

KUOPION YLIOPISTON JULKAISUJA D. LÄÄKETIEDE 320
KUOPIO UNIVERSITY PUBLICATIONS D. MEDICAL SCIENCES 320

MATTI SUISTOMAA

Clinical Course and Outcome in Intensive Care

Methodological Aspects with Special Reference
to Early Circulatory Failure



UNIVERSITY OF KUOPIO

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Doctoral dissertation

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ABSTRACT

The aim of this study was to evaluate patterns and consequences of acute circulatory failure and to study possible problems in the calculation of the severity scores and outcome prediction based on them. The signs of acute circulatory failure were studied with the pattern of lactate and lactate/pyruvate ratio in emergency admission patients. Hemodynamic profile and oxygen transport variables of patients with acute circulatory were studied in relation to resuscitation outcome and development of multiple organ failure. The bias resulting from different data collection methods for the severity score calculation was studied by stepwise elevation of the sampling rate. The accuracy of outcome prediction based on the severity scores was studied in patients with prolonged stay using recalibrated models of outcome prediction in a large national intensive care database.

Prolongation of lactate elevation over 6 hours was associated with increased risk of death compared to patients with normal lactate. Simultaneous elevation of lactate and lactate/pyruvate ratio was associated with increased mortality, but the predictive value of lactate and lactate/pyruvate ratio was similar to the measurement of lactate with acid-base status. Responders of resuscitation of acute circulatory failure defined as clearance of elevated lactate and base deficit in 24 hours showed higher mean arterial pressure at 24 hours after admission but no other differences in parameters of circulation and oxygen transport could be found. Non-responders of resuscitation developed a more severe multiple organ failure. The severity of multiple organ failure and late propagation of organ failures were associated with increased mortality. Severity scores are biased if the sampling methods are changed because increasing the sampling rate of data collection for the severity score calculation resulted in higher APACHE II and SAPS II scores. Outcome prediction based on the severity scores collected on the first day of ICU care can not be used in patients with prolonged care because the prediction models lose their predictive power as their stay in intensive care prolongs.

National Library of Medicine Classification: WG 106, WX 218

Medical Subject Headings: shock; multiple organ failure; severity of illness index; treatment outcome; predictive value of tests; hospital mortality; acute disease; hemodynamics; intensive care; intensive care units; length of stay; lactate; lactic acidosis; Finland; human

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List of abbreviations

ADP	adenosine diphosphate
ALI	acute lung injury
AMP	adenosine monophosphate
APACHE	acute physiologic and chronic health evaluation
ARDS	acute respiratory distress syndrome
ATP	adenosine triphosphate
AUC	area under the curve
CI	cardiac index
CIMS	clinical information management system
CNS	central nervous system
CO	cardiac output
CVP	central venous pressure
DNR	do not resuscitate
DO ₂ I	oxygen delivery index
GCS	Glasgow coma scale
HR	heart rate
ICU	intensive care unit
ICU-LOS	intensive care unit length of stay
IQR	interquartile range
ISS	injury severity score
LDH	lactate dehydrogenase
L/P-ratio	lactate/pyruvate ratio
LODS	logistic organ dysfunction system
LR+	positive likelihood ratio
MAP	mean arterial pressure
MODS	multiple organ dysfunction syndrome

MOF	multiple organ failure
MPM	mortality prediction model
NAD	nicotinamine adenine dinucleotide
PaCO ₂	partial pressure of carbon dioxide
PaO ₂	partial pressure of oxygen
PAOP	pulmonary artery occlusion pressure
PAR	pressure adjusted heart rate
pHi	intramucosal pH
RBC	red blood cells
ROC	receiver operating characteristic curve
SAPS	simplified acute physiologic scoring
SIRS	systemic inflammatory response syndrome
SOFA	sequential organ failure assessment
SvO ₂	mixed venous oxygen saturation
TISS	therapeutic intervention scoring system
TMS	total maximal SOFA
VO ₂ I	oxygen consumption index

List of original articles

The thesis is based on the following articles which are referenced to in the text with their roman numerals

I Suistomaa Matti, Ruokonen Esko, Kari Aarno, Takala Jukka. Time-pattern of lactate and lactate to pyruvate ratio in the first 24 hours of intensive care emergency admissions. *Shock* 2000;14:8-12.

II Suistomaa Matti, Uusaro Ari, Parviainen Ilkka, Ruokonen Esko. Resolution and outcome of acute circulatory failure does not correlate with hemodynamics. *Critical Care* 2003, 7:R52-R58 (16 June 2003).

III Suistomaa Matti, Kari Aarno, Ruokonen Esko, Takala Jukka. Sampling rate causes bias in APACHE II and SAPS II scores. *Intensive Care Med* 2000; 26:1773-1778.

IV Suistomaa Matti, Niskanen Minna, Kari Aarno, Hynynen Markku, Takala Jukka. Customised prediction models based on APACHE II and SAPS II scores in patients with prolonged length of stay in the ICU. *Intensive Care Med* 2002; 28:479-485.

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1 INTRODUCTION

Before the advent of modern intensive care methods and technology, patients with severe injury or illness were most likely to die during the initial resuscitation period. Today patients survive the first days after insult through sophisticated therapeutic interventions. A prolonged resuscitation period activates several defence mechanisms in the human body, which then lead to a series of secondary reactions. The clinical picture resulting from the activation of these cascades and defence mechanisms (systemic inflammatory response syndrome or SIRS) is a reaction of the organism to the triggering insult and is very similar to the response to an infection (Bone, et al. 1992b). If the activation period is long and severe enough, the cells become temporarily malfunctioning and focal necrosis can occur leading to clinically manifest organ dysfunction (Fry 2000, Koch and Funk 2001). This syndrome is today known as multiple organ failure or MOF. MOF is the main cause of death after prolonged intensive care and it has been in the focus of intensive scientific work for more than 2 decades (Deitch 1992). MOF concerns all main functions of the body. Because of the multitude of clinical pictures of MOF, several scoring systems have been developed with the aim to describe the syndrome in a better way (Marshall, et al. 1995, Vincent, et al. 1996). The pattern of MOF may influence the ultimate outcome of the patient and scoring systems can be used to describe the course of the syndrome.

Most acute disorders leading to intensive care admission are either directly or indirectly related to circulation. The term shock is defined as a state where blood circulation cannot maintain sufficient oxygen supply to the tissues and organs. Clinical signs of shock are therefore more closely related to the consequences of shock rather than hemodynamic alterations leading to it. The signs of shock become apparent when compensatory mechanisms of oxygen supply are exhausted. Metabolic indicators of shock and circulatory failure include signs of anaerobic metabolism, such as increased arterial concentrations of lactate (Weil and Afifi 1970) and metabolic acidosis (Kincaid, et al. 1998), especially lactic acidosis (Mizock and Falk 1992). The role of lactate in health and disease has been studied extensively during the last century and information of the etiology of hyperlactatemia in various settings has emphasised its role as a

valuable variable in the monitoring of critical care patients. Most often lactate elevation is related to hypoperfusion. However, new evidence suggests that lactate can be produced in compartments of well-perfused tissues through epinephrine-stimulated Na^+ , K^+ -ATPase activity in patients with injury and sepsis (James, et al. 1999). Elevated lactate levels with or without concomitant metabolic acidosis as a measure of exhaustion of compensatory mechanisms and its pattern during the resuscitation period is under ongoing debate.

Objective assessment of the severity of acute illness is challenging. Several scoring systems have been developed for the purposes of assessing this severity. The most widely used systems are the APACHE II (Knaus, et al. 1985a) and SAPS II (Le Gall, et al. 1993). These systems combine variables of acute physiological alterations with measures of chronic illness and age of the patient. Because many of the variables contained in the scores may change rapidly during critical illness, the sampling rate may have a great impact on the resulting score, and thus on the perceived severity of the illness (Bosman, et al. 1998). Computer technology has made it possible to collect data automatically with high resolution, daily providing large amounts of data points for each patient. The selection of the appropriate data points for the severity score variables may have a fundamental impact on the severity scores and is a major potential cause of bias. Though the issue itself has been recognised, its quantification is still lacking. Mortality prediction models based on severity scores emerged from the assumption that severity of acute illness is directly related to mortality. The performance of commonly used severity scores, measured on their discriminatory power and calibration, is good in many patient populations (Wong, et al. 1995). The bias resulting from different patient populations can partly be eliminated with recalibration of the prediction models to the patient population on which they will be used. Because many patients die in the very first days of their stay in the ICU, the developed models might be biased to favour this group of patients. Patients staying for more than 7 days in the ICU are a minority in number but consume half of all ICU –resources. Therefore, the prediction of mortality in this patient population might be even more warranted (Oye and Bellamy 1991). The impact of ICU-length of stay on the prediction tools has not been studied with recalibrated models in sufficiently large patient populations yet.

The aims of this study were to study the patterns of lactate and L/P-ratio in the early phase of emergency admissions to the ICU and their role as predictors of outcome. Second aim was to study the hemodynamic profiles associated with the success of resuscitation of acute circulatory failure and the outcome of acute circulatory failure in terms of mortality and MOF. Third aim was to measure the bias caused by different data collection methods of APACHE II and SAPS II scores. The fourth aim was to study the reliability of the mortality prediction tools based on APACHE II and SAPS II scores in patients with prolonged length of stay in the ICU.

2 REVIEW OF THE LITERATURE

2.1 Multiple organ failure

2.1.1 MOF and the use of ICU-resources

Multiple organ failure (MOF) or multiple organ dysfunction syndrome (MODS) is the leading cause of death in patients with prolonged length of stay in the intensive care unit (ICU - LOS, Deitch 1993). Nearly 100% of patients with ICU-length of stay (ICU-LOS) over 10 days have MOF and the more severe the MOF the longer the ICU-LOS (Barie and Hydo 1996). MOF was initially understood as an uncontrolled infection (Fry, et al. 1980) but is recently considered as a potentially temporary malfunction of organs and organ systems distant from the initial event (Baue 1994, Bone, et al. 1992b). The term MODS (multiple organ dysfunction syndrome) was introduced to replace the term failure as it was emphasised that the organ systems were not capable of maintaining sufficient organ function and homeostasis and that the organ dysfunction was sometimes only relative (Bone, et al. 1992b). Dysfunction can also be understood as being something temporary and dynamic, not a state but a process (Bone, et al. 1992b). It is a syndrome in the sense that MOF forms a group of symptoms that together are characteristic of a specific condition (Webster's Encyclopedic Unabridged Dictionary, Gramery Books, New York, 1996). MOF is triggered by various initial insults like trauma, surgery, infection, sepsis, septic shock, burn injury and intoxication among others. MOF associated with trauma has served as a model for investigation because the interval between triggering event and development of MOF can be assessed precisely and primary organ injury can be easily separated from remote organ dysfunctions. Also, trauma patients are younger and comorbid conditions do not compromise the possibilities of the patients to survive (Suaia, et al. 1996). In recent years, research has focused on 3 aspects of MOF; 1) association between initial event especially SIRS and development of MOF, 2) factors associated with the severity of MOF and 3) attempt to describe and grade the course of MOF during the ICU-stay.

2.1.2 Quantification of MOF

Because the clinical picture of MOF is different in every patient and degree of organ failure varies, scoring systems have been developed with the aim to characterise MOF in terms of

numbers and degrees of severity. These systems may also help to analyse the course of the syndrome in large patient groups and identify general characteristics among them. Organ failure assessment has followed two principally different approaches; 1) by a dichotomous assessment of failure as present or absent or 2) by grading of organ systems dysfunction into varying levels of severity and by forming a sum figure to grade the severity of multiple organ failure. The first organ failure assessment, OSF (organ system failure) graded 5 organ system failures (circulation, respiration, renal, hematological, neurological) as present or absent based on definitions for each organ failure (Knaus, et al. 1985b). This grading system was used on a daily basis. The results of the first publication based on analysis of 5677 ICU-admissions in 13 hospitals from the year 1979 to 1982 revealed that there is a relationship between duration and number of organ failures and mortality. If 3 or more organs were failing for longer than 3 days, mortality was over 90%. The results of this report were used for several years as a criterion to withdraw intensive care of patients with sustained organ system failures. The same group published an analysis of 7703 patients from the year 1988 to 1990 using the same organ failure assessment (Zimmerman, et al. 1996). They showed that the survival rate of patients with three or more organ failures lasting 4 days or longer was better than in patients one decade earlier. However, the mortality of patients with three or more organ failures for at least 4 days was still over 80% indicating that MOF still was the main cause of death after prolonged intensive care. Though the mortality of patients with more than 3 organ failures for several days is high, it is not 100% and therefore the decision to withdraw treatment cannot be based on the OSF-scores alone. High risk of death indicates that many of the patients will die, but it cannot answer exactly who are the survivors.

Several semi-quantitative scoring systems have been developed for grading of MOF. Three scoring systems that have gained most popularity are MODS-score, (Marshall, et al. 1995), SOFA-score (Vincent, et al. 1996) and logistic organ dysfunction (LOD)-score (Le Gall, et al. 1996). MODS- and SOFA-scores are based on quantification of organ failures into 5 grades of severity based on physiologic or laboratory threshold values (Table 2-1). There are minor differences between these two systems about which variables are used to describe organ dysfunction. Neither of them contains gastrointestinal failure.

Table 2-1 Comparison of MODS score and SOFA scores.

SOFA	Variable	1	2	3	4
Respiratory	PaO ₂ /FiO ₂	<400	<300	<200 ^a	<100 ^a
Hematologic	Platelets 10 ⁹ /L	<150	<100	<50	<20
Hepatic	Bilirubin μmol/L	20-32	33-101	102-204	>204
Cardiovascular	Hypotension/ Inotropes	MAP <70mmHg	D <5 or DB (any dose) ^b	D >5, or E <0.1 or NE <0.1 ^b	D > 15 or E >0.1 or NE > 0.1 ^b
Cerebral	GCS	13-14	10-12	6-9	<6
Renal	Creatinine μmol/L Urine output ml/d	110-170	171-299	300-440 or < 500	>440 or < 200
MODS		1	2	3	4
Respiratory	PaO ₂ /FiO ₂	226-300	151-225	76-150	<76
Hematologic	Platelets 10 ⁹ /L	81-120	51-80	21-50	<21
Hepatic	Bilirubin μmol/L	21-60	61-120	121-240	>240
Cardiovascular	PAR	10.1-15.0	15.1-20.0	20.1-30.0	>30.0
Cerebral	GCS	13-14	10-12	7-9	<7
Renal	Creatinine μmol/L	101-200	201-350	351-500	>500

PAR (pressure adjusted heart rate) = HR x CVP/MAP

HR = heart rate

CVP = central venous pressure

MAP = mean arterial pressure

^a on respirator

^b D = dopamine, DB = dobutamine, E = epinephrine, NE = nor-epinephrine, dosages expressed in μg/kg/min. Vasoactive infusion must last for at least 1 hour.

MODS-score was developed in a single unit using data of 692 patients. For MODS-score six organ systems are graded into 5 levels of severity ranging from zero, which equals to normal function, to 4, which equals to most severe failure. The organ specific scores are summed to give the final score. The maximum of MODS-score is thus 24. MODS-score was primarily constructed to quantify MOF for the whole period of ICU-stay but can also be calculated on a daily basis.

SOFA-scores were initially calculated daily and later applications constructed sum-functions for quantification of MOF for the whole ICU-period. The SOFA-score is calculated in a similar fashion as the MODS-score. The original abbreviation of the SOFA (Vincent, et al. 1996, Moreno, et al. 1999), Sepsis-related Organ Failure Assessment score was later modified to indicate Sequential Organ Failure Assessment. (Moreno, et al. 1999, Vincent, et al. 1998).

The third organ failure assessment system, the logistic organ dysfunction system (LOD-score), which was based solely on the data of the first ICU-day, graded the 6 organ failures from 1 to 3 levels of severity and LOD-points were assigned according to the level of severity from 0 to 5. (Le Gall, et al. 1996). Relative weights were determined using logistic regression techniques. The final score ranging from 0 to 22 was converted to a probability of hospital death. LOD-score was more a method to describe organ dysfunction very early during the ICU-stay. This review will concentrate on the SOFA and MOD-scores, because the data collection of the original LOD-score is limited to the first ICU-day and is therefore not a method to describe later development of MOF as a consequence of a primary insult.

The most important difference between the two systems of MODS and SOFA in selection of the threshold values lies in the assessment of circulatory failure. The PAR or “pressure-adjusted heart rate” of the MODS-score (Table 2-1) is calculated as the product of heart rate and CVP divided by MAP. PAR increases if signs of hypovolemia, such as tachycardia, low CVP and low MAP are present. The higher the PAR the more points are assigned to the score. Such an interim value is not calculated on a routine basis and in order to find the “worst” value during each 24 hours period it has to be recorded at least once an hour. On the lowest level of severity the SOFA-score for the circulatory failure is graded related to a threshold level of mean arterial pressure and on the higher levels of severity to the need and doses of sympathomimetic medication. A time-related condition is defined only for sympathomimetic medication; the threshold dose has to last 1 hour at least. For other organ failures in SOFA-score and MODS-score applies that duration of any status is not predefined in order to be qualified for inclusion to the scoring. In MODS-score the clinical and laboratory data were collected at a certain time each day. The importance of this is diminished by the fact that renal, hepatic and hematologic organ system failures are improving or

worsening slowly and a rapid progression in either direction within 24 hours is not anticipated. In contrast, circulatory failure (measured as PAR or mean arterial pressure and sympathomimetic drug infusion), respiratory failure (measured as PaO₂/FiO₂) and neurological condition (measured as GCS) can change rapidly and short episodes of deterioration are possible.

None of the grading systems of MOF include a measure for intestinal failure. Because of difficulties in determining the level of intestinal failure on continuous or semi-continuous basis it has been omitted in the scores (Marshall, et al. 1995). Intestinal failure seems not to be the most important risk factor of mortality in patients with MOF (Tran, et al. 1990, Hebert, et al. 1993, Kollef and Sherman 1999). However, the intestinal tract is an important trigger or amplifier of distant organ failures (Moore 1999). The changes in the intestinal region induced by SIRS play an important role in the development of MOF (Doig, et al. 1998). The circulation of splanchnic area is reduced as a result of compensatory reactions during various states of shock and if the resuscitation is prolonged or insufficient, a protracted period of splanchnic ischemia with release of inflammatory mediators results (Kirton, et al. 1998). This is followed by the development of remote organ failures. Also, nutritional issues aiming at conserving the integrity of the mucosal layer of the intestinal tract play a role in the development of MOF. Early enteral nutrition (Kudsk 1994, Borum, et al. 2000) and parenteral glutamine supplementation (Griffiths 1997) can reduce severity of MOF, complications and mortality in specific patients groups.

