The Prediction and Prevention of Postinjury Multiple Organ Failure

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PhD Thesis

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Scientific publications related to the thesis:

I. **Balogh Z**, Tomka J, Varga E, Simonka J.A.
Advanced Trauma Life Support (ATLS): koncepció és ideológia.
Magyar Traumatol. Ortop. Kézseb. Plasztikai Seb. 1999;42:338-344.

II. **Balogh Z,** Offner PJ, Moore EE, Biffl WL.
The NISS Predicts Postinjury Multiple Organ Failure Better Than the ISS.
J Trauma. 2000;48:624-627; discussion 627-628.

III. **Balogh Z**, Wolfárd A, Szalay L, Simonka JA, Boros M.
Sodium Dalteparin treatment during resuscitation inhibits hemorrhagic shock-induced leukocyte rolling and adhesion in the mesenteric microcirculation
J Trauma. 2002;52:1062-1070.

IV. **Balogh Z**, Varga E, Süveges G, Tomka J. Tóth L, Simonka JA.
The New Injury Severity Score is a Better Predictor of Extended Hospitalization and ICU Admission than the ISS in Patients with Multiple Orthopedic Injuries.
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List of abbreviations:

AIS	Abbreviated Injury Scale
AP	Anatomic Profile
ASCOT	A Severity Characterization of Trauma
H-L	Hosmer-Lemeshow statistics
HS	haemorrhagic shock
ICU	intensive care unit
I/R	ischaemia-reperfusion injury
ISS	Injury Severity Score
i.v.	intravenous
IVM	intravital video-microscopy
LOS	length of stay
LMWH	low molecular weight heparin
LR	lactated-Ringer's solution
MAP	mean arterial pressure
MOF	multiple organ failure
MOI	multiple orthopaedic injuries
NISS	New Injury Severity Score
PMN	polymorphonuclear neutrophil leukocyte
PRBC	packed red blood cells
ROC	receiver-operating characteristic
s.c.	subcutaneous
SEM	standard error of mean
SIRS	systemic inflammatory response syndrome
UFH	unfractionated heparin

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INTRODUCTION

Considering all age groups trauma is the third most frequent cause of death after cardiovascular and malignant diseases[1]. Even more significant is the fact that injury is the leading cause of mortality in people less than 40 years old with enormous socioeconomic consequences[1]. The postinjury mortality follows a trimodal distribution including prehospital mortality, early hospital mortality and late hospital mortality[2]. The first peak – prehospital mortality, responsible for 50% of all deaths – is caused by immediate deaths from high spinal cord injury, massive head injury, airway obstruction and exsanguinations from major vascular injury. This is the area where primary prevention such as education, vehicle and road safety and firearm control could make improvements. The second peak – early hospital mortality (0-48 hours), responsible for up to 30% of all deaths – is related to severe head injury and exsanguinations from uncontrollable bleeding and postinjury coagulopathy. To address these problems very efficient prehospital care with dedicated in-hospital trauma teams are required to work in a trauma system. The third peak – late postinjury deaths (usually 7-14 days), responsible for up to 20% of all deaths – is due to complications such as sepsis and postinjury multiple organ failure (MOF). In regions where highly developed trauma system exist with excellent prevention, education and prehospital care, the prehospital mortality is decreased, but more patients *in extremis* reach the hospital equalizing the magnitude of the first and second mortality peaks[3]. Despite the significant improvements in prehospital care, shock resuscitation and critical care, the incidence of posttraumatic MOF continues to be unchanged and the mortality remains high. This resulted a third peak with constant height in the postinjury trimodal death distribution during the last 30 years[4]. When MOF develops, no specific therapy can be instituted; the treatment modalities merely support the failing organs[5]. Extensive investigative efforts have advanced our understanding of the pathophysiology of MOF[6-13]. The initial overactivation and consequent depression of the immune system is recognized today as the overall mechanism of postinjury MOF[7] and polymorphonuclear neutrophil leukocytes (PMN) are identified as pivotal cellular elements of the postinjury inflammatory response[12-13]. Unfortunately, these advancement in understanding the pathophysiology are not translated into improved outcome[9]. The results of clinical trials of newer therapeutic modalities aimed at modulating the inflammatory response are disappointing[14–18]. This failure could be largely related to the complexity of the

inflammatory response;[6,10-11, 19-20] but the early identification of high-risk patients is problematic as well[7]. Thus, **1.** the identification of trauma patients at high-risk for the development of MOF, and **2.** to concentrate our preventive efforts on the early modulation of the key elements of the inflammatory response in high-risk individuals are promising approaches to this complex problem.

The purpose of this thesis is to discuss the improved technique of MOF prediction ("clinical core") and a new approach to modulate postinjury inflammatory response via the inhibition of PMN – endothelial cell interactions. ("basic science core")

CLINICAL CORE

1. The prediction of postinjury multiple organ failure

Background

Based on clinical observations and extensive basic science research, the current hypothesis is that a dysfunctional systemic inflammatory response syndrome (SIRS) is central to the pathogenesis of MOF[21]. After the initially recommended uncontrolled infection concept[22,23] it became obvious that postinjury MOF can occur without infections and infections are rather symptoms than cause of MOF[24,25]. However, the results of large clinical trials aimed at modulating the early SIRS and ultimately decreasing the incidence of MOF are not encouraging[14–18]. This is partly due to the inability to identify the population at risk at an early stage when intervention could be effective. The Denver group of trauma surgeons and researchers showed that postinjury MOF can be predicted as early as 12 hours after admission with 63% sensitivity and 84% specificity[26]. They identified age, shock severity (transfusion requirement, metabolic acidosis) and tissue injury as independent predictors for MOF[26-28]. Age can be exactly determined and is a surrogate of physiologic reserves and co-morbidities which were previously shown to have poor predicting power for postinjury MOF[27-29]. Parameters used for describing shock severity are either therapy-dependent, such as transfusion requirements, resuscitative fluid requirements and the need for inotropes or have limited discriminative power such as traditional measurements like blood pressure and heart rate[30]. Measures of tissue injury, in particular the Injury Severity Score (ISS), have consistently emerged as robust predictors of postinjury MOF[26-28, 31-32]. However, the ISS has been plagued by several inadequacies[33]. In particular, it fails to account for multiple injuries to the same body region, limiting its usefulness in penetrating trauma[34]. The ISS is defined as the sum of the squares of the single highest injury score in each of the three most severely injured body regions. As such, the ISS fails to consider the second most severe injury from the already coded region in favor of less severe injuries that occur in other body regions. The unnatural division of the human body into regions complicates calculations and diminishes the predictive power. Novel measures like the Anatomic Profile (AP)[35,36] and a Severity Characterization of Trauma (ASCOT)[37] were introduced to address these shortcomings; however, they offered only modest gains in predicting trauma mortality[38,39]. Moreover, their computational complexity further hindered general acceptance as an alternative to the ISS.

Recently, Osler *et al.* reported a new ISS (NISS) based on the three most severe injuries, regardless of body region[40]. This simple modification of the ISS was demonstrated to improve mortality prediction, especially after penetrating trauma. We hypothesized that the NISS is also a superior predictor of postinjury MOF compared with the ISS.

MATERIALS AND METHODS

Since 1992, Denver Health Medical Center, a regional Level I trauma center, has prospectively collected data on injured patients at risk for developing MOF. The goal of this prospective computerized database was to characterize the epidemiology of and identify risk factors for postinjury MOF. Inclusion criteria for the MOF database include age greater than 15 years, ISS greater than 15 and survival for more than 48 hours. The present study included all patients entered into the database over the 5-year period ending November of 1998. The ISS was calculated in the standard manner as the sum squares of the highest Abbreviated Injury Scale (AIS) score in the three most severely injured body regions[41]. The NISS was computed as the sum of the squares of the three highest AIS scores regardless of body region[40]. Both the ISS and the NISS were based on AIS-90 scores[42]. **Table 1** shows an example of a multiply-injured patient's scores; the NISS computation uses the three most severe injuries regardless of the body region.

Table 1. Clinical example of a multiple injured patient.

AIS region	Injuries	AIS	ISS	NISS
Head	Concussion	2	2^2	
Face	Lip laceration	1		
Chest	Two fractured ribs	2	2^2	
Abdomen	No injury	0		
Extremities	Type C pelvic fracture	4	4^2	4^2
	Femoral shaft fracture	3		3^2
	IIIB open tibia/fibula fracture	3		3^2
External	Multiple abrasions	1		
Total			24	34

MOF was defined by using the Denver MOF score[21]. In brief, four organ systems (pulmonary, hepatic, renal, and cardiac) are evaluated daily throughout a patient's intensive care unit stay and organ dysfunction is graded on a scale from 0 to 3 (0= no dysfunction and 3= severe dysfunction). MOF is defined as the sum of simultaneously obtained individual organ dysfunction grades greater than or equal to 4. MOF is not determined before 48 hours,

because indices of organ dysfunction may represent incomplete or ongoing resuscitation. The MOF database is maintained on an IBM-compatible computer by using Microsoft Access 97 (Microsoft Corp., Redmond, Wash). Statistical analysis was performed by using SPSS for Windows, Version 8.0 (SPSS, Inc., Chicago, Ill) and Arcus Quickstat Biomedical for Windows, Version 1.0 (Research Solutions, Cambridge, UK). Where appropriate, univariate analysis was performed by using Student's t test for continuous data and χ^2 square for categorical data. The predictive performance of the NISS was compared with that of ISS by substituting it into a multiple logistic regression model containing the ISS as well as other risk factors for postinjury MOF. The change in predictive performance was assessed by using the Hosmer-Lemeshow (H-L) statistic and receiver operating characteristic (ROC) curve analysis[43-45]. The ROC statistic is a standard measure used in trauma outcome research of the power of a test to separate two mutually exclusive populations. The value of the ROC means the area under the graph of sensitivity × 1 - specificity. A ROC value of 1 corresponds to a test that perfectly separates two subpopulations, whereas the value of 0.5 describes a completely inadequate test. The H-L statistic is used to determine how well calibrated a model is. The lower the value of the H-L statistic result, the better the model calibrated.

