CLINICAL STUDIES IN PATIENTS AT RISK FOR ARDS AND MOF

"WE HAVE MET THE ENEMY AND HE IS US."

...POGO

R.M.H. ROUMEN

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With emphasis on scoring systems, inflammatory mediators

and the role of the digestive tract.

RMH ROUMEN

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CLINICAL STUDIES IN PATIENTS

AT RISK FOR ARDS AND MOF

With emphasis on scoring systems, inflammatory mediators
and the role of the digestive tract.

Een wetenschappelijke proeve
op het gebied van de Medische Wetenschappen

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volgens besluit van het College van Decanen
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"We have found the enemy, and he is us"
(Pogo, Walt kelly, 1970)

In memory to my father

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GENERAL INTRODUCTION

Introduction

There is a lot of evidence indicating that Adult Respiratory Distress Syndrome (ARDS) and Multiple Organ Failure (MOF) are the result of one common pathophysiological pathway (1-3). Respiratory failure merely is the first organ failure apparent in the sequence of events leading to MOF and therefore is of special interest (4). The MOF syndrome was first recognised as an entity by Tilney et al. (1973), who described the post-operative course of patients with ruptured abdominal aortic aneurysms (5). Later Baue (1975) wrote a famous editorial on the syndrome of sequential and progressive failure of function of several organ systems, finally resulting in death (6). MOF has become the syndrome of the last decades. It actually is a consequence of the successful resuscitation of critically ill and severely traumatized patients with up to date intensive care treatment. In fact, in this way intensive care medicine has created its own disease (7).

From a historical point of view, every era has known its own medical limitations. Acute blood loss was the main cause of death in World War I. After prevention and treatment of this type of shock during the World War II and the late fifties, renal insufficiency appeared to be the major limiting factor for survival. During the Vietnam conflict increased administration of large amounts of crystalloids prevented acute renal failure, but now survival of patients was limited by the development of ARDS (the so called "Da Nung-lung"). Later in the seventies, when increasing numbers of patients survived ARDS - because of adequate mechanical ventilation with positive end expiratory pressure (PEEP) - the limiting problem was not a single organ failure anymore, but a complex of sequential organ failures: MOF (9,10).

ARDS and MOF are responsible for more than 70% of the ventilator days spent in the intensive care unit (ICU) (4,8). Today MOF represents the number 1 cause of death in a surgical ICU and is responsible for 50% to 80% of all surgical ICU deaths (9). The costs are estimated to exceed $ 150,000 per MOF patient in the USA.

Clinical presentation of ARDS and MOF

The sequence of events leading to ARDS and MOF is best illustrated by several extensive clinical case reports.

Case 1

Patient P was a 48-year-old man, who was admitted to another hospital, because of acute abdominal discomfort and severe shock (systolic blood pressure 80 mmHg and pulse rate 140/minute). Since one day he had developed jaundice and had produced dark coloured urine and discoloured stools. Blood analysis showed a marked hyperamylasemia and hypocalcemia. Severe acute pancreatitis was diagnosed and because of respiratory failure and renal insufficiency the patient was transferred to our hospital.

An explorative laparotomy was performed: a severe hemorrhagic necrotizing pancreatitis was present throughout the whole pancreas; the retroperitoneal space was extensively infiltrated from the diaphragm into the pelvis and a high number of calcium deposits were found intra-abdominally. The galbladder was filled with stones and sludge. A cholecystectomy and additional choledochotomy with drainage were carried out.

On admission to the ICU, the man was hemodynamically stable with no need for vaso-active agents. Mechanical ventilation was continued with a FiO_2 of 50% and 6 cm H_2O PEEP, resulting in normal blood gasses. Urine production was about 30 ml/hour. The third day a second look operation was performed and necrotic tissue was removed. Bacterial cultures of material taken during the first operation were negative, while necrosis of the second laparotomy appeared to be infected with Escherichia coli. Over the next days the patient developed a progressive renal failure (creatinine > 600 μmol/l and BUN > 50 mmol/l) and hemodialysis was necessary.

On day 6 the pulmonary function deteriorated further: with an FiO_2 of 60% and 10 cm H_2O PEEP the PaO_2 was only 8.6 kPa. A chest X-ray showed diffuse bilateral patchy infiltrates and ARDS was diagnosed. In this period increasing amounts of Dopamine[R] were necessary to maintain an adequate systolic blood pressure. Meanwhile, from day 1 to 4, the patient's positive fluid balance had exceeded 10 liters, while central venous pressure was normal. The patient had developed a generalized edema and his central body temperature varied from 36.8°C to 39.2°C. After the first operation the initially raised bilirubin levels -due to biliary obstruction- had decreased. From day 5 however, bilirubin levels started to increase again together with transaminases. Jaundice was present. During the whole ICU admission the patient was on total parenteral nutrition. At day 5 a hemorrhagic gastritis was diagnosed. On days 8 and 10, respectively, a third and fourth laparotomy for removal of necrotic tissue were performed. From day 5 on several blood cultures grew E.coli, as well as Pseudomonas species.

In the seond week the patient further deteriorated with diminished cerebral responsiveness and increasing cardiovascular instability. Platelet count was decreasing (at day 12 below 30,000 x 10^9/l) and the initial leukocytosis (21,400 x 10^9/l) changed into a leukopenia at day 12: 2,100 x 10^9/l. At day 16 the man had several arhythmic episodes and bradycardia with persisting low systolic blood presurres. Cerebral responsiveness was further diminished and his pupils were anisocoric and showed only a slight reaction to light. At day 17 the patient died of irreversible shock. Permission for post mortem examination was not obtained.

Case 2 (11)

Patient T was an 18-year-old man, who was hit by a car when riding his bicycle. He was admitted to another hospital in severe shock (systolic blood pressure < 70 mmHg). A left-sided tension hemopneumothorax and 6 fractured ribs were diagnosed, together with a hemoperitoneum, an unstable pelvic fracture and a fracture of the left scapula. Blood loss through a thoracostomy tube was so extensive that a thoracotomy had to be performed for hemostasis. Explorative laparotomy revealed a laceration of the inferior mesenteric artery and an extensive retroperitoneal hematoma. The artery was ligated and no significant ischemia of the large bowel resulted. The blood pressure returned to normal and an adequate diuresis followed. Seven liters of blood were administered during the first 24 hours.

Subsequently the patient was carefully observed, while breathing spontaneously. Two days later, however, the man developed progressive pulmonary insufficiency requiring mechanical ventilation. Because of this the patient was transferred to our hospital. On admission, a left-sided pneumothorax was relieved by a new thoracostomy tube. Because of hemodynamic instability a second laparotomy was performed and the spleen was removed because of a ruptured subcapsular hemotoma. Complete inspection of the abdomen revealed no further abnormalities. The displaced pelvic fracture was then reduced by suspension in a hammock sling and traction to one leg. After admission to the ICU, mechanical ventilation with FiO_2 of 100% and 20 cm H_2O PEEP was necessary to obtain a PaO_2 of 8.0 kPa. Intravenous hyperalimentation was started. During the following 5 days, FiO_2 could progressively be diminished to 40% and PEEP to 12 cm H_2O. The platelet count remained below 50,000 x 10^9/l during the next 7 days. From then on the leukocyte count slowly increased from 12,000 x 10^9/l to 70,000 x 10^9/l. Central body temperatures were between 37.2°C and 39.8°C.

At day 10, bacterial cultures of sputum grew E.coli, which was also cultured in the urine at day 12. Pus from an infected maxillary sinus also contained E.coli. Weaning

from the ventilator was not possible. In the third and fourth week sputum cultures revealed multi-resistent E.coli, together with Klebsiella pneumoniae and Pseudomonas aeruginosa. Blood cultures remained negative until day 42, when Staphylococcus epidermidis was cultured. Extensive pulmonary fibrosis resulted in hypertension with cardiopulmonary failure, not responding to treatment with digitalis. Progressive renal failure developed at the end of week 3, necessitating hemodialysis. Jaundice developed with increasing levels of bilirubine and transaminases. At 7 weeks a tender mass could be felt in the right subcostal area, and acalculous cholecystitis was confirmed ultrasonographically. Other disorders found in the patient included spontaneous hemorrhage from the rectum, lungs, trachea, nose and ears, requiring blood transfusions, bilateral otitis media needing paracentesis, ulceration and spontaneous perforation of the cornea, despite adequate local care and extensive herpes zoster. Because of the "destroyed lung" operation for the acalculous cholecystitis was not performed and the patient subsequently died 58 days after the injury.

At post mortem examination, there was extensive consolidation of both lungs, which weigthed 1200 g and 990 g. The kidneys were large and swollen. The liver weigth was 2580 g. An acute phlegmonous necrotizing cholecystitis was present with recent perforation and biliary peritonitis. A bile trombus was present in the cystic duct. The major intra- and extra-hepatic bile ducts were patent and of normal calibre. Microscopy of the liver demonstrated biliary stasis, mainly with pericentral localization. Multiple petechiae were seen in the gastric mucosa, the bladder mucosa and subepicardially.

Case 3

Patient A was a 74 year old man, who was seen at the emergency department, because of acute abdominal tenderness and moderate shock (systolic blood pressure 90 mmHg and pulse rate 120/minute). Analysis of blood taken on admission showed a lactate concentration of 6800 μmol/l, hemoglobine concentration of 6.5 mmol/l, creatinin 130 μmol/l, platelet count of 187 x 10^9/l, leukocyte count of 22,800 x 10^9/l, with the following arterial blood gas analysis: PO_2 12.2 kPa, PCO_2 4.1 kPa, pH 7.35, HCO_3^- 16.8 mmol/l and base excess - 7.0 mmol/l.

A ruptured abdominal aortic aneurysm was diagnosed and an emergency laparotomy was carried out without delay. The aorta was cross-clamped infrarenally and the aneurysm was repaired with an inlay graft. The whole operation took 145 minutes and total blood loss was 4.5 liters. By use of a cell saver, 1000 ml of homologous blood could be returned to the patient, together with 8 units of autologous blood.

The post-operative course was complicated by an insufficient arterial blood supply to

both legs. Therefore a bilateral arterial embolectomy had to be performed, three hours after the initial operation. The peripheral circulation could be restored adequately and a four compartment fasciotomy was carried out bilaterally to prevent compartment syndromes. During this procedure, two more units of packed cells were transfused.

On admission to the ICU the patient was hemodynamically stable, with a systolic blood pressure of 170 mmHg, pulse rate of 100/minute and central venous pressure of 5 cm H_2O, with intravenous Dopamin^R administration in renal dosage. Central core temperature was 32,3°C. At that moment urine production was more than 200 ml/hour. Mechanical ventilation was performed with FiO_2 of 40% and 2 cm H_2O PEEP, resulting in a PaO_2 of 15.0 kPa. Over the next few hours urine production diminished and 24 hours postoperatively the patient was practically anuric (urine production less than 5 ml/hour), probably due to acute tubular necrosis.

At day 2, the use of vasopressor agents had to be increased to maintain the systolic blood pressure between 130 and 140 mmHg; central venous pressure was normal (10 cm H_2O), but the pulmonary condition deteriorated: with a FiO_2 of 55% and 8 cm H_2O PEEP, PaO_2 was only 8.2 kPa. A chest X-ray showed bilateral patchy infiltrates, features compatible with the diagnosis ARDS. From days 1 to 4 the patient's positive fluid balance exceeded 12 liters and generalized edema was present. Because serum creatinin rose above 400 μmol/l and BUN above 24 mmol/l hemodialysis was started. Bacteriologic cultures of blood, sputum and urine did not reveal any microorganism. Except for the prophylactic use of a cephalosporin peri-operatively, no other antibiotic drug was used at that time.

The patient's condition remained unchanged until day 9. Cultures of sputum showed Serratia marcescens and ß-hemolytic streptococci. At day 10, a blood culture grew S. marcescens and antibiotic treatment was started. At day 14 a wound abscess was diagnosed and drainage performed (cultures: S. marcescens). These two weeks central body temperature remained below 38°C. Meanwhile the leukocyte count rose progressively from 12,000 to above 24,000 x 10^9/l and bilirubin levels rose above 200 μmol/l. Clinical jaundice was present.

At day 19 the patient had several episodes of bradycardia, while cardiac output was over 8 l/minute (cardiac index > 4,0). At that day a relaparotomy was performed for the search of a "septic" focus. Because of acalculous cholecystitis a cholecystectomy had to be performed. Postoperatively the patient seemed more stable, the use of vasopressive agents could be diminished and no episodes of bradycardia occured. At day 23, because of the suspicion of a renewed intra-abdominal sepsis, a second relaparotomy was carried out. However, the operation did not reveal any abnormal

infectious focus. Up to this period S. marcescens grew in all cultures, while at day 23 P. aeruginosa could also be cultured from the dialysis fluid.

Over the next days the patient deteriorated further, requiring maximal support of the cardiovascular system by various vasoactive medication, pulmonary support with mechanical ventilation (FiO_2 60%, 10 cm H_2O PEEP), renal support by dialysis, need of parenteral feeding because of gastro-intestinal failure with ileus, liver failure with jaundice, leukocytosis and trombopenia, and diminished cerebral responsiveness.

After consultation of the patient's family, it was decided not to resuscitate further. The patient subsequently succumbed at day 31. Post mortem autopsy was refused.

Comment

Although the three cases represent different etiologic entities (acute pancreatitis/inflammation, multiple trauma/extensive tissue injury, hemorrhagic shock/ischemia-reperfusion injury) all three ended in progressive failure of several organ systems.

In all three patients acute pulmonary failure played an early role. In two patients (P and A) acute renal failure was already present in the early stage, while in patient T renal insufficiency developed in the third week.

During the first days these patients developed a marked positive fluid balance and had an appearance of total body edema. This was not caused by cardiac failure (normal venous pressures and high cardiac output), but probably by a generalized increased micro-vascular permeability.

Liver failure occured next, which was mainly indicated by the rising (unconjugated) bilirubin levels. Obviously, patient P presented with initial liver failure, due to obstruction of the biliary tract which also caused the pancreatitis, but after a tendency to normalize, a secondary liver failure appeared at the end of the first week.

All three patients also showed increasing cardiovascular instability, mainly expressed by the increasing need for vaso-active medication to maintain an adequate systolic blood pressure.

In all patients the function of the gastro-intestinal tract deteriorated, resulting in ileus and in the necessity of total parenteral nutrition. Patient P developed hemorrhagic gastritis and patients T and A acalculous cholecystitis.

The hematologic and clotting systems subsequently deteriorated, as indicated by the leukocytosis or leukopenia, trombopenia and general bleeding disorders (patient T). The impairment and dysregulation of the immunological functions is demonstrated by the various types of infections that developed. Logically, in patient P the necrotic

tissue was infected very rapidly. But in patients T and A bacteria could not be cultured from sputum, urine, blood or other body fluids before the beginning of the second week.

In general patients developing MOF frequently show dysregulation of the central and peripheral neurological functions, although it is difficult to evaluate these functions in sedated patients at an ICU. The Glasgow Coma Scale can be very helpfull in this respect (see apppendix).

In summary, the patients described above showed a progressive and sequential failure of seven organ systems, including the pulmonary, renal, cardiovascular, hepatic, gastro-intestinal, hematologic-immunologic, and neurological system with the clinical signs of generalized inflammation i.e. 'rubor' (generalized vasodilatation), 'calor' (fever), 'tumor' (generalized edema), and 'functio laesa' (MOF). Based on these observations Goris et al. developed the MOF score to grade the severity of organ failure (12) (see appendix).

It should be noticed that, although the systemic responses are similar among patients developing MOF, the exact sequence of organ failures can be influenced by the patient's acute disease process or physiological reserve (9).

Incidence and severity grading of ARDS and MOF.

Data on the incidence of ARDS and MOF and of their respective mortality are confusing. This is mainly caused by the use of different definitions of ARDS and MOF and the wide range of patient populations studied. Patient populations generally known to be at risk for development of ARDS and MOF are: patients with sepsis (infection - septic shock), with multiple trauma or extensive burn wounds, after major elective surgery, with severe pancreatitis, or with hemorrhagic shock, such as due to ruptured aneurysms or with ongoing blood loss needing multiple blood transfusions. Within these different patient groups, the reported incidence of ARDS and MOF may vary from 5% in trauma patients to 65% in septic patients (13,14).

The relationship between MOF and mortality can be illustrated by studying the number of organs that have failed. Mortality of a single organ failure has been reported to vary from 16 - 40%, two organ failures 57 - 60%, three organ failures 80 - 85% and four or more organ failures 88 - 100% (12-15), while the length of time a patient suffered from organ failure has also been demonstrated to correlate with mortality (15). To compare different reports and studies on ARDS and MOF consensus about

the definition of these syndromes is necessary.

Since Ashbaugh and coworkers in 1967 described the first patients with this type of acute pulmonary failure (16) this entity has been recognized throughout the world (16-18). Yet, there still exists controversy concerning a satisfactory definition of this syndrome. In general it has been called ARDS or "acute respiratory failure due to non-cardiogenic pulmonary edema" (16). Recently, it has been proposed to rename it to "Acute Lung Injury" (19).

Current definitions rely mostly on the following features:

1.   Hypoxemia, measured either by the PaO2 / FiO$_2$ ratio or by the alveolar -arterial oxygen quotient, and the necessity for PEEP ventilation to maintain an acceptable PaO$_2$,

2.   Diffuse bilateral röntgenographic infiltrates on the chest X-rays,

3.   Decreased pulmonary compliance (though almost never measured),

4.   Normal pulmonary capillary wedge presssure (values vary from less than 12 mm Hg to less than 18 mm Hg),

5.   Pulmonary shunting (shunt fraction higher than 15% or 20%), and

6.   A clinical condition associated with the risk for development of ARDS.

Other definitions use the necessity of mechanical ventilation for more than a certain number of days and grade the intensity of ventilatory support by using various PaO$_2$ / FiO$_2$ / PEEP indexes (3,16,20,21).

MOF has been defined as a syndrome consisting of the sequential failure of two or more organ systems in patients with clinical signs of "sepsis" (10). Originally, the term sepsis implied the systemic, clinical response arising from infection. Confusion developed when the term was also used for patients with this clinical syndrome, but without clear signs of infection or bacterial invasion. An additional source of confusion was the use of various other terms, such as bacteremia, septicemia, septic syndrome, septic shock. Recently, a consensus conference held by the American College of Chest Physicians and Society of Critical Care Medicine proposed the use of the term Systemic Inflammatory Response Syndrome (SIRS) to describe the inflammatory reaction of the organism, independent of its cause (22). It would therefore be better to decribe MOF as a frequent complication and late consequence of SIRS.

The organ systems involved in definitions of MOF are usually the ventilatory (ARDS), cardiovascular, renal, hepatic, gastro-intestinal, coagulation, hematological, immune, central nervous, metabolic and musculoskeletal systems. The grading of severity of

these organ failures varies in the same way as outlined before for ARDS. Many scoring systems have been published to grade the severity of organ dysfunction, one sometimes being a slight modification of another.

The following is a list of parameters that are mostly used to grade the intensity of dysfunction of a specified organ system (2,9,12-14,23-37):

(for **ventilatory** system see ARDS),

Cardiovascular: systolic blood pressure or mean arterial pressure, pulse rate, cardiac output or cardiac index, cardiac filling pressure, decreased ejection fraction, arhythmias, use of vaso-active drugs, myocardial infarction, need for reanimation.

Renal: urine output, body urea nitrogen, serum creatinine, serum potassium, creatinine-clearance, effect of diuretics, requirement for dialysis, ultra- or hemofiltration.

Hepatic: rise of enzymes, such as alkaline phosphatase or transaminases, serum bilirubine, ketone body ratio, serum ammonia, serum albumin.

Gastro-intestinal: stress ulcer (by endoscopy or necessity of blood transfusion), ileus (gastric retention fluid or intolerance to enteral feeding), acalculous cholecystitis, pancreatitis, raise of serum or urine amylase, enterocolitis, bowel perforation, mesenteric vein trombosis.

Central nervous: polyneuropathy, pathological reflexes, mental state, progressive coma, Glasgow Coma Scale.

Coagulation: platelets, serum fibrinogen and fibrinogen split products, serum antitrombine III, clotting time, requirement of fresh frozen plasma, disseminated intravascular coagulation.

Hematologic: platelets, leukocytes, hematocrit, P50 (PO_2 when 50% of the hemoglobin is oxygenated).

Immunologic: B and T cell function, skin tests (delayed hypersensitivity test).

Metabolic / musculoskeletal: occurence of decubitus, weigth loss, hyperglycemia or need of insuline, ketone body ratio, aminoacid-, carbohydrate-, and fat metabolism.

Next to these more or less organ specific parameters, some scoring systems use additive data such as central temperature, serum electrolytes (calcium, sodium, potassium) or hemoglobin or total protein concentration, number of positive blood cultures, local effects of tissue infection and metabolic acidosis (compensated or not) (23-25,29,35,36).

The variability in criteria used to define organ failure causes the confusion about the exact data on the incidence and prevalence of ARDS and MOF.

It is worthwhile to consider the morphologic alterations seen in different organs involved in ARDS and MOF. We will discuss morphological changes of organs reported in autopsy studies of patients succumbed after trauma and information gathered from organs studied after experimental hypovolemic - traumatic shock or experimentally induced ARDS and MOF (38-43). An important finding is the general increase of organ weights and swollen appearance of these organs found in patients dying of ARDS and MOF, compared to "normal" values of organ weights obtained from other autopsies (39).

For the **lung** the most prominent features associated with ARDS or early lung failure are the sequestration, aggregation and degranulation of polymorphonuclear granulocytes (PMNs) in the pulmonary microcirculation. This leads to damage of the pulmonary capillary endothelium and alveolo - capillary membrane, with interstitial edema and protein-rich fluid migrating into the alveolar space. In a later stage, fibrin deposition and platelet accumulation take place, leading to progressive and diffuse fibrosis. Also monocyte invasion occurs, more extensively so in patients developing MOF.

Morphologic changes seen in the **liver** after injury or shock also consist of accumulation and aggregation of PMNs, endothelial cell and Kupffer cell swelling, impairment of sinusoidal function and focal areas of hepatocyte necrosis. The latter changes increase in severity with the length of survival after injury.

In the **kidneys** PMN accumulation has also been observed in the glomeruli, whereas the tubuli showed vacuolar nephrotubulopathy. Endothelial cell swelling with bleb formation can occur, leading to blocking of the intravascular spaces.

In the **heart** increased numbers of PMNs have been found occassionally, concomitant with interstitial and cellular edema. Focal cellular necrosis has also been demonstrated and increasingly so in patients dying late after trauma.

In the **spleen** an excessive number of PMNs and macrophages can be found, next to depletion of red and white pulpa. Pathologists attributed these findings to "sepsis", though these features also occurred in patients who died within 24 hours after trauma, without clinical signs of infection.

The **Intestines,** after a period of trauma or shock (low flow syndrome), macroscopically show hemorrhagic mucosal damage. Microscopically there is mucosal edema formation, necrosis, loss of epithelium, interstitial hemorrhage, and edema, features that are also observed in the intestines of patients dying of MOF (44).

Skeletal muscle after a period of shock and reperfusion shows markedly increased

endothelial cell swelling, however without increased accumulation of PMNs.

After septic shock extensive perivascular edema with PMN infiltration is found in the **brain** (45).

Many of the above mentioned alterations in various organs could also be observed in experimental circumstances, such as after infusion of complement activated plasma with additional hypoxia in rabbits, after intraperitoneal injection of zymosan in rats and mice, after hemorrhagic shock in rabbits, after endotoxin administration in rats or after cecal ligature and puncture in sheep (46-50).

The morphologic alterations observed share several common findings: 1. endothelial cell damage and generalized edema formation, and 2. the presence of PMN infiltration (except in the musculoskeletal system). These features are compatible with a generalized inflammatory reaction with microvascular injury (14,38,39).

Oxygen metabolism in relation to ARDS and MOF

Circulatory failure (shock) and especially insufficient peripheral circulation result in a reduction of oxygen supply to the cells. This oxygen supply is vital, as 95% of the energy generated by the body normally originates from aerobic pathways (51). In conditions associated with sepsis, trauma or extensive surgery, oxygen demand may be elevated. However, it has been demonstrated, e.g. in fully resuscitated trauma patients, that although oxygen supply was normal or even above normal, oxygen consumption was decreased (52). It has also been shown that in these patients oxygen consumption depends on oxygen supply, a condition called pathologic oxygen-supply-dependency (53). This process has been attributed to an impaired oxygen extraction and is associated with "hidden tissue hypoxia", causing deterioration of organ functions leading to MOF (54). In patients with ARDS such supply-dependency has also been demonstrated (55).

When oxygen supply decreases below a critical threshold, excess lactate is generated (56). Many clinical studies have indicated that blood lactate levels are increased in circulatory failure and are directly correlated with the severity of shock (57). In septic shock, lactate reliably predicts outcome (57). In ARDS oxygen extraction is low, despite a supra-normal oxygen supply, while lactic acidosis is present (59).

When, after a period of shock, ischemia and hypoxia, tissues are reperfused, they will also be reoxygenated. During hypoxia, ATP is broken down to hypoxanthine. Meanwhile an enzyme system is activated, leading to the production of xanthine oxidase, which after reoxygenation converts hypoxanthine into xanthine (urate). During this

process highly reactive oxygen free radicals are produced (60). These oxygen free radicals will induce the oxydation of plasma membrane associated arachidonic acid by the lipoxygenase and cycloxygenase pathways, resulting in an excess production of metabolites, such as lipid peroxides, prostaglandins and tromboxanes (60). The process of ischemia and reperfusion has also been shown to be associated with impaired oxygen extraction (51). The involvement of oxygen free radicals in the pathogenesis of ARDS is suggested by the finding of increased levels of H_2O_2 in the expired breath and increased carbon exhalation in patients with ARDS (61,62).

Ischemia, resulting in tissue hypoxia, may ultimately lead to cell destruction. The intestine is highly susceptible to splanchnic ischemia, which can very rapidly lead to mucosal damage and finally transmural infarction (63). The adequacy of this mucosal oxygenation can be investigated indirectly by pH measurement of the mucosa. This pHi (intramucosal pH) determination, using an intraluminally placed balloon catheter permeable to CO_2, is called tonometry (64). Tonometry has been demonstrated to be usefull in monitoring ICU patients to guide therapy (65) and to provide predictive information towards the development of complications, such as sepsis and MOF, in patients after cardiac or abdominal aortic operations (64,66).

Role of humoral and cellular systems in ARDS and MOF

The primary reaction of the organism to any type of tissue damage can be summarized as an inflammatory response. Experimental and clinical evidence indicates that activation of humoral systems precedes activation of cellular systems (38). The various local interacting humoral systems (complement, coagulation, fibrinolytic and kinin-kallikrein) in turn are potent activators of circulating inflammatory cells, such as PMNs and monocytes.

The complement system can be activated by either the classical or the alternative pathway. Both routes lead to conversion of C3 to C3a, which is a very strong anaphylatoxin (67,68). Next in the cascade is the production of C5a (from C5) and terminal complement complexes, which are an assembly of C5b to C9. The level of complement activation has been positively correlated to severity of trauma (69,70), while in patients with established ARDS higher levels of activated complement products could be demonstrated compared with patients without ARDS (68,71). Continuous infusion of complement activated plasma with additional hypoxia in the rabbit, resulted not only in ARDS-like changes in the lungs, but also in a generalized

inflammatory response in many other organs, such as the liver, kidneys, spleen and heart (46). In another report it was shown that complement activation positively correlated to the first signs of MOF (72).

The generation of complement activated products (C3a and C5a) leads to the activation of PMNs, which aggregate and stick to endothelial cells. This process accounts for the PMN margination, resulting in pulmonary leukostasis seen in ARDS and the early leukopenia observed at the onset of sepsis or immediately after hypovolemic-traumatic shock (73,74). Adherence of PMNs to the endothelium appears to create an inflammatory microenvironment in which numerous active substances are released, such as proteolytic enzymes (elastase), vaso-active substances (platelet activating factor, leukotrienes, prostaglandins), wound hormones (granulocyte macrophage - colony stimulating factor) and oxygen free radicals. These substances lead to endothelial damage, thus creating microvascular injury, resulting in increased permeability with edema formation (7,38).

Especially elastase seems to be a factor of direct relevance in this type of tissue injury. Experimental administration of elastase results in elevated pulmonary vascular resistance, decreased cardiac output, pulmonary leukostasis, disseminated intravascular coagulation and increased venous oxygen content (75). In many studies a positive correlation between plasma elastase levels (measured as the elastase-α1-antiprotease inhibitor complex) and severity of trauma, sepsis, ARDS and MOF could be demonstrated (76-79). Some authors even reported elastase levels to be predictive for subsequent ARDS and MOF (76,78). Free circulating elastase might harm endothelial tissue in remote organs, thereby contributing to the development of MOF.

In response to inflammatory stimuli, human PMNs produce large amounts of oxygen free radicals, importantly more than bovine, ovine or porcine PMNs (80). The hydroxyl radical probably is the most important oxidant involved in PMN-induced endothelial cell injury (81). Thus, the cell damage observed in the post-traumatic or post-ischemia/reperfusion period is aggravated by the contribution of oxygen free radicals produced by activated PMNs (38).

After chemoattraction to the inflammatory scene, circulating monocytes differentiate locally into macrophages. Fixed tissue macrophages are present in most tissues, such as the liver (Kupffer cells, comprising 70% of the total population of fixed macrophages), brain (glia cells), kidneys (mesangial cells), or peritoneum, lung and spleen. Monocytes and macrophages in turn also are activated by C5a and a score of signals from PMNs (82). Other strong activators of macrophages are tissue hypoxia and endotoxin (82). Upon stimulation, macrophages may release large amounts of

secretory products, including pro-inflammatory (such as cytokines), anti-inflammatory, immunosuppresive or pro-coagulatory substances (83). In contrast to PMNs, it apparently takes several days after activation to develop the full inflammatory capacity of macrophages (83).

Neopterin is a stable inactive end product of macrophage metabolism and neopterin levels reflect macrophage activity (84). As neopterin is cleared from the circulation in a creatinin-like manner it probably is more correct to use the neopterin/creatinin ratio, when using neopterin as a marker of macrophage activity (76,84). Increased plasma neopterin concentrations have been associated with poor outcome in patients with viral infection (including AIDS), auto-immune disease, graft vs host reaction, and multiple trauma and sepsis (76,85).

Recently the role of cytokines - such as tumor necrosis factor (TNFα), interleukine-1ß and -6 (IL-1ß and IL-6) - in the inflammatory process has been subject of extensive study. Monocytes (macrophages) and endothelial cells are the primary source of these cytokines, but many other cells involved in the inflammatory reaction such as fibroblasts, T and B cells and various mesenchymal cells also produce cytokines (86). Of course cytokines have various beneficial effects and cannot only be detrimental to the host. For example, they are essential for normal antimicrobial and immune activity, wound healing and optimal substrate mobilisation (9). The understanding of cytokine effects is complicated by several factors:

* the cytokine cascade is characterized by many feedback loops, in which cytokines can modulate each other;
* combinations of cytokines can be inhibitory, additive or synergistic;
* cytokine producing cells may be primed or just tolerant to new triggers;
* the sequence of cytokine release influences the target cells, and
* cytokine effects are dose related (9).

Until now of all cytokines IL-1ß, TNFα and IL-6 have been well studied in the clinical setting. Elevated levels have been demonstrated in patients with sepsis, after trauma or burn injury, shock, inflammation in the absence of infection and even in chronic diseases (87-93). There is ample evidence that TNFα appears to be a key messenger in activating and orchestrating the "septic" or inflammatory response (9,38). Administration of TNFα induces a cascade of factors that modulate multiple humoral systems, resulting in organ damage closely mimicking MOF (94).

IL-6 has been shown to correlate positively with the severity of injury and its levels are more closely tied to soft tissue trauma than the other cytokines (88,95,96). IL-6 is the main regulator of the acute phase response in human adult hepatocytes, which

release acute phase proteins, including C reactive protein (CRP) (97). CRP levels have also been shown to correlate well with the severity of injury or the magnitude of surgical intervention (95,98) and were predictable of subsequent MOF in one study of multiple trauma patients (76).

Bacteriological aspects of MOF

By the late 1970s, surgeons started to think of MOF as a septic syndrome. Many of the critically ill surgical patients had occult, usually intra-abdominal infections and MOF came to be regarded as the external expression of an occult septic focus and as an indicator for abdominal exploration. In 1980, Fry et al.(27) published the results of 553 patients who underwent emergency operations, 38 of whom had developed MOF. Thirty four (89%) of these patients showed signs of infections and the authors concluded that infection and its systemic manifestations were the most crucial factor in the evolution of MOF in patients after surgery. The first investigators to describe ARDS noticed that these patients often died of sepsis (99) and in a necropsy study of patients with lethal ARDS, infection was found in 46 of 47 patients (100). As time went on, however, it was found that increasing numbers of patients were explored in whom no abscess could be found intra-abdominally, even though florid MOF was evident (101).

In 1980, Meakins et al. (102) described a group of patients who manifested the characteristic clinical findings of sepsis, yet who had persistently negative blood cultures. This phenomenon was then termed 'non-bacterial clinical sepsis'. Several studies, especially on multiple trauma patients, showed that the relation between infection, sepsis and MOF is not so evident. Goris et al. (12) documented that a focus of uncontrolled infection was present in only 31 (56%) of 55 severely injured patients with MOF. Border (103) found negative blood cultures in two thirds and no septic focus in one third of his patients with MOF following trauma. Fowler et al. (104) reported that 49 (56%) of 88 patients with ARDS did not show signs of infection. In an excellent study of 100 multiple trauma patients Waydhas et al. (75) concluded that in about one quarter of patients with MOF infection did not play a role at any time, and that in those patients with infection three quarter showed early onset of MOF long before infection started. In addition, nine (9%) patients suffered from sepsis, but did not develop any organ dysfunction at all.

There appear to be no essential clinical, biochemical or morphological differences

between patients with non-bacterial sepsis (or SIRS) (22) and patients with bacterial sepsis (12,105,106). It has been demonstrated that the correlation of sepsis scores to mortality depends only on organ failure data, not on bacteriologic data (107). In patients at risk of or with ARDS/MOF, bacterial invasion occurs relatively late and infection is often caused by organisms of relatively low virulence, such as Staphyloccocus epidermidis and Candida species (12,108). In these circumstances the finding of bacteremia actually may be an expression of failed host defenses, rather than of infection in the traditional sense (9).

The apparent paradox why no septic focus can be identified clinically or at autopsy in more than 30% of bacteremic patients, led to the concept of the gut being the source of translocating bacteria and thus being the 'motor' of MOF (9,109).

The gut and its association with MOF

Under normal conditions the splanchnic circulation receives about 30% of the cardiac output and contains approximately one-third of the total circulating blood volume (110). Hypovolemic or cardiogenic shock results in a profound splanchnic vasospasm, generating an effective autotransfusion to the systemic circulation. However, the resulting splanchnic ischemia may lead to mucosal damage throughout the whole intestine, finally resulting in transmural infarction (63). It has been suggested that the gastro-intestinal tract is not only a target organ in critical illness, but that it may have a more active role in the pathogenesis of MOF (109). This is attributed to the presence of large amounts of bacteria and endotoxins in the bowel.

Living bacteria have been shown to cross the intact intestinal mucosal barrier and to appear in mesenteric lymph nodes, peritoneal fluid and other organs. This process is called bacterial translocation and it has been demonstrated to occur under a variety of conditions, such as hemorrhagic shock, severe burns, pancreatitis, severe inflammation, abdominal abscesses and after endotoxin administration (9,111-115).

Endotoxins are lipopolysaccharide compounds of the outer membrane of Gram-negative bacteria. They can cause numerous deleterious biological effects and are thought to be responsible for the detrimental changes observed in Gram-negative septic shock (116). Michie et al. (84) showed that endotoxin and TNFα induce similar metabolic responses in human beings, resulting in organ damage. Under pathological circumstances endotoxin can penetrate the mucosal barrier, leading to portal and systemic endotoxemia (117,118).

Since bacteria and endotoxin can play a significant role in the initiation and perpetuation of the inflammatory cascade, the gut barrier function seems to be important. As discussed above, conditions such as trauma and shock may lead to mucosal damage by splanchnic ischemia, which in turn may result in loss of barrier function. Alterations of intestinal permeability have been demonstrated to occur under various pathological conditions (for review see chapter 8). Some authors reported an association between increased intestinal permeability, endotoxemia, bacterial translocation and infectious complications (114,119,120). However, Alexander et al. (118) elegantly demonstrated that the process of microbial and endotoxin translocation is different from the absorption of for instance inert sugars, which are frequently used in investigations on intestinal permeability. Nevertheless, it is often suggested that the finding of increased intestinal permeability will probably also mean bacterial and endotoxin translocation and thus contribute to the development of MOF (9,99,121).

In this respect data on selective decontamination of the gastro-intestinal tract are interesting. This procedure aims to selectively eradicate the Enterobacteriaceae - organisms most likely to translocate -, while leaving intact the more harmless anaerobes to prevent bacterial overgrowth of pathogens (122). Selective decontamination has resulted in an impressive decrease in incidence of nosocomial infections in ICU patients, but sofar it has not been demonstrated conclusively to be effective in the prevention of MOF (123).

