Thesis for doctoral degree (Ph.D.) 2007

Hemodynamic, Respiratory and Neurophysiological Reactions after High-Velocity Behind Armor Blunt Trauma

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“The pen is mightier than the sword”

Edward Bulwer-Lytton

To my family

Abstract

This thesis is addressing Behind Armor Blunt Trauma (BABT), defined as the non-penetrating injury resulting from a ballistic impact on personal body armor. The protective vest may impede the projectile, but some of the kinetic energy is transferred to the body, causing effects such as pulmonary contusion, apnea, hypotension and occasionally death.

Our aims of these studies have been to investigate physiological responses after high-velocity BABT, including EEG (study I). Furthermore, the safety criterion of 44 mm for protective vests (study II), effects of vagotomy (study III), and fluid resuscitation (study IV) has been evaluated.

Anaesthetized pigs, wearing body armor on the right side of thorax, were shot with a standard 7.62 mm assault rifle (velocity approx. 800 m/s). We used body armors corresponding to 28 mm impression in clay placed behind the vest (study I and III), 34 mm and 40 mm (study II), and 42 mm (study IV). Several physiological parameters were thereafter monitored during two hours after the shot. Experimental protocol was similar in all studies, except from study III (in which one group received bilateral cervical vagotomy) and study IV, in which 2 groups received Ringer´s acetate (RA) or hypertonic saline with dextrane (HSD).

In all studies we observed an immediate drop of blood pressure, desaturation, increased pressure in the lung circulation, suppressed EEG-pattern and pulmonary contusion. In study II and IV, severe hyperkalemia was seen early after the trauma and several animals had serious arrhythmias. Our observed EEG-changes indicate that high-velocity BABT induces brain dysfunction, for at least a couple of minutes. Based on our results, the safety criteria of 44 mm should be considered insufficient when a vest is exposed to high-velocity bullets. Our results show that apnea after BABT is a vagally mediated reflex, that can be inhibited by vagotomy. Fluid resuscitation has limited effects on physiological parameters in our model, although HSD induces less edema formation and a tendency to improved saturation compared to RA.

List of publications

This thesis is based on the following papers, which will be referred to in the text by their Roman numerals:

I. Dan Drobin,* Dan Gryth,* Jonas KE Persson, David Rocksén, Ulf P Arborelius, Lars-Gunnar Olsson, Jenny Bursell, B Thomas Kjellström.
***** These authors contributed equally to the study.
Electroencephalogram, circulation and lung function after high-velocity Behind Armor Blunt Trauma (BABT).
J Trauma. 2007. 63:405-13.

II. Dan Gryth, David Rocksén, Jonas KE Persson, Ulf P Arborelius, Dan Drobin, Jenny Bursell, Lars-Gunnar Olsson, Thomas B Kjellström.
Severe lung contusion and death after high-velocity Behind-Armor Blunt Trauma (BABT) – relation to protection level.
Military Medicine: International Journal of AMSUS 2007. 172(10):1110-16.

III. Dan Gryth, David Rocksén, Ulf P Arborelius, Dan Drobin, Jonas KE Persson, Anders Sondén, Jenny Bursell, Lars-Gunnar Olsson, B Thomas Kjellström.
Bilateral vagotomy inhibits apnea and attenuates other physiological responses after blunt chest trauma.
J Trauma (in press)

IV. Dan Gryth, David Rocksén, Dan Drobin, Henrik Druid, Eddie Weitzberg, Jenny Bursell, Lars-Gunnar Olsson, Ulf P Arborelius.
Effects of fluid resuscitation with hypertonic saline-dextran or Ringer acetate after pulmonary contusion and shock.
Submitted August 2007

Contents

Abbreviations

ARDS	Acute respiratory distress syndrome
ATP	Adenosine triphosphate
BABT	Behind armor blunt trauma
BE	Base excess
CO	Cardiac output
CPR	Cardio-pulmonary resuscitation
CT	Computer tomography
CVP	Central venous pressure
DAB	3,3'- Diaminobenzidine
DO_2	Oxygen delivery
ECG	Electrocardiogram
EDTA	Ethylenediamine tetraacetic acid
EEG	Electroencephalogram
ELISA	Enzyme-linked immunosorbent assay
ET-1	Endothelin-1
Hb	Hemoglobin
HSD	Hypertonic saline with dextran
ICU	Intensive care unit
IL- 6	Interleukin-6
i.v.	Intravenously
MAP	Mean arterial blood pressure
MPAP	Mean pulmonary artery pressure
NATO	North Atlantic Treaty Organization
NIJ	National Institute of Justice (USA)
NO	Nitric oxide
PA	Pulmonary artery
$PaCO_2$	Partial pressure of carbon dioxide in arterial blood
PaO_2	Partial pressure of oxygen in arterial blood
PEEP	Positive end-expiratory pressure
RA	Ringer's acetate solution
S-100	S-100 protein
SaO_2	Arterial oxygen saturation
SvO_2	Mixed venous oxygen saturation
SVR	Systemic vascular resistance
TNF-α	Tumour necrosis factor-alpha
VF	Ventricular fibrillation

Introduction

"Wisdom is a treasure
that follows its owner everywhere"

Chinese proverb

The history of body armors

This thesis focuses on Behind Armor Blunt Trauma (BABT), which is defined as the non-penetrating injury resulting from a ballistic impact into personal body armor[1].

The development of modern body armors, which began during the First World War, initially involved soft armors made from silk and other natural fibers.

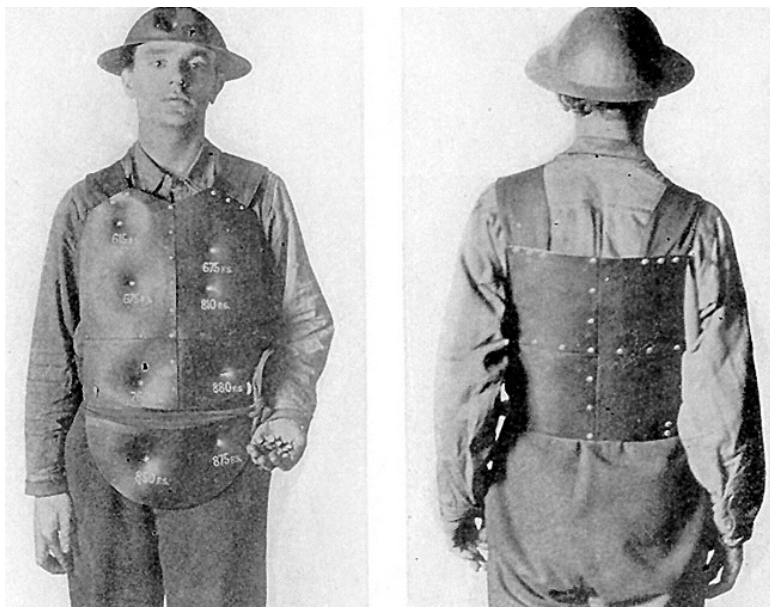

Figure 1. British Dayfield body shield (front and rear view) (reproduced from "Modern body armour and helmets: An introduction", with permission from Michael Iremonger).

Furthermore, rigid armors containing one large or several small metal plates were produced. Some of these were heavy and bulky and could weigh as much as 12 kg [2] (*figure 1 and 2*).

Figure 2. US Brewster shield (reproduced from "Modern body armour and helmets: An introduction", with permission from Michael Iremonger).

Further development, during the Second World War, involved reductions in weight, achieved by using new materials, such as strong aluminum plates surrounded by nylon. *Figure 3* depicts such an armor (M12), designed for ground troops, weighing 5.5 kg.

During the Korean War there was a real breakthrough regarding protection of ground troops with personal body armors. Field trials of body armor and battle casualties were well monitored. It was recognized that fragments were the main cause of casualties (85%) and that the majority of these were relatively easy to prevent[3]. The US Army developed a vest referred to as T-52-1 (*figure 3*), which weighed about 3.6 kg and was made of nylon textile, together with additional hard plates (glassfiber-reinforced composite)[2]. The strategy was to protect the most vulnerable regions of the chest and upper abdomen with hard plates and cover the upper chest and shoulders with nylon textile alone. This armor proved capable of preventing penetration by 75% of fragments and nearly 25% of bullets[2]. This successful introduction of body armor for American ground troops in Korea led to more extensive use in the Vietnam War. A study of soldiers killed in the Lebanon war revealed that 45 % of all hits by shrapnel and bullets were against the torso, which is slightly more than the torso's proportion of total body-surface[4].

Figure 3. US armor vests: M12 and T-52-1 (reproduced from "Modern body armour and helmets: An introduction", with permission from Michael Iremonger).

Today, body armor is used by police, military, journalists and civilians all over the world, when there is a high risk for assault with hand-guns, rifles or explosives. The potential to increase survival rate is revealed when comparing number of causalties among US soldiers in the Vietnam War to survivors equipped with modern body armor in Somalia[5]. However, new threats such as armor-penetrating ammunition and the desire to reduce armor weight, create challenges when developing new body armors[6, 7]. Thus, adaptation to meet the demands from newer weapons and projectiles requires continuous research on body armor and BABT.

Body armor design

Modern body protection can be categorized into soft or hard body armors. Soft armors consist of fiber materials such as aramid, polyethylenes or high-strength plastics. These armors are designed to protect against knifes, fragments or low-velocity bullets. Hard body armors are constructed specifically for protection against high-velocity bullets, such as 5.56 and 7.62 mm NATO bullets. The hard plates in these vests consist primarily of ceramic materials, such as aluminum oxide, boron carbide or polyethylene composite.