RESULTS

During the 60-month study period, 558 patients admitted to the Denver Health Medical Center's shock/trauma ICU who met inclusion criteria and were entered into the MOF database. The mean age was 36 years, and the injury was blunt in 74% **(Table 2)**.

Table 2. Patient demographic stratified by MOF status.

Parameter	All (n = 558)	MOF (n = 101)	No NOF (n = 457)	*p* Value
Age (yr)	36 ± 0.7	39.9 ± 1.9	35.5 ± 0.7	0.018[b]
Mechanism (% blunt)	74	74	73	0.923[c]
ISS	27 ± 0.4	33 ± 1.4	26 ± 0.4	<0.0001[b]
NISS	33 ± 0.5	43 ± 1.4	32 ± 0.6	<0.0001[b]
Transfusion (pRBC units/first 12 hours)	5.3 ± 0.4	12.6 ± 1.5	3.9 ± 0.4	<0.0001[b]
MOF (%)	18			
Mortality (%)	9	35	2	<0.0001[c]

[a] Continuous data shown as mean ± SEM. pRBC, packed red blood cell.
[b] *t* test MOF vs. no MOF.
[c] χ^2 test MOF vs. no MOF.

These patients were severely injured, as reflected by the mean ISS of 27 and average transfusion requirement of 5.3 units of packed red blood cells in the first 12 hours after injury. The mortality rate was 9%. A total of 101 patients (18%) developed MOF. Patients who developed MOF were older, more severely injured, and required greater transfusions compared with those who did not develop MOF. The mortality rate was significantly greater in patients who developed MOF (35% vs. 2%). The NISS and ISS scores were identical in 271 patients (48.6%), and the NISS exceeded the ISS in 287 patients (51.4%). The subgroup of patients with discrepant scores differed significantly from patients with identical scores **(Table 3)**.

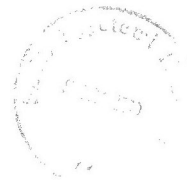


Table 3. Characteristics of patients with and without NISS/ISS scores

Parameter	NISS = ISS (n = 271)	NISS > ISS (n = 287)	*p* Value
Age (yr)	37 ± 1	36 ± 0.9	0.34[b]
Mechanism (% blunt)	80	67	0.001[c]
Transfusion (pRBC units/first 12 hours)	3.7 ± 0.5	6.8 ± 0.6	<0.0001[b]
MOF (%)	8.7	22.3	<0.0001[c]
Mortality (%)	4.9	13.2	0.001[c]

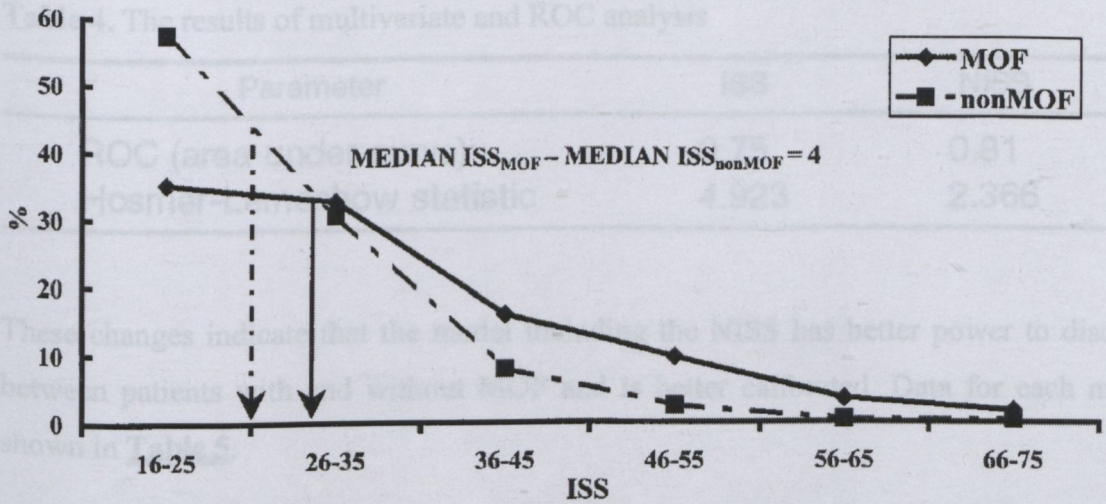
[a] Continuous data shown as mean ± SEM. pRBC, packed red blood cell.

[b] *t* test NISS = ISS vs. NISS > ISS.

[c] χ^2 test NISS = ISS vs. NISS > ISS.

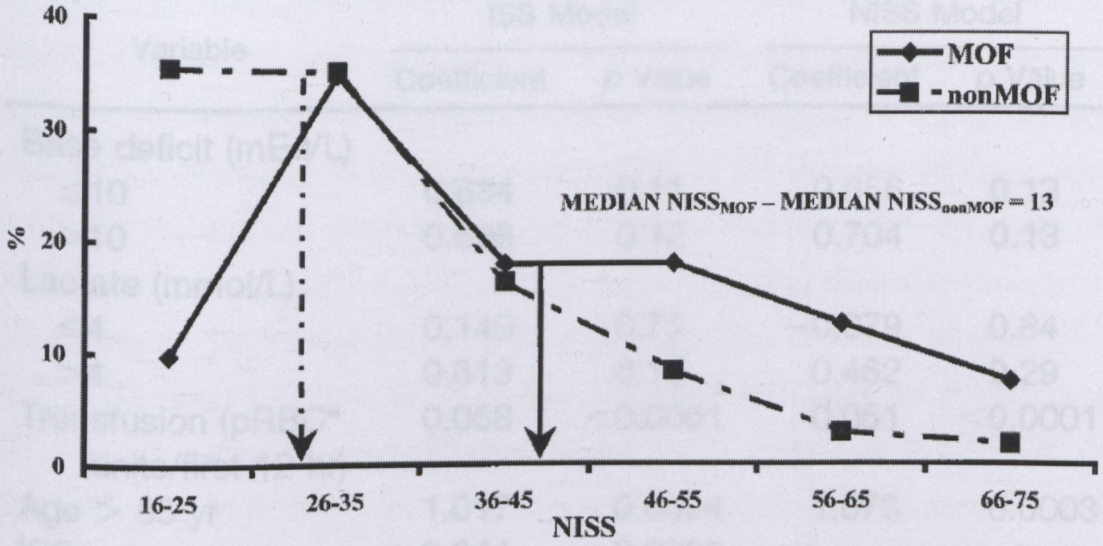
Patients with discrepant scores were more likely to have suffered penetrating injuries and had a greater early transfusion requirement. Moreover, this group of patients had over 2.5-fold increase in both MOF and mortality. Graphic examination of the data demonstrates that the NISS discriminates between patients who did and did not develop MOF **(Figs. 1 and 2)**.

Figure 1. Frequency distribution of ISS for patients with and without MOF.



Arrows indicate median values. He difference in median ISS scores for patients with and without MOF is 4 (29 - 25 = 4)

Figure 2. Frequency distribution of NISS for patients with and without MOF.



Arrows indicate median values. He difference in median NISS scores for patients with and without MOF is 13 (42 - 29 =13)

The difference in median NISS values between patients with and without MOF was 13, whereas the same difference in median ISS was only 4. When the NISS was substituted for the ISS in a multivariate predictive model for MOF, the area under the ROC curve increased and the H-L statistic decreased, respectively **(Table 4)**.

Table 4. The results of multivariate and ROC analysis

Parameter	ISS	NISS
ROC (area under curve)	0.75	0.81
Hosmer-Lemeshow statistic	4.923	2.366

These changes indicate that the model including the NISS has better power to discriminate between patients with and without MOF and is better calibrated. Data for each model are shown in **Table 5**.

Table 5. Full multiple logistic regression models for predicting postinjury MOF using ISS and NISS.

Variable	ISS Model		NISS Model	
	Coefficient	*p* Value	Coefficient	*p* Value
Base deficit (mEq/L)				
≤10	0.684	0.11	0.656	0.13
>10	0.696	0.12	0.704	0.13
Lactate (mmol/L)				
≤4	0.140	0.71	−0.079	0.84
>4	0.613	0.15	0.462	0.29
Transfusion (pRBC[a] units/first 12 hr)	0.058	<0.0001	0.051	<0.0001
Age > 55 yr	1.017	0.0004	1.073	0.0003
ISS	0.044	0.0001	—	—
NISS	—	—	0.055	<0.0001

[a] pRBC, packed red blood cells.