Pathophysiological theories on the mechanisms leading to ARDS and MOF

Based on the observations discussed in the previous paragraphs several hypotheses about the pathophysiological mechanisms leading to ARDS/MOF have been developed. Some of these theories can be summarized as follows (9,10,99,124):

* Sepsis theory. Invading bacteria or their toxic products, such as endotoxin or exotoxin are thought to be the primary cause that trigger the cascade leading to ARDS/MOF. It remains a matter of debate, however, whether patients with ARDS/MOF die **from** bacterial infection, or just **with** infection.

* The gut as "the motor of MOF". Intestinally derived bacteria and endotoxins serve as a trigger to initiate, perpetuate or exacerbate the "septic" state. There is of course an overlap with the first hypothesis. This theory yields an attractive explanation for the fact that in a lot of patients with clinical signs of sepsis and lethal MOF no bacterial focus can be found. However, the clinical relevance of the role of bacterial trans-

location and endotoxemia - both extensively demonstrated experimentally - is yet to be elucidated.

* Microcirculatory hypothesis. Organ dysfunction is related to ischemia or microvascular-endothelial injury. This includes the mechanism of inadequate tissue and cellular oxygen delivery (125), ischemia-reperfusion injury (38,60), and tissue injury due to endothelial-leukocyte interactions (126). There are many overlapping points in this hypothesis with the following two theories (9). An important clinical observation that supports this theory is that circulatory shock with resulting tissue hypoxia is one of the most common clinical events that precedes MOF (6,9). In addition, autopsy data show evidence of diffuse microvascular injury in patients with lethal MOF (39).

* Uncontrolled inflammatory response by an excessive and prolonged activation or stimulation of humoral and cellular systems. In this theory the activation of humoral and cellular inflammatory systems is exaggerated and out of control. Teleologically, inflammation is intended to be a local process, but after an overwhelming stimulus a systemic activation of inflammatory cells and thus a systemic spill-over of inflammatory products and mediators may be present. This may then lead to whole body inflammation with damage to remote organs not primarily involved in the primary injury (4,7,12). The macrophage is thought to play a major role in this process (127).

* Two hit phenomenon. An initial insult primes the host such that on a second subsequent event the host's response is greatly amplified, resulting in an autodestructive inflammatory response. In fact, this represents a combination of the hypotheses mentioned above.

At the moment there is no consensus what key factor is responsible for the final common pathophysiological pathway observed in the development of ARDS and MOF. But, whatever theory or mechanism fits this key role, there is agreement that a cascade of events precedes MOF. In addition, it is important to realize that ARDS and MOF are entities that represent a pathophysiologic continuum of progressively increasing severity.

According to Goris (4) we can schematically represent this proces in time by discriminating several events (or stimuli or triggers) that can be graded by scoring systems. Each event can be characterized by increased levels of circulating biochemical substances, which are then called markers of that event.

If these substances are actively involved in the development or triggering of a next event by inducing damage to otherwise healthy tissues they are mediators of that

process. If increased amounts of mediators are detected prior to subsequent ARDS and MOF, these substances then are underlined predictors of ARDS and MOF.

For example, elastase - a protease released by activated PMNs - can cause damage to proteins, such as elastin, and mediates endothelial cell injury. Elevated serum elastase levels have been shown to correlate well with injury severity and the final development of ARDS and MOF. Thus, elastase is a marker of PMN activity and trauma severity, a mediator for endothelial injury and a predictor of ARDS and MOF (7).

To fully analyze the sequence of events, the following procedures should be performed.

* A time scale should be set to separate cause from effect.
* Primary insults have to be identified and graded according to severity, such as the severity of trauma, shock, pancreatitis, peritonitis.
* The physiological responses to these primary events need to be graded also, for instance by APACHE II score, Glasgow Coma Scale, or sepsis scores (see appendix).
* Body fluids, mainly blood, should be sampled sequentially to detect substances that could serve as markers, mediators or even as predictors.
* Finally, parameters adequately defining organ function are necessary, and scoring systems to quantify the degree of organ (dys)function during follow up of the patient's clinical course.

With this concept and on the basis of the literature (3,4,10,38,44,99), we constructed figure 1.1, which is a diagram showing the interrelations of several events, risk factors, scoring systems, (potential) markers, mediators and predictors in relation to the development of ARDS and MOF. Instead of a fixed time scale we used levels that range from the initial level 1 (primary, causative event) to the final level 7, being the effect, viz. ARDS, MOF and/or death.

Questions and aim of the study.

The aim of this thesis was to further delineate several components of the aforementioned levels of the cascade resulting in ARDS and MOF. The accent was put on clinical observations and determinations in patients known to be at risk of ARDS and MOF, such as patients with severe trauma, in hemorrhagic shock due to a ruptured abdominal aneurysm, undergoing major elective vascular surgery, or with severe

pancreatitis. We were especially interested in these patients, because they primary have a non-bacterial challenge, allowing to study the time-relation between primary event, inflammatory response, evential occurring infection-endotoxemia-sepsis and subsequent complications, such as ARDS/MOF.

The following three main issues and various connected questions will be addressed in the respective chapters:

1. <u>What is the role of scoring systems, grading the severity of trauma, disease and organ dysfunction in relation to subsequent ARDS/MOF ?</u> (level 1 to 7).

a. What is the (predictive) value of several scoring systems towards final outcome, i.e. either ARDS, MOF or death. Do disease-specific scoring systems (e.g. for pancreatitis) provide more information about outcome than non-specific scoring systems, like the APACHE II score? (chapter 2)

b. Is there a difference between anatomical severity grading and physiological response grading concerning the predictive value for outcome after severe trauma? (chapter 3)

c. What is the difference in prognostic information of severity of disease classification systems, like the APACHE II score, and organ failure scoring systems, like the MOF score? (chapters 2 and 3)

2. <u>What is the relation of various circulating products of the inflammatory cascade with subsequent ARDS/MOF ?</u> (level 1, 3 and 4).

a. The predictive value of <u>lactate concentrations</u> in multiple trauma patients towards subsequent ARDS/MOF. (chapter 2)

b. Evaluation of <u>complement activation, acute phase reaction, eicosanoid production and PMN and macrophage activation</u> after multiple trauma. (chapter 4)

c. <u>Cytokine production</u> after multiple trauma, hemorrhagic shock and major vascular surgery. (chapter 5)

d. Serum <u>lipofuscin concentrations</u> as indicator of lipid peroxidation following severe trauma and acute and elective major vascular surgery. (chapter 6)

Figure 1.1

* = asterisks indicate parameters that are evaluated in this thesis.

Level

Cause → **Event** ----→ **Effect**

Severity Grading

Potential
- markers
- mediators
- predictors

1
Trauma
Major surgery
Sepsis
Endotoxemia
Hem shock
Pancreatitis

Injury severity scores
ISS PTS *
Sepsis scores *

Extracellular ATP

Endotoxin *

2
HYPOXIA

Activation
Humoral systems
Complement
Coagulation
Kallikrein - kinin
Arachidonic acid

Shock scores
Ranson, Imrie score *

Proteases

PaO₂/FiO₂ ratio *
Art Ven O₂ saturation
Muscle PO₂
Tonometry *

Lactate *

3
Activation
Cellular systems
PMNs
Macrophages
Platelets

Disseminated intravascular
Coagulation, need for
clotting factors
Platelet count

Activated complement (C3/C3a) *
Terminal Compl Complexes *
Fibrin, fibrin split products
Leukotrienes, Prostaglandins
Tromboxanes *
Oxygen radicals, Lipofuscin *
Elastase, Neopterin *
Cytokines *

PHYSIOLOGICAL

RESPONSE SCORES

4
ENDOTHELIAL
CELL DAMAGE

APACHE II, TS GCS

ELAM, ICAM
Nitric oxyde, PAF
Fibronectin
Cytokines *

5
Barrier disruption
Permeability change
Interstitial edema

Δ O₂ Diffusion

Permeability tests
(lung, kidney, intestine)

Tonometry *

Labelled albumen,
Indium III-IgG
Proteinuria
Lactulose/Mannitol ratio *

6
Bacterial translocation

ORGAN DAMAGE
ARDS - MOF

ARDS and MOF
scores *

Organ specific parameters
like   bilirubin,
creatinin

7
OUTCOME

DEAD / ALIVE

32

3.   **What is the role of the gut in relation to the development of ARDS/MOF with emphasis on its barrier function (intestinal permeability) ?** (level 1, 2 and 5).

a.   Does endotoxemia occur after severe trauma or major vascular surgery? If so, is there evidence that endotoxin plays a key role in the cascade leading to ARDS and MOF? (chapters 7 and 9)

b.   Is intestinal permeability altered after multiple trauma, hemorrhagic shock or major vascular surgery? (chapters 9 and 10) What is the value of intestinal permeability in relation to bacterial translocation and subsequent complications? (chapter 8) Does altered intestinal permeability relate to subsequent ARDS and MOF? (chapters 8, 9 ,10)

c.   What information is provided by measurements that give an indication of the splanchnic ischemic insult (gastric tonometry) in multiple trauma patients? Does the latter measurement correlate with changes in intestinal permeability? (chapter 11)

In the general discussion (chapter 12) we will address the question whether our clinical studies provide evidence that ARDS and MOF are the result of an overwhelming generalized autodestructive inflammatory response of the host to the primary insult.

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SCORING SYSTEMS FOR PREDICTING OUTCOME IN ACUTE HEMORRHAGIC NECROTIZING PANCREATITIS

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Abstract

Between 1980 and 1990, 39 patients, admitted to the ICU of the St.Radboud University Hospital, Nijmegen, were surgically treated for acute hemorrhagic necrotizing pancreatitis (AHNP).

Five scoring systems were retrospectively investigated for the prediction of severity and outcome: Ranson score, Imrie score, APACHE II, MOF score and SSS.

Twenty-two of the patients died (56%). The survivors were significantly younger than the non-survivors, of whom 68% died within 3 weeks of admission to the Intensive Care Unit (ICU). Stay in the ICU was significantly longer ICU in the former group.

Sensitivity in prediction of death was best with the APACHE II score > 9 (96%) and Ranson score ≥ 3 (95%). Of the five scores the MOF score ≥ 4 gave the best equilibration between sensitivity (73%) and specificity (76%) and the strongest prediction of lethal outcome (80%).

Although the independent factor age had low sensitivity (55%) it showed the highest specificity (88%) and prediction of death (86%).

APACHE II score is concluded to be the best for grading the severity of disease on admission to the ICU, while the MOF score is best for monitoring the degree of organ dysfunction and the intensity of supportive treatment.

Introduction

Acute pancreatitis presents a broad clinical spectrum ranging from a mild disorder to a fulminant lethal disease resulting in multi-organ failure and death. Mortality rates reported in large series of acute pancreatitis range from less than 3% to 10% (1-5). The actual mortality rate even may be higher as cases diagnosed at necropsy are not included in most series (6). In patients with acute hemorrhagic necrotizing pancreatitis (AHNP) mortality varies from 30% to 90% depending on the extent of necrosis of the (peri-)pancreatic tissue and the severity of organ failures (2,7,8). Sepsis and MOF still are the main cause of death in this group of patients (2).

Surgical treatment is indicated in AHNP when the patient's condition deteriorates. In one case series AHNP was fatal in 100% of patients without, and 63% of those with surgical treatment (9). To accurately evaluate the effects of therapeutic intervention, therefore, it is of the utmost importance to grade the severity of pancreatitis and to identify potential non-survivors. In the present study, we retrospectively investigated

several scoring systems for predicting outcome in 39 patients with laparotomy proven AHNP.

Scoring systems (see appendix, chapter 14)

The widely accepted **APACHE II** system was originally devised for classification of severity in acute diseases and to predicting hospital mortality among cases admitted to ICU (10). The system has of three components, viz. an acute physiology score, that can be influenced by therapeutic interventions; and non-dynamic components such as age and chronic health evaluation. The system is well suited for the stratification of patients and comparison of treatment methods. Although it was not designed for following the clinical course, many studies showed it to be usefull for monitoring this course and the response to therapy (3,4). Nevertheless the score may improve while the number and intensity of therapeutic interventions increase.

The **Ranson** (11,12) and **Imrie** (13,14) scoring systems were evolved for evaluating acute pancreatitis. They respectively comprise 11 and nine clinical and biochemical criteria collected within 48 hours from the onset of the disease and permit identification of patients with mild or severe pancreatitis. Mortality was shown to increase with the numbers of positive criteria. The scores consist of factors as age, specific pancreatitis linked parameters (i.e. serum calcium and glucose levels), and criteria of remote organ dysfunction like pulmonary (arterial pO2), renal (BUN), and liver (serum LDH and AST levels) function parameters. The scores indicate the severity at onset of the disease and are not intended for monitoring the clinical course.

The **Sepsis Severity Score (SSS)** (15) was developed to grade the severity of sepsis at any given time and to permit follow up of the patient's progress. Its four components are: local effects of tissue infection, pyrexia, secondary effects of sepsis and laboratory data. As both the cause and the effects of sepsis are used to compute the total score, some conditions are scored multiply, e.g. a positive bloodculture with fever and leucocytosis. Furthermore "secondary effects of sepsis" and "laboratory data" concern mainly alterations in the function of several organ systems (liver, kidney, CNS and blood), but do not include data from the most important sources such as the pulmonary, cardiovascular and gastro-intestinal organ systems.

The **Multiple Organ Failure score (MOF score)** (16), was developed to grade the function of the seven main organ systems: the pulmonary, cardiovascular, hepatic, renal, nervous, hematologic and gastro-intestinal system. It comprises a three-point scale. The score can be used at any time and is well suited for following the clinical course during ICU treatment. Included in the score are laboratory data, a few clinical diagnoses and the number and intensity of several therapeutic interventions necessary to support organ functions.

Patients and methods

During a ten year period (1980-1990) 39 patients with AHNP were admitted and treated in the departments of General Surgery and Intensive Care. This selected group of patients required mechanical ventilation for more than 24 hours because of respiratory failure: 22 had been referred from other hospitals for intensive care treatment. AHNP was diagnosed at the first laparotomy in all patients. At the time of the initial hospital admission the severity of acute pancreatitis was defined according to Ranson and Imrie criteria.

On the day of ICU admission patients were scored using the APACHE II system. MOF score and SSS were determined daily. For each patient these latter scores were calculated to give an average for the entire ICU-stay and also for the first four days of ICU-stay. Survivors were defined as patients discharged alive from the hospital and non-survivors as those who died from AHNP or its complications during hospitalization.

Differences between groups were tested using the Mann - Whitney U-test. Correlations were calculated using the Spearman's correlation coefficients. Probability values of less than 0.05 were regarded as significant.

Results

Twenty-two (56%) of the 39 patients died. Mortality among primarily treated patients in our ICU was 59% and 55% patients referred from elsewhere (table 2.2). The median age of survivors was 40 years and of non-survivors 57 years (p=0.0048). Of the 17 patients aged over 55 years survived only two survived.

Table 2.2

Age and sex of 39 patients with AHNP.

	number of patients	Sex (female/male)	Age	Referred
Survivors	17	7/10	40 (19-69)	10
Non-survivors	22	6/16	57 (24-83)**	12
Total	39	13/26		22

** : p = 0.0048

The average Ranson score for survivors was 3.5 and for non-survivors 4.6 (p = 0.037), while the respective Imrie averages were 2.7 and 4.0 (p = 0.021) (table 2.3).
On ICU admission APACHE II scores averaged 9.8 (12-17) in the survivors and 14.1 (7-24) in the non-survivors (P < 0.001). When the contribution of age points to the APACHE II score was excluded, these figures became 8.9 (5-15) and 11.0 (4-21), respectively (p = 0.057). The factor age in APACHE II, thus, contributed significantly in prediction of outcome in AHNP.

Table 2.3

Number of positive criteria according to Ranson et al. and Imrie et al. in 39 patients with AHNP. Difference between groups according to Ranson: p = 0.037, and according to Imrie: p = 0.021.

Ranson:

	0	1	2	3	4	5	6	≥ 7
Survivors (n=17) (mean 3.5)	-	1	3	6	2	4	1	-
Non-survivors (n=22) (mean 4.6)	-	-	1	6	5	3	2	5

Imrie:

	0	1	2	3	4	5	6	≥ 7
Survivors (n=17) (mean 2.7)	1	3	7	1	2	3	-	-
Non-survivors (n=22) (mean 4.0)	-	1	3	4	7	2	3	2

The stay in the ICU was significantly shorter for non-survivors than for survivors (mean 21 days versus 51 days, p = 0014). Of the non-survivors, 68% died during the first 3 weeks of ICU admission, while during this same period only two of the 17 survivors could be discharged from the ICU.

A good correlation was found between the MOF score and SSS (Spearman's corr.coef. r = 0.65, p < 0.001).

The average daily values of MOF score and SSS for the entire ICU-stay significantly differed between survivors and non-survivors (p < 0.001) (table 2.4A). The average for the first 4 days of ICU-stay (table 2.4B) showed significant intergroup difference for MOF score (p = 0.012), but only an indication of significance for SSS (p = 0.054).

Table 2.4

Average MOF scores and SSS (median - range) in 39 patients with AHNP.

Table 2.4A: For the entire ICU-stay. ** = p < 0.001

	MOF score	SSS
Survivors (n=17)	2.0 (1.2 - 3.5)	12.3 (7.2 - 17.3)
Non-survivors (n=22)	4.5 (1.7 - 8.2)**	20.4 (11.9 - 27.6)**

Table 2.4B: For the first 4 days in ICU. * : p 0.012, and (*) : p = 0.054

	MOF score	SSS
Survivors (n=17)	3.0 (0.8 - 6.8)	16.5 (9.0 - 28.0)
Non-survivors (n=22)	4.7 (1.3 - 8.0)*	21.8 (10.3 - 27.0)(*)

Table 2.5 summarizes the sensitivity, specificity and the positive and negative p-redictive values. In figure 2.1 the average MOF score of the first four days is plotted versus age: 16 of 20 patients (80%) with an average MOF score ≥ 4 died. Of the patients older than 60 years, only the patient with the lowest MOF score (1.5) survived.

When clinical deterioration occurred, relaparotomy was performed for debridement or to search for a septic focus. Excluding the reoperations for technical reasons like wound closure or restoration of bowel continuity, all patients underwent one or more (1-13) relaparotomies, averaging 4.8 in the non-survivors and 6.2 in the survivors. In 82% of the relaparotomies debridement was performed or a septic focus was found. Between survivors and non-survivors there was no difference in the incidence of these intra-abdominal findings.

Table 2.5

Sensitivity, specificity, and predictive values with five scoring systems, and age as an independent factor, in 39 patients with AHNP. Between [ ] the values are shown when age as a contributing factor was excluded for calculations.

Score	Sensitivity (%)	Specificity (%)	Positive predictive value (%) (death)	Negative predictive value (%) (survival)
APACHE II > 9	96 [73]	59 [65]	75 [73]	91 [65]
Ranson ≥ 3	95 [77]	24 [29]	62 [57]	80 [50]
Imrie ≥ 3	82 [68]	65 [71]	75 [75]	73 [63]
SSS ≥ 20	55	76	75	57
MOF ≥ 4	73	76	80	68
Age > 55	55	88	86	60

Comment

Prediction of outcome in acute pancreatitis has been extensively reported (1,3-5,11-1-4). Some of these studies compared and evaluated different scoring systems (3-5). We have found no reports on the evaluation of such scoring systems in the subgroup of patients with the most severe form of of the disease: acute hemorrhagic necrotizing pancreatitis (AHNP). The present group of AHNP patients was highly selected, because of the need for more than 24 hours of mechanical ventilation. Previous authors (2) reported 38% mortality in a series of AHNP, but only 12 needed mechanical ventilation for more than 24 hours and developed MOF, and eigth (67%) died. This example emphasizes the need for stratification and classification of AHNP patients by the use of scoring systems.

Figure 2.1

Average MOF score for the first 4 days of ICU-stay versus age in 39 patients with AHNP.
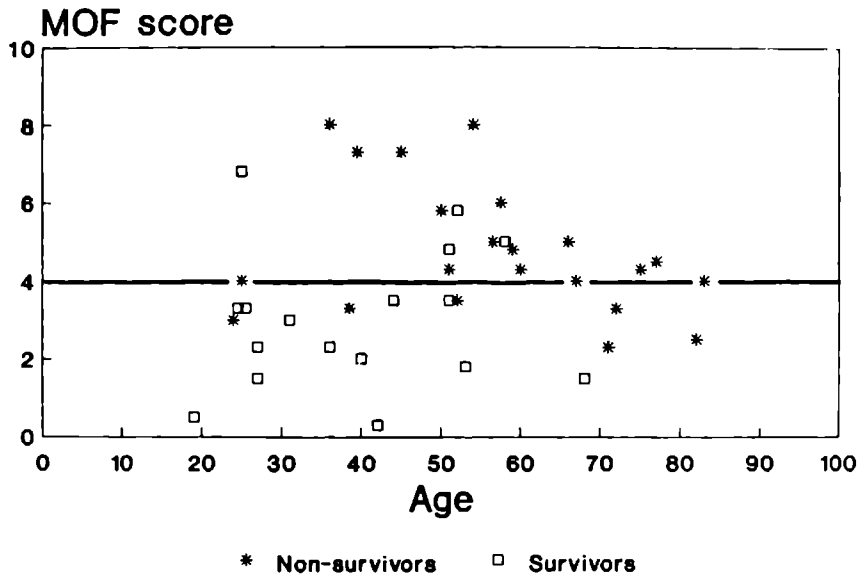
Such systems can be useful for predicting mortality, severity of disease and intensity of its complications.

The 56% mortality rate in our series is comparable to the rates in other studies of patients treated by total pancreatectomy (60-75%) or by excision of necrotic tissue (37-64%) (8,17,18).

To illustrate the listed aspects we compiled data of several large series of acute pancreatitis, where classification as severe occurred in 16% to 26%, using the Ranson and/or Imrie scores (1,3-5,14). Among the patients with severe pancreatitis mortality was 31% to 50% and AHNP developed in 18% to 68% (2-5,8,9,14,19). On the other hand, only 76% to 79% of proven AHNP cases were originally classified as severe (2,14). Of our cases, 87% were classified as severe according to Ranson score, but only 62% with Imrie score. Thus, there is a considerable group of patients with pancreatitis apparently mild at the onset which later evolves to AHNP. These scoring methods gave a reasonable indication of the severity of pancreatitis, but our results (24% and 65%) confirmed the poor specificity shown by others (3).

Peak APACHE II score, recorded during the first 3 post-admission days, was used in a recent study of acute pancreatitis (4). When the peak score was more than 9, the negative predictive value was very good for survival (95%), but low for death (45%). In the present study we used the APACHE II score on ICU admission and at more than 9 obtained similar prediction of survival (91%), but a higher figure for death (75%). We thus can confirm the statement that the APACHE II score provides a higher accuracy and better prediction of outcome than Ranson and Imrie scores do (4). The MOF score was the most accurate predictor of death (80%), and gave a well equilibrated sensitivity (73%) and specificity (76%). The most important difference between the MOF score and APACHE II score is the fact that the MOF score includes intensity of therapeutic interventions and grades the severity of organ dysfunction. Thus, it is possible that an ICU-patient may have a high MOF score but a low APACHE II score. Therefore the MOF score is the more informative of the two as regards the severity of illness.

The SSS showed the lowest sensitivity (55%) and the difference with the MOF score has already been pointed out.

It is well known that age is a factor significantly contributing to the prediction of outcome in patients with AHNP (1,2). As this factor is an independent variable and cannot be influenced, prediction of outcome should be possible irrespective of age (1). Moreover, increasing mortality in relation to age is not always due to the specific complications of the pancreatitis per se (20). Our results show that, though sensitivity

was low (55%), the factor age showed the highest specificity (88%) and positive predictive value for death (86%). Age is not included in MOF and SSS scoring, but the influence of this variable as part of the APACHE II score, and Ranson and Imrie score is clear from table 5. When age was excluded the sensitivity of these scores was greatly reduced.

Our results demonstrate that prolonged ICU-stay was not necessarily an unfavourable prognostic factor, as 68% of the non-survivors died during the first 3 weeks in the ICU, whereas only two of the 17 survivors could be discharged from the ICU in the same period.

In conclusion, we advocate the APACHE II score for grading the severity of disease on admission hospital or ICU. For monitoring the grade of organ dysfunction and intensity of supportive treatment the MOF score is well suited. Use of these two scoring methods with consideration of the patient's age permits a fairly good prediction of outcome in patients with AHNP.

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SCORING SYSTEMS AND BLOOD LACTATE IN RELATION TO THE DEVELOPMENT OF ARDS AND MOF IN SEVERELY TRAUMATIZED PATIENTS

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Abstract

In 56 polytraumatized patients with an ISS ≥ 33 we prospectively collected data of seven scoring systems (ISS, TS, TRISS, GCS, PTS, APACHE II, SSS) and sequentially determined blood lactate concentrations. These data were analysed in relation to later developing Adult Respiratory Distress Syndrome (ARDS) and Multiple Organ Failure (MOF).

Twenty-two patients developed ARDS and 18 MOF. Of the mentioned scoring systems only ISS, PTS and SSS were predictive of subsequent ARDS, and only ISS and SSS of subsequent MOF. Lactate concentrations at day 2, 3 and 4 were significantly different between patients with and without subsequent ARDS and/or MOF. Surprisingly, APACHE II did not correlate with subsequent ARDS and/or MOF, nor showed any significant relation with lactate concentration at any time. By stepwise regression analysis ISS, SSS and lactate at day 3 were the most significant variables toward the development of ARDS and MOF.

It is concluded that scoring systems directly grading the severity of groups of trauma patients have predictive value for late and remote complications such as ARDS and MOF, while scoring systems that grade the physiologic response to trauma - though clearly related to mortality - have no such predictive value.

Introduction

Measuring the severity of illness, the degree of sepsis, the severity of trauma or the intensity of organ failure by scoring systems has been subject of many studies. Most of these studies had mortality as endpoint. As ARDS and MOF are the major cause of prolonged intensive care treatment and put a heavy burden on health care, it is imperative to identify markers that predict these syndromes (1,2). In polytraumatized patients at risk of death and late and/or remote complications, such as ARDS and MOF, almost any of these scoring systems may be applied, depending on the time after injury or the topic of interest during the clinical course.

Multiple trauma often leads to shock with ischemic injury and tissue hypoxia. As soon as oxygen supply falls below the critical level, blood lactate starts to rise, reflecting anaerobic metabolism as response to the oxygen debt (3-5). A clear correlation between blood lactate levels and circulatory shock has frequently been shown and in septic shock lactate is one of the most reliable predictors of outcome (3,4,6,7). Regar-

ding polytrauma only a few reports studied the correlation between the severity of injury and plasma lactate concentrations (8-10).

In the present study we evaluate the relative value of several scoring systems for severity of injury or illness and plasma lactate concentrations in relation to the development of ARDS and/or MOF in severe polytraumatized patients.

Scoring systems (see appendix)

Injury Severity Score

In 1974 Baker et al. devised the Injury Severity Score (ISS) based upon the Abbreviated Injury Scale (AIS) by summing the squares of the 3 highest values obtained in five body regions, with 0 points for no injury and 5 points for a critical lesion (11). The maximal ISS then is 75. ISS scores the severity of anatomical injury in victims of blunt trauma and correlates well with mortality (10-14). The Hospital Trauma Index (HTI) is an adaptation of AIS, containing both anatomical and physiological elements in six body regions (15). As HTI utilizes more objective diagnoses, its use instead of AIS was advocated (12). Nevertheless, a very good correlation between ISS-HTI and ISS-AIS has been shown (13). The main criticism on ISS concentrates on two elements: 1. there is a systematical underprediction of death, as ISS fails to identify the patient population in which death occurs from head injury (12,16,17); 2. there is no adjustment for age as a risk factor. A solution to this latter problem has been offered by Bull's probit method, weighting age and ISS, or by the TRISS method (14,18). ISS is the most widely used system for grading the severity of injury. Attempts to improve the score by adding biochemical data or varying AIS values have failed until today (10).

Trauma Score

The Trauma Score (TS) was developed in 1980 by Champion et al. for rapid assessment and field triage of the injured patient (16). The score also can be used for reviewing prehospital care. TS measures physiological changes caused by the injury. It consists of simple respiratory and hemodynamic information, combined with the Glasgow Coma Scale. The score ranges from 1 (worst) to 16 (best prognosis). TS has been shown to have a high predictive power as to survival and death (16,19,20).

TRISS method

Physiologic (TS), as well as anatomic characteristics (ISS) and age are combined in the TRISS method, which is used to quantify probability of survival after injury (18,20). The method was especially developed for evaluating trauma care, but can of course be applied to any individual patient to estimate the probability of survival. The formula is:

$$Ps = 1 / (1 + e^{-b})$$

where Ps is the probability of survival, $b = b0 + b1(TS) + b2(ISS) + b3(A)$, with A = 0 if the patient's age is ≤ 54 and A = 1 if the age is > 55; b0...3 are coefficients derived from the Walker-Duncan regression analysis applied to data from thousands of analyzed polytrauma patients. These coefficients can change over time, as improved trauma care may lead to a decreased mortality. By substituting the calculated TS, ISS, age and the latest published coefficients the probability of survival (Ps) or death (1-Ps) can be calculated. More recently the Trauma Score has been replaced by the Revised Trauma Score (RTS) and in combination with new coefficients, this led to an improvement of prediction (18). At this time calculation of the RTS is reserved for after the fact evaluation of trauma care (18).

Glasgow Coma Scale

In 1974 Teasdale and Jennet introduced the Glasgow Coma Scale (GCS), a simple, reliable and generally applicable method for assessment and recording of the altered level of consciousness (21). Three aspects of behavior are scored independently: eye opening, best motor response and best verbal response. The scale ranges from 3 (worst) to 15 (best). One must realise that additional injuries can negatively influence brain function as measured by GCS on admission (22). But as approximately 50% of the patients with severe head injury die, the information provided by the GCS is essential (10,12,20). The GCS also showed a good correlation with functional outcome of the survivors (21,23,24). The interobserver disagreement of GCS is very low, even in inexperienced or unskilled hands (19,21). Undoubtedly therefore, the GCS has been incorporated in other scoring systems, such as the Trauma Score, APACHE II and Polytrauma Score.

The Polytrauma Score

The Polytrauma Score (PTS), developed in Hannover, Germany, in 1985, is an anatomical injury severity score including an age classification (17). In later publications the score was revised, with inclusion of the Horrowitz index (PaO2 / FiO2) and Base Excess, while the GCS was used to grade the severity of head injury (25). The score is thought to be more practicable than the ISS, while featuring an excellent correlation with the ISS (17,26,27). A recent study revealed that the interobserver disagreement in PTS was significantly less compared to ISS (27). In the present study we used the original PTS.

APACHE II

In 1985 Knaus et al. presented APACHE II, being a revised version of APACHE (Acute Physiologic And Chronic Health Evaluation), a severity of disease classification system developed to stratify acutely ill patients admitted to the ICU (28). Increasing scores (range 0 to 71) closely correlate with subsequent hospital death. The score consists of an acute physiologic score (APS), an age score and a chronic health score. APS is determined from the most deranged physiologic values during the initial 24 hours after ICU admission. While APACHE II was not developed for follow up of the clinical course, many studies showed that it is usefull in this respect (using daily APACHE II) and for studying the response to treatment (29).

Sepsis Severity Score

In 1983 Stevens developed the Sepsis Severity Score (SSS) for grading the severity of surgical sepsis (30). The system consists of a 6 point scale in seven important organ systems: lung, kidney, coagulation, cardiovascular, liver, GI tract and neurologic.
The final score is calculated by adding the squares of the 3 highest values of the 3 organs with the most severe dysfunction. Several studies showed significantly different scores in survivors versus non-survivors and the score correlated well with the length of hospital stay in survivors (26,30,31). In fact the SSS scores the degree of multiple organ failure (26). In the present study we used a modification of the score by summing the points obtained in all 7 organ systems, leading to a maximum score of 35 points.

Multiple Organ Failure score

The Multiple Organ Failure score (MOF score) was developed by Goris et al. in 1985 to grade the (dys)function of the 7 main organ systems: the pulmonary, cardiovascular, hepatic, renal, central-nervous, hematologic and gastro-intestinal system (1). It consists of a 3 point scale (maximum score is 14). As the MOF score includes the intensity of therapeutic interventions necessary to support organ function as well as the severity of organ dysfunctions, this system accurately assesses the severity of MOF. It is well suited for follow up during ICU treatment and correlates well with outcome (1,29).

Patients and methods

During a two year period, data from 56 polytraumatized patients were prospectively collected as part of a multicentre trial on the evaluation of inflammatory mediators. Patients with blunt trauma, were admitted to 3 trauma hospitals in Europe (Innsbruck, Nijmegen and Vienna). Patients were included in the study if ISS (HTI) ≥ 33, which equals at least two severe lesions in different body regions or one severe and two major lesions in three different regions. Extensive data collection was performed on admission and further daily during ICU admission. Bloodsampling was done daily in the first week and every other day in the second week. Three aspects were subject of our study: mortality, ARDS and MOF.

Late lung failure or ARDS was defined as an average Benzer Quotient > 0.45, from day 5 to day 14. The "Benzer Quotient" is the alveolar-arterial oxygen quotient: PAO2 - PaO2/ PAO2 (32). This Quotient has been shown to differentiate patients with acute lung failure (ARDS) from those with other pulmonary dysfunctions like, e.g. obstructive airway diseases (32).

Multiple organ failure (MOF) was defined as an average MOF score ≥ 4 from day 5 to day 14. According to this definition, in our study all patients with a MOF score of 5 or more (a definition used before) were included, while patients that had only an incidental MOF score of 5 were excluded (1,29,33).

Scoring systems were utilized as described above. Table 3.1 gives an overview of the time relation of the application of the scores.

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Table 3.1

Time table that shows the application of scores, lactate determinations and definition of ARDS and MOF.

	On admission	Within 24 hours	Daily	Average day 5-14
ISS		x		
TS	x			
TRISS		x		
GCS	x			
PTS		x		
APACHE II		x		
SSS		x		
MOF Score			x	x
Benzer Quotient			x	x
Lactate			x	

TS and GCS were scored on admission. ISS, PTS and TRISS were calculated from data collected on the first day of admission; for APACHE II and SSS we used the highest values within the first 24 hours after admission.

Statistical analyses were performed using the Kruskall Wallis test and Wilcoxon two sample test for comparison between groups. Spearman's correlation coefficients were calculated to assess correlations between several parameters. A p value < 0.05 was considered to be significant.

Results

Fifty-six patients entered the study, 10 women and 46 men. The mean age was 33 years (range 14-71). By inclusion criteria all patients had an ISS of ≥ 33.

Mortality was 14%, as only 8 patients died. Table 3.2 shows the cause of death in these patients. ARDS was diagnosed in 22 patients; 29 patients had no ARDS,

whereas 5 patients already died before day 5. The mean (± SD) ICU stay of patients with ARDS was 29 ± 15 days, and without ARDS 14 ± 12 days (p < 0.0001).

Table 3.2

Causes and day of death, ISS, age, GCS on admission and probability of survival (TRISS) of eigth patients with severe polytrauma.

patient number	age	day of death	ISS	GCS	Probability of survival, TRISS (%)	cause of death
1	16	1	50	10	1%	severe thoracic injury ruptured lungs
2	19	3	38	5	30%	brain death
3	23	3	75	3	2%	severe thoracic injury and brain death
4	26	3	57	3	15%	brain death
5	50	3	57	15	70%	coagulopathy, ARDS + acute renal failure (= early MOF)
6	29	6	57	3	15%	acute renal failure and brain death
7	29	9	50	3	2%	MOF
8	37	37	57	3	1%	MOF

According to the definition utilized, 18 patients developed MOF. The average ICU stay of MOF patients was 32 ± 18 days, and 15 ± 9 days (p = 0.0003) in 33 patients without MOF.

Table 3.3 shows the mean values (± SD) of seven scores as regards mortality. All scoring systems, except PTS and GCS, showed a significant difference between survivors and non-survivors. PTS and GCS showed only an indication of significance with p values of 0.07 and 0.09, respectively.

Table 3.3

Mean values (± SD) of seven scoring systems in survivors (n=48) and non-survivors (n=8).

	Survivors	Non-survivors	P-value
ISS	44.3 ± 9.8	55.1 ± 10.1	0.006**
TS	10.3 ± 3.3	6.6 ± 3.4	0.009**
TRISS	0.53 ± 0.34	0.18 ± 0.23	0.004**
GCS	8.5 ± 4.8	5.6 ± 4.5	0.09
PTS	39.1 ± 17.0	49.8 ± 17.2	0.07
APACHE II	15.7 ± 7.7	24.3 ± 7.7	0.02*
SSS	10.5 ± 2.9	14.1 ± 4.1	0.01*

$*$ = $p < 0.05$ and $**$ = $p < 0.01$, by Wilcoxon's test.

In table 3.4 and 3.5 the results of the scores are presented concerning ARDS and MOF. Only ISS and PTS showed significant differences between patients with and without ARDS. ISS and SSS were the only two scores that significantly differentiated between patients with and without MOF.