Several models of body armors are made in the form of a vest composed of soft armor materials. A common way to meet threats from high-velocity bullets is to add (permanently or in a pocket), hard plates that cover the front and back of thorax, upper abdomen and the back. The neck and side of the trunk is usually only protected by soft fibers. Additional soft plates can also be attached for protection of genitalia, groins and gluteal region. The armor mostly used by the Swedish Armed Forces, in international operations, weighs 11kg and is classified as protection-level III+, according to the National Institute of Justice (NIJ) classification system, in which level IV is the best protection. Note that level III+ is only valid for the surface covered by ballistic insert plates (*figure 4*).

Figure 4. Complete body armor m/94, with aramid fiber layers, and ceramic plates in front and back.

Biomechanical aspects of behind armor blunt trauma

Deformation of the projectile and of the armor itself is a part of the retardation and energy absorbing process that captures the projectile[1]. In the process of stopping the missile, the backside of the armor will be deformed to a certain degree, with the temporary deformation being generally more extensive than the permanent. The kinetic energy causes rapid deflection of the chest wall and sends shock-waves throughout the body, causing acceleration, shear deformation and retardation of tissues in the body wall and underlying organs, resulting in internal injuries and occasionally death[1, 8-11].

Energy transferred to the body of the individual wearing the protective vest is considered to be linked to the degree of injury sustained[8, 10-12]. To investigate the relation between energy and resulting injury, tests has been conducted in a chest model, using an injury criterion originally developed to assess thoracic impacts within the automobile industry. This criterion is called the "Viscous criterion", and is dependent on the amount of chest deflection, but also the rate at which it occurs[13].

Experimental models of behind armor blunt trauma

In order to increase knowledge regarding BABT, research on animals is crucial. During the 1970´s goats were used routinely in these kind of experiments. But today, swine are more commonly used, due to their ready availability, similarities to human anatomy and physiology.

In addition to animal experiments, there exist other ways to study BABT, including human corpses. Although not frequently used, corpses can provide certain information about structural injuries[14], but no data on pathophysiological effects. Computerized simulation models are also utilized[15, 16], but such models are no better than their input data, and it is obvious that the existing knowledge about the mechanisms is too weak, to permit reliable descriptions of the relationship between applied violence and resulting injury. Therefore, these models are mostly used to investigate mechanistic characteristics of different impacts.

Safety criteria for body armors

Protection efficiency of body armors is categorized into 4 levels (I-IV), based on the type of ammunition that can be defeated. Level IV is the highest protection level and can resist bullets with calibers as large as 12.7 mm.

At present, the most commonly used safety criterion for body armors is the so-called ”44 mm-criterion”, originating from the USA. The criterion was established after BABT studies on goats[17], protected by a soft body armor (aramide) and exposed to handgun ammunition (caliber 0.22 and 0.38). Physiological results were compared to the impression made in a block of ballistic plasticine placed behind the armor. It was concluded that the injury sustained is tolerable if the impact does not generate an impression deeper than 44 mm.

The recommended method for testing whether body armor fulfills this criterion is described in the report “NIJ Standard-0101.44, Ballistic Resistance of Personal Armor”. The body armor should be fixed to the front of a block of ballistic plasticine (Roma Plasteline No.1), and the projectile of interest should be fired from a distance of 10 m. If the impression in clay is deeper than 44 mm, the body armor should be considered inadequate[16].

This criterion was originally validated for hand-gun bullets or fragments, but has been extended far beyond the original limited bullet energy levels, without proper consideration of the energy delivered to the tissue, the projectile speed, body mass, gender or the location at which the body is hit[13, 16, 18].

Pathophysiology of behind armor blunt trauma

As mentioned above, experimental animals and human corpses have been used to evaluate biomechanical aspects and physiological consequences of BABT. Projectiles aimed at the lungs, heart or spine cause subcutaneous hematomas, rib fractures, pulmonary contusions, heart contusions and spinal fractures. Physiological effects have only been studied in animal models, for obvious reasons. The results have shown decreased systolic blood pressure, slightly slower heart rate and arrhythmias, as well as apnea and decreased saturation of the blood[19, 20].

The triad of apnea, bradycardia and hypotension has also been described in a number of studies investigating primary blast injury to the chest[21-25]. The pathophysiological effects has been shown to be a reflex mediated via the vagus nerve[22]. Activation of C-fiber receptors in the lung parenchyma are involved in that reflex. These receptors are located in the alveolar interstitial space, close to the pulmonary capillaries [26, 27], and are triggered by various stimuli, for example by elevations in pulmonary capillary pressure[28], increase in the lung interstitial pressure[29] and intravenous injections of certain chemical substances[30]. The afferent pathways from the lung stretch-receptors and the C-fibers are conducted through the vagus nerve to the respiratory center in the brain stem. Consequently, bilateral transection of the vagus nerve might prevent apnea and other pathophysiological effects, resulting from BABT[24, 30, 31].

Brain function might also be affected by pressure waves propagated through the body after high-velocity trauma. Thus, Göransson et al. demonstrated suppressed activity of electroencephalogram (EEG) directly following impact of a high-velocity bullet on the hind leg of pigs[32]. Pronounced depression of EEG has also been described in pigs after blast trauma[33]. However, no data have been published previously, concerning the effects of high-velocity chest impact on EEG.

BABT and its pathophysiological consequences have similarities to civilian blunt chest trauma. Pulmonary contusion, one of the most significant effects of BABT, is also a common finding in trauma patients, especially after traffic accidents and fall from heights, occurring in nearly 20% of all individuals suffering multiple injuries (i.e with an Injury severity score > 15) [1, 34]. However, in contrast to these examples, impact velocity is higher and the area of impact smaller in our studies, although peak velocity of the chest wall movement should not be considered equal to bullet velocity. In warfare and in connection with terrorist attacks, pulmonary contusions are also observed after shock waves produced by explosions[35]. Pulmonary damage caused by such trauma is characterized by disruption of microvasculature, resulting in local flooding of alveoli and interstitial extravasation of red cells and plasma[36].

Incidence of behind armor blunt trauma

The first modern clinical report on BABT was written by Carrol et al.1978[8]. This report described five cases of policemen who were hit by handgun bullets (caliber 0.38 and 0.22). The policemen were carrying soft body armors, made by 7- 18 layers of Kevlar®, and were hit at different regions of the chest. They were hospitalized for 2 to 3 days, due to bruises and superficial bleedings, but no subject had any signs of pulmonary or cardiac contusion.

Figure 5 depicts a subcutaneous hematoma resulting from BABT, but the circumstances and injuries of the subject are unknown to us. IACP/DuPont Kevlar Survivors' Club is a voluntary association for policemen who survived assault due to protection by body armor. To date, 207 persons have survived hits from different types of ammunition and are members in this association. The injuries described are often bruises and hematomas, but some suffered more serious damage. It is difficult to draw conclusions from the material, because different weapons, distances, angles and target areas were involved. Bir and coworkers made an attempt to evaluate policemen in the Survivors' Club, with the aim to determine whether there is any gender difference in susceptibility to injury from BABT. In the report only 3 women and 8 men protected by soft body armor met the inclusion criteria, e.g. known weapon and distance. Described injuries were bruises, rib fractures, pulmonary contusions

and hemoptyse, but all patients survived after hospital care[37]. In that study, it was difficult to determine whether any gender difference exists. However, it seems likely that gender (or mass) is a parameter that might affect outcome after BABT.

Beside reports about soft armors, there exists some reports concerning BABT occurring behind rigid armors, after impact of high-velocity bullets. The earliest reported case of lethal BABT, due to a high-velocity bullet, was described 1969 by Shepard et al.[38]. During the Vietnam War, they described a US sergeant that was accidentally shot with a M-16 from close range. This report provides no description of his body armor, but the bullet did not penetrate the pleural cavity. After a short period of respiratory and hemodynamic stability the patient rapidly deteriorated, and died within 45 minutes after admission to the hospital.

In 1995 the French military reported that during the war in former Yugoslavia, a civilian voluntary worker had worn body armor (with a ceramic plate), that defeated a 14.5 mm bullet. This individual survived with large areas of myocutaneous necrosis beneath the plate and minor haemothorax[1].

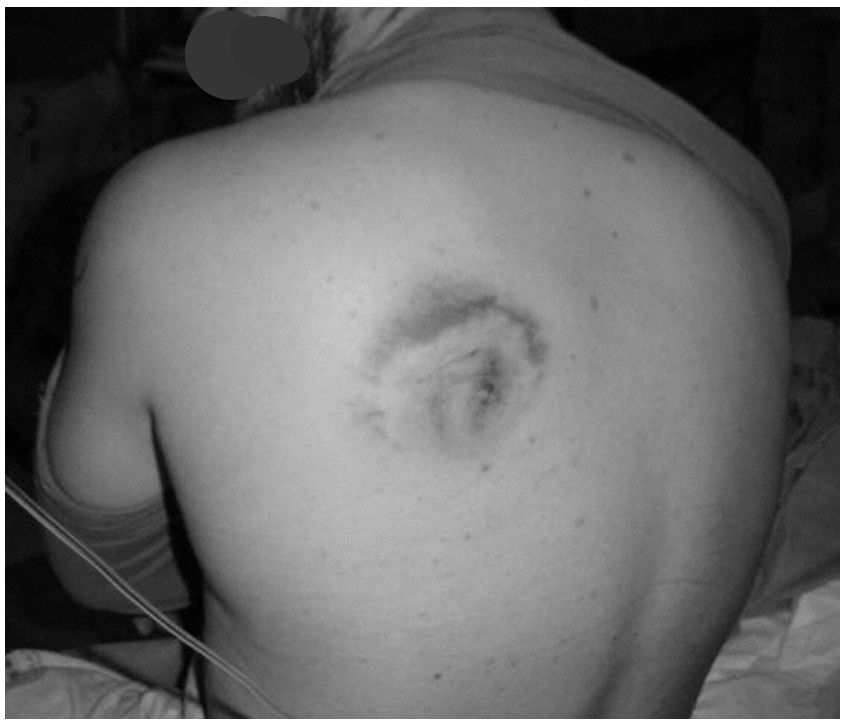

Figure 5. A soldier with subcutaneous hematoma resulting from BABT.