DISCUSSION

The ISS has remained the standard anatomic measure of injury severity since its introduction over three decades ago[41]. Perhaps the most notable limitation of the ISS is that it excludes multiple injuries of a single body region by allowing only the most severe injury in each body region to be considered[34,35]. Moreover, when multiple body regions are injured, the ISS will ignore more severe injuries in one body region in favor of less severe injuries of another body region[34]. The AP was developed to address these limitations[35,36]. However, the AP is complicated and difficult to calculate[36]. In addition, it was shown to be only marginally superior to the ISS when combined with physiologic data to predict survival[37-39]. Although the ISS has been used classically to predict mortality from trauma, we and others have noted it to be a consistently good indicator of risk for postinjury MOF[26-28,31]. In developing predictive models for MOF, the risk factors were categorized as being related to tissue injury severity, cellular shock severity, the magnitude of the systemic inflammatory response to the injury, and host factors (including age, sex, and co-morbidity)[7,27,28]. Tissue injury severity is a major component of the MOF predictive models; and we have considered it to be readily quantifiable by using the ISS. Recognizing the limitations of the ISS, the AP was subsequently investigated AP as an alternative measure of tissue injury severity. However, we observed that the AP offered no advantage over the ISS in predicting postinjury MOF[28]. Moreover, the AP is difficult to calculate with greater inter-rater variability compared with the ISS[28]. The NISS is a simple but significant modification of the ISS[30]. By considering the three most severe injuries regardless of body region, it avoids many of the previously acknowledged limitations of the ISS. By preserving the AIS as the framework for injury severity scoring, the NISS remains familiar and "user friendly." Preliminary studies suggest that the NISS is a more accurate predictor of trauma mortality than the ISS[40,46]. Osler *et al.* recommended that the NISS replace the ISS as the standard anatomic measure of injury severity[40]. This report extends these observations and demonstrates that the NISS is a superior predictor of postinjury MOF. The difference in median NISS scores between patients with and without MOF was greater than the difference in median ISS scores; thus, better separating these two groups of patients. Moreover, a multivariate predictive model incorporating other risk factors for postinjury MOF showed that substituting the NISS for the ISS in the model yielded better predictive performance. This improvement is reflected in an

increase in the area under the ROC curve and a decrease in H-L statistic. Over half of the patients had NISS scores exceeding their ISS scores. This subgroup of patients had an almost threefold higher incidence of MOF and mortality compared with the group in whom the ISS equaled the NISS. There were more male patients in the NISS>ISS group, most likely reflecting the greater frequency of penetrating injuries among men. Our observation that penetrating injuries were greater in the NISS>ISS group (33% vs. 20%) supports this assumption. Moreover, further examination of our MOF database showed penetrating injury in 32% of male patients compared with 11% of female patients. We conclude that the NISS is superior to the ISS in the prediction of postinjury MOF. Given its greater simplicity and ease of calculation, it should replace the ISS as the preferred measure of tissue injury severity. Moreover, it seems that the subgroup of patients whose NISS exceeds their ISS is at high risk for MOF and deserves closer study.

2. The predictive power of NISS applied for the entire trauma population - the Szeged experience

Background

The improved predictive power of the NISS over the ISS has been demonstrated in mortality and MOF prediction[40,46,47]. The ISS also underestimates multiple orthopedic injuries (MOI) in polytrauma scenarios and has been found to be a poor predictor of postinjury hospital length of stay (LOS)[33,48]. The NISS was never tested in the European trauma system where the dominant injury mechanism is blunt and all minor and low energy traumas are managed in the trauma departments. In Hungary the regionalized trauma system is under development. The other important feature of the Hungarian trauma care is that extended hospital length of stay (LOS) on trauma departments often occurs because of multiple orthopedic trauma. With the use of the traditional ISS (only the single highest injury is counted in a region) this problem is not recognized. Based on the German and the United States experience it is essential to designate trauma centers with adequate patient load to maintain the trauma care personnel's injury management skills[49,50]. The establishment of the trauma system is key contributor to the prevention of MOF. Firstly, it is supposed to decrease the time until hemorrhage control (shock is an independent predictor of MOF) and secondly, the high risk patients could get access to the specialized critical care environment. The accurate trauma center and intensive care unit (ICU) design mandates the estimation of the injury severity–matched length of hospitalization and the need for ICU beds of a given region's trauma population. Unfortunately this calculation can not be accurately performed on the basis of international figures where the injury mechanisms and hospital and ICU LOS days are not applicable because of the local social, economic and infrastructural characteristics. We aimed 1. to compare the scoring efficacy of the ISS and the NISS in predicting extended hospital LOS and ICU admission, and 2. to determine the effect of MOI on the discrepancies between the ISS and NISS (the previously described high risk NISS>ISS group) and their impact on extended LOS and ICU admission in the region of Szeged.

MATERIALS AND METHODS

A total of 3,100 consecutive patients over the two years period ending on December 31, 2000, admitted to the Department of Traumatology, University of Szeged, who met the inclusion criteria of age older than 14 years and survival greater than 24 hours were entered into the study. Data on gender, age, co-morbid conditions, all AIS scores for each of the six body regions, hospital LOS, and ICU admission were collected prospectively in the study registry, unaffected by the discharge coding and financial interest of the department. The ISS and the NISS were prospectively calculated. The ISS was calculated in the standard fashion as the sum of the squares of the highest AIS scores in the three most severely injured body regions[41]. The NISS was computed as the sum of the squares of the three highest AIS scores regardless of body region[40]. For the computation of both scores, the AIS-90 version was used[47]. When a patient's NISS was higher than the ISS, the responsible AIS region was noted (in the example in **Table 1**, the marked region is the extremity region). The computation of the scores was performed prospectively by three physicians of the department. Intra-rater and inter-rater reliability studies showed excellent reproducibility (>95% for ISS and >98% for NISS). Where appropriate, univariate analysis was performed using Student's *t* test for continuous data, and χ^2 square for categorical data. Data are depicted as percentages or mean ± standard error of mean (SEM). The ISS and NISS were compared as univariate predictors of extended hospital LOS and ICU admission. Multivariate analysis was used to determine if substitution of the NISS for the ISS resulted in a superior predictive model. The predictive performance of the NISS was compared with that of the ISS by substituting it into a multiple logistic regression model containing the ISS and other possible risk factors for postinjury extended LOS and ICU admission. The ISS model included age, gender, co-morbidity, and the ISS. The NISS model included the same, but the ISS was replaced by the NISS. The change in predictive performance was assessed using the H-L goodness-of-fit statistics and ROC)curve analysis[43-45]. The subgroup of patients with discrepant scores (NISS > ISS) was evaluated further to determine the potential input of MOI in patients with extended LOS and ICU admission. The prospective database was maintained on an IBM compatible computer using Microsoft Access 97 (Microsoft Corp, Redmond, WA). Statistical analysis was performed using SPSS for Windows, Version 8.0 (SPSS, Inc, Chicago, IL).

RESULTS

3,100 consecutive patients with the average ISS of 6 ± 0.13 (median 6, range 1–48) were included into this prospective study. There were 1,799 (58%) male patients; the average age of the population was 48 ± 0.5 years (range 15–94). Within the cohort, 42% had significant co-morbidity requiring medication during the hospitalization. Only patients, 230 (7.5%) had a higher NISS (mean 12.8 ± 0.8, median 13, range 2–54) than ISS (mean 7.1 ± 0.6, median 6, range 1–43); while 2,870 cases (92.5%) had equal NISS and ISS (mean 5.8 ± 0.1, median 6, range 1–48).

The incidence of MOI among patients with identical scores was only 0.8% (230 of 2,870 patients) compared with 70% (161 of 230) of patients with discrepant scores ($p < 0.0001$) (Fig. 1). The results of the univariate analysis comparing NISS = ISS and NISS > ISS groups **(Table 6)** showed a significantly longer hospital LOS (8 ± 0.2 versus 22 ± 1.6 days; $p < 0.001$ – and ICU LOS (0.1 ± 0.02 versus 3.4 ± 0.6 days; $p < 0.001$) and more frequent ICU admission (1.8% versus 34%; $P < 0.001$) in the group with discrepant scores.

Table 6. Univariate comparison of patients with equal (NISS = ISS) and discrepant (NISS > ISS) scores.

	Age	ISS	Comorbidity	Mortality	Hospital LOS	ICU admission	ICU LOS
NISS > ISS	48 ± 2	7.2 ± 0.6	41%	8%*	22 ± 1.6*	34%*	3.4 ± 0.6*
NISS = ISS	50 ± 1	5.8 ± 0.1	42%	1.2%	8 ± 0.2	1.8%	0.1 ± 0.02

*$P < 0.001$.

The NISS > ISS group had a significantly ($p< 0.001$) higher mortality (8%) than the NISS = ISS group (1.2%) despite their similar age, ISS, and co-morbidity. Data for the extended hospital LOS and ICU admission multivariate models for the entire cohort are shown in **Tables 7 and 8**.

Table 7. Multiple logistic regression analysis for predicting extended (≥ 10 days) hospital length of stay.

	ISS model		NISS model	
	Coefficient	*P* value	Coefficient	*P* value
Gender	–0.206	0.113	–0.232	0.0766
Age	0.025	<0.0001	0.026	<0.0001
Comorbidity	0.876	0.233	0.692	0.198
ISS	0.165	<0.0001	—	—
NISS	—	—	0.146	<0.0001

Table 8. Multiple logistic regression analysis for predicting intensive care unit admission.

	ISS model		NISS model	
	Coefficient	*P* value	Coefficient	*P* value
Gender	0.577	0.0742	0.492	0.141
Age	0.0017	0.807	0.0075	0.331
Comorbidity	0.267	0.764	0.414	0.627
ISS	0.317	<0.0001	—	—
NISS	—	—	0.275	<0.0001

Based on multiple logistic regression analysis, the independent predictors ($P < 0.0001$) of extended hospital LOS are age, ISS, and NISS; the independent predictors ($P < 0.0001$) for ICU admission are the anatomic injury measures, ISS, and NISS. The model that included NISS was found to be more predictive of longer (≥10 days) LOS (ROC: NISS = 0.794, ISS = 0.782; $P < 0.0001$) and ICU admission (ROC: NISS = 0.944, ISS = 0.918; $P < 0.0001$). The multivariate predictive model that included NISS showed a better goodness of fit (H-L for long LOS NISS = 11.58, ISS = 14.82; H-L for ICU admission NISS = 5.42, ISS = 6.32) compared with the same model that included ISS. In both multivariate predictive models when the NISS was substituted for the ISS, the areas under the ROC curves increased, and the H-L statistics decreased **(Table 9)**.

Table 9. Results of multivariate ROC analysis.

	Extended LOS prediction		ICU admission prediction	
	ISS	NISS	ISS	NISS
ROC (area under the curve)	0.772	0.788*	0.918	0.944*
Hosmer-Lemeshow statistic	14.82	11.58	6.32	5.42

*$P < 0.001$.