Table 3.6 shows the relationship between the scoring systems and later developing ARDS (average Benzer Quotient) or multiple organ failure (average MOF score). Again significant correlations only existed between ISS and ARDS ($r = 0.40$) and between ISS ($r = 0.38$), SSS ($r = 0.43$) and MOF.

Table 3.4

Mean values (± SD) of 7 scoring systems in 51 patients with ARDS (n=22) and without ARDS (n=29).

	No ARDS	ARDS	P-value
ISS	42.1 ± 7.2	48.5 ± 11.6	0.04*
TS	9.5 ± 3.7	10.6 ± 3.4	0.22
TRISS	0.51 ± 0.36	0.50 ± 0.34	0.84
GCS	7.6 ± 4.9	8.9 ± 4.7	0.31
PTS	39.5 ± 14.2	45.8 ± 18.9	0.03*
APACHE II	17.2 ± 8.6	15.3 ± 8.0	0.45
SSS	10.5 ± 3.4	11.3 ± 3.1	0.21

* = p <0.05, by Wilcoxon's test.

Table 3.5

Mean values (± SD) of 7 scoring systems in 51 patients with MOF (n=18) and without MOF (n=33).

	No MOF	MOF	P-value
ISS	42.6 ± 8.1	49.1 ± 11.5	0.03*
TS	10.5 ± 3.5	9.0 ± 3.7	0.19
TRISS	0.55 ± 0.34	0.42 ± 0.36	0.11
GCS	9.1 ± 4.9	6.3 ± 4.2	0.06
PTS	40.5 ± 18.5	38.6 ± 14.3	0.97
APACHE II	15.7 ± 7.5	17.6 ± 9.8	0.63
SSS	9.9 ± 2.8	12.6 ± 3.5	0.01*

* = p <0.05, by Wilcoxon's test.

Table 3.6

Relationship expressed by Spearman's correlation coefficients (r.) of seven scoring systems and mean values of scoring for MOF and ARDS (Benzer Quotient) in 51 patients.

	Mean MOF score		Mean Benzer Quotient	
	r.	P-value	r.	P-value
ISS	0.38	0.005	0.40*	0.003
TS	-0.28	0.04	0.04	0.78
TRISS	-0.32	0.02	0.19	0.17
GCS	-0.34	0.01	-0.03	0.80
PTS	0.01	0.93	0.25	0.07
APACHE II	0.13	0.35	0.12	0.41
SSS	0.43*	0.001	0.17	0.21

(* = significant and relevant correlation with r ≥ 0.4 and p < 0.05).

As regards mortality, lactate levels were significantly different between survivors and non-survivors at day 2 (p < 0.05). Figures 3.1 and 3.2 illustrate the lactate levels during the first week of admission. Lactate levels in patients later developing ARDS showed an indication of significance at day 2 (p = 0.08) and were significantly higher at day 3, 4 and 5. Lactate levels were significantly higher in patients later developing MOF, beginning at day 2 and persistend so at day 3 and 4. Lactate concentrations correlated well with the mean MOF score (from day 5 to 14): at day 2 (r = 0.56, p = 0.0001; at day 3 (r = 0.49, p < 0.001); and at day 4 (r = 0.45, p < 0.005). The correlation between lactate concentrations and mean Benzer Quotient was only relevant at day 3 (r = 0.37 p = 0.01).

Table 3.7

Relationship expressed by Spearman's correlation coefficients (r.) of seven scoring systems and serum lactate concentrations of the first three days of admission in 56 patients after severe poly-trauma.

	Lactate day 1		Lactate day 2		Lactate day 3	
	r.	P-value	r.	P-value	r.	P-value
ISS	0.23	0.11	0.23	0.09	0.43*	0.002
TS	-0.13	0.39	-0.18	0.19	-0.15	0.28
TRISS	-0.18	0.23	-0.22	0.09	-0.29	0.04
GCS	-0.16	0.26	-0.27	0.04	-0.23	0.10
PTS	0.29	0.05	0.07	0.58	0.19	0.18
APACHE II	-0.002	0.99	-0.10	0.48	-0.001	0.99
SSS	0.15	0.30	0.37	0.004	0.43*	0.001

(* = significant and relevant correlation with $r \geq 0.4$ and $p < 0.05$).

In table 3.7 the relations between the seven scores and lactate concentrations of the first three days are given. Relevant correlations ($r \geq 0.4$ and $p < 0.05$) were only found between ISS and SSS and lactate concentration of day 3.

Strikingly, APACHE II (highest value within 24 hours) - although significantly different between survivors and non-survivors - had no correlation with subsequent ARDS or MOF, nor showed any significant differences between patients with and without ARDS and/or MOF. Moreover, it had no significant correlation with any lactate concentration measured at any time.

Finally, stepwise regression procedures showed lactate levels at day 3 and SSS (highest value within 24 hours) to be the best predictors of MOF, and ISS to be the best predictor of ARDS ($p < 0.05$).

Figure 3.1

Mean lactate levels (+ SD) of 51 polytraumatized patients divided into patients with ARDS (n=22) and without ARDS (n=29), (* = p < 0.05).
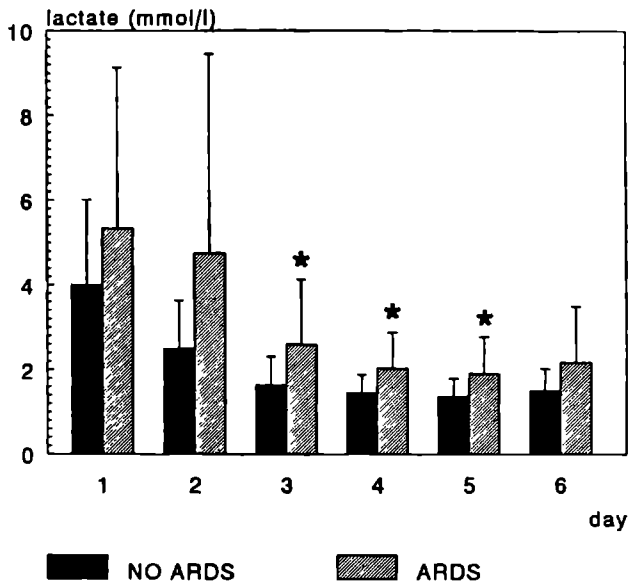
Figure 3.2

Mean lactate levels (+ SD) of 51 polytraumatized patients divided into patients with MOF (n=18) and without MOF (n=33), (* = p < 0.05).
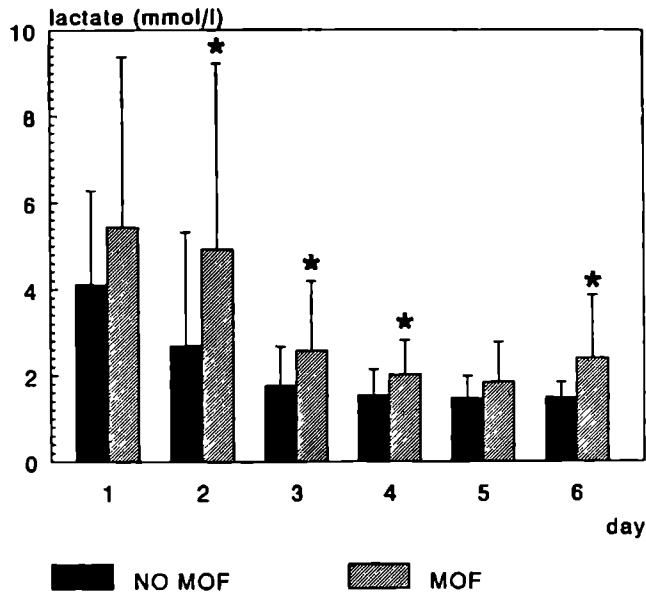
Discussion

In the present study we evaluated the relevance of several scoring systems and blood lactate concentrations in relation to the development of ARDS and/or MOF in polytraumatized patients. Evidence is accumulating that a multicascade of inflammatory responses to different initiating events, such as trauma, sepsis, pancreatitis, and hemorrhagic shock, finally may lead to ARDS and MOF (2,34). We were specially interested to study mediators and markers (risk factors) of this inflammatory cascade to unravel the possible correlations with and predictive values for subsequent ARDS and/or MOF. For trauma patients, the primary event in the inflammatory cascade of course is the injury and tissue damage itself. Severity of injury scoring systems may grade the intensity of this event. Circulatory shock and tissue hypoxia are directly associated with polytrauma. In this respect blood lactate level could be an informative marker. We will discuss the relevance of injury severity scoring (event-grading) and lactate (marker) for subsequent ARDS and MOF (see figure 3.3).

Figure 3.3

Schematic diagram illustrating the relations of subsequent events, severity grading and markers for the development of Multiple Organ Failure after polytrauma.
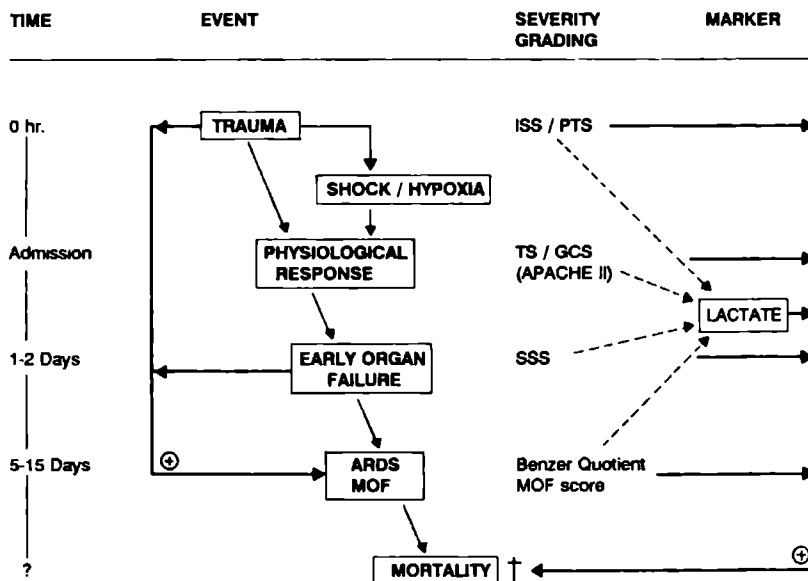
It should be emphazised that ISS and PTS particularly score the anatomical severity of injury, while TS scores the physiologic reactions of the organism to trauma at a certain moment. Also the GCS scores the physiologic response of one organ system: the central nervous system. TRISS compiles anatomical severity of trauma with the physiologic response, considering the patient's age. APACHE II includes no information on the severity of injury, but grades the physiological dysregulation - whatever the intensity of treatment - in combination with prehospital condition and age. In contrast to APACHE II, SSS grades not only the degree of physiological dysregulation in 7 organ systems, but also incorporates the intensity of treatment, necessary to support these organ systems. In this aspect it is similar to the MOF score.

The present study demonstrates that the only relevant scoring systems, accurately predicting ARDS and/or MOF in groups of patients with severe polytrauma, are the anatomical severity (and quantity) of injury scores (ISS and PTS) on one hand, and SSS that grades the intensity of initial organ dysfunction and support on the other hand. As SSS in fact is an organ failure scoring system it seems logical that it significantly correlates with later developing MOF.

But the importance of SSS for subsequent ARDS and/or MOF fits within the concept that early organ failure, which is partly reversible, is the prerequisite for late MOF (34). It must be emphazised, however, that the statistically significant differences found between patients at the group level are likely to be very helpful in the individual patient, due to the large degree of overlap between the groups (table 4 and 5). The same is true for the statistically significant correlations found between scoring systems and ARDS/MOF, which actually are weak correlations, especially when considered in an individual patient. Nonetheless, despite these limitations the application of these scores in groups of patients reveals relevant information.

Surprisingly, the physiological dysregulations measured initially by TS, GCS or APACHE II have no predictive value at all toward ARDS and MOF. These data confirm the findings of Cerra et al., who showed that APACHE II had no relevant ability to predict the development of MOF in postoperative surgical patients (35). A possible explanation for this finding in the present study of polytraumatized patients concentrates on three important aspects of APACHE II: age, chronic health evaluation and GCS. We studied relatively young patients with healthy prehospital status. The patients had been operatively stabilized before admission to ICU. In this postoperative setting it is difficult to score GCS adequately. A recent study showed that GCS soon after arrival at the emergency department had no predictive power toward outcome in patients after severe head injury (24). These authors pointed out that the GCS

originally was proposed to be applied at least 6 hours after trauma. But in postoperative polytraumatized patients, who are ventilated and heavily sedated, this is hardly possible. On the other hand, the GCS on admission may negatively be influenced by factors not related to the anatomical severity of brain injury, such as additional injuries, shock and hypoxemia (22). Although in the present study 6 of 8 patients that died, had a very low GCS ($\leq$ 5) on admission and 4 of them died because of the severity of brain injury, GCS did not identify patients later developing ARDS and/or MOF.

Next to the severity of the traumatic event, tissue hypoxia as reflected by lactate concentrations was studied in correlation to subsequent ARDS and MOF. Some studies pointed out a positive correlation of lactate levels with mortality in polytraumatized patients, but only few studies showed a correlation between lactate and later developing ARDS and MOF (8-10,33,35).

It must be realised that the cause of high lactate levels in the initial phase after trauma is different from high lactate levels seen in patients with established ARDS and MOF (36). The latter probably is the consequence of the inability of the tissues to extract oxygen and to use it efficiently (37). This type of hypoxia with elevated blood lactate - found at the end of the cascade that leads to MOF - closes a vicious cicle as it causes more organ dysfunction. The higher lactate levels found at day 5 and 6 in patients with ARDS and/or MOF support this concept. Our data further demonstrate that persisting high lactate levels in the first three days post-injury not only correlate well with the most relevant scoring systems ISS and SSS (table 3.7), but also confirm the predictive value of lactate levels toward subsequent ARDS and/or MOF (fig. 3.1 and 3.2). Moreover, stepwise regression procedures showed that both parameters (ISS - SSS and lactate at day 3) independently were of significant importance for the development of these two syndromes.

Finally, we conclude that in polytraumatized patients anatomical injury severity scoring systems (like ISS) positively correlate with subsequent ARDS and MOF. Scoring systems that grade the degree of early organ failure (like SSS) and serial lactate measurements similarly predict ARDS and/or MOF. Because therapeutical efforts to improve outcome of established ARDS and MOF have failed until now, the focus must be on prevention of these syndromes. As the severity of injury itself cannot be changed, agressive early and rapid resuscitation is necessary to diminish the accompaning hypoxic injury.

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INFLAMMATORY MEDIATORS IN RELATION TO THE DEVELOPMENT OF MOF IN PATIENTS FOLLOWING SEVERE BLUNT TRAUMA

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Abstract

We prospectively evaluated several inflammatory mediators or markers (C3, C3a, terminal complement complex -TCC-, thromboxane B2 -TxB2-, C-reactive protein - CRP-, elastase, and neopterin) in 56 patients following severe blunt trauma (ISS ≥ 33). Major aims of study were the analysis of the relation between inflammatory mediators and scoring systems, multiple organ failure (MOF) and mortality.

Elastase levels showed the best correlation with severity of injury (corr. coefficient at day 1 with ISS r = 0.50, with Trauma Score r = -0.63).

Non-survivors (n=8) had significantly higher C3a and elastase levels on the first post-injury day, compared with survivors (n=48). No difference between these groups was found for TCC, TxB2, CRP, and the neopterin/creatinine ratio.

Five patients died before day 5. Eigthteen patients developed MOF, which was diagnosed from day 5 onwards, leaving 33 patients without MOF. The patients with subsequent MOF showed significantly higher (mean ± SEM) levels of C3a (914 ± 190 ng/ml), TCC (57 ± 17 U/ml), and TxB2 (275 ± 37 pg/ml) at the first post-injury day, than the patients without MOF (566 ± 110 ng/ml, 27 ± 2 U/ml, and 169 ± 14 pg/ml, respectively). In patients with MOF elastase levels were significantly higher at day 2, 3, 4, and 5 post-injury. Neopterin/creatinine ratios, on the other hand, were significantly higher in patients with MOF when MOF already had established (at day 8 and 10).

From the present data it is concluded that in polytrauma patients excessive triggering of the inflammatory cascade, as expressed by complement activation and stimulation of polymorphonuclear leukocytes producing elastase, plays an important and early role in the development of MOF.

Introduction

Death after polytrauma occurs either immediately at the scene of the accident or within hours after the event when patients are hospitalized (1). These fatalities are mainly due to the severity of injury or to direct complications from the primary injury. The third possibility then is late death after days or even weeks, because of complications in remote organ systems not necessarily affected by the primary trauma. In the latter group most patients die of adult respiratory distress syndrome (ARDS) and multiple organ failure (MOF), syndromes that are thought to have one common pathophysiological background (2,3). This group is of special interest, not only

because of the great impact these patients have on ICU occupation, but also because the mechanisms leading to ARDS/MOF and subsequent death still have to be unravelled.

In polytrauma patients head injury accounts for approximately 50% of the deaths, hemorrhage for about 10 - 15% and ARDS, MOF and sepsis for approximately 30 - 35% (4,5). The incidence of MOF after polytrauma varies from 21 - 47% (4-7) and mortality within this group from 20 - 30%, depending on patient populations studied and definitions used. Unfortunately, there is still no general consensus about the definition of this syndrome and therefore conclusions of various reports are difficult to compare and can lead to contradictory findings.

It remains puzzling why in two patients, with equal preexisting condition, similar trauma and treatment, one recovers within few days and the other develops ARDS and MOF and subsequently dies. One hypothesis on this paradigm is that a varying inflammatory reaction following trauma may lead to a sequential autodestructive process in various organ systems (2).

The present study on polytrauma patients was performed to investigate the role of mediators and markers of the inflammatory cascades in relation to scoring systems for severity of injury and disease, the development of MOF, and mortality. The following parts of the inflammatory cascades were studied: complement activation, acute phase protein synthesis, thromboxane production, polymorphonuclear leukocyte (PMN) and macrophage activation.

Complement activation

Complement activation plays a central role in the inflammatory cascade, because of the release of anaphylatoxins, that trigger a series of other biological events (8).

C3 is the initial key component that is activated either by the classical or the alternative pathway, the latter being the main route after trauma (8). From the activated split products we chose C3a for measurement, because other products are more rapidly cleared from the circulation (9). C3a and its ratio with C3 (C3a/C3) has been shown to correlate positively with outcome after trauma or septic shock (8-10). In addition, we measured the Terminal Complement Complex (TCC), which is a complex formed by C5b, C6, C7, C8 and C9 and indicates the activation of the terminal complement pathway (11). Since the generation of TCC requires activation of C5 to C5a and C5b, TCC can be used as an indirect indicator of C5a formation (12).

C-Reactive Protein

The acute phase reaction is a general and non-specific response to most forms of infective and non-infective inflammatory processes, trauma, tissue necrosis and neoplasias (13). C-reactive protein (CRP) is a fast reacting acute phase protein, synthesized by hepatocytes under the influence of humoral mediators, such as prostaglandin-E1 or, especially, interleukin-6 (14). It may play a vital role as an opsonic protein in the immediate post-injury period when complement is consumed (15). It probably acts primarily as a protective mechanism, but in some circumstances CRP may also initiate or exacerbate inflammatory lesions (13). Some studies showed a positive correlation between the severity of (surgical) trauma and levels of CRP (16,17).

Thromboxane B2

Eicosanoids, with a broad spectrum of biological activities, represent a class of lipid mediators, derived from polyunsaturated fatty acids (18). The major natural source is arachidonic acid. Enzymatic catalysation of arachidonic acid leads to either prostaglandins and thromboxanes by the cyclooxygenase pathway, or to leukotrienes by the lipoxygenase pathway. In the present study thromboxane B2 (TxB2), which is the inactive metabolite of the main biologically active product thromboxane A2 that is known to have strong vasoactive and platelet stimulatory effects (18), was chosen to evaluate the cyclooxygenase pathway. Many different inflammatory triggers (e.g. allergic reactions, toxic oxygen radicals, endotoxin) and especially septic or circulatory shock are associated with enhanced eicosanoid formation (18,19).

Elastase

There is plenty of evidence that PMNs play a major part in triggering complications in septic or post-traumatic patients (6,9). The enzyme elastase is released from stimulated PMN's at the site of injury, infection or inflammation and can cause tissue damage and subsequent organ dysfunction. By measuring the complex of elastase with its inhibitor α1-proteinase (Elastase-α1 PI) in plasma, the degree of PMN activation can be quantified (20,21).

Neopterin

There is increasing evidence that activated macrophages play a key role in the autodestructive inflammatory response to traumatic or septic events (3). After immune stimulation, e.g. by endotoxin or τ-interferon, activated macrophages produce and excrete the inactive metabolite neopterin (22). Neopterin is cleared from the circulation in a creatinine-like manner and can be measured in blood as well as urine (23,24). To correct for possible renal insufficiency, we therefore used the neopterin / creatinine ratio to grade macrophage activation.

Patients and methods

During a two year period, data from 56 polytraumatized patients were prospectively collected as part of a multicenter trial on the evaluation of inflammatory mediators and scoring systems (25). Patients with blunt trauma were admitted to 3 trauma hospitals in Europe (Innsbruck, Nijmegen and Vienna). Patients were included in the study if Injury Severity Score (ISS) (26) calculated from the Hospital Trauma Index (HTI) (27) was $\geq$ 33, which represents at least two severe lesions in different body regions or one severe and two major lesions in three different regions. On admission the severity of injury was graded by the ISS as well as the Trauma Score (TS) (28). Extensive data collection was performed on admission and daily during ICU admission, up to two weeks after injury.

Blood sampling at the ICU was done daily in the first week and every other day in the second week. Biochemical measurements were performed as follows: C3a was determined by ELISA technique according to Zilow et al.(29), C3 by radio-immuno-diffusion (NOR-Partigen, Behring Diagnostics, FRG) and TCC according to Deppisch et al.(30), CRP by an immuno-turbidometric assay (Orion Diagnostica, Espoo, Finland), thromboxane B2 by RIA as described by Flynn et al.(31), elastase-α1 proteinase inhibitor complex by ELISA (Merck, Darmstadt, FRG) and neopterin was determined using a RIA (Henning, Berlin, FRG) with neopterin/creatinine ratio expressed as μmol/mol.

Three items were subject of our mediator study: scoring systems, MOF and mortality. Survivors were defined as patients discharged from hospital alive; non-survivors were patients that died in hospital because of any post-traumatic complication.

For all patients APACHE II score (32) and MOF score (2,33) were calculated daily. For

determination of the MOF score and APACHE II the most deranged values of the various contributing parameters of each day were used.

The MOF score according to Goris et al.(2) grades organ function as normal (0 point), moderately disturbed (1 point) or severely disturbed (2 points), with a maximum of 14 points in seven main organ systems (table 1). MOF was defined as an average MOF score ≥ 4, from day 5 to day 14 (25).

Statistical analyses were performed using the Wilcoxon two sample test for comparison between groups. Spearman's correlation coefficients were calculated to assess correlations between several parameters. $P < 0.05$ was considered to be significant.

Results

Fifty six patients entered the study, 10 women and 46 men. The mean age was 33 years (range 14 - 71). The mean ($\pm$SD) ISS of all patients was 46 $\pm$ 10 (range 33 - 75). Mortality was 14%, as 8 patients died. Table 4.2 shows the cause of death and the day after admission these patients died. Mean ISS of survivors was 44 $\pm$ 10 and of non-survivors 55 $\pm$ 10 ($p < 0.01$).

As five patients died early (within 3 days) we only provide data concerning inflammatory mediators in relation to mortality of the first day of admission. Differences between survivors and non-survivors for the various mediators are shown in table 4.3. At day 1 only complement activation, expressed by C3a/C3 ratios, and elastase levels were significantly different between survivors and non-survivors. The differences for the C3a/C3 ratios were mainly caused by significantly increased levels of C3a in the non-survivors. TCC showed a tendency towards higher levels in non-survivors compared to survivors ($p = 0.07$).

Correlation analyses of mediators during the first four post-injury days and injury severity scoring systems (ISS and TS) are shown in table 4.4. ISS correlated significantly with TCC on day 1, 2 and 4 and with elastase on the first three days post-injury. No significant correlations were found between ISS and the other mediators during this period. TS on the other hand, showed significant correlations with C3a/C3 ratios almost continously during the whole observation period, mainly because of significantly inverse correlations between TS and C3a. (The higher levels of activated complement correlate with a worse (lower) Trauma Score). The same was true for TS and elastase. Except for a significant correlation between TS and CRP levels on day 3 and 4, no other mediators showed significant correlations with TS in the early post-

injury period.

Table 4.2

Injury Severity Scores (ISS), cause and day of death in the eight patients that died.

patient nr.	ISS	day	cause
1	50	1	severe thoracic injury ruptured lungs
2	38	3	brain death
3	75	3	severe thoracic Injury and brain death
4	57	3	brain death
5	57	3	coagulopathy, ARDS + acute renal failure (= early MOF)
6	57	6	acute renal failure and brain death
7	50	9	MOF
8	57	37	MOF

Table 4.3

Inflammatory mediators (mean ± SD) in survivors (n=48) and non-survivors (n=8) determined on the first day after injury. * = $p < 0.05$ and ** = $p < 0.01$, by Wilcoxon.

	Survivors	Non-survivors	P-value
C3 (mg/ml)	0.67 (0.31)	0.71 (0.28)	0.32
C3a (ng/ml)	604 (571)	1331 (619)	0.01*
C3a/C3 x 1000	0.96 (0.79)	3.23 (4.24)	< 0.001**
TCC (U/ml)	36 (34)	53 (28)	0.07
CRP (mg/l)	55 (51)	33 (24)	0.41
TxB2 (pg/ml)	194 (92)	237 (155)	0.19
Elastase (ng/ml)	539 (337)	1006 (287)	0.03*
Neop/creat (μmol/mol)	837 (488)	906 (476)	0.71

Table 4.4

Spearman's correlation coefficients between several mediators and two injury severity grading systems applied on admission: Injury Severity Score (ISS) and Trauma Score (TS), during the first four days of admission (* = $p < 0.05$ and ** = $p < 0.01$).

(4.4 a) ISS

MEDIATOR	DAY			
	1	2	3	4
C3	0.15	0.19	0.05	-0.05
C3a	0.19	0.30*	0.12	0.15
C3a/C3 x 1000	0.10	0.25	0.18	0.20
TCC	0.53**	0.38*	0.25	0.44**
CRP	-0.01	0.11	0.19	0.14
Elastase	0.50*	0.53*	0.43*	0.28
Neop/creat	0.16	0.15	0.14	0.009
TxB2	0.28	-0.11	-0.02	-0.15

(4.4 b) TS

MEDIATOR	DAY			
	1	2	3	4
C3	0.01	0.09	0.05	0.22
C3a	-0.29	-0.39*	-0.29*	-0.22
C3a/C3 x 1000	-0.36*	-0.46**	-0.41**	-0.35*
TCC	-0.05	-0.08	-0.06	-0.09
CRP	-0.12	0.17	0.36*	0.47**
Elastase	-0.63*	-0.62**	-0.35*	-0.72**
Neop/creat	-0.23	0.007	0.14	0.15
TxB2	-0.04	-0.11	-0.06	0.09

Significant correlations ($r \geq 0.3$ and $p < 0.05$) were found in the early post-injury period between APACHE II and complement activation (expressed by C3a/C3) (day 1: $r = -0.40$; day 2: $r = -0.48$) and elastase levels (day 1: $r = 0.39$; day 2: $r = 0.33$), but not between APACHE II and TCC, CRP, TxB2 or neopterin/creatinine.

Since five patients died before day 5, 51 patients were left for classification of subgroups with or without MOF. Of these 51 patients, MOF was diagnosed in 18 cases. Figure 4.1 (a+b) shows the mean values ($\pm$ SEM) of six mediators during the two week study period in patients with and without MOF. On day 1 TCC, TxB2 and C3a were significantly higher in patients with MOF, while CRP was lower on day 1 and 2. The most protracted differences between patients with and without MOF were found for elastase: practically the whole first week post-injury the levels were significantly higher in patients with MOF. Neopterin/creatinine ratios did not show any significant difference between both groups during the first week. However, significantly higher neopterin/creatinine ratios were found in patients with MOF at day 8 ($p = 0.04$) and day 10 ($p = 0.005$), while there was an indication of significance at day 12 ($p = 0.06$).

Discussion

In the present report we prospectively evaluated inflammatory mediators in relation to scoring systems for severity of injury and disease, subsequent MOF and mortality.

It should be emphasized that we studied a homogeneous group of severely traumatized patients, who at least had two severe or one severe plus two major lesions in different body regions (= ISS $\geq$ 33). This is in contrast to most other reports, that evaluate a much wider range of "multiple" injured patients, even including those with an ISS of less than 18 points (7,9,12,34). This might implicate that in the present study differences between groups will become less easily evident. On the other hand, if differences between groups occur, they could be pathophysiologically more relevant.

Complement and PMN activation, expressed by C3a or C3a/C3 ratios and elastase levels, respectively, appeared to be the most significant mediators for differentiation between survivors and non-survivors. This is in line with other studies, not only reporting on trauma patients, but also about patients after major elective surgery and sepsis (8,10-12,20,21,35,36).

Figure 4.1 (a)

Mean (± SEM) values of C3a, TCC, CRP, TxB2, Elastase and Neopterin/creatinine ration during a two week ICU observation period in 51 multiple trauma patients with MOF (solid line, n = 18) and without MOF (broken line, n = 33). P values are indicated by asterisks: (*) = 0.05 ≤ p < 0.10, * = p < 0.05 and ** = p < 0.01, by Wilcoxon.
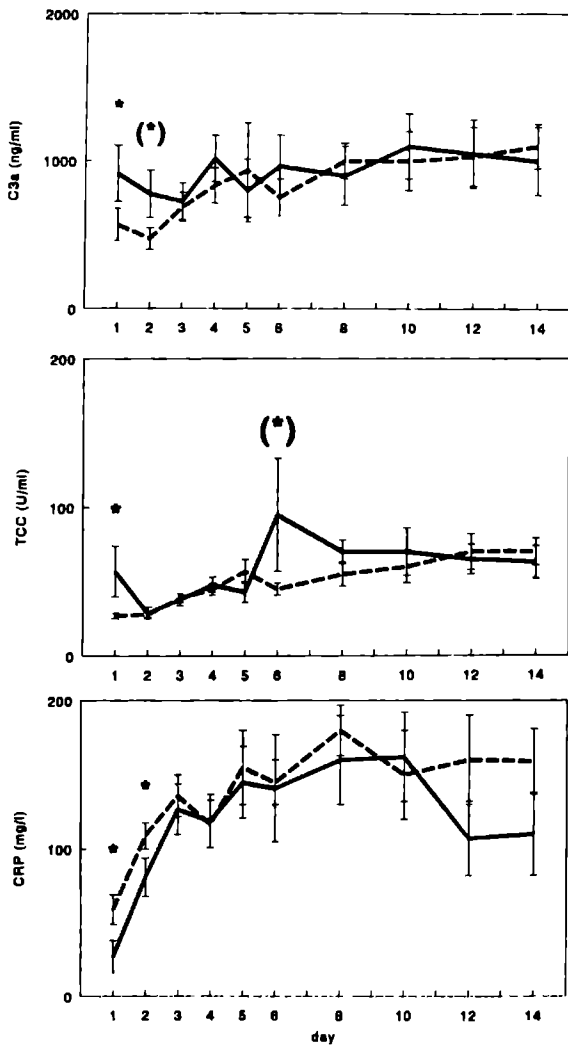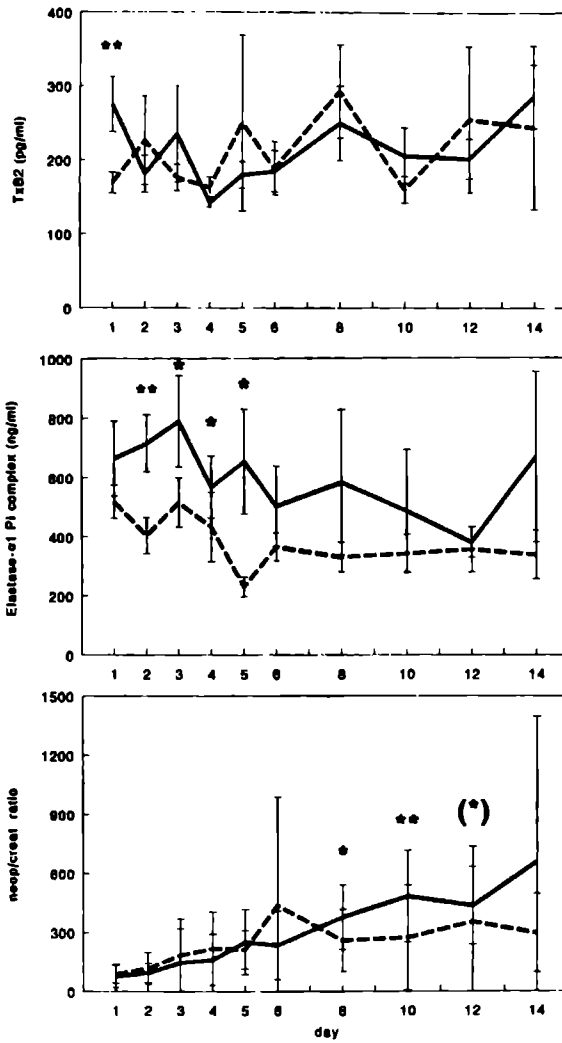
Figure 4.1 (b)

Previously we reported that ISS and TS both could significantly discriminate between survivors and non-survivors, but that only ISS - mainly grading the anatomical severity of injury - showed a good correlation with subsequent ARDS and MOF (25). For TS however - scoring the physiologic reaction of the organism to injury at a certain moment - this relation could not be demonstrated. However, both anatomical (ISS) and physiological (TS) scoring systems showed reasonable correlations with complement activation and elastase levels, but not with CRP, TxB2 or neopterin/creatinine ratio. Good correlations have been demonstrated between the severity of trauma and elastase (6,9,37) and between complement activation and tissue trauma (11,12,34). The importance of the activation of the complement system and PMNs in the post-traumatic course is further underlined by the moderate correlations found with the APACHE II scoring system. This latter scoring system, originally meant for disease classification, gives information about the physiological derangement and necessity of treatment (32).

The most important observation is, that we found significantly higher levels of complement activation (C3a and TCC), as well as TxB2 levels at the first post-injury day in patients with subsequent MOF compared to those without subsequent MOF, while elastase levels were significantly elevated practically the whole first week in the former patients.

CRP concentrations, on the other hand, were initially higher in patients without MOF. This latter finding is not in agreement with a previous report, that showed a similar rise of CRP levels in both patient group with and without MOF during the first four days post-injury, with a significant elevation in MOF patients from day 5 onwards (6). We also could not demonstrate a positive correlation between severity of injury (expressed by ISS and TS) and CRP, while other reports clearly showed that the magnitude of (surgical) trauma correlated well with the levels of CRP production (15-17). A possible explanation could be that the patients in the present study all had such a severe trauma that this led to similar CRP levels according to the "all or nothing phenomenon" theory of Colley et al. (38). On the other hand, it remains questionable to what extent liver damage and insufficiency may contribute to the initial lower CRP production in patients developing MOF.

The role of the prostanoid TxB2 in the development of ARDS and MOF remains unclear. Some authors reported a positive correlation with subsequent ARDS (19,39), while others could not confirm this (40). We could only demonstrate a significantly higher level of TxB2 on the first post-traumatic day in patients with subsequent MOF.

Neopterin concentrations in blood and urine have been shown to predict outcome of

patients with viral infections (including AIDS), autoimmune diseases and graft vs host reactions (41). Also, in multiple trauma and sepsis patients it was demonstrated that increased levels of neopterin are associated with poor outcome (6,7,41). Since neopterin is exclusively eliminated by the kidneys in a creatinine-like manner (23,24), it remains questionable whether the plasma neopterin concentrations may be used as an independent parameter. Nast-Kolb et al.(6) concluded in their study on 69 multiple trauma patients that neopterin was a reliable parameter in predicting subsequent organ failure from day 2 to 5, but after this period elevated neopterin levels were mainly caused by retention due to renal insufficiency (6). In the present series we therefore used the corrected neopterin concentrations during the whole observation period. We could only demonstrate a significant rise of the neopterin/creatinine ratio in MOF patients in the second week. This is in line with the finding of Nathan (42) who concluded that it apparently takes several days for macrophages after activation to fully develop their inflammatory capacity.

The good correlation between neopterin/creatinine and APACHE II during the second observation week indicates that ongoing macrophage activation is related to physiological derangement and organ dysfunction.

The present data support the view that complement activation plays a central and early role in the inflammatory cascade leading to complications and poor outcome in multiple trauma patients. Complement activation is fundamental for bacterial opsonisation and recruitment of inflammatory cells by chemoattraction and elicits the release of lysosomal enzymes, like elastase, and oxygen radicals by PMNs, thus contributing to the defense against microorganisms, but also leading to cell and tissue damage, that ultimately may result in organ failure (11,35).