2.1.3 The clinical picture and time-pattern of MOF

The 1992 consensus conference report outlines the associations between SIRS, sepsis and MOF (Bone, et al. 1992b). SIRS is a reaction of the body to an insult (Table 2-2). Any severe insult like trauma, circulatory shock, pancreatitis, burn injury or infection can lead to SIRS. If SIRS is associated with infection the condition is defined as sepsis. The definition of SIRS contains 5 aspects of a very complex clinical condition and the variables are weighted as present or absent. The duration of the SIRS-variables has not been defined but they have been recorded as present if they appear on the patient records. SIRS is present if two or more of the variables are present simultaneously and thus a grading of SIRS into categories of severity is possible according

to the number of variables exceeding the threshold limit. The general nature of SIRS is demonstrated by the fact that many physiological and normal situations of healthy people fulfil the criteria of SIRS e.g. heavy physical exercise. As such the SIRS is not a syndrome because it does not have a unique cause but it is more a context, and it is quite sensitive but non-specific (Marshall2000, Levy, et al. 2003b).

Table 2-2 The definition of systemic inflammatory response syndrome (SIRS).

At least two of the following need to be present.

Variables	Limits
Temperature	> 38 or < 36°C
Heart rate	> 90/min
Respiratory rate or PaCO ₂	>20/min <4.3kPa
White blood cells	12 000/mm ³ or < 4000/mm ³ or > 10% immature forms

Almost all patients are admitted to the ICU with the picture of SIRS (Pittet, et al. 1995). If the duration of SIRS prolongs there is a greater danger for the development of MOF (Haga, et al. 1997, Bown, et al. 2003). Successful resuscitation of the early ICU-care can be documented by a decrease of SIRS-score, which is equal to the number of SIRS-elements (Talmor, et al. 1999). It seems that the prolongation or reappearance of SIRS is more important in terms of MOF-development than the severity of SIRS per se. SIRS often precedes sepsis and septic shock. This was shown by Rangel-Frausto et al. According to their research, nearly half of patients with sepsis had a preceding SIRS several days before (Rangel-Frausto, et al. 1995). The study showed further that the more criteria of SIRS were present, the higher was the rate of ARDS, acute renal failure, disseminated intravascular coagulation and shock. Mortality increased in a stepwise fashion from 3 to 17% as the number of SIRS-components increased from 0 to 4. In contrast, the presence or the number of inflammatory response criteria during sepsis were not prognostic for the outcome in a large multicenter study by Alberti et al. in patients with sepsis (Alberti et al. 2003). They

identified comorbid conditions, severity of acute illness, organ dysfunction, presence of infection and the type of microbes to be prognostic for the outcome.

The scoring systems of MOF do not include limitations that consider the term MOF as a secondary phenomenon only. Organ failures are scored if they meet the definitions irrespective of the time point. Many patients fulfill the criteria of organ failure already on the day of admission. This is very possible if the patient has been treated at least some days in hospital and the triggering insult has occurred in the ward e.g. as a result of infection and operation. It could also be possible that an infectious disease has started at home and patient will be admitted to hospital with established organ failures. However, this has led to the confusing discussion about primary and secondary MOF. If MOF is considered e.g. a consequence of injury or shock, it should not be present in patients admitted to the ICU directly from the trauma scene. Knaus (Knaus, et al. 1985b) reported that 79% of patients with organ failures entered the ICU with at least one organ system failing and 21% of patients developed organ failures after the first day in the ICU. From those who developed organ system failures later, did so on the third day at the latest. In a study using a modified MODS-score in trauma patients (Cryer, et al. 1999), 72% of patients had MOF on the first day. Patients with severe MOF reached that level in 67% of the cases on the first day of ICU care. In order to avoid primary SIRS and incomplete resuscitation to be mixed up with MOF, other investigators have included MOF only, if it appears after 48 hours of care (Sauaia, et al. 1996).

In order to separate MOF from SIRS many studies of post-injury MOF have used a modified MODS-score omitting the assessment of neurological and coagulation systems (Sauaia, et al. 1998, Cryer, et al. 1999). The grading of neurological failure using Glasgow coma scale (GCS) is always subjective and can be hampered by sedative drugs. The most applied MODS-score for trauma patients consists thus from 4 organ failures: 1) respiratory, 2) renal, 3) hepatic and 4) cardiac failure (Sauaia, et al. 1994). Respiratory dysfunction is graded with an ARDS-score including radiological findings, oxygenation, minute ventilation, level of positive end expiratory pressure and static compliance. Cardiac function is graded using dosages of inotropic medication. Renal function is measured with creatinine and hepatic function with bilirubin levels. This score

should be used after 48 hours from the injury only, in order not to include rapidly reversible abnormalities of the early SIRS (Sauaia, et al. 1994). Patients of older age develop a more severe posttraumatic MOF than younger patients after injury of similar severity (Goris, et al. 1985). The age might not be independently associated with MOF because older patients have often concomitant diseases, which complicate the resuscitation and stabilisation period and make them prone to developing a more severe MOF (Tran, et al. 1993). The development of posttraumatic MOF is related to the severity of the trauma (Sauaia, et al. 1994). Need for blood transfusions in the early resuscitation period is shown to be associated with the development of MOF and the need of blood transfusions can be seen as an surrogate of trauma severity (Sauaia, et al. 1998, Tran, et al. 1993). Also the need of crystalloids is associated with the severity of injury and thus also with severity of MOF (Regel, et al. 1996). In patients with severe trauma (ISS > 24) the incidence of MOF was 45% in patients receiving more than 6 units of RBC but 10 % in patients receiving 6 units or less. One exception in the association of trauma severity and MOF is brain damage. Severe brain damage (GCS <8) is not associated with the development of MOF (Sauaia, et al. 1994). Lactate can be seen as an indicator of the severity of shock. Lactate levels of first ICU-day are associated with the risk of MOF (Sauaia, et al. 1994, Sauaia, et al. 1996, Moore, et al. 1996). Because base deficit values can be considered surrogates of the severity of shock as well, their association with development of MOF is not surprising (Moore, et al. 1996, Sauaia, et al. 1996, Regel, et al. 1996, Cryer, et al. 1999).

The respiratory failure has a unique role in the development of MOF. The first organ failure to show deterioration is the respiratory system (Fry, et al. 1980, Sauaia, et al. 1994, Regel, et al. 1996, Russell, et al. 2000). This view is very uniformly established in the literature. The maximum failure of respiratory function is reached within few days of ICU-care (Vincent, et al. 1998, Russell, et al. 2000). The position of the lungs in the circulation as the first filter to receive the debris, toxins, activated leukocytes and cytokines predisposes them as the place of action. As a result there are changes of permeability and albumin extravasation with the clinical picture of non-cardiogenic pulmonary oedema (Wisner and Sturm 1986, Regel, et al. 1996). Occasionally the lungs are directly affected by the trauma as in the cases with pulmonary contusion, aspiration of

blood or gastric contents and smoke inhalation. The definitions of ALI and ARDS contain same quantification variables of oxygenation failure as MOF-scores. If the oxygenation failure is accompanied with radiological findings of the lungs, the case fulfils the criteria of ARDS. The order of appearance of other organ dysfunctions after respiratory failure is less uniform. Many publications place the liver on the second place in the order of appearance in trauma patients (Fry, et al. 1980, Goris, et al. 1985, Regel, et al. 1996). If liver failure is present, it is commonly developed after third day post-injury (Moore, et al. 1996) and the maximum of the liver failure is commonly reached after 4 to 5 days of ICU-care (Marshall, et al. 1995, Vincent, et al. 1998). Renal, hematological and cardiovascular failures reach their peak values of SOFA and MODS-scores in 3 to 4 days of ICU-care. The differences of the patient populations and patient selection in the studies of Marshall et al and of Moreno et al could explain the great difference in the occurrence and timing of CNS-failure. In surgical patients the maximum CNS-failure was reached in 4.1 days (Marshall, et al. 1995). In contrast, mixed ICU-patients reached their maximum CNS-failure after 1.6 days. (Moreno et al, 1999)

The contribution of specific organ failures to the risk of death is not equal and can vary in different patient populations. Though the respiratory failure is highly associated with mortality in trauma patients (Regel, et al. 1996), its role is not so important in mixed ICU patients (Moreno, et al. 1999). Also, the time of treatment has an impact. The association of the respiratory failure with mortality is present only if a worsening of the respiratory dysfunction occurs in the second week of treatment (Cook, et al. 2001). There is a strong association of the circulatory dysfunction with mortality and this association is not time-dependent. (Marshall, et al. 1995, Moreno, et al. 1999, Cook, et al. 2001). The late circulatory dysfunction and resistance to inotropic support in the late stages of MOF are often signs of final decompensation of MOF and precede death. CNS dysfunction is highly associated with mortality in surgical patients (Marshall, et al. 1995) as well as in mixed ICU patients (Moreno, et al. 1999). In medical patients the organ systems with the strongest contribution to hospital mortality were hepatic, cardiovascular and respiratory failures in the order of decreasing risk ratio (Janssens, et al. 2000). Russels used a different study approach and estimated organ failures at baseline and 3 days later as worsening or improving of the status.

He showed that 30-day mortality of patients with sepsis was associated with worsening of neurological, coagulation and renal function over the first 3 days of the ICU care (Russell, et al. 2000). Interestingly, the severity of the first day respiratory failure or worsening respiratory function over the first 3 days was not associated with mortality, which finding is similar to that of Cook et al. (Cook, et al. 2001).

2.1.4 Repeated measurement of organ failure scores

MODS- score and SOFA-score are very similar to each other especially after calculation of total maximal SOFA-score, abbreviated as TMS-score. TMS score is calculated by summing the maximum individual organ scores ever reached during the ICU-stay. Thus, TMS and MODS-score both represent the total of organ failures during the whole ICU-stay. Delta-SOFA, understood as the TMS minus admission SOFA is the same as delta-MODS, calculated as the increase of the MODS-score from the admission to the total MODS-score. Two reports, one dealing with delta-MODS (Marshall, et al. 1995) and the other with delta-SOFA (Moreno, et al. 1999) have found exactly the same association between organ failure score increase after admission and mortality. Both found a nearly linear rise of mortality from 0 or 10%, up to 80% as the score either remained the same or increased maximally. The admission scores contributed as strongly as the difference of the scores between admission and the maximum scores to the predictive power.

When comparing the variables contained in severity scores and MOF-scores one can notice that the differences are small. The variables of the severity scores are more often rapidly changing than those of MOF-scores, except of PaO₂/FiO₂, GCS and PAR, respectively, MAP or dose of inotropic medication. Because MOF-scores contain also rapidly changing variables they can be sensitive to differences in the data collection practices. If MOF-scores are collected on a fixed time point of the day, it is important that the time point reflects the average of the patients' status. The duration of each failure has not been addressed in the literature.

2.2 Circulatory failure as the cause of multiple organ failure

2.2.1 Tissue hypoxia and hypoperfusion

A shock is present if the perfusion and thus the oxygenation of vital organs is threatened or compromised. Traditionally shock is divided into hypovolemic, cardiogenic, obstructive and distributive shock. These are, however, not mutually exclusive entities but often also simultaneously present as e.g. in patients with sepsis or severe trauma, where hypovolemic, cardiogenic, and distributive components all are present. The definition of shock based on the oxygenation of organs implies also that a predefined level of blood flow or blood pressure, which could be considered sufficient to guarantee organ oxygenation, cannot be determined. It depends on the temporary needs of the organs and they vary e.g. in relation to temperature and metabolic activity. The main determinant of oxygen delivery at the whole body level is cardiac output because it can vary in a much larger scale than the components of oxygen content, SaO₂ and hemoglobin.

2.2.2 Blood pressure and flow

All severity scores include variables of blood pressure. Blood pressure is directly related to stroke volume and vascular resistance and dependent on a multitude of control and compensation mechanisms of the body. A seemingly adequate blood pressure does not guarantee sufficient blood flow. The correlation between cardiac index and blood pressure is poor (Wo, et al. 1993) and thus cardiac index cannot be estimated from blood pressure (Abou-Khalil, et al. 1994). Low blood pressure is often quoted as shock and the degree of shock is a measure for the severity of trauma. Many studies have found an association between shock and development of MOF (Faist, et al. 1983, Henaou, et al. 1991, Tran, et al. 1993, Sauaia, et al. 1994, Moore, et al. 1996). Other investigators were unable to find an association between minimal systolic blood pressure in the first 24 hours after injury and severity of MOF in severely injured patients (Cryer, et al. 1999). Low flow state can be present even if blood pressure and filling pressures are within normal range and occasionally, a low flow state can be suspected with simple clinical indicators such as skin temperature (Kaplan, et al. 2001). The pattern of blood pressure of the first day is the result of patient physiology and its manipulation by various therapeutic interventions. In selected patient

groups even the control of high blood pressure and decreasing peripheral vascular resistance might be the key elements of the resuscitation in order to reach good results (Ruokonen, et al. 1993a, McKinley, et al. 2000). Tachycardia can be a sign of impaired circulatory function and a sign of hypovolemia or impaired cardiac function. In a series of 48 mixed type septic patients, Parker et al found that heart rate was predictive to survival (Parker, et al. 1987). Heart rate of the survivors was lower and a decreasing heart rate and cardiac index in the 24 hours interval were predictive to survival. MAP initially or during 24 hours was not associated with survival.

2.2.3 Regional circulation

Hypovolemia and hypoperfusion cause a series of adaptive mechanisms in the body, which aim to support the perfusion of vital organs like heart and brain. This is accomplished by diverting blood flow away from less vital regions like the splanchnic region, which leads to ischemia, cellular dysfunction and disruption of the intestinal barrier (Moore, et al. 1994).

Ischemia/reperfusion injuries induce activation of the neutrophils and endothelial cells which lead to augmented cellular damage. Bacterial translocation and leakage of endotoxins to the blood circulation are thought to be major contributing factors to remote organ failures (Swank and Deitch 1996). Several studies showed that mucosal ischemia measured with gastric intramucosal pH (pHi) or with pCO₂-gradient between arterial blood and mucosa (Fiddian-Green 1993), can predict MOF and death in various critically ill patient populations (Marik 1993, Maynard, et al. 1993, Kirton, et al. 1998, Poeze, et al. 2000, Levy, et al. 2003a). Gutierrez et al studied a group of sepsis patients with a pHi < 7.32 (Gutierrez, et al. 1994). This level is often considered to be associated with impaired splanchnic circulation. Dobutamine infusion increased oxygen delivery with no changes in oxygen consumption. High lactate levels decreased. Gastric pHi values increased in patients with normal as well as high lactate levels. Others have not repeated these results with similar consistency. Measurement of pCO₂ gradient can serve as a predictor of outcome, but probably not as a goal of treatment (Mythen and Webb 1994, Mythen, et al. 1993). The unpredictability of regional circulation by hemodynamic manipulation has limited the clinical usefulness of pCO₂-gap measurement in patient care (Jakob, et al. 2000, Marik and Mohedin 1994, Ruokonen, et al. 1993b). Development and propagation of MOF is not solely resulting from

circulatory impairment but the activation of cytokine response and other defence mechanisms are much involved. This was brought up by Gebbert et al. who found that the cytokine levels of patients in MOF resulting from cardiogenic shock were as high as of patients with sepsis (Geppert, et al. 2002).

2.2.4 Oxygen debt and flow-dependency

Oxygen debt was introduced into the medical practice by Shoemaker who showed in high risk surgical patients that the greater the oxygen debt, the worse the outcome in terms of mortality and MOF (Shoemaker, et al. 1992). This cumulative oxygen deficit or oxygen debt, introduced in the sixties through animal studies, is calculated as the time integral between estimated oxygen need and actual oxygen delivery. The most important hemodynamic variable related to the oxygen debt and associated with outcome has been shown to be cardiac index (Shoemaker, et al. 1992). The concept of oxygen debt has been criticised because debt is considered as something that can be paid back. Triggering events for the development of MOF emerge during the hypoperfusion and the development of MOF cannot be prevented even though the period of hypoperfusion is followed by a period of hyperperfusion and thus oxygen debt cannot be paid back. Oxygen consumption can vary considerably and significant increases can be induced e.g. by physiotherapy resembling changes seen during physical exercise (Weissman and Kemper 1993). During hypoperfusion, blood flow is diverted to vital tissues and augmentation of flow will subsequently improve the blood flow through tissues, whose circulation was temporarily impaired.

Oxygen consumption is flow-dependent if oxygen delivery to the tissues is limiting the oxygen consumption. Oxygen delivery is mainly influenced by the blood flow. If oxygen delivery is enhanced in a flow-dependent situation, oxygen consumption will rise, revealing occult sites of hypoperfusion. Oxygen consumption becomes flow-dependent when the physiological compensation mechanisms, like local adaptation of regional circulation, microcirculation and increased oxygen extraction, are exhausted. Oxygenation is non-flow dependent if blood lactate is normal and oxygen consumption does not rise as a result of augmentation of circulation (Abramson, et al. 1993). Non-flow-dependency has been used as a proof that all organs are sufficiently perfused. Flow-dependency might be different in sepsis and septic shock than in other

patients with critical illness, especially trauma. Some early studies demonstrated the presence of flow-dependency also in sepsis (Haupt, et al. 1985, Astiz, et al. 1987), but later studies have questioned this (Manthous, et al. 1993, Ronco, et al. 1993b, Gore, et al. 1996). Incomplete hemodynamic resuscitation can simulate the flow-dependency (Ronco, et al. 1993b). Using same parameters for the measurement of oxygen delivery and oxygen consumption will lead to mathematical coupling of the data (Archie 1981). This is the case, if reversed Fick-principle is used for the determination of oxygen consumption because CI is used for calculation of oxygen delivery as well as for oxygen consumption. Also ARDS patients showed no flow-dependency as oxygen delivery was improved by changes of respirator settings and oxygen consumption was measured independently from delivery measurement by mass spectrometry (Annat, et al. 1986). The impairment of cellular oxygenation during sepsis is often not related to circulation at all. Sepsis can induce malfunction of the mitochondria by disturbing cellular respiration and energy production leading to cellular death and organ dysfunction (Brealey, et al. 2002).

