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The effect of permissive hypotension in combined traumatic brain injury and blunt abdominal trauma: an experimental study in swines

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Abstract. – OBJECTIVE: Optimal hemodynamic resuscitation strategy of the trauma patient with uncontrolled hemorrhage and severe head injury in the pre-hospital setting remains a special challenge. Permissive hypotension prior to definite surgical haemostasis promotes coagulation, decreases blood loss and favors survival. However, hypotension is associated with poor outcome in severe head injury. The purpose of this experimental animal study was to assess the impact of permissive hypotension on survival, hemodynamic profile and brain oxygenation parameters before and/or after definite surgical haemostasis.

PATIENTS AND METHODS: Six-week-old pigs (n=12) underwent general anesthesia and brain injury was produced by the fluid percussion model. Animals were instrumented to measure hemodynamic parameters and cerebral blood flow. All animals (n=12) were subjected to laparotomy and a surgical knot was placed through the abdominal aorta wall. Uncontrolled hemorrhage was simulated by pulling out the intentionally left protruding free ends of the suture (goal MAP=30 mmHg). Animals were randomly divided into two groups; group A (n=6) was subjected to aggressive fluid resuscitation (goal SAP >80 mmHg) and group B (n=6) was left hypotensive (permissive hypotension). Animals who survived one hour of hypotensive shock underwent definite surgical haemostasis and were resuscitated for one hour. We measured survival, hemodynamic and brain oxygenation parameters at different time points before and after surgical haemostasis.

RESULTS: All animals from Group A and 50% from Group B died before surgical haemostasis. In surviving animals (Group B, 50%, p=0.033), MAP, CO, rCBF, SjO_2 and $AVDO_2$ were restored to pre-procedural levels.

CONCLUSIONS: Permissive hypotension by delaying fluid resuscitation up to definite surgical haemostasis improves survival, hemodynamics and allows restoration of cerebral oxygenation in severe head injury.

Key words:
Traumatic brain injury, Permissive hypotension, Hemorrhagic shock, Swine.

Abbreviations

$AVDO_2$ = arteriovenous difference of oxygen; BE = base excess; CaO_2 = arterial oxygen content; CBF = cerebral blood flow; CO = cardiac output; CvO_2 = venous oxygen content; DAP = diastolic arterial pressure; Hb = haemoglobin; HR = heart rate; LA = lactic acid; MAP = mean arterial pressure; MPAP = mean pulmonary artery pressure; $PaCO_2$ = partial pressure of CO_2 in arterial blood; PaO_2 = partial pressure of O_2 in arterial blood; PCWP = pulmonary capillary wedge pressure; rCBF = regional cerebral blood flow; SD = standard deviation; SAP = systolic arterial pressure; SjO_2 = oxygen saturation at the jugular bulb; SVO_2 = oxygen saturation at the mixed venous blood.

Introduction

Brain injury and hemorrhage are the predominant causes of mortality and disability following trauma[1]. Clinicians are often confronted with these two conflicting clinical entities in the same patient. Primary brain injury at the time of trauma results in impairment of cerebrovascular carbon dioxide reactivity and autoregulation, thus, rendering the brain more vulnerable to secondary insults including hypotension, hypoxia, anaemia and hypercarbia[2]. On initial presentation, 35% of patients are hemodynamically unstable and hy-