Elastase indeed appears to be not only a marker of severity of injury and a mediator leading to proteolysis of a great variety of normal tissue substances, but also a factor significantly correlating with final outcome.

The present study therefore underlines the importance of the complement system and PMN activity in the early post-traumatic phase, not only towards mortality, but also towards the major complicating syndrome: MOF.

Finally, these data support the hypothesis that MOF is the result of an excessive uncontrolled autodestructive activation of inflammatory cells and mediators (2).

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CYTOKINE PATTERNS IN PATIENTS AFTER MAJOR VASCULAR SURGERY, HEMORRHAGIC SHOCK AND SEVERE BLUNT TRAUMA: RELATION WITH SUBSEQUENT ARDS AND MOF.

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Abstract

Adult respiratory distress syndrome (ARDS) and multiple organ failure (MOF) following severe trauma, hemorrhagic shock or ischemia-reperfusion injury are thought to be the result of an excessive uncontrolled activation of inflammatory cells and mediators. In the present study we investigated the plasma patterns of the cytokines $TNF\alpha$, IL-1ß and IL-6 during these events.

Of 28 multiple trauma patients, 20 patients admitted in shock because of a ruptured abdominal aortic aneurysm (AAA) and 18 patients undergoing elective AAA repair, arterial blood was serially sampled on admission or at the start of the elective operation, after 6 hours and on day 1, 2, 3, 4, 5, 7, 9, 11, and 13 at the ICU.

Twenty-two patients died, 15 within 48 hours and 7 after several weeks, due to ARDS/MOF. On hospital admission and after 6 hours these non-survivors had significantly higher plasma $TNF\alpha$ and IL-1ß levels than the survivors, while the differences in IL-6 levels did not reach statistical significance. At the same measuring points $TNF\alpha$ and IL-1ß were significantly more elevated in patients with ruptured AAA compared with the patients with trauma. On the contrary, IL-6 was significantly higher in the patients with trauma.

Ten patients developed ARDS/MOF and 41 had an uncomplicated course in this respect. The patients with ARDS/MOF exhibited significantly different cytokine patterns in the early post-injury phase. $TNF\alpha$ and IL-1ß were higher mainly the first day of admission, while IL-6 appeared to be significantly elevated in patients with ARDS/MOF from the second day onwards. The latter cytokine showed a very good correlation with the daily MOF score during the whole two week observation period.

It is concluded that in the early post-injury phase higher concentrations of the cytokines are not only associated with increased mortality, but also with an increased risk for subsequent ARDS and MOF. These data therefore support the concept that these syndromes are caused by an overwhelming autodestructive inflammatory response.

Introduction

Evidence is accumulating that the adult respiratory distress syndrome (ARDS) and multiple organ failure (MOF) are the result of a severe generalized autodestructive inflammation, in which micro-organisms may or may not be involved (1). Trauma,

shock and infection initiate a complex inflammatory response, in which the pro-inflammatory cytokines TNFα, IL-1ß and IL-6 are thought to play a pivotal role (2,3). The role of these cytokines has almost exclusively been studied in relation to the pathogenesis of infection and septic shock. Only a few studies deal with cytokinemia following trauma or hemorrhagic shock (5-10). Most of these - clinical and experimental - studies have mortality as endpoint. However, ARDS and MOF represent an important part of morbidity in the intensive care unit (ICU), being responsible for more than 70% of the ventilator days spent on the ICU (1,11,12). In addition, ARDS and MOF are the main cause of late death in surgical ICU patients and put a very heavy burden on health care (12). Therefore, unraveling the pathophysiology of these syndromes should be a major objective of study. We have investigated the role of circulating cytokines (TNFα, IL-1ß and IL-6) in relation to the development of ARDS and MOF in patients with essentially a non-bacterial challenge: severe blunt trauma, hemorrhagic shock and major vascular surgery.

Patients and methods

Sixty-six patients were studied prospectively, including 18 patients undergoing elective aortic surgery (16 abdominal aortic aneurysms and 2 thoraco-abdominal aortic aneurysms), 20 patients with hemorrhagic shock because of a ruptured abdominal aortic aneurysm (AAA) and 28 patients with severe blunt trauma (Hospital Trauma Index - Injury Severity Score [HTI-ISS] > 25) (13,14). All patients or their relatives gave informed consent to draw blood for analyses.

Arterial blood was withdrawn from the patients undergoing elective aortic surgery at the time of incision, when they had already been anaesthesized (0h) and after 6 hours and 24 hours. Subsequently, samples were collected daily during the first week and every other day during the second week, as long as patients were at the ICU with a maximum of two weeks. For the other patients, the first sampling point (0h) was immediately after hospital admission. Thereafter, the same schedule was followed as for the patients undergoing elective surgery.

Definitions

An APACHE II score (15) was calculated for all patients at the time of hospital and subsequent ICU admission and further daily throughout the ICU stay. In order to

grade the intensity of organ failure a daily MOF score was calculated (1). Patients were diagnosed to have MOF, if the average MOF score between days 5 and 14 was ≥4 (16). ARDS was diagnosed when patients had bilateral diffuse infiltrates on the chest radiography, and progressive hypoxemia requiring mechanical ventilation resulting in a PaO_2 / FiO_2 ratio ≤ 175 with PEEP ≥ 10 cm H_2O and - in case of prior cardiac disease - did not have a pulmonary artery wedge pressure exceeding 18 mm Hg (17).

A shock score was defined to grade the severity of hemodynamic derangement after admission (16). For this purpose the Allgöwer shock index (heart frequency / systolic blood pressure) (18) and the systolic blood pressure were used: (0) no shock: index ≤ 1.0 and systolic blood pressure ≥ 100 mm Hg, (1) mild, compensated shock: index > 1.0 and systolic blood pressure ≥ 100 mm Hg, (2) moderate shock: systolic blood pressure 80 - 100 mm Hg, (3) severe shock: systolic blood pressure < 80 mm Hg, (4) severe, prolonged shock: more than one hour systolic blood pressure < 80 mm Hg.

Blood analysis

Arterial blood was collected in sterile 4 ml tubes containing 0.048 ml EDTA-K_3 (Vacutainer Systems, Becton and Dickinson, Rutherford, New Jersey, USA) and 250 μl aprotinin (final concentration 625 kallikrein inactivating units per ml; Bayer, Leverkusen, Germany). After centrifugation at 2000 g for 10 minutes the resulting platelet-poor plasma was transferred into sterile 1.5 ml tubes and samples were stored at -20°C until further analysis. The samples were analyzed by fluidphase radio-immuno-assay (RIA) for TNFα and IL-1ß, as described by Van der Meer et al. (19) and Cannon et al. (20). Prior to the IL-1ß measurement the plasma was extracted with chloroform according to Cannon et al. (20). Detection levels in the assays were: TNFα, 60 pg/ml and IL-1ß, 200 pg/ml.

Arterial blood for IL-6 assay was collected in sterile 4 ml tubes and processed as described above. IL-6 was quantitated by ELISA technique. Microtiter flatbottom plates (Costar) were coated with anti-IL-6 monclonal (Moab) BE-8 (7 μg/ml) in phosphate buffered saline (PBS) pH 7.4 (100μl/well). After 24 hour incubation at 4 °C, plates were washed with PBS with 0.02% (v/v) Tween-20, followed by a 60 minute/room temperature incubation of PBS with 5% bovine serum albumen (BSA) (200μl/well). After washing serial dilutions of standard recombinant human IL-6 (kind gift of Dr. L. Aarden, CLB, Amsterdam) or serum samples were added to the plates and incubation proceeded for 1 hour at 37°C. After washing, 100 μl PBS/BSA with biotinilated anti-IL-6

Moab BE-4 (2μg/ml) was added to the wells. BE-4 and BE-8 recognize different epitopes. Following a 60 minute incubation and a washing step, 100 μl strepavidin horseradish peroxidase in PBS/BSA was added, followed by 45 minutes incubation. After washing a citric-acid buffer pH 5.2 with 0.003% H_2O and ortho-phenyl diamine was added. The reaction was terminated with 4 mol/l H_2SO_4 and the absorbance was read at 495 nm in an automated ELISA reader (Titertek). The detection level of this assay was 20 pg/ml.

Arterial blood lactate was measured in deproteinized samples (0.6 mol/l perchloric acid) by enzymatic conversion of lactate into pyruvate.

Statistical analysis

The Kruskal-Wallis test and Wilcoxon two sample test were used to examine differences between patient groups when indicated. Pearson's correlation coefficients were used for correlation analysis. P values of less than 0.05 were considered to be significant.

Results

Demographic data of the 66 patients are presented in table 5.1. We differentiated between early (the first or second day of admission) and late mortality. Fifteen patients (8 with trauma and 7 with ruptured AAA) died early. Of the remaining 51 patients, ARDS/MOF developed in ten. Two patients with trauma developed ARDS without subsequent MOF and survived. One patient with a ruptured AAA had ARDS without MOF and survived as well. The remaining seven patients all had MOF (six including ARDS) and they succumbed between days 28 and 60 at ICU. Thus, total mortality was 22 of 66 patients (33%). The 41 survivors who did not develop ARDS/MOF were considered as patients with an uncomplicated clinical course.

Table 5.1

Demographic data of the study population. Data are expressed as mean ± SD.

	N	Age	Sex F/M	APACHE II (ICU)	ISS	Early death	ARDS MOF	Late death	Uncomplicated
Elective	18	64±11	3/15	6.2±4.0	-	0	3	3	15
Ruptured	20	70±7	1/19	11.6±5.4	-	7	5	4	8
Trauma	28	31±14	6/22	9.9±7.0	38±11	8	2	0	18
total	66		10/56			15	10	7	41

The course of the cytokine concentrations during the first two days in the three separate patients groups is depicted in Figure 5.1. On admission IL-1β and after 6 hours TNFα were at a significantly higher level in patients with ruptured AAA compared with the patients with trauma ($p = 0.03$ and 0.02, respectively). In this early postinjury period (0h), however, IL-6 was significantly more elevated in the patients with trauma compared with both vascular patient groups ($p < 0.001$). On day 1 and 2 the differences between groups concerning TNFα and IL-1β disappeared, but now IL-6 was increased in the vascular patient groups, while in the patients with trauma a decrease could be observed.

Figure 5.2 illustrates the course of cytokine concentrations during the first day of admission in relation to mortality. The corresponding p-values of these measurements are listed in table 5.2. Non-survivors had significantly higher TNFα and IL-1β concentrations, both on admission and 6 hours later. With respect to IL-1β, this difference was mainly caused by the contribution of the late non-survivors who died of ARDS/MOF; in the case of TNFα both early and late non-survivors appeared to contribute equally to the observed difference with survivors. The differences in IL-6 concentrations between non-survivors and survivors did not reach statistical significance ($p = 0.07$ and 0.08 at 6h and 24h, respectively).

In addition, we did not find any significant difference in cytokine concentrations between early and late non-survivors.

Table 5.2

P-values of Wilcoxon two sample tests for analysis of differences between cytokine concentrations of survivors and non-survivors (including early and late non-survivors). Corresponding cytokine concentrations are demonstrated in figure 5.2.

	Time (hr)	All Non-Survivors (NS)	Early NS (N = 15)	Late NS (N = 7)
IL-1β	0	0.04*	0.32	0.007**
	6	0.001**	0.26	0.004**
	24	0.02*	0.15	0.10
TNFα	0	0.003**	0.01*	0.08
	6	0.002**	0.06	0.01*
	24	0.67	0.12	0.15
IL-6	0	0.75	0.44	0.17
	6	0.07	0.006**	0.86
	24	0.08	0.18	0.29

(* = $p < 0.05$ and ** = $p < 0.01$).

Figure 5.3 shows the course of the cytokine concentrations during the first two weeks at ICU in the group of 10 patients with ARDS/MOF and the 41 patients with an uncomplicated course. IL-1β was increased in patients with ARDS/MOF at 6 hours and at day 1, but the difference did not reach statistical significance ($p = 0.056$ and 0.087, respectively). This difference completely disappeared between day 2 and 4 because the patients with an uncomplicated course showed a rise of IL-1β. In the subsequent period IL-1β levels went down again in the "uncomplicated" group, while the levels remained elevated in patients with ARDS/MOF.

Figure 5.1

Plasma cytokine concentrations in three patient groups during the first two days of admission. Data are expressed as medians in box plots ranging from the 25th to 75th percentile. Bars indicate 5th and 95th percentile. Dotted lines indicate the detection limit of the various cytokine assays.

☐ trauma patients; ☐ patients with ruptured AAA;
▨ patients after elective AAA repair.

(*) = 0.05 ≤ p < 0.10; * = 0.01 ≤ p < 0.05 and ** = p < 0.01

Figure 5.2

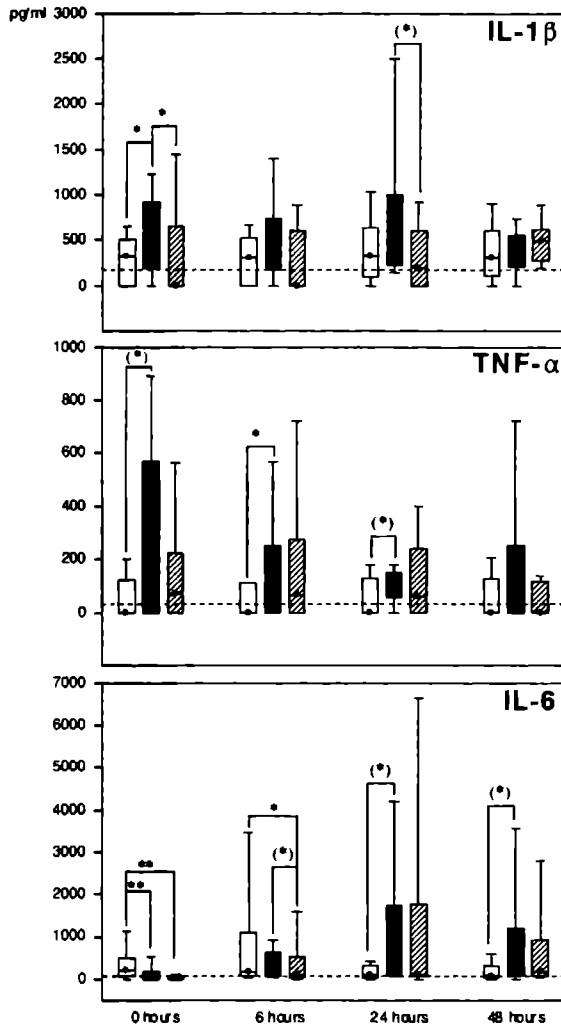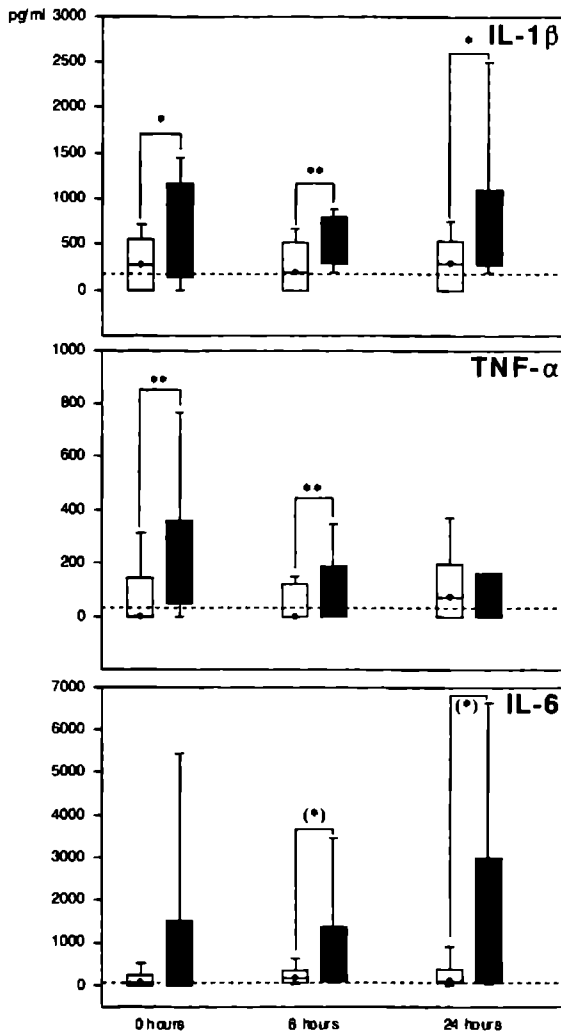Plasma cytokine concentrations on the first day of admission in survivors and non-survivors. Data are expressed as medians in box plots ranging from the 25th to 75th percentile. Bars indicate 5th and 95th percentile. Dotted lines indicate the detection limit of the various cytokine assays.

[ ] survivors; [ ] non-survivors.

(*) = $0.05 \leq p < 0.10$; * = $0.01 \leq p < 0.05$ and ** = $p < 0.01$

TNFα showed a somewhat similar picture. There was a significant difference in TNFα levels at 6 hours ($p < 0.005$) and an almost significant difference at day 1 and 2 ($p = 0.055$ and 0.051, respectively). In the second week, TNFα levels rose in patients with ARDS/MOF and tended to normalize in the "uncomplicated" group.

IL-6 levels showed a completely different course. At all measuring points the IL-6 concentrations were significantly higher in the patients with ARDS/MOF than in the patients with an uncomplicated course, except for the first 24 hours, due to the large variation.

A good correlation was found between ISS and IL-6 on admission, as well as 6 and 24 hours later ($r = 0.52$, 0.43, and 0.53, respectively; all $p < 0.05$). A highly significant correlation ($r = 0.83$, $p < 0.001$) was found between IL-6 and lactate concentration at 24 hours. Further correlation analysis between cytokines and ISS, shock score, lactate concentrations or APACHE II score did not show any consistent pattern of significant correlations.

In all patients a daily MOF score was calculated and we correlated these values with the cytokine levels measured at different days. In the second week IL-1ß and TNFα showed very good correlations with the MOF score, for instance: IL-1ß at day 9 and MOF score at day 9 ($r = 0.63$, $p = 0.02$); IL-1ß at day 11 and MOF score at day 13 ($r = 0.68$, $p = 0.02$); TNFα at day 7 and MOF score at day 7 ($r = 0.77$, $p = 0.005$); and TNFα at day 9 and MOF score at day 11 ($r = 0.84$, $p = 0.001$).

Finally, striking correlations (all $p < 0.01$) were found between IL-6 concentrations and MOF scores from the second day onwards: day 2 ($r = 0.64$); day 3 ($r = 0.53$); day 4 ($r = 0.60$); day 5 ($r = 0.77$); day 7 ($r = 0.77$); day 9 ($r = 0.59$); and day 11 ($r = 0.63$). Correlation analysis between the cytokine concentrations of all samples at various time points did not reveal any significant correlation.

Figure 5.3

Plasma cytokine concentrations during the first two weeks of ICU admission in 10 patients with ARDS/MOF (—-0—) and 41 patients without ARDS/MOF (—*—). Data are expressed as mean ± SEM. (*) = 0.05 ≤ p < 0.10; * = 0.01 ≤ p < 0.05 and ** = p < 0.01
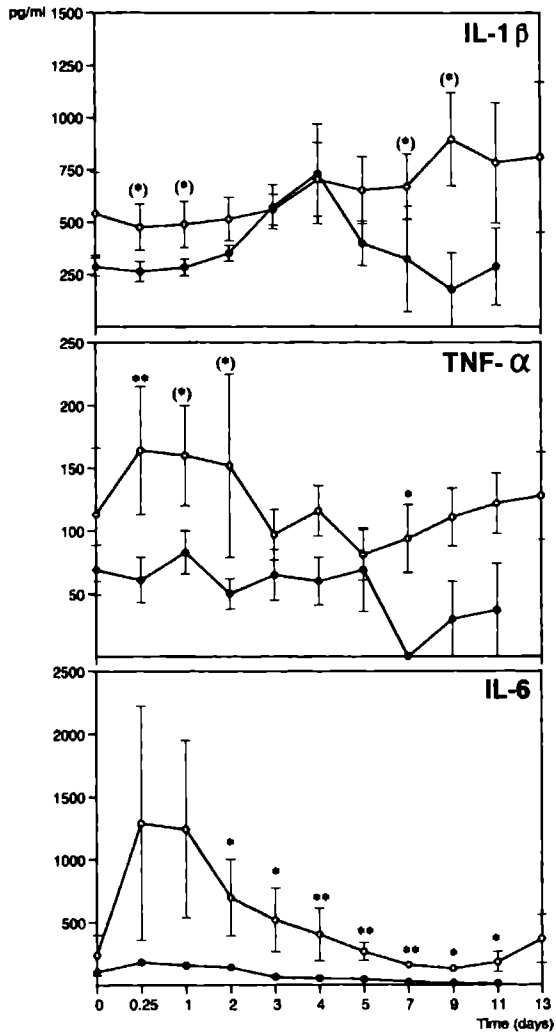
Discussion

In the present study we found intriguing differences in cytokine profiles between three different patient groups representing different pathogenic conditions associated with an increased risk for subsequent ARDS/MOF: severe trauma, hemorrhagic shock (ruptured AAA) and ischemia-reperfusion injury (elective AAA). On admission and after 6 hours, TNFα concentrations were significantly higher in patients after hemorrhagic shock than after trauma. In the former patients, higher IL-1ß concentrations were also found on admission. These findings are in accordance with animal experiments showing that the induction of TNFα release after trauma is significantly enhanced when hemorrhagic shock is also present (4). Apparently, shock is the main factor leading to production and release of TNFα by macrophages. Experimentally, it has also been demonstrated that intestinal ischemia and reperfusion injury leads to 5 to 10 fold increases of circulating TNFα (21), and that hypoxia alone is a major stimulus for human peripheral blood monocytes to produce and secrete IL-1ß and TNFα (22).

The ischemia and reperfusion injury is likely to be responsible for the elevated levels of TNFα and IL-1ß found in patients after elective aortic aneurysm repair. However, it remains unclear why in some of these patients after induction of anaesthesia and at the start of the operation increased TNFα and IL-1ß concentrations were found. The use of specific medication, like cyclooxygenase inhibitors, or the presence of chronic heart failure has been shown to lead to raised levels of circulating TNFα (23,24). However, only one patient (TNFα < 60 pg/ml) regularly used cyclooxygenase inhibitors, while one other patient exhibited signs of mild chronic heart failure (TNFα = 110 pg/ml). Certainly, the role of anaesthesia in relation to the release of these cytokines needs further investigation.

Our observations of increased IL-1ß concentrations after major trauma are in agreement with the findings of Baigrie et al. (25), who demonstrated short-lived IL-1ß responses to major surgical injury. It is more difficult to explain how our data relate to those of Faist et al. (9), who showed that the elevated number of circulating monocytes found post-injury were not able to produce adequate amounts of IL-1ß within the first eigth to ten days following trauma. This process was attributed to elevated concentrations of PGE$_2$, downregulating TNFα and IL-1ß synthesis (8,9). However, it is currently unclear to what extent circulating monocytes contribute to in-vivo production of cytokines. Bitterman et al. (10) could only detect TNFα and IL-6, but no IL-1ß activity, in a rat model of major surgery and shock. An explanation could be that we used chloroform extraction (20) to show IL-1ß activity. In addition, there may be diffe-

rences between the cytokine responses in rats and humans.

We found quite a different profile for IL-6. Trauma patients exhibited the highest concentrations of IL-6 directly post-injury and 6 hours later. These data support the idea that IL-6 production is more closely tied to soft tissue trauma than other cytokines (4). The IL-6 profiles observed are also in agreement with the reports describing a relation between post-operative concentrations of IL-6 and the magnitude of surgical trauma (26,27). The delay in the IL-6 peak in the patients with ruptured and elective AAA might be explained by the fact that here IL-6 was mainly released by the surgical trauma of the vascular reconstruction, and also because IL-6 levels tend to follow $TNF\alpha$ and IL-1ß peaks with some delay (2,25). It is of interest that the occurrence of shock apparently did not contribute significantly to the release of IL-6, since we found no difference between patients undergoing acute or elective major vascular surgery.

The role of translocating bacterial endotoxin in the production and release of the cytokines in the present patient population remains unclarified. In 28 individuals (11 patients with trauma, 10 with ruptured AAA and 7 undergoing elective AAA repair) we were able to look for blood endotoxin concentrations at 0, 6, 24 and 48 hours (16,28). In 15 patients (4 with trauma, 6 with ruptured AAA and 5 after elective AAA repair) endotoxemia could be detected (mostly at 0 or 6 hours) and all but two patients exhibited circulating $TNF\alpha$ at the same moment (data not shown). On the other hand, in 10 of the 13 patients without detectable circulating endotoxin we also found increased $TNF\alpha$ concentrations at one or more of the same time points. Thus, endotoxemia may be indicative for the presence of subsequent circulating $TNF\alpha$, but it surely is not a prerequisite. Endotoxemia has been shown to occur after hemorrhagic shock, intestinal ischemia and reperfusion injury and even after elective aortic aneurysm repair (16,21,28-30), but it was only rarely detected in multiple trauma patients (31). There is ample evidence that endotoxin induces the production and secretion of $TNF\alpha$, but it is clear that endotoxin is not the only factor responsible for the cytokine production in our patients. A great variety of microbial and non-microbial factors is known to be able to lead to cytokine production.

The present data demonstrate that patients who succumb eventually exhibit much higher levels of $TNF\alpha$, IL-1ß and IL-6 in the early post-traumatic phase than survivors. But the finding of increased cytokine levels in non-survivors was probably not an independent phenomenon. The fact is that the large standard deviations indicate that the finding of elevated cytokine concentrations can hardly be expected to better predict prognosis in an individual patient than for instance the ISS or APACHE II score would

do. Nevertheless, the present data may help to elucidate the mechanism of inflammatory response to trauma and shock.

Finally, our data demonstrate a good correlation between cytokine levels and the development of ARDS and MOF. On the first two days after admission, TNFα was significantly elevated in patients with subsequent ARDS/MOF. This is in agreement with previous reports, in which TNFα levels were found to correlate with subsequent sepsis or septic episodes in post-injury patients (8,32,33). From these studies, however, it is not clear whether this phenomenon was linked to bacterial or non-bacterial sepsis, since the presence of bacteria was not obligatory for the definition of sepsis in these studies. Such obscure use of the term sepsis and septic syndrome has already led to a lot of confusion in the discussion about the relation between bacterial sepsis (infection) and MOF. It would, therefore, probably be better to utilize a term like Systemic Inflammatory Response Syndrome (SIRS) as recently proposed by Bone et al.(34).

With respect to the IL-1ß levels, there only was an indication of a significant elevation in patients with subsequent ARDS/MOF on the first day after admission. An interesting finding was the rise of chloroform extractable IL-1ß between days 2 and 4 in the patients with an uncomplicated clinical course. A similar phenomenon was observed during the recovery phase in patients with meningococcal infections (35). This finding might suggest a protective effect of IL-1ß necessary in the course of reconvalescence, which is in line with the proposition that several cytokines not only synerge but also counterregulate each other (2,36). However, this observation might also be influenced by the assay method used and therefore this phenomenon is presently investigated further. Patients with ARDS/MOF, on the other hand, showed a trend of sustained elevated TNFα and IL-1ß levels in the second week. This protracted cytokine release is probably associated with the organ damage observed in those patients.

The presence of significantly increased IL-6 concentrations in the patients with subsequent ARDS/MOF is remarkable. This is also reflected by the striking correlation between IL-6 and the MOF score during the two weeks studied. While the patients with an uncomplicated clinical course showed a normalization of IL-6 in the second week, the release of IL-6 in the patients with ARDS/MOF remained abnormally high during this period. The same has been demonstrated in patients after major thermal injury (6) and septic shock (37).

We could not demonstrate any relevant correlation between the concentrations of the three cytokines. This finding has also been reported previously (23,38) and therefore

our data support the concept that the production of these cytokines is regulated independently (38).

In conclusion, after major trauma, hemorrhagic shock due to a ruptured AAA and after elective aortic aneurysm repair increased concentrations of the cytokines TNFα, IL-1β and IL-6 are a common finding. The higher concentrations found in the early post-injury time course are not only associated with increased mortality, but also with an increased risk for the development of ARDS and MOF. The present study therefore supports the concept that ARDS and MOF are syndromes caused by an excessive uncontrolled activation of endogenous inflammatory cells and mediators (1).

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SERUM LIPOFUSCIN IS INCREASED AFTER MAJOR VASCULAR SURGERY, HEMORRHAGIC SHOCK AND SEVERE TRAUMA AND IS RELATED TO SUBSEQUENT ARDS AND MOF.

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Abstract

Toxic oxygen radical damage is thought to play an important role in events like trauma and sepsis, where ARDS and multiple organ failure (MOF) are the major cause of late mortality. Serum lipofuscin has been proposed as a parameter to assess lipid peroxidation caused by toxic oxygen radicals.

Serum lipofuscin levels were measured in 75 healthy controls of various ages and sequentially in 66 patients: the latter include 18 patients after elective major vascular surgery, 20 with a ruptured abdominal aortic aneurysm and 28 with severe blunt trauma.

Fifteen of the 66 patients died early (within two days). Ten of the remaining 51 patients developed ARDS and/or MOF and 41 patients had an uncomplicated postoperative course. Serum lipofuscin concentrations in controls showed a positive correlation with age. Compared with controls all three patient groups showed significantly increased lipofuscin concentrations during the first day after major vascular surgery, trauma or shock, respectively. In addition, the 10 patients who subsequently developed ARDS and/or MOF showed significantly enhanced lipofuscin levels on day 1, compared with the 41 patients with an uncomplicated clinical course.

Thus, we conclude that serum lipofuscin, which compound may act as a simple and valuable measure for grading the oxidative stress in human studies, is positively related to subsequent ARDS and/or MOF in patients at risk for these syndromes.

Introduction

It is well known that cell damage caused by toxic oxygen radicals takes place in many disorders, especially when inflammatory reactions or ischemia and reperfusion play a key role (1-3). Events such as severe trauma, shock and sepsis, trigger the activation of polymorphonuclear leukocytes, resulting in an respiratory burst with the generation of large quantities of toxic oxygen radicals (4-6). The release of these toxic oxygen radicals in vivo is thought to cause peroxidation of membrane lipids, resulting in cell damage (7,8). Because free radicals are highly reactive and have an extremely short half-life, unequivocal evidence that lipid peroxidation caused by radicals occurs in humans, is technically very difficult to obtain (9,10). The present evidence is mainly based on the measurement of degradation products of lipid peroxidation such as conjugated dienes and malondialdehyde in blood or tissue, or penthanes and ethanes

in expired breath. However, these assays all have their limitations and specific problems (9).

Lipofuscin is a pigment which is formed as an end result of in vivo lipid peroxidation in organelles (11). Lipofuscin is defined as being a yellowish brown, lipid-soluble, cytoplasmic granular pigment having an intense yellow autofluorescence when exposed to ultraviolet light. The fluorescence measurement of these lipofuscin pigments has been used as a parameter of lipid peroxidation in vitro as well as in vivo (11).

Both adult respiratory distress syndrome (ARDS) and multiple organ failure (MOF), which syndromes are thought to have one common underlying pathophysiological pathway (12), are probably associated with a significant increase in oxidative stress (6). So far, limited data are available on lipid peroxidation in patients at risk for these syndromes. Patients after severe trauma or undergoing major elective or acute vascular surgery represent three different etiologic entities: tissue trauma, ischemia-reperfusion injury and hemorrhagic shock, respectively. Therefore we studied the course of serum lipofuscin concentrations in these three patient groups and investigated its relation with clinical symptoms, in particular with respect to the development of ARDS and MOF.

Patients and methods

Normal values of serum lipofuscin were measured in healthy humans of different ages. For this purpose, venous blood was collected of 75 persons (22 females and 53 males), who had no acute disease and were otherwise considered in good condition.

In order to investigate the correlation in lipofuscin levels between arterial and venous blood, samples of both were withdrawn simultaneously from 14 hospitalized patients, who had indwelling arterial and venous catheters.

Day to day variation in serum lipofuscin was examined in venous blood from five healthy volunteers collected on four consecutive days.

Sixty six patients were studied prospectively, including 18 patients after elective aortic surgery (16 abdominal aortic aneurysms and 2 thoraco-abdominal aortic aneurysms), 20 with hemorrhagic shock because of a ruptured abdominal aortic aneurysm and 28 with severe blunt trauma (ISS-HTI > 25) (13,14).

From the patients undergoing elective operation arterial blood was withdrawn at the time of incision (0h), when patients had already been anaesthesized and after 6h and

24h. Subsequently, samples were collected daily during the first week and every other day during the second week, as long as patients were admitted to the ICU. From patients with a ruptured aneurysm and with trauma the first samples were obtained immediately after hospital admission (0h). Thereafter, the same schedule was followed as for the patients undergoing elective surgery. Informed consent was obtained from all subjects or their relatives prior to the study.

Definitions

An APACHE II score was established in all patients at the time of hospital admission, of ICU admission and further daily throughout the ICU stay (15). In order to grade the intensity of organ failures a daily MOF score was calculated (12). Patients were diagnosed to have MOF, if the average MOF score between days 5 and 14 was ≥ 4. ARDS was diagnosed when patients had bilateral diffuse infiltrates on the chest radiography, and progressive hypoxemia requiring mechanical ventilation resulting in a PaO_2 / FiO_2 ratio ≤ 175 with a PEEP ≥ 10 cm H_2O and - in case of prior cardiac disease - did not have a pulmonary artery wedge pressure exceeding 18 mm Hg (16). The PaO_2 / FiO_2 ratio was calculated daily in order to grade the pulmonary gas exchange.

Lipofuscin assay

Serum lipofuscin was measured essentially according to Tsuchida et al (11). Five ml ethanol/ether (3:1, v/v) were added to 150 μl serum and the mixture was shaken vigorously. After centrifugation (5 min. at 3000 g) the supernatant was discarded and the sediment washed once with 5 ml ethanol/ether. The final sediment was dissolved in 3 ml 67 mM phosphate buffer, pH 7.0. The fluorescence intensity of the solution was measured at excitation and emission wavelengths of 345 and 430 nm, respectively, in a Hitachi F-3000 fluorescence spectrophotometer. A quinine sulphate solution, 1 mg/ml 0.1 M H_2SO_4 and further diluted with phosphate buffer, was used to construct a standard curve (0.05 - 40 μg quinine sulphate/ml). The lipofuscin concentrations are expressed as arbitrary units relative to the fluorescence of quinine sulphate. All samples were measured in duplicate, which showed less than 5% variation.

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Statistical analysis

The differences between the lipofuscin levels measured and the levels predicted (see methods section) for each patient group were tested by the Wilcoxon two sample test. The Kruskal-Wallis test was used to examine differences between patient groups. Pearson's correlation coefficients were used for correlation analysis. P values of less than 0.05 were considered to be significant. The formula of Bayes was used to calculate the predictive value from sensitivity, specificity and prevalence.

Figure 6.1

Relation between age and serum lipofuscin concentration. The latter is expressed as arbitrary units relative to the fluorescence of quinine sulphate (Pearson's correlation coefficient $r = 0.39$, $p < 0.01$).
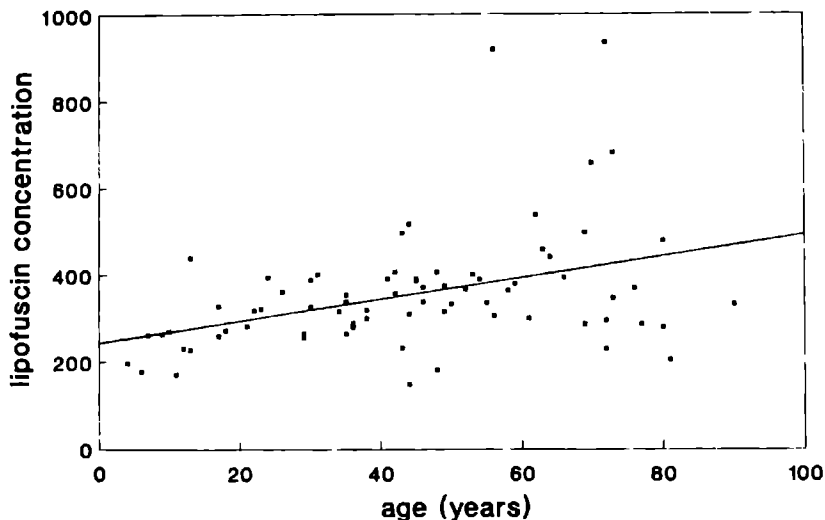
Figure 6.2

Relation between lipofuscin concentrations in venous and arterial serum sampled simultaneously from 14 different ICU patients (Pearson's correlation coefficient r = 0.51, p < 0.001).
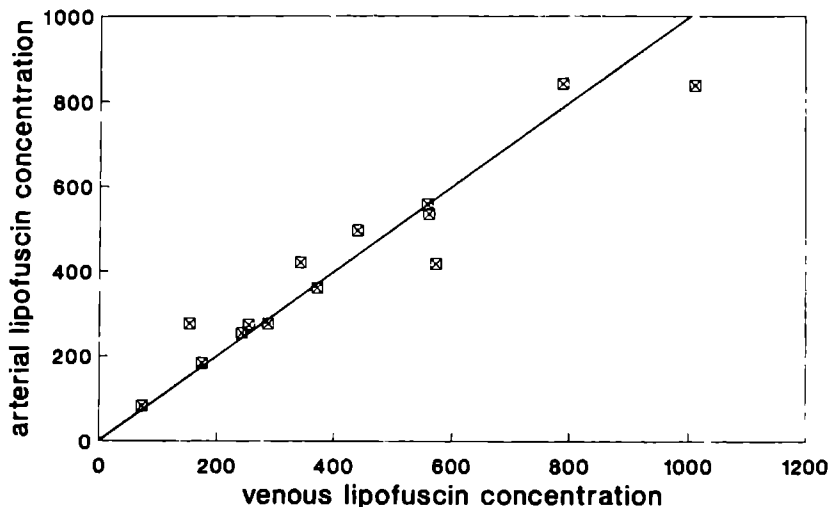
Results

Sera from healthy controls contained significant levels of lipofuscin. Values measured in persons of different ages are shown in figure 6.1. The Pearson correlation coefficient was r = 0.39, p < 0.01, indicating that the serum lipofucsin concentration increases significantly with age. The regression line of this equation was: y = 244 + 2.5 x. The day to day variation, as measured on four consecutive days in five controls, was small: the coefficients of variation ranged from 1.6% to 6.5% (mean 3.6%). Figure 6.2 illustrates that a satisfactory correlation existed between arterial and venous lipofuscin concentrations (r = 0.51, p < 0.001). The regression line through the origin was: y = 0.95 x .

