. Clinical trials in emergency and critical care settings frequently involve patients with acute catastrophic injuries or life threatening illnesses causing loss of decision-making capacity and, given the emergency nature of the conditions, facing (very) short therapeutic time frames. Examples are hemorrhagic shock, septic shock, circulatory arrest, subarachnoid hemorrhage, trauma and traumatic brain injury.

All clinical trials are subject to the ethical and juridical principles of Good Clinical Practice and international and national regulations. The guiding ethical principles underlying clinical trials are respect for autonomy of the subject, protection against discomfort, harm, risk and exploitation and the prospect of potential benefit.

Informed consent in emergency critical care research can, given the emergency nature and severity of the condition or due to pharmacological sedation, seldom be obtained from patients themselves. Delaying acute experimental treatment to obtain informed patient or proxy consent might jeopardize the trial results. Several solutions are in use for obtaining consent in emergency situations. Proxies (legal representatives) or an independent physician can give consent before inclusion in research, or (patient or proxy) consent can be deferred for some time or consent can even be waived. The prospect of benefit can even be complicated by the equipoise underpinning the statistical null hypothesis of pharmacological trials: the hope that an individual patient will benefit, being evenly certain as the chance of no benefit.

In this article we will argue that using deferred proxy consent is the preferable substitute for informed patient consent in emergency critical care research. We will address two problems, which researchers can face when using deferred proxy consent. First, can proxies give a valid judgment for consent or refusal in the acute phase of the

life threatening illness of their relative and second, what should researchers do with already obtained data when study procedures are finished (e.g. because the patient has died) before proxies can be informed and consent be sought? We propose some recommendations regarding these two dilemmas.

THE CONCEPT OF PROXY CONSENT

Most ethical committees in European countries consider consent by legal representatives valid. The moral basis for such proxy consent is restricted to the substituted judgment about inclusion into the trial. Theoretically the proxy is supposed to act as the patient, if competent, would have decided. The question remains if the patient wants to be represented by relatives for inclusion in a trial. Roupie et al. [1] found that only 41% of 1089 patients would want their spouse/partner to be their surrogate, whereas 28% wanted to be represented by the physician in charge of their care. Furthermore, many proxies do not seem to know what the patient's wishes are [2]. For instance, Coppolino & Ackerson concluded that surrogate decision makers for critical care research resulted in false-positive consent rates in up to 20% [3]. In the study by Sulamsy et al. [4] agreement between patients and proxies varied between 57% and 81%, depending on whether previous discussions had taken place on similar situations. It is unlikely that such existential discussions occur frequently in the target population resulting in lack of evidence what their relative would have wanted in case of severe illness.

THE CONCEPT OF DEFERRED (PROXY) CONSENT IN EMERGENCY CRITICAL CARE RESEARCH

Proxies are not always available in the first hours of hospital or intensive care admission or are too overwhelmed to understand the provided information to give a valid consent. This prompted investigators and ethical committees to use deferred proxy consent and

waiver of consent in emergency critical care research facing short therapeutic windows. With deferred (proxy) consent, patients are included into the research without prior consent. After inclusion, the patient (deferred patient consent) or his/her representatives (deferred proxy consent) should be informed as soon as possible and subsequent consent should be requested. With waiver of consent, consent is waived at all. Emergency research without prior consent (deferred consent or waiver of consent) can morally be accepted on the principles of fairness, justice and beneficence. Furthermore, the requirement for all patients to give written informed (proxy) consent before enrolment can result in a significant selection biases, such that research populations are not representative anymore of the typical patient [5]. A study searching for public views on emergency exception to informed consent found that 49% of 530 people believed that enrolling patients without prior consent in an emergency situation would be acceptable and 70% would not object to be entered into such a study without providing prospective informed consent [6].

The implementation of waiver or deferred consent strategies was successful in terms of enrolment rates and therapeutic windows: the adoption of waiver of consent in the National Acute Brain Injury Study- Hypothermia (NABIS-H) resulted in a higher enrolment and it reduced the time between injury and treatment [7]. In this study, relatives of only 11 out of 113 patients arrived within 6 hours of the injury. In the CRASH trial, mean time to randomization was significantly longer and patient recruitment higher in those hospitals where consent was required compared with those where it was not required (8). In a septic shock trial the investigators could not contact the proxies within the inclusion time in 74% of the cases, and these were included under waiver of consent [9].

DILEMMA 1. ARE PROXIES COMPETENT ENOUGH DURING THE ACUTE PHASE OF A SUDDEN AND UNEXPECTED EMERGENCY SITUATION?

The emotional nature of an emergency situation has been shown to limit the reliability of proxy consent for clinical research [2,10,11]. In addition, only 48% of 79 representatives of European Brain Injury Consortium (EBIC) associated neuro-trauma centers in 19 European countries felt that relatives could make a balanced decision in an emergency situation [12]. Also in our own experience the validity of informed consent and proxy consent given in an emergency situation is at least troubling. Therefore, under emergency circumstances, proxy consent does not always seem to secure proper patient/subject protection.

The process of obtaining consent for inclusion into an emergency critical care trial contains three phases. First information about the trial is provided, second the investigator asks the proxies for consent, and third the proxies give consent or refusal. However, when consent for clinical research is sought during an emergency situation, comprehension is generally less than optimal [13,14,15,16]. Patients enter an intensive care in physiological crisis, while their families enter the intensive care in a psychological crisis [17]. Admission to an intensive care triggers a variety of emotional and psychological responses in the relatives that often manifest in the form of distress, anxiety, anger, guilt and fear. Such responses can impede the ability of family members to exercise effective coping strategies [18]. In many cases relatives are so distressed or overwhelmed in the first chaotic phase of admission of their loved one, that they cannot fully understand the information provided during the acute phase, at least their understanding is selective. They have a need for information about the diagnosis and prognosis [19], but most probably have no interest in the pro's and cons of inclusion into a clinical trial. Uncertainty as to whether the patient will survive has a profound influence on the relative's reactions, actions and strategies [20].