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potension is demonstrated to be and independent prognostic factor that doubles the mortality rate following severe traumatic brain injury (TBI)[3,4]. Even short episodes of hypotension prior to hemodynamic stabilization may result in persistent brain ischemia and are predictive of increased mortality and poor functional outcome[5,6]. Since cerebral perfusion in TBI depends strictly on systemic blood pressure, a cut-off for systolic arterial pressure (SAP) ≥ 90 mmHg is recommended by the American Brain Trauma Foundation to maintain adequate cerebral perfusion pressure[7]. Early and aggressive restoration of circulating blood volume is the standard immediate treatment in hemorrhagic shock in order to maintain vital organ perfusion until bleeding is surgically controlled. However, a clinical study in humans suffering penetrating torso wounds showed that normotensive fluid resuscitation increased mortality and postoperative complications[8]. More data from animal studies showed that early and aggressive fluid resuscitation was associated with increased blood volume loss[9-11], which in turn may worsen cerebrovascular parameters The strategy to limit or withhold resuscitation prior to surgical intervention is advantageous in many aspects; it limits the depletion and dilution of coagulation factors, favors the formation and stabilization of the blood clot and impedes trauma-related inflammatory cascade, thereby, decreasing short and long-term mortality[12]. Decreased blood loss, stable hemodynamics and increased survival have also been demonstrated in animals for target resuscitation mean arterial pressure (MAP) 50-60 mmHg[11,13]. However, permissive hypotension in the TBI patient has the risk of significant secondary ischemic brain insult. Due to the lack of well-performed, randomized, controlled trials, current recommendations in regard to resuscitation of patients with both TBI and uncontrolled hemorrhage are still mainly based on expert opinion, pathophysiological mechanisms and small studies in humans and animals. However, some animal studies showed that early and aggressive resuscitation didn't improve cerebral hemodynamics, whereas hypotensive resuscitation didn't result in neuronal deficits and histological brain damage[11,14]. Here, the authors present a pilot study in swines with severe TBI and uncontrolled intra-abdominal hemorrhage in order to evaluate the effect of permissive hypotension by withholding fluid resuscitation on survival, hemodynamic profile and brain oxygenation parameters prior to - and post-surgical haemostasis.

Materials and methods

The study was approved by the Animal Research and Ethics Committee of the Federal University of Patras, Greece, and conducted under stringent animal ethics protocol.

Animals and preparation

A total of 12 female swines (25-30 kg) were used. Animals were acclimated for 3 days before the experiment. Food was withheld the night before surgery and water was provided *ad-libitum.* The day of the experiment animals were placed in the supine position and premedicated with midazolam 2 mg/kg i.m. (Roche Pharmaceuticals, Basel, Switzerland). Anesthesia was induced with fentanyl 4-5 μg/kg (Janssen Pharmaceuticals, Beerse, Belgium), cis-atracurium 0.5 mg/kg (GlaxoSmithKline, London, United Kingdom) and intramuscular injection of ketamine 10 mg/kg (Pfizer, New York, USA). Animals were intubated and volume-cycled mechanical ventilation was initiated (Engström Erica I.C.U ventilator, Engström, Sweden). Initial ventilator settings included a tidal volume of 15 ml/kg body weight, peak pressure of 20 cm H_2O and the respiratory rate was adjusted to maintain an end-tidal PCO_2 of 35-45 mmHg. Anesthesia was maintained with propofol 10 mg/kg/h and fentanyl 5 μg/kg/h (Abbott Lifecare 5000 infusion pump, Abbott, Illinois, North Chicago, USA). Drugs and fluids were administered via the internal jugular vein catheter.

Brain injury model and instrumentation

We used the fluid percussion model to produce traumatic brain injury as described elsewhere[15]. A 90 mm craniotomy was made centrally around the midline between the bregma and lambda suture to expose the intact dura. A plexiglass tube 5cm in diameter and 40 cm in length was attached to the dura matter and filled with isotonic saline. A metal piston was stably adjusted at one end of the tube (peripheral) and the opposite end was connected to a pressure transducer. A metal pendulum of 6.2 kg struck the free edge of the piston so that a pulse pressure of 3.5 ± 0.3 atm was transferred to the surface of the dura matter. A thermal diffusion cerebral blood flow sensor (Micro Saber Plus, Flowtronics, Phoenix, Arizona, USA) was inserted in the subdural space and the open dura was carefully sutured. Cerebral blood flow (CBF) was measured via the cerebral blood flow sensor. Following