As a consequence of these findings we concluded that the serum lipofuscin levels in our patients should be corrected for age using the regression line calculated above. Since venous samples were used to construct this line and patient samples were obtained from arterial catheters the regression line was corrected for the venous-

arterial difference reported above. Thus, each patient is expected to show an arterial lipofuscin level of: [232 + 2.4 x age] units/150μl serum. A deviation from this expected value then indicates enhanced (or suppressed) production of lipofuscin compared with healthy controls. Accordingly, we calculated for each patient the difference between the serum lipofuscin concentration actually measured and the concentration predicted. These data were used for statistical analysis.

Table 6.1

Demographic data of the study population. Data are expressed as mean ± SD.

	N	Age	Sex F/M	APACHE II (ICU)	ISS	Early death	ARDS MOF	Late death	Uncom-pli-cated
Elective	18	64±11	3/15	6.2±4.0	-	0	3	3	15
Ruptured	20	70±7	1/19	11.6±5.4	-	7	5	4	8
Trauma	28	31±14	6/22	9.9±7.0	38±11	8	2	0	18
total	66		10/56			15	10	7	41

Table 6.1 shows the demographic data of the three patient groups. We differentiated between early mortality (the first or second day after admission) and late mortality. Fifteen patients died early, ten within the first 6 hours. Late mortality - in all cases due to ARDS and MOF - was seen in seven patients, which died between day 28 and 60 at the ICU. In ten patients ARDS and/or MOF was diagnosed. Two trauma patients developed ARDS without subsequent MOF and survived. One patient with a ruptured aneurysm had ARDS without MOF and survived as well. The remaining seven patients all had MOF (six including ARDS) and none survived. Survivors who did not develop ARDS or MOF were considered as patients with an uncomplicated clinical course.
We found no significant difference of lipofuscin levels on the first two days of admission between patients that died early and all other patients.

Figure 6.3

Serum lipofuscin concentrations in the three patient groups during the first two days after admission. The numbers within the bars represent the number of patients in the various group. Concentrations are expressed (in arbitrary units) as the difference between the level measured and the level predicted and the mean ± SEM is given. For each group the difference between values measured and values predicted was tested for significance using a Wilcoxon two sample test:

(*): $0.05 < p \leq 0.10$; *: $0.01 < p \leq 0.05$; **: $0.001 < p \leq 0.01$; ***: $p \leq 0.001$.
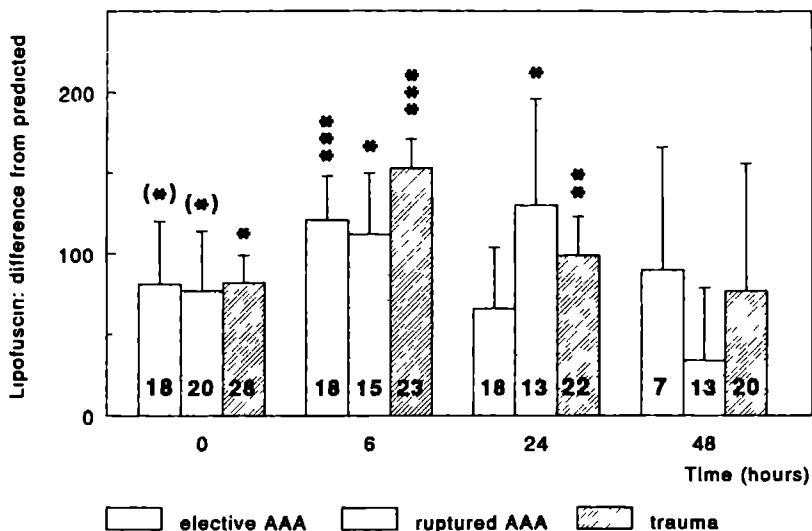
Figure 6.3 shows the course of the lipofuscin concentrations, represented as the difference between the value actually measured and the value predicted, on the first two days in the three patient groups. No significant differences between the three groups were found at any of the sampling points. Six hours after the start of operation, elective patients showed a significantly increased lipofuscin concentration. Both patient groups with trauma and ruptured aneurysm showed significantly increased lipofuscin levels at 6h and at 24h. Although all patients showed enhanced levels at time 0, the difference with the predicted values was only significant in the trauma group. Betweeen the three patient groups mutually no significant differences were found at any of the sampling points (Kruskal-Wallis).

The APACHE II score on hospital admission in patients with ARDS/MOF (12.1 ± 4.6) was significantly higher ($p < 0.01$) than patients with a subsequent uncomplicated

recovery (7.9 ± 4.5); the same was true for the APACHE II score at ICU admission (13.1 ± 5.4 versus 7.2 ± 4.9).

Figure 6.4

Serum lipofuscin concentrations in patients with and without ARDS/MOF. The numbers above/below the bars represent the number of patients in the various group. Concentrations are expressed (in arbitrary units) as the difference between the level measured and the level predicted and the mean ± SEM is given. For each group the difference between values measured and values predicted was tested for significance using a Wilcoxon two sample test: (*): 0.05 < p ≤ 0.10; *: 0.01 < p ≤ 0.05; **: 0.001 < p ≤ 0.01; ***: p ≤ 0.001.
Differences between groups were tested for significance using a Wilcoxon test: #: 0.01 < p ≤ 0.05; ##: 0.001 < p ≤ 0.01.
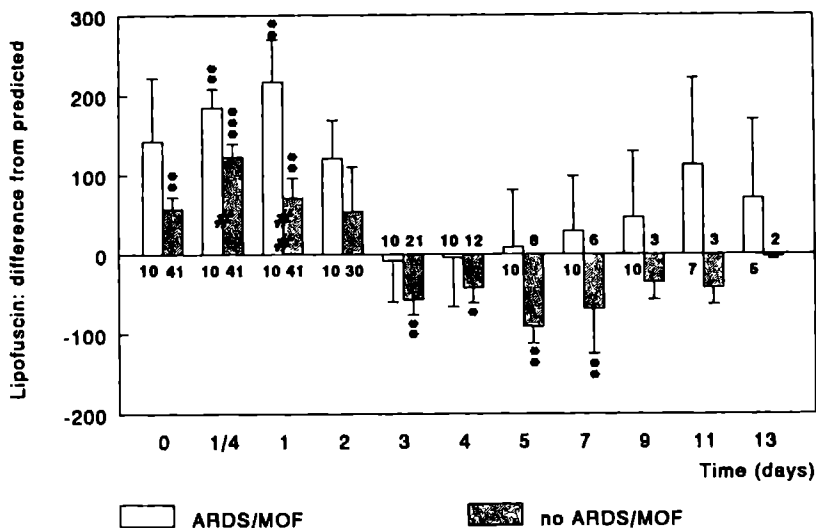
In figure 6.4 the course in serum lipofuscin levels is compared between patients with an uncomplicated clinical course (n=41 at day 1) and patients who developed ARDS and/or MOF (n=10). Compared with controls in the patient group without complicati-ons serum lipofuscin levels were significantly elevated after 6h and 24h, but signifi-cantly lower between day 3 and 7. During the second week serum lipofuscin levels tended to normalize to baseline levels. The patients with subsequent ARDS/MOF also showed significantly increased lipofuscin levels at 6h and 24h compared with controls, but also higher levels than the patients with an uncomplicated clinical course. In addition, the patients with ARDS/MOF did not exhibit the decrease observed between

days 3 and 7, but their serum lipofuscin levels showed a renewed tendency to increase to supranormal levels in the second week, although these differences from predicted did not reach statistical significancy. Figure 6.5 illustrates the course of lipofuscin concentrations in three different patients: one trauma patient (S) with head injury, who had an uneventfull recovery and another trauma patient (B) who developed ARDS in the second week without MOF and who finally could be discharged rom ICU at day 26. The third patient (R) with a ruptured AAA developed ARDS and MOF and finally died on the ICU at day 31.

Evaluation of sensitivity and specificity showed that the cut off point of 100 age-corrected lipofuscin units/150μl serum at 24 hours after admission appeared to be the best predictive value towards subsequent ARDS/MOF. Eigth of ten ARDS/MOF patients had lipofuscin levels above the discrimination value of 100 units and 32 of the 41 patients with an uncomplicated course below this cut off point. This resulted in a sensitivity of 80%, with a specificity of 78% and an overall accuracy of 78%. As the prevalence of ARDS/MOF in this patient population was 20% (10/51) the positive predictive value for the development of ARDS/MOF of > 100 units lipofuscin difference from predicted was 47% and the predictive value for an uncomplicated course was 94% (calculated by the formula of Bayes).

Finally, correlation analysis showed that lipofuscin concentration significantly correlated with APACHE II score, not only on the first day of ICU admission, but also on day three, four, five and seven (day 1: r = 0.50, day 2 r = 0.21, day 3 r = 0.74, day 4 r = 0.60, day 5 r = 0.69 and day 7 r = 0.52, all p values < 0.01, except day 2). In addition, lipofuscin concentration showed a significantly negative correlation (r = -0.38, p < 0.01) with PaO_2 / FiO_2 ratio on the first day of ICU admission, indicating the pulmonary (dys)function of that day.

Discussion

Toxic oxygen radicals are the major cause of neutrophil-mediated cell damage, which has been documented to occur after trauma, shock, cardiopulmonary bypass surgery and ischemia and reperfusion injury (6,10,17,18). The plasma membrane, especially that of the endothelial cells, is the critical site of toxic oxygen radical reactions (3). The end products of their reaction with polyunsaturated fatty acids are lipid peroxidation products like conjugated dienes, malondialdehydes, 4-hydroxynonenals and fluorescent products like lipofuscin (3,6,11).

Figure 6.5

Course of serum lipofuscin concentrations in three individual patients during two weeks of ICU admission. Dotted line is the predicted value of the patient.

Patient S, aged 20 years, polytrauma with headinjury, ISS = 34 and APACHE II day 1 (ICU) = 20; the patient had an uneventfull recovery with a mean MOF score of 3.0 and stayed 17 days at ICU; survivor.

Patient B, aged 55 years, polytrauma with an ISS = 41 and APACHE II day 1 (ICU) = 21; the patient developed ARDS in the second week without subsequent MOF (mean MOF score = 3.8). Discharge from ICU at day 26; survivor.

Patient R, aged 74 years, ruptured AAA admitted in shock, APACHE II day 1 (ICU) = 16; the patient developed ARDS and subsequent MOF (mean MOF score = 9.2) and died in ICU on day 31; non-survivor.
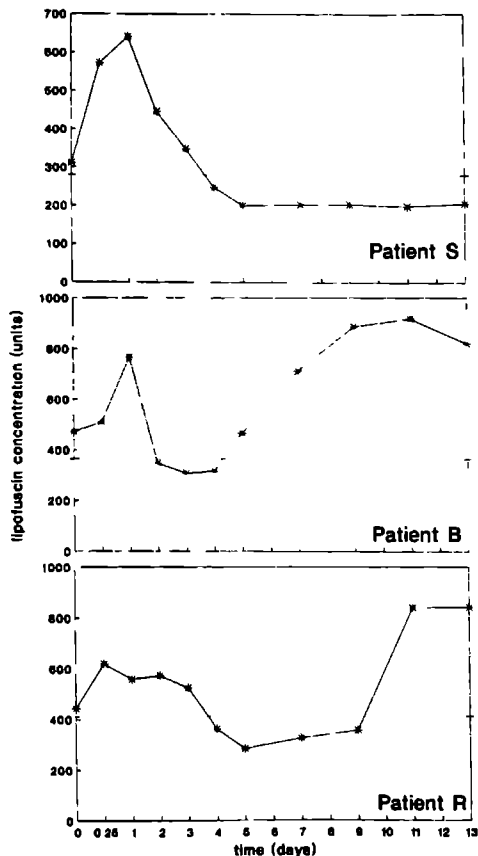
Involvement of toxic oxygen radicals in the pathogenesis of ARDS is suggested by the finding of increased levels of H_2O_2 in the expired breath and increased hydrocarbon exhalation in patients with ARDS (9,19) and by significant malondialdehyde elevation in trauma patients dying of ARDS and sepsis (10). Furthermore, experimental administration of agents liberating free radicals, induces a syndrome which closely resembles ARDS and MOF (20,21). Fluorescent substances like lipofuscin have been shown to be significantly elevated in an animal model of in vivo lipid peroxidation induced by carbon tetrachloride (11).

It is known that the cellular lipofuscin content increases with age. However, the consideration that lipofuscin is an age pigment is primarily based on histological observations (22). So far, no data are available on the age dependent nature of serum lipofuscin concentrations. The present data show that serum lipofuscin concentration indeed increases with age, although the positive correlation is admittedly a weak one.

The present study is the first to show that the serum lipofuscin concentration is markedly increased after trauma and hemorrhagic shock and even after major elective surgery such as aortic aneurysm repair. The latter group of patients were perioperatively hemodynamically stable, but must have sustained some form of reperfusion injury after declamping of the aorta. The role of (the induction of) anaesthesia in the explanation of the initial elevation (at 0 hours) of lipofuscin concentration remains unclear.

It is remarkable that patients who subsequently develop ARDS and MOF initially show significantly higher lipofuscin levels than patients whose clinical course over the next period will be uncomplicated. This finding suggests that in patients with subsequent ARDS and MOF, free radical damage initially may take place on a larger scale, leading to early cell damage, which is the prerequisite of later organ failures (6). This concept is underlined by the finding of an inverse correlation between pulmonary gas exchange and lipofuscin concentration on the first day of ICU admission.

Moreover, we found a cut off point of lipofuscin concentration at 24 hours after hospital admission that predicts reasonably well the absence of subsequent ARDS/MOF (94%). However, the prediction of the occurence of ARDS/MOF was weak (47%). Nonetheless, since the prevalence of ARDS/MOF in this patient population was 20%, the lipofuscin concentration could give additional information for the prediction of subsequent ARDS/MOF. Of course the number of patients is to small to draw a definitive conclusion about the predictive value of the present lipofuscin cut off point.

Furthermore we demonstrated a significant decrease of lipofuscin concentration in patients with an uncomplicated course during the second half of the first week.

Patients with subsequent ARDS and/or MOF did not show such a bifasic lipofuscin course, but - on the contrary - showed an elevation of lipofuscin levels again in the second week of admission, when ARDS and MOF were established.

Oxidative stress with subsequent cell damage and the disturbance of the equilibrium between oxidants and anti-oxidants plays an important role in (the development of) ARDS and MOF (6,23). For instance, in critically ill patients significantly depressed levels of vitamin E, an exogenous anti-oxidant, were demonstrated and these levels were shown to be significantly decreased in patients with ARDS if compared to non-ARDS patients (23). Glutathione is one of the most important endogenous oxygen radical scavengers; its biosynthesis occurs mainly in the liver (24). The anti-oxidant capacity is correlated with the total glutathione content of cells (25). In an ischemia-reperfusion acute lung injury model in rats glutathione was shown to be decreased and oxidized glutathione to be significantly elevated (24). Nakagawa et al. showed that the amount of lipofuscin-like pigments induced by chloroquine administration in mice was roughly inverse to the glutathione content in liver and kidney (26). In mice fed diets containing different amounts of vitamin E, the serum fluorescence intensity varied inversely with the level of vitamin E administered in the diet (11) and in a study on diabetic rats an inverse relation between vitamin E and lipofuscin contents of erythrocytes was demonstrated (27).

We therefore hypothesize that a traumatic insult can lead to such an oxidative stress that the balance between oxidants and anti-oxidants is disturbed, resulting in lipid peroxidation with increased lipofuscin production. Patients that have the capability to restore this balance, either because the insult is not so severe or by a compensatory mechanism of supply and/or production of anti-oxidants, like vitamin E and glutathione, are those who subsequently will show an uneventfull clinical course. If, however, the triggering event is to intense (as indicated in our patients by APACHE II score at day 1) or the capacity to supply and/or produce enough compensatory anti-oxidants is insufficient, the balance turns to increased oxidative stress with more cell damage, resulting in enhanced levels of serum lipofuscin and finally complications like ARDS and MOF.

We conclude that lipofuscin measurements could serve as a valuable parameter in the evaluation of the oxidative stress in patients at risk for ARDS and MOF. However, much work remains to be done to unravel the exact biochemical background of lipofuscin substances. Additional studies are required to investigate the relation of free

radical damage, plasma lipofuscin concentration and outcome of patients after severe trauma and shock.

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ENDOTOXEMIA AFTER MAJOR VASCULAR OPERATIONS

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Abstract

Endotoxemia has been associated with syndromes like ARDS and MOF. Translocation of endotoxins from the gut has been demonstrated to occur experimentally in animals after splanchnic ischemia. We investigated endotoxemia in eleven patients with hemorrhagic shock due to a ruptured abdominal aortic aneurysm and in five patients after elective abdominal aortic aneurysm repair. Endotoxin was measured quantitatively using a limulus assay with a detection limit of 12.5 pg/ml.

In 7 of the eleven patients admitted to the hospital with an acute condition endotoxin was present on admission (range 15-25 pg/ml), even before resuscitation and operation were started. In patients treated electively endotoxin was noticed after cross-clamping of the aorta in four of five patients (mean ± SEM: 18.9 ± 4.6 pg/ml). After reperfusion endotoxemia increased and was present in all patients (mean ± SEM: 22.8 ± 2.8 pg/ml). All five patients treated electively had an uneventful recovery without specific organ failures or infectious complications.

It is concluded that systemic endotoxemia as monitored by the Limulus assay is a common finding in patients after major vascular surgery. Hemorrhagic shock resulting in splanchnic ischemia may lead to endotoxemia. Ischemia and especially reperfusion after aortic cross-clamping also result in endotoxin translocation. However, the low concentrations of systemic circulating endotoxin found were not related to subsequent adverse effects in either the patients treated for acute conditions or in the electively treated patients.

Introduction

Adult respiratory distress syndrome (ARDS) and multiple organ failure (MOF) are the main causes of late hospital death after major vascular surgery (1,2). The gut, which contains large quantities of endotoxin, has been implicated to play a major role in the etiology of MOF (3). Endotoxin can cause an inflammatory cascade with a deleterious effect on endothelial cells, which results in increased microvascular permeability leading to ARDS and MOF (4,5). Recently we have demonstrated that intestinal permeability is markedly increased in patients after acute and elective aortic aneurysm repair (6). O'Dwyer et al. showed that intravenous endotoxin administration in healthy human subjects significantly increased gut permeability (7). In addition, endotoxemia was demonstrated to occur rapidly after intestinal ischemia caused by superior

mesenteric artery occlusion in cats and after colon devascularization in dogs (8-10). The present study was done to determine whether endotoxemia occurs in human beings after acute and elective major vascular operation and, if so, to investigate its relation to possible adverse effects in these patients.

Patients and methods

Two patient groups were enrolled in the study. Informed consent was obtained from all patients or their relatives before the study. The first group consisted of 11 male patients (69 ± 6 years of age), admitted to the hospital in hemorrhagic shock caused by rupture of an abdominal aortic aneurysm. Arterial blood was withdrawn under sterile conditions immediately after hospital admission (0 hours) and after 6, 24 and 48 hours. The second group consisted of five male patients (71 ± 5 years of age) who underwent elective repair of an aneurysm of the infrarenal aorta. From these patients arterial blood was withdrawn under sterile conditions at eigth standardized time points: (I) before anaesthesia was induced; (II) immediately after skin incision; (III) after manipulation of the intestines and before cross-clamping of the aorta; (IV) 15 to 20 minutes after cross-clamping of the aorta; (V) 2 to 3 minutes after reperfusion following declamping of the aorta; (VI) at the end of the operation; (VII) 4 hours after the initial incision and (VIII) six hours after the incision.

Blood for endotoxin determinations was collected in special storage tubes (Kabi Diagnostica, Mölndal, Sweden), centrifuged, and immediately frozen at -20°C as described by Redl et al. (11). Endotoxin was measured quantitatively after dilution (10%) and heat pretreatment by a limulus assay with chromogenic substrate (Coatest Endotoxin, Kabi Diagnostica, Mölndal, Sweden). Each assay was run in duplicate. The detection limit of this assay is 12.5 pg/ml.

Postoperatively, after admission to the ICU, the APACHE II score was determined in all cases (12). As long as patients were admitted to the ICU, a daily MOF score was calculated (13). A patient was diagnosed as having MOF, if the average MOF score from day 5 to 14 was ≥ 4.

Results

Three patients with a ruptured aneurysm died within six hours of hospital admision. The mean APACHE II score on ICU admission of the remaining eight patients from this group was 14.5 ± 6.9.

Table 7.1

Demographic data and endotoxin concentrations at 0 and 6 hours after hospital admission in eleven patients with hemorrhagic shock caused by a ruptured abdominal aortic aneurysm. At 24 and 48 hours no circulating endotoxin could be detected in any patient. (*): patient died before 6 hours after hospital admission; #: no detectable endotoxin with a detection limit of 12.5 pg/ml.

PATIENT	AGE (years)	APACHE II score	ENDOTOXIN concentration (pg/ml) 0 h	6 h	ICU stay (days)	MOF	DEATH
1.	82	17	25	(*)	0	-	early
2.	69	21	#	#	59	yes	late
3.	60	3	20	(*)	0	-	early
4.	62	6	21	16	3	no	-
5.	64	14	#	#	46	yes	late
6.	65	11	#	#	3	no	-
7.	73	12	15	#	30	yes	late
8.	64	18	24	#	48	no	-
9.	76	30	15	25	3	no	-
10.	66	13	#	#	30	yes	late
11.	74	14	24	(*)	0	-	early

Table 7.1 presents the circulating endotoxin concentrations of all eleven patients. Seven patients had measurable endotoxin levels (range 15 to 25 pg/ml) immediately after hospital admission, before operation was started. At 6 hours only two of the remaining eigth survivors still showed circulating endotoxin levels. At 24 and 48 hours no systemic circulating endotoxin could be detected in any of the patients. In four of

the eight initial survivors MOF developed and none of these patients survived. From table 7.1 it is evident that the patients with MOF did not exhibit a different initial endotoxin pattern compared with that of the patients who did not have MOF.

The APACHE II score of the five patients treated electively for aneurysm was 5.8 ± 2.3 on ICU admission. Table 7.2 shows the endotoxin concentrations in all five patients at the eigth defined sampling points. The course (mean ± SEM) is graphically represented in figure 7.1.

No systemic circulating endotoxin could be discovered before operation (point I) in any patient. After manipulation of the intestines, but before cross-clamping of the aorta (III) a slight elevation of endotoxin was noticed in two patients. After infrarenal cross-clamping of the aorta (IV), four of five patients showed measurable levels of endotoxin, with a slight increase after reperfusion when the aortic clamp was removed (V). At this point, endotoxin was detectable in all patients. Endotoxemia was present until 4 hours after the initial incision (VII) in all patients and still detectable in four of five patients at 6 hours from incision (VIII).

All five patients undergoing elective operation stayed in the ICU less than 2 days and were discharged from hospital between 11 and 14 days postoperatively after an uneventfull recovery, without any infectious complications.

Discussion

Bacterial endotoxins, lipopolysaccharide components of the outer membrane of Gram-negative bacteria, are thought to be responsible for the detrimental changes observed in patients with Gram-negative septic shock, which is still associated with a high mortality in patients admitted to a surgical ICU (14,15). Although there are many reports on a variety of effects of endotoxin in experimental circumstances, relatively few studies document endotoxemia in human diseases.

Endotoxemia has been documented in patients with Gram-negative sepsis, with inflammatory bowel disease, with liver failure, after colonoscopy or colectomy and with burn wounds (5,16-20). In severely traumatized patients endotoxemia was only exceptionally found after severe hemorrhagic shock (21,22). Surprisingly, hardly any data are available on the evaluation of endotoxemia in patients after major vascular surgery. Van Deventer et al. investigated endotoxemia in a series of 21 patients without liver disease including nine patients who had undergone aortic bifurcation implantation (23).

Table 7.2

Endotoxin concentrations in five patients during elective aortic aneurysm repair. See text for the definition of the sampling points I to VIII. #: no detectable endotoxin with a detection limit of 12.5 pg/ml.

PATIENT	I	II	III	IV	V	VI	VII	VIII
A.	#	#	16	30	24	31	21	17
B.	#	16	26	20	17	17	16	20
C.	#	#	#	20	23	27	18	20
D.	#	#	#	25	34	#	13	#
E.	#	#	#	#	16	37	28	26

Figure 7.1

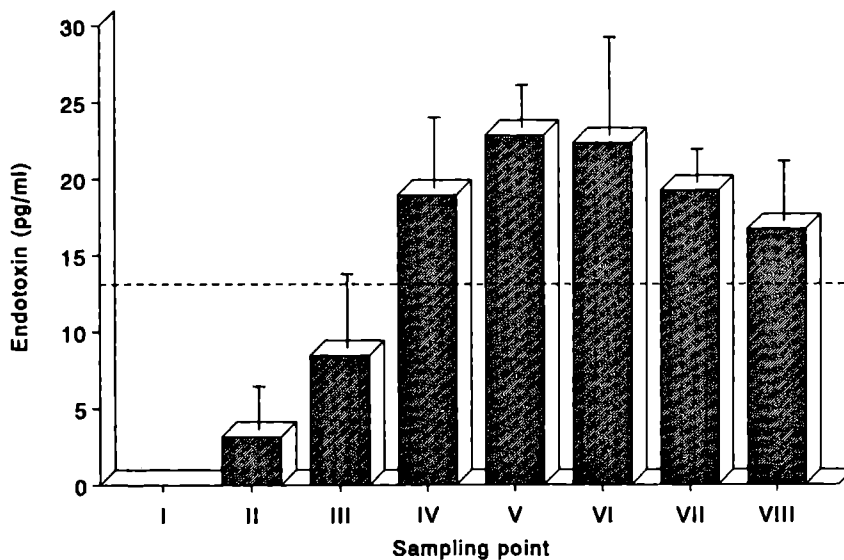Mean (± SEM) endotoxin concentrations in five patients during elective aortic aneurysm repair. See text for the definition of the sampling points I to VIII. Dotted line represents detection limit of endotoxin assay (12.5 pg/ml).

In only two of those nine patients portal and peripheral endotoxemia was detected after aortic cross-clamping with subsequent reperfusion.

The reticuloendothelial system of the liver effectively removes small amounts of endotoxin that have been absorbed into the portal circulation (5). However, it has been shown experimentally, that also the thoracic duct is also a potential route for endotoxin to enter the systemic circulation, thus bypassing the liver (5).

From the present data, we conclude that systemic endotoxemia is a common finding in patients after elective aneurysm repair. This already occurs in the period of bowel ischemia but is quantitatively more important during the reperfusion period. This major contribution to endotoxemia of the reperfusion period was also demonstrated experimentally in cats (10). That hemorrhagic shock leading to splanchnic ischemia plays a role in the translocation of endotoxin is demonstrated by the finding of systemic endotoxemia in patients admitted to the hospital with a ruptured aortic aneurysm, even before resuscitation and emergency operation. Of course, in this period intestinal perfusion must have been impaired.

The direct relation of endotoxemia with the increased intestinal permeability that has been demonstrated to occur between 24 and 36 hours in patients after major vascular operation in previous studies remains unclear (6,24). Endotoxemia was detected mainly before, but not at the very moment of the documented gut permeability itself, which indicates that endotoxemia and increased gut permeability may be independent phenomena (24). On the other hand, endotoxemia could have contributed to a rise in the already enhanced intestinal permeability (7).

Recently endotoxemia was noticed in 20% of patients one hour after cardiopulmonary bypass surgery (25). This endotoxemia was without relation to subsequent complications. Another study documented a significant increase of plasma TNF concentrations after release of the aortic cross-clamp, a phenomenon that could be prevented by dexamethason administration (26). It is well known that endotoxin is one of the most important inductors of mediator release, such as TNF (27,28). In experimental circumstances, intestinal reperfusion injury led to portal vein endotoxemia with subsequent systemic plasma TNF levels, resulting in acute lung injury, which suggests a pathogenetic role for these substances (28). On the other hand, in an animal model of experimentally induced MOF, caused by a severe systemic inflammatory response induced by intraperitoneal zymosan, it was shown that endotoxin sensitivity and thus probably endotoxin itself was not essential in the pathogenesis of subsequent MOF, in as much as the clinical outcome and mortality rate were not different between endotoxin-responsive mice and endotoxin-hyporesponsive mice (29).

Though the number of patients in this study is limited, we conclude from our observations that endotoxin in low concentrations, as found in the initial period of shock in patients with acute conditions, was not related to the development of subsequent MOF or associated with adverse effects in the patients undergoing elective operation. We, therefore, do not support the hypothesis that endotoxin plays the key role in the pathogenesis of ARDS and MOF.

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INTESTINAL PERMEABILITY AND BACTERIAL TRANSLOCATION: THEIR ROLE IN THE DEVELOPMENT OF MOF.

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Introduction

Today multiple organ failure (MOF) represents the number one cause of death in a surgical intensive care unit (ICU). However, the basic pathophysiology of this syndrome still remains to be elucidated (1). Hypotheses on the pathogenesis of MOF include "generalized inflammation" resulting from an excessive activation of endogenous inflammatory mediators and cells (2), and "the gut as the motor of MOF", implicating the role of translocating gut bacteria and endotoxins triggering the septic state (3). In this respect, alterations of intestinal permeability (IP) have been shown to be associated with translocation of intraluminally present toxic substances and micro-organisms. The role of splanchnic ischemia, inducing increased IP, has been stressed (4), while monitoring intestinal mucosal metabolism (for instance by gastric intra-mucosal pH measurements) has been shown to provide for early prognostic information (5,6), and for a guideline in therapy, thereby improving outcome in ICU patients (7).

Since MOF is associated with a generalized permeability problem (2,8), the role of IP in relation to this syndrome needs further clarification. IP can be defined as that property of the intestinal wall which modifies the permeation of a solute across or into the intestine (9).

In the present review the following questions will be addressed: under what circumstances has IP been shown to be altered; what is the relation of IP to bacterial translocation and what is the relation of these phenomena to subsequent MOF.

Measurements of Intestinal Permeability

Several methods to study IP non-invasively have been described. Intestinal absorption can be measured using non-metabolizable substances of different molecular size, like polyethyleneglycol polymers (PEG) (10-12). After urinary excretion of PEG, however, complex deterministic mathemathical models are required to reflect intestinal absortion (12) and the validity of these calculations is questionable (13).

Another possibility to study IP is the use of the isotope [51] Cr-labelled ethylenediamine-tetra-acetate ([51] Cr-EDTA) (14,15). This radio-active labelled solution is also given orally and after absorption, urinary excretion after a standardized period (e.g. 24h) is measured by the gamma activity uniformly assessed for 100 seconds in a low back ground chamber along with an appropriate standard (9,15). The total excretion then is expressed as a percentage of the ingested dose. A great advantage of this test is the

opportunity to study IP in vitro: in biopsy specimens of intestine (9).

A major advantage of using a ratio of two probes like in the dual sugar absorption tests (DSA) is the fact that by indexing the excretion of one sugar to that of another it is possible to correct for factors unrelated to IP, such as gastric emptying, intestinal transit time, mucosal surface area, cardiac output and renal function (9,16,17). Single probe tests of IP, like [51] Cr-EDTA and PEG, have as a major drawback a lack in correction for the above mentioned factors, thus resulting in a wide variation in urinary recovery of these molecules.

Most of the DSA tests use lactulose and mannitol (other combinations with e.g. rhamnose or cellobiose have been described). Since most studies on IP in surgical and critically ill patients have been performed using DSA tests, especially with lactulose and mannitol as markers, and because of the advantages of the two probes tests mentioned above, we will further concentrate on this test.

IP is graded by the ratio of lactulose to mannitol (L/M ratio), while both sugars represent different absorption routes (9,18). Lactulose, the larger molecule (m.w. 342) is absorbed passively: paracellularly via the tight junctions and extrusion zones at the villous tips (figure 8.1). Alterations in lactulose absorption (mainly increased levels) in fact reflect mucosal leakiness, resulting from a disruption of the anatomical barrier. Mannitol, the smaller molecule (m.w. 182), passes actively through aqueous pores in the cell membrane. This process requires energy and therefore depends on the functional absorptive capacity of the mucosa. Thus, decreased mannitol absorption reflects decreased mucosal function.

An abnormal L/M ratio indicating an abnormally increased IP, therefore, can be due to increased lactulose absorption (anatomical disruption) or decreased mannitol absorption (functional impairment) or a combination of both. Considering reports on alterations in IP, one should keep in mind these different absorption routes and look at conclusions of altered IP with caution.

Figure 8.1

Illustration of transport routes of lactulose and mannitol through the intestinal mucosal layer.

MANNITOL
TRANSCELLULAR

(FUNCTIONAL)

LACTULOSE
PARACELLULAR

(ANATOMICAL BARRIER)
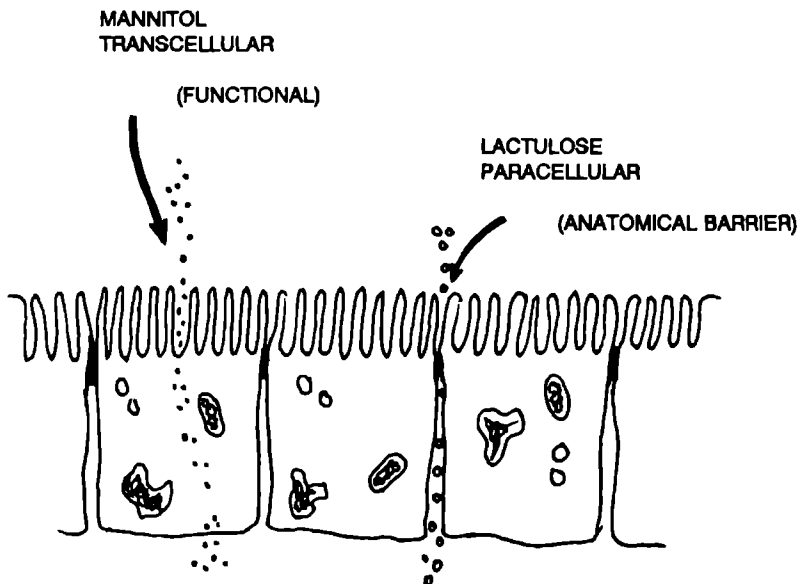
Quantitative analyses of Lactulose and Mannitol

The widespread use of the L/M test is limited by the difficulties of analyses for carbohydrates in urine at low concentrations (19). At present, three different methods are available to quantify these sugars. The enzymatic method for lactulose is based on hydrolysis by ß-galactosidase into fructose, which then is enzymatically assayed (20). Urinary mannitol can be analyzed by an enzymatic-spectrophotometric method, using mannitol dehydrogenase, which can be purified from mycelia of Aspergillus parasiticus (21). The other techniques are by gas-liquid chromatoghraphy (22) or by high pressure liquid-chromatography, in which anion exchange chromatography and pulsed amperometric detection are used (19). The advantage of the latter technique compared to the gas-liquid chromatography is that prior derivatization is not necessary (19).

Normally, lactulose is not present in human urinary samples, while mannitol may occur naturally in human urine (23). Therefore it is advised to take pretest urinary samples to correct for the mannitol determinations. Under normal conditions 0.1 - 0.5% of the

administered lactulose and 6 - 18% of the mannitol is excreted in 6 hourly collected urine (24). Thus, reported L/M ratios of healthy human control groups vary from 0.006 to 0.035 (24).