Decision making competence is based on factual understanding, evidencing a choice (consent or refusal) and reasoning and appreciation of the situation. We argue that some family members in emotional distress are temporarily incompetent in these three points. Hence, relatives of a patient who is in a life-threatening situation can be temporarily incompetent for valid proxy consent during the acute phase.

DILEMMA 2. WHAT IF STUDY PROCEDURES ARE FINISHED BEFORE PROXIES CAN BE INFORMED AND CONSENT BE SOUGHT? USE THE DATA OR NOT?

Clinicians and investigators may encounter another important practical and ethical problem when enrolling patients in a study under deferred (proxy) consent: should the researcher use the study data if study procedures are already finished before it was possible to inform proxies and ask consent? This includes the situation in which the patient has died early.

- A recently finished clinical trial as an example

The clinical importance of this dilemma is illustrated by the enrolment process of a recently completed Dutch multi-center randomized controlled trial ("early lactate-directed therapy in the ICU" - study: <http://www.clinicaltrials.gov/ct/show/NCT00270673?order=1>). In this clinical trial using deferred consent, which was approved by the local Ethics Committee referring to the Dutch revised "Medical Research in Human Subjects Act" [21], approximately 10% of the randomized patients died before consent could be sought [22,23], in comparison with an estimated overall study mortality rate of 40%. In another 5% of the enrolled patients, it was not possible to inform proxies and ask consent within the period of study procedures (in our example study this lasted 72 hours from randomization)