In connection with the present work, we discovered how difficult it is to obtain high-quality epidemiological data regarding BABT. Military cases are usually classified, so most open reports focuses on the interaction between low-velocity projectiles and soft protective vests[39-41]. Due to the lack of research and epidemiological data, NATO formed a research group on BABT in 1995. There is still a lack of knowledge regarding BABT caused by high velocity weapons, emphasizing the importance of the research conducted in this thesis.

Diagnos and treatment of pulmonary contusion

The clinical presentation of a trauma patient, suffering from severe pulmonary contusion, includes respiratory distress, hemoptysis, decreased oxygenation of the blood and radiographic abnormalities of the lungs, that appear within hours after the injury[35]. The most definitive means of diagnosing pulmonary contusion is by computer tomography (CT)[35, 42].

Severe pulmonary contusion often requires mechanical assistance in breathing, together with supplementary oxygen. Respiratory support can be maintained by non-invasive ventilatory support, such as continuous positive airway pressure (CPAP), Bi-level positive airway pressure (BiPAP) or mechanical ventilation[43, 44]. During ventilation, moderate inspiratory pressure should be employed in order to avoid barotraumas, since the lungs are more sensible in patients with pulmonary contusion[45]. In addition, positive end-expiratory pressure (PEEP) is often utilized to avoid atelactasis and improve oxygenation of arterial blood[46-48].

In the later phase, after a pulmonary contusion, patients might develop pneumonia or acute respiratory distress syndrome (ARDS)[35, 49]. Avoidance of endotracheal intubation leads to a significant reduction in ventilator-associated pneumonia and other infections[50]. Other treatment strategies is to use ventilatory suport that generates limited elevation in peak inspiratory pressure, which is associated with a decreased incidence of late post-traumatic ARDS[45]. Moreover, patients with severe acute lung insufficiency treated in the prone position have shown positive effects on blood oxygenation[51].

In acute lung injury (ALI) and ARDS there is a marked maldistribution of pulmonary perfusion, in favor of poorly or non-ventilated lung areas[52]. Inhaled nitric oxide (iNO) therapy offers the possible to selectively modulate the pulmonary blood flow, reduce pulmonary hypertension and improve matching of ventilation/perfusion[53]. Clinical studies have demonstrated improved arterial oxygenation and pulmonary hemodynamics in ARDS-patients treated with NO[54-56]. However, this increase in PaO_2 was only transient, and no improvement in mortality or ventilator-free days

were found[57]. Nevertheless, the European expert group for inhaled nitric oxide therapy, recommend to use iNO as a rescue treatment in adults with severe refractory ALI/ARDS[58].

Many investigators have proposed a linkage between ARDS and the "two-hit" theory, suggesting that one injury alters cell and organ function, so that the response to a second injury is exacerbated[59, 60]. To avoid that, some studies recommend preventive treatment with corticosteroids[61], although evidence concerning effectiveness of this approach is insubstantial[62, 63]. In the last decade, corticosteroids has not been recommended in the management of pulmonary contusion[35, 64].

In some cases the pulmonary contusion is accompanied by other injuries, for example hemorrhage, requiring fluid treatment. However, infusion of fluids should be performed with caution[34, 35, 45, 65], since the lungs are more sensible after a contusion[66]. Lung edema can occur when fluids are administrated to patients sustaining multitrauma and lung contusion, leading to decreased saturation[67]. Negative effects of fluid management in patients with lung contusion have been discussed since World War II[68]. During the Vietnam War it was described as "shock lung" or "DaNang lung" [69]. Certain clinical findings support these observations[70], whereas other studies conclude that fluids could be administrated safely[36, 71]. Prehospital resuscitation during trauma treatment until recently consisted of early and aggressive fluid administration, to stabilize the patient and normalize the blood pressure before arrival at the hospital[72]. In recent years this strategy has been challenged, and clinical and experimental models have shown possible deleterious effects if fluids is administrated before hemorrhage is under control. Emphasis has shifted from aggressive fluid administration, to early hemorrhage control[73, 74] together with fast admission to trauma hospital[75]. Furthermore, timing of the infusion must be considered[76].

Fluids commonly used for resuscitation are isotonic crystalloid solutions, such as Ringer's acetate (RA) or lactated Ringer's (LR) solution. These fluids are distributed throughout the entire extracellular space, with no preference for the intravascular space. Consequently, these solutions can occasionally cause tissue edema, which in turn impairs oxygenation[42, 77]. It has been proposed that hypertonic saline solutions containing colloids, such as hypertonic saline with dextrane (HSD), can be used to increase the blood pressure, cardiac output and peripheral tissue perfusion, without causing edema formation[78, 79]. The hyper-osmotic effects of such solutions have been shown to expand plasma volume three to four times the volume infused, by influx of extravascular fluid[80]. Resuscitation with HSD has shown a tendency to improve survival rate in severely injured patients[81] and improve outcome in patients with severe head trauma[82]. In contrast, Bunn et al. concluded that hypertonic fluid

resuscitation in critically ill patients was not more efficient than resuscitation with isotonic crystalloid fluids[83]. However, hypertonic saline has been shown to reduce the inflammatory response after severe hemorrhagic shock in animal models[84-86]. HSD has also other advantages, particularly in pre-hospital and military circumstances, as it is easy to carry and store[79]. One might also speculate that infusion of a small volume HSD decreases the risk that hypothermia will develop, or be aggravated, in a cold environment.

Aims of the thesis

General aim:
To develop an animal model for high-velocity BABT, and in this experimental set-up investigate pathophysiological effects and mechanisms.

Specific aims:

- Study I: Evaluate physiological effects after high-velocity BABT in pigs wearing "complete protection" (M94), with particular focus on EEG-changes.

- Study II: To determine whether the 44 mm-criterion provides sufficient protection when body armors is exposed to high-velocity ammunition.

- Study III: To examine whether the vagus nerve is involved in apnea and other pathophysiological effects caused by BABT.

- Study IV: To compare fluid resuscitation with Hypertonic saline-Dextran (HSD) or Ringer's acetate (RA) solution, for treatment of pulmonary contusion accompanied by shock.

Material and methods

Detailed descriptions regarding methods used in this thesis is included in papers I-IV. Only a brief summary of methodological principles and considerations is given here. Most aspects of methodology were identical in the four studies and the experimental setting is displayed in *figure 6*. Specific differences between the studies are described in the section "Methods specific for studies I-IV".

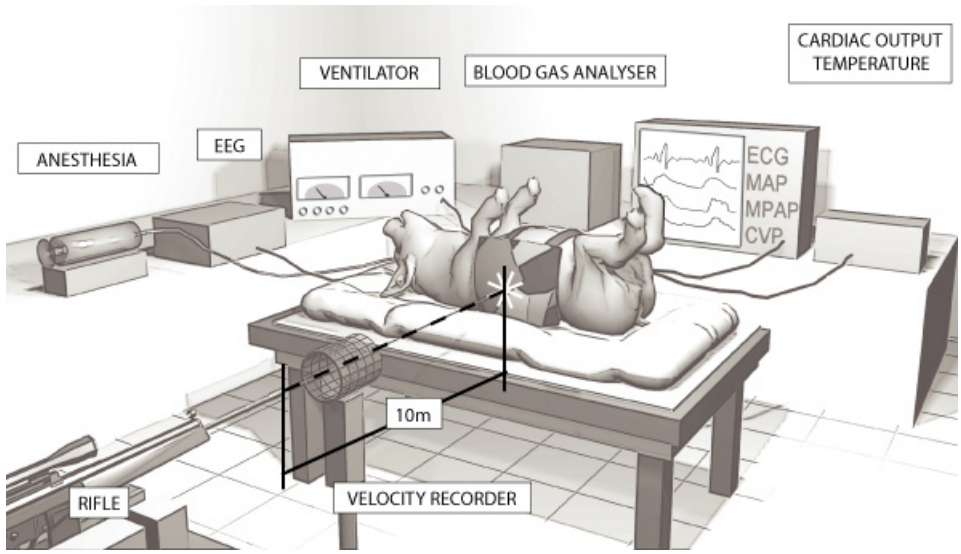

Figure 6. An illustration of our experimental set-up.

Measurement of back-face deformation

These tests were performed prior to the animal experiments, to evaluate the deformation behind the body armor (measured as impression in ballistic plasticine), following the standard developed by National Institute of Justice in USA (Standard 0101.04). The same procedure was used in study I-IV and only one shot was fired at each armor.

Shooting procedure in ballistic plasticine

A standard assault rifle (Swedish Armed Forces Mark AK4) equipped with a laser aiming device (Diode laser type S 1889) was used in all experiments. The weapon was

mounted on a gun-carriage placed 10 meters in front of the target. All ammunition was of Danish issue, NATO type, 7.62 × 51 mm (M/94). This is standard "ball" ammunition with a lead core and a bullet weight of 9.5 g. Projectile velocity was measured with an optical shutter device (Chronograph Beta model). The recorded bullet velocities, during all reported shootings, were very close to 800 m/s (range 787-811). This velocity is associated with a kinetic energy of 3kJ, which was reduced to 0 within approximately 25 microseconds after impact.

Body armors

In all studies a layer of cotton fabric was placed tight between the block of plasticine and the armor, to simulate a field shirt. The manner in which the various components of protection were used in the four studies is summarized in table 1, where the resulting impression in plasticine is also given.

In study I, we used a specially manufactured vest segment, corresponding to the Swedish Armed Forces standard issue, m/94 consisting of three layers of uniform fabric, a ceramic ballistic insert plate (Aluminum oxide, 255 x 300 mm), and behind the plate 14 layers of aramid fabric (Kevlar®). This body armor is normally used by the Swedish Army during international operations and consists of a vest, covering the trunk, containing the aramid pack. On the front and back of the trunk there are pockets for the additional ballistic insert plates.