Clinical data on altered Intestinal Permeability

IP of humans has been studied extensively and was shown to be altered after various disorders. Increased IP was documented in patients with several types of gastro-enterologic diseases, like Crohn's disease (10,12,25,26), celiac disease (27-29), gastro-enteritis (30,31), persistent (29) and diabetic diarrhoea (32) and exocrine pancreas dysfunction (33). In patients with ulcerative colitis, however, L/M ratios appeared to be normal (25,27). Oral administration of chenodeoxycholic acid (34), a drug clinically used for dissolution of gallstones, and intravenous administration of endotoxin (35) both led to a significant increase of IP. The influence of diets on IP (36) has been demonstrated by the fact that IP normalizes in patients with celic disease who take a gluten-free diet (28). Total starvation led to significantly higher L/M ratios in children with diarrhoea, compared to those who were still enterally fed (30). Allergic conditions, such as cow's milk intolerance, food allergy or atopic dermatitis are associated with an abnormal increase of IP (29,37).

Additionally, also patients without gastro-enterologic disorders showed abnormally altered IP: patients with AIDS (25), chronic renal failure (11), or critically ill patients admitted at an ICU because of various underlying disorders (38). Trauma, like burn injury (16,17,39), blunt polytrauma (40), surgery for elective aortic aneurysm repair (24) and even long distance running (15) have been demonstrated to be associated with increased IP (table 8.1).

Attempts have been made to correlate the degree of abnormally increased IP, expressed by L/M ratio, with other parameters associated with the investigated diseases. In this respect L/M ratios could be correlated with the severity of disease in a study on patients with Crohn's disease (26). L/M ratios were also related to the degree of histological alterations in jejunal biopsies (29) and showed an inverse relation to growth in Gambian children (31).

Table 8.1

AUTHOR	YEAR	PATIENT GROUP STUDIED	TEST	COMMENT
Sundqvist[12]	1980	Crohn's disease	PEG	increased absorption of higher weights PEG polymers
Ukabam[27]	1983	Crohn's disease	L/M	sign. increased
		Ulcerative colitis	L/M	normal
Cooper[32]	1987	Diabetic diarrhoea	L/M	normal in uncomplicated diabetes
Elia[38]	1987	Total starvation	L/M	sign. increased;
			^{51}Cr-EDTA	no diff. between lean and obese; prevented by low calorie diets
Erickson[34]	1988	Oral chenodeoxy-cholic acid	L/M	sign. increased
O'Dwyer[35]	1988	Endotoxin administration	L/M	sign. increased in healthy humans
Olaison[10]	1988	Crohn's disease	PEG	increased absorption of higher weights PEG polymers
Ziegler[16]	1988	Burn patients	L/M	from day 2 - 45, related to infections
Akinbami[29]	1989	Celiac disease Cow's milk intolerance Food allergy Persistent diarrhoea	L/M	related to histology of jejenal biopsy
Dupont[37]	1989	Cow's milk sensitive enteropathy	L/M	sign. increased after provocation test, normal under diet
		Atopic dermatitis	L/M	sign. increased
Isolauri[30]	1989	Gastro-enteritis children	L/M	sign. different between feeded and fasted children

Table 8.1 (continued)

AUTHOR	YEAR	PATIENT GROUP STUDIED	TEST	COMMENT
Murphy[29]	1989	Crohn's disease	L/M	correlation with activity of disease index
Deitch[30]	1990	Burn patients	L/M	16 - 30 hr. post-injury sign. increased
Lunn[31]	1991	Children with growth faltering + diarrhoea	L/M	growth inversely related to L/M ratio
Magnusson[11]	1991	Chronic renal failure	PEG	relatively more higher weigths PEG polymers absorbed
Harris[38]	1992	Critically ill ICU	L/M	no correlation with severity of disease or sepsis scores
Leke[28]	1992	Celiac disease	L/M	normalization of L/M ratio during gluten-free diet
LeVoyer[17]	1992	Burn patients	L/M	sign. increased in patients with infections
Mack[33]	1992	Cystic fibrosis Shwachman syndrome	L/M	sign. increased in patients with exocrine pancreas dysfunction
Oktedale[15]	1992	Long distance runners	^{51}Cr-EDTA	after marathon sign. increased, related to gastric mucosal erosions
Ott[25]	1992	AIDS Crohn's disease Ulcerative colitis	L/M	sign. increased sign. increased normal
Roumen[24,40]	1993	Polytrauma Major vascular surgery	L/M	sign. increased at day 1 sign. increased at day 1, no difference between acute and elective major vascular surgery

In some studies on burn patients an association with infectious complications could be demonstrated (16,17), although in polytrauma patients and patients with hemorrhagic shock due to a ruptured aortic aneurysm, no difference in L/M ratios was found between patients with and without subsequent infections (40). Also, no correlations could be found between L/M ratios and severity of shock (24,40), injury (24), or disease (38), total body surface area burned (17), APACHE II scores (38,40), sepsis scores (38) or subsequent ARDS and MOF (24,40).

From the present data we therefore must conclude that increased IP is a common phenomenon seen in many patients, with different conditions and at various time points during the course of their diseases. Today, no clear conclusions or predictive value towards the severity of disease can be drawn from the severity of increased IP, ie. the height of L/M ratios.

Relation between Intestinal Permeability, Endotoxin and Bacterial Translocation

Since the first investigators to describe ARDS noticed that these patients often died of sepsis (41), a consensus developed that bacterial overgrowth is the cause of ARDS and MOF. Later, the frustration in not finding bacteria in obviously septic patients led to a concept of 'non-bacterial' clinical sepsis (3). In this setting the gut was hypothesized to be the source of bacteria and endotoxins and to play the key role in MOF (3). Indeed, the gut contains large amounts of intraluminal endotoxin, that may cause deleterious biological effects, possibly inducing the clinical and laboratory manifestations of septic shock (42). The process in which bacteria, normally confined to the gastro-intestinal tract can cross the mucosal barrier and appear in mesenteric lymph nodes and other organs has been termed bacterial translocation (43).

From several studies it is obvious that endotoxemia (or endotoxin translocation), bacterial translocation and IP are three associated phenomena. O'Dwyer et al. (35) showed that intravenous endotoxin administration in human volunteers significantly increased IP. Deitch and coworkers (43) demonstrated that endotoxin administration in mice promoted bacterial translocation and Navaratham et al. (44) showed that endotoxemia increased mesenteric vascular resistance in sheep and promoted bacterial translocation, suggesting a causative role for splanchnic ischemia in this process. Fink et al. (45), however, concluded from their experiments with pigs that the increased IP, observed after endotoxin administration, could be due to factors other than (or in addition to) mesenteric hypoperfusion. Induction of colonic ischemia (46)

or hemorrhagic shock (47) in dogs led to significant transmural migration of endo-toxin, whereas ischemia reperfusion injury after lower limb ischemia has been shown to result in increased IP in cats (48). Gathiram et al. (49) additionally showed that administration of anti - LPS during the reperfusion period after superior mesenteric artery occlusion in rats completely reversed endotoxemia. Rats subjected to he-morrhagic shock showed bacterial translocation, with a positive correlation between the degree of translocation and duration of shock (50,51). These findings were associated with shockinduced gut mucosal injury, subepithelial edema and focal areas of necrosis (51). On behalf of these observations it was hypothezised that a systemic challenge like shock or sepsis, causing splanchnic ischemia, may result in increased IP, bacterial translocation and endotoxemia. Endotoxemia on its turn aggravates the mucosal permeability, thereby generating a recurrent circle of gut derived infections (35).

However, no single human study has clearly demonstrated that increased IP in itself was positively and causatively correlated with endotoxemia and bacterial translocation. Observations in 50 polytrauma patients showed that positive blood cultures were present in 56% when admission systolic pressure was below 80 mm Hg (52). However, in only two of these patients endotoxemia was noticed. Peitzman et al. (53) concluded from their study on 25 trauma patients, that bacterial translocation to the mesenteric lymph nodes (MLN) was not a common occurrence in acutely injured patients and they could not demonstrate a relation between positive MLN cultures, later infectious complications and outcome. In a prospective clinical study on major torso trauma, Moore et al. (54) could not confirm portal or systemic bacteremia within the first 5 days postinjury, despite an eventual 30% incidence of MOF. In polytrauma patients and patients in shock due to a ruptured abdominal aortic aneurysm, IP is significantly increased 24 to 36 hours postinjury (40). In some of these patients systemic circulating endotoxin could be detected, but only immediately after hospital admission and 6 hours later. At 24 hours, when IP was demonstrated to be signifi-cantly increased, and at 48 hours no endotoxemia could be noticed anymore (40).

These data from the clinical situations in humans, therefore, do not support the above mentioned hypothesis, in which IP, bacterial translocation and endotoxemia are parts of a vicious circle ultimately leading to MOF (35).

Experimental data on Bacterial Translocation

Alexander et al. (55) elegantly demonstrated that Candida albicans and E. coli trans-

locate by direct penetration of the enterocyte, a proces different from classical phagocytosis. Translocation in between enterocytes was not observed. The same observation was done for endotoxin penetration. This finding was also observed by others (56,57), indicating that bacterial translocation is a process requiring an energetic contribution from the enterocyte. Surprisingly, for some unknown reason, the host thus seems to contribute actively to bacterial translocation. In this respect it has been suggested that bacterial translocation could be a normal function of the gut associated lymphoid tissue (GALT), in which macrophages are very important (56,58). In an experimental study on mice, Wells et al. (56) demonstrated that intestinal macrophages play the key role in the transport of intestinal particles, including bacteria, into extraintestinal sites.

In a recent study on the effects of ischemia-reperfusion in bacterial translocation in a hemorrhagic shock pig model, it was shown that bacterial translocation did not occur in the early post shock and post reperfusion period, despite significant evidence of lipid peroxidation in gut tissues after resuscitation (58). It should be notified that most of the work on bacterial translocation has been performed in rodents, animals that essentially differ in their purine metabolism from for instance pigs and humans, who are more similar in this respect (58). Also in one study with intravenous endotoxin administration in mice, no increased bacterial translocation could be demonstrated (59).

Since Enterobacteriaceae are thought most likely to translocate, selective decontamination (SD) of the gastro-intestinal tract has gained wide popularity as a method to selectively kill off these bacteria (60), while leaving intact the more harmless anaerobes (61). This method has resulted in an impressive decrease in the incidence of nosocomial infections in treated ICU patients (62). However, there are still doubts on the clinical relevance of SD in ICU patients, because no significant reduction of ICU days and ventilator days was observed, and mortality was reduced only in a few subgroups of patients (62). Moreover, untill today, SD has not been conclusively demonstrated to be effective in preventing MOF (62).

Experimentally, MOF may be induced by a non-bacterial, non-endotoxic inflammatory stimulus, even in germ-free rats (63). This ZIGI (Zymosan-Induced Generalized Inflammation) model has been shown to be a suitable one, not only of MOF but also of bacterial translocation and was extensively validated by others (64,65). Conclusions from several studies with this model (62,66) are, that, although bacterial translocation

was a common finding, the development of MOF did not depent on bacterial translocation. Suppression of bacterial translocation by SD did not prevent MOF, while streptomycine significantly reduced mortality, even in the presence of an overgrowth by Enterobacteriaceae (67). This latter result could be explained by the beneficial effect of streptomycin on the phagocytic activity of macrophages (68). In an experiment with endotoxin-hyporesponsive and endotoxin-responsive mice, bacterial translocation was barely seen and the mice were surprisingly resistant to zymosan-induced MOF (66). The most likely explanation is that zymosan does not induce macrophage activation in these mice, as was shown in vitro (69). Macrophage depletion by the administration of liposome-encapsulated dimethylene-diphosphonate prior to zymosan, resulted in an important increase in bacterial translocation, but in an almost total prevention of mortality from MOF (70). In all these experiments only control or modulation of the inflammatory response prevented both bacterial translocation and MOF, while these two phenomena were not causatively related.

Conclusion

The above described data indicate that IP, measured by the permeation of non-metabolizable substances, can be altered during many different disordes and circumstances. Moreover, it has been demonstrated that it is a phenomenon different from bacterial translocation and endotoxin penetration. At present it is still unknown whether these processes always occur concomitantly or whether some pathological conditions are associated with abnormal IP in the absence of increased translocation or vice versa (18). We further conclude that increased permeability is a phenomenon not necessarily associated with subsequent MOF. The same conclusion is made for bacterial translocation. Since the gut is an organ very susceptible to disturbances of homeostasis (4), altered IP merely could be a process that is part of a general permeability problem seen in many patients with or at risk of MOF. Finally, we suggest that IP, bacterial translocation and endotoxemia should not be bracketed together unconditionally, because these processes do not implicate causatively related phenemona.

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INTESTINAL PERMEABILITY AFTER SEVERE TRAUMA AND HEMORRHAGIC SHOCK IS INCREASED WITHOUT RELATION TO SEPTIC COMPLICATIONS

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Abstract

After thermal injury, alterations in intestinal permeability have been demonstrated and correlated with subsequent infections. We measured intestinal permeability on the second day after severe trauma and hemorrhagic shock (ruptured abdominal aneurysm). The mean ($\pm$ SD) lactulose/mannitol (L/M) excretion ratio was 0.012 ± 0.005 in seven healthy control subjects, 0.069 ± 0.034 in eleven severely traumatized patients and 0.098 ± 0.093 in eight patients with aneurysm, indicating a significant increase of intestinal permeability in both patient groups ($p < 0.005$). No significant correlation was found between L/M ratios and age, severity of injury or shock, lactate levels on admission, APACHE II score, daily pulmonary gas exchange parameters or mean multiple organ failure scores. No difference in intestinal permeability between patients with and without subsequent infections could be demonstrated. In eleven patients we looked for endotoxin in the systemic circulation. In six patients endotoxemia was present immediately after admission and before the L/M test. However, during the L/M test and one day afterward, no circulating endotoxin was observed. The present data provide evidence for the hypothesis that increased intestinal permeability and subsequent infectious complications are independent phenomena, frequently seen in patients after severe trauma or hemorrhagic shock.

Introduction

Severe trauma and hemorrhagic shock may initiate a cascade of events, leading to septic complications, the Adult Respiratory Distress Syndrome (ARDS), Multiple Organ Failure (MOF), and ultimately death. One of these events may be failure of the barrier function of the gastrointestinal tract, resulting in increased intestinal permeability and associated with subsequent translocation of bacteria and endotoxins from the gut (1). Increased intestinal permeability is well documented in humans after thermal injury (1-3) and correlates positively with septic complications (2,3). In addition, experimental administration of intravenous endotoxin in humans results in increased intestinal permeability (4). Therefore, the gut may be an important source of infection in patients at risk, and may be the "motor of MOF" (5). However, at present no data are available on changes in intestinal permeability in patients with severe trauma and/or hemorrhaghic shock.

We investigated intestinal permeability after severe trauma and hemorrhaghic shock

and its relation to the severity of injury or shock, to infectious complications, ARDS and MOF, and to endotoxemia.

Patients and methods

Subjects

Three groups of subjects were studied. The control group consisted of seven healthy volunteers. The trauma group consisted of 11 patients with severe blunt injury, resulting in an Injury Severity Score (ISS) (6), calculated from the Hospital Trauma Index (7), above 24 points. The third group, admitted in hemorrhaghic shock, consisted of eight patients, who underwent an emergency operation because of a ruptured abdominal aortic aneurysm. The study was approved by the local ethical committee and informed consent was obtained from all patients or their relatives prior to the study.

Study design

On admission, severity of injury in patients with trauma was graded with the ISS (6). At the time of admission to the ICU, the APACHE II score (8) was determined. On admission (0 hours = baseline) and at 6, 24 and 48 hours after admission, arterial blood was withdrawn under sterile conditions for determination of lactate and endotoxin concentrations. On the second day, 24 to 36 hours after admission to the hospital, intestinal permeability was assessed by measuring the absorption of two orally administered inert markers, lactulose (L) and mannitol (M), and their ratio (L/M ratio) (2,9). The patients were followed up for 2 weeks after admission with regard to the development of infectious complications, ARDS and MOF.

Lactulose and mannitol assays

The test solution consisted of 10 grams of lactulose and 5 grams of mannitol mixed in 60 ml of distilled water, which was instilled via a nasogastric tube. Until then the patients had been fasting. The healthy volunteers received the test solution orally after an overnight fast. Before administration, the urinary bladder was emptied and a pretest urine sample was taken. During the next 6 hours all urine was collected and

pooled. From this pooled urine a sample was taken. Both urine samples were frozen at -20°C until analysis. Urinary lactulose and mannitol concentrations were determined using capillary gas chromatography (10). Mannitol excretion was corrected by subtraction of baseline values determined in the pretest samples.

Blood analysis

Arterial blood lactate levels were measured in deproteinized samples (0.6 mol/l perchloric acid) by enzymatic conversion of lactate into pyruvate. Blood for endotoxin determinations was collected in special storage tubes (Kabi Diagnostica, Mölndal, Sweden), centrifuged, and immediately frozen at -20°C as described by Redl et al (11). Endotoxin was measured quantitatively using a limulus assay with chromogenic substrate (Coatest Endotoxin, Kabi Diagnostica, Mölndal, Sweden). Each assay was run in duplicate. The detection limit of this assay is 12.5 pg/ml.

Definitions

A shock score was defined to grade the severity of hemodynamic derangement after admission. For this purpose the Allgöwer shock index (heart frequency / systolic blood pressure) (12) and the systolic blood pressure were used: (0) indicates no shock: index $\leq$ 1.0 and systolic blood pressure $\geq$ 100 mm Hg; (1) mild, compensated shock: index > 1.0 and systolic blood pressure $\geq$ 100 mm Hg; (2) moderate shock: systolic blood pressure 80 to 100 mm Hg; (3) severe shock: systolic blood pressure < 80 mm Hg; (4) severe, prolonged shock: more than one hour systolic blood pressure < 80 mm Hg.

ARDS was diagnosed when patients had bilateral diffuse infiltrates on the chest roentgenograms, and progressive hypoxemia requiring mechanical ventilation that resulted in a PaO_2/FiO_2 ratio $\leq$ 175 with PEEP $\geq$ 10 cm H_2O and, in patients with a history of cardiac disease, a pulmonary artery wedge pressure that did not exceed 18 mm Hg (13). The PaO_2/FiO_2 ratio was calculated daily to grade pulmonary gas exchange.

For every patient a daily MOF score was calculated to grade the intensity of organ failure (14). A patient was diagnosed as having MOF, if the mean MOF score from day 5 to 14 was $\geq$ 4.

Infectious complications were defined as follows:

-   bronchopneumonia: rectal temp. ≥ 39°C and positive sputum cultures and/or infiltrates on the chest roentgenograms;
-   septicemia: rectal temp. ≥ 39°C and one or more positive blood cultures;
-   wound infection: rectal temp. ≥ 38°C and purulent discharge;
-   urinary tract infection: rectal temp. ≥ 38°C and > 10 [5] micro-organisms/ml urine;
-   intra-abdominal sepsis: rectal temp. ≥ 39°C and positive cultures from abdominal fluid (using laparotomy or ultrasonographic puncture).

Statistical analyses

The Kruskal-Wallis test, Wilcoxon two sample test, and Spearman's rank correlation analysis were used as indicated. Differences were considered significant at $p < 0.05$.

Results

The demographic data of the study population are given in table 9.1. The mean APACHE II score in the aneurysm group was 6 points higher than in the trauma group, mainly because of the higher age of the patients with aneurysm (APACHE II scores 5 additional points for age between 65-74 years).

The data on excretion of administered lactulose and mannitol are given in table 9.2. Lactulose excretion was higher in both study groups than in the control group, and significantly higher in the aneurysm group. Mannitol excretion was significantly lower in both study groups. The mean (± SD) L/M ratio in controls was 0.012 ± 0.005; in the trauma group 0.069 ± 0.034 and in the aneurysm group 0.098 ± 0.093 ($p < 0.005$, by Wilcoxon's test) (figure 9.1).

Table 9.1

Demographics of the study population. Data are expressed as mean ± SD.

	n	Sex M/F	Age (yr)	APACHE II on admission	ISS (HTI)
Control	7	7/0	31 ± 9	—	—
Trauma	11	7/4	33 ± 15	8.1 ± 3.5	34 ± 5
Aneurysm	8	8/0	69 ± 6	14.6 ± 7	—

Figure 9.1

Lactulose/mannitol urinary excretion ratios in normal controls and in patients with severe trauma or ruptured abdominal aortic aneurysm. Horizontal bars indicate mean values. Differences between groups are as follows: control vs trauma: $p = 0.0006$; control vs aneurysm: $p = 0.003$; aneurysm vs trauma = not significant, by Wilcoxon's test.
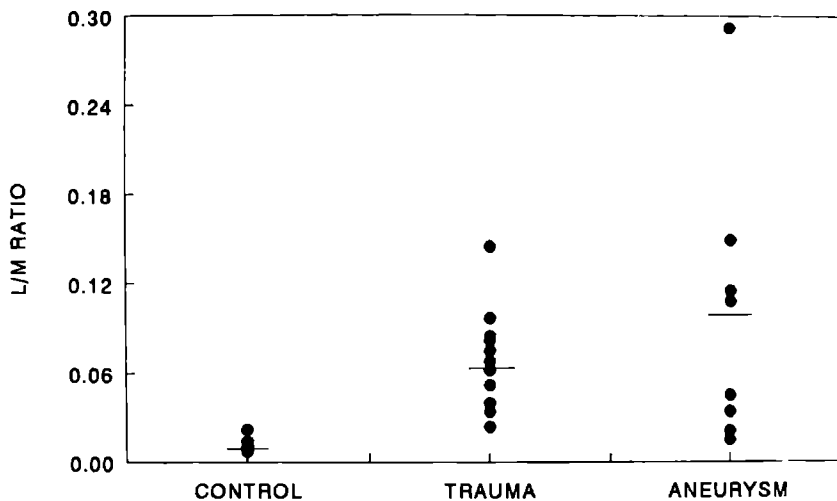
Table 9.2

Lactulose and mannitol excretion in 6 hour urine collection of the study population. Data are expressed as mean ± SD.

	Control (n=7)	Trauma (n=11)	Aneurysm (n=8)
Lactulose excreted %	0.22 ± 0.09	0.69 ± 1.17	0.44 ± 0.20 *
Mannitol excreted %	21.9 ± 8.3	9.2 ± 11.6 *	9.6 ± 8.3 *
Lactulose / mannitol excretion ratio	0.012 ± 0.005	0.069 ± 0.034 **	0.098 ± 0.093 **

* = p < 0.05 and ** = p < 0.005 versus controls, by Wilcoxon's test.

In nine patients, 12 infectious complications were diagnosed during the 2-week study period, including five cases of pneumonia, four urinary tract infections, two cases of septicemia and one intra-abdominal infection (table 9.3). Of the 16 bacterial species cultured, seven (44%) probably were of enteric origin and nine (56%) of non-enteric origin.

The mean L/M ratio on day 2 in the nine patients who later developed infectious complications was 0.059 ± 0.032 and in the 10 patients without infectious complications 0.101 ± 0.080 (not significant, by Kruskal-Wallis test). No significant differences were found between infected and non-infected patients with regard to age, APACHE II, severity of shock or plasma lactate levels (data not shown).

The degree of the altered intestinal permeability, expressed by the L/M ratio, did not show any significant correlation with ISS, APACHE II score, shock score, plasma lactate levels, PaO2/FiO2 ratios at days 1,2 and 3, or mean MOF scores from days 5 to 14. None of the patients died during the two week study period. Four patients with aneurysm developed ARDS and MOF, while none of the patients with trauma fulfilled the criteria for ARDS and/or MOF. The L/M ratios of the four aneurysm patients developing ARDS/MOF (0.047 ± 0.038) were not significantly different from those of the other patients (0.090 ± 0.065, by Kruskal-Wallis test).

In 11 patients (5 with aneurysm, 6 with trauma) a complete set of blood samples (at 0, 6, 24 and 48 hours) was available for endotoxin determination. In 6 patients (5 with aneurysm, 1 with trauma) endotoxemia was demonstrated at either 0 h (in 6 patients the mean endotoxin level was 21 pg/ml, range 15 to 25 pg/ml) or 6 h (in 2 patients

the endotoxin levels were 16 and 25 pg/ml). In the other 5 patients, no circulating endotoxin could be detected at any time. In patients with endotoxemia, the mean L/M ratio was 0.112 ± 0.100, versus 0.051 ± 0.028 in patients without measurable endotoxin. The mean shock score and blood lactate concentration on admission in patients with endotoxemia were 2.3 ± 1.2 and 5665 ± 4005 μmol/l, versus 1.4 ± 0.5 and 3167 ± 2218 μmol/l in patients without endotoxemia. Since the groups were small, no statistical analysis is provided.

Table 9.3

Type of infection in patients after ruptured abdominal aneurysm (patient nr. 1 through 3) and in severely traumatized patients (patient nr. 4 through 9), the day the infections became obvious and the micro-organisms that were cultured together with the individual data on lactulose and mannitol excretion (expressed as %) and their ratio.

Patient nr.	Type of Infection	Day	Micro-organism (Gram stain)	Enteric yes/no	Lactulose/mannitol excretion (% / %)
1	Intra-abdominal sepsis	14	Bacteroides sp. (-)	yes	0.85 / 18.8
			Enterococcus sp. (+)	yes	
2	Septicaemia	4	S. epidermidis (+)	no	0.54 / 4.9
	Pneumonia	14	Ps. aeruginosa (-)	no	
3	Pneumonia	5	K. pneumoniae (-)	yes	0.13 / 8.8
			P. mirabilis (-)	yes	
	Urinary tract	8	Enterococcus sp. (+)	yes	
4	Pneumonia	10	S. aureus (+)	no	0.31 / 5.9
			Strept. pyogenes (+)	no	
	Septicaemia	10	S. aureus (+)	no	
5	Pneumonia	8	H. influenzae (-)	no	0.25 / 10.5
6	Urinary tract	11	Enterococcus sp. (+)	yes	4.35 / 44.9
7	Urinary tract	8	Enterococcus sp. (+)	yes	0.08 / 1.0
8	Pneumonia	3	S. aureus (+)	no	0.07 / 1.8
			Ps. aeruginosa (-)	no	
9	Urinary tract	5	Ps. aeruginosa (-)	no	0.49 / 7.7

(sp. = species)

Discussion

The lactulose-mannitol test is based on the different absorption routes of the two sugars. Mannitol, the smaller molecule, passes through aqueous pores in the cell membrane, while lactulose, the larger molecule, is absorbed paracellularly via the tight junctions and extrusion zones at the villous tips (1). By indexing the excretion of lactulose to that of mannitol (using the L/M ratio), it is possible to correct for factors unrelated to intestinal permeability, such as gastric emptying, intestinal transit time, mucosal surface area, cardiac output and renal function (2).

Alterations in absorption of lactulose reflect mucosal leakiness, whereas decreased absorption of mannitol correlates with a decrease in functional absorptive area (3,9,15). The L/M ratio may be increased because of decreased mannitol absorption (functional impairment) as in celiac disease and in malnourished children with diarrhoea (9,15), or because of an increased lactulose absorption due to mucosal damage (physical impairment) as occurs after burn injury (3). Under normal conditions, 0.1 to 0.5% of the administered lactulose and 6 to 18% of the mannitol is excreted in the urine during the first 6 hours after administration, the L/M ratios reported varying from 0.006 to 0.035 (1-4,15,16). In the present study, the controls showed similar excretion and L/M ratios.

Both patients with trauma and aneurysm showed significantly increased L/M ratios on the second day after the event, the first documentation, to our knowledge, of increased intestinal permeability in these patient populations. In this respect, the patients responded like thermally injured patients (1-3) and experimental animals after hemorrhaghic shock (16).

No significant correlation was found between the severity of injury as documented by the ISS or shock as documented by the shock score and lactate levels on admission on one hand and the degree of increase in intestinal permeability on the other hand. This finding is in agreement with the post-burn injury studies, which did not show a burn-size-related effect on intestinal permeability (1-3).

Since only a few patients in our study developed ARDS and subsequent MOF and these patients did not display a significantly different pattern of intestinal permeability compared with other patients, we looked at pulmonary gas exchange (PaO_2 / FiO_2) and mean MOF scores of all patients. No correlation was found between L/M ratios and either impaired pulmonary function within the first 3 days of admission or with a later increase of mean MOF scores.

In contrast to other reports (2,3), our data demonstrate that there is no significant

difference in intestinal permeability between patients with and without subsequent infections. A type II error is unlikely because the direction of the trends in the L/M ratios was even opposite to that suggested by the other reports, ie., intestines of infected patients were less permeable than those of non-infected patients. LeVoyer et al. reported an increased intestinal permeability prior to the episode of infection in patients with burn (3). However, in their series only six of the 13 infections were caused by enteric organisms. Ziegler et al. also suggested a correlation between increased intestinal permeability and infections (2). However, in the latter study L/M ratios were measured after the first postburn week and thus at the time of infection itself.

In our present study only five (42%) of the 12 documented infections (seven (44%) of 16 infecting micro-organisms) were caused by enteric organisms. The remaining infections were caused by other non-enteric Gram-positive or Gram-negative species. Thus, we suggest that increased intestinal permeability and subsequent infections are independent phenomena, seen in patients after severe trauma or hemorrhagic shock. This hypothesis is supported by the observations that the process of microbial translocation occurs by direct penetration of the enterocyte, which is a process different from classical phagocytosis (17). Additionally, it has been demonstrated that the macrophage may play a key role in this translocation process (18). Thus, increased intestinal permeability as reflected in the L/M ratio may have little relevance to the mechanism of bacterial uptake by the intestinal epithelium.

In six (54%) out of 11 patients in whom endotoxin was measured, detectable levels were found at the time of admission and/or 6 hours later. However, at the time increased intestinal permeability was demonstrated, and 1 day after the L/M test, no circulating endotoxin was found in any patient. Although the number of patients was limited, we found a trend toward higher L/M ratios in patients with prior positive endotoxemia test results. This is in agreement with the observations of O'Dwyer et al., who showed an increased intestinal permeability after a single dose of intravenous endotoxin in healthy humans (4). However, the present study provides no support for the hypothesis that endotoxin creates a positive feedback loop, in which damage to the intestinal barrier leads to translocation of endotoxins, with infectious complications and a septic response (4,5). We found endotoxemia, especially in patients after severe hemodynamic derangement (mainly ruptured abdominal aneurysms, with higher shockscores and lactate levels). In these patients splanchnic flow and especially liver perfusion generally are impaired in the shock phase (19). Therefore, endotoxin that entered the systemic circulation either by portal vein route or lymphatic transport

could be less rapidly inactivated by the liver, which normally plays a key role in this aspect (20). Once endotoxemia has occurred, this leads to an increase of mesenteric vascular resistance, resulting in a reduction of mesenteric blood flow of more than 50% (21). After reperfusion and stabilization of hemodynamics, or in patients with less splanchnic flow impairment, endotoxin inactivation by the liver could be such that systemic circulating endotoxin levels do not exceed the threshold of detection. This effect may explain why in a recent study on major trauma patients no endotoxin could be detected in the circulation within the first 48 hours, since the first samples were taken no sooner than 6 hours after trauma (22). In one of our patients with trauma endotoxemia was found, but only immediately after the injury. After 6 hours this patient did not exhibit any detectable circulating endotoxin anymore. Our findings are in agreement with the data of Rush et al., who took blood specimens within 3 hours of admission in 10 patients with hemorrhagic shock (23). In the latter study only significant endotoxin levels were measured in two of these patients, who had very low blood pressures on admission (less than 80 mm Hg).

The finding of increased intestinal permeability without subsequent detectable endotoxemia may be explained in several ways. First, after trauma and shock both increased intestinal permeability as well as endotoxemia are phenomena that primarily occur independently of each other. In patients with endotoxemia, a factor previously shown to promote bacterial translocation (19,24), the intestinal permeability can be increased or show a sustained elevation. However, increased intestinal permeability itself does not necessarily lead to more endotoxemia. Within this concept fits the finding that translocation of endotoxin does not require loss of mucosal integrity as such, since endotoxin has been shown to translocate directly across the enterocyte (17). The second explanation could be that immediately after trauma and shock intestinal permeability is so much elevated that it leads to endotoxemia. Twenty-four hours later some reconvalescence of the intestinal mucosa has taken place, but intestinal permeability is still significantly increased, although not enough to lead to endotoxemia. The latter proces could be enhanced by the fact that small amounts of entered endotoxin are cleared by the liver and do not exceed the detection limit of the systemic circulation.

Conclusions

In patients with severe trauma or a ruptured aortic aneurysm, intestinal permeability, as measured by the lactulose/mannitol test, was significantly increased at day 2.

However, increased intestinal permeability did not correlate with the severity of injury and/or shock, or with subsequent infectious complications, ARDS and/or MOF. Endotoxemia was only demonstrated before the measurement of increased intestinal permeability, not at the time of measurement or afterward. We therefore hypothesize that in the patient population studied, increased intestinal permeability and subsequent infectious complications are independent phenomena.

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INTESTINAL PERMEABILITY IS INCREASED
AFTER MAJOR VASCULAR SURGERY

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Abstract

In experimental animals increased intestinal permeability has been demonstrated after ischemia and reperfusion injury. In this study we determined intestinal permeability in patients after elective or emergency aortic aneurysm repair: the latter patients were in severe shock on hospital admission. A dual sugar absorption test with lactulose (L) and mannitol (M) as markers was used to measure intestinal permeability on the second day between 24 and 36 hours after hospital admission. The lactulose/mannitol (L/M) excretion ratio was 0.012 ± 0.005 in seven healthy control subjects, 0.118 ± 0.116 in seven patients undergoing elective operation and 0.098 ± 0.093 in eight patients having emergency operation, indicating a significant increase of intestinal permeability in both patient groups ($p < 0.01$). No significant difference was found in intestinal permeability between patients of the elective and emergency groups. It is concluded that a significant increase in intestinal permeability commonly occurs in patients after elective and emergency major vascular surgery. It is suggested that this is mainly due to reperfusion injury rather than the ischemic period of the intestine itself.

Introduction

Late hospital death after major vascular surgery is mainly due to multiple organ failure (MOF) (1,2). It has been hypothezised, that the gut may play a leading role in the origin of MOF (3). This contribution of the intestine in situations leading to MOF is associated with two phenomena: bacterial translocation and endotoxemia (4-6). Bacterial translocation has been demonstrated in experimental animals after trauma and shock,(4) but in humans with major trauma this could not be confirmed (7). Endotoxemia was documented to occur after intestinal ischemia in cats (8). Experimentally, bacterial translocation is also promoted by endotoxin administration (5,9), whereas intravenous injection of endotoxin in human volunteers increased intestinal permeability (6). These findings have led to the hypothesis that injury and shock, endotoxemia, intestinal permeability and bacterial translocation are parts of a vicious circle, finally leading to remote organ damage and death (6).

Recently it was demonstrated that intestinal permeability is increased in rats after lower limb ischemia and reperfusion injury (10). The present human study was undertaken to investigate whether gut permeability is altered after major vascular

surgery, in particular after abdominal aortic aneurysm repair.

Patients and methods

Subjects

Three groups were studied. The control group for studying intestinal permeability consisted of seven healthy volunteers, all men with a mean (±SD) age of 31 ± 9 years. The second group consisted of seven patients (6 men and 1 woman: 65 ± 12 years of age), who underwent elective repair of an aneurysm of the infrarenal aorta. The third group consisted of eight male patients (69 ± 6 years of age), who were admitted in hemorrhagic shock and had an emergency operation because of a ruptured infrarenal aortic aneurysm. The study was approved by the local ethics committee, and informed consent was obtained from all patients or their relatives prior to the study.

Study design

After operation, after admission to the ICU, the APACHE II score was determined in all cases (11). On the second day, 24-36 hours after operation, intestinal permeability was assessed by measuring the absorption of two orally administered inert markers lactulose and mannitol (6,12).

The test solution consisted of 10 grams of lactulose and 5 grams of mannitol mixed in 60 ml of distilled water, and was instilled via a nasogastric tube. Until then the patients had been fasting. The healthy volunteers received the test solution orally after an overnight fast. Before administration, the urinary bladder was emptied and a pretest urine sample was taken. During the next 6 hours, all urine was collected and pooled. A sample was taken from this pooled urine. Both urine samples were frozen at -20°C until analysis. Urinary lactulose and mannitol concentrations were determined, by use of capillary gas chromatography (13). Mannitol excretion was corrected by subtraction of baseline values determined in the pretest samples. Finally the lactulose/mannitol excretion ratios (L/M ratio) were calculated.

As long as patients were admitted at the ICU, a daily MOF score was calculated (14). A patient was diagnosed as having MOF if the average MOF score from day 5 to 14 was ≥ 4.

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Statistical analyses

The Kruskal-Wallis test and Wilcoxon's two sample test were used for comparison of groups. Differences were considered significant at $p < 0.05$.

Results

The mean ($\pm$ SD) APACHE II score on ICU admission was 5.3 ± 2.4 in the elective group and 8.4 ± 2.5 in the emergency group ($p = 0.09$, by Kruskal-Wallis).

The excretion of administered lactulose and mannitol is shown in table 10.1. Lactulose excretion was increased in both study groups as compared with the control group and significantly so in the emergency group. Mannitol excretion was significantly lower in both study groups. The mean L/M ratio in controls was 0.012 ± 0.005, in the elective group 0.118 ± 0.116 and in the emergency group 0.098 ± 0.093 ($p < 0.01$, by Wilcoxon's test) (figure 10.1).