2.2.5 Goal directed therapy

A series of studies started in the seventies by the Shoemaker group found that survivors of shock (Shoemaker, et al. 1973), injury (Bishop, et al. 1993), high risk surgery (Shoemaker, et al. 1988) and sepsis (Shoemaker, et al. 1993) had higher oxygen delivery and oxygen consumption as well as higher cardiac output in early phases of their illness compared to non-survivors. This observation led to the concept of supranormal values of oxygen delivery and cardiac output as goals of treatment in various patient populations. Augmentation of oxygen delivery can be accomplished by optimising cardiac filling pressures, by increasing the hemoglobin concentration and by giving inotropic agents. This concept was widely accepted and studied in various patient populations. Better outcomes have been reported in patients with septic shock (Edwards, et al. 1989), with severe trauma (Fleming, et al. 1992, Bishop, et al. 1995) and with high-risk surgery (Shoemaker, et al. 1988, Boyd, et al. 1993). Most often hemodynamic goals were set to oxygen delivery of 600ml/min/m² and oxygen consumption of 150-170 ml/min/m². All studies could not confirm a favourable effect of this concept on outcome (Hayes, et al. 1994, Gattinoni, et al. 1995, Durham, et al. 1996, Alia, et al. 1999, Takala, et al. 2000, Velmahos, et al. 2000). Intention to

treat basis of the study set-up was often disturbed by spontaneous reaction of some patients to reach the study goals without manipulation. This led to the need of subgroup analysis and to the conclusion that patients who can, whether induced or spontaneously, elevate their oxygen delivery have better outcome (Yu, et al. 1993). Younger patients might have greater benefit of this approach or elderly patients do not tolerate the inotropic medication (Hayes, et al. 1994, Durham, et al. 1996, Yu, et al. 1998). Younger patients are more often capable to reach optimal goals (Velmahos, et al. 2000). In order to be effective, goal directed therapy must be started early and the risk of death must be high enough. (Shoemaker, et al. 1988, Bishop, et al. 1995). If organ failures are established, augmentation of oxygen delivery to supranormal levels has no effect on outcome. The start of goal directed therapy was very early in the study by Rivers in patients with severe sepsis and septic shock (Rivers, et al. 2001). Target levels were set to CVP 8-12 mmHg, MAP 65-90 mmHg, urine output $> 0,5$ ml/kg/h and central venous oxygen saturation (measured with a specially designed catheter) to $> 70\%$. If the latter goal was not reached with volume and red cell substitution, dobutamine was infused. This strategy was started roughly 1.5 hours after arrival to the emergency department and used until patients were admitted to ICU, which occurred 6 to 8 hours later. The goal directed group showed lower hospital, 28-day and 60-day mortality and less patients were on respirator during the first 3 days in the ICU. In order to reach the target goals, more fluids and blood products will be needed (Bishop, et al. 1995). Negative results in elderly patients might reflect diminished cardiac reserves. If the cardiac and metabolic reserves are totally exhausted with the disease process or with chronic illness, cardiac function cannot be augmented with any kind of therapeutic intervention. Some evidence leading to this direction can be seen in the dobutamine-stress-test (Vallet, et al. 1993, Rhodes, et al. 1999). Patients unable to increase their oxygen consumption by more than 15% with dobutamine infusion were considered non-responders. The mortality of the non-responders was 44.4% compared to 8.7% ($p < 0.05$) of the responders in the study by Vallet and 91% and 15% ($p < 0.01$) in the study by Rhodes, respectively. The responders were younger and fewer had cancer.

There are some published attempts to define a critical level of oxygen delivery below which tissue oxygenation is not sufficient. Rashkin found in critically ill patients that oxygen delivery

below 8 ml/kg/min was associated with marked increases of blood lactate and poor survival rate (Rashkin, et al. 1985). In patients anaesthetised for coronary by-pass surgery, the critical level of oxygen delivery was estimated by finding the lowest threshold value of oxygen delivery below which oxygen consumption started to decline (Shibutani, et al. 1983). The critical level was set at 330ml/min/m², which is close to the 8ml/kg/min found by Rashkin. Using the same approach, Ronco et al found a critical level of 3,8 ml/kg/min in septic and 4,5 ml/kg/min in non-septic patients (Ronco, et al. 1993a). This study was conducted when life support measures were gradually withdrawn in patients considered not to be able to survive. Septic shock patients with DO₂ below 8.5 ml/min/kg had 100% mortality in the series of Tuchs Schmidt et al (Tuchs Schmidt, et al. 1992). These critical values are far from the optimal goals for oxygen delivery recommended e.g. by Shoemaker which might reflect the need for an extra compensation for increased oxygen demand because of the stress reaction induced by surgery, trauma and pain as well as by respiratory work.

2.3 Lactate and acid-base abnormalities as signs of circulatory failure

2.3.1 Lactate as a sign of circulatory failure

Lactic acid production has been known to be associated with e.g. hypoxia for over 100 years (Araki, 1890, referenced by Huckabee 1958a). The most important cause of blood lactate elevation is poor tissue perfusion and accompanying lack of oxygen in the tissues. The elevation of blood lactate with simultaneous metabolic acidosis is termed as lactic acidosis in contrast to states of lactate elevation without acidosis (Stacpoole, et al. 1994). The latter situation is often quoted as hyperlactatemia. A precise definition of lactic acidosis does not exist. One definition is the combination of metabolic acidosis with arterial lactate > 5 mmol/L (Stacpoole, et al. 1994).

Pyruvate is the product of glycolytic pathway in the degradation process of glucose in the cells' energy production. Lactate is produced from pyruvate and the reaction is catalysed by the enzyme LDH (lactic dehydrogenase). By the reaction NADH⁺ is oxygenated to NAD. The further oxidation of pyruvate to CoA is catalysed by the enzyme PDH (pyruvate dehydrogenase). All cells are capable of lactate production. Whether pyruvate is converted to lactate or oxidised depends on the concentration of pyruvate and the ratio of NAD/NADH. Other possibilities in the

pyruvate metabolism are its transamination to alanine or carboxylation to oxaloacetate or malate. The energy the cells need is produced by hydrolysis of ATP to ADP during which P_i and H^+ are produced in equimolar quantities. If the oxygen supply is adequate the produced ADP is reconstituted to ATP by utilising H^+ and P_i in the mitochondria. If oxygen supply is inadequate, the restitution of ATP is prevented and H^+ and P_i are accumulated in the cells, which leads to acidosis. The glycolytic pathway of glucose to lactate produces 2 moles lactate and 2 moles ATP. If this ATP is used for energy production, again ADP, P_i and H^+ are produced and in states with adequate oxygen supply, the ADP is regenerated to ATP. As a net result, lactate is produced without concomitant acidosis. In cases with cellular hypoxia, energy production by glycolysis of glucose to lactate produces also hydrogen ions. The myokinase reaction (or adenylate kinase reaction) is present in most cells and can produce energy by hydrolysis of ADP to AMP during which H^+ is produced but not lactate. This can explain situations where acidosis develops without increases in lactate concentrations. (Gutierrez and Wulf 1996) The main cause of lactate production in the tissues is the lack of oxygen, which leads to anaerobic metabolism because of inhibition of oxydation of pyruvate to acetyl CoA.

In physiological situations such as after exercise, the accumulated lactate is very rapidly taken up by liver, kidney, myocardium, and muscles (Wasserman, et al. 1985, Brooks 1986). The same occurs in patients after epileptic convulsions (Vincent, et al. 1983). In both of these situations the circulation itself is functioning properly. As mentioned above, the most important cause of lactate elevation in intensive care patients is considered to be impaired tissue perfusion, but because of the complexity of lactate metabolism and because of the key role of lactate in many metabolic pathways, the exact causes of lactate elevation e.g. in trauma patients can be several. In order to be able to distinguish between impaired tissue perfusion and other causes of hyperlactatemia, the concomitant measurement of lactate to pyruvate ratio (L/P- ratio) has been proposed. L/P-ratio was introduced over 40 years ago (Huckabee1958a, Huckabee1958b) with the concept that it would reflect the redox-state within the cells. Redox-state is reflected in the relation of oxidised to reduced nicotinamide nucleotides (NAD/NADH^+). In states with diminished

oxygen availability, the balance of the synthesis of lactate from pyruvate would favour the production of lactate with resulting increase of L/P-ratio.

2.3.2 Lactate in sepsis and septic shock

It was noted decades ago that lactate production can also occur in states where there is no obvious lack of oxygen. In septic patients, hyperlactatemia can be found in patients with no signs of impaired tissue perfusion and at the extremes also in patients with profoundly hyperdynamic hemodynamic pattern. The three basic mechanisms of lactate elevation, diminished uptake by the liver, increased production stimulated by catecholamines as well as by other factors, and insufficient tissue perfusion because of abnormal distribution of blood flow between organs and in organs all play a role. Furthermore, disturbances of oxygen transport within the cell induced by sepsis contribute to the lactate elevation. The latter has been demonstrated in studies showing that the lactate elevation cannot be cured by augmentation of the hemodynamic function. There are several pathophysiological mechanisms for lactate elevation in sepsis and septic shock patients. First of all, lactate can be produced because of insufficient oxygen transport in relation to oxygen demands of the tissues as discussed above. The role of cellular hypoxia as the only cause of blood lactate elevation during sepsis was challenged e.g. by Hotchkiss and Karl (Hotchkiss and Karl 1992). They noted, based on studies with nuclear magnetic resonance spectroscopy during sepsis, that cellular hypoxia can be present with normal lactate levels, because normally oxygenated cells can uptake lactate, and that moderate increases of lactate levels are often not associated with metabolic acidosis. Lactate can be produced by direct stimulation of glycolysis (Gore, et al. 1996), which can further be augmented by sympathetic stimulation. Lactate uptake by the liver can be diminished and result in elevated blood lactate levels (Levrant, et al. 1998). In a more recent study, Levrant et al showed by infusion of exogenous lactate that lactate clearance of patients with sepsis is low and results in normal or mildly elevated blood lactate levels (Levrant, et al. 2003). In this study the basal lactate levels between survivors and non-survivors were equal but low lactate clearance was independently related to poor outcome. The presence of lactic acidosis or hyperlactatemia has been used as a proof for impaired tissue perfusion and oxygenation, because patients with lactic acidosis can increase the oxygen consumption as a result of augmentation of

oxygen delivery with fluid therapy and catecholamines. (Haupt, et al. 1985, Gilbert, et al. 1986, Astiz, et al. 1987). Lactate can, however, be produced also in hyperdynamic circulatory states (Subramanian and Kellum 2000), which diminishes the role of lactate as a sign of impaired perfusion. In certain situations, augmentation of oxygen transport by manipulation of circulation does not lower the elevated lactate levels as expected or do not result in increased oxygen consumption (Ronco, et al. 1993b). In the clinical setting the improvement of systemic circulation might not be directed to regional areas with insufficient perfusion (Ruokonen, et al. 1993b). If this is the case, the enhancement of oxygen consumption and clearance of hyperlactatemia are no longer interrelated. This was shown by Silverman in patients with lactic acidosis and sepsis syndrome. The patients received fluids, red cells and dobutamine to increase the oxygen delivery. There was no correlation between changes of oxygen consumption and changes in lactate levels (Silverman 1991). Especially, the role of catecholamines and the stimulation of glycolysis by catecholamines in skeletal muscles as the cause of hyperlactatemia in sepsis has been advocated recently (James, et al. 1999) and animal models support this opinion (Luchette, et al. 1998). During physical exercise the association of catecholamine levels and lactate levels is well proven (Brooks 1986, Brooks 1991, di Prampero and Ferretti 1999). The energy production of the cells and mitochondrial function are impaired during sepsis leading to cellular oxygen deficit irrespective of hemodynamic status (Brealey, et al. 2002). Although lactate elevation and metabolic acidosis occur often simultaneously, in various shock states they result via different metabolic pathways. The lack of oxygen leads to accumulation of hydrogen ions because the regeneration of high-energy phosphates is inhibited leading to acidosis (Zilva 1978, Vincent 1995, Gutierrez and Wulf 1996). Also physical-chemical changes in the concentrations of strong ions like potassium, sodium, chloride and lactate of the extracellular fluid have been addressed to be responsible for the development of acidosis during lactic acidosis (Balasubramanian, et al. 1999, Kellum, et al. 1998). The lungs of patients with acute lung injury produce large amounts of lactate and the lactate production is proportional to the severity of lung injury (Brown, et al. 1996, De Backer, et al. 1997, Kellum, et al. 1997, Routsis, et al. 1999). Respiratory muscles contribute to the blood lactate levels in respiratory distress and if the oxygen delivery to the muscles cannot match

this increase, marked lactate elevation and acidosis develop (Aubier, et al. 1982). Lactate elevation in the critically ill patient is thus not only associated with hypoperfusion and tissue hypoxia. Lactate elevation is associated with a number of critical situations of intensive care and the etiology of hyperlactatemia and lactic acidosis is not uniform. Lactate is a non-specific but sensitive indicator of patient's well being in the intensive care setting.

2.3.3 Using laboratory test for outcome prediction

A large number of laboratory tests are taken daily and repeatedly from patients in intensive care. Some of the blood tests are essential and routine part of diagnostic and are taken to guide the therapy, whereas some are more closely associated with scientific interests. Laboratory tests are also used for outcome prediction in the intensive care setting and are an important part of severity scores, which will be discussed later. For testing the diagnostic accuracy of a prediction tool recommendations have been published (Fischer, et al. 2003, Randolph, et al. 1998). The validity and reliability of the prediction has to be reported. Study population and raw data has to be reported in detail to allow comparisons to an other group of patients (Fischer, et al. 2003). Sensitivity and specificity are calculated. Positive likelihood ratio (LR+) reflects the ratio of the probability of having a positive test result with the disease to the probability of showing a positive test without the disease. It calculates as $LR+ = \text{sensitivity}/(1-\text{specificity})$ and it can be calculated on several levels of the test result. LR can always be calculated if the original data is reported to allow the construction of a 2 x 2 table with the test result and the outcome. Discriminative power of the test is studied with ROC-curves calculating the AUC (area under the curve). The level of the test with the best discrimination can be roughly estimated using the curve. The best cut-off point is the level where the sum of sensitivity and specificity is maximal.

Scientific work has identified a number of cytokines which are especially involved with the pathogenesis of sepsis and septic shock and thus also with the prognosis of the patients. Severe trauma triggers a metabolic response resulting in the clinical picture of SIRS. The metabolic response can be measured by determining the levels of host response markers. Tumor necrosis factor- α (TNF- α) and interleukin-6 (IL-6) are central mediators of sepsis. Marecaux et al compared their prognostic significance with lactate in 38 patients with sepsis (Marecaux, et al.

1996). They found that the TNF-levels were elevated at admission to the ICU, but the levels decreased similarly in survivors and non-survivors during the first 48 hours after onset of shock. Lactate levels of the non-survivors were higher and decreased less than the lactate levels of the survivors. IL-6 values were not associated with mortality. Some of the inflammatory mediators remain elevated for prolonged periods of time, especially if the clinical course is complicated. Oberhofer et al showed in sepsis patients who were treated for longer than 2 days in the ICU that TNF- α , IL-6 and procalcitonin levels were good predictors of death as assessed with ROC-curves (Oberhoffer, et al. 1999). Also C-reactive protein had a similar ROC-AUC in this study. The date of blood sampling was randomly chosen and every patient was presented by one sample only. The results of Pettilä et al studying the predictive role of procalcitonin and IL-6, among others, supports the finding that inflammatory markers are better predictors after some days of ICU-care. Procalcitonin and IL-6 values of the ICU-day 2 showed a reasonable good discriminatory power reflected in relatively large (>0.75) ROC-AUCs (Pettilä, et al. 2002a). Dunham et al showed that the mean C-reactive protein level of days 3 and 7 was correlated with the development of MOF in trauma patients (Dunham, et al. 1994). This study indicates that C-reactive protein is not an early prognostic marker of adverse outcome in trauma patients. Pettilä et al found a similar result in patients with suspected sepsis; admission C-reactive protein levels were similar in survivors and non-survivors (Pettilä, et al, 2002b). The timing of sampling of these laboratory markers is of importance for the outcome prediction because some of the cytokines are very short lived and the inflammatory markers elevate after a latency period.

2.3.4 Lactate levels and prediction of ICU-outcome

The role of lactate as a predictive instrument is well established. Table 2-1 summarises studies on the role of lactate as a predictor of ICU-outcome. The initial lactate levels, peak lactate levels and prolonged clearance of lactate, are all associated with complicated outcome. Already 1965, Peretz et al demonstrated an association of lactate levels with outcome in patients with shock syndrome and patients unable to normalise their lactate levels had a 100% mortality (Peretz, et al. 1965). Elevated lactate levels are associated with increased mortality in trauma patients when measured at the time of initial resuscitation (Duff, et al. 1966, Blow, et al. 1999). Peak

lactate levels during resuscitation of trauma patients are also associated with the outcome (Vitek and Cowley 1971, Manikis, et al. 1995). Delayed lactate clearance after trauma is associated with increased probability of death and development of MOF (Abramson, et al. 1993, Manikis, et al. 1995, Blow, et al. 1999, Claridge, et al. 2000). In shock states of different origins, lactate is a good prognostic tool (Vitek and Cowley 1971, Vincent, et al. 1983, Bakker, et al. 1991). Elevated lactate values at ICU-admission are indicators of poor outcome in patients with acute myocardial infarction (Henning, et al. 1982). Elevated admission lactate in patients with suspected myocardial infarction is highly specific in identifying patients with myocardial compromise needing closer attention and care (Schmiechen, et al. 1997). An earlier study by Kessler et al, showed that resting lactate levels after cardiac arrest were higher in patients who experienced a recurrent cardiac event and peak lactate levels after exercise were higher in patients dying of cardiac causes (Kessler, et al. 1987). More recently, Smith et al examined the role of lactate and base deficit in a rigorous way as prognostic tools in 148 mixed intensive care patients (Smith, et al. 2001). They determined a threshold value for admission lactate most closely associated with mortality arbitrarily by inspection of ROC-curves and came up with 1.5 mmol/L. ROC-AUC for mortality of admission lactate was 0.78 with a sensitivity of 69.0% and specificity of 77.3% with this cut-off value (LR+ 3.0). Patients with admission lactate > 1.5 mmol/L had a mortality of 61.4% compared with 17.6%

Table 2-3. Studies of lactate as a predictor of ICU-outcome. LR+ was calculated, if possible.