These changes indicate that the model including the NISS has a better power to discriminate between patients with extended and non-extended hospital LOS and between patients who were admitted and were not admitted to the ICU. We evaluated further the high-risk group of patients with NISS > ISS. Among patients with discrepant scores, 61% (140 patients) had MOI (extremities) responsible for the NISS > ISS. The other AIS body regions responsible for score discrepancies were abdomen, 15% (34 patients); head, 8% (18 patients); external, 6% (14 patients); chest, 5% (12 patients); and face, 5% (12 patients).

DISCUSSION

The ISS underestimates MOI in polytrauma scenarios and is found to be a poor predictor of postinjury LOS[44,51]. The unnatural division of the human body into regions complicates the calculation and diminishes the predictive power[40]. The Anatomic Profile (AP) and the combined anatomic and physiologic scores, such as TRISS and ASCOT (A Severity Characterization of Trauma) were introduced to address these shortcomings; however, they offered only modest gains in predicting trauma mortality[38]. Their computational complexity and poorer intra-rater and inter-rater reciprocity further hinder general acceptance as an alternative to the ISS[52]. These facts helped the ISS to survive for three decades as the most extensively used anatomic measure. Recently the NISS has been proved to be a better predictor of postinjury death and MOF. The ISS is unable to discriminate patients with multiple extremity trauma from the rest of the trauma population. Although this group can be the major cause of increased health care costs, it is still undiscovered by the traditional injury scoring[48,51,53]. Simultaneous calculation of the ISS and the NISS in the present study revealed that patients with discrepant scores (NISS > ISS) spent a longer time in the hospital and in the ICU and were admitted to the ICU more frequently. By definition, the NISS is always equal to or higher than the ISS; if the NISS is higher, it means that a significant injury or injuries are taken into account that would have been neglected by the ISS **(Table 1)**. Our results on mortality support the finding of other groups that the NISS > ISS group is more likely to have a poor outcome. The ISS and NISS were defined as independent predictors of extended hospital LOS and ICU admission. The multivariate predictive models that included the NISS outperformed models that included the ISS. The areas under the ROC curves are significantly higher in the NISS models than the ISS models. Both scores did better in predicting ICU admission than extended hospital LOS. The reason for this could be that ICU admission is more closely related to threat of life than extended hospital LOS. The ISS was not designed for the evaluation of resource utilization, but the NISS did better in this field. Many studies showed that the ISS underestimates the increased morbidity and resource utilization related to multiple extremity injuries[48,51,53]. The application of the NISS offers an answer to this problem. In most (61%) of the patients with NISS > ISS, the orthopedic injuries were responsible for the higher value of the new scoring system. The high-risk group causing extra hospital charges (two thirds of the NISS > ISS group spent >10 days in the hospital, and 37%

of the patients were admitted to the ICU) is recognized by the use of the NISS but hidden for an ISS-based database. Similar to previous comparisons of ISS and NISS for predicting postinjury death and MOF, our results indicate that the NISS is a superior predictor for extended posttraumatic hospitalization and the need for ICU admission.

In summary it can be concluded that:

1. The NISS is a better predictor of the postinjury extended hospital LOS and ICU admission than the ISS.
2. Trauma patients with discrepant (NISS > ISS) scores are admitted to the ICU more frequently and have longer hospital and ICU LOS with increased mortality rate.
3. Because in most patients the discrepancy between ISS and NISS is due to MOI, orthopaedic trauma has a major effect on trauma outcomes such as hospital and ICU LOS, ICU admission, and mortality rate.
4. Since the NISS disregards the anatomic regions, calculations are easier and give extra accuracy to the new anatomic measure.

Most importantly, our study adds a further reason to consider the replacement of the traditional ISS by the NISS in trauma outcome research.

BASIC SCIENCE CORE: Modulation of the postinjury immune response for the prevention of multiple organ failure

Background

The combination of posttraumatic/hemorrhagic shock (HS) and subsequent resuscitation is associated with ischemia-reperfusion (I/R) injury in the systemic circulation. I/R-induced PMN adhesion and extravasation are strongly associated with posttraumatic complications, including systemic inflammatory response syndrome, multiple organ dysfunction syndrome, and MOF[7,13]. For the initiation of leukocyte migration and activation, interaction with the endothelial layer is necessary[54]. The first phase of PMN adhesion is mainly dependent on selectins[55]. These adhesion molecules share a common primary structure with an N-terminal lectin domain that interacts with various glycoconjugated ligands, including heparan sulfate and heparin[56], and this raises the possibility that heparin-like oligosaccharides can inhibit L-selectin– and P-selectin–mediated PMN adhesion[57]. Although the potential to inhibit leukocyte-endothelial cell interactions could alter the harmful consequences of I/R, the clinical applicability of conventional heparin is limited because of the increased risk of bleeding. Low-molecular weight heparins (LMWHs) are much safer in this regard[58-62]. LMWHs are used extensively in posttraumatic situations, as they are potent and safe thromboprophylactic agents[63]. However, it may be hypothesized that the advantageous properties might include a so far unknown effect on leukocyte-endothelial cell interactions. Accordingly, the aims of our experimental work were

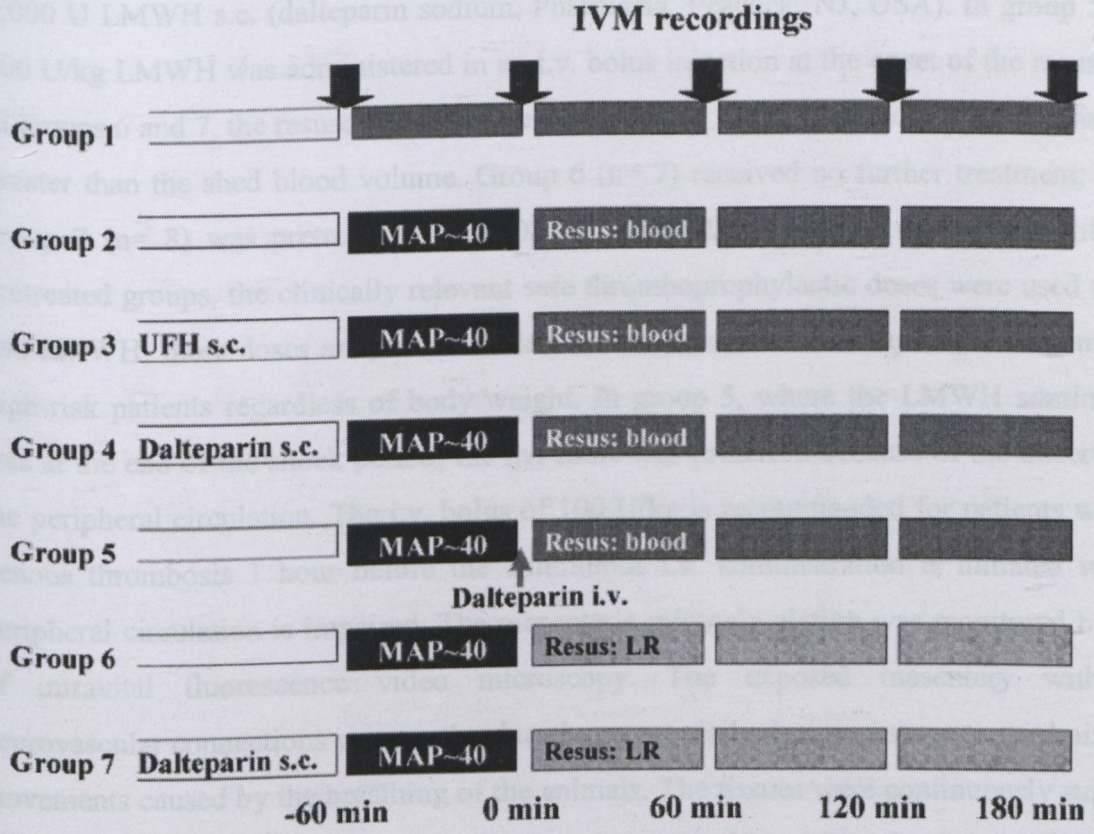
1. to observe and quantify HS and reinfusion-induced leukocyte-endothelial cell interactions in the mesentery in a large animal model;
2. to evaluate the consequences of LMWH pretreatment on leukocyte-endothelial cell interactions after HS;
3. to compare the effects of LMWH and conventional UFH (heparin sodium) pretreatments;
4. and to evaluate the effectiveness of late LMWH therapy, when the treatment was initiated only after HS and resuscitation was performed with crystalloid.

MATERIALS AND METHODS

The experiments were performed in adherence to the National Institutes of Health guidelines for the use of experimental animals. The study was approved by the Ethical Committee for the Protection of Animals in Scientific Research of the University of Szeged. Seven groups of healthy mongrel dogs (mean body weight, 12.5 kg; range, 9.8–14.3 kg) were used **(Fig. 3)**

Figure 3. Experimental group and protocol (See Material and Methods for the description of the groups)

MAP~ 40, 60 minutes shock period with mean arterial pressure of 40 mmHg; UFH, unfractionated heparin; Dalteparin, Dalteparin sodium; Resus: blood, resuscitation with shed blood; Resus LR, resuscitation with lactated Ringer's solution, s.c., subcutaneous; i.v., intravenous; IVM, intravital video microscopy.