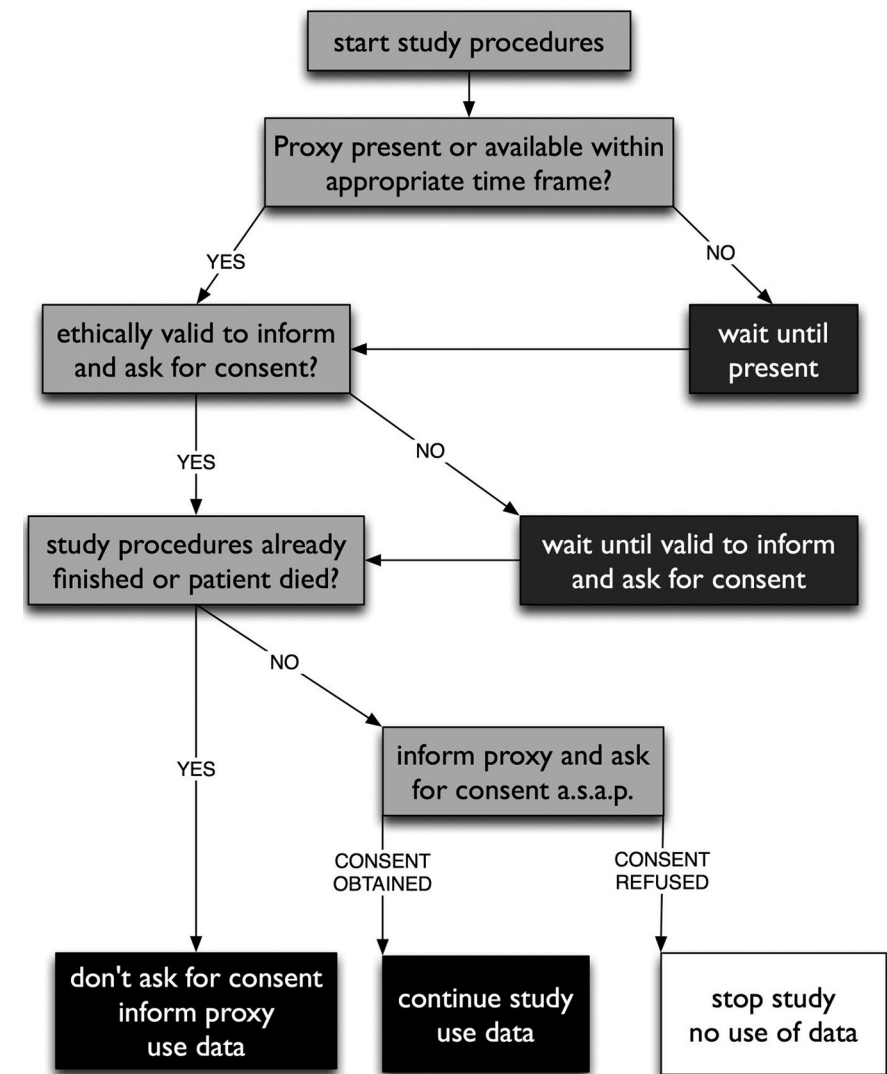
- Ethical considerations

The question is whether the arguments in favor of *not using* data are outweighed by the following arguments in favor of *using* data, which can be particularly important in the specific situation that a patient has died. First, not using these data will probably introduce selection bias, make randomization arms asymmetrical and jeopardize trial results. Moreover, the intention-to-treat principle implies that the primary analysis should include all randomized subjects [24]. Second, the validity of proxy consent obtained from bereaved relatives can be ethically questioned. As already mentioned in dilemma 1, the risk exists that consent by relatives in emergency ICU situations reflects rather a regime of bureaucracy (consent is required, we need a signature), than true ethical concern (by obtaining consent the relatives act in the patients interests); how then can we value consent in the tragic situation in which the patient has died? Third, very few patients or relatives refuse consent for the use of already obtained data in emergency situations [22,25,26,27]. Furthermore, using data will not harm the patient or relatives, provided that appropriate confidentiality and privacy measures have been applied. Fourth, jeopardizing studies by not using data might harm future patients and society. Degrading a study in this fashion also devalues the contribution made by subjects who do consent to take part in the study, which is an ethically undesirable consequence. While this premise probably cannot provide an argument for including data when research subjects expressly deny consent, it does make an ethically valid case for including data where such explicit denial of consent does not exist. Fifth, since confronting bereaved relatives represents additional burden, which health care providers have the duty to relieve or prevent, it seems morally correct to adopt policies that prevent seeking consent from proxy's after their relatives have died. Sixth, the individual's decision about the privacy of their medical information (whether made by the individual him/herself or his/her proxy) is not absolutely binding if the processing is necessary and proportionate for "the protection of health" (Article 8 of the European Convention on Human Rights), if sufficient safeguards apply (EU Data Protection Directive) or if it is necessary and proportionate for the goals of medical research (UK Data Protection Act 1998).

- Back to our example

The Central Committee on research involving Human Subjects (CCMO, "the Dutch national Ethics Committee") was asked for a judgment on the use of already obtained data of the patients who died before consent could be sought. The Committee stated that

Figure 1. Proposed flow-chart for use of proxy deferred consent in emergency critical care research. We recommend this flow-chart in the circumstance 1) that the emergency nature of the disease prevents a priori obtaining of informed consent and 2) that patients are mentally incapacitated.



this situation is comparable with the situation in which the research project has already been finished at the time that deferred consent can be sought. They judged that in such case relatives should be notified about the research project (in line with the responsibility of a good health care provider), but that seeking consent was not useful anymore because of the lack of consequences.

Recommendations

We propose approaching the relatives with information about the trial and asking them for consent only if it is ethically valid to do so. The first psychological distress may prohibit a complete understanding of the information, which is necessary for true and valid informed proxy consent. In addition, we recommend using the study data if study procedures are finished (including the situation in which a patient has died) before proxies can be informed and consent be sought, provided sufficient privacy measures have been applied. Using these two recommendations, we have constructed a flow-chart for the conduct of emergency critical care research in an ethically valid and practically feasible way (figure 1).

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SUMMARY AND CONCLUSIONS

Blood lactate has first been measured in human blood by the German physician-chemist Johann Joseph Scherer in 1843. In **chapter 2**, we describe his forgotten observations on a lethal case of fulminant septic shock due to puerperal fever in a young woman and describe the influence of his findings on further research on blood lactate measurement. Since then, more than 150 years have passed and still important unanswered questions remain regarding lactate monitoring. To address these issues, we present in **chapter 3** a systematic review, conducted using the format of a Health Technology Assessment. Following an explicit search and selection strategy, we reviewed a substantial amount of articles (>150) and concluded that blood lactate measurement in critically ill patients:

- I) Is accurate in terms of measurement technique but adequate understanding of the (an)aerobic etiology is required for its correct interpretation
- II) Provides not only diagnostic but also important prognostic information
- III) Should be directly measured instead of estimated from other acid-base variables
- IV) Has an unknown effect on healthcare workers confidence
- V) Can alter therapeutic decisions
- VI) Could potentially improve patient outcome when combined with a treatment algorithm to optimize oxygen delivery, but this has only indirectly been shown
- VII) Is likely to have similar benefits in critical care settings worldwide
- VIII) Has an unknown cost-effectiveness.

The International Network of Agencies for Health Technology Assessment describes a Health Technology Assessment as *“the systematic evaluation of properties, effects, and/or impacts of health care technology. It may address the direct, intended consequences of technologies as well as their indirect, unintended consequences. Its main purpose is to inform technology-related policymaking in health care”* [1]. Hence, by conducting this Health Technology Assessment, it not only allowed us to systematically review the literature on the clinical value of blood lactate measurement, but it ad-

ditionally provides a framework for future efforts on local or (inter) national policy decision-making on the use of lactate monitoring in critically ill patients [2].

One of the important findings of the Health Technology Assessment, the consistency of the prognostic value of lactate, implies that its measurement certainly has a place in the risk-stratification of critically ill patients in the Intensive Care Unit or the Emergency Department.

As early identification of critical illness is widely acknowledged as a vital step towards improving survival [3-5], we aimed at transferring this prognostic ability of lactate monitoring from the hospital to the pre-hospital setting. In **Chapter 4** we present the results of a prospective observational pilot study (n=124), in which emergency medical services nurses measured pre-hospital blood lactate levels. We found that pre-hospital lactate levels were significantly associated with in-hospital mortality and that a level of 3.5 mmol/L was the best cut-off value to discriminate survivors from non-survivors. Importantly, the prognostic value was superior to that of heart rate and systolic blood pressure. In pre-hospital care, the process of risk-estimation is particularly challenging because limitations of time, equipment, available skill set and environment render the objective diagnosis of haemodynamic shock difficult [6]. Our preliminary data therefore indicate a new avenue of research into the earliest possible treatment of haemodynamic shock [6]. Further studies are required to evaluate whether the use of blood lactate measurement in Emergency Medical Services has potential for triage decisions, earlier detection of occult shock and earlier start of goal-directed therapy in order to, ultimately, influence patient outcome.