Author(s) /Year	Number of patients	Population	Study outcome	Threshold value of lactate or goal of treatment	Compared groups or study design
Pereta /1995	52	Circulatory shock	Mortality		Association between lactate and mortality
Weil adn Afifi /1970	142	Circulatory shock	Mortality	4.8 (determined by discriminant analysis)	Discriminant analysis
Vitek and Cowly /1970	126	Shock	Mortality	NA	Logistic analysis
Henning et al /1982	28	Acute myocardial infarction	Mortality	NA	Survivors vs. nonsurvivors at admission and at maximal CO
Siegel et al /1990	185	Blunt trauma	Mortality	NA	Linear regression
Bakker et a l/1991	48	Septic shock	Mortality	NA	Survivors vs. nonsurvivors. Admission vs. postresuscitation
Stacpoole at al /1993	126	Patients with lactic acidosis	Mortality	NA	Survivors vs. nonsurvivors
Abramson et al /1993	76	Trauma	Mortality	Therapeutic goal <2.0	Survivors vs. nonsurvivos
Sauaia et al /1994	106 with lactate values	Trauma	MOF	2.5	Univar. analysis and logistic regression to identify riskfactors
Manikis et al /1995	129	Trauma	Mortality and MOF	1.5	Association between mortality and lactate
Bakker et al /1996	74 surviving >24h, Total 87	Septic shock	Mortality	NA	Survivors vs. nonsurvivors
Marecaux et al. / 1996	38	Septic shock	Mortality	NA	Survivors vs. nonsurvivors
Bernardin /1996	32	Septic shock	10-days mortality	After 24h treatment <3.5	Survival analysis
Blow et al /1999	85	Major trauma	Mortality, MOF, resp. complications	Therapeutic goal <2.5	Survivors vs. nonsurvivors Clearance of lactate after 6, 12, 24 hours or later
Claridge /2000	381	Major trauma	Infection rate	2.4 at 12 hours	Risk of infection
McNelis et al. /2001	95	Consecutive SICU patients	Mortality	NA	Stepwise regression analysis
Kobayashi et al. /2001	22	Consecutive patients with SIRS	Mortality	Second day lactate 2.5	Survivors vs. nonsurvivors With or without DIC
Smith et al. /2001	148	Consecutive mixed ICU patients	Mortality	1.5 at admission 1.0 at 24 hours	Prognostic value of lactate at admission and at 24 h
Bernal /2002	107	Paracetamol induced liver failure	Mortality	Admission 3.5, Late 3.0	Risk of death
Husain et al. /2002	137	Surgical ICU	Mortality and morbidity	Normal < 2.0	Survivors vs. nonsurvivors Clearance time (hours)

Author(s) /Year	Result (Lactate values in mmol/L)	Comments	LR+ for the outcome
Peretz/1995	Stepwise increase of mortality with increasing lactate levels		
Weil and Afifi /1970	Correct classification rate 88% with a reference value of 4.2		
Vitek and Cowly /1970	Stepwise increase of mortality with increasing lactate levels	SL50 4.9, Time-point of blood sampling not reported	
Henning et al /1982	Admission lactate 3.5 vs. 4.3(p<0.05), at highest CO 2.5 vs. 4.7(p<0.01), 4 h before discharge 1.9 vs. 8.8(p<0.01)		
Siegel et al /1990	P < 0.0001	LD50 9.5	
Bakker et al /1991	Early: surv/nonsurv. 5.1/8.2(p<0.05), Late surv/nonsurv. 2.6/7.3(p<0.001)	Admission values 1 4 hours, Postresusc. Values when SAP >90 without inotropes or before death	
Stacpoole et al /1993	Mean lactate: surv/nonsurv. 9.2±4.9/12.2±5.9 (p=0.004)	Lactate not significant after controlling for APACHE II, SAP and arterial pH	
Abramson et al /1993	Initially no difference, Lactate elevated for < 24h, mortality 0%, for 24-48h, mortality 22.2%, for >48h, mortality 86.4% (p<0.0001)	Lactate measured at 8 h intervals for 48 hours	
Sauaia et al /1994	Lactate at 12 to 24 hours after admission an independent predictor of MOF, OR 5.9(1.92-12.35, p=0.0012)		
Manikis et al /1995	Initial lactate surv/nonsurv 2.8/4.0 (p<0.05), maximal lactate lactate surv/nonsurv 3.4/4.6 (p<0.05). Initial lactate MOF/no-MOF: 3.4/2.4 (p<0.01)	Lactate measured at least 2 times/day until normal. Lactime (Number of days with lactate > 1.5 determined)	
Bakker et al /1996	Initial lactate: no difference. Lactime(= hours with lactate >2.0) and AUC of lactime curve higher in nonsurvivors	Additional 13 patients died in the first 24 hours and were excluded. Curve constructed with two values assuming linear trend	
Marecaux et al. / 1996	Lactate higher in nonsurvivors (p<0.05)	No difference in TN-α and IL.-6	
Bernardin /1996	If 24h lactate >3.5: mortality 80.8%, if < 3.5: mortality 30.7% (p=0.0019). Surv/nonsurv at 24h: 2.4±1.4/5.7±3.9(p>0.05)	Lactate cut-off 3.5 at 24hours. MAP at 24h < 85mmHg associated with increased mortality	
Blow et al /1999	Mortality 43 vs 0%, MOF 64 vs 5%, respiratory complications 50 vs 15% if lactate clearance < or > 24 hours	Lactate measured at 6 hours intervals	
Claridge /2000	OR for infection if lactate elevated > 12 hours 5.33 (CI 3.07-9.26)	Correction of lactate(<2.4) at 12, 24 hours or later. Population mortality low (3.3%)	
McNelis et al. /2001	Initial lactate surv/nonsurv 4.3±2.1/7.3±5.4 (p<0.01). Time to lactate clearance surv/nonsurv 17.0±22.2/48.0±30 hours(p<0.0001)	Initial lactate not significant for mortality, if lactate clearance included	
Kobayashi et al. /2001	Admission and first day lactate no difference. 2 nd and 4 th day lactate higher in nonsurvivors	Lactate values every 4 hours for 4 days	
Smith et al. /2001	Admission lactate: ROC-AUC 0.78, Sensitivity 69.0%, Specificity 77.3%. If admission lactate >1.5 and 24-hours lactate >1.0, mortality 81.5% compare to 23.8% if 24-hours lactate < 1.0	Threshold values determined from the ROC curves	Adm lactate >1.5: 3.0 Adm lactate >1.5 and 24h lact > 1, compared to adm lactate < 1.5 and 24h lactate < 1.0, LR+ 9.4.
Bernal /2002	Early lactate >3.5: OR 43(9.1-201, p <0.0001), Sens 67%, Spec 95%. Postresuscitation lactate >3: OR 63(10.4-385, p<0.0001). Sens 76%, Spec 97%	Early = first 4 hours, Postresuscitation 12 hours after admission	Early LR+ 13, Postresuscitation LR? 30.
Husain et al. /2002	Initial lactate surv/nonsurv 2.8/4.2(p=0.002), 24-h lactate 2.2/5.1(p<0.001). Mortality if lactate clearance in 24 h 10%, in 48h 20%, in >48h 23%, never 67%. Independent predictor of death: 24h lactate	Retrospective analysis. Initial lactate higher and clearance time longer in patients with complicated outcome. Lactate not predictive in major abdominal surgery patients.	

in patients with lower lactate ($p < 0.05$). The mortality of patients with admission lactate over 1.5 mmol/L and with the 24 hours lactate above 1.0 mmol/L was 81.5% compared with 23.8% ($p < 0.05$) if the lactate after 24 hours was less than 1.0 mmol/l (LR+ 3.4). Both these cut-off values are lower than in previous reports. Differences of case-mix might have resulted in these lower threshold values with fewer patients after trauma or hemorrhagic shock of other etiologies which can easily be corrected by fluid resuscitation. A similar study was done by Husain et al, who showed in surgical ICU-patients that initial and 24-hour lactate levels were higher in non-survivors than in survivors (Husain, et al. 2003). Lactate clearance in 24 hours was associated with 10% mortality compared to 24% if lactate normalised in more than 48 hours and to 67% if lactate failed to normalise.

Despite the fact that lactate elevation can arrive through several pathways, the clearance of lactate after circulatory failure can be considered as a sign of success of resuscitation. A number of reports show that prolonged elevation of lactate levels is highly correlated with mortality and development of MOF or ARDS (Vincent, et al. 1983, Pasch, et al. 1987, Moore, et al. 1992, Roumen, et al. 1993, Manikis, et al. 1995, Bakker, et al. 1996). A prolongation of lactate clearance for longer than 12 hours in trauma patients and longer than 48 hours in septic shock predisposes the patients to the development of MOF (Tuchschmidt, et al. 1989, Sauaia, et al. 1996), whereas lactate normalisation in 24 hours practically leads to a 100% survival rate (Abramson, et al. 1993). The duration of lactate elevation is a better predictor of outcome than peak lactate values (Bakker, et al. 1996). Lactate clearance is also associated with the use of ICU-resources. McNelis et al found a 100% mortality rate among surgical ICU patients who were unable to normalise their lactate values in 98 hours (McNelis, et al. 2001). One third of the non-survivors spent more than 50 days in the ICU.

The presence and duration of metabolic acidosis with elevated base deficit without concomitant hyperlactatemia has been shown to be associated with adverse outcome as well. This is to be expected because hyperlactatemia and development of acidosis are both related to impaired tissue oxygenation though not to same biochemical processes. Prolonged metabolic acidosis after resuscitation of trauma patients with normal lactate levels is associated with

increased mortality and incidence of MOF (Kincaid, et al. 1998) and ARDS (Eberhard, et al. 2000). Elevated base deficit has been identified as an early indicator of hemodynamic instability and it is associated with the need of blood transfusions and with high probability of death in trauma patients (Rixen, et al. 2001). The study of Smith et al has shown that the admission base deficit has a ROC-AUC of 0.73 for mortality in mixed ICU-patients (Smith, et al 2001). The same groups found a critical cut-off level for admission base deficit of 4 mmol/L and for the 24-hours base deficit of 2.5mmol/L. These points were close to the upper left corner of the ROC-curve. The admission cut-off value had a sensitivity of 70.6% and a specificity of 72.2 in predicting death (LR+ 2.5). If the patients with the admission base deficit of more than 4 mmol/L could not clear their acidosis to a level less than 2.5 mmol/L, the mortality was 70.6% in contrast to 11.1% ($p<0.05$) in patients who could clear the acidosis in 24 hours (LR+ 2.4). In the study of Husain et al, initial base deficit was not different between survivors and non-survivors but there was a difference in base deficit after 24-hours (Husain et al. 2003).

The main reason for using base deficit instead of lactate is the better availability of blood gas measurements compared to lactate. Though some studies have proposed that base deficit should be used as a prognostic marker instead of lactate after injury (Siegel, et al. 1990, Kincaid, et al. 1998), lactate is more closely associated with different aspects of acute illness through its several pathways of production. Lactate level cannot be predicted with acid base status (Mikulaschek, et al. 1996, Husain, et al 2003).

Early studies indicated that the L/P-ratio was normal, if it was below 10 to 15:1. (Huckabee 1958a). Predictive use of L/P-ratio was estimated already in early studies, which found the addition of L/P-ratio not to improve the predictive power of lactate (Weil and Afifi 1970). The most critical practical point concerning the use of L/P-ratio in the clinical setting is the need for cautious handling of the pyruvate sample (Chariot, et al. 1994). The pyruvate samples have to be deproteinised and deep frozen very quickly. It seems that L/P-ratio elevations in circulatory failure occur simultaneously with lactic acidosis (Levy, et al. 2000) but how this contributes to its predictive use is not well understood.

2.3.5 Confounding factors in the interpretation of lactate and L/P-ratio values.

Sympathomimetic substances, either endogenously or exogenously, affect lactate and pyruvate metabolism. In healthy volunteers during exercise the epinephrine levels correlate with the levels of lactate and L/P-ratio (Wasserman, et al. 1985). An epinephrine infusion increases the levels of lactate and L/P-ratio in a similar fashion but the increase of lactate is relatively greater than the increase of pyruvate (Levy, et al. 1997). The pyruvate declines more slowly than lactate during the recovery phase after an exercise. In sepsis patients, endogenous epinephrine levels are related to the elevations of lactate (James, et al. 1999). However, epinephrine infusion during septic shock might be responsible for impaired splanchnic oxygen transport (Levy, et al. 1997, Meier-Hellmann, et al. 1997) indicating that lactate elevations of septic patients caused by epinephrine are not simply related to its metabolic action. Respiratory alkalosis elevates the lactate levels by interfering with the clearance of lactate (Goldstein, et al. 1972, Druml, et al. 1991) and lactate release from the splanchnic region (Karlsson, et al. 1995). Lactate elimination occurs mainly in the liver and acute liver failure is associated with lactate elevation also without circulatory impairment. Lactate elevation in patients with acute liver failure caused by paracetamol is an accurate predictor of death (Bernal, et al. 2002). The retrospective study by DeJonghe et al showed that patients with early (during the first 48 hours) hepatic dysfunction induced by circulatory failure had higher lactate levels. Independent predictors of serum lactate were hepatic dysfunction, non-distributive type of shock and use of epinephrine (De Jonghe, et al. 1999). Ethanol ingestion interferes with the metabolism of carbohydrates (Goldfrank and Starke 1991) and moderate levels of hyperlactatemia have been found in patients with acute alcohol intoxication (Fulop, et al. 1986). From the clinical point of view, it is important that other causes than alcohol consumption are to be sought for as the cause of lactate elevation also in intoxicated patients (MacDonald, et al. 1994). Ethanol ingestion induces an inhibition of the gluconeogenesis from pyruvate resulting in markedly elevated L/P-ratio values (Lecky, et al. 2002). This interference hampers the use of L/P-ratio as a predictor of outcome in this patient category.

2.4 Outcome prediction using severity scores

2.4.1 General aspects

Prediction of ICU and hospital outcome has the aim to estimate patients' outcome based on the available data. Aside of the present diagnosis, patients have a history of chronic illnesses influencing their abilities to survive. Furthermore, outcome is affected by the severity of the present illness and quality of care. The patients whose therapy has been withdrawn with subsequent fatal outcome are difficult to handle in outcome prediction studies and occasionally DNR patients were eliminated from study population (Knaus, et al. 1985b). If treatment has been continued up to time point of withdrawal, DNR patients should not be excluded. Similar problems may arise with cases not receiving full-scale treatment. Outcome of intensive care is most often reported as ICU mortality, hospital mortality or mortality on a specified day. Intensive care mortality can be strongly biased through different treatment policies of hospitals and practices to handle patients with poor prognosis vary considerably. Hospital outcome is considered to be less affected by bias, although many patients are discharged from hospital to other institutions for rehabilitation or continued care. In these cases the final outcome of the patients might remain unknown or the transferred patients are considered as survivors, because they leave the hospital in question alive. Also patient transferrals to other intensive care facilities take place. Most often, outcome prediction is related to the mortality during the same hospitalisation period or status at hospital discharge but it could be related also to the length of stay in the ICU or in hospital (Barie, et al. 1996b, Woods, et al. 2000), the quality of life (Buist 1994)) and costs (Zimmerman, et al. 1995). An optimal prediction instrument should be easily obtainable and objective (Kollef and Schuster 1994). The latter property implies that every person performing the data collection finds the same value. This is true for variables which do not include subjective assessment. Some variables are subjective in their nature. E.g. urine output in 24 hours is an objective value, but grading of somnolence or agitation is not. The prediction instruments should be applicable in many patient categories i.e. they should not be specific for one group of patients only. The differences of health care systems between countries and continents make uniform and bias-free systems nearly impossible. Because of variability in patient population and in ICU-and healthcare

environment the prediction models can be used only in the surroundings where they were developed. Each model should be recalibrated before being used in a new population (Kollef and Schuster 1994, Moreno and Apolone 1997, Moreno, et al. 1998).

2.4.2 The APACHE and SAPS systems

The first generation severity score, acute physiologic and chronic health evaluation, APACHE, was introduced in 1981 (Knaus, et al. 1981). The main aim was to introduce a method for describing severity of illness for groups of patients. APACHE consisted of 34 physiological variables and a four step grading for the severity of the chronic disease. The selection of the physiological variables and the weights of them ranging from 0 to 4 were determined by a small group of experts. The observation period for finding the worst value was 32 hours because it included 4 working shifts. It was primarily tested in 582 admissions and a clear correlation between APACHE-score and mortality could be detected. Only patients staying longer than 24 hours in the ICU were included. An analysis of APACHE system was published a year later (Knaus, et al. 1982). The risk coefficients were calculated using data of 613 patients originating from one hospital and the predictive performance was tested in 795 patients from 5 other hospitals. There was a good correlation between acute physiological score of APACHE and mortality. APACHE proved to be a good predictor of outcome in many disease categories (Wagner, et al. 1983). The APACHE system included also arterial lactate concentration with a normal range (giving zero points) below 3.4 mmol/L.

APACHE II was introduced 1985 and was intended to be clinically more useful, simpler and still accurate enough for patient classification (Knaus, et al. 1985a). The data of 5815 patients from 13 hospitals were collected. The set of variables for the acute physiologic score (APS) were reduced to 12 and the staging from 0 to 4 points was used as in the APACHE system. Lactate was omitted because, as it was noted, it was not routinely measured. For age and chronic health status points were assigned. Accordingly, the APACHE II sum consisted of APS, chronic health points and age points. The admission diagnosis was included into the risk calculation in form of a weight. Twenty-nine non-operative and 16 operative diagnoses were given weights and if not available, one of 5 main vital organ systems responsible for the admission, should be selected.

Emergency operative status was given a special coefficient. APACHE II model had a correct classification rate of 85.5% with a specificity of 94.9% and a sensitivity of 47.0%, (Knaus, et al. 1985a). The association of APS with outcome is depending on the diagnostic group and in patients with pulmonary embolism and diabetic ketoacidosis the association is poor (Wagner, et al. 1986).

Apache III is the latest development in the field of severity scores (Knaus, et al. 1991). Unfortunately, the logistic regression coefficients and details of the weights of disease categories are private property and thus not freely available. This has limited the acceptance and utilisation of this system considerably. Apache III has corrected some of the limitations in the Apache II system. It consists of acute physiological score with 17 variables, of age-points, of 7 comorbid conditions and of score for the location prior to ICU-admission. The acid-base status incorporates pH and carbon dioxide levels. In the scoring of neurological abnormality, instead of the GCS, a special scheme of the neurological evaluation has to be used. For the calculation of the probability of death one of the 78 disease categories is selected. The performance of the Apache III system was excellent with a ROC-AUC of 0.9 and correct classification rate of 88.2% in a database of 17440 admissions (Knaus, et al. 1991).