The animals were intubated and anesthetized with sodium pentobarbital (30 mg/kg intravenously [i.v.] for induction, 2 mg/kg for supplementary doses); the body temperature was maintained at 37°C with a homeothermic blanket. The left femoral artery and vein were cannulated for the measurement of mean arterial pressure (MAP), and for the administration

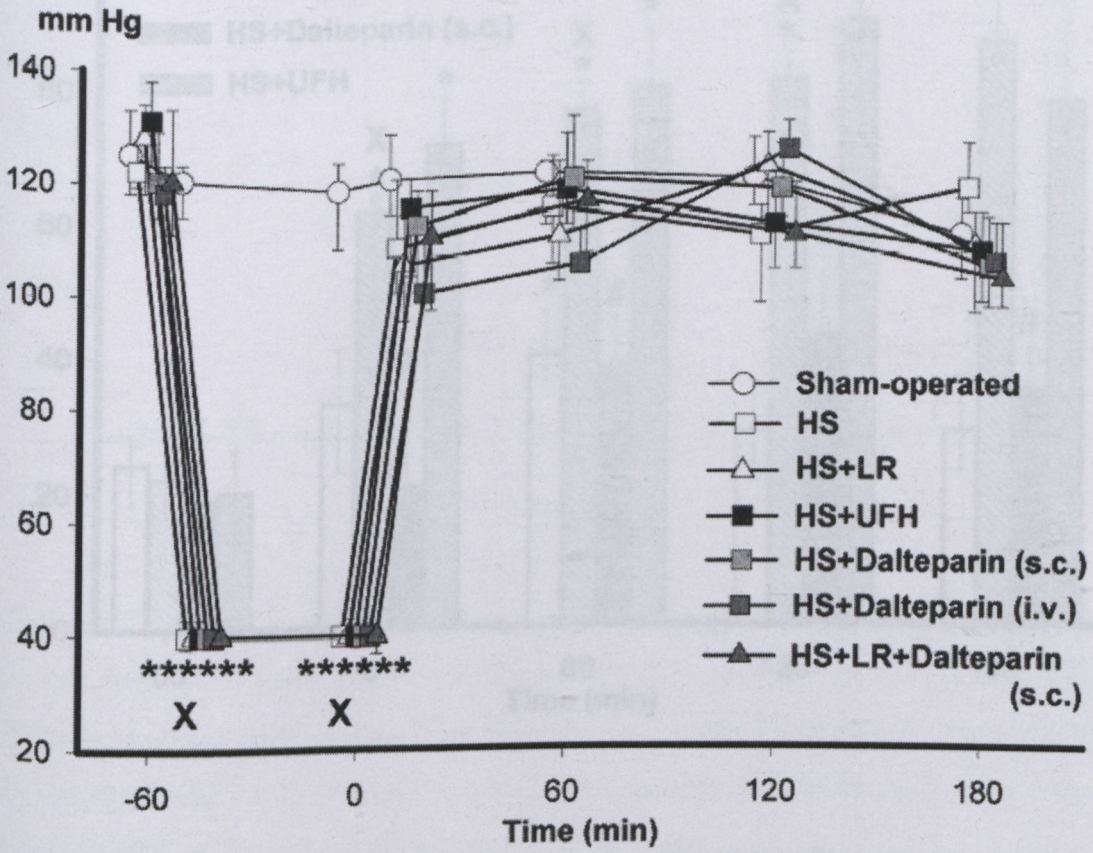
of fluid (7 mL/kg/h lactated Ringer's [LR] solution; B. Braun, Melsungen, Germany) or drugs, the reinfusion of shed blood, and resuscitation with LR solution, respectively. The right femoral artery was cannulated and connected to a reservoir, and a midline laparotomy was performed for visualization of the mesenteric microcirculation of the small bowel. Group 1 (n= 5) served as sham-operated control to exclude hemodynamic changes attributable to the time elapsed. In groups 2 through 7, HS was achieved by bleeding the animals into the reservoir (to MAP ~ 40 mm Hg), and after hypotension lasting 60 minutes, the shed blood was reinfused (groups 2–5) or resuscitation was performed with LR solution (groups 6 and 7). In group 2 (n= 8), no additional treatment was given (untreated controls). Group 3 (n= 7) was treated with 5,000 IU UFH subcutaneously (s.c.) (heparin sodium, Merckle-Ratiopharm, Ulm, Germany) before the induction of hemorrhage. Group 4 (n= 7) was pretreated with 5,000 U LMWH s.c. (dalteparin sodium, Pharmacia, Peapack, NJ, USA). In group 5 (n= 8), 100 U/kg LMWH was administered in an i.v. bolus injection at the onset of the resuscitation. In groups 6 and 7, the resuscitation was performed with LR solution with a volume four times greater than the shed blood volume. Group 6 (n= 7) received no further treatment, whereas group 7 (n= 8) was pretreated with 5,000 U LMWH s.c. During the experiments in the pretreated groups, the clinically relevant safe thromboprophylactic doses were used for UFH and LMWH; these doses are recommended for the prevention of deep venous thrombosis in high-risk patients regardless of body weight. In group 5, where the LMWH administration was at the end of the shock period, the i.v. route was preferred because of the uncertainty of the peripheral circulation. The i.v. bolus of 100 U/kg is recommended for patients with deep venous thrombosis 1 hour before the continuous i.v. administration is initiated when the peripheral circulation is impaired. The mesenteric microcirculation was monitored by means of intravital fluorescence video microscopy. The exposed mesentery with intact neurovascular connections was gently placed on a specially designed stage to minimize organ movements caused by the breathing of the animals. The tissues were continuously superfused with 36.5°C saline to avoid drying and exposure to ambient air and to maintain the water immersion of the microscope objectives. Any exposed tissue not protected by glass was covered by plastic sheets. Leukocytes were stained in vivo by means of rhodamine-6G (Mw 479, Sigma Chemical Co., St. Louis, MO; 0.2%, 1 mL i.v. 2 minutes before measurements) and the mesenteric microcirculatory network was visualized using a high-resolution Zeiss

Axiotech Vario 100HD (Carl Zeiss, Thornwood, NY) fluorescence intravital microscope (100 W HBO mercury lamp, Acroplan (Carl Zeiss) water immersion objective). The microscopic images were recorded by a charge-coupled device video camera (AVT HORN-BC 12 [AVT HORN, Aalen, Germany]) attached to an S-VHS video recorder (Panasonic AG-MD 830) and a personal computer. Quantitative assessment of the microcirculatory parameters was performed off-line by frame-to-frame analysis of the videotaped images using a computer-assisted image analysis system (IVM Pictron, Budapest, Hungary). Leukocyte-endothelial cell interactions were analyzed within five fields per animal, including the observation of non-adherent, adherent, and rolling leukocytes in five postcapillary venules per field. Adherent leukocytes (stickers) were defined in each vessel segment as cells that did not move or detach from the endothelial lining within an observation period of 30 seconds, and are given as numbers of cells per square millimeter of endothelial surface, calculated from the diameter and length of the vessel segment observed, with the assumption of cylindrical geometry. Rolling leukocytes were defined as cells moving at a velocity less than two fifths that of erythrocytes in the centerline of the microvessel, and are given as percentages of non-adherent leukocytes passing through the observed vessel segment within 30 seconds. The animals were randomly assigned to the various experimental groups. After a stabilization period, basal cardiovascular parameters were measured for 20 minutes, IVM was then performed to establish the baseline microvascular variables in all groups. Video microscopic images were recorded before hemorrhage (-60 minutes), at the end of the 60-minute HS period just before reinfusion/resuscitation (0 minutes), and at 60, 120, and 180 minutes after resuscitation. At the end of the experiments, the animals were killed with an overdose of pentobarbital. The statistical analysis was performed with a statistical software package (SigmaStat for Windows, Jandel Scientific, Erkrath, Germany). Friedman repeated measures analysis of variance on ranks was applied within the groups. Time dependent differences from the baseline (0 minutes) for each group were assessed by the Dunn method. Differences between groups were analyzed with Kruskal-Wallis one-way analysis of variance on ranks, followed by the Dunn method for pair wise multiple comparison. Figures present median values and 75th and 25th percentiles; p values < 0.05 were considered significant.

RESULTS

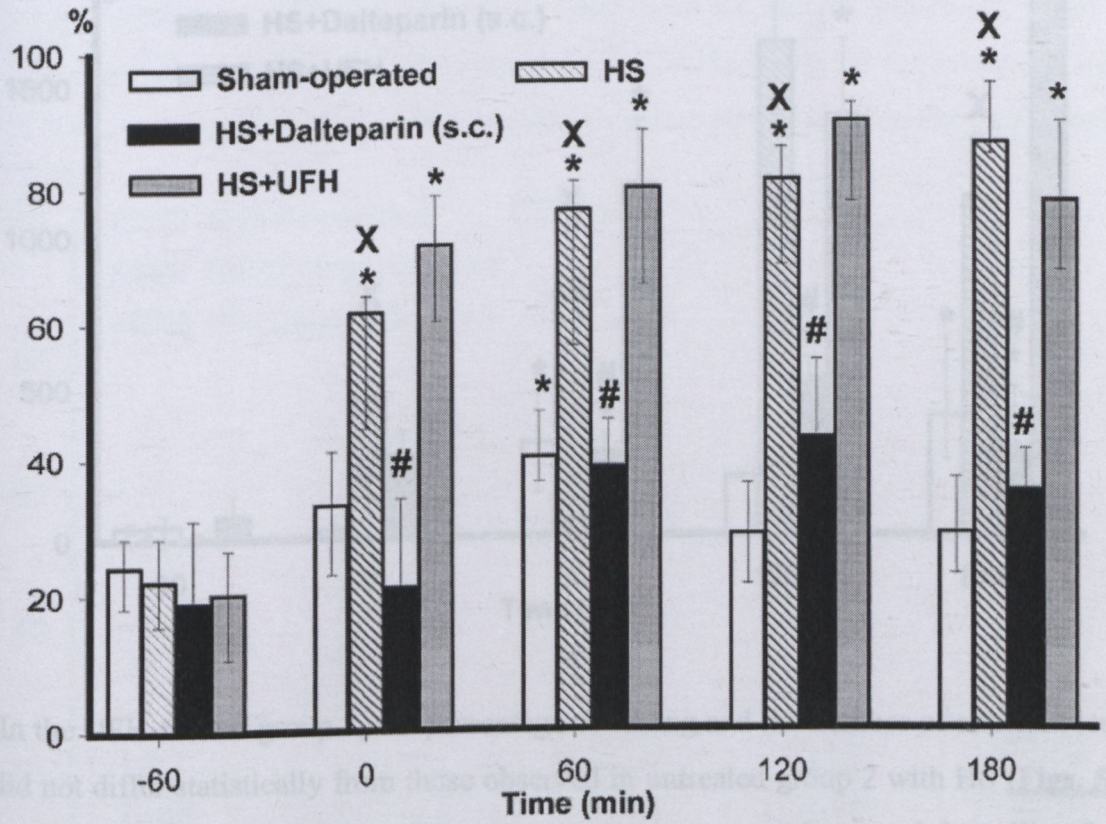
MAP was unchanged in the sham-operated group (group 1) during the examination period, and no changes in leukocyte-endothelial cell interactions were observed as compared with the baseline level. In groups 2 through 7, MAP was kept at 40 mm Hg during the HS period; after resuscitation, MAP values reached the pre-HS level regardless of the type of resuscitation (Fig. 4).