Although blood lactate levels in ICU patients are generally associated with mortality, it was unknown whether lactate performs equally well in different diagnostic categories of the heterogeneous group of critically ill patients. In **chapter 5** the results are shown of a prospective observational two-center study (n=394). We found that lactate reduction during the first 24 hours of ICU stay was associated with improved outcome only in septic patients, but not in patients

with haemorrhage or other conditions generally associated with low oxygen-transport. We hypothesized that in this particular group of patients this could be due to irreversible damage already present at ICU admission. Potentially, for this reason, lactate-directed therapy might not be as beneficial in this particular group of patients, or should be started in an earlier phase in the emergency department. However, the study was limited in providing pathophysiological rationale as no data were collected on oxygen delivery and consumption or on indices that suggest aerobic or anaerobic etiology (e.g. lactate to pyruvate ratio, liver function test, serum catecholamine concentration, or microcirculation imaging).

In our search on why patients with hyperlactataemia have a worse outcome, we focused on the association between blood lactate levels and multiple organ failure and more specifically, on how the individual failing organs relate to hyperlactataemia. We showed in a retrospective observational study (n=134), described in **chapter 6**, that both the duration and level of hyperlactataemia were associated with the Sequential Organ Failure Assessment score. This association appeared stronger in the early phase of ICU stay than in the late phase. Of all individual SOFA organ components, respiratory and coagulation components, were most strongly associated with lactate. Further prospective research is warranted to elucidate why elevated lactate levels are related to adverse outcome and, most importantly, to study whether early blood lactate level-guided resuscitation can actually prevent organ dysfunction and, ultimately, improve patient survival.

This brings us to the central part of the thesis, which is presented in **chapter 7**. In a two-year, multi-centre, open-label, randomized controlled trial conducted in four centres in the region of Rotterdam, 348 patients were randomly allocated to either lactate-guided monitoring (lactate group) or non-lactate guided monitoring (control group) during the first eight hours of ICU stay. In the lactate group, treatment was guided by lactate levels with the objective to decrease lactate by 20% or more per two hours whereas in the control group, the treatment team had no knowledge of lactate levels (except for the admission value) during the first eight hours. In the

unadjusted primary outcome analysis we found a non-significant 9.6% absolute mortality reduction ($p=0.067$), which was consistent with a highly significant mortality reduction in the pre-defined multivariable analysis and with a decrease in important secondary outcome measures as organ failure, duration of mechanical ventilation and length of ICU-stay. Two study results need particular attention. First, there was a discrepancy in significance between the unadjusted and adjusted primary outcome analysis. We hypothesize that the power of this study to show a treatment benefit on a dichotomous endpoint as mortality might have been insufficient. In our sample size calculation we targeted a 15% absolute in-hospital mortality difference based on the results of Rivers' early goal-directed therapy study [7]. To be able to detect 10% absolute mortality reduction such as found in our study, approximately 800 patients would have been required. For a 5% difference, which would still be clinically relevant, around 3600 enrolled patients would have been needed. However, the statistical method of predefined co-variate adjustment allowed us to increase the power of the study without requiring increased sample size [8]. This technique makes treatment effect estimation more individualized, reduces noise in the analysis and thereby improves the statistical power (i.e. the ability to identify a smaller treatment effect when it really exists). The second study finding that needs attention is the similar course of lactate levels in the two groups, despite that the treatment strategy in the experimental arm was particularly aimed at reducing lactate levels and that lactate levels in the control arm were not available to the treating doctors and nurses. This suggests that there was no causal relationship between the administered therapy (i.e. additional fluid resuscitation and vasodilator therapy) and hyperlactataemia in our study participants. Instead, lactate might be an epiphenomenon of severity of disease. By acting as a warning signal, clinicians might interpret hyperlactataemia or the lack of its subsequent reduction over time as a warning that their patients do not clinically improve or even deteriorate in the presence of stable hemodynamic parameters. This could trigger intensified resuscitation or attention to other causes than inadequate tissue perfusion that could be associated with impaired lactate reduction (e.g. non-controlled septic focus). Unfortunately, the design of the study does not allow us to draw

definite conclusions on the mechanism behind the clinical outcome benefit found in this study.

Conducting this randomized controlled trial required great effort of the participating centers on a 24/7 basis. This resulted in steady patient recruitment leading to completion of the trial within two years. Other strengths of the study include the immediate start of the study treatment following ICU admission, the use of hospital mortality as the primary endpoint and its multi-centre design, as growing concerns have been raised regarding adoption of single-center studies in clinical guidelines [9]. Additionally, the study findings are important for clinical practice given that lactate levels are already commonly obtained in the critically ill, and thus, the proposed model for early goal-directed therapy could be implemented widely at little additional costs. The study is also a good example on the use of biomarkers to tailor treatment to each individual ICU patient. Finally, the results extend the concept of Rivers' early-goal-directed therapy from the Emergency Department to the ICU and to other patient groups besides severe sepsis or septic shock.

On the other hand, some concerns remain when interpreting the study results. First, although unavoidable when investigating such a treatment protocol, the unblinded design imposes an inherent risk of bias. Second, the difference in terms of treatment intensity between the groups was smaller than in Rivers' EGDT therapy study, possibly explaining the lack of difference in any of the physiological endpoints. Third, the treatment mechanism responsible for the reduced mortality remains to be further elucidated, as the difference in fluid resuscitation between the two groups was rather small and the efficacy of vasodilators therapy to improve poor microcirculatory perfusion remains open to discussion [10]. Additionally, as ScvO₂ monitoring was mandatory in the lactate group and facultative in the control group, we cannot exclude the possibility that this had an impact on the observed outcome difference. Finally, it is uncertain whether the treatment components in general were beneficial (i.e. the fluids or vasodilators) or whether the lactate monitoring itself, where lactate acted as a individual biomarker of severe illness, was successful by tailoring ICU treatment to the patients' needs.