Le Gall et al. constructed a simplified version of scoring (simplified acute physiology score) which was based on the first APACHE system (Le Gall, et al. 1984). Instead of 34 variables, SAPS contained 14 variables and the weights were similar to those in APACHE. SAPS was not extensively used, because it was published only 1 year before APACHE II which became the preferred instrument for several years. One additional negative feature of SAPS was that it was not convertible to a probability of mortality.

The new version of SAPS, the SAPS II was based on a large European – North American population of 13152 patients (Le Gall, et al. 1993). A statistical modelling was used for defining the weights of the variables. Only 3 diagnostic categories, metastatic cancer, hematological malignancy and AIDS as well as 3 types of admissions, scheduled surgical, unscheduled surgical and medical, were included and they were incorporated to the scoring system. The sum score could be transformed to a probability of hospital death using a logistic regression formula and the model contained an extra variable, $\ln(\text{SAPS} + 1)$, for correction of the skewed distribution of

SAPS II scores. The weights of the included variables were calculated through statistical procedures and in all cases each variable was represented by one “worst” value.

A third prediction model, the mortality probability model or MPM was based on statistical analyses of a large series of variables associated with the outcome (Lemeshow, et al. 1985). The main goal of the process was to build a prediction model for mortality, not a measure of severity of illness. The second version, the MPM II was based on the same database as the SAPS II complemented with data of six ICUs in the USA (Lemeshow, et al. 1993). In a further developmental step the same group implemented data collected at 24-hour intervals after admission and developed the MPM24 and MPM72 models (Lemeshow, et al. 1994). In the MPM model patient status is estimated dichotomously as a presence or absence of a variable like coma, infection, vasoactive medication, mechanical ventilation, heart rate above and blood pressure below a threshold value etc. Only age is a continuous variable. This review will focus on the SAPS II and APACHE II scoring systems, because they are commonly used and they can be used to describe the SIRS and circulatory failure in a more detailed form.

2.4.3 Calculation of the probability of death

The association between probability of death and with the severity score is not linear. The severity score is transformed to a logit following principles of logistic regression analysis. The equation of logit is of the form (Le Gall, et al. 1993):

$$\text{Logit} = \beta_0 + \beta_1 \times \text{severity score} + \beta_2 \times \text{dependent variable}_1 + \beta_3 \times \text{dependent variable}_2 .$$

In this formula β_0 is a constant, and dependent variables are weights of admission diagnosis, emergency operative status and for the SAPS equation the variable $\ln(\text{SAPS} + 1)$. This was included into the equation to correct the skewed distribution of the SAPS II scores. (Le Gall, et al. 1993). The logit is converted to a probability of death using the formula:

$$\text{Probability} = e^{\text{logit}} / (1 + e^{\text{logit}}) .$$

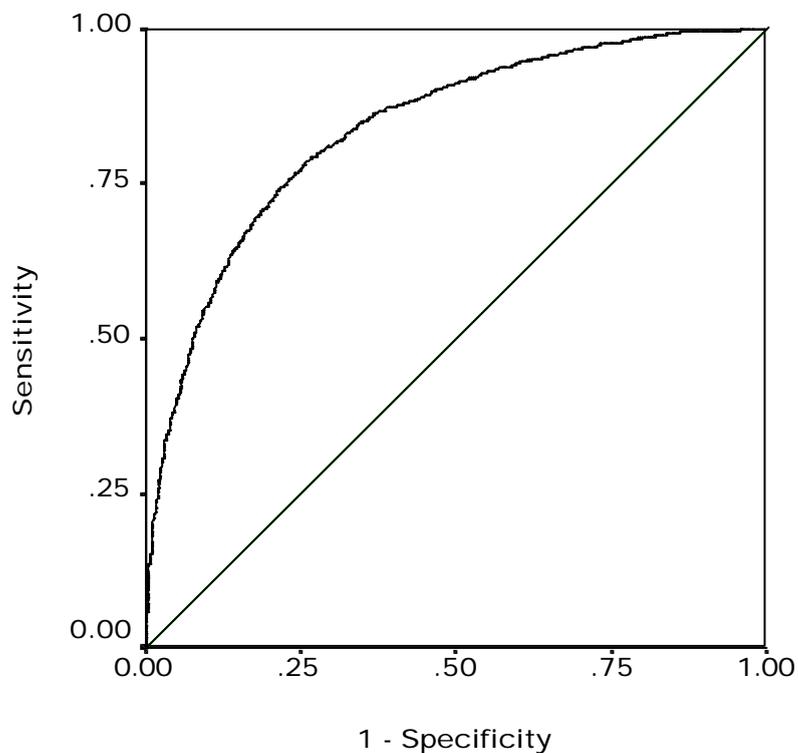
From this equation follows that the probability of death is a S-shaped curve and the nearly linear mid-section of the curve lies at the probability of death of 0.5. Because the admission diagnosis is separately included into the APACHE II prediction equation, a whole spectrum of curves is produced, the location of which on the x-axis determines the association between risk of

death and APACHE II score. The prediction of survival or non-survival in 2x2 tables is done at the decision point 0.5 of risk which means that one point increase in severity score at this point might shift the patient from those predicted to survive to those predicted to die.

2.4.4 Calculation of the performance of prediction models

The two cornerstones in estimating the performance of predictive tools is to have a measure of discrimination and a measure of calibration. Discrimination is the ability of the prediction instrument to correctly identify survivors and non-survivors. This is done by constructing a diagram combining sensitivity and specificity, the receiver operating characteristic curve, ROC-curve (Figure 2-1) and by calculating the area under the ROC-curve, ROC-AUC (Hanley and McNeil1982).

FIGURE 2-1 The ROC-curve combines the sensitivity and specificity of an outcome variable to one graph. The area under the curve, the ROC-AUC of this curve is 0.839 (SE 0.831-0.848)



The closer the ROC-AUC is to 1.0 the better is the discrimination. ROC-AUC of 0.5 means a discriminatory performance equal to pure chance or tossing a coin. If the ROC-AUC is above 0.8, the discriminator is considered excellent (Le Gall, et al 1993). The second objective, the calibration means that the prediction instrument performs well over the whole range of risk. For this purpose, the goodness-of-fit procedure has been used with calculation of applied chi-square statistics as proposed by Hosmer and Lemeshow (Lemeshow and Hosmer 1982, Hosmer and Lemeshow 1989). To do this the population is divided into 10 strata of increasing risk, either in equally sized groups or in deciles of increasing risk of death. The former gives the C* statistics and the latter the H* statistics when the chi-square values of each strata are summed. H* statistics is the mathematical expression for the calibration curve as it is drawn after division of the population into deciles of increasing probability of death on x-axis and observed mortality of each strata on y-axis. The expected mortality is compared to the observed one over the whole range of risk. The better the calibration the lower the H* respectively C* value. If the fit of the calibration curve is good, it is not statistically different from an ideal line with a p-value >0.05. Recalibration or customisation can be done by development of a new equation for outcome prediction using logistic regression analysis and including all the independent variables contained in the original model. This is termed as second level customisation. First level customisation includes development of a new model with the original logit as the independent variable (Zhu, et al. 1996).

2.4.5 Limitations and problems in severity scores in outcome prediction

2.4.5.1 Finding the correct values for the variables and the rate of sampling

The concept of severity scoring in the prediction of outcome includes the assumption that the severity of illness on the initial phase of ICU care is an important determinant of mortality (Knaus, et al. 1985c, Wagner, et al. 1986, Wong, et al. 1995). The association of hospital mortality and severity of acute illness seems to be well documented for general ICU populations (Le Gall, et al. 1993, Rowan, et al. 1994, Beck, et al. 1997) and also for other critically ill patients like patients in intermediate care and coronary care units (Schuster, et al. 1997, Auriant, et al. 1998), and patients with myocardial infarction (Ludwigs and Hulting 1995). The association of the severity of acute illness and outcome is not necessarily straightforward. As described with

lactate, the highest value, which is very often the first value as well, might not always be the value most strongly related to the outcome. The clearance of lactate, which is reflected in the last value of the initial 24 hours, is more clearly associated with mortality than the highest value per se (Vincent, et al. 1983, Abramson, et al. 1993, Bakker, et al. 1996, Bernardin, et al. 1996). Only the variables in the MPM models have been tested statistically in relation to mortality. Theoretically, the change of values in time, in contrast to worst values, e.g. of pH, pO₂ and base excess could reflect a unsuccessful resuscitation (Kincaid, et al. 1998) and thus be more closely associated with mortality than the worst values. The effect of treatment is not included in the severity scores (Cowen and Kelley 1994). The effect of treatment can to some extent be studied by measuring severity scores repeatedly. Increased severity of illness is associated with high mortality (Bion, et al. 1988, Chang, et al. 1988). However, a subsequent study with the same approach in a larger database was not able to repeat the good result of the previous study (Rogers and Fuller 1994). Using severity scores repeatedly has never been validated and is very much subject to bias caused by therapeutic measures. The approach of repeated measurement of risk has been included into the APACHE III system (Knaus, et al. 1991). Because most often the worst values are the first ones, repeated measurement does not bring in new information (Knaus, et al. 1985a). In contrast to the severity scores, the impact of treatment is included in the SOFA-scores in the form of vasoactive medication (Vincent, et al. 1996). The authors of the APACHE II indicate in their original publication that an as early as possible time point would be the best for scoring e.g. the emergency department in order to eliminate the effect of treatment to the scores (Knaus, et al. 1985a). Some more confusion arrives to this issue in the technical protocol of the APACHE III data collection (Knaus, et al. 1991). According to the protocol, admission values were those taken during the initial 1 hour of ICU stay. If there were no values available the previous, pre-ICU 1 hour time period was used. The worst value of the first day was either an admission value or the value taken during the next 23 hours. Whether this approach was used also during the collection for APACHE II, has not been clarified in the literature (Rowan 1996).

Route of admission or the location of the patient prior to admission to ICU is included in the APACHE III scoring system. Preliminary studies have shown that the location from which the

patient is transferred to the ICU is related to the outcome (Dragsted, et al. 1989, Escarce and Kelley 1990). Escarce could clearly show that patients transferred from hospital areas, where they could be stabilised for a longer period of time, had higher than expected mortality (Escarce and Kelley 1990). This finding emphasises the fact that if patients can be stabilised prior to admission, the severity scores are low and the expected death rate as well. The mortality of patients in the study by Escarce transferred directly from the emergency department was close to the predicted mortality. The impact of early resuscitation on severity scores is also reflected in the study by Rivers et al who used a goal directed therapy for septic shock patients required to wait about 6 hours to be admitted to the ICU (Rivers, et al. 2001). Aside of lactate values, also the APACHE II and SAPS II scores of the treatment group were lower than of the control group.

The application of computer technology for automated data collection has increased the sampling rate considerably and omitted the need of professional personnel to interpret and record the clinical data. All continuous variables can be measured with high resolution, which necessitates also the use of different techniques to solve the problem of artefact recognition (Sukuvaara, et al. 1993). The high resolution of collected data of continuous variables results in higher scores because abnormal values are found more often (Bosman, et al. 1998). The clinical significance of the recorded alterations is not considered. There are no commonly accepted agreements of the duration of an alteration to be included into the severity scores (Marik and Varon 1999).

The relative contribution of the predictor variables to the risk estimation varies from variable to variable and is dependent on the patient group for which the risk is estimated. Among the risk predictors, the Glasgow Coma Scale (GCS) has a very unique role. In trauma patients, 75% of the predictive power of APACHE II system is explained by the GCS alone (Vassar, et al. 1992). In cardiac arrest patients, the GCS alone is as good a predictor of hospital outcome as APACHE II score (Niskanen, et al. 1991). The non-linear fashion of the weights of the scores and lack of consistency in the relative importance of different variables in relation to outcome interfere with the mathematical calculation of the risk of death. E.g. core temperature change in APACHE II scoring with an increase by one step from 1 to 2 points bears not the same increase of risk of

hospital death as the rise by one step from 3 to 4. Similarly, two points of the score in GCS are most likely not similarly related to mortality as two points resulting from serum sodium or age of 45 years.

Some studies have compared the ability of the care personnel, physicians and nurses, with prediction models to predict hospital outcome. If the data collection for both, the clinical and APACHE II assessment were performed simultaneously and shortly after admission, the ability for correct prediction was identical (Kruse, et al. 1988). If the physicians had information of the whole first day, the clinical prediction was better than the APACHE II system (Brannen, et al. 1989). This difference can partly be explained by the knowledge of the response to treatment, which made the prediction in the latter study more exact.

2.4.5.2 Case mix

The development and validation populations determine the case-mix which the model is designed for. Case-mix differences can be very obvious, like patients in specialised units designed for subgroups of patients like surgical (Meyer, et al. 1992), cardiac (Schuster, et al. 1997), trauma (McAnena, et al. 1992, Roumen, et al. 1993), respiratory (Del Bufalo, et al. 1995) and neurologic (Weingarten, et al. 1990). If the mortality rate of the study population is far different from the original one, this is also a case-mix difference and the model does not perform well unless it is customised for the new population (Zhu, et al. 1996). As the time of death is far apart from ICU-admission or patients are treated for prolonged time in the ICU, the prediction models are not accurate (Sleigh, et al. 1992, Sicignano, et al. 1996). Sleigh et al studied 383 patients in two ICUs and measured APACHE II scores on the first ICU-day. Thirty-five % of patients stayed in the ICU one day or less. Patients treated shorter than for 4 to 5 days were in more than 80% of cases correctly classified to die. In contrast, in patients with an ICU-LOS of 6 days or more, correct classification rate fell to 62%. Sicignano et al used the first generation SAPS-score in a group of 8059 patients. Patients with an ICU-LOS of less than 24 hours were excluded. The investigators developed a prediction model for SAPS. ROC-curves were constructed for patient groups with increasing ICU-LOS. The ROC-AUC for the whole population was 0.79. The group with ICU-LOS longer than 4 days had a ROC-AUC less than 0.7 and the group with ICU-LOS longer than 7

days a ROC-AUC round 0.66, which indicates that the discriminative power was lost as the ICU-LOS prolonged.

Patients treated longer than 24 hours only were included into the original APACHE score, but the APACHE III included all patients treated longer than 4 hours as mentioned earlier. If a large proportion of dying patients is treated a very short time e.g. less than 2 days, the prediction models will focus on the risk of death of this group. Only few studies have given detailed information on the distribution of ICU-LOS (Meyer, et al. 1992, Barie, et al. 1996b, Wong, et al. 1999). In the study of Barie, 57% of patients stayed less than 3 days and in the study of Wong, 60% of patients stayed less or equal to 2 days showing that majority of patients are treated for short time only. The costs of intensive care are associated with prolonged stay and development of MOF (Oye and Bellamy 1991, Barie and Hydo 1996). In the study of Oye et al, outcome prediction using the APACHE II model for high cost patients, predicted death for 43.4% of patients whereas the observed mortality was 70.6%. High cost patients consumed 50% of total ICU resources but consisted of only 8% of the total number of patients. The predicted and observed mortality rates of the low-cost patients were 24.6% and 20.0%, respectively. The prediction of the outcome of the high-consumers of ICU resources with prolonged stay is less accurate than of those receiving only a short period of treatment.

It is evident from the early studies on that aside from the severity of acute illness, also the admission diagnosis is important for the prognosis (Knaus, et al. 1985c). A certain severity of illness measured with severity score in one diagnostic group is not associated with the same risk of death in some other diagnostic group. Typically, patients with intoxication have a lower risk of death than patients with GI perforation with the same severity score. Elective surgical admissions bear a lower risk of death than emergency surgical admissions and medical admissions (Knaus, et al. 1985a, Cerra, et al. 1990). Elective admissions are selected and planned and patients can be prepared for the surgery and ICU admission, which ultimately should be accompanied by lower risk compared to emergency admissions. In some diagnostic groups of APACHE II, like diabetic ketoacidosis, pulmonary embolism and respiratory arrest patients, there is no relationship between severity of illness and mortality (Wagner, et al. 1986). In these diagnostic categories the mortality

prediction based on severity scores is misleading because it is depending on the admission diagnosis only. For APACHE III, in patients with pneumonia, subarachnoid hemorrhage and acute myocardial infarction or unstable angina the predicted death rate was higher than the observed mortality. In patients with cardiac arrest, sepsis of urinary tract origin, head trauma, multiple trauma, GI bleeding and especially with drug overdose, the observed death rate was higher than the predicted one (Zimmerman, et al. 1998). The weights of diagnostic groups in the original publication of Apache II have not been questioned over the years although the risk of death associated with each diagnostic group might have changed over the years. As is evident from the previous citation, also the weights of diagnostic categories in APACHE III might not be accurate. The APACHE-systems have been criticised for the difficulty of selecting the only one admission diagnosis because the relative importance of several possible admission diagnoses is often not obvious (Vassar and Holcroft 1994).

2.4.5.3 Lead time bias

Lead time bias is a term normally associated with the results of cancer treatment. Lead-time bias is present when e.g. an improvement of diagnostic capabilities results in an earlier detection of patients with cancer and an earlier start of medication and care. When the survival time is calculated from time of diagnosis to death, it looks as if the survival time has increased, when it actually has remained the same; only the diagnosis is done earlier. This approach transferred to the ICU surrounding would mean that the predicted risk is dependent on the time when it is determined. Pre-ICU treatment and location of the patient before ICU admission were already discussed above. It is much more difficult to assess the timing of the resuscitative efforts in relation to the disease process as a whole. As discussed earlier, resuscitation of trauma patients and association of trauma-resuscitation with MOF and mortality is easier to study because the time-relations are precise (Shoemaker 1996). The exact timing of a community acquired pneumonia with sepsis or SIRS is much more difficult to assess. Delays before contacting medical personnel and delays in the hospital until admission to ICU for care and making the risk prediction are often obscure.

All of the scoring systems assume that data for scoring is collected solely during the ICU stay with the exceptions mentioned above. The timing of scoring is one of the crucial points. The effect of lead-time bias on the severity scores by inclusion of pre-ICU values to the set of variables was studied by Tunnell et al (Tunnell, et al. 1998). They included data 2 hours prior to ICU-admission for vital signs and 6 hours prior to admission for laboratory data to the scores and found significant increases in the scores of APACHE II, APACHE III and SAPS II as well as for predicted mortality. The risk estimates are not correct for patients who have been treated effectively prior to admission if the pre-admission treatment does not lower the risk equally. The pre-admission values e.g. of laboratory tests should be included into the data set because these values often confirm the indication for the ICU-admission and to initiate resuscitation efforts and are not repeated before treatment is started. It is clear that treatment immediately before ICU admission, either by the ICU staff or others, lowers the severity of illness if only data obtained in the ICU is included (Rowan1998). The same applies to patients transferred from other hospitals, especially if they have received effective treatment in the referring hospital or during the transportation (Uusaro, et al. 2002) Effective treatment in the emergency department results in better stabilisation of patients and lowering severity scores (Dragsted, et al. 1989, Rivers, et al. 2001). If the real risk remains unchanged but the timing of data collection results in lower scores, lead-time bias is present.