Figure 4. Mean arterial pressure changes during the observation period.
p <0.05 within group; ^{X}p <0.05 between sham-operated and HS groups. See Materials and Methods section for statistical evaluation. HS, hemorrhagic shock; UFH, unfractionated heparin; Dalteparin, dalteparin sodium; LR, lactated Ringer's (solution); s.c., subcutaneous; i.v., intravenous.



In the untreated control group, HS and reinfusion significantly increased leukocyte rolling in the mesenteric postcapillary venules, from a mean baseline value (-60 minutes) of 22.5% to 61%, 76%, 80%, and 87% at 0, 60, 120, and 180 minutes, respectively **(Fig. 5)**.

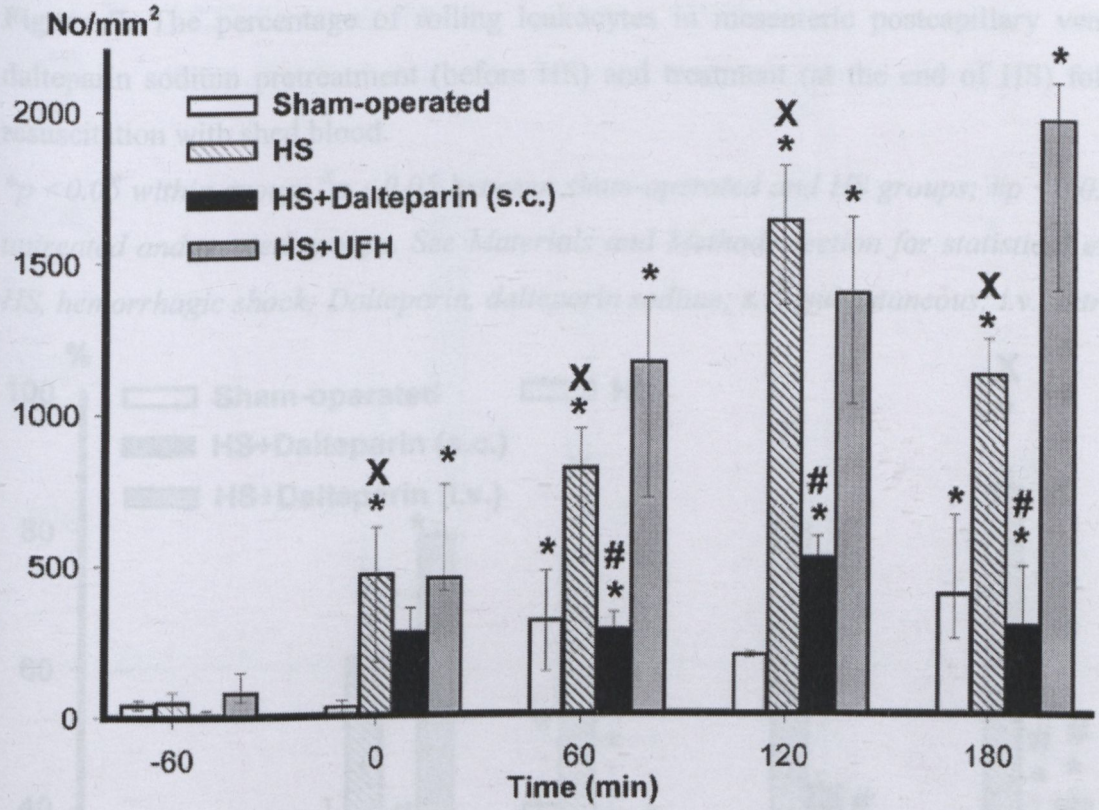
Figure 5. The percentage of rolling leukocytes in mesenteric postcapillary venules with UFH or dalteparin sodium pretreatment before HS
followed by resuscitation with shed blood.
**p <0.05 within group; ^{X}p <0.05 between sham-operated and HS groups; #p <0.05 between untreated and treated groups. See Materials and Methods section for statistical evaluation. HS, hemorrhagic shock; UFH, unfractionated heparin; Dalteparin, dalteparin sodium; s.c., subcutaneous.*



Firm adhesion increased from a baseline value of 56 cells/mm^2 to 479, 818, 1,636, and 1,128 cells/mm^2 at 0, 60, 120, and 180 minutes after hemorrhage, respectively **(Fig. 6)**.

Figure 6. The number of adherent leukocytes in mesenteric postcapillary venules with UFH or dalteparin sodium pretreatment before HS followed by resuscitation with shed blood (in 1 mm^2 vessel area).

**p <0.05 within group; ^{X}p <0.05 between sham-operated and HS groups; #p <0.05 between untreated and treated groups. See Materials and Methods section for statistical evaluation. HS, hemorrhagic shock; UFH, unfractionated heparin; Dalteparin, dalteparin sodium; s.c., subcutaneous.*



In the UFH-treated group 3, the percentage of rolling and the number of adherent leukocytes did not differ statistically from those observed in untreated group 2 with HS **(Figs. 5 and 6)**. The subcutaneous dalteparin sodium pretreatment in group 4 decreased the rolling fraction of the leukocytes to 21%, 39%, 43%, and 35.5%, and the firm adhesion to 282, 290, 522, and 296 cells/mm^2 at the same consecutive recording times.

In group 5, when LMWH was administered at the time of resuscitation, the number of leukocyte-endothelial interactions did not differ from that in the untreated group 2 at _60 minutes and 0 minutes. However, at the postresuscitation time points (60, 120, and 180 minutes), the rolling fraction decreased to 24.5%, 28%, and 49%, respectively, and the absolute numbers of adherent leukocytes were significantly lower (367, 345, and 409 cells/mm^2, respectively) **(Figs. 7 and 8)**.

Figure 7. The percentage of rolling leukocytes in mesenteric postcapillary venules with dalteparin sodium pretreatment (before HS) and treatment (at the end of HS) followed by resuscitation with shed blood.

**p <0.05 within group; ^{X}p <0.05 between sham-operated and HS groups; #p <0.05 between untreated and treated groups. See Materials and Methods section for statistical evaluation. HS, hemorrhagic shock; Dalteparin, dalteparin sodium; s.c., subcutaneous; i.v., intravenous.*