In study II the aim was to evaluate the "44 mm-criterion". In order to obtain an impression with a depth as close to 44 mm as possible, the components of the "complete protection" were successively stripped away. 40 mm deep impression was achieved by using only the ceramic plate. This group was compared to the 34 mm-group, where the impression was slightly less (34 mm). This change was accomplished by adding three layers of uniform fabric.

In study III the same complete body armor as in study I (m/94) was used.

In study IV a ballistic insert plate (size 300 x 255 mm), made of polyethylene, (Swedish m/98) was used with 4 additional layers of aramid fabric at the backside, resulting in an impression of 42 mm. The goal with this set-up was a more severe BABT-injury than in earlier studies (I-III).

Table 1. The armor panels used in the different studies, the number of test shots to measure impression in plasticine, and the resulting impression.

Study	I	II (40 mm)	II (34 mm)	III	IV
Protection	Complete vest (m/94) (including ceramic plate)	Ceramic plate (m/94)	Ceramic plate (m/94) + 3 layers of uniform fabric	Complete vest (m/94) (including ceramic plate)	Polyethylene plate (m/98) + 4 layers of aramid
Shots	n=4	n=6	n=2	n=4	n=2
Impression (mm)	28 (24-31)	40 (38-43)	34 (33-34)	28 (24-31)	42 (41-42)

Animals

The pigs were all of Swedish landrace type (females or castrated males), obtained from a commercial breeder. Pigs weighing around 60 kg were used because their thorax size mimics human anatomy and physiology[87]. The experimental protocols were all approved by the Ethics Committee on Animal Research, Umeå, Sweden. Animals were accommodated in an accredited animal facility at least 2 days prior to the experiment and fed a standard diet with free access to tap water. Ambient room temperature were maintained at 21-22° C with a photoperiod of 12 h light/12 h darkness.

Table 2. Subjects and groups in the four studies. Controls in I and II are the same group.

Study	I	II	III	IV
Shot groups and number of animals	Exposed (8) Control (4)	40 mm (10) 34 mm (8) Control (4)	Vagotomized (5) Non-vagotomized (11) Control (8)	HSD (9) RA (10) Shot control (10) Unshot control (5)
Unshot groups and number of animals	Control (4)	Control (4)	Control (8)	Unshot control (5)
Weight in kg	BM = 63 (50-91)	BM = 54 (43-72)	BM = 62 (45-79)	BM = 66 (56-76)

Anesthesia and ventilation

All animals got premedication before further handling and transport to the laboratory. A solution consisting of tiletamin 25 mg/ml, zolazepam 25 mg/ml and medetomidinhydrochlorid 1 mg/ml, was used. A dose of approximately 0.06 ml/kg was administered intramuscularly in the dorsum of the neck.

The general anesthesia was started with pentobarbital sodium 6 mg/kg, and 0.5 mg atropine sulphate intravenously (i.v.). The anesthesia was maintained with intravenous infusion of ketamine hydrochloride 50 mg/ml, and pethidin hydrochloride 50 mg/ml. 1 ml pethidin was added to every 30 ml of ketamine, and the infusion rate was 0.5 ml / (kg h).

In study III and IV, the pethidin was excluded to minimize deprivation of the respiratory drive, since these animals were spontaneously breathing during the whole, or part, of the experimental course.

In general anesthesia the animals were tracheotomized and mechanically ventilated in a volume controlled mode with room air (Siemens Servo Ventilator 900C), at a rate of 20 breaths per minute. The tidal volume was adjusted to achieve normoventilation. In all four studies the ventilation started in the same mode.

In study I and II, the ventilation was continued in the same mode as described above, through the whole experiment (120 min).

In study III, after the preparation, the ventilator was switched to spontaneously breathing (30 minutes before the shot), and was maintained so throughout the whole experiment. A small pressure support was set to compensate for the air flow resistance in the tubes. The length of the apnea period was visually registrated.

In study IV, the ventilator was switched to spontaneous breathing mode 30 minutes before the shot, but 1 minute before the shot the ventilator was disconnected until 5 minutes after the shot. After that they were connected again to the ventilator in a volume controlled mode. This ventilatory strategy was performed since our aim was to mimic field conditions, where an exposed person would receive assisted ventilation 5 min after impact. The length of the apnea period was visually registrated.

Catheterization

One catheter was introduced in an ear margin vein and used for induction of general anesthesia. Through a paramedian left neck incision, a polyethylene catheter was introduced into the left external jugular vein, to be used for continuous infusion of the ketamine. The same incision, as for the tracheotomy, was used for introduction of a polyethylene catheter into the left common carotid artery, for blood sampling and mean arterial blood pressure (MAP) monitoring. Trough a right paramedian neck incision, an optical pulmonary thermo dilution catheter (Opticath, Abbot) was inserted into the right external jugular vein, for measurements of central venous pressure (CVP), mean pulmonary artery pressure (MPAP), cardiac output (CO), mixed venous saturation (SvO_2) and body core temperature. The cardiac output was measured using thermo dilution technique.

After the preparation was completed, animals were allowed 30 minutes rest to achieve steady state.

Recording of circulatory parameters

Electrocardiography (ECG), heart rate (HR), mean arterial pressure (MAP), central venous pressure (CVP) and mean pulmonary artery pressure (MPAP) were measured and monitored with a Sirecust 960 (Siemens Medical Electronics). Cardiac output (CO), mixed venous saturation (SvO_2) and core temperature were measured and monitored with an Oximetrix 3 (Abbott Critical Care Systems). CO was measured by duplicate injection of 10 ml of 0.9 % saline with ambient room temperature. Measurements were accepted if both injections agreed within 10 %, otherwise additional measurements were obtained. The mean of the two accepted measurements was registered.

Calculated variables

Table 3. Calculated variables in the present study.

Abbreviation	Variable	Source	Unit
SV	Stroke volume	CO/HR	mL/stroke
SVR	Systemic vascular resistance	80 x (MAP - CVP) / CO	mmHg/(L/min)
Vo_2	Oxygen uptake	CO x 0.0139 x Hb x (SaO_2-SvO_2)	mL/minute
DO_2	Oxygen delivery	CO x (0.0139 x Hb x SaO_2)	mL/minute
O_2ER	Oxygen extraction ratio	Vo_2 / Do_2 x 100	%

Recording of electroencephalogram (EEG)

Electrical activity from the brain cortex was registered by bipolar electroencephalogram (EEG) in study I-III. Registration of the EEG-signal was carried out with five electrodes screwed into the outer part of the skull bone in the midline over the frontal and parietal lobes, bilaterally over the temporal lobes and at the vertex. The registration was made with a mobile eight-channel EEG recorder (Model No. EEG-7209, Nihon Kohden Corporation). Two ground electrodes were placed subcutaneously in the neck. An equilibration time of 30 minutes was allowed before start of the EEG-recording.

The EEG-recording started five minutes before firing of the weapon, to get a baseline-pattern, and was continued until 15 minutes after the impact, followed by two-minute recordings every 15 minute, until the animal died or was euthanized at 120 minutes. As a control for artifacts in the EEG-curve, ECG was recorded simultaneously from two electrodes placed subcutaneously, one on the right shoulder and another on the left chest. The EEG-sheets were manually analyzed by an experienced specialist in clinical neurophysiology.

The EEG-pattern was graded into one out of five levels, according to the estimated change in frequency and amplitude over time:

1 Slight to moderate reduction in frequencies, i.e. a reduction of the fast frequency band (*slowing in frequency range*).
2 Pronounced reduction in frequencies, i.e. a dominance of the slow frequency band (*marked slowing in frequency range*).
3 Overall reduction in amplitudes of 50% or more (*depression pattern*).
4 Short bursts of slow activity with an otherwise global suppression of all cortical activity (*burst-suppression pattern*).
5 A totally suppressed EEG-pattern (*iso-electric pattern*).

The pre-exposure baseline pattern was always graded as zero (0). An illustration of the EEG-levels is outlined in *figure 7.*

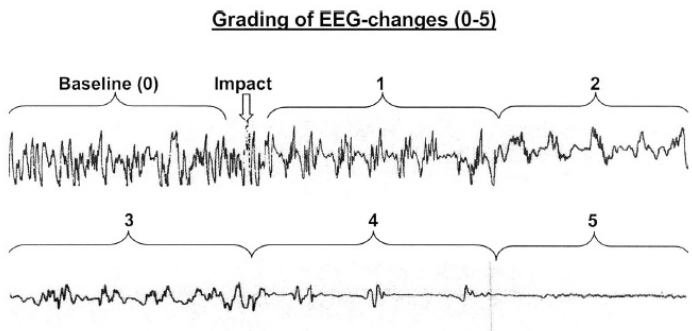

Figure 7. Grading of EEG-changes. Recorded EEG in an exposed animal is outlined. The EEG-levels 0 (baseline) – 5 (iso-electric EEG) is depicted.

This grading was based on earlier observed changes in EEG-pattern, following experimental concussion in awake animals[88], which in its turn was graded according to a previously established staging system for concussion in humans[89].

Blood sampling

Blood samples were obtained from the arterial line for analysis of SaO_2, PaO_2, $PaCO_2$, Na^+, K^+, Ca^{2+}, pH, base excess (BE) (GEM Premier Plus analyzer), lactate (Miniphotometer, 8), blood glucose (B-Glucose analyzer, Hemocue AB, Ängelholm, Sweden), and whole blood hemoglobin (Hb) (Hemoglobin Photometer, Electrolux). In study IV we used a new blood gas machine (GEM Premier 3000), which could measure all the samples mentioned above except blood hemoglobin, for which we used the same method as previously.

These parameters and physiological data were recorded at baseline, 1, 5, 10 and 15 minutes following impact, and thereafter every 15 minutes until the end of the experiment at 120 minutes. However, in study IV, due to practical reasons, no blood sample was taken 1 min after impact.