2.4.5.4 Variability in data collection

The collection of data for the severity scores is mainly accomplished by transferring data from medical records to databases. If the data transfer is reliable the collected data reflects the true variance of the sample (Damiano, et al. 1992). Damiano et al found that the reproducibility of data collection for APS and age is good but less good for chronic health points. In this study the collected data were reassessed by an data abstractor of APACHE Medical Systems. In multicenter studies ambiguities of definitions and problems of translation and conversion to other units than in the original system has been identified as a source of bias (Fery-Lemonnier, et al. 1995, Chen, et al 1999). Inter-observer variability can be improved by strict guidelines and training (Polderman, et al. 2001a). Polderman et al found that the intra-observer variability is 15% for APACHE II

scores and concluded that this amount of variability is inherent to the scores (Polderman, et al. 2001b). This was studied in a set-up where the same persons collected data at intervals from the same records.

3 AIMS OF THE STUDY

The purpose of this study was to investigate factors associated with the acute circulatory failure and the outcome of acute circulatory failure in terms of multiple organ failure and hospital outcome. Circulatory failure was studied with special reference to its indicators, lactate and metabolic acidosis, and its association with the development of multiple organ failure. The commonly used severity scores lack precise definition of the sampling method and therefore the impact of sampling rate on the scores was assessed. Because the patients with multiple organ failure stay in intensive care for a prolonged time and consume high amounts of resources, the accurate prediction of outcome of this patient group is of major importance. Hence, the impact of length of stay in intensive care on the performance of the severity scores was investigated in a large national database.

The specific aims of this study were to answer the following questions:

- What is the role of lactate, L/P-ratio and lactic acidosis as signs of circulatory failure in the first ICU day?
- Is the clearance of lactate and/or metabolic acidosis associated with differences in hemodynamic profiles of patients in the first day of ICU-care?
- What are the consequences of resuscitation success in terms of development of multiple organ failure and mortality?
- What is the magnitude of bias caused by increased sampling rate on the APACHE II and SAPS II scores?
- Are recalibrated outcome prediction models based on APACHE II and SAPS II scores reliable for patients in prolonged ICU care?

4 MATERIAL AND METHODS

4.1 Study subjects

The time-pattern of lactate and L/P-ratio (Study I) was studied in 98 consecutive emergency admission patients above the age of 16 with a mean age of 54 ± 2 . Sixty-five (66%) of them were men. A subgroup of sixty-nine of these patients formed the study population for study III.

The consequences of early resuscitation on the eventual development of MOF and survival (Study II) was studied by reconstructing the patient records of 83 patients using the CIMS (clinical information management system) of the ICU in Kuopio University Hospital (Clinisoft, Instrumentarium Helsinki Finland) and by retrieving data from written patient records. The study population was selected from emergent admitted patients above the age of 15 who were monitored invasively during the first ICU day and who stayed in the ICU for longer than 24 hours. The records of all patients admitted between 1st of August 1998 and 31th July 1999 were checked in order to identify candidates for the study. Open heart surgery patients, neurosurgical patients, intoxication patients and patients who were transferred from other hospitals after having received intensive care for longer than 12 hours before transportation were excluded. Patients with multiple admissions were analysed only once and if more than one admission fulfilled the inclusion criteria, the latest admission was selected. Only patients with a circulatory failure defined as arterial lactate > 2 mmol/L and/or base deficit > 4 mmol/L at any point during the first ICU-day were selected. From 210 candidates 83 fulfilled all the inclusion criteria and formed the study population.

The effect of sampling rate to the APACHE II and SAPS II scores (Study III) was studied in 69 consecutive emergency admission patients above the age of 16 years. The group sampled had a mean age of 54 ± 2 and a 42 over 27 male to female ratio.

The effect of prolonged ICU-LOS (Study IV) on the predictive performance of APACHE II and SAPS II scores was studied in a prospectively collected database consisting of 23953 admissions in 13 ICUs in non-university hospitals in Finland. The database was collected by The Finnish Consortium of Intensive Care Data with the aim to compare ICU performance and quality of care in Finnish ICUs. The database was collected during the years 1994 to 1999.

Table 4-1 Summary of the study populations

Study	Number	Study period	Inclusion criteria	Mortality n(%)	MOF n(%)	ICU-LOS >5d n(%)
I	98	5th Aug -15th Sept 1996	Consecutive	13(13.3)	14 ^b (14.3)	17(17.3)
II	83	1st Aug 1998-31th July 1999	Lact >2 and/or BE <4	33(39.8)	47 ^a (56.6)	27(32.5)
Total	181			46(25.4)	84(46.4)	44(24.3)
III	69 ^c	5th Aug -1st Sept 1996	Consecutive	8(11.6)	12 ^b (17.4)	14(20.2)
IV	23953 ^d	From 1994 to 1999	All patients with full data	2356(19.8)	No data	1915(16.1)

a Definition: Sofa score > 2 of 2 or more organ systems

b Definition of Ruokonen et al. Crit Care Med 1991

c First 69 consecutive patients of the Study I patients

d Split into calibration and validation data of equal size

4.2 Sample size considerations

For the lactate study (study I), sample size was estimated based on the patient selection of emergency admissions of ICU of Kuopio University Hospital. Hospital mortality at the institution is 8-12 % in elective patients and higher in emergency patients. The study group of 100 patients was estimated to include more than 10 patients ultimately dying in hospital and to be large enough to allow conclusions about the predictive role of hyperlactatemia in terms of mortality. The study patients for the sampling rate study (study III) were a subgroup of 69 patients of the lactate study group. The study population of the Study II was formed retrospectively by studying patient records. The ICU of Kuopio University Hospital receives about 940 emergency admissions per year. One third of these are neurosurgical patients. The ICU-LOS of 250 patients exceeds 2 days and they are thus at risk of having MOF. The first check of patient records of one year identified 210 candidates for the study. Patients not having pulmonary artery catheter monitoring and not fulfilling the inclusion criteria of the study reduced the number of study patients to 83. Because the emergency patients have a hospital mortality of 20%, this group was estimated to include at least 20 deaths. The prediction model study (study IV) was based on a large national database and all admissions at the end of previous year before the start of the study were included.

4.3 Ethical considerations

Informed consent was waived in studies I and III because no therapeutic manipulations were done and because only minimal amounts of blood were collected from indwelling arterial lines. Arterial lines were part of the routine protocol in the care of the patients. The study II was a retrospective analysis of patient data. The study IV was carried out in a large national database and the use of the database for research purposes was approved by the board of the Consortium and by responsible authorities of all participating ICUs. All studies were approved by the ethics committee of the Kuopio University Hospital.

4.4 Study protocol

4.4.1 Time-pattern on lactate and L/P-ratio (Study I)

4.4.1.1 Sampling protocol

In order to study the time-pattern of lactate and L/P-ratio in 98 emergency admission patients, blood samples for the measurement of arterial lactate, pyruvate and the blood gases were taken at the time of admission and at two hours intervals during the next 24 hours or until earlier discharge or death of the patient. The attending physician had access only to the lactate and blood gas values taken on clinical basis. On average 20.5% (range 15.6 – 28.1% between diagnostic groups) of the total number of lactate samples were taken on clinical basis.

4.4.1.2 Laboratory analysis

The blood samples for the lactate and pyruvate determination were drawn from indwelling arterial lines and put in ice immediately after sampling. The blood lactate samples were analysed without delay in the ICU using an amperometric enzyme sensor method (YSI 2300 Stat Plus, YSI Incorporated, Yellow Springs, Ohio, USA). The lactate measurements had an intra-assay coefficient of variation of 1.9% and 1.7% with control samples of 2.0 and 11.4 mmol/L, respectively. The inter-assay coefficient of variation was 3.6% and 1.8% with control samples of 2.0 and 10.7 mmol/L, respectively. The blood pyruvate samples were deproteinised and centrifuged without delay in the clinical laboratory of the ICU and the supernatants were frozen to -80°C. They were analysed after a maximum of 4 days of storage in sets using an enzymatic colour reaction (Sigma UV-706 kit, Sigma Diagnostics, St.Louis, MO, USA) and a

spectrophotometer (Shimadzu CL-750, Shimadzu Corporation, Kyoto, Japan). Analyses of each individual patient were performed within the same set of tests. The pyruvate-analyses had an inter-assay coefficient of variation of 2.7%, 2.9% and 5.0% with control samples of 200, 169 and 100 $\mu\text{mol/L}$, respectively. The intra-assay coefficient of variation was 4.4%. The blood gas measurements were done immediately after sampling in the laboratory of the intensive care unit (Radiometer ABL-500, Radiometer, Copenhagen, Denmark).

4.4.1.3 Determination of the cut-off values for lactate and L/P-ratio

The lactate value less than 2 mmol/L was considered normal, which has been commonly used as a cut-off value for lactate in intensive care studies. The reference value of L/P-ratio was determined in 50 healthy volunteers. The median value of L/P-ratio of the volunteers was 10.0 (IQR 8.1-11.5). Because of not normal distribution of the L/P-ratio, calculation of a mean value and determination of 2.5 and 97.5 percentiles was performed with logarithmic values. These calculations gave a reference range of 5.1-18.0 for the L/P-ratio in healthy volunteers and that was used in the study.

4.4.1.4 Definitions

Circulatory shock was defined either as hypovolemic shock or as the need for sympathomimetic drugs and/or vasodilators (excluding vasodilator treatment for arterial hypertension alone) to support circulation (septic and cardiogenic shock). Hypovolemic shock was defined based on a clinical history of acute bleeding requiring surgical intervention and fluid resuscitation. Septic shock was defined as sepsis with the need for adrenergic drugs to maintain blood pressure (Ruokonen et al 1991). Circulatory shock was considered to be cardiogenic if the patient received inotropes or vasodilators to enhance cardiac performance and was not in hypovolemic or septic shock. In the study I, MOF was considered to be present if the ICU-stay was more than 2 days and at least two of the following were present at the same time: a) Glasgow Coma Scale < 10 in the absence of sedation; b) dependence on mechanical ventilation; c) vasoactive drug infusion to treat hypotension or decreased cardiac output; d) serum bilirubin concentration > 40 $\mu\text{mol/L}$ and serum alanine aminotransferase > 40 U/L; e) serum creatinine concentration > 200 $\mu\text{mol/L}$, urine output < 750 mL/24hrs in the absence of hypovolemia or the

need for acute dialysis; f) platelet count $< 80 \times 10^9/L$ and leukocyte count $< .5 \times 10^9/L$; g) macroscopic gastrointestinal bleeding or paralytic ileus (Ruokonen et al 1991).

4.4.2 Circulatory failure (Study II)

The first ICU-day of each study patient was reconstructed by producing identical sets of trend curves as in the original clinical situation using the CIMS (Clinical information management system, Clinisoft Datex-Ohmeda, Helsinki, Finland) of the unit. The trend curves consisted of all hemodynamic data, temperatures, urine output, Glasgow Coma Scale (GCS), blood gases, arterial lactate, pulse oximetry readings and infusions rates of vasoactive drugs. Continuously measured variables were stored in the database as two-minute median values and other variables were stored as often as they were measured. The nursing staff performed hourly controls of patient status. These included cardiac filling pressures, cardiac output, urine output and GCS and they were stored in the data management system as well. Laboratory tests were taken when clinically indicated. Treatment recordings consisted of vasoactive therapy and other medication, as well as of volumes of infusions of crystalloids, colloids and blood products given. The dosages of vasoactive treatment were calculated as far as they were necessary for SOFA scoring. A combination medication could be administered simultaneously or in sequence. Dobutamine or dopamine were used as inotropes and as other sympathomimetic drugs norepinephrine or epinephrine were used. Sodium nitroprusside or nitroglycerin were used as vasodilators. For the purpose of describing patient characteristics, patients were divided into 6 diagnostic categories based on the immediate cause of admission: cardiovascular, respiratory, infection, trauma, cardiac arrest and others. These categories are used in our ICU with the exception that trauma and surgical patients were put into the same group. Patients were considered to have sepsis if at least two of the following were present simultaneously: body temperature $> 38^\circ C$ or $< 36^\circ C$, heart rate > 90 beat/min, respiratory rate > 20 breaths/min or $p_aCO_2 < 4.3$ kPa, WBC $> 12,000$ cells/ mm^3 or $> 10\%$ immature forms and a known source of infection (Bone, et al. 1992a). In all cases either a positive microbial culture or obvious source of infection was identified. The later course of the ICU-care and possible development of MOF of each patient were characterised with daily SOFA-scores. SOFA-scores were calculated using the published threshold values and using the available

laboratory tests and CIMS (Vincent, et al. 1996). If adjacent values were present, the missing value was interpolated. If more than one value was missing, they were not interpolated and were scored as missing and giving 0 points. This process of interpolation was necessary only for bilirubin values. If more than one value was available for the particular day, the worst i.e. the most points giving value was chosen. In order to describe the involvement and severity of different organ failures, the total maximal SOFA-score (TMS-score) was calculated. This was done by summing the maximum scores of each 6 organ systems during the whole ICU-period. The theoretical maximum of TMS-score is thus 24. In order to describe the evolution of MOF, an extra variable, time to peak-TMS was determined as the ICU-day during which the TMS-score reached its maximum.

4.4.3 The effect of sampling rate on the severity scores (Study III)

Two regimes of sampling of laboratory values and of monitored values contained in the severity scores were followed. The first set of laboratory tests was collected taking the needed tests by the time of admission and thereafter only when prescribed by the clinical staff. In addition the laboratory tests were collected at two hours intervals for the first 24 hours or until earlier discharge or death of the patient. Monitored values of hemodynamic and respiratory status as well as of temperature were recorded in two different ways. First, all monitored variables needed for the severity score calculation were manually stored into the database of the ICU at one hour intervals by the attending nurse, simulating a traditional manual record keeping. Simultaneously, a second set of data was collected automatically with the CIMS as two-minute median values. Using the obtained values, three sets of APACHE II and SAPS II scores were calculated. Manually collected hemodynamic data and clinically indicated laboratory data were used to calculate traditional severity scores ($APACHE_{TRAD}$ and $SAPS_{TRAD}$). Automatically collected monitor data and clinically indicated laboratory data were used to calculate a set of severity scores describing the effect of CIMS ($APACHE_{CIMS}$ and $SAPS_{CIMS}$). A high sampling rate data was collected when automatically collected monitor data and laboratory values on 2 hours intervals were used ($APACHE_{HIGH}$ and $SAPS_{HIGH}$). SAPS II and APACHE II scores were used to calculate the risk of hospital death according to the original formulae. For the calculation of the risks of

hospital death, 2 patients with burn injuries and 3 coronary surgery patients were excluded because no diagnostic category weight is determined. One of these patients died.

4.4.4 The effect of prolonged ICU stay on the mortality prediction using severity scores (Study IV)

4.4.4.1 Data collection

ICUs in nine central hospitals in Finland started the “Finnish Consortium of Intensive Care Data” by collecting data for Acute Physiology and Chronic Health Evaluation II (APACHE II) and Simplified Acute Physiologic Score II (SAPS II) calculations in the year 1994. For the study, data of the years from 1994 to 1999 was used and during that time the number of participating units increased to 13. The practice of data collection was standardised and advised before the start of the process and at least once a year thereafter in collaborative meetings. Data was collected by a trained nurse or a physician. Data for Therapeutic Intervention Scoring System (TISS) was also collected and used as a sum of each ICU admission to reflect the consumption of ICU-resources. In the years 1994 and 1995 the most deranged values for the score calculations were picked up by the responsible doctors in each unit. Starting 1996, both the highest and the lowest value of each variable were recorded and the most points giving values picked up automatically by a tailor-made computer program. In 1994-1996 data were entered to the database manually by three specially trained assistants who checked the forms for major errors. In 1997-1998 optical character recognition and centralised computerised error checking were performed, and in 1999 computerised checks for major errors were done during the data entry procedure. The study database was formed after exclusion of patients under the age of 18, patients admitted for observation only as well as re-admissions and coronary surgery patients. Data of 1036 admissions were missing or not complete. From 30333 admissions collected, 23953 formed the study population.

4.4.4.2 Customisation of the APACHE II and SAPS II prediction models

The performance of the risk calculations of hospital death with the published formulae was tested: Risk calculations with the original formulae (Knaus, et al. 1985, Le Gall, et al. 1993):

$$\text{APACHE II: } R/(1-R) = e^{-3,517 + (\text{APACHE II} * 0.146) + 0.603 (\text{if emergency surgery}) + \text{diagnostic category weight}}$$

$$\text{SAPS II: } R/(1-R) = e^{-7,7631 + (0.0737 * \text{SAPS II}) + 0.9971 * \ln(\text{SAPS} + 1)}$$

R = Risk of hospital death

Performance of these original scores was not satisfactory and therefore a customisation process was undertaken. This was done by dividing the study population randomly into two equally sized halves, a calibration data set of 12064 admissions and a validation data set of 11889 admissions. Random division was performed with the SPSS-statistical program. The only difference between the calibration and validation data set was the slightly higher mean age of men in the validation data set. Logistic regression analysis was performed in the calibration data by using hospital death as the outcome variable. For the customised APACHE model, APACHE II score, diagnostic category weight as originally published by Knaus (Knaus, et al. 1985a) and emergency operative status were entered simultaneously as independent variables. For the customisation of the SAPS model, SAPS II score and the $\ln(\text{SAPS} + 1)$ variable were entered. The logistic regression analysis resulted in correction factors for all the independent variables and using these new coefficients, new formulae for the calculation of the risk of hospital death were formed.

Customised APACHE model:

$$R/(1-R) = e^{-4.0032 + (\text{APACHE II} * 0.1483) + (0.0143 \text{ if emergency surgery}) + (0.6792 * \text{diagnostic category weight})}$$

Customised SAPS model:

$$R/(1-R) = e^{-4.5051 + (0.0817 * \text{SAPS II}) - 0.0183 * \ln(\text{SAPS} + 1)}$$

These formulae were used for the calculation of risk of hospital death in the validation data set.