However, although there are clues of responsible mechanisms for the improved outcome in lactate-monitored patients, these are only suggestive and not conclusive. In order to unfold this, a new randomized controlled trial should be designed, controlling for these specific mechanisms in a pre-specified way.

In the last part of the thesis three studies are presented on ethical aspects of informed consent in emergency critical care research. The process of obtaining ethically valid informed consent for participation in research is particularly challenging in intensive care patients. In **chapter 8**, we present the practical dilemma of using or not using data from patients who died early after start of the study without obtained deferred consent. Although it is our conviction that the obligation to obtain consent should be respected as thoroughly as possible, we identified a variety of arguments in favor of using the data without consent in these extraordinary circumstances:

- (a) not using data will probably introduce selection bias
- (b) the validity of proxy consent obtained during emergency situations can be ethically questioned
- (c) using data of patients who died and for whom deferred consent was not yet obtained will not harm the patient or relatives (provided that appropriate confidentiality and privacy measures have been applied)
- (d) using data will probably benefit future patients and society
- (e) confronting bereaved relatives to obtain consent is an additional burden
- (f) an individual's decision about the privacy of their medical information is not absolutely binding.

To test the first and arguably most important hypothesis, that not using these data will introduce selection bias and hereby jeopardize study results, we present in **chapter 9** the results of our randomized controlled multi-centre trial when including or excluding patients in who deferred consent could not be obtained. The level of significance in the unadjusted primary outcome analysis was reduced from $p=0.067$ to $p=0.42$ when the patients with missing deferred consent were excluded. In the adjusted primary outcome analysis, a

significant treatment effect ($p=0.006$) even became non-significant ($p=0.35$).

Based on the thorough consideration of **chapter 8** and the trial data of **chapter 9**, we present a decision tree in **chapter 10** for the consent procedure of emergency critical care research in an ethically valid and practically feasible way. Herein, it is proposed to approach the relatives for consent only if it is ethically valid to do so. It is also proposed to use the data if study procedures are finished before proxies can be informed and consent be sought, provided sufficient privacy measures have been applied.

Finally we return to the case presentation, which was described in the **introduction section**. Despite the haemodynamic stability for the first few hours, the resident should have diagnosed a severe disturbance in the homeostasis of his patient already 30 minutes following admission at the moment when the first lactate level became available. This thesis provides support for early lactate monitoring and lactate-guided resuscitation in this patient. The intensivist could then perhaps have made a bigger impact on the outcome of this patient, who died several days following admission.

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SAMENVATTING EN CONCLUSIE

Lactaat werd voor het eerst in humaan bloed aangetoond in 1843 door de Duitse klinisch-chemicus Johann Joseph Scherer. In **hoofdstuk 2** van dit proefschrift wordt zijn vergeten observatie beschreven van een dodelijk geval van kraamvrouwenkoorts bij een jonge vrouw en wordt de invloed hiervan op de geschiedenis van onderzoek naar lactaat monitoring toegelicht. Sinds die tijd zijn meer dan 150 jaar voorbijgegaan en nog steeds zijn er belangrijke onbeantwoorde vragen omtrent het meten van lactaat. Om deze vragen te verhelderen, wordt in **hoofdstuk 3** een systematisch overzicht gepresenteerd in de vorm van een zogenaamd Health Technology Assessment. Gebruikmakend van een expliciete zoek- en selectiestrategie werden meer dan 150 wetenschappelijke artikelen beoordeeld. Op basis hiervan kunnen we concluderen dat:

- I) Het serum lactaat gehalte betrouwbaar gemeten kan worden, maar dat voldoende kennis nodig is van de anaerobe en aerobe etiologie van lactaat voor een correcte interpretatie van de waarde.
- II) Het lactaat gehalte niet alleen diagnostische maar ook belangrijke prognostische informatie oplevert.
- III) Lactaat direct gemeten dient te worden, en niet geschat op basis van andere zuur-base variabelen.
- IV) Het meten van lactaat een onbekend effect heeft op het ervaren van (on)zekerheid door gezondheidszorg medewerkers.
- V) Lactaat de potentie heeft om therapeutische beslissingen te beïnvloeden.
- VI) Het meten van lactaat mogelijk de prognose van een patiënt kan verbeteren wanneer dit gecombineerd wordt met een behandelingsprotocol waarbij zuurstofaanbod aan de weefsels geoptimaliseerd wordt. Dit is echter slechts indirect aangetoond in de wetenschappelijke literatuur.
- VII) Het aannemelijk is dat lactaat monitoring wereldwijd dezelfde voordelen biedt aan ernstig zieke patiënten
- VIII) De kosten-effectiviteit van het meten van lactaat onbekend is.

Het INAHTA (International Network of Agencies for Health Technology Assessment) beschrijft een Health Technology Assessment

als een "systematische evaluatie van eigenschappen, effecten en/of gevolgen van gezondheidszorg technologie. Het kan hierbij zowel gaan om de directe, bedoelde consequenties van een technologie, als om de indirecte, onbedoelde gevolgen. Het hoofddoel is informatie verstrekking ten behoeve van beleidsvorming in de gezondheidszorg" [1]. Derhalve, door een dergelijk Health Technology Assessment uit te voeren, kon niet alleen de wetenschappelijke literatuur op een systematische wijze geanalyseerd worden, maar kon daarnaast ook een kader opgesteld worden voor toekomstige lokale of (inter)nationale beleidsvorming ten aanzien van het gebruik van lactaat monitoring bij ernstig zieke patiënten [2].