Analysis of Endothelin-1, TNF-α, IL-6 and S-100

These measurements were only performed in study IV. For analysis of endothelin-1, blood was drawn separately from the arterial line and the PA line at baseline, 7, 30, 60 and 120 minutes after shot. Collected blood samples were mixed with EDTA (final concentration 10 mM) and kept on ice until centrifuged at + 4°C. Plasma was stored at -20°C for analysis of endothelin-1 as described earlier[90].

Venous blood samples for TNF-α and IL-6 determinations were taken at baseline and 120 minutes after the shot, and were centrifuged at 15,000 rpm for 20 minutes at 4°C. Serum was thereafter kept at -70°C until final processing. Cytokine levels were determined using commercial enzyme-linked immunosorbent assay (ELISA) kits (Quantiqine M Immunoassay), specific for murine TNF-α and IL-6. All assays were performed in duplicate.

Blood samples for the determination of S-100 were drawn from the arterial line at 7, 30, 60 and 120 minutes after shot and allowed to clot for 30 minutes at room temperature. Tubes were then centrifuged in 3,000g for 10 min. The supernatant was stored in aliquots at - 70°C until analysis. Serum concentrations of S-100 were measured with a commercially available, automated immunoluminometric assay (Byk-Sangtec Diagnostica).

Armor and shooting procedure in the animal experiments

The same specially made armor panels used for measurements of back-face deformation were used for the animal experiments. In all four studies the weapon, ammunition and shooting distance (10 m) were the same and, hence, also the incoming energy. Consequently, the actual energy transferred to the swine thorax, as well as other loading characteristics in the different studies, were determined by the characteristics of the used armor panel. The armor was firmly attached to the right side of thorax with two 3 cm broad girdles. Care was taken not to cause restriction of the ventilation.

The conditions were kept identical to the ones of the plasticine impact tests, and agreed in general with those determined by the NATO task group BABT, as standard for these kind of experiments[87].

The control animals were subjected to a rifle shot with the same weapon but using blank ammunition. The amount of gunpowder in the blanks was adjusted to produce a similar sound level as the live ammunition.

The animals were randomized, immediately before the shooting, to live ammunition or to blank ammunition, except for the vagotomized group in study III, which was exposed only to live ammunition. The target point was over the eighth rib at the right side of thorax, generating an adequate exposure of the right lung. The firing of the rifle was synchronized to the endpoint of the inspiratory phase.

After two hours observation time, the animals were euthanized with pentobarbital 60 mg/ml, 70 ml i.v. or more until the ECG became iso-electric.

Post mortal examination

Directly following death, an autopsy was performed in all studies (I-IV), in which the swine were examined for gross pathology. The thorax wall, lungs, heart, liver and bowels of the upper part of the trunk were examined.

Histology

In study IV, histology was performed on the lung, heart and kidney. Small pieces, averaging 1 x 1 x 0.5 cm, were collected from both lungs, the myocardium and from the right kidney and put into phosphate-buffered formalin. Paraffin sections

were stained with Hematoxylin-eosin, and with anti-myeloperoxidase antibodies (myoclonal, 1:200, Chemicon, Stockholm, Sweden), followed by a goat-anti-mouse secondary antibody, labeled with horseradish peroxidase, and a DAB detection kit. Neurophils in lungs were counted in five fields at 600x magnification, whereas other morphometry was based on semiquantitative grading.

Methods specific to studies I-IV

Below are descriptions of methods that are specific for the individual studies (I-IV), and differences from the general methodology, described above.

The specific methodology in study I

Study I followed the previously described methodology. The aim of this study was to test our new experimental model and evaluate the effects of BABT on physiological parameters, including EEG. The shot animals were protected by the complete body armor (vest + insert plate) and were compared to unshot animals.

The specific methodology in study II

Study II followed the previously described methodology. The aim of this study was to test if the 44-mm criterion is valid for protection against high-velocity bullets. Unshot controls (same as in study I) were compared to two groups who had protection panels that were stripped down, in order to obtain deeper impression behind the armor (34 and 40 mm).

The specific methodology in study III

Study III had basically the same design as study I, except that all animals were spontaneously breathing and that pethidin was excluded from the medication. Since the aim of study III was to investigate the role of the vagus nerve, in causing apnea, one of three groups received bilateral cervical vagotomy. This preparation was performed on five animals. The nerves were accessed through the same midline incision that was used for tracheotomy.

The specific methodology in study IV

As in study III, in this study the animals were spontaneously breathing and the pethidin was excluded from the medication. There were four groups receiving different treatment (see below and *table 2*). This was the only study where we used a

polyethylene ballistic insert plate. Four aramid layers where added to get a protection allowing approximately 50 % lethality after BABT (42 mm).

Exposed animals were shot with live ammunition and divided into three groups:

- Receiving Hypertonic saline containing Dextran (HSD group, n=9).
- Receiving Ringer's acetate solution (RA group, n=10).
- Shot control group, receiving no fluid (SC, n= 10).

Blank ammunition and no fluid were used in the unshot control group (C, n=5).

The treatment protocol was chosen to mimic the earliest possible initial medical care during battlefield conditions. One minute after shot the animal was positioned, lying on the right side, to prevent blood from flooding the unharmed lung. Suction of the airways began after three minutes and was repeated when required. After five minutes the pig was connected to the ventilator, in volume control mode at the same adjusting as earlier. Fluid treatment started 10 minutes after impact. In the HSD-group, 250 ml (~4ml/kg) was infused intravenously during 5 minutes, which is a recommended volume and infusion rate[78].

In the RA-group, 2000 ml (~32ml/kg) was infused intravenously during 30 minutes, following the recommended administration of 2 L bolus of intravenous fluid for trauma patients in shock[91].

Fluid treatment with HSD results in an initial plasma expansion of 3-4 times the volume of infused fluid[80], which is roughly equivalent to the plasma expansion caused by 2 L of isotonic solution[69].

In study IV, wet/dry weight weight ratio of the injured lung was examined by the following method: A small piece of lung tissue was taken from the middle lobe, 3 cm from the border of the hemorrhagic edge of the pulmonary contusion. From the left lung was also a small piece taken from the similar location. These samples were weighed and dried in an incubator at 45° C, until a constant weight was achieved[92]. The amount of water in the lung was calculated by the relation between wet and dry weight (wet/dry weight).

Statistical methods

All groups of animals were followed over time and measurements were performed at 12 pre-defined time-points. The data were analyzed using a linear mixed-effects model[93], because some data were missing at the late phase of the experiment in study I, and due to animals dying in study II-IV. PROC MIXED in the statistical package SAS was used for the analysis. In text and figures, the least square means are depicted inside 95% confidence intervals. *p* values of 0.05 or less were considered significant.

Results and Discussion

Injuries

The injuries and physiological responses of the animals were well related to body armor protection in study I-IV. Beneath the point of impact at the body armor, an almost circular subcutaneous hematoma was seen in all studies. With the best protection (study I and III), the mean diameter of the hematoma was 6 cm. The weakest protection in study IV resulted in a mean diameter of 7 cm. We also observed fractures of one to three ribs and a lung contusion in all four studies. The largest lung contusions were seen in study IV (*figure 8*), with a mean size of 13 cm in length, 8 cm broad and 6 cm deep. Compared to full protection (study I and III), the mean size was 8 cm in length, 7 cm broad and 4.5 cm deep. In study IV, a minor lung laceration was seen in five of twenty-nine animals and eight had slight traumatic emphysema, compared to study III (full protection) where one of sixteen animals had a lung laceration and only one had emphysema. Cut sections of the lung contusion had an appearance similar to liver tissue i.e "hepatization of the lung"[35].

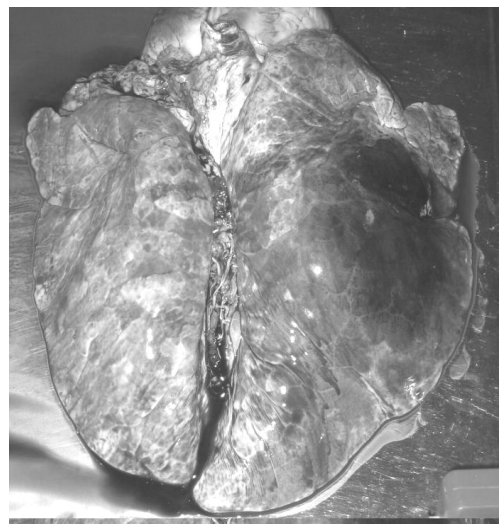

Figure 8. Circular hematoma in right lung behind the point of impact. Left lung is not affected by any hematoma. The view is from the dorsal side and the hematoma is on the lateral side.

In study II and IV some exposed animals demonstrated dense cardiac tissue, in other studies referred to as a "stone heart"[94]. This change was only seen in deceased animals that suffered from low PaO_2 for a longer period during the experiment. In study II, dense cardiac tissue was observed in 3 of 18 exposed animals, and in study IV in 11 of 29 exposed animals. In the control groups and in study I and III, there were no observations of dense cardiac tissue.

Myocardial stunning has also been described after global myocardial ischemia[95]. The cause of myocardial stunning is probably myocardial hypoxia leading to depletion of adenosine triphosphate (ATP), making actin-myosin binding irreversible. Myocardial stunning has been shown to occur *in vivo* with as little as 50% depletion of ATP[95, 96]. Therefore, one might hypothesize that dense cardiac tissue could be an important tool for forensic scientists, to evaluate if a person suffered from grave hypoxia before cardiac arrest. Hypothetically, the dense heart and death can perhaps be prevented by early ventilation with extra oxygen content.

Mortality

Mortality caused by BABT was documented in study II and IV (worst injury), and in study III in which one animal died. In study II, 2/8 (25 %) of animals in the 34mm-group and 5/10 (50 %) in the 40mm-group died due to the trauma. In study IV, 13 of 29 (45 %) exposed animals died due to the trauma. Fluid resuscitation did not improve survival rate in study IV. The animals who died from the injuries, except three, died within 60 minutes.