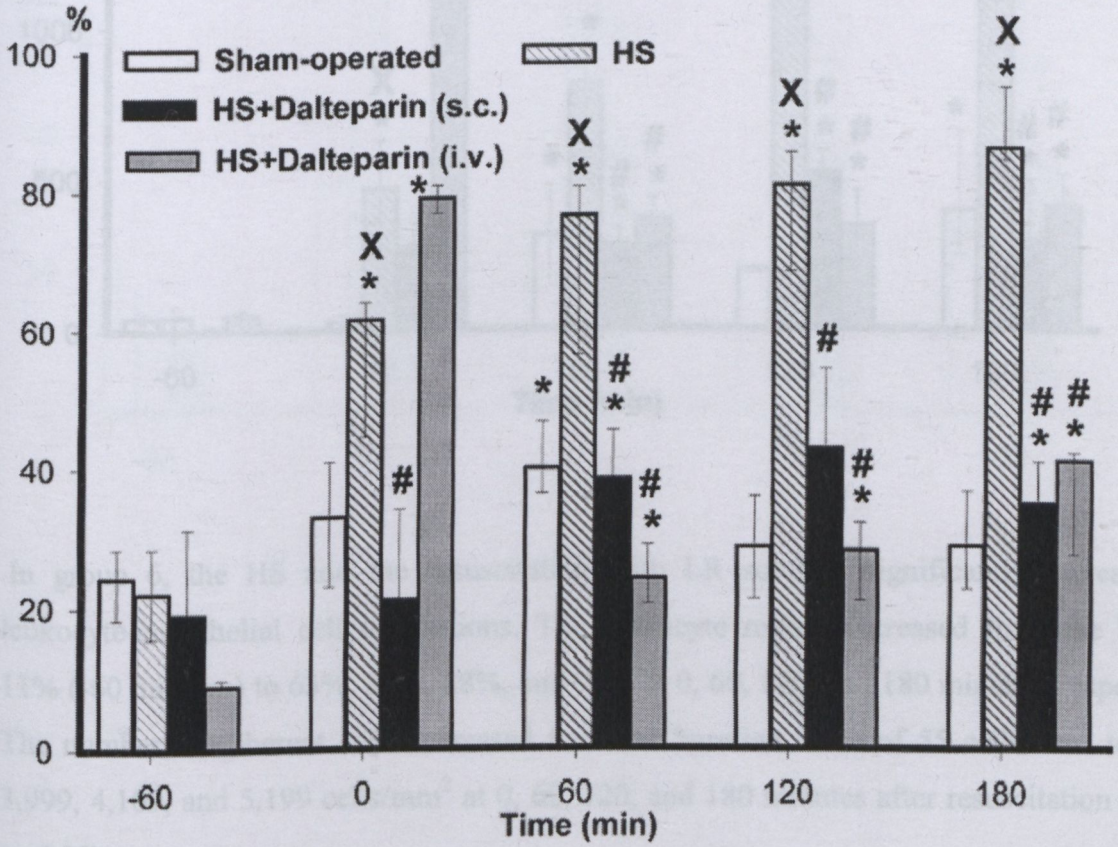
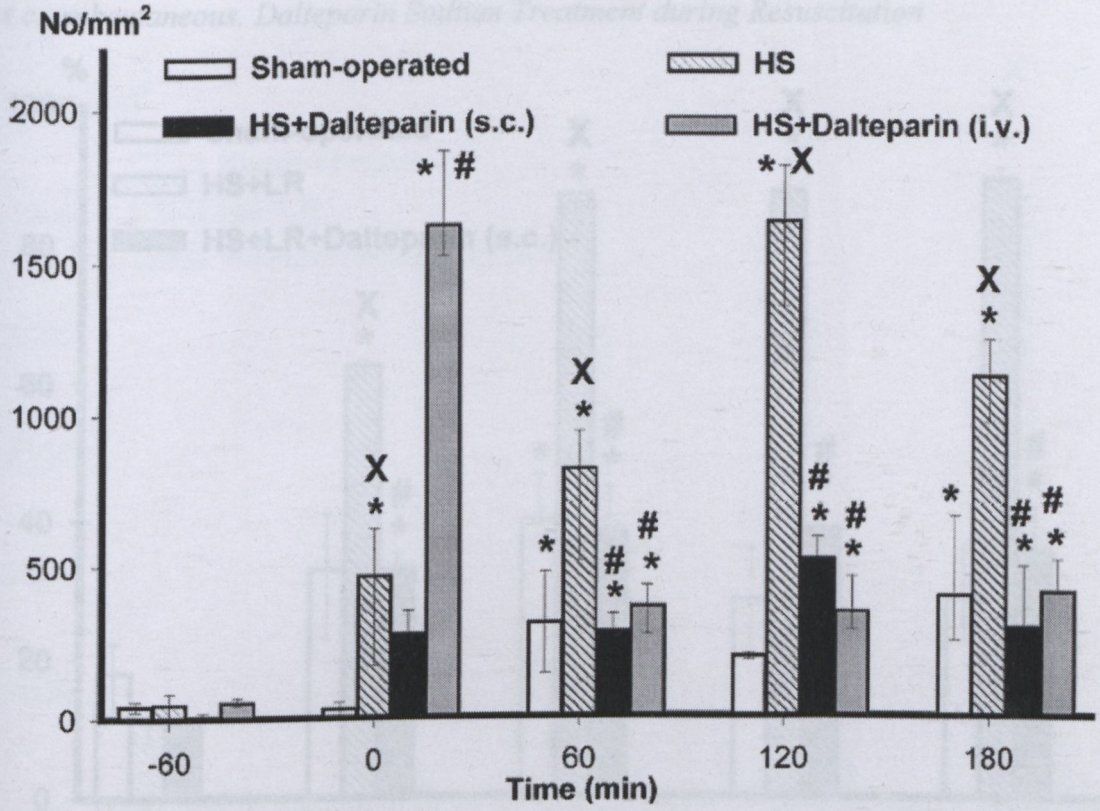


Figure 8. The number of adherent leukocytes in mesenteric postcapillary venules with dalteparin sodium pretreatment (before HS) and treatment (at the end of HS) followed by resuscitation with shed blood (in 1 mm2 vessel area).

**p <0.05 within group; ^{X}p <0.05 between sham-operated and HS groups; #p <0.05 between untreated and treated groups. See Materials and Methods section for statistical evaluation. HS, hemorrhagic shock; Dalteparin, dalteparin sodium; s.c., subcutaneous; i.v., intravenous.*



In group 6, the HS and the resuscitation with LR solution significantly increased the leukocyte-endothelial cell interactions. The leukocyte rolling increased from the baseline 11% (-60 minutes) to 63%, 87%, 88%, and 90% at 0, 60, 120, and 180 minutes, respectively. The number of adherent cells increased from the baseline value of 55 cells/mm^2 to 1,818, 3,999, 4,109, and 5,199 cells/mm^2 at 0, 60, 120, and 180 minutes after resuscitation **(Figs. 9 and 10)**.

Figure 9. The percentage of rolling leukocytes in mesenteric postcapillary venules with or without dalteparin sodium pretreatment before HS followed by resuscitation with lactated Ringer's solution.

**p <0.05 within group; ^{X}p <0.05 between sham-operated and HS groups; #p <0.05 between untreated and treated groups. See Materials and Methods section for statistical evaluation. HS, hemorrhagic shock; Dalteparin, dalteparin sodium; LR, lactated Ringer's (solution); s.c., subcutaneous. Dalteparin Sodium Treatment during Resuscitation*

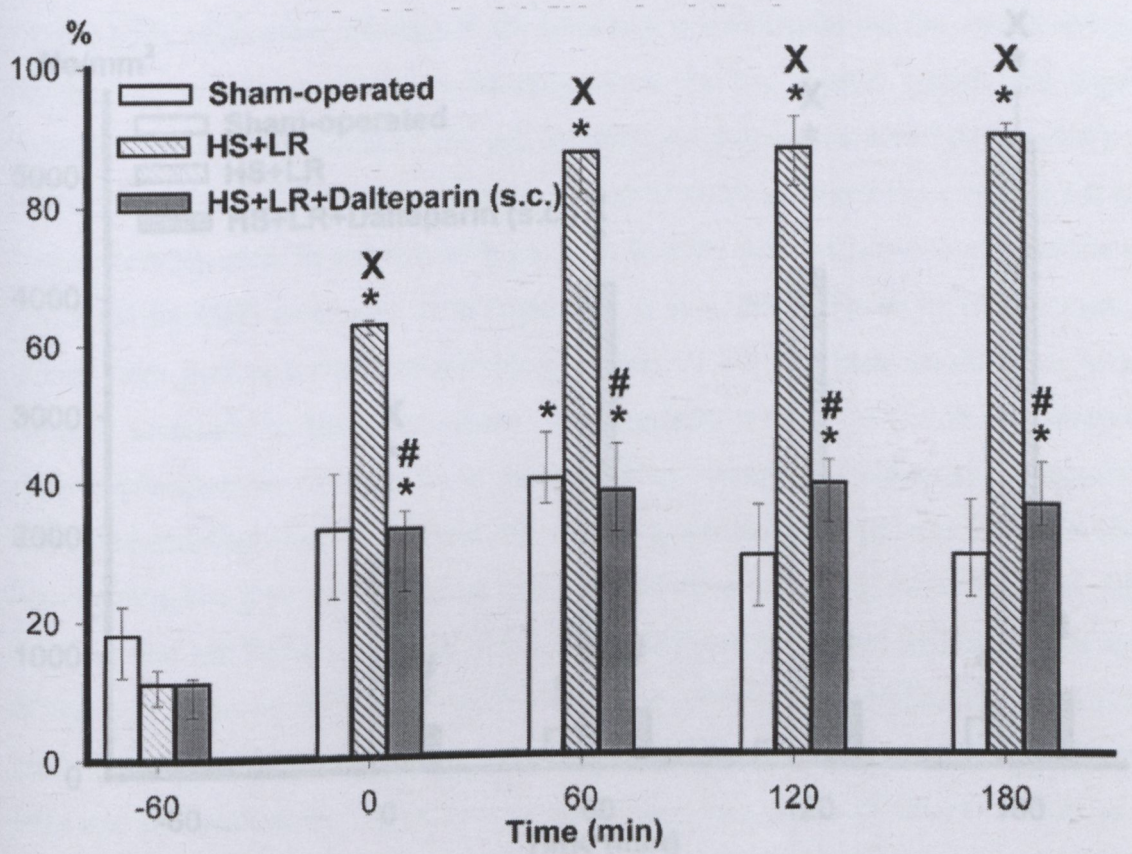
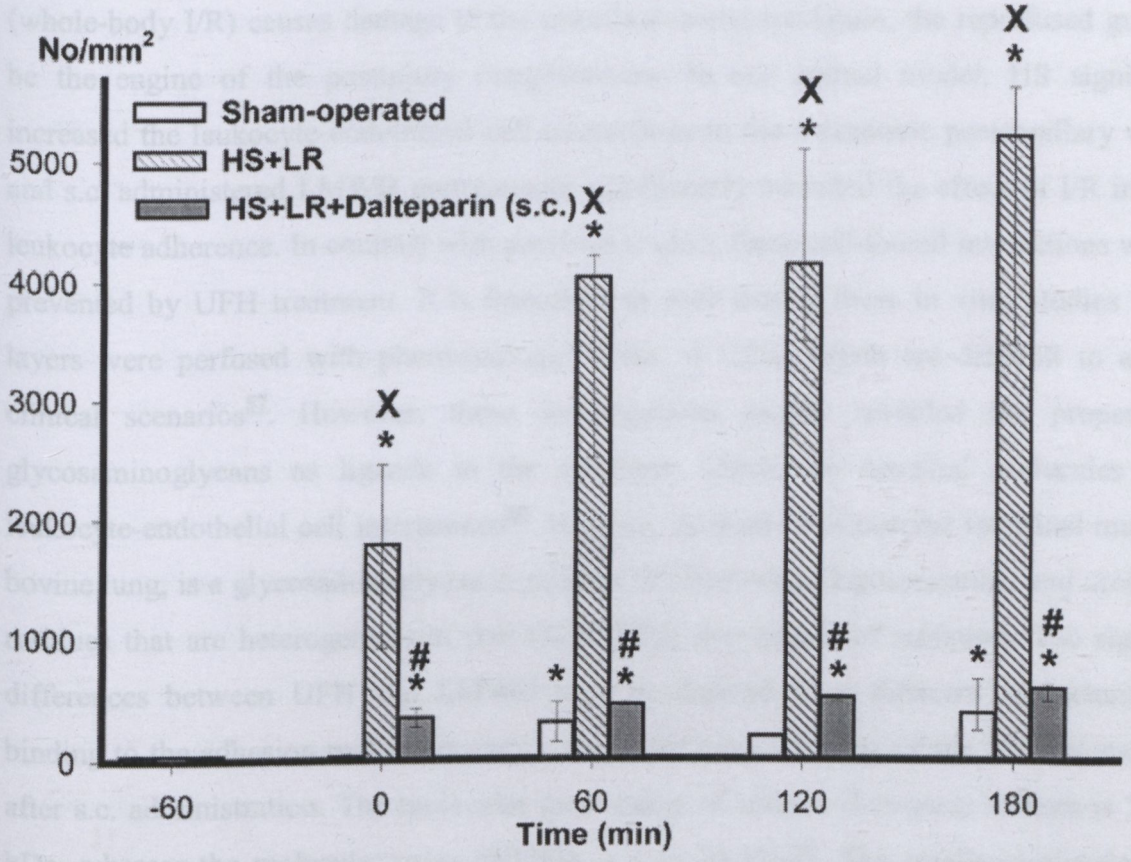


Figure 10. The number of adherent leukocytes in mesenteric postcapillary venules with or without dalteparin sodium pretreatment before HS followed by resuscitation with lactated Ringer's solution (in 1 mm2 vessel area).