Een van de belangrijke bevindingen van dit Health Technology Assessment, de consistente prognostische waarde van lactaat, houdt in dat het meten van lactaat absoluut van waarde is bij de risicostratificatie van ernstig zieke patiënten op de intensive care of de spoedeisende hulp. Omdat vroeger identificatie van ernstige ziekte algemeen geaccepteerd is als een essentiële stap in de verbetering van de overlevingskansen [3-5], hadden wij als doel gesteld om de prognostische mogelijkheden van lactaat te verplaatsen van het ziekenhuis naar de pre-hospitale fase. In **hoofdstuk 4** worden de resultaten gepresenteerd van een prospectieve observationele pilot studie (n=124), waarin ambulance verpleegkundigen het pre-hospitale bloed lactaat gehalte bepaalden. Het bleek dat het pre-hospitale lactaat gehalte significant geassocieerd was met ziekenhuissterfte en dat een waarde van 3.5 mmol/L de beste afkap waarde was om onderscheid te maken tussen patiënten die overleefden of overleden. Het is belangrijk dat de prognostische waarde superieur bleek aan die van de hartfrequentie en de systolische bloeddruk. In de pre-hospitale zorg wordt het proces van risico-inschatting extra bemoeilijkt door het gebrek aan tijd, materiaal en ervaren personeel. Hierdoor is de objectieve diagnose van haemodynamische shock in deze fase problematisch [6]. Deze preliminaire data initiëren daarom een nieuwe mogelijkheid van onderzoek naar de eerst mogelijke behandeling van haemodynamische shock [6]. Er zijn meer studies nodig om te evalueren of het gebruik van lactaat in de ambulance zorg potentie heeft voor triage beslissingen, vroegere detectie van 'verborgen' shock en voor vroegere start van doelgerichte haemo-

dynamische therapie om, uiteindelijk, de prognose van patiënten te verbeteren.

Ook al is het bloed lactaat gehalte bij IC patiënten in het algemeen geassocieerd met mortaliteit, het was vooralsnog onbekend of dit in dezelfde mate gold voor de verschillende patiënten categorieën van de heterogene groep ernstig zieke patiënten die op een IC opgenomen worden. In **hoofdstuk 5** worden de resultaten getoond van een prospectief observationele studie uitgevoerd in twee ziekenhuizen (n=394). Het bleek dat de daling van het lactaatgehalte gedurende de eerste 24 uur van IC opname alleen bij septische patiënten, en niet bij patiënten met een bloeding (of een andere aandoening waarbij het zuurstofaanbod normaliter laag is), geassocieerd was met een verbeterde klinische uitkomst. Onze hypothese is dat dit in deze laatste groep patiënten veroorzaakt kan zijn door irreversibele schade die al aanwezig was bij opname op de IC. Mogelijk zal hierdoor lactaat-gerichte haemodynamische therapie niet even effectief zijn in deze specifieke groep patiënten, of zou dit in een eerdere fase gestart moeten worden. De studie is echter beperkt in het geven van een pathofysiologische verklaring door het ontbreken van gegevens over zuurstoftransport en variabelen die een aerobe of anaerobe etiologie suggereren (bijvoorbeeld lactaat/pyruvaat ratio, lever functie testen, serum catecholamine concentratie of microcirculatie monitoring).

Bij het zoeken naar een verklaring voor de slechte prognose van patiënten met hyperlactatemie, hebben we gefocust op de associatie tussen lactaat en multi-orgaan falen en de rol die de verschillende orgaansystemen hierin spelen. Uit een retrospectieve observationele studie (n=134), beschreven in **hoofdstuk 6**, bleek dat zowel de duur als de hoogte van hyperlactatemie geassocieerd waren met de SOFA (Sequential Organ Failure Assessment) score. Deze associatie was sterker in de vroege dan in de late fase van IC opname. Van alle individuele SOFA orgaan systemen waren de respiratoire en coagulatie componenten het sterkst geassocieerd met lactaat. Er is meer prospectief onderzoek nodig naar de slechte prognose van hyperlactatemie en, nog belangrijker, naar de vraag of haemodynamische therapie, specifiek gericht op het verlagen van lactaat,

ook daadwerkelijk kan leiden tot een reductie in orgaan falen en uiteindelijk mortaliteit.

Dit brengt ons bij het belangrijkste gedeelte van het proefschrift dat beschreven wordt in **hoofdstuk 7**. In een twee jaar durende, multicentrische, open-label, gerandomiseerd gecontroleerde studie, uitgevoerd in vier ziekenhuizen in de regio Rotterdam, werden 348 patiënten willekeurig behandeld met behulp van lactaat-gerichte hemodynamische monitoring (lactaat groep) of met haemodynamische monitoring zonder lactaat (controle groep) gedurende de eerste acht uur van de IC opname. In the lactaat groep was de behandeling gebaseerd op het lactaat gehalte met als doel een daling van lactaat van 20% of meer per twee uur, terwijl de behandelaars in de controle groep niet op de hoogte waren van de lactaat gehalte (behalve de waarde bij opname) gedurende de eerste acht uur. Het resultaat van de ongecorrigeerde primaire uitkomst analyse was een niet-significante absolute mortaliteit reductie van 9,6% (p=0.067). Daarbij werd een sterk significante daling in mortaliteit gevonden in de vooraf gedefinieerde multi-variabele analyse met tevens een daling in belangrijke secundaire eindpunten zoals orgaan falen, beademingsduur en van de duur van IC opname. Twee studieresultaten behoeven speciale aandacht. Ten eerste was er een verschil in statistische significantie tussen de ongecorrigeerde en de gecorrigeerde primaire uitkomst analyse. Onze hypothese is dat de 'power' van deze studie om een behandelingseffect op een dichotoom eindpunt als mortaliteit aan te tonen, onvoldoende groot geweest kan zijn. In de 'sample size' berekening werd uitgegaan van een 15% absoluut verschil in ziekenhuissterfte, gebaseerd op de resultaten van Rivers' studie naar vroege doelgerichte therapie [7]. Om een 10% absolute sterfte reductie te kunnen detecteren, zoals gevonden in onze studie, zouden ongeveer 800 patiënten hebben moeten deelnemen. Voor een verschil van 5%, dat nog steeds klinisch relevant geweest zou zijn, zouden ongeveer 3600 patiënten nodig geweest zijn. Echter, door toepassing van de statistische methode van a priori gedefinieerde co-variate correctie kon de 'power' van de studie vergroot worden zonder werkelijke uitbreiding van de studiepopulatie [8]. Deze techniek zorgt voor een meer geïndividualiseerde schatting van het behandelingseffect, reduceert ruis in de analyse en