Respiration

Apnea was only detectable in study III and IV, since the respiration of animals in study I and II where regulated by a ventilator. This experimental set-up resulted in an apnea of 22 (6-44) seconds in study III and 146 (46-210) seconds in study (IV). More energy was transferred to the lung tissue in study IV, indicating that more stretching of the lung and the C-fibers give a longer apnea period. This has also been published by Adams et al. 1987 and Jaffin et al. 1987, showing that the apnea period was proportional to the load of hyperinflation or blast distance[30, 97].
In this thesis, vagotomized animals in study III were protected from apnea, clearly

showing that apnea during BABT is a vagally mediated reflex. Based on the results from our studies, it is a fair assumption that early supported ventilation might reduce other pathophysiological effects of BABT. This hypothesis is supported by the observation that desaturation was more pronounced in groups suffering from apnea. In study IV all animals had apnea, but some started the breathing with gasping by means of very low respiratory rate, until the animals were supported by the ventilator. 13 of 29 animals in study IV died during the experiment and showed immediately before death yet again a breathing pattern of gasping. Gasping is an universal phenomenon in mammals (also known as agonal respirations), originating in the medulla of the central nervous system, and is the terminal breathing pattern that occurs after anoxia or ischemia[98]. In humans, gasping is prevalent during cardiac arrest and has been recognized in 30-40 % of witnessed episodes of cardiac arrest in adults[99]. Thus, when gasping occur, it is an important sign for bystanders to start resuscitation[99].

Arterial oxygen saturation (SaO_2) decreased directly after the trauma in all studies, a result well related to body protection and size of lung contusion. A contributing factor for the desaturation was probably increased "dead space ventilation", due to the lung contusion. Furthermore, bleeding inside airways resulted in flooding of non-injured parts of the lungs, which probably caused occlusion of the alveoli (shunt). Such ventilation-perfusion changes have recently been reported in another experimental pulmonary contusion model[42]. In our studies, hemoptysis was only observed in exposed animals in study II (n=10/18) and IV (n=29/29). In the ventilated studies (I and II), the lowest SaO_2 was observed after 30 minutes, measuring 91% and 60%, respectively. For animals in study III and IV, SaO_2 was most depressed after 1 minute, measuring 83% (non-vagotomized animals in study III) and 35% (study IV). SaO_2 was improving over time in surviving animals in all four experiments. An explanation might be that in the later phase ventilation/perfusion (V/Q) developed a better matching. In contrast, Mosely et al. 1970 observed decreasing partial pressure of oxygen in arterial blood (PaO_2) until 2 hours after the lung contusion[19], possibly because the animals were ventilated by 100% oxygen which can create further atelectasis and increase the shunt[100]. However, during routine induction of general anesthesia, 80% oxygen content caused minimal increase of atelectasis[100].

It should be mentioned that the animals that died in study II and IV demonstrated more severe arterail oxygenation desaturation than surviving animals, an observation indicating that low SaO_2 is an important cause of death in our studies.
PaO_2 and mixed venous oxygen saturation (SvO_2) showed similar pattern as SaO_2 in

all four studies, although data for these parameters is shown only in study I (SvO_2) and IV (PaO_2). In study IV there was a marked decrease of PaO_2 after the trauma in all three exposed groups. Between 30 and 120 min post impact, HSD-treated animals displayed significantly better recovery of PaO_2, compared to the shot control group, and a tendency ($p = 0.09$) toward better recovery compared to the RA group.

Although the evidence are not clear-cut, study IV indicate that it is possible that edema formation contribute to the desaturation after BABT. Our study showed that the group treated with RA significantly increased the relative water content of the injured lung, when compared to the HSD, shot control and unshot control group. This difference between the RA and HSD groups is an important finding in study IV, since it shows that fluid resuscitation with RA might increase edema after a pulmonary contusion, compared to treatment with HSD. Previous studies show conflicting data regarding the effectiveness of HSD in preventing lung edema[92, 101]. It should also be mentioned that there were no significant differences between the groups, in the amount of lung water in the corresponding left unharmed lung, indicating that the fluids did not induce edema in non-injured tissue.

Oxygen delivery (DO_2) and oxygen extraction (O_2ER) were reported in study I. These parameters are influenced by changes in SaO_2 and CO. The SaO_2 and CO was deteriorated due to the trauma, leading to a marked drop in DO_2 early after impact in study I. An increased O_2ER compensated for the reduced DO_2, but this compensation did not seem to be sufficient, since the blood lactate level increased, as a sign of peripheral anaerobic metabolism.

Hemodynamics

Mean arterial pressure (MAP) decreased immediately after the trauma in all four studies. In study II and IV, MAP declined about 50% during the first minute. With full protection (study I and III), the decrease of MAP was only about 25%. At 5 min post impact, exposed animals in study II-IV had almost recovered to baseline level, followed by a subsequent decrease. Animals in study I differed from the other animals, since MAP was stable after the 5 minute period.

MPAP increased directly after the hit in all four studies. In study IV (worst injury),

it increased from 22 to 32 mmHg, in exposed groups. After 15-30 minutes MPAP had decreased back to baseline level in all studies. The rationale for the decrease is probably redistribution of lung circulation, i.e increased blood flow in parts of the lung not affected by the trauma. Furthermore, connections between lung arteries and lung veins (von Hayeks vessels), has been suggested to open if MPAP is markedly elevated [102].

Cardiac output (CO) was also affected in all four studies, decreasing in study II from approximately 5.5 to 3.5 L/min after 1 minute. In this study, CO did not recover to baseline for the rest of the experiment. In study II and IV, systemic vascular resistance (SVR) showed a similar pattern as MAP, with an initial drop (approximately from 2000 to 1500 mmHg/L/min), recovery, and a subsequent slow decrease (data not shown).

In study IV, we observed a striking tackycardia, from approximately 90 to 150 beats/minute, 10 minutes after the hit. The tackycardia was maintained for the rest of the experiment in the shot control group, but there was a significant decrease of HR in groups receiving fluids. We monitored heart frequency directly (0-1 min) after the trauma only in study III. This was done using the ECG-recordings, since we considered it necessary to compare our data to other studies showing decreased heart rate early after trauma[19, 20]. We observed a slight decrease the first half minute, although only in the non-vagotomized group in study III.

In our studies we have undoubtly shown that the circulation has been affected by the trauma. One explanation might be pulmonary vascular occlusion, due to the lung contusion, leading to derange of lung circulation. This hypothesis is supported by the increased MPAP directly after impact, as well as the decrease in MAP and CO. These changes has also been shown after blast trauma against the right thorax[103]. Furthermore, our manual examination of lung tissue showed coagulation and occlusion of the lung circulation, as well as disrupted vessels in the area of the pulmonary contusion.

Another possible explanation to the fast circulatory failure is a neurological reflex after the trauma, inducing bradycardia and rapid relaxing of the vascular tonus. It has been previously suggested that the vagus nerve is involved in the hypotension after blast trauma[22, 24, 104]. An early study by Clemedson et al. showed that hypotension after blast trauma could be prevented by a combination of bilateral vagotomy and blocking of the carotid sinus region, with local anesthesia[105]. Furthermore, Daly

and Kirkman showed that stimulation of C-fibers results in a symphatho-inhibition, leading to decreased peripheral vascular resistance and hypotension[106]. In our studies, we noted a fast decrease of MAP, and a slight, but significant, decrease in heart rate during the first minute in study III. In this study, the vagotomy prevented animals from decreased heart rate, but had no effect on MAP or MPAP.

A third theoretical contribution to the circulatory effects is release of inflammatory mediators after trauma. Cell destruction after a lung contusion can induce an outflow of stored mediators, for example endothelin-1. This is a potent vasoconstrictive and pro-inflammatory peptide, which is produced in the vascular endothelium. The plasma half-life of endothelin-1 is only approximately 2 min *in vivo,* but the effects persist up to 60 min after administration in humans[107]. It has been demonstrated that the production of endothelin-1 is increased after trauma[108] and sepsis[90]. In study IV, we found a rapid and short-lived increase of endothelin-1 in two out of three groups 7 min after impact. Hypothetically, the short half-life of endothelin *in vivo* suggests that these levels could have been even higher earlier after impact. In agreement with this finding, a previous study of experimental cardiac ischemia showed that the highest levels of endothelin could be measured already after 2 min[109]. Albeit the short elevation in plasma, the effects of endothelin may have persisted for a longer time-period, thus contributing to the pulmonary hypertension.

A fourth contributing mechanism to increased MPAP can be hypoxic pulmonary vasoconstriction (HPV)[110, 111].

In study II-IV we also noted a subsequent, slower decrease of MAP and CO, following the first recovery. Hypothetically, the decrease in this second phase could be an effect of ATP-deficiency, caused by low oxygen in the blood. Deficiency in ATP causes decreased constrictive effect in vessels and reduced contractile ability of heart muscles, leading to lower CO and MAP. Furthermore, severe hypoxia increase the adenosine in blood and can stimulate the adenosine-receptors A_{2A} and A_{2B} in extreme conditions, leading to vasodilatation[112]. These theories is supported by study I, where SaO_2 was only modestly affected, with no subsequent decrease of MAP.

In contrast to other studies[19, 34, 92], fluid treatment in study IV had no effect on MAP, CO or survival rate in our shock model. The explanation is probably that our lung contusion was more severe, inducing more severe hypoxia that caused failure of circulation in the delayed, second phase. Supported ventilation with extra oxygen would most likely have led to a positive effect on circulatory parameters.