**p <0.05 within group; ^{X}p <0.05 between sham-operated and HS groups; #p <0.05 between untreated and treated groups. See Materials and Methods section for statistical evaluation. HS, hemorrhagic shock; Dalteparin, dalteparin sodium; LR, lactated Ringer's (solution); s.c., subcutaneous.*



In group 7, the dalteparin sodium pretreatment significantly reduced the interactions in the small bowel mesenteric microcirculation after LR resuscitation, similar to that observed in shed blood-resuscitated group 4. After LMWH pretreatment, the rolling fraction of 11% (-60 minutes) increased to 34% (0 minutes), 39% (60 minutes), 39% (120 minutes), and 37% (180 minutes), and the adherent cell number of 60 cells/mm^2 (-60 minutes) increased to 327 cells/mm2 (0 minutes), 473 cells/mm^2 (60 minutes), 545 cells/mm^2 (120 minutes), and 618 cells/mm^2 (180 minutes) in the LR-resuscitated group 7 **(Figs. 9 and 10)**.

DISCUSSION

Despite the improvements in perioperative and postoperative care, the incidence of posttraumatic MOF continues unchanged and the mortality remains high[4]. When MOF develops, no specific therapy can be instituted; the treatment modalities merely support the failing organs[5]. Thus, the prevention of postinjury organ dysfunction with adequate resuscitative methods must be a key element of early interventions to achieve effective modulation of the inflammatory response[64]. As the combination of HS and resuscitation (whole-body I/R) causes damage to the intestinal microcirculation, the reperfused gut might be the engine of the postinjury complications. In our animal model, HS significantly increased the leukocyte-endothelial cell interactions in the mesenteric postcapillary venules, and s.c. administered LMWH pretreatment significantly inhibited the effect of I/R injury on leukocyte adherence. In contrast with previous studies, these cell-to-cell interactions were not prevented by UFH treatment. It is important to note that in these in vitro studies the cell layers were perfused with pharmacologic doses of UFH, which are difficult to apply in clinical scenarios[57]. However, these investigations clearly revealed the properties of glycosaminoglycans as ligands to the selectins, which are essential molecules of the leukocyte-endothelial cell interactions[65]. Heparin, isolated form porcine intestinal mucosa or bovine lung, is a glycosaminoglycan composed of alternating D-glucosamine and uronic acid residues that are heterogenous in size (3–30 kDa) and degree of sulfation. The significant differences between UFH and LMWH may be derived from different characteristics of binding to the adhesion molecules and/or the better bioavailability of the LMWH molecules after s.c. administration. The molecular mass range of sodium dalteparin sodium is 3 to 8.5 kDa, whereas the molecular mass of UFH is 3 to 30 kDa[66]. The smaller molecules cause fewer bleeding complications, but the compounds are still too heavily sulfated to be effective ligands for adhesion molecules. The pharmacokinetics of s.c. LMWH are also favorable. Dalteparin sodium exhibits dose-independent monoexponential first-order pharmacokinetic characteristics, usually expressed in terms of plasma anti-factor Xa activity. A mean maximum plasma anti-factor Xa activity value of 290 U/L was reported after s.c. administration of 5,000 U dalteparin, and 180 U/L after the same dose of UFH. The bioavailability of dalteparin sodium after s.c. administration is 87%, as compared with approximately 25% for UFH[67]. Pretreatment with anticoagulants and resuscitation with

autologous blood is very different from routine clinical practice. Our study involved three additional groups (groups 5–7) to eliminate these biases. An important secondary finding was that, in the untreated groups, the number of adherent cells was about three times higher if resuscitation was performed with LR solution (group 6) compared with shed blood resuscitation (group 2). Nevertheless, the type of resuscitation (shed blood vs. crystalloid) did not affect the tendencies to leukocyte rolling and adhesion after hemorrhagic shock (but did affect the absolute number of adherent cells), and did not influence the effectiveness of LMWH to prevent adhesion. The post-HS dalteparin sodium treatment was administered i.v., because of uncertain absorption from subcutaneous sites during the shock state. Without LMWH pretreatment, similar leukocyte reaction occurred before and during HS to those observed in the untreated controls. However, i.v. dalteparin sodium administration at the time of resuscitation significantly decreased the number of interactions in the postresuscitation period. It is unlikely that the molecule has any effect on an established leukocyte-endothelial cell interaction, but our results suggest that this treatment can prevent amplification of the process. The significant decrease in the number of adherent cells is because of the extravasation of previously adhering leukocytes and the LMWH medication-induced relative decrease in newly evolving adhesions. It should be mentioned here that LMWHs are not interchangeable: their pharmacologic characteristics might differ in association with their different structural properties[68]. In view of the effectiveness of LMWH treatment, the inhibitory effects of dalteparin sodium on leukocyte rolling and adherence deserve further investigation. Our further studies should focus on showing that the decrease of leukocyte-endothelial cell interactions could result in lower incidence of MOF. In conclusion:

1. We propose that pharmacologically relevant doses of the LMWH compound (in addition to thromboprophylaxis) exert beneficial effects through modulation of the leukocyte-mediated early inflammatory responses, and this property may be important for the prevention of posttraumatic complications in human clinical practice.
2. In the absence of contraindication, the initiation of LMWH administration should be considered in trauma patients after hemorrhage control.

CLINICAL IMPLICATIONS AND FUTURE DIRECTIONS

Prospective data analyzed with uni- and multivariate methods consistently prove age, shock severity and injury severity as independent risk factors for postinjury MOF[26,47].

Elderly patients (>55 years is independent risk factor) present significant challenge to European and North American trauma care providers where increasing proportion of the population falls into this category. The aging of the population is an important reason for the consistency of MOF incidence despite the more sophisticated intensive care knowledge and technology[4].

Basic and clinical research indicates that traumatic shock is a major contributor of postinjury MOF[7]. The timely recognition and control of hemorrhage together with optimal resuscitation are essential parts of the prevention of HS related complications such as MOF. To achieve this universal systematic response is required to all major trauma patients' resuscitation. The already proven approach is recommended by the Advanced Trauma Life Support Program (ATLS), which standardizes the first hour of trauma patients' inhospital evaluation and management driven by priorities[69]. This is a very different approach compared to our medical training where after the detailed history one performs meticulous physical examination, order tests, requests consults from other specialties and finally have a diagnosis which makes it possible to initiate treatment. The ATLS supports the standardized diagnostic test simultaneously with the focused history and checking the vital organ systems. Invasive interventions (therapy) are encouraged on the basis of clinical signs without diagnosis (i.e. decreased breath sounds on the right chest means chest tube insertion without knowing what is the underlying cause). Based on the explored inadequacies in the Hungarian trauma care the introduction of the ATLS program is an appropriate next step to address the shortcomings[70]. Our working group's efforts since 1997 have led the promulgation process to the first Hungarian course in 2005. Finding the ideal approach to traumatic resuscitation is complex and well exceeding the aims of this thesis. Our basic science findings however indicate that LMWH administration is a useful adjunct to shock resuscitation in preventing leukocyte-endothelial cell interactions the known initial step of PMN (key cellular element in the mechanism of postinjury MOF) activation[71]. The fact that the magnitude of interactions (both rolling and adhesion) is higher if resuscitation is performed with LR than shed blood is an important additional finding which a potential impact on our clinical trauma care.

Independently from our results other groups in different models have proven the pro-inflammatory characteristics of LR. Given the fact that LR is one of our first-line resuscitation crystalloid fluid this finding has significant clinical relevance[72,73].

It is not possible to modulate the anatomical injury after the trauma but it can be exactly described and compared within and between centers. The latter fact makes anatomical scores very important in trauma outcome and prediction research[41]. Contrary its widespread application during the last three decades the ISS has several inadequacies[40,46]. We could show that the NISS preserves and even further develops the ISS simplicity and improves its accuracy and predictive power. The NISS is a superior predictor of MOF over the ISS[47]. Our study performed on the entire trauma population showed that the NISS is more accurate in predicting general trauma outcomes such as mortality, hospital LOS and ICU admission[74].

SUMMARY

The thesis presents NISS, a new, improved anatomic measure to predict postinjury MOF, which helps to concentrate our preventive and therapeutic efforts to the right population of patients. In addition, new areas are opened for further research to prevent postinjury MOF. We propose new adjuvant therapy with sodium dalteparin, a potent modulator of the uncontrolled leukocyte-endothelial cell interactions; and we draw attention to the potential threats of LR as a pro-inflammatory agent in resuscitation and trauma care.

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