5 STATISTICAL METHODS

5.1 Data presentation and statistical tests

Data are presented as mean \pm SD or as median with IQR (inter quartile range) depending on the distribution characteristics of the data. Logarithmic or square root transformations of the data were performed if it was necessary to get the data normally distributed for the analyses. Data were analysed with T-test or with Mann-Whitney test, according to the distribution characteristic of data. Data in 2x2 and 2x3 tables were analysed with chi-square test and Yates correction was applied if appropriate. Per cent distributions between two groups were analysed with Fisher's-exact test. Standardised mortality ratio (SMR) was calculated by dividing the number of observed deaths by the number of expected deaths. The number of expected deaths was calculated by summing the probabilities of death. Confidence intervals of the SMR were calculated using the proposed methods (Gardner and Altman 1989).

5.2 Special statistical considerations.

Study I

The L/P-ratio values refer to the concurrent L/P-ratio values coinciding with the peak lactate values. A univariate logistic regression model was used to calculate the odds ratio for hospital death comparing hyperlactatemic and subgroups of hyperlactatemic patients with normolactatemic patients. The risk coefficients are reported with 95% confidence intervals and p-values.

Study III

The contribution of the variables to the changes of the scores between high and low sampling rate was calculated by relating the change of the score of every variable to the total change of the score and separately to the hemodynamic or laboratory scores.

Study IV

The calibration of the prediction models was tested using Hosmer-Lemeshow goodness-of-fit procedure. The H* statistics was calculated by dividing the admissions into 10 deciles according to increasing risk of death. The chi-square statistics was determined for each decile and summing the 10 chi-square values resulted in H*. A high p-value (>0.05) indicates a good fit of the model.

The discrimination of the models was studied by Receiver Operating Characteristic (ROC)-curves and corresponding areas under the curves (AUC).

All statistical procedures were performed using SPSS 9.0 statistical package (SPSS Inc., Chicago, Illinois USA).

6 RESULTS

6.1 Lactate and L/P-ratio in emergency ICU-admissions

Thirty patients had circulatory shock: Hypovolemic shock was found in 8 patients, septic shock in 8 patients and cardiogenic shock in 14 patients. There were 31 neurosurgical patients and 37 patients in other diagnostic groups. Forty-eight patients (49%) had lactate values above the cut-off value of 2 mmol/L during the first ICU-day. Thirty-one patients had hyperlactatemia at the time of admission and 17 developed lactate elevations during the first day. In 16 patients the hyperlactatemia was accompanied with L/P-ratio elevation at some point during the observation period. The majority of patients with circulatory shock (76.7%) had hyperlactatemia at some time point and in 16 cases (53%) it was present at the time of admission. The patients with circulatory shock had in 8 cases (27% of all patients with circulatory shock) a simultaneously elevated lactate and L/P-ratio. In 8 out of 9 cases with lactic acidosis, the lactate elevation was accompanied with L/P-ratio elevation. The non-survivors had higher peak lactate values (5.3[1.9-7.5]mmol/L) than the survivors (1.9[1.3-2.9]mmol/L, $p=0.003$). If the admission hyperlactatemia persisted longer than 6 hours, the mortality was 36.8% in contrast to short lasting admission hyperlactatemia, which was not associated with mortality ($p=0.032$). Hyperlactatemia developing during the first ICU-day after admission was not associated with significant mortality (1 patient, 5.9%). The risk estimates of patterns of hyperlactatemia with and without L/P-ratio elevation compared to patients with normal lactate levels is presented in Table 6-1. The OR of lactic acidosis compared to patients with normal lactate was 31.3(CI95% 5.1-191.8, $p= 0.0002$) and LR+ was 11.1.

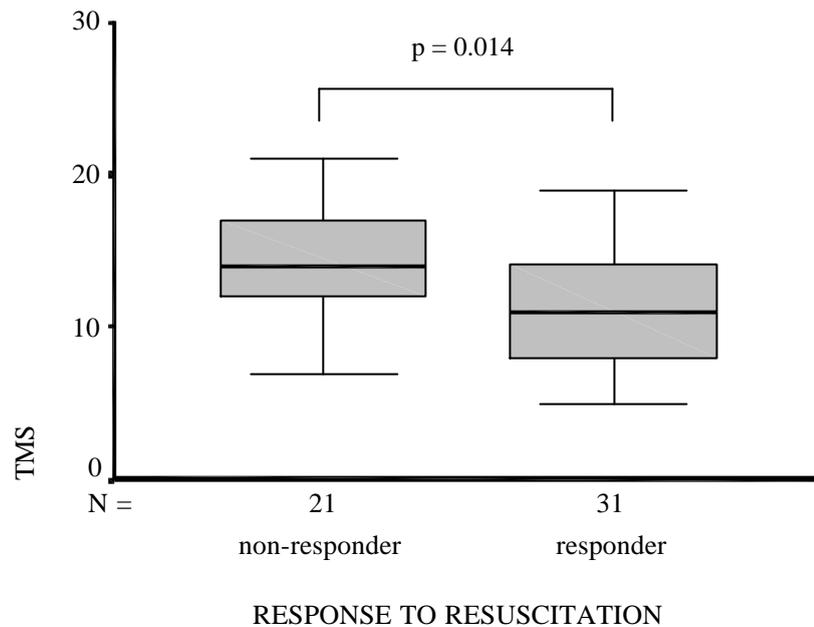
Table 6-1 The association of different patterns of lactate elevation with or without L/P-ratio elevation with mortality. Odds ratio and p-values refer to risk of dying of patients with lactate elevation with or without L/P-ratio elevation compared to patients with normal lactate. LR+ refers to subgroups of patients with hyperlactatemia compared to patients without lactate elevation for prediction of hospital death.

	Number /non-surv.	ODDs ratio (95% CI)	p-value	Mortality	LR+
Lactate > 2	48/13	4.1 (1.1-16.0)	0.04	13.3%	1.9
Admission hyperlactatemia persisting > 6 hours	19/7	13.4 (2.5-73.1)	0.003	36.8%	3.6
Lactate >2 and L/P-ratio > 18	16/6	9.4 (2.0-44.0)	0.003	37.3%	3.8

6.2 Results of the acute circulatory failure study

ICU mortality of the study group was 33.7% (28 out of 83) and hospital mortality 39.8% (33 out of 83). Fifty-two patients (63%) responded to the treatment and the signs of perfusion failure subsided during the first 24 hours, while 31 patients (37%) were non-responders with a persisting circulatory failure. There was no difference in APACHE II scores between these groups ($p = 0.1$). The ICU-LOS of responders and non-responders were equal ($p = 0.38$). There was a trend towards higher hospital mortality of the non-responders compared to the responders (55% vs. 33%, $p = 0.07$, LR+ 1.6). The only hemodynamic measure with significance in terms of resuscitation outcome or mortality was the mean arterial pressure at 24 hours after admission and it was higher in responders than in non-responders. The variables measured with PA-catheter were not associated with the resolution of perfusion failure. DO2I did not differ between responders and non-responders or between survivors and non-survivors. The non-responders received more crystalloids (3254ml[1300-7096] vs. 1489[383-2992], $p = 0.0006$) and colloids (950ml[475-1900] vs. 475ml[202-950], $p = 0.001$) than the responders, respectively. TMS-scores of the non-responders (12[9-16]) were higher than of the responders (10[7-12], $p=0.019$) and the difference was enhanced if only patients with ICU-LOS > 2 days were considered (Figure 6-1).

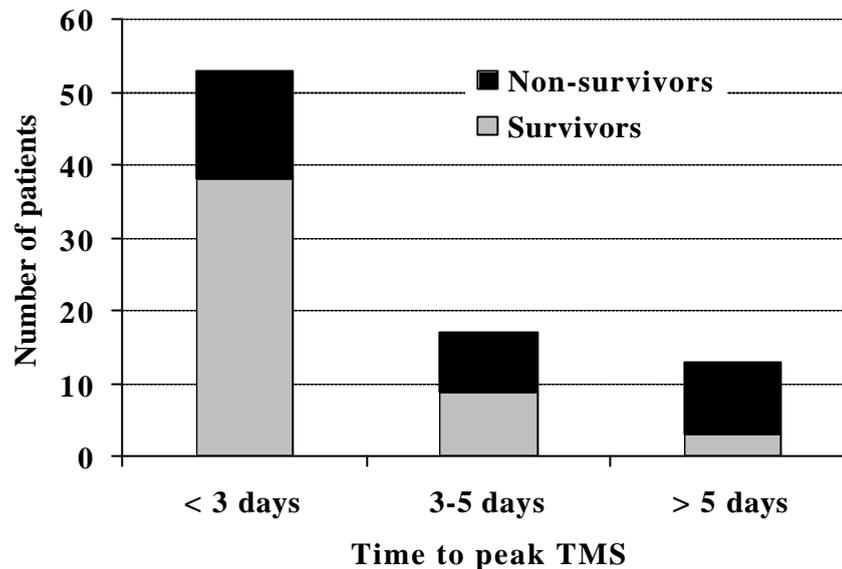
Figure 6-1 The development of MOF as described with TMS-scores in responders and non-responders of the resuscitation from acute circulatory failure. Only patients with ICU-LOS > 2 days are included. p-value refers to Mann-Whitney U-test.



The responders had lower daily SOFA-scores on days 1 ($p = 0.006$), 2 ($p < 0.001$) and 3 ($p = 0.001$) than the non-responders but not later on. In order to find remote organ failures, emerged as a consequence of the circulatory failure, TMS scores were calculated without the inclusion of circulatory failure points. TMS-scores without circulatory failure were higher in the non-responders (9[8-12]) than in the responders (8[6-10], $p = 0.014$). TMS-scores of the non-survivors were higher (13.0 [11-17]) than of the survivors (8.0 [7-12], $p < 0.001$). Hospital mortality of patients with TMS-scores ≤ 5 , 6 - 10, 11 - 15 and > 15 were 0%, 27%, 45% and 79%, respectively. TMS-score without circulatory failure of the non-survivors (10[9-13]) was higher than of the survivors (7[6-9], $p < 0.001$). The organ specific components of TMS- score were analysed separately. Points of coagulation (2[1-3] vs. 3[2-4], $p = 0.02$), central nervous system (1[0-2] vs. 3[3-4], $p < 0.001$), renal (1[0-2] vs. 2[2-3], $p = 0.04$) and cardiovascular function (2[1-3] vs. 3[3-4], $p = 0.005$) were different between the survivors and the non-survivors, respectively.

There were no differences in respiratory and liver points between the survivors and the non-survivors. Mortality increased with time from admission to peak-TMS (Figure 6-2).

Figure 6-2 The effect of the time to reach the peak TMS on mortality.



$p = 0.005$ for a difference in mortality between groups, Chi square-test.

When the time to peak-TMS was less than 3 days, the mortality was 28% and when the time to peak-TMS was 3 – 5 days, the mortality was 47%. In patients with the time to peak-TMS over 5 days, only 3 out of 13 patients were discharged alive from the hospital. Daily SOFA-scores of the non-survivors were higher than the scores of the survivors on days 1 ($p < 0.001$), 2 ($p > 0.001$) and 3 ($p = 0.001$). Later on there was no difference in SOFA-scores between survivors and non-survivors. The non-survivors had higher APACHE II scores (27[24-31] than the survivors (21[17-26], $p < 0.001$).

6.3 Results of the sampling-rate study

The APACHE II and SAPS II scores increased stepwise as sampling rate was elevated. The APACHE II score changed from 15.3 +/- 7.8 to 16.5 +/- 7.9 (+7.8%, $p < 0.001$) if CIMS was used for collection of continuously measured variables and further to 17.5 +/- 8.3 (+14.4%, $p < 0.001$) if also laboratory data was collected in 2 hours intervals. The SAPS II scored increased from 35.0 +/-

16.6 to 39.1 \pm 17.8 (+11.5%, $p < 0.001$) by applying high-resolution data collection with CIMS and to 40.5 \pm 18.6 (+14.5%, $p < 0.001$) when also laboratory data was collected with elevated resolution. The relative contribution of the variables of the severity scores to the maximum effect of increase in sampling rate is presented in Table 6-2.

Table 6-2 The relative contribution of the variables of the severity scores to difference between traditional and high sampling rate of data collection.

		APACHE II	SAPS II
Hemodynamic and respiratory variables	Heart rate	35.2 %	29.6 %
	Blood pressure	56.2 %	70.4 %
	Temperature	1.0 %	0.0 %
	Respiratory rate	7.6 %	
	Contribution to the total difference	55 %	75 %
Laboratory variables	Oxygenation	21.5 %	52.1 %
	Leukocytes	18.5 %	16.4 %
	Renal function	4.6 %	9.6 %
	Potassium	15.4 %	17.8 %
	Sodium	0.0 %	4.1 %
	pH/HCO ₃	7.7 %	0.0 %
	Hematocrit	32.3 %	
	Contribution to the total difference	45 %	25 %

The risk of hospital death calculated from APACHE_{TRAD} and APACHE_{HIGH} was 0.21 ± 0.22 and 0.25 ± 0.25 , respectively (difference 19.5%, $p < 0.001$). The risk of hospital death calculated from SAPS_{TRAD} and SAPS_{HIGH} was 0.23 ± 0.24 and 0.31 ± 0.28 , respectively (difference 34.8%, $p < 0.001$). Because eight patients died in hospital, the SMR decreased from 0.60 (CI95% 0.25-1.18) to 0.50 (CI95% 0.21-0.99) when APACHE_{HIGH} values were used instead of APACHE_{TRAD} values and from 0.53 (CI95% 0.23-1.07) to 0.41 (CI95% 0.17-0.81) when using the SAPS_{HIGH} values instead of the SAPS_{TRAD} values. Because of the small number of patients in the study, the differences of SMR were not significant.

6.4 Results of the APACHE and SAPS models in patients with prolonged ICU-LOS

The resource utilisation of the validation population is presented in Table 6-3. Patients with ICU-LOS over 7 days were 11% in number but consumed 56.2% of ICU-days and collected 51.7% of all TISS-points. Performance of the recalibrated prediction models is presented in Table 6-4 and Figure 6-3.

As the ICU-LOS increased up to 7 days, the prediction models lost their predictive power. Fifty-two per cent of all deaths occurred in patients who stayed in the ICU less than 2 days (Figure 6-4).

Table 6-3 Resource utilization and outcome of the predictive models according to the length of ICU stay (ICU-LOS) in the validation database.

	ICU-LOS (days)					
	All	≤1	>1, ≤2	>2, ≤3	>3, ≤7	> 7
Number of admissions	11889	4639	2784	1264	1890	1312
Resource utilisation						
Per cent of admissions	100	39.0	23.4	10.6	15.9	11.0
Per cent of ICU-days	100	7.4	10.4	7.9	21.6	52.6
Per cent of TISS-points	100	9.9	10.5	7.4	20.6	51.7
Outcome						
Number of non-survivors	2356	813	423	243	419	458
Hospital mortality %	19.8	17.5	15.2	19.2	22.2	34.9

Table 6-4 Performance of the recalibrated prediction models in patients with varying ICU-LOS

	ICU-LOS (days)					
	All	≤1	>1, ≤2	>2, ≤3	>3, ≤7	> 7
APACHE model						
H* statistic	11.1	105.6	24.1	13.1	36.1	221.5
p-value, df 9	0.27	<0.001	0.004	0.158	<0.001	<0.001
ROC-AUC	0.84	0.91	0.86	0.81	0.76	0.65
(95%CI of AUC)	(0.83-0.85)	(0.89-0.92)	(0.84-0.88)	(0.78-0.84)	(0.74-0.79)	(0.61-0.68)
SAPS model						
H* statistic ^b	8.9	112.7	30.6	6.8	41.6	306.3
p-value, df 9	0.447	<0.001	<0.001	0.658	<0.001	<0.001
ROC-AUC	0.83	0.91	0.85	0.79	0.74	0.62
(95%CI of AUC)	(0.82-0.84)	(0.90-0.92)	(0.83-0.87)	(0.76-0.83)	(0.72-0.77)	(0.59-0.66)

Figure 6-3 Calibration curves of the customised APACHE (above) and SAPS (below) models in patients with varying ICU-LOS. The corresponding statistics of the curves is presented in table 6-4.