No significant difference in either lactulose or mannitol excretion or in the L/M ratios was found between patients of the elective and of the emergency group.

Mof developed in 4 patients, all from the emergency group. Their L/M ratios (0.047 ± 0.038) did not significantly differ from other patients, in whom subsequent MOF did not develop (0.128 ± 0.110).

Table 10.1

Lactulose and mannitol excretion in 6 hour urine collection of the study population. Values are expressed as mean $\pm$ SD.

	Control (n=7)	Elective (n=7)	Emergency (n=8)
Lactulose excreted %	0.22 ± 0.09	0.85 ± 1.52	0.44 ± 0.20 *
Mannitol excreted %	21.9 ± 8.3	7.1 ± 4.9 *	9.6 ± 8.3 *
Lactulose / mannitol excretion ratio	0.012 ± 0.005	0.118 ± 0.116 **	0.098 ± 0.093 **

* = $p < 0.05$ and ** = $p < 0.01$ versus controls, by Wilcoxon's test.

Figure 10.1

Lactulose/mannitol urinary excretion ratios in healthy controls, patients after elective aneurysm repair and patients after emergency repair, because of a ruptured aneurysm. Horizontal bars indicate mean values. Differences between groups: control vs elective: $p = 0.003$; control vs emergency: $p = 0.009$; elective vs emergency: $p = 0.52$, not significant, by Wilcoxon's test.
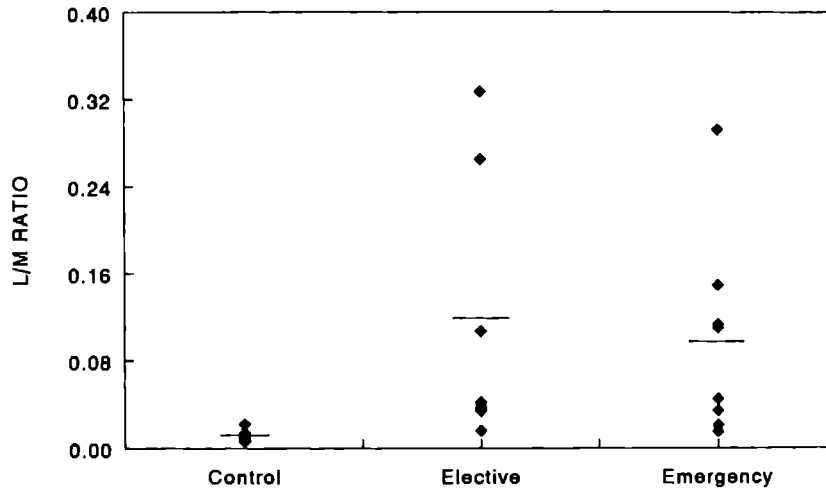
Discussion

The lactulose-mannitol test is a generally accepted tool for assessing intestinal permeability and is based on the different absorption routes of the two sugars (6,12,15-18). Mannitol, the smaller molecule of the two agents, passes through aqueous pores in the cell membrane, whereas lactulose, the larger molecule, is absorbed paracellularly via the tight junctions and extrusion zones at the villous tips (12). By indexing the excretion of lactulose to that of mannitol (with use of the L/M ratio), it is possible to correct for factors unrelated to intestinal permeability, such as gastric emptying, intestinal transit time, mucosal surface area, cardiac output and renal function (16).

Under normal conditions, 0.1-0.5% of the administered lactulose and 6-18% of the

mannitol is excreted in the urine during the first 6 hours after administration (18). The reported L/M ratios vary from 0.006 to 0.035 and appear to be independent of age (18). In the present study the controls showed similar excretion and L/M ratios as in the reviewed literature.

Increased intestinal permeability has been reported to occur in patients with several gastro-intestinal disorders, like Crohn's and celiac disease (19) and in malnourished children with diarrhoea (17). In like manner, patients after thermal injury showed a marked increase of intestinal permeability (12,15,16). In these latter patients intestinal permeability could be related to subsequent infectious complications (15,16). We recently also reported such an increase of intestinal permeability in patients after severe trauma, but we could not confirm the relation of this increased permeability with septic complications (18).

The present report demonstrates that after major vascular surgery intestinal permeability is markedly increased. We found no difference in intestinal permeability in patients with an elective aortic aneurysm repair, compared to those admitted in shock and operated on for a ruptured aneurysm. In both patient groups the aneurysm and the clamp placed before operation on the aorta were located below the renal arteries, so in both groups the flow through the superior mesenteric artery - and thus through the small intestines - was affected in a similar way by the operation itself. This finding indicates that the factor of hemodynamic instability and shock in patients of the emergency group did not contribute significantly to intestinal permeability. These data confirm the hypothesis that the reperfusion injury, that must have occurred in both patient groups may be the most important factor leading to gut mucosal damage and increased permeability (10). This is in agreement with animal studies that showed that the effects of ischemia occurred largely at the time of reperfusion and reoxygenation rather than during the ischemic period itself (20).

Additional human studies are required to investigate whether intestinal permeability is changed also after lower limb ischemia and reperfusion as it is in patients who undergo femoral artery operation. Furthermore, attempts should be undertaken to unravel the role of anti-oxydants and other antagonists of mediators that are released after ischemia and reperfusion injury, with emphasis on intestinal permeability changes.

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GASTRIC TONOMETRY IN MULTIPLE TRAUMA PATIENTS

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Abstract

Splanchnic ischemia, leading to intestinal mucosal damage, is thought to be a common condition in patients after severe trauma. The adequacy of mucosal oxygenation can indirectly be determined by gastric intramucosal pH (pHi) measurement. We prospectively examined the post-traumatic gastric pHi values in 15 multiple trauma patients. In all patients gastric pHi was measured using a tonometer applied via the nasogastric route. A pHi value ≤ 7.32 was used to differentiate between normal and low gastric pHi.

Six hours after the injury four patients showed abnormally low pHi levels. Four other patients with normal initial pHi values exhibited low pHi values during one or more of the next measuring periods. Three of these eigth patients developed major complications (2x ARDS) and two of them subsequently died. The seven remaining patients never had abnormal pHi levels and all patients had an uncomplicated recovery.

Although intestinal ischemia was expected to be a common condition in multiple trauma patients, no consistent pattern of abnormal pHi measurements in the direct post-traumatic course could be discovered. No correlation was found between initial pHi values (at 6h) and ISS, shock and lactate concentrations or APACHE II score on admission. It is concluded that monitoring gastric pHi is usefull in severely injured patients admitted to ICU.

Introduction

Intestinal ischemia is a common condition in critically ill patients (1). It induces a spectrum of mucosal injury ranging from subtle changes in capillary permeability to gross transmural infarction depending on the severity and duration of the ischemic challenge (2). The mucosal damage consists of two components: the injury induced by ischemia (hypoxia) and that produced by oxygen free radicals on reperfusion of the ischemic tissue (2,3). In previous studies we showed that human intestinal permeability is markedly increased 24 to 36 hours after severe blunt trauma (4). In another study, significant increases of serum lipofuscin levels at 6 and 24 hours after severe trauma were demonstrated, with a predictive value for subsequent ARDS and multiple organ failure (MOF) (5). The presence of increased lipofuscin concentration in these patients suggests a pathogenic role for lipid peroxidation caused by oxygen free radicals (5,6). Thus, one might expect that splanchnic ischemia is a common

condition in the direct post-traumatic course of multiple trauma patients.

Indirect measurement of pH in gut mucosa (pHi) has been shown to provide a measure of the adequacy of mucosal oxygenation (1,7,8). By means of an intraluminally placed balloon catheter permeable to CO2 pHi can be measured (9,10).

The present study was undertaken to investigate the post-traumatic course of tonometrically measured pHi in patients after severe blunt trauma. In addition we studied the relation between pHi and parameters for severity of injury, shock, lactate levels and physiological derangement.

Patients and Methods

Fifteen patients with multiple blunt trauma, with an ISS-HTI > 25 (11,12), who had to be operated upon because of one or more injuries, were enrolled in the study. Informed consent was obtained from all patients or their relatives prior to the study. The study was approved by the local ethical committee.

On hospital admission ISS-HTI, APACHE II (13) (also calculated on ICU admission) and a shock score (4) were determined. The latter score was defined to grade the severity of hemodynamic derangement on admission. For this purpose the Allgöwer shock index (heart frequency / systolic blood pressure) (14) and the systolic blood pressure were used: (0) no shock: index ≤ 1.0 and systolic blood pressure ≥ 100 mm Hg, (1) mild, compensated shock: index > 1.0 and systolic blood pressure ≥ 100 mm Hg, (2) moderate shock: systolic blood pressure 80 - 100 mm Hg, (3) severe shock: systolic blood pressure < 80 mm Hg, (4) severe, prolonged shock: more than one hour systolic blood pressure < 80 mm Hg. During general anaesthesia a tonometer (Tonomitor, Tonometrics, Inc. Bethesda, Maryland, USA) was inserted via the nasogastric route in all patients. The position of the balloon was confirmed radiographically. PCO_2 was assessed by inflating the balloon with physiologic saline, precisely according to the instructions of the tonometer users manual. After an equilibration period of 30 minutes, a saline sample was withdrawn anaerobically and PCO_2 measured immediately by a standard blood gas analyzer (Corning 278, Ciba Corning Diagnostics N.V., Houten, The Netherlands). Arterial blood was withdrawn simultaneously for determination of pHa, blood gases and bicarbonate concentration, as well as lactate concentration. After correcting the PCO_2 according to the equilibration period the pHi was calculated with the modified Henderson-Hasselbalch equation:

$pHi = 6.1 + Log_{10} \{ [HCO3^-] / PCO_2 \times 0.03 \}$.

PHi and lactate measurements were performed at 6, 12, 24, 36 and 48 hours after hospital admission. None of the patients received histamine-receptor-blocking agents throughout the study period (15). A pHi value of $\leq$ 7.32 was considered as an indication of inadequate tissue oxygenation (9,10,16,17). Arterial blood lactate was measured in deproteinized samples (0.6 mol/l perchloric acid) by enzymatic conversion of lactate into pyruvate.

Pearson's correlation coefficients were used for correlation analysis. P values less than 0.05 were considered to be significant.

Results

Demographic data and initial pHi values (at 6 hours) of all 15 patients are shown in table 11.1. The patients had a mean ($\pm$ SD) age of 36 $\pm$ 7 years and ISS of 35.5 $\pm$ 8.8. APACHE II score was 10.6 $\pm$ 4.9 on hospital admission and 7.4 $\pm$ 6.4 after admission to the ICU. Figure 11.1 illustrates the pHi course of the whole patient group during 48 hours.

Four patients had an initial abnormal pHi value of less than 7.32. Two of these patients showed a correction of pHi to normal values in the next measuring periods. They had an uncomplicated recovery and were discharged from ICU at day 3 and 5, respectively. One patient had a persistently low pHi at 12 hours with normalization in later periods; however, there were no specific complications and he was discharged from ICU at day 11. The fourth patient showed a further decrease of pHi (lowest pHi = 7.08), brain death was diagnosed subsequently and he died of cardiopulmonary instability at day 3 in ICU. In four other patients, who initially showed a normal pHi at 6 hours, a decrease below pHi 7.32 occurred during one of the next measuring periods. Two of these patients also had an uncomplicated recovery with discharges from ICU at day 3 and 4, respectively. The two other patients, however, developed complications: one developed ARDS with a prolonged ICU stay (26 days) and the other patient -77 years of age- also developed ARDS with subsequent sepsis due to acalculous cholecystitis and died at day 12 in ICU.

Thus, eight of the 15 patients showed one or more abnormal pHi values during the first 48 hours after trauma, of whom three patients had a complicated course. In the remaining seven patients in whom no abnormal pHi values were measured all had an uncomplicated clinical reconvalescence.

Table 11.1

Demographic data and gastric intramucosal pH (pHi) values of 15 patients with multiple blunt trauma. # Indicates an abnormally low pHi value (≤ 7.32), (+) indicates that the patient died.

Patient	Age (years)	ISS (HTI)	Shock score (0-4)	Lactate at 6 hours (μmol/l)	pHi at 6 hours	Next lowest pHi	Compli-cation
1	25	41	1	1900	7.12 #	7.11 #	-
2	26	34	1	1738	7.23 #	7.34	-
3 (+)	43	57	4	10260	7.31 #	7.08 #	brain death
4	31	41	2	3129	7.32 #	7.37	-
5	46	25	0	3917	7.34	7.46	-
6	36	41	2	3660	7.35	7.43	-
7	41	34	2	2238	7.39	7.44	-
8	21	29	1	3623	7.41	7.18 #	-
9	19	34	1	1500	7.42	7.15 #	-
10	21	25	1	1700	7.44	7.46	-
11	33	34	2	3015	7.46	7.41	-
12	52	29	1	3121	7.49	7.34	-
13	16	33	1	2178	7.52	7.36	-
14	55	41	3	4954	7.54	7.10 #	ARDS
15 (+)	77	27	0	1200	7.66	7.06 #	ARDS-sepsis

Their ICU stay ranged from 2 to 6 days, except for one patient with severe brain damage, who stayed in the ICU for 27 days.

No significant correlations could be found between initial pHi values (at 6 hours) and ISS (r = -0.36), shockscore (r = -0.13), lactate concentration on admission (r = -0.25) or at 6 hours (r = -0.14) or APACHE II score on hospital and ICU admission (r = +0.17 and r = +0.39, respectively).

Figure 11.2

Course of pHi values (mean ± SD) in 15 multiple trauma patients at five consecutive sampling periods: 6, 12, 24, 36 and 48 hours after the injury. The dotted line indicates the pHi value (7.32) that was used to differentiate between normal and low gastric pHi.
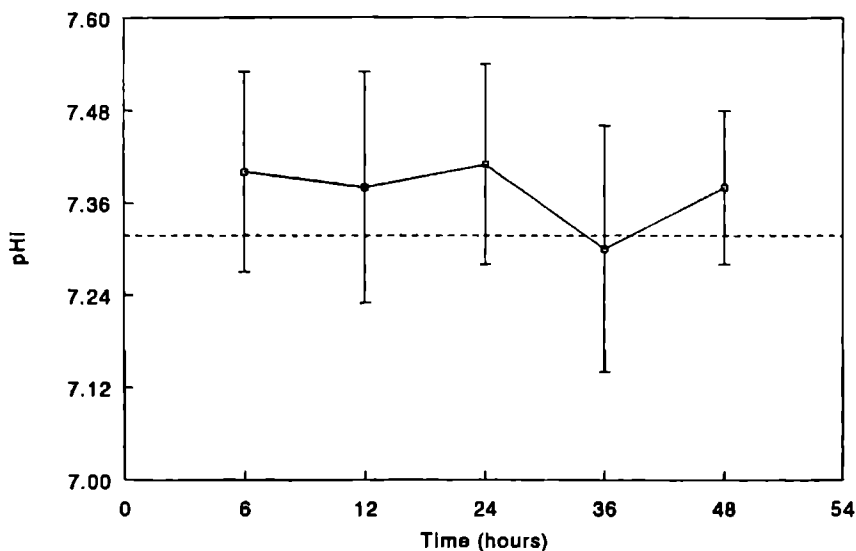
Discussion

Several -experimental and clinical- reports have demonstrated that monitoring the intramucosal pH (pHi) of the gastro-intestinal tract provides reliable information on the local anaerobic activity during situations of systemic hypoxia (7,8,18). Gastric tonometric data have been shown to correlate with sepsis and mortality in critically ill patients (16,17) and to be of predictive value of complications after cardic surgery (9). Sigmoid tonometry was of prognostic value in patients after abdominal aortic operations not only regarding the development of subsequent colitis, but also towards postoperative infections with intestinal organisms (19,20). Experimentally, it has been shown that pHi reflects reduced gastro-intestinal mucosal perfusion (21) and the degree of pHi decrease to correlate well with the histologic degree of ischemic mucosal injury (7,8). The method also has been demonstrated to be reliable in the setting of tissue acidosis induced by endotoxemia (18).

Recently, Gutierrez et al. (10) reported that therapy guided by gastric pHi measurements could significantly improve survival in critically ill patients. This was true in those patients in whom pHi on admission to the ICU was normal ($\geq$ 7.35), but subsequently had levels falling below this level and in whom pHi could be restored to normal by treatment aiming at an increase of systemic oxygen transport or reduction of oxygen demand (10). We could not find a single study that reported on the phenomenon of gastric tonometry in patients after multiple trauma.

It has been shown that mucosal injury leads to increased intestinal permeability (2,21). This phenomenon is thought to play a role in the development of multiple organ failure, since the gastro-intestinal tract is an occult reservoir of pathogens and large amounts of endotoxins (22). Recently, our group demonstrated a significant increase of intestinal permeability, measured by the lactulose/mannitol urine excretion ratio, in trauma patients 24 to 36 hours after severe blunt injury (4). Eigth of the present 15 patients studied, took part in that study on intestinal permeability and all these patients showed abnormally increased intestinal permeability (data not shown) (4). Only two of these eigth patients had initially low pHi values, whereas all belonged to the group of patients with uncomplicated recovery.

Since practically all severe trauma patients exhibit abnormally increased post-traumatic intestinal permeability, we expected to find consistently abnormal pHi levels in the direct post-traumatic course. Surprisingly, this was not the case. This discrepancy may be explained by the fact that tonometry monitors the metabolic process of the mucosal cells. This process may fluctuate in time -depending on the splanchnic blood

flow- and abnormal levels can be restored within a short period (21). Intestinal permeability measurement, on the other hand, reflects either mucosal barrier damage expressed by increased passive lactulose absorption and/or decreased mucosal cell function expressed by decreased active mannitol absorption (4,23). Once this mucosal surface is damaged it probably takes much more time to be restored than the underlying metabolic process that reflects pHi.

Like other reports we also could not find a sigificant relation between initial pHi values and lactate concentrations, severity of previous shock or APACHE II scores (10,16,17). Also the severity of injury did not correlate with subsequent pHi levels. Apparently these parameters do not significantly influence or reflect splanchnic blood flow.

Since monitoring and even therapy guided by pHi values clearly has been demonstrated to be of value in critically ill patients, tonometry may also be indicated and useful in monitoring patients after severe blunt trauma. This is illustrated by the fact that the three patients with a complicated course all had one or more abnormal post-traumatic pHi levels.

The present report, however, shows that tonometry and measurements of intestinal permeability are two different methods to study the role of the gut in relation to post-traumatic complications. Therefore conclusions of such measurements should be interpreted with caution.

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GENERAL DISCUSSION

The clinical studies presented in this thesis are a part of the clinical and experimental work on ARDS and MOF that is performed at the Department of Surgery of the University Hospital Nijmegen under the supervision of Prof. Dr. RJA Goris.

Based on clinical and experimental work this group was the first to formulate the hypothesis that ARDS and MOF are **one** syndrome resulting from an uncontrolled and general inflammatory response to a variety of stimuli (1,2). They emphasized the importance of the activation of the complement system and the specific role of PMNs (expressed by their elastase release) (3). These observations could be confirmed in our clinical study on severely traumatized patients. In addition, they demonstrated the importance of hypoxia in experimental work on rabbits (4). Since blood lactate is a generally accepted parameter of tissue hypoxia (5), the finding that in trauma patients elevated blood lactate concentrations during the early post-injury phase are an independent and significant determinant of subsequent ARDS and MOF confirms the role of tissue hypoxia.

Nuytinck et al. also were the first to point out that autopsy findings of trauma patients and patients succumbed of MOF, frequently show features of a generalized inflammatory process in the lungs, liver, kidneys, heart and spleen (6). This observation was made not only in those patients dying late of sepsis and MOF, but also in patients who died within hours post-injury, or without any sign of clinical sepsis.

Also an experimental animal model was developed, in which a MOF-like syndrome was induced by means of a non-bacterial, non-endotoxic, local inflammatory stimulus, i.e. intraperitoneal injection of Zymosan suspended in paraffin (7,8). The usefulness of this animal model has been confirmed by others (9). Morphological studies of lungs, liver, kidneys and spleen showed the same features of generalized inflammation as observed in the post-mortem studies of Nuytinck et al.(6).

Another important aspect of this experimental work is that it was demonstrated that MOF is not obligatorily dependent on the presence of bacteria or endotoxin. Selective decontamination of the gut, although very effective in preventing bacterial translocation, did not prevent the development of MOF in this model (10).

The problem with experimental studies is that the findings and conclusions can not simply be extrapolated to the human clinical situation. This is mainly because 1) in experimental circumstances one variable is changed throughout the experiment, whereas all other variables are kept as constant as possible with a fixed time scale and 2) the responses of various species - and even between individuals within one species - may show huge variations.

ad 1). It is clear that in clinical studies we deal with patients of varying ages, with

varying preexistent (pathological) conditions, with different degrees of trauma or insult, and who enter the study protocols at various time points. This may explain why the clinical significance of several inflammatory mediators varies from series to series. For example: cytokines, like TNFα, have a short half-life and therefore peak concentrations can be overlooked due to random sampling. Samples may be taken at the "wrong" time point, because the disease process has already been established. Moreover, circulating levels do not necessarily reflect local tissue levels or biological activity (11). ad 2). A few examples may illustrate this point: mutation of a single gene is responsible for the change of an endotoxin-sensitive mouse into an endotoxin-hyporesponsive mouse (12). Thromboxane B2 production during sepsis and septic shock varies significantly between rats, dogs, pigs and humans (13). From studies on cytokine responses to endotoxin stimulation it is known that human individuals can be divided into high-responders and low-responders (14). Human PMNs generate free radicals at a much higher level than bovine, ovine and porcine PMNs (15).

Nonetheless, animal experiments remain essential and are necessary to discover or explain underlying pathophysiological mechanisms. Despite the miscellaneous circumstances in clinical practice, clinical studies are required to prove pathophysiological theories and to demonstrate their clinical relevance. For instance, bacterial translocation is a phenomenon which has been demonstrated to occur in experimental circumstances (16), but its clinical relevance remains unclear. The studies of Peitzman et al. (17) and Moore et al. (18) on trauma patients showed that bacterial translocation to mesenteric lymph nodes was not a common occurrence, nor was systemic or portal bacteremia. Moreover, in those cases where bacterial translocation did occur, no correlation with subsequent complications (such as MOF) could be discovered.

The goal of the present thesis is the search for factors significantly associated with the development of MOF in the clinical setting. Bone et al.(19) recently emphasized the urgency to achieve uniform definitions, to standardize research protocols and to compare information from different clinical studies. The problem resulting from the absence of such uniformity can be illustrated by the use of the ARDS definitions in our own studies. In chapter 3 we used the alveolar-arterial oxygen quotient (20) to describe patients with and without ARDS, while in chapter 5, 6 and 9 the definition according to Pepe (21) was used. The use of these different definitions was prompted by the fact that the data in chapter 3 were collected from a multi-center study in

cooperation with two Austrian trauma hospitals, routinely utilizing the parameter mentioned first.

The role of scoring systems, grading the severity of trauma, diseases and organ dysfunction in relation to subsequent ARDS and MOF.

In our retrospective analysis of patients with acute hemorrhagic necrotizing pancreatitis (AHNP), who are most prone to develop ARDS and MOF, we demonstrated the usefulness of the MOF score developed by Goris et al. (1) and its accuracy in the early prediction of death or survival. In addition, we compared the MOF score with other scoring systems, such as APACHE II and SSS (see appendix), in order to illustrate that different aspects are graded, thus resulting in different information and conclusions. The APACHE II score, which is a generally accepted tool for classification of ICU patients and for prediction and comparison of ICU mortality rates (22), is less useful for follow up, especially when MOF occurs. It is possible that a patient with a high MOF score - indicating the necessity of organ support and intensive treatment - may exhibit a normal or low APACHE II score, because most parameters have been normalized due to effective organ support.

On the other hand, we could demonstrate that the APACHE II score provides more prognostic information in patients with AHNP than the pancreatitis-specific-scoring systems developed by Ranson et al. and Imrie et al.(see appendix).

Another aspect of scoring systems is that they may grade the severity of an insult according to objective criteria (such as grading the anatomical severity of lesions), or the physiological response of the organism to the insult. The first score is once for all fixed and will only be influenced by the accuracy of diagnosis. The latter scoring system will yield varying values in time, due to the clinical evolution of the patient and to the effects of treatment. This may explain the different predictive values of the Injury Severity Score and Trauma Score (see appendix) towards the development of ARDS and MOF found in our study on patients with multiple trauma.

The relation of various circulating biochemical products of the inflammatory cascade with subsequent ARDS and MOF.

The role of hypoxia, expressed by elevated lactate concentrations, was demonstrated in multiple trauma patients: significantly higher blood lactate levels were found in those patients who subsequently developed ARDS/MOF.

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Data on increased serum lipofuscin concentrations may also illustrate the important role of hypoxia (leading to ischemia) with subsequent reperfusion resulting in oxygen free radical production. Since PMNs are known to be an important source of oxygen free radical production, serum lipofuscin concentrations might also be an expression of the significant role of PMNs in the early post-injury phase. We found that lipofuscin levels were not only significantly elevated in patients with subsequent ARDS/MOF, but also to have a great accuracy in the prediction of these syndromes.

The important involvement of PMNs in the early post-injury phase, and more significantly so in patients who subsequently developed ARDS/MOF, could be demonstrated in the study on patients with multiple trauma. Elastase-α1 proteinase inhibitor complex levels can be used as a marker of the severity of injury and our data support the hypothesis that elastase may act as an important mediator in the inflammatory cascade leading to ARDS/MOF. In other reports it was even concluded that elastase can be a predictor of these complications (23). In the same multicenter study on trauma patients we could demonstrate the significant role of complement activation in the early post-injury phase, associated with an increased incidence of ARDS/MOF.

In our final study on inflammatory mediators, i.e. the cytokines TNFα, IL-1ß and IL-6, we found intriguing differences between the three patient groups investigated (patients with multiple trauma, ruptured AAA and undergoing elective AAA repair): we observed significantly higher cytokine levels during the early post-injury phase in non-survivors, as well as in patients who developed ARDS/MOF at a later stage.

These studies on inflammatory mediators support the view that the basic elements involved in the evolution of organ failure are the uncontrolled and persistent immuno-inflammatory response and tissue hypoxia following a traumatic event. In this concept the host is not an innocent bystander or victim who is invaded by bacteria and products of injured tissue, but is an active participant in this destructive process (1,11).

The role of the gut in relation to the development of ARDS/MOF with emphasis on its barrier function (intestinal permeability).

In the discussion about pathophysiological mechanisms resulting in ARDS/MOF endotoxin plays an important role. This might be because of the paradoxical position it has. In fact, it is a true exogenous toxin, but we carry along with us an abundancy of lethal doses of this toxin inside the lumen of our own intestines.

Experimental work has provided extensive evidence of the toxicity of endotoxin.

Intravenous endotoxin administration causes a myriad of biological effects (24) clinically resembling sepsis or a shock-like state and thus potentially resulting in MOF (25). At present, endotoxin is thought to be the main denominator of the effects seen in gram-negative sepsis (26). It has also been demonstrated that endotoxemia results in a significant and consistent cytokine release (TNF, IL-1ß) (27). Conversely, experimental administration of these cytokines produces a response that largely mimicks the response to endotoxin or clinical septic shock (28). Therefore, at present it remains unclear to what extent endotoxemia (due to endotoxin translocation from the gut) is responsible for some or all effects observed in our patients after a severe trauma or in hemorrhagic shock.

Our study on patients undergoing elective aortic aneurysm repair revealed a consistent systemic endotoxemia after clamping and declamping of the infrarenal abdominal aorta. This endotoxemia, however, was without specific adverse clinical effects. Moreover, in patients admitted in shock due to a ruptured abdominal aortic aneurysm or after a severe trauma, systemic endotoxemia could also been demonstrated. The concentrations found were not higher than in the elective patients, and did not correlate with subsequent MOF. In addition, when systemic circulating endotoxin was present, no correlation was found to the presence of TNFα. On the other hand, in 77% of the patients without measurable endotoxin we were able to demonstrate systemic circulating TNFα. These data may illustrate that endotoxin is not the only factor that is responsible for the cytokine release observed in our patient populations.

This debatable role of endotoxin in the process leading to organ failure brings up the role of the barrier function of the gastro-intestinal tract in the pathogenesis of MOF. Those who advocated the significant role of infections and sepsis in the development of MOF were confronted with the fact that in more than 30% of patients dying of MOF no septic focus could be identified (1,23). The demonstration of bacterial and endotoxin translocation from the gut may then explain this apparent paradox of negative septic foci. The study of O'Dwyer et al., (29) who demonstrated that intravenous endotoxin administration resulted in a significant increase of intestinal permeability and the reports on the promotion of bacterial translocation by endotoxin application (30), made the confusion about the role of intestinal permeability complete. From that time on, many reports appeared stating that increased intestinal permeability would probably mean increased bacterial and endotoxin translocation. A literature review on this subject and our own clinical studies revealed that such is not the case.

The gut apparently is an organ highly susceptible to disturbances of homeostasis resulting in functional and anatomical mucosal damage, that can easily be measured

by the absorption and excretion of two orally administered inert sugars (29). However, this measure of intestinal barrier function does not implicate that patients with increased permeability have a higher chance of developing gut derived infections, septic complications or MOF. In addition, our studies demonstrated that there is no correlation between the increase in permeability and parameters that grade the severity of injury and/or shock. In a study on gastric intramucosal pH measurements (pHi) in polytrauma patients, we could confirm that monitoring gastric pHi in ICU patients is valuable and can be predictive of subsequent complications, such as MOF (31, 32). This fits within the concept that hypoxia - and in this case true tissue hypoxia - may aggravate the initial insult as was shown by the study of Nuytinck et al. (3). But again we could not demonstrate a correlation between the degree of intestinal permeability and gastric pHi values. These observations on the role of the gut suggest that the gut is not the key organ or motor of MOF (33), but that the associated processes of bacterial translocation, endotoxemia, altered intestinal permeability and gut-derived-infections merely are epiphenomena frequently seen in patients at risk for ARDS and MOF.

Notwithstanding the fact that prevention of MOF should have the highest priority, and that foci of bacteria and endotoxin should be treated early and vigorously, it appears that the inflammatory response of the human body to severe injury, shock and infections importantly contributes to subsequent morbidity and mortality. Therefore, future studies should address the development of strategies that influence or interfere with the potentially harmful inflammatory response of the host itself.

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SUMMARY

Adult respiratory distress syndrome (ARDS) and multiple organ failure (MOF), both syndromes considered to be the result of one common pathophysiological pathway, represent the number one cause of death in a surgical ICU. Despite the increasing quality of intensive care treatment, the mortality rates of patients with established MOF have not appreciably improved during the last two decades. It therefore is a challenge to unravel factors that significantly contribute to the development of ARDS/MOF.

In this thesis the role of scoring systems, various inflammatory mediators and the gut is scrutinized in relation to the development of ARDS/MOF in patients known to have an increased risk for developing these syndromes.

In **chapter 1** the definition and clinical presentation of ARDS and MOF are outlined. It is demonstrated that in patients with different etiological entities a sequential and progressive failure of several organ systems may develop, resulting in a common end stage.

The role of oxygen metabolism and toxic oxygen free radicals, probably produced by stimulated PMNs and in various tissues after ischemia and reperfusion injury, is discussed.

Further attention is payed to the role of humoral and cellular systems, to bacteriological aspects and to the role of the gut (containing large amounts of bacteria and endotoxin that may translocate).

Several theories on the mechanisms that may lead to ARDS and MOF are summarized. Finally, the aim of the thesis and the questions that will be addressed in the following chapters are outlined.

Chapter 2 provides a retrospective analysis of patients admitted to the ICU because of severe acute hemorrhagic necrotizing pancreatitis requiring mechanical ventilation.

Several scoring systems are compared: Ranson and Imrie scores (grading the severity of pancreatitis), Sepsis Severity Score and APACHE II (grading the severity of any disease process), and the MOF score (grading the severity of organ dysfunction and intensity of organ support).

It is concluded that on admission to ICU the APACHE II score is better for grading the severity of disease than the so-called disease-specific scoring systems (Ranson and Imrie), which should be applied during the first 48 hours of hospital admission. The MOF score had the best accuracy and yielded the best prediction of death within the first four days of ICU admission.

Chapter 3 reports on the evaluation of seven scoring systems in 56 patients, who sustained severe blunt trauma, in relation to subsequent ARDS and MOF. It is shown that the scoring systems that directly grade the anatomical severity of trauma correlate best with subsequent ARDS and MOF. This was not the case for scoring systems that grade the physiological response of the organism to the injury.

In addition, it was demonstrated that lactate concentrations -indicating the hypoxic injury- were significantly elevated during the first three days post-injury in patients who subsequently developed ARDS/MOF, in comparison with patients who did not develop ARDS/MOF.

Chapter 4 describes the patterns of various inflammatory mediators (complement, thromboxane B2, C-reactive protein, elastase and neopterin) in the same 56 patients as reported in chapter 3.

We could demonstrate that non-survivors had significantly higher levels of complement activation at day 1 post-injury, if compared to survivors. The same was true for elastase, indicating enhanced activation of PMNs. Moreover, we found significantly higher concentrations of C3a, terminal complement complexes, thromboxane B2, and elastase at day 1 in patients with subsequent MOF, compared to those who did not develop MOF. Neopterin concentrations, indicating macrophage activation, were significantly higher during the second week in patients with established MOF.

In **chapter 5** the cytokines TNFα, IL-1ß and IL-6 are studied. Three patients groups were enrolled in the study: 28 patients after severe blunt trauma, 20 patients with a ruptured AAA and 18 patients undergoing major elective aortic aneurysm repair. Of the total of 66 patients 22 died (15 $\leq$ 2 days and 7 later). The remaining 51 patients were divided in patients who developed ARDS/MOF (n=10) and patients who did not develop ARDS/MOF (n=41).

Intriguing differences between patient groups were found for the various cytokines. IL-6 appeared to be elevated significantly in trauma patients, compared to the patients who presented with a ruptured AAA. These latter patients showed higher levels of TNFα and IL-1ß on hospital admission. Non-survivors showed significantly higher levels of IL-1ß and TNFα on hospital admission, whereas the differences in IL-6 did not reach statistical significance.

Most interesting was the finding of significantly different cytokine patterns in the early post-injury phase in patients who later developed ARDS/MOF. TNFα and IL-1ß were significantly higher on admission and after 6 hours in ARDS/MOF patients, while IL-6

levels were significantly elevated in these patients from the second day onwards.

Chapter 6 describes the data on serum lipofuscin measurements in the same patient population as outlined in chapter 5. Lipofuscin has been proposed to be a parameter of lipid peroxydation caused by toxic oxygen radical production.

Additionally, blood was drawn from 75 "healthy" persons, ranging in age from 4 to 90 years, for determination of normal serum lipofuscin concentrations. It appeared that serum lipofuscin levels increase significantly with age.

Especially 6 hours after the trauma, rupture of an AAA or the elective operation of an AAA, serum lipofuscin levels (corrected for age) were significantly elevated in all three patient groups, as compared with the controls.

In the group of patients with subsequent ARDS/MOF significantly higher levels of serum lipofuscin could be found during the first 24 hours post-injury, compared to patients without ARDS/MOF.

This might indicate that oxidative stress (leading to increased lipid peroxidation) plays an important role in the development of ARDS and MOF in these patient populations.

In **Chapter 7** we report on systemic endotoxemia in patients undergoing major vascular surgery (elective and emergency aortic aneurysm repair). Endotoxemia was regularly present in patients in shock due to a ruptured AAA on hospital admission, even before resuscitation or operation was performed.

Secondly, in patients undergoing elective surgery of the infrarenal aorta, systemic endotoxemia was demonstrated especially immediately after ischemia and reperfusion (clamping and declamping of the aorta). However, the concentrations of systemic circulating endotoxin were low and were within the same range in both elective and emergency patients. We could not find adverse effects of endotoxemia in the studied patient population.

Chapter 8 contains an overview of the literature on intestinal permeability, the methods used to measure it, the clinical data and relevance, and its relation with endotoxin and bacterial translocation.

It is concluded that altered (increased) intestinal permeability is a phenomenon that occurs under various circumstances and in many pathological conditions, while it cannot conclusively be related to endotoxemia and/or bacterial translocation.

In **Chapter 9** we report on intestinal permeability in patients with severe blunt trauma

and with a ruptured AAA. It is shown that intestinal permeability is significantly increased 24 to 36 hours post-injury in these patient groups. We could not demonstrate any difference in intestinal permeability in patients with subsequent infections, compared to those who did not develop such infectious complications. Additionally, we studied endotoxemia in relation to increased intestinal permeability. Systemic circulating endotoxin was only found before the increased intestinal permeability was demonstrated. At the very moment of increased intestinal permeability, and one day later, no endotoxin could be demonstrated in the systemic circulation anymore.

In **chapter 10** we report on intestinal permeability in patients after major elective and emergency AAA repair. No difference was found in intestinal permeability between patients operated electively and patients undergoing emergency operation because of shock, due to a ruptured AAA.
This finding suggests that the factor shock did not contribute importantly to increased intestinal permeability, whereas the reperfusion injury probably was the significant factor in this respect.