verhoogt hierbij de statistische 'power' (d.w.z. de potentie om een kleiner behandelingseffect aan te tonen als dit er in werkelijkheid is). Het tweede studieresultaat dat aandacht verdient is het gelijke beloop in lactaatgehalte bij de beide randomisatie groepen, terwijl in de lactaatgroep de behandelingsstrategie specifiek gericht was op het verlagen van lactaat en in de controlegroep de behandelde dokters en verpleegkundigen juist niet op de hoogte waren van het lactaatgehalte. Dit suggereert dat er geen causaal verband was tussen de gebruikte therapie (d.w.z. meer vloeistofresuscitatie en meer vasodilatoren) en hyperlactatemie in onze studiepatiënten. In plaats daarvan zou lactaat kunnen fungeren als een epifenomeen van ernst van ziekte. Door de functie als waarschuwingssignaal kunnen klinici de aanwezigheid van hyperlactatemie (of het gebrek aan daling van lactaat gedurende een bepaalde tijd) beschouwen als een waarschuwing dat hun patiënt klinisch niet verbeterd of zelfs verslechterd terwijl de patiënt op dat moment nog haemodynamisch stabiel lijkt. Dit zou kunnen leiden tot vroegere, intensievere resuscitatie of tot aandacht voor andere oorzaken (dan inadequate weefsel perfusie) van een gestoorde daling van het lactaatgehalte (bijvoorbeeld een ongecontroleerd septisch focus). Helaas kan er door de opzet van de studie geen verklaring gegeven worden voor het verantwoordelijke mechanisme achter de aangetoonde verbetering in klinische uitkomst.

De uitvoering van deze gerandomiseerde gecontroleerde studie vergde een grote inspanning van de deelnemende ziekenhuizen. Dit heeft geresulteerd in een voorspoedige patiënten rekrutering met afronding van de studie binnen twee jaar. Andere sterke kanten van de studie zijn onder andere de zeer snelle inclusie van patiënten direct na opname op de intensive care, het gebruik van ziekenhuissterfte als primair eindpunt en de multi-centrische studieopzet, zeker aangezien toenemende zorgen geuit zijn ten aanzien van gebruik van één-centrum studies bij het opstellen van (inter)nationale richtlijnen [9]. Hiernaast zijn de studieresultaten belangrijk voor de klinische praktijk omdat lactaat al vaak gemeten wordt bij ernstig zieke patiënten en hierdoor kan deze vorm van vroege doelgerichte therapie gemakkelijk geïmplementeerd worden tegen lage bijkomende kosten. De studie is ook een goed voorbeeld van hoe het gebruik

van biomarkers op de IC tot aanpassing van de behandeling aan de individuele patiënt kan leiden. Tenslotte verruimen onze resultaten het concept van Rivers' doelgerichte therapie van de spoed eisende hulp naar de intensive care en naar andere patiëntencategorieën dan ernstige sepsis en septische shock.

Aan de andere kant zijn er ook bepaalde beperkingen als men de studie resultaten interpreteert. Ten eerste, ook al is dit onoverkomelijk bij het onderzoeken van een dergelijke behandelingsprotocol, de ongeblindeerde studie opzet heeft een inherent risico op bias. Ten tweede was het verschil in behandelingsintensiteit tussen de twee randomisatie groepen kleiner dan bij Rivers' studie, hetgeen mogelijk verklaart waarom er geen verschil was in fysiologische eindpunten. Ten derde dient er verder onderzoek plaats te vinden naar het verantwoordelijke werkingsmechanisme achter de verlaagde mortaliteit, aangezien het verschil in vloeistofresuscitatie tussen de twee groepen vrij klein was en de effectiviteit van vasodilatatie therapie om de microcirculatoire perfusie te verbeteren nog ter discussie staat [10]. Aangezien meting van ScvO₂ verplicht was in de lactaat groep en slechts facultatief in de controle groep, bestaat er daarnaast de mogelijkheid dat dit invloed gehad heeft op het geobserveerde verschil in klinische uitkomst. Tenslotte is het onzeker of de verschillende therapiecomponenten (bijvoorbeeld de vloeistof- of vasodilatatie toediening) effectief waren of dat het meten van lactaat op zichzelf, als biomarker van ernstige ziekte, succesvol was bij het aanpassen van de IC behandeling op de individuele behoefte van de patiënt. Echter dient opnieuw opgemerkt te worden dat, ook al zijn er aanwijzingen ten aanzien van verantwoordelijke mechanismen, deze enkel suggestief en niet conclusief kunnen zijn. Om deze te bevestigen dient een nieuwe gerandomiseerd gecontroleerde studie opgezet te worden waarbij op een vooraf gespecificeerde wijze voor deze mechanismen gecontroleerd wordt.