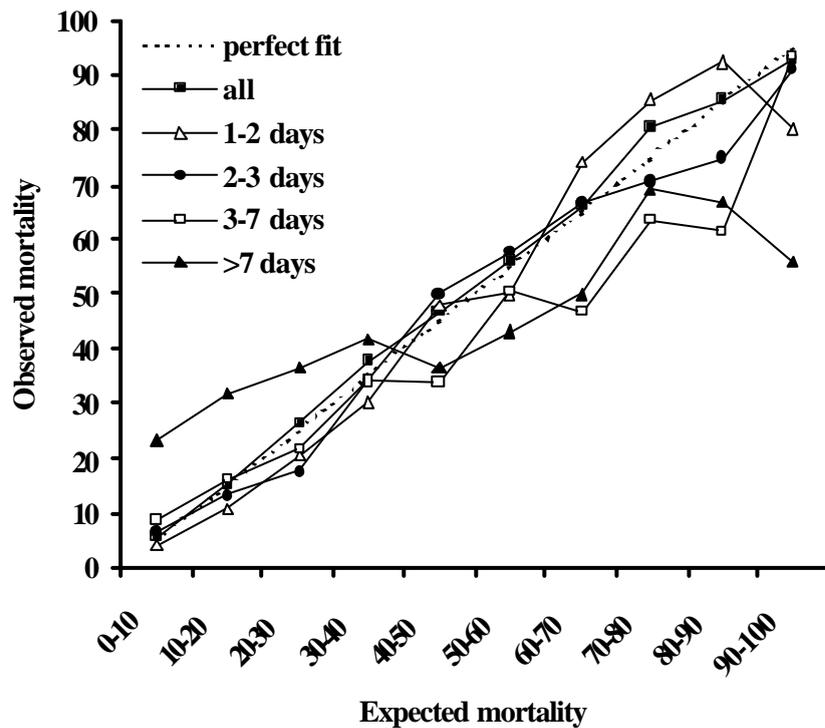
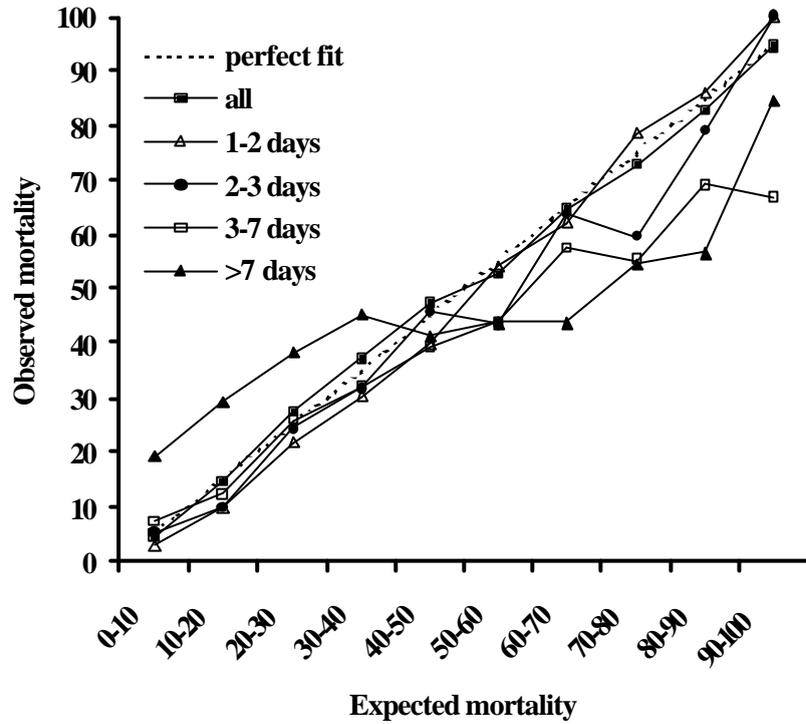
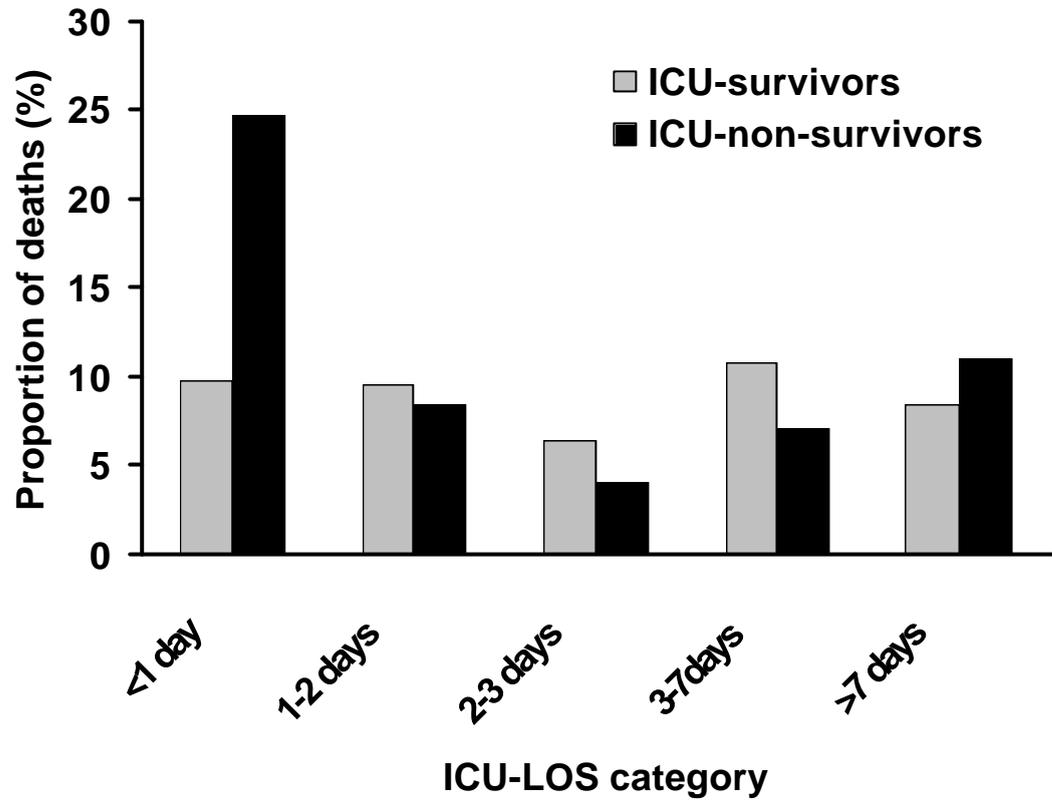


Figure 6-4 The relative proportions of ICU and hospital deaths in patients with varying ICU-LOS



7 DISCUSSION

This study shows that lactate elevation is often caused by circulatory failure and that rapid resolution of hyperlactatemia is associated with more favourable outcome than long persisting hyperlactatemia. Hyperlactatemia with simultaneous L/P-ratio elevation is often seen in patients with serious circulatory impairment and these patients have often a lactic acidosis as well. Success of resuscitation from acute circulatory failure is not associated with any circulatory pattern obtainable with pulmonary artery catheter. Failed resuscitation from acute circulatory failure in 24 hours is associated with increased risk of MOF as reflected in TMS-scores. Late worsening of MOF is associated with increased risk of death. The more organ failures are involved and the more severe the present organ failures are, the higher is the mortality. Increasing the sampling rate of data collection for the APACHE II and SAPS II scores results in higher scores and alters the outcome prediction. Mortality prediction models based on APACHE II and SAPS II scores are not reliable in patients with prolonged ICU stay even after recalibration to local patient population.

Circulatory failure is the main cause of lactate elevation. Other causes of lactate elevation, such as the use or endogenic production of epinephrine, respiratory alkalosis, diminished lactate clearance in acute liver failure and most importantly, lactate production induced by metabolic alterations in sepsis, are all associated with the acute phase of critically ill patients. The etiology of lactate elevation cannot be determined in detail in a clinical situation. In the study, sepsis was only rarely causing hyperlactatemia. In hypovolemic and cardiogenic shock, increased blood lactate concentrations can reflect anaerobic metabolism due to hypoperfusion, but the interpretation of blood lactate concentrations in septic patients is more complicated. Increased lactate concentration may result from cellular metabolic changes impairing the oxygen availability rather than from global hypoperfusion and in those circumstances increasing systemic oxygen delivery fails to normalise increased lactate concentrations (Gore, et al. 1996, Brealey, et al. 2002).

The rate of lactate clearance, despite of the etiology of hyperlactatemia, is of utmost importance to the outcome of the patients. If the admission hyperlactatemia lasted longer than 6 hours, the risk of death was markedly higher than in patients with normal lactate values. None of

the patients who could clear their lactate values in 6 hours died and only one patient with subsequent hyperlactatemia died. The hyperlactatemia developing during the first ICU day is often of low level and caused by metabolic changes induced by therapy. Because the neurosurgical patients had most often either cerebral trauma or subarachnoid bleeding, the applied hyperventilation might have triggered the moderate level lactate elevations (Druml, et al. 1991).

Hyperlactatemia was rarely (33% of all hyperlactatemic patients) associated with L/P-ratio elevation. There was no support for the assumption that increased L/P-ratio is more common in patients with circulatory failure (Hotchkiss and Karl 1992) because the share of patients in circulatory failure and with hyperlactatemia combined with L/P-ratio elevation was not different from patients without circulatory impairment. Though the addition of L/P-ratio to the lactate measurement increased the predictive power of lactate alone, simultaneously elevated L/P-ratio and lactate was overlapped by lactic acidosis and thus, its diagnostic value in daily practice is diminished by this. The patients with lactic acidosis were often severely sick and often had circulatory failure. Because of its difficult handling, L/P-ratio is prone to pre-analytical errors, which makes it an unpractical tool for everyday use.

Most studies on lactate have dealt with specific patient groups like trauma (Abramson, et al. 1993) and sepsis or septic shock (Tuchschmidt, et al. 1989, Bakker, et al. 1991, Bernardin, et al. 1996). Most studies have used sampling intervals determined by clinical practice or the clinical course of the patients (Bakker, et al. 1991) or timely fixed sampling times such as every 8 (Abramson, et al. 1993, Manikis, et al. 1995) or 24 hours (Bernardin, et al. 1996). Smaller intervals have been used only in brief studies (Vincent, et al. 1983). The applied approach of this study facilitated the description of the pattern of lactate and L/P-ratio in detail during the first day and also to detect hyperlactatemia developing after admission.

The normal range of lactate in healthy volunteers is considerably lower than the generally accepted threshold range of 2 – 2.5 mmol/L in critically ill patients. For this study the hyperlactatemia was considered to be present if lactate was over 2 mmol/L (Abramson, et al. 1993, Bakker, et al. 1996). The normal range of L/P-ratio is more complicated. The normal value of L/P-ratio has been set to a level of 10 since the times of Huckabee (Huckabee1958a) and we

found similar mean values in healthy volunteers. L/P-ratio has been shown to be in the range of 20 in patients with sepsis and around 40 in patients with cardiogenic shock (Levy, et al. 2000). The level of 10 is according to our results too low for intensive care patients and we used the level of 18 after it was determined in healthy volunteers.

Previous studies of the association of L/P-ratio with mortality have revealed contradicting results. Early studies of circulatory shock patients of various etiologies has showed that the power of lactate in predicting mortality was not significantly improved by adding L/P-ratio values to the discriminant function analysis (Weil and Afifi 1970). The ROC-AUC of L/P-ratio was slightly larger than that of lactate in predicting hospital outcome but the curves were not compared statistically with those of lactate alone in later studies (Levy, et al. 2000).

The present study showed that the successful resolution of circulatory failure defined as clearance of hyperlactatemia and/or metabolic acidosis is associated with lower risk of MOF. More severe and progressive MOF is associated with increased mortality. Manipulation of circulation is the cornerstone of patient care in the intensive care. Most acute problems in intensive care are directly resulting from impaired circulation or at least related to circulation as a facilitator of tissue oxygenation. Response to treatment in acute circulatory failure, defined as disappearance of hyperlactatemia or metabolic acidosis can be used as a measure of successful treatment. The definition of acute circulatory failure in our study attempted to identify a group of severely sick patients with a high risk of MOF and/or mortality. Previous study has shown that resolution of hyperlactatemia and/or metabolic acidosis is associated with favourable outcome (Abramson, et al. 1993, Sauaia, et al. 1994, Bakker, et al. 1996). Persistence of occult hypoperfusion defined as the presence of elevated lactate levels despite therapeutic efforts have been shown to be associated with respiratory complications, MOF and death (Blow, et al. 1999) as well as with infectious complications (Claridge, et al. 2000). The findings of our study are in agreement with previous studies showing that lactate clearance is not associated with any particular pattern of oxygen transport and cardiac performance (Levy, et al. 2000, Bernardin, et al. 1996). This study does not support the concept of supranormal oxygen delivery as a therapeutic

goal to improve mortality or to lower the risk of MOF (Tuchschmidt, et al. 1992, Yu, et al. 1993, Boyd, et al. 1993).

Grading of MOF with SOFA-scores and its sophistication, the TMS-score is suitable for clinical trials (Moreno, et al. 1999). The use of daily SOFA score might lead to underestimation of the cumulative failures. In TMS scores all organ failures ever present during the ICU-stay in question are included. TMS-scores are good predictors of ICU-outcome and the ROC-AUC has been shown to be above 0.8 in predicting death (Janssens, et al. 2000). Other studies have found that MODS-score and TMS-score are comparable in predicting hospital death (Pettilä, et al. 2002) and their basic idea is similar. TMS-score of 15 was associated with high mortality in the present study, which is in accordance with previous studies (Moreno, et al. 1999). Also the timing of accumulation pattern of MOF measured as the time-to peak TMS was related to mortality. If new organ failures appeared or present organ failures worsened after 5 days of care, the prognosis was poor. The present results are similar to those found by others (Moreno, et al. 1999, Janssens, et al. 2000). In the context of MOF-development it is of interest to look for remote organ failures from the initial event. The initiating event in our patients was the circulatory failure and with our definition all patients had some form of circulatory impairment on the first ICU-day. In order to concentrate on the remote organ failures, TMS-scores without cardiovascular points were calculated. A similar difference between responders and non-responders was found as with total TMS-scores and we can conclude that circulatory failure triggered the organ failures in remote organ systems.

MOF is the most important cause of prolonged ICU-stay. Because MOF patients consume large amounts of ICU resources, the prediction of outcome in this patient category is most warranted. Accurate prediction of poor outcome would spare the patient unnecessary suffering and the hospital wasted resources. Outcome prediction based on the severity scores starts with estimation of the severity of acute illness on the day of admission. The severity of acute illness together with host factors like admission diagnosis and age is transferred to a probability of death. Prediction of outcome can be biased if the score is inaccurate and does not correctly reflect the patients status or if the prediction model does not apply to all groups of patients equally. Modern

computer technology can save data with nearly unlimited resolution. If the daily measured continuous data is stored automatically at two-minute intervals, there are 720 measuring points compared to 24 measurements with the traditional rate of once per hour. The present results indicate that severity scores are subject to a substantial bias if the sampling rate is changed. The results are in accordance with those of Bosman (Bosman, et al. 1998). Adding to his results, the impact of increasing the sampling rate of laboratory tests could be estimated separately. High sampling resolution of computerised systems includes that all brief events including artefacts are also stored. One method of artefact elimination is median filtering, which was used in the technology applied in this study (Mäkivirta, et al. 1991). There is no agreement or standard on the extent or duration a measurement fluctuation should attain in order to be considered a relevant piece of information and not an artefact. The inter-observer variability in the study III was eliminated because all data were collected and analysed by the author. Great emphasis was put to control the inter-observer variability of data of the study IV. Data collection, definitions and interpretation of data were advised and discussed in detail at the start of the project and rehearsed thereafter in yearly collaborative meetings. This was especially necessary because of the length of the project.

Patients with prolonged stay form a special group of patients in different ways. Nearly one quarter of our patients in studies I and II stayed in the ICU for longer than 5 days. The association of MOF and mortality is well documented (Ferreira, et al 2001, Metniz, et al. 2001, Pettilä, et al. 2002c, Timsit, et al. 2002). The mortality of the patients with prolonged stay is most often related to the course of MOF and to host factors (Goins, et al. 1991). If the severity of acute illness and the course of MOF are controlled, the differences in outcome are then closely related to differences in factors related with organisation, management and quality of care. (Shortell, et al. 1994, Dimick, et al. 2001). Because the quality of provided care is important for the outcome during the prolonged treatment, the outcome of MOF-patients can be a marker of quality of care (Johnson and Mayers 2001). The mortality of patients with prolonged stay is higher than of other patient groups (Stricker, et al. 2003). These multiple factors can impair the performance of prediction models that are based on the data of the first ICU day. (Zhu, et al. 1996). The results of

our study showed that prediction models based on APACHE II and SAPS II scores of the first ICU day are not applicable in patients staying longer than 7 days in the ICU, though the models performed well in patients with short stay in the ICU. This finding is in accordance with previous studies (Sleigh, et al. 1992, Sicignano, et al. 1996). Similar results have been found in patients with perforated viscus (Barie, et al. 1996a). The weights of the severity scores have not been statistically analysed in relation to outcome after prolonged stay and actually most of the weights of the APACHE II scores were directly taken from the original APACHE (Knaus, et al. 1985a). Barie studied predictions of prolonged critical care in surgical patients and found that APACHE III score, emergency admission status and organ failures were independent predictors of prolonged stay (Barie, et al. 1996b). Only admission APACHE III score and organ failures were independently associated with mortality and the authors state that more weight should be given to parameters of organ failures in future predictive models. All non-survivors had MOF and the mean ICU-LOS was 12 days, which emphasises the role of MOF as the main cause of prolonged stay. Though the mortality of patients with short ICU stay is normally lower than of patients with long ICU stay, their high proportion means that majority of deaths occur to patients with short stay (Figure 6-5). The performance of prediction models was also satisfactory in these short-staying patients. It is noteworthy that 57 % of all deaths occurred to patients with a predictive risk of death of less than 50%. The predictive instruments in their present form cannot be used to predict death in a single patient. The outcome of patients after prolonged ICU care is the result of numerous factors. The severity of acute illness, as it is assessed with the severity scores, does not allow prediction of outcome. The present study indicates that outcome prediction of patients with prolonged ICU should include variables containing response to therapy and development of MOF. An important indicator of a positive response to therapeutic measures is the clearance of lactate.

The present study has some limitations. The small sample size and large number of patients with short ICU-LOS in the study I prevents a more rigorous presenting of data according to recommendations of using laboratory tests for outcome prediction. ROC-curves could have been presented to demonstrate the independent and combined predictive power of lactate and L/P-ratio for outcome prediction. In the study II, the most critical question is the possibility of a selection

bias, which can arise in post-hoc analysis. It can not be excluded that the selection method picked up patients with MOF already developing at the time of admission and that the later therapeutic interventions could not have been able to change the course of these patients. This is especially true for the patients with re-admissions to the ICU. An analysis of predictive factors using logistic models could have identified the independent predictors of mortality and MOF in more detail. However, in the early phase of ICU-care, it is not possible to distinguish an early MOF from other temporary organ dysfunctions.

8 CONCLUSIONS

On the basis of the present study following conclusions can be drawn.

- Lactate elevation in unselected emergency admission patients is common and it is often a sign of circulatory failure.
- Prolonged lactate clearance on the first ICU day is associated with increased risk for development of multiple organ failure and death.
- Addition of L/P-ratio to lactate measurement improves the predictive role of lactate measurement.
- Failure in the early resuscitation of circulatory failure increases the risk of MOF but the development and progression of MOF determines the final the outcome.
- General severity scores are subject to considerable bias if the sampling rate of the values for variables is changed.
- Mortality prediction models based on the first day severity scores cannot be used in patients with prolonged ICU-stay.

9 FUTURE IMPLICATIONS

The results of this study implicate that the variables of the severity scores should be tested for their correlation with the outcome after prolonged intensive care and if they prove not to have prognostic significance, other variables should be looked for. Arterial lactate and its evolution during the first ICU-day have proved to be a good predictor of outcome. Because of the difficulty in determining the exact phase of MOF, the severity scores can actually measure the severity of MOF. Severity of the acute disease can be mixed up with developing MOF, which results in errors of outcome prediction. Therapeutic efforts are sensitive to the phase of the disease process when they are applied (Rivers, et al. 2001). Logistic models can only include variables that are independent, linearly associated with the outcome and limited in number. New prediction models based on analysis of non-linear complex systems (Seely and Christou, 2000) and on neural networks (Dybowski, et al. 1996, Hanisch, et al. 1998) may result in improved outcome prediction also in patients with prolonged ICU-stay. These methods are able to handle the great amount of data that can be collected and that has value alone or in combinations with other variables for the outcome prediction.

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