Cerebral effects

EEG

Electroencephalogram (EEG) was recorded before and after impact in study I-III. To our knowledge was study I the first scientific article that demonstrates EEG-changes after chest BABT. An immediate slowing of the EEG-activity has been previously described in pigs following blast wave exposure caused by detonation of explosives[33], and after high energy missile trauma in the hind limb of pigs[32].

In all our three studies the EEG became affected as early as 15-30 seconds after impact. These changes from the baseline pattern, indicates that the trauma almost instantly induced a global cerebral dysfunction. The changes were in most cases temporary, but some of the most affected animals never recovered from the isoelectric pattern. Other showed a depressed EEG-activity that gradually demonstrated a further decrease down to iso-electric pattern.

When comparing EEG-changes in study I, against study III (equal protection), the non-vagotomized group in study III was more affected by the trauma (table 4). The methodological differences between study I and III were that in study I the respiration was controlled by a ventilator, and in study III the animals were breathing spontaneously. Therefore, non-vagotomized animals in study III suffered from apnea, resulting in lower oxygenation of the blood, and consequently generating a slightly negative influence on EEG, compared to study I. In contrast, the bilaterally vagotomized group in study III was protected from apnea. These vagotomized animals showed slightly reduced EEG-changes after trauma compared to the other two groups (table 4).

One likely reason for the reduced EEG-changes in vagotomized animals might be that this group were protected from apnea. Another, or contributing, possibility is that the EEG-changes are mediated through the vagus nerve. Support for this hypothesis is the fact that vagal afferent nerve fibres is linked to several different parts of the brain[28, 113, 114] and can therefore affect EEG. Balzamo et. al showed that electrical and chemical stimulation of afferent vagal C-fibres in cats causes an immediate depression of the background EEG-rhythms, unrelated to changes in cardiovascular parameters[113, 114]. Bilateral vagotomy markedly reduced these EEG-changes, despite a persistence of cardiovascular effects, indicating that vagal afferent signals might directly affect the EEG-rhythm.

That the EEG-changes in our study is caused solely by direct influence from a shock wave transmitted from the area of impact to the brain, either through the blood ves-

Table 4. Comparing the EEG-results at 1 minute post insult, between the groups in study I-III.

Study and impression	EEG-level	Subjects
I (28 mm)	0	2
	1	3
	2	2
II (40 mm)	1	3
	2	1
	3	1
	5	5
II (34 mm)	1	3
	2	2
	3	1
	4	1
	5	1
III, vagotomized (28 mm)	0	1
	1	4
III, non-vagotomized (28 mm)	1	8
	3	1
	4	2

sels[115] or via soft tissues[116], is unlikely because the EEG-changes would then have been similar irrespectively of vagotomy or not.

In most animals in study I and III there were gradual returns to baseline EEG-pattern within two minutes (study I) and five minutes (study III). These animals remained at baseline (level 0), during the rest of the observation period. The only exception was one non-vagotomized animal in study III, which had apnea and never started to breath (died after 9 minutes).

In study II, with less protection, the changes in EEG were considerably more pronounced and with longer duration, compared to study I and III. Five of 18 animals in study II dropped directly to EEG-level 5 (iso-electric pattern).
Four of these returned to level 1-2 in 5 minutes but one stayed at level 5 and died 13 minutes after the trauma. Three of the animals that had recovered demonstrated a subsequent depression of EEG and died between 15 and 45 minutes. There were

also two other animals that showed only minor changes initially, but demonstrated a slow subsequent decrease down to iso-electric pattern (died at 62 and 103 minutes respectively). The first change in EEG was seen as early as 15 seconds after trauma. After only 15 seconds the blood was not desaturated, so it seems likely that the main cause of EEG changes in study II is the fast drop of MAP or/and a direct nerve reflex to CNS.

As previously mentioned, we also observed a subsequent depression of EEG in study II, after the first recovery. This change in EEG was seen in both deceased and surviving animals, but more frequently among the deceased animals. During this phase of the experimental course, blood pressure and desaturation decreased slowly. Serious hypotension or hypoxia did not affect EEG separetely, but a combination of the two parameters seems to induce EEG-depression.

There were no EEG-changes in two of the exposed pigs in study I and one in study III. Although our experimental protocol is standardized, small differences in body weight or where the impact was on the torso must be taken into account. Biological variation in sensitivity to trauma might also cause some deviation in our results.

In conclusion, our results indicate that an early effect on EEG is probably from vagal influence on CNS and/or the fast hypotension. It seems likely that these changes can be aggravated by hypoxia. The results from study III support that hypothesis, since vagotomy provided some protection from the depression of EEG, either as a direct effect on CNS or indirectly by preventing apnea. The delayed effect on EEG in the second phase is probably due to influence of serious hypotension and hypoxia, especially in combination of these.

The EEG-pattern is registered from the brain cortex, but since the cortical activity is dependent on input from subcortical brain structures, the observed changes could reflect a direct effect on vital centers in the brainstem, such as the centre for wakefulness. The fact that the EEG-changes were general could be an indication that the signals were elicited from deep brain structures, and consequently not being signs of local processes from more superficial structures of the hemispheres.

Our opinion is that a human suffering from the observed EEG changes would be incapacitated for a number of minutes, due to the cerebral effects only. The initial

incapacitation can be lethal, if this person lose the ability to return fire or move to shelter. These results clearly demonstrate the importance of studying a possible influence on the cerebral function also in trauma not directed to the head.

In situations where the victims is conscious (but have apnea), there is no need for ventilatory support, because they will soon start to breathe spontaneously and there is no risk for sever hypoxia. However, EEG-changes of level 3-5 should probably result in unconsciousness and such a victim might have problems with obstructed airways if they begin to breathe before they are conscious. Our results in this thesis emphasize the importance of creating free airways if unconscious persons seems to have breathing difficulties. Furthermore, supported ventilation should be administrated to unconscious persons with apnea.

S-100

In study I we hypothesized that our observed negative effects on EEG might induce brain injury. A marker for brain injury is S-100, a protein mainly produced in the central nervous system by neurons and/or glial cells[117]. It has been suggested that S-100 can be measured in blood as a biomarker for traumatic brain damage and leakage of the blood-brain barrier[118, 119]. We sampled S-100 in study IV, where we had the most severe shock and hypoxia. About 50% of the animals died due to the trauma, but we detected no increase of S-100 in any of the animals. We therefore conclude that no leakage of the blood-brain barrier occurs in our experimental set-up, even though we observed severe EEG-changes.

Blood samples

Lactate

Blood lactate increased after impact and was reported in study I, II and IV. Lactate increases when the blood flow decreases in the microcirculation, leading to impaired oxygen delivery and the generation of lactic acid, via anaerobic glycolysis[120]. Serum lactate measurement is recommended as a test to estimate and monitor shock[75], but also as a prognostic parameter in septic shock[121].

Baseline values of blood lactate in our studies was approximately 1 mmol/L. Blood lactate increased in study I to 2 mmol/L at 120 min. Study II showed an increase to approximately 4 mmol/L, for both exposed groups, at 60 minutes. In

study IV blood lactate increased significantly in all exposed groups, compared to the unshot control group. The shot control group reached the level of 9 mmol/L at the end of the experiment, the HSD group 5.5 mmol/L and the RA group 4 mmol/L. It should be mentioned that these values in study IV are very high and reflect the low oxygenation and deteriorated circulation in that study. It was somewhat surprising that blood lactate was higher in the HSD group, compared to the RA group, since HSD has been shown to improve the microcirculation in other studies[78].

Potassium

Potassium levels in serum was reported in study II and IV. In study II, both exposed groups showed a transient increase of serum potassium after the trauma, with the peak value at 5 minutes (the 40 mm-group increased from 4.2 to 5.0 mmol/L). Study IV showed the same pattern, but the peak was much higher with the three exposed groups increasing from 4.1 mmol/L to 7.7 mmol/L. Several animals had serum potassium close to 9 mmol/L and the highest level was 11.4 mmol/L. We believe that massive cell destruction in lung tissue induced the elevated S-potassium 5 min after the hit. Several animals showed elevated T-waves, widened QRS-complexes and flattened P-waves, on the ECG-recordings, which is typical for hyperkalemia[122]. The high S-potassium levels observed in our studies should be considered life-threatening, since it may lead to lethal arrhythmias[123]. The most serious arrhythmias we noticed on ECG-recordings were ventricular fibrillation (VF) and asystoli. In study (IV) there were two animals with VF 3 minutes after the hit and one with asystole. These arrhythmias sustained approximately one minute and converted spontaneously to sinus rhythm, which is rare according to previous studies[124, 125]. Two other animals died before 10 minutes and were excluded from the study (one had VF and the other asystole). In study II, one animal died after 13 minutes, due to VF, with a serum potassium level of 8.6 mmol/L at 5 minutes, and 6.7 mmol/L at 10 minutes.

In study I and III (full protection), the pulmonary contusion were much less extensive than in study II and IV. Potassium in serum only increased from 3.9 mmol/L to 4.2 mmol/L (study I) and from 4.1 mmol/L to 4.3 mmol/L in study III. The results indicate that serum potassium is related to the size of pulmonary injury.

Our observation of massive hyperkalemia shortly after a lung contusion seems to be a new finding. It has been shown previously that some patients with crush injuries, as well as other injuries, have developed hyperkalemia[126], but not to the level we observed in study IV. The short-lived peak observed in our studies have never been documented in authentic trauma cases, which is not surprising, since it is usually

not possible to collect blood samples immediately after an accident. Human victims who sustain high-energy blunt chest trauma (traffic accidents or fall from heights) would probably get similar levels of hyperkalemia in the blood, and this might hypothetically be the explanation to some unclear deaths in human trauma victims. These findings tell us that it might be beneficial to perform cardio-pulmonary resuscitation (CPR) early after isolated blunt chest trauma, if there is no pulse. This may be efficient since the potassium decrease very fast, so the possibility exists that the arrhythmias spontaneously convert to sinus rhythm (as we observed in study IV), while CPR protects from hypoxic brain damage in the meantime.