Chapter 11 provides data on gastric intramucosal pH (pHi) measurements in 15 polytraumatized patients. Although we expected that splanchnic ichemia was a common finding in multiple trauma patients, no consistent pattern of abnormally low pHi values was present.
However, in those patients in whom abnormally low pHi values were found, either 6 hours after hospital admission and resuscitation or later, significantly more complications developed. Patients that never showed any abnormal pHi values, all had an uncomplicated recovery. It is concluded that monitoring gastric pHi in severely injured patients admitted to an ICU may be usefull.

Finally, in **chapter 12** the results of the presented studies are discussed. Especially the data on circulating inflammatory mediators, such as activated complement, elastase, lactate, lipofuscin and cytokines, which products were all significantly elevated in the early post-injury phase in patients that later developed complications, such as ARDS and MOF, provide evidence that these syndromes are the consequence of a overwhelming generalized autodestructive inflammatory response of the host itself.

SAMENVATTING

Adult Respiratory Distress Syndrome (ARDS) en Multiple Organ Failure (MOF) zijn twee syndromen, waarvan men tegenwoordig aanneemt dat er één gemeenschappelijk pathofysiologisch mechanisme aan ten grondslag ligt. Zij vertegenwoordigen de belangrijkste vorm van morbiditeit en mortaliteit op een chirurgische Intensive Care afdeling. Ondanks een indrukwekkende toename in kwaliteit van intensieve zorg zijn de mortaliteitscijfers van patienten met een volledig ontwikkeld beeld van MOF gedurende de laatste decennia niet in gunstige zin veranderd.

Het is daarom zeker een uitdaging om de onderliggende pathofysiologische mechanismen van het ontstaan van ARDS en MOF te ontrafelen en factoren te identificeren die een wezenlijke bijdrage aan dit proces leveren.

In deze dissertatie wordt onderzoek beschreven met betrekking tot een drietal onderscheiden deelgebieden, te weten: 1. de waarde van scorings-systemen ten aanzien van het ontstaan van ARDS/MOF; 2. de rol van diverse circulerende verbindingen, welke onderdeel uitmaken van ontstekingsreacties (de zogenaamde inflammatoire mediatoren), in relatie tot het ontstaan van bedoelde syndromen; en 3. de rol die de tractus digestivus in dit geheel speelt.

Hoofdstuk 1 behandelt, uitgaande van de thans beschikbare literatuur, enkele algemene aspecten van ARDS en MOF. De klinische presentatie van ARDS en MOF wordt gedemonstreerd aan de hand van een drietal patienten casus en we gaan in op de veelheid aan definities van deze syndromen.

Voorts wordt de rol van het zuurstofmetabolisme en toxische zuurstofradicalen besproken. Deze radicalen worden geproduceerd door gestimuleerde polymorfonucleaire leukocyten en gevormd in diverse weefsels, na doorgemaakte ischemie en reperfusie.

De huidige stand van zaken omtrent de rol van humorale en cellulaire systemen, welke geassocieerd zijn met het ontstaan van ARDS/MOF, wordt behandeld. Bovendien wordt ingegaan op de discussie omtrent het belang van bacteriën, endotoxinen en derhalve ook de tractus digestivus bij het ontstaan van ARDS/MOF.

Tot slot wordt een overzicht gegeven van de theoriën omtrent mechanismen die ten grondslag zouden liggen aan beide syndromen, waarna het doel van de studie en de basale vragen worden toegelicht.

Hoofdstuk 2 is een verslag van een retrospectieve studie verricht bij 39 patienten die op de Intensive Care afdeling werden opgenomen in verband met een ernstige acute

hemorrhagisch necrotiserende pancreatitis (AHNP) met beademingsnoodzaak. Het doel van deze studie was uit te zoeken welke van een vijftal gebruikelijke scorings-systemen de meest relevante informatie opleverde ten aanzien van de prognose (morbiditeit en mortaliteit) van deze patienten. Het betrof de score volgens Ranson en Imrie (beide ontwikkeld om specifiek de ernst en prognose van acute pancreatitis in te schatten), de Sepsis Severity Score (volgens Elebute en Stoner) en de APACHE II score, welke beide ontwikkeld zijn om in zijn algemeenheid de ernst van ziekte bij ICU patienten aan te geven. Tot slot de in Nijmegen ontwikkelde MOF score, die de ernst van orgaanfalen en de intensiteit van orgaan ondersteunend handelen scoort.

De conclusies van dit onderzoek zijn dat de APACHE II score een betere informatie geeft omtrent de prognose quo ad vitam van patienten met een AHNP dan de score volgens Ranson en Imrie, en dat de MOF score (het gemiddelde van de eerste 4 dagen op de ICU) de best predictieve waarde heeft ten aanzien van overlijden.

In **hoofdstuk 3** doen wij verslag van een evaluatie van 7 scorings-systemen toegepast bij 56 multi-trauma patienten, wederom in relatie tot ARDS/MOF. Er kon worden aangetoond dat scoringssystemen die de anatomische ernst van letsel graderen het best correleerden met later ontstaan van ARDS en MOF. Dit was niet het geval voor scorings-systemen die de fysiologische reactie van het organisme op trauma grade-ren. Bovendien onderzochten wij lactaatconcentraties, welke een goede maat zijn voor de doorgemaakte hypoxie bij deze patienten. Het bleek dat patienten die in de tweede week ARDS en/of MOF ontwikkelden, reeds gedurende de eerste drie dagen na het ongeval significant hogere lactaatspiegels hadden in vergelijking met patienten, die niet aan de criteria van ARDS/MOF voldeden.

In **hoofdstuk 4** doen wij verslag van onze studie van diverse inflammatoire mediatoren (in serum) bij dezelfde groep patienten als uit hoofdstuk 3. Het betrof het comple-mentsysteem, thromboxaan-B2, C-reactieve proteine, elastase en neopterine.

Patienten die overleden hadden op de eerste dag na het trauma significant hogere waarden voor complementactivatie en elastaseconcentraties, in vergelijking met de overlevenden.

Bij vergelijking van de patienten die MOF hadden ontwikkeld met diegenen zonder deze complicatie, bleek de eerste groep op dag 1 significant hogere serum concen-traties te hebben van geactiveerd complement (C3a), terminaal complement complex (C5 t/m C9), thromboxaan-B2 en elastase. Bovendien hadden deze patienten in week 2, dus op het moment van een reeds ontwikkeld MOF beeld, hogere neopterinewaar-

den, hetgeen een indicatie geeft over macrophagen activatie.

Hoofdstuk 5 handelt over cytokinen: TNFα, IL-1ß en IL-6. Wij bestudeerden drie patienten groepen: a. 28 multi-trauma patienten, b. 20 patienten met een gebarsten aneurysma van de abdominale aorta (AAA) en c. 18 patienten die een electief herstel van een AAA ondergingen. Van deze 66 patienten overleden er uiteindelijk 22, namelijk 15 vóór de tweede dag en 7 ten gevolge van MOF na ruim één maand ICU opname. Er waren derhalve 51 patienten over voor indeling in een groep met ARDS/MOF (n=10) en een groep die wat ARDS/MOF betreft een ongecompliceerd beloop had (n=41).

De volgende opvallende verschillen in cytokine-patronen werden gevonden. IL-6 concentraties bleken bij trauma patienten direkt na opname in het ziekenhuis en 6 uur later een significant hoger niveau te hebben, dan de patienten die in shock werden opgenomen ten gevolge van hun gebarsten AAA. Deze laatste patienten hadden juist hogere TNFα en IL-1ß waarden op deze tijdstippen.

Vergelijking tussen overleden patienten en overlevenden toonde bij opname significant hogere TNFα en IL-1ß spiegels in de groep overledenen. De verschillen in IL-6 concentraties waren niet significant.

De belangrijkste bevinding was evenwel dat de patientengroep die later ARDS/MOF ontwikkelde, reeds op de eerste dagen na het trauma wezenlijk andere cytokine-patronen had. Patienten uit deze groep hadden significant hogere TNFα en IL-1ß spiegels bij ziekenhuisopname en 6 uur later, terwijl er vanaf de tweede dag voortdurend hogere spiegels IL-6 spiegels werden gevonden.

In **hoofdstuk 6** bespreken wij serum lipofuscine metingen verricht bij dezelfde patientengroepen als vermeld in hoofdstuk 5. Bovendien was er een controle groep gevormd, bestaande uit 75 "gezonde" personen in leeftijd varierend van 4 tot 90 jaar.

Uit andere in vitro en in vivo studies blijkt dat serum lipofuscine een maat is voor lipiden peroxidatie ten gevolge van toxische zuurstofradicalen, en dus voor de oxidatieve stress die heeft plaatsgevonden.

Op grond van analyse van de controle groep bleek dat serum lipofuscine spiegels toenemen met de leeftijd. Derhalve werden voor verdere vergelijkingen de gevonden-waarden voor leeftijd gecorrigeerd.

Reeds 6 uur na trauma, ruptuur van het aneurysma of de electieve operatie voor een AAA bleken de serum lipofuscineconcentraties in alle drie patienten groepen significant verhoogd te zijn in vergelijking met de controle groep.

De groep van 10 patienten die ARDS/MOF ontwikkelde had de eerste 24 uur na trauma, ruptuur of operatie significant hogere serum lipofuscinespiegels dan de patienten zonder later ARDS/MOF.

Er wordt geconcludeerd dat oxidatieve stress in de vroege "post-traumatische" fase een rol kan spelen bij het ontstaan van ARDS en MOF.

In **hoofdstuk 7** doen wij verslag van serum endotoxine metingen bij patienten die vasculaire reconstructies van de abdominale aorta ondergingen. Er wordt aangetoond dat bij patienten met een gebarsten AAA reeds systemisch circulerend endotoxine aanwezig is bij ziekenhuisopname, nog vóór dat resuscitatie of spoed operatie heeft plaatsgevonden.

Voorts werden monsters genomen op zorgvuldig vastgestelde tijdstippen tijdens electieve operatie voor een AAA. Wij observeerden een systematische endotoxemie bij deze patienten ten tijde van de ischemie (met infrarenale afklemming van de aorta) en met name ook in de reperfusie fase (na het verwijderen van de aortaklem). De gevonden endotoxineconcentraties waren laag en in hetzelfde bereik als bij de patienten met een gebarsten AAA.

We konden geen klinisch negatieve effecten van endotoxemie waarnemen.

Hoofdstuk 8 is een overzicht van de recente literatuur betreffende intestinale permeabiliteit. De meet methoden en de klinische relevantie van abnormale intestinale permeabiliteit worden besproken. Verder wordt er ingegaan op de relatie tussen intestinale permeabiliteit, endotoxinen en bacteriële translocatie.

Wij concluderen dat abnormaal toegenomen intestinale permeabiliteit een fenomeen is dat onder zeer uiteenlopende omstandigheden en bij diverse aandoeningen kan worden waargenomen, zonder dat er aanwijzingen zijn dat er een causale relatie bestaat met translocatie van bacteriën en/of endotoxinen -en dientengevolge infectieuze complicaties-, noch met het ontstaan van MOF.

Hoofdstuk 9 bevat gegevens over intestinale permeabiliteitsmetingen bij multitrauma patienten en patienten met een gebarsten AAA. Wij vonden een significant verhoogde intestinale permeabiliteit, gemeten met behulp van de Lactulose/Mannitol test, bij beide patienten groepen tussen de 24 en 36 uur na trauma of ruptuur. Alle patienten werden vervolgens verdeeld in twee groepen afhankelijk van het al of niet ontwikkelen van infectieuze complicaties. Tussen deze twee groepen werd absoluut geen verschil in intestinale permeabiliteit gevonden. Bovendien werden endotoxinemetingen verricht.

Endotoxemie kon alleen waargenomen worden op tijdstippen vóór de permeabiliteits-metingen, echter niet meer ten tijde van deze metingen of 24 uur later.

In **hoofdstuk 10** doen we verslag van onze intestinale permeabiliteitsmetingen bij twee groepen patienten die een vasculaire ingreep aan de abdominale aorta ondergingen: te weten een electieve reconstructie van een AAA of een spoedoperatie wegens een gebarsten AAA. In beide groepen werd een abnormaal verhoogde intestinale permea-biliteit geconstateerd, zonder wezenlijk verschil tussen de groepen onderling.

Deze bevinding suggereert dat niet shock, maar veeleer reperfusieschade een belangrijke rol speelt bij het ontstaan van abnormale intestinale permeabiliteit.

In **hoofdstuk 11** bestuderen we de intramucosale pH (pHi) van de maag(wand) bij 15 multitrauma patienten. De pHi is een maat voor de oxygenatietoestand van het desbe-treffende orgaan, waarin gemeten wordt. Wij verwachtten bij multitrauma patienten een verminderde doorbloeding van het splanchnicusbed, met dientengevolge aanwijzingen voor (doorgemaakte) ischemie.

In onze patienten groep kon evenwel geen evident patroon van een dergelijk ischemie aangetoond worden. Wel bleken de patienten bij wie eenmaal of vaker een abnormaal lage pHi werd gemeten, diegenen te zijn met een later optredend gecompliceerd beloop (ARDS, sepsis, overlijden). Patienten bij wie nooit een abnormale pHi waarde werd gemeten, hadden allen een ongecompliceerd herstel.

Intramucosale pHi metingen van de maag kunnen derhalve een zinvol additionele vorm van monitoring betekenen bij ICU patienten.

Tot slot wordt in **hoofdstuk 12** een algemene beschouwing gegeven over de verrichte studies en de daaruit getrokken conclusies.

Met name menen wij te mogen constateren dat de gegevens over de diverse circulerende inflammatoire mediatoren, zoals geactiveerd complement, elastase, lipofuscine, lactaat en cytokinen - welke allemaal in de vroege "post-traumatische" periode significant verhoogd bleken te zijn - een extra ondersteuning zijn voor de hypothese dat ARDS en MOF het gevolg zijn van een gegeneraliseerde, uit de hand gelopen, autodestructieve ontstekingsreactie van het eigen organisme.

APPENDIX

A. SCORING SYSTEMS

RANSON score (1)

On admission:

> Age > 55 years
>
> White cell count > 16000/mm^3
>
> LDH > 600 units/l
>
> ASAT > 120 units/l
>
> Glucose > 10 mmol/l

Within 48 hours:

> hematocrit fall > 10%
>
> Urea rise > 0.9 mmol/l
>
> Calcium < 2 mmol/l
>
> PO$_2$ < 8 kPa
>
> base deficit > 4 mEq/l
>
> Fluid sequestration > 6000 ml

Sum of the score ranges from 0 to 11.

0-2 points indicates mild pancreatitis, ≥ 3 points severe pancreatitis.

IMRIE score (2)

On admission:

      Age > 55 years

Within 48 hours:

      White cell count > 15 x 10^9/l

      Blood glucose > 10 mmol/l (no diabetic history)

      Serum urea > 16 mmol/l (no response to i.v. fluids)

      PO_2 < 8 kPa

      Serum calcium < 2 mmol/l

      Serum albumin < 32 g/l

      LDH > 600 μ/l

      ASAT/ALAT > 100 μ/l

Sum of the score ranges from 0 to 9.

0-2 points indicates mild pancreatitis, ≥ 3 points severe pancreatitis.

APACHE II score (3)

PHYSIOLOGIC VARIABLE	HIGH ABNORMAL RANGE				0	LOW ABNORMAL RANGE			
	+4	+3	+2	+1	0	+1	+2	+3	+4
TEMPERATURE - rectal	≥41	39-40.9		38.5-38.9	36-38.4	34-35.9	32-33.9	30-31.9	≤29.9
MEAN ARTERIAL PRESSURE - mmHg	≥160	130-159	110-129		70-109		50-69		≤49
HEART RATE (ventricular response)	≥180	140-179	110-139		70-109		55-69	40-54	≤39
RESPIRATORY RATE (non-ventilated or ventilated)	≥50	35-49		25-34	12-24	10-11	6-9		≤5
OXYGENATION A-aDO2 or PaO2 (mmHg) a. FiO2 ≥0.5 record A-aDO2	≥500	350-499	200-349		<200				
b. FiO2 <0.5 record only PaO2					PO2 >70	PO2 61-70		PO2 55-60	PO2 <55
ARTERIAL pH	≥7.7	7.6-7.69		7.5-7.59	7.33-7.49		7.25-7.32	7.16-7.24	<7.15
SERUM SODIUM (mMol/L)	≥180	160-179	155-159	150-154	130-149		120-129	111-119	≤110
SERUM POTASSIUM (mMol/L)	≥7	6-6.9		5.5-5.9	3.5-5.4	3-3.4	2.5-2.9		<2.5
SERUM CREATININE (mg/100ml)(Double point score for acute renal failure)	≥3.5	2-3.4	1.5-1.9		0.6-1.4		<0.6		
HEMATOCRIT (%)	≥60		50-59.9	46-49.9	30-45.9		20-29.9		<20
WHITE BLOOD COUNT (total/mm³) in 1,000s	≥40		20-39.9	15-19.9	3-14.9		1-2.9		<1
GLASGOW COMA SCORE (GCS) Score = 15 minus actual GCS									
A Total ACUTE PHYSIOLOGY SCORE (APS) Sum of the 12 Individual variable points									
Serum HCO3 (venous mMol/L) (Not preferred, use if no ABGs)	≥52	41-51.9		32-40.9	22-31.9		18-21.9	15-17.9	<15

B AGE POINTS
Assign points to age as follows

AGE (yrs)	Points
≤44	0
45-54	2
55-64	3
65-74	5
≥75	6

C CHRONIC HEALTH POINTS
If the patient has a history of severe organ system insufficiency or is immuno-compromised assign points as follows

a. for nonoperative or emergency postoperative patients - 5 points or
b. for elective postoperative patients - 2 points

DEFINITIONS
Organ insufficiency or immuno-compromised state must have been evident prior to this hospital admission and conform to the following criteria
LIVER: Biopsy proven cirrhosis and documented portal hypertension; episodes of past upper GI bleeding attributed to portal hypertension; or prior episodes of hepatic failure/encephalopathy/coma

CARDIOVASCULAR: New York Heart Association Class IV
RESPIRATORY: Chronic restrictive obstructive or vascular disease resulting in severe exercise restriction, i.e., unable to climb stairs or perform household duties; or documented chronic hypoxia, hypercapnia, secondary polycythemia, severe pulmonary hypertension (>40 mmHg) or respirator dependency
RENAL: Receiving chronic dialysis
IMMUNO-COMPROMISED: The patient has received therapy that suppresses resistance to infection, e.g. immuno-suppression, chemotherapy, radiation, long term or recent high dose steroids, or has a disease that is sufficiently advanced to suppress resistance to infection, e.g. leukemia, lymphoma, AIDS

APACHE II SCORE
Sum of A + B + C
A APS points _____
B Age points _____
C Chronic Health points _____
Total APACHE II _____

MULTIPLE ORGAN FAILURE score (4)

Organ system

	Grade 1	Grade 2
Pulmonary	mech. ventilation with PEEP ≤ 10 cm H2O FiO2 ≤ 0.4	mech. ventilation with PEEP > 10 cm H2O FiO2 > 0.4
Cardiac	hypotension > 100 mmHg dopamine ≤ 10 μg/kg/min nitroglycerine ≤ 20 μg/kg/min	hypotension ≤ 100 mmHg dopamine > 10 μg/kg/min nitroglycerine > 20 μg/kg/min
Renal	serum creatinine ≥ 2 mg/dl	dialysis
Hepatic	serum bilirubin ≥ 2 mg/dl or SGOT ≥ 25 U/l	serum bilirubin ≥ 6 mg/dl or SGOT ≥ 50 U/l
Hematologic	platelets < 50x10^9/l and/or leuco's ≥ 30x10^9/l	disseminated intravascular coagulation leuco's < 2.5x10^9/l or ≥ 60x10^9/l
Gastro-Intestinal	acalculous cholecystitis stress ulcer	perforation gallbladder bleeding from ulcer > 2 units blood/24 hr necrotizing enterocolitis pancreatitis
Central nervous	diminished responsiveness	severely disturbed responsiveness and/or diffuse neuropathy

No failure = grade 0; moderate failure = grade 1; severe failure = grade 2.
MOF score is total of 7 organ failure scores, with a maximum of 14 points.

SEPSIS SEVERITY SCORE

according to Elebute and Stoner (5)

Table I: *SCORING OF LOCAL EFFECTS OF TISSUE INFECTION*

Attribute	Score
Wound infection with purulent discharge/ enterocutaneous fistula	
Requiring only light dressing changed not more than once daily	2
Requiring to be dressed with a pack, dressing needing to be changed more than once daily, requiring application of a bag and/or requiring suction	4
Peritonitis	
Localized peritonitis	2
Generalized peritonitis	6
Chest infection	
Clinical or radiological signs of chest infection without productive cough	2
Clinical or radiological signs of chest infection with a cough producing purulent sputum	4
Full clinical manifestations of lobar/ bronchpneumonia	6
Deep-seated infection (e g subphrenic abscess, pelvic abscess, empyema thoracis, acute or chronic osteomylitis)	6

Table II: *SCORING OF PYREXIA (ORAL TEMPERATURE)*

Attribute	Score
Maximum daily temperature (° C)	
36–37 4	0
37 5–38 4	1
38 5–39	2
>39	3
<36	3
	Add
Minimum daily temperature >37 5 °C	1
If 2 or more temperature peaks above 38 4 °C in 1 day	1
If any rigours occur in a day	1

Temperature should be recorded at least 4 times in 24 h The record for the 24 h period is assessed as above and pyrexia score computed

Table III: *SCORING OF SECONDARY EFFECTS OF SEPSIS*

Attribute	Score
Obvious jaundice (in the absence of established hepatobiliary disease)	2
Metabolic acidosis	
Compensated	1
Uncompensated	2
Renal failure	3
Gross disturbance of mental orientation/level of consciousness (e g delirium, coma) and/or other focal neurological manifestations of pyaemia/ septicaemia (having excluded other causes)	3
Bleeding diathesis (from disseminated intravascular coagulation)	3

Table IV: *SCORING OF LABORATORY DATA*

Attribute	Score
Blood culture	
Single positive culture	1
Two or more positive cultures separated by 24 h	3
Single positive culture + history of invasive procedure	3
Single positive culture + cardiac murmur and/or tender enlarged spleen	3
Leucocyte count (× 10^9/l)	
12–30	1
>30	2
<2 5	3
Haemoglobin level in the absence of obvious bleeding (g/dl)	
7–10	1
<7	2
Platelet count (× 10^9/l)	
100–150	1
<100	2
Plasma albumin level (g/l)	
31–35	1
25–30	2
<25	3
Plasma total bilirubin level in the absence of clinically obvious jaundice	
>25 µmol/l	1

INJURY SEVERITY SCORE (6)

according to Hospital Trauma Index (7)

HOSPITAL TRAUMA INDEX (HTI) - INJURY SEVERITY SCORE (ISS)

SYSTEM	INJURY	CLASS	INDEX	square of highest Index
RESPIRATORY	no injury	no injury	0	
	chest discomfort, minimal findings	minor	1	
	simple rib or sternal fracture (fx), chest wall contusion with pleuritic pain	moderate	2	
	first or multiple fx, hemothorax, pneumothorax	major	3	
	open chest wounds, flail chest, tension pneumothorax c normal (+)t, subpressure (bp), simple fx c diaphragm	severe	4	
	acute resp failure (primosis), aspiration, tension pneumo c bp, bilateral flail c(s) diaphragm	critical	5	
CARDIOVASCULAR	NO INJURY	no injury	0	
	10% (bld vol) blood volume (bv) loss, no change in vein perfusion	minor	1	
	10 to 20% bv loss (500cc, 1000cc) c vein perfusion, urine normal c 30cc/M, myocard. cont. bp nl	moderate	2	
	20%-30% bv loss (1000cc - 1500cc) c vein perfusion, urine (<30cc) temperature, bp (>30cc)	major	3	
	30%-40% bv loss ((1500cc, 2000cc) c vein perfusion, anuria (<10cc) tamponade, connection, bp < 80	severe	4	
	40%, 50% bv loss, restless, agitated, coma, cardiac contusion or arrythmia, bp not obtainable	critical	5	
	50% bv loss Coma. Cardiac arst. No vital signs	fatal	6	
NERVOUS SYSTEM	NO INJURY	no injury	0	
	head trauma c or c scalp lacin, no loss consciousness (coma) no fracture (fx)	minor	1	
	head injury c brief coma (<15') skull fx, cervical pain c minimal findings	moderate	2	
	cerebral injury c coma (+15'), depressed skull fx, cervical fx c neuro findings, multi facial fx	major	3	
	cerebral injury c coma (+60') or neuro findings, cervical fx c major findings, (+) paraplegia	severe	4	
	cerebral injury c coma c no response to stimuli up to 24 hours. Cervical fx c quadriplegia	critical	5	
	cerebral injury c no response to stimuli & c dilated fixed pupil (s)	fatal	6	

SYSTEM	INJURY	CLASS	INDEX	square of highest Index
ABDOMINAL	NO INJURY	no injury	0	
	mild abdominal wall, flank or back pain & tenderness c peritoneal signs	minor	1	
	acute flank, back or abdominal discomfort and tenderness, h of a rib 7 12	moderate	2	
	one of minor lesion, pn, bowel, spleen, kidney, body pancreas mesentery, ureter, urethra, fax 7 12 rib	major	3	
	2 major rupture liver, bladder head pancreas, duodenum, colon, mesentery (large)	severe	4	
	2 severe crush liver. Major vessels including thor & abdom aorta, clamp back, hepatic veins	critical	5	
EXTREMITIES	NO INJURY	no injury	0	
	minor sprains & fx(s) no long bones	minor	1	
	simple fx(s) humerus, clavicle, radius, ulna, tibia, ulula, single nerve	moderate	2	
	h(s) multiple moderate, c p/o moderate femur (simple) pelfc (stable) dislocation major major nerve	major	3	
	fx(s) two major c pd femur c into crush or amputation, unstable pelfc fx	severe	4	
	fx(s) two severe, multiple major	critical	5	
SKIN & SUBCUTANEOUS	NO INJURY	no injury	0	
	< 5% burn abrasions contusions lacerations	minor	1	
	5%, 15% burn extensive contusions avulsions 3"-6" extensive lacerations (total 12'2)	moderate	2	
	15%, 30% burn avulsions 12'2 +	major	3	
	30%-45% burn avulsions entire leg, thigh or arm	severe	4	
	45% 60% burn (3rd degree)	critical	5	
	60% + burn (3rd degree)	fatal	6	

ISS =

DEFINITIONS:

minor = trivial injury
moderate = minimal injury, short hospitalization anticipated
major = major injury, not immediately life-threatening
severe = life-threatening but survival probable
critical = survival uncertain
fatal = survival unlikely

ABBREVIATIONS

*bp - blood pressure
bv - blood volume
cpd - compound
c - with
d - days

fndgs - findings
fx - fracture
i p - intraperitoneal
lac-lacina - lacerations
multi - multiple

nl - normal
rds - resp distress synd
s - without
u - units

vent - ventilator
wnd - wound
I - decreased
> - greater than
< - less than

* Obtained before emergency operations

Calculations: When multiple lesions are present in one organ system of HTI, the final index is determined by assimilating 2 major lesions (HTI3) to 1 severe (HTI4) and 2 severe lesions to 1 critical (HTI5). The ISS is then calculated by summing the squares of 3 highest HTI indices.

GLASGOW COMA SCALE *(8)*

Eyes open

spontaneously	4
on spoken command	3
on pain	2
no response	1

Best motor response

to spoken command	6
to pain stimulus:	
* localised pain	5
* flexion withdrawal	4
* flexion abnormal	3
* extension	2
* no response	1

Best verbal response

oriënted + converses	5
disoriënted + converses	4
inappropriate words	3
incomprehensible sounds	2
no response	1

Sum of the score ranges from 3 to 15.

TRAUMA score (9)

Respiratory rate

	10 - 24 / min	4
	24 - 35 / min	3
	≥ 36 / min	2
	< 10 / min	1
	0	0

Respiratory effort

	normal	1
	shallow or retractive	0

Systolic blood pressure

	≥ 100 mm Hg	4
	80 - 99 mm Hg	3
	60 - 79 mm Hg	2
	< 60	1
	no pressure	0

Capillary refill

	normal	2
	delayed	1
	none	0

Glasgow Coma Scale

	14 - 15	5
	11 - 13	4
	8 - 10	3
	5 - 7	2
	3 - 4	1

Sum of the score ranges from 1 to 16

POLY-TRAUMA SCHLüSSEL *(10)*

Schädel

SHT 1 oder GCS 9-12	2
SHT 2 oder GCS 6-8	4
SHT 3 oder GCS 3-5	12
Mittelgesichtsfraktur	1
Schwere Mittelgesichts- fraktur	2

Abdomen

Milzruptur	5
Leberruptur	8
Ausgedehnte Leberruptur	10
Pankreasverletzung	8
Magen- Darm- Nieren- Mesenterialverletzung	5

Extremitäten

Oberschenkeltrümmerfraktur	8
Oberschenkelfraktur	6
Oberarm, Schulter	
Unterschenkelfraktur	1
Patella- OSG-Fraktur	
Kniebandruptur, Unterarm- und Ellenbogenfraktur	1
Gefässverletzung	
Oberschenkel	5
Oberarm	4
Unterschenkel, Unterarm	2
2' und 3' offene Fraktur	3
Weichteilverletzung	1

PaO_2/FIO_2

< 50	22
50 - 99	12
100 - 149	8
150 - 199	5
200 - 249	3
250 - 299	2
300 - 349	1
≥ 350	0

Thorax

Sternum, Rippenfrakturen(1-3)	1
Rippenserienfraktur	4
Rippenserienfraktur bds.	10
Pneumothorax	2
Hämatothorax	1
Lungenkontusion	3
Lungenkontusion bds.	5
Aortenruptur	16

Becken

Beckenfraktur (einfach)	2
Beckenfraktur (kombiniert)	5
Becken-u. Urogenitalverletzung	8
Wirbelfraktur	2
Querschnittslähmung	8
Beckenquetschung	12

Alter

≤ 40	0
40 - 49	1
50 - 54	1
55 - 59	2
60 - 64	3
65 - 69	5
70 - 74	8
≥ 75	17

Base excess

≤ -16	26
-14 .. -15,9	20
-12 .. -13,9	14
-10 .. -11,9	9
- 8 .. - 9,9	5
- 6 .. - 7,9	3
- 4 .. - 5,9	1
≥ - 3,9	0

SEPSIS SEVERITY SCORE
according to Stevens (11)

Levels of Dysfunction in Seven Organ Systems for Determining SSS*					
	Rating of Dysfunction				
System	1	2	3	4	5
Lung	O₂ by mask	Intubated, no PEEP	PEEP, 0%-10%	PEEP, >10%, Po₂, >50 mm Hg	Maximal PEEP, Po₂, <50 mm Hg
Kidney	CL, 1 5-2 5 mg/dL	CL, 2 6-3 5 mg/dL	CL, >3 6 mg/dL, adequate urine volume	CL, >3 6 mg/dL, urine volume, 20-50 mL/hr	CL, >3 6 mg/dL, urine volume, 20 mL/hr
Coagulation	Ecchymoses, PT, PTT, and platelet count, normal	PTT, 45-65 s, PT, 12-14 s	Platelets, 20,000-100,000/cu mm, PTT, >50 s, PT, >14 s	Platelets, 20,000/cu mm, elevated PT and PTT	Increased FSP and euglobulin, bleeding
Cardiovascular	Slight hypotension	Livedo, moderate hypotension	Vasopressors, moderate doses	Vasopressors, large doses	Profound BP decrease despite vasopressors
Liver	LDH and SGOT increased, bilirubin, normal	Bilirubin, 1 5-2 5 mg/dL	Bilirubin, 2 6-4 0 mg/dL	Bilirubin, 4 9-8 0 mg/dL	Precoma bilirubin, >8 0 mg/dL
GI tract	Mild ileus	Moderate ileus	Severe ileus	Bleeding due to erosive gastritis	Mensenteric venous thrombosis
Neurologic	Obtunded	Disoriented	Irrational	Hyporeactive	Coma

*SSS indicates septic severity score, CL, creatinine level, PT, prothrombin time, GI, gastrointestinal, PTT, partial thromboplastin time, PEEP, positive end-expiratory pressure, LDH, lactate dehydrogenase, and FSP, fibrin split products Sum of the squares of the three highest dysfunction ratings equals SSS

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B. LIST OF ABBREVIATIONS

AAA	Abdominal Aortic Aneurysm
AHNP	Acute Hemorrhagic Necrotizing Pancreatitis
AIS	Abbreviated Injury Scale
AL(A)T	ALanine (Amino)-Transferase (=SGPT)
APACHE II	Acute Physiology And Chronic Health Evaluation
APS	Acute Physiology Score
ARDS	Adult Respiratory Distress Syndrome
AS(A)T	ASpartate (Amino)-Transferase (=SGOT)
BUN	Body Urea Nitrogen
C3(a)	Complement factor 3 (activated)
CNS	Central Nervous System
^{51}Cr-EDTA	Chrome-labelled EthyleneDiamineTetra-Acetate
CRP	C-Reactive Protein
E.Coli	Escherichia coli
Elastase-α1 PI	Elastase-α1 Proteinase Inhibitor Complex
ELISA	Enzyme Linked ImmunoSorbent Assay
FiO$_2$	Inspired Oxygen Fraction
GCS	Glasgow Coma Scale
HTI	Hospital Trauma Index
ICU	Intensive Care Unit
IL-1ß	Interleukin-1ß
IL-6	Interleukin-6
IP	Intestinal Permeability
ISS	Injury Severity Score
kPa	kilo Pascal
LDH	Lactic DeHydrogenase
L/M ratio	Lactulose/Mannitol ratio
LPS	LipoPolySaccharide (=endotoxin)
MOF	Multiple Organ Failure
M.W.	Molecular Weight
Neop/creat	Neopterin/creatinine ratio
PaO$_2$	Arterial Oxygen Pressure
PEEP	Positive End Expiratory Pressure
PEG	PolyEthyleneGlycol

pHi	Intramucosal pH
PMN	PolyMorphoNuclear (leukocytes)
Ps	Probability of survival
PTS	PolyTraumaSchlüssel
r	Correlation coefficient
RTS	Revised Trauma Score
SD	Standard Deviation
	Selective Decontamination
SEM	Standard Error of the Mean
SGOT	Serum Glutamate Oxalo-acetate Transaminase (=ASAT)
SIRS	Systemic Inflammatory Response Syndrome
Sp	Species
SSS	Sepsis Severity Score
TCC	Terminal Complement Complex
TNFα	Tumor Necrosis Factor α (=cachectin)
TRISS	Trauma Score or Revised TS and Injury Severity Score
TS	Trauma Score
TxB2	Thromboxane B2
vs	versus

DANKWOORD

Een proefschrift maak je niet alleen. Bij het opstellen van studieprotocollen, het verzamelen van gegevens, het uitvoeren van laboratoriumbepalingen, het uitwerken van data en het opschrijven van een en ander tot een leesbaar geheel zijn vele personen betrokken. *Allen* die mij op een op andere manier hierbij ondersteund hebben en die hier niet expliciet met name genoemd worden, wil ik mijn dank overbrengen.

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CURRICULUM VITAE

Rudi Roumen werd op 3 juni 1957 geboren te Heerlen. Na het behalen van het Gymnasium-ß diploma aan het St. Bernardinus College te Heerlen werd in 1975 gestart met de studie Geneeskunde aan de Katholieke Universiteit van Nijmegen.

Na eerst een periode als co-assistent met veel voldoening in het St. Anthony's Hospital, Dzodze, Ghana gewerkt te hebben, werd het arts-examen in 1983 met goed gevolg afgelegd.

Als docent o.a. anatomie en fysiologie was hij menig jaar verbonden aan diverse opleidingen voor O.K.-assistenten en Verpleegkunde in de regio Nijmegen.

Van 1984 t/m 1986 was hij als AGNIO Algemene Heelkunde eerst in het Lukas Ziekenhuis te Apeldoorn en later in het Academisch Ziekenhuis Sint Radboud, te Nijmegen werkzaam.

De opleiding tot algemeen chirurg werd gestart op 1 januari 1987, waarbij de eerste 3 "perifere" jaren werden genoten in het Canisius Wilhelmina Ziekenhuis (Hoofd: Dr. HJM Joosten) en vervolgens de 3 "academische" jaren in het Universiteits-Ziekenhuis (Hoofd: Prof. Dr. RJA Goris), beide gelocaliseerd in Nijmegen.

Gedurende deze laatste periode werd klinisch onderzoek verricht bij patienten met een verhoogd risico op het ontstaan van ARDS en MOF.

In 1992 won hij de Schoemakerprijs voor de beste publikatie in het jaar 1991: "Unstable Colles fractures in elderly patients", n.a.v. onderzoek uitgevoerd in het Canisius Wilhelmina Ziekenhuis, te Nijmegen.

Hij is getrouwd met Desirée van den Akker en is vader van Roger, Paul en Daniëlle.

Vanaf 1 januari 1994 zal hij als Algemeen Chirurg werkzaam zijn in het Sint Joseph Ziekenhuis, te Veldhoven (Hoofd afd. Algemene Heelkunde: Dr. CMA Bruyninckx).

Nunc est bibendum !