In het laatste gedeelte van dit proefschrift worden drie studies beschreven over de ethische aspecten van toestemmingsprocedures bij spoedeisend onderzoek bij ernstig zieke patiënten. Het verkrijgen van ethisch valide geïnformeerde toestemming voor inclusie in een wetenschappelijk onderzoek is namelijk gecompliceerd bij intensive

care patiënten. In **hoofdstuk 8** wordt het praktische dilemma beschreven van het al dan niet gebruiken van studiedata van patiënten die kort na de start van een studie overleden zijn, maar waarbij nog geen geïnformeerde toestemming gevraagd kon worden. Ook al is het onze sterke overtuiging dat de verplichting om geïnformeerde toestemming te verkrijgen zo goed mogelijk gerespecteerd dient te worden, toch hebben we in deze buitengewone omstandigheden een aantal argumenten opgesteld voor het gebruik van data zonder toestemming:

- (a) Het niet gebruiken van de data zal waarschijnlijk leiden tot een selectie bias.
- (b) De validiteit van toestemming door naaste familieleden of wettelijke vertegenwoordigers (proxy consent), verkregen tijdens spoedeisende situaties, is ethisch gezien twijfelachtig.
- (c) Het gebruik van data van patiënten die gestorven zijn en waarbij geen uitgestelde toestemming verkregen kon worden, zal de patiënt of zijn/haar familie niet schaden mits er voldoende privacy gewaarborgd wordt.
- (d) Het gebruik van data zal waarschijnlijk gunstig zijn voor toekomstige patiënten.
- (e) Het benaderen van rouwende nabestaanden om achteraf toestemming te vragen is een additionele belasting voor deze nabestaanden.
- (f) Een individuele beslissing over het gebruik van medische informatie is niet ten alle tijden bindend.

Om de eerste en ogenschijnlijk belangrijkste hypothese te toetsen, dat het niet gebruiken van de data zal leiden tot een selectie bias en hiermee de validiteit van de studieresultaten schaadt, worden in **hoofdstuk 9** de resultaten beschreven van de gerandomiseerd gecontroleerde lactaatstudie met en zonder inclusie van patiënten waarbij geen geïnformeerde toestemming gevraagd kon worden. Het niveau van statistische significantie van de ongecorrigeerde primaire uitkomst analyse werd verlaagd van $p=0.067$ tot $p=0.42$ als de patiënten met ontbrekende geïnformeerde toestemming geëxcludeerd werden. Bij de gecorrigeerde primaire uitkomst analyse werd een significant behandelingseffect ($p=0.006$) zelfs niet-significant ($p=0.35$).

Gebaseerd op grondige beschouwing van de argumenten beschreven in **hoofdstuk 8** en de studie data van **hoofdstuk 9**, wordt in **hoofdstuk 10** een beslisboom beschreven voor een ethisch valide en praktisch uitvoerbare toestemmingsprocedure bij spoedeisend onderzoek bij ernstig zieke patiënten. Hierin wordt voorgesteld om de vertegenwoordiger van de patiënt alleen te benaderen voor toestemming als het ethisch valide is om dit op dat specifieke moment te doen. Er wordt ook aanbevolen om de studiedata te gebruiken als de studieprocedures beëindigd zijn alvorens de patiënt of zijn/haar vertegenwoordiger geïnformeerd kon worden en om toestemming gevraagd. Hierbij dienen wel voldoende privacy maatregelen genomen te worden.

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'...want zij die bijvoorbeeld een proefschrift schrijven, dat immers alleen bestemd is om aan het oordeel van enige professoren te worden onderworpen, en die de strengste en meest deskundige critici niet vrezen, zijn, dunkt me, meer te beklagen dan te benijden, daar ze zich eindeloos aftobben. Ze voegen toe, veranderen, schrappen, herstellen weer, herzien, werken het weer geheel en al om, laten het graag anderen zien, houden het negen jaar in portefeuille en zijn nooit tevreden met het resultaat. De beloning, die ze er tenslotte voor krijgen - immers de lof van een enkeling - is wel heel duur betaald met al hun zwoegen, zweten en gebrek aan het zoetste, wat er bestaat: de slaap. Voeg hierbij nog dat dit alles gaat ten koste van hun gezondheid, dat ze daardoor humeurig, lelijk, bijziende of zelfs blind worden, tot armoede vervallen, bij ieder uit de gunst zijn, dat ze alle genoegens moeten verzaken, dat ze vóór hun tijd oud zijn, ontijdig sterven en wat dies meer zij..'

Dit citaat van Desiderius Erasmus uit Lof der Zotheid (1515) schetst het lot van een promovendus. Maar gelukkig stond ik er niet helemaal alleen voor. Graag wil ik daarom van de gelegenheid gebruik maken om een aantal personen te bedanken die een belangrijke rol gespeeld hebben bij de totstandkoming van dit proefschrift.

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CURRICULUM VITAE

Tim Christiaan Jansen was born on April 20th 1978 in Nijmegen. After graduating from secondary school (VWO, Kandinsky College, Nijmegen) he studied Medicine from 1996 to 2003 at the University of Maastricht. He obtained his qualification as a Medical Doctor Cum Laude. Before starting a research career, he worked as a resident (ANIOS) Intensive Care at the Erasmus MC University Medical Center Rotterdam from 2004 to 2005. Subsequently, he started his PhD trajectory as described in this thesis at the department of Intensive Care of the Erasmus MC University Medical Center Rotterdam, under supervision of Prof.dr. J. Bakker. In 2007, he founded Nosce Orbis B.V., a consultancy and assessment company for medical professionals. In May 2008, he started his specialty training in Internal Medicine under supervision of Prof.dr. J.L.C.M. van Saase (Erasmus MC University Medical Center, Rotterdam) and drs. A.P. Rietveld (Sint Franciscus Gasthuis, Rotterdam).