Hemoglobin

In study IV we observed a marked increase of hemoglobin in all exposed groups, which was a surprising finding. As an example, hemoglobin increased in the RA group from 113 mg/L to 133 mg/L after 5 minutes, but was back at baseline level at 30 minutes. We also observed increased hematocrite which is in agreement with the results from hemoglobin.

Surprisingly, Hb did not increase in study II although the trauma was nearly the same. One difference was that the respiration in study II was controlled by a ventilator, compared to study IV where the animals were breathing spontaneously. After 5 minutes, PaO_2 was 6 kPa in the 40 mm-group in study II, and 4 kPa in study IV. MAP was approximately 55 mmHg in both studies. Our hypothesis is that the pigs have a compensatory mechanism to counteract hypoxia and fast circulatory failure by releasing red blood cells from the liver and/or spleen. The purpose of such a mechanism could be to increase oxygen transporting capacity in life-threatening situations. Later in the experimental course of both study II and IV, MAP and PaO_2 decreased slowly to similar levels, but no increase of Hb was observed. Therefore, our hypothesis is that the fast drop of MAP and PaO_2, early in the experimental course of study IV, is an important factor for the increase of Hb in that study.

It has previously been shown that stimulation of sympathetic nerves mobilizes blood from the liver[127]. Perhaps a fast and potent drop of MAP and PaO_2 stimulates the sympathetic activation to mobilize blood from the liver and/or the spleen. A pure reflex is not likely because the traumatic impact was powerful in both studies (II and IV), but Hb was only increased in study IV.

To our knowledge, a similar fast increase of blood hemoglobin after trauma has not been described previously. It has been shown that hemolysis occurs after blast trauma, particularly after fast shock waves[128]. However, it is unlikely that the early increase

of hemoglobin in our study is due to hemolysis of red blood cells, since we measured both intracellular and free hemoglobin. Another, or supplementary, explanation is that the trauma induces rapid leakage of fluid through the endothelium and therefore results in a higher concentration of red blood cells. It would be very interesting to prevent circulation from the liver/spleen to investigate if the red blood cells are recruited from these organs in our experimental model. Another interesting question for the future is if a sympathetic acting drug as epinephrine given intravenously can increase Hb.

Glucose

Only in study II and IV, we observed significantly increased levels of glucose in blood. Between 5 to 30 minutes after impact, all exposed groups in study IV and the 40 mm-group in study II had significantly higher blood glucose, compared to the unshot control group. Both the HSD and the RA groups in study IV had lower B-glucose, compared to the shot control group, and the reason might be dilution of B-glucose after resuscitation.

Circulatory shock and stress release catecholamines, glucocorticoid and glucagon which all contribute to release glucose from the liver. Moreover, it has been shown that catecholamines can induce insulin resistance, thus potentiating the concentration of glucose[129]. However, glucose can also be metabolized via biosynthesis pathways, leading to the synthesis of O-linked beta-N-acetyl-glucosamine (O-GlcNAc). It has been suggested that increased levels of O-GlcNAc improves cell survival after ischemia/perfusion injury, and improves cardiac function, organ perfusion and attenuates the inflammatory response in rodent models of trauma-hemorrhage[130].

Trauma patients submitted to the intensive care unit (ICU) often present hyperglycemia and hyperinsulinemia, suggesting overall insulin resistance and possibly impaired compensatory response of ß-cells[131]. Two large, prospective, randomized, controlled clinical studies of critically ill patients, have demonstrated that strict maintenance of normoglycemia with insulin infusion, for at least a few days, reduce morbidity and mortality[132, 133]. Although these studies indicated that persisting hyperglycemia exert negative effects on patient outcome, it is tempting to speculate that hyperglycemia generate a positive effect on morbidity and mortality in the short perspective, early after a life-threating trauma.

Inflammatory response

When planning study IV, we hypothesized that we could detect an inflammatory

response after the lung contusion. Furthermore, the HSD-solution has been shown to cause anti-inflammatory effects[84, 86, 134], so our aim was also to investigate if we could observe such an effect in our resuscitation study. Blood was taken after two hours and analyzed for cytokines, and lung tissue was dissected post mortem to investigate recruitment of neutrophils. TNF-α was significantly increased in the shot control group, compared to the unshot control group. The RA and HSD groups displayed also increased TNF-α, although not significantly, compared to unshot controls. This indicates that the chest trauma in our model induced an inflammatory response, that could be detected in the systemic circulation. We can only speculate if the lower cytokine level in groups receiving fluid was an effect of dilution or if fluid treatment down-regulate the inflammatory response after BABT. Resuscitation with lactated Ringer's solution after hemorrhagic shock has been shown to induce an upregulation of various neutrophil and endothelial adhesion molecules[135]. However, in contrast to some previous publications[136], we can conclude that fluid treatment did not induce an augmented systemic inflammatory response in the systemic circulation, when measured 2 hours after impact.

IL-6 was not increased in any of the groups and no neutrophil accumulation was observed in the lungs. Most likely is a 2 hours surveillance period too short to discover any rise in IL-6 or neutrophil accumulation. This assumption is supported by a previous experiment in rats, studying isolated bilateral lung contusion. After 12 hours they did not observe any increased IL-6 in BAL, but noted a significant elevation after 24 hours[137]. In a similar experiment, Raghavendran et al. found significantly increased number of leukocytes in BAL after 24 hours[138].

It is well known that severely injured trauma patients have activated neutrophils[135]. TNF-α is a key mediator in the early inflammatory response, suggesting that activation of neutrophiles were induced at least in the shot control group in study IV. It is also likely that a similar response was induced in the other studies, especially in study II (with similar protection as study IV).

Microscopic examination of lung tissue showed no significant differences between the exposed groups regarding the degree of congestion, edema or atelectasis in the specimens from right lungs. In the kidneys, no fibrin deposition could be demonstrated, and there were no signs of tubular obstruction or necrosis. Biopsies from the left heart ventricle demonstrated microscopically scarce, focal contraction band necrosis, but no reactive inflammatory changes. With this staining we could not

find any evidence, why some heart had dense contracted tissue in study II and IV. We probably need other staining methods to investigate this interesting phenomenon, and this could hopefully be done in future studies.

Conclusions

This thesis is based on a model of behind armor blunt trauma (BABT), that was originally developed by the NATO Task Group on BABT. Our group was the first to set up this model of lung contusion in Sweden. Besides the parameters measured by the NATO task group, we have further developed the model and included EEG, insertment of an optical pulmonary thermo dilution catheter to measure central venous pressure (CVP), mean pulmonary artery pressure (MPAP), cardiac output (CO) and mixed venous saturation (SvO_2). Moreover, sampling of blood to analyze endothelin-1, TNF- α, IL- 6 and S-100 have not been done before, when studying BABT. We have also performed bilateral cervical vagotomy in pigs exposed to BABT, and explored the physiological response (study III). In study IV, we have used our model to investigate effects of fluid resuscitation after a pulmonary contusion, accompanied by shock. Other findings in this thesis include some previously unknown physiological responses after BABT, which has given us better understanding of body reactions after severe injuries.

In all studies included in this thesis, the pulmonary contusion has been the central injury. Our opinion is that the observed injuries and physiological responses after the trauma are accurately related to level of protection in study I-IV. Our physiological results, especially when monitoring severe BABT, showed apnea for several minutes with serious desaturation, immediate hypotension, decreased CO, increased MPAP and depressed EEG-activity. The circulatory system did some recovery after trauma, but showed a subsequent decrease, probably due to the lack of oxygen.

Early after the lung contusion, the damage of cells caused a short peak of hyperkalemia, causing in some cases lethal arrhythmias. This short-lived peak of potassium, following cell damage, seems to be a new finding and has to our knowledge never been documented before.

Animals that suffered from severe hypoxia for a longer period and then died, demonstrated dense contracted cardiac tissue during autopsy. This is a surprising finding that should be investigated in further studies.

Blood hemoglobin showed an early peak after 5 min, hypothetically as a defense mechanism in a life-threatening situation. To our knowledge this is also a new finding.

This thesis has also been the first to document EEG-changes after BABT. EEG has been graded from 0 (normal EEG) to 5 (isoelectric EEG). We can conclude that even with "full protection", spontaneously breathing pigs showed EEG-pattern that was depressed to level 4 in some animals. Our data indicate that the trauma almost instantly elicited a global cerebral dysfunction. This is probably caused by a fast decrease of blood pressure and/or a nerve reflex. Desaturation is likely contributing to the depressed EEG, especially in combination with low MAP late in the experimental course. It should be mentioned that it is complex to transfer the results from anaesthesised pigs directly to awake human subjects. However, it seems that a human suffering from the observed EEG-changes would be incapacitated for at least a number of minutes.

From study I, combined with study II, we have documented an effect on pathophysiology and mortality in conformity with the level of body armor protection. In these studies the impression in clay, placed behind the different body armors, were 28 mm (study I), 34 mm and 40 mm (study II). The mortality was 0% (28 mm), 25% (34 mm) and 50% (40 mm). Our data is clearly demonstrating that the safety criterion of 44 mm impression for body armor is insufficient when they are exposed to high velocity projectiles.

The bilateral vagotomy in study III prevented apnea, and induced a slight, positive effect on the EEG-depression. We can conclude that the apnea after BABT is a vagally mediated reflex.

None of the fluids given in study IV had any significant effect on MAP or CO in this type of shock. The HSD-group displayed significantly improved PaO_2 compared to the shot control group, and a tendency compared to the RA-group. Moreover, the group treated with RA significantly increased the lung wet/dry weight in the injured lung, when compared to the other groups. We also observed lower TNF-a release and decreased HR in animals receiving fluid. However, given the fact that we did not observe striking effects, it seems like fluid resuscitation has limited therapeutic effects for treatment of BABT.

Who dares wins!

SAS - Special forces

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