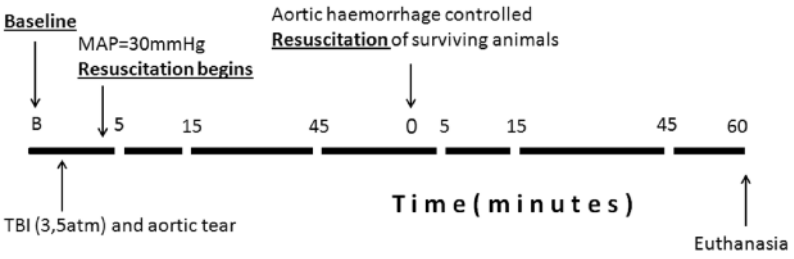

Figure 1. Timeline of the model.

surgical preparation, the common carotid artery was catheterized with a 1.5 mm diameter polyurethane tube for invasive blood pressure monitoring, oxymetry measurements and serial arterial and laboratory blood sampling. The inferior vena cava was cannulated with a triple-lumen pulmonary artery polyurethane catheter 7.5 Fr (OptiQ continuous cardiac output system, Abbott, North Chicago, IL, USA) for the measurement of hemodynamic parameters and blood sampling. Retrograde catheterization of the right internal jugular bulb was used for oxymetry measurements. Heart rate (HR) was monitored using a 3-lead ECG and animals were placed under heating lamps in order to maintain a body temperature (T) of 36°C.

Hemorrhage and resuscitation protocol

The animals were fixed on the surgical table in the supine position. After adequate sterilization with iodine alcohol solution a midline incision was performed and infra-renal aorta was exposed to the surgical field. A 4 mm surgical knot was placed on the ventral surface of the aorta with a 3-0 nylon suture. Following catheterization of the inferior vena cava a continuous full thickness running suture was placed through the edges of the laparotomy to close the abdominal wall. Both free ends of the suture were exteriorized through the abdominal incision. Free intra-abdominal hemorrhage was induced by pulling out the sutures[11]. When MAP reached the target value of 30 mmHg, animals were randomly assigned into two groups (n=6 animals per group). For the next 6 minutes no fluids were infused to simulate the average time for platelet thrombi formation. Group A was resuscitated with lactated Ringer's solution (3:1 crystalloids *vs*. estimated blood loss) to a goal SAP of > 80 mmHg, whereas Group B was left hypotensive (permissive hypotension). Animals who survived one hour of haemorrhage underwent definite surgical haemostasis and were further resuscitated for one hour with lactated Ringer's solution to a goal SAP of > 80 mmHg (Figure 1). Animals were then euthanized with intravenous administration of potassium chloride at the end of the experiment.

Physiologic measurements

Measurements for CO (cardiac output), systolic arterial pressure (SAP), diastolic arterial pressure (DAP), mean arterial pressure (MAP), heart rate (HR), mean pulmonary artery pressure (MPAP), pulmonary capillary wedge pressure (PCWP), oxygen saturation (sO_2) at the mixed venous blood (S_VO_2) and the jugular bulb (S_jO_2), pH, $PaCO_2$ (partial pressure of CO_2 in arterial blood), PaO_2 (partial pressure of O_2 in arterial blood), haemoglobin (Hb), base excess (BE), lactic acid (LA), regional cerebral blood flow (rCBF) were obtained at 0 (baseline) and time points 5, 15 and 45 min following haemorrhage and after surgical haemostasis. MAP, CaO_2, CvO_2, and $AVDO_2$ were calculated using standard formulas.

Statistical Analysis

Results were presented as mean ± standard deviation (SD) and analyzed by multivariate ANOVA with repeated measures and covariance design was used to determine if a variable changed significantly with respect to time. This test was performed after homogeneity of variances determined. When significant differences between groups were found, multiple comparison tests (Student-Newman-Keuls, $p<0.05$ was considered statistically significant) were used. Analysis was completed with a statistical software package for desktop computers (SPSS 13.0, SPSS Inc., Chicago, IL, USA).

Table I. Baseline physiological parameters in 12 swines. Values are expressed as the mean ± SD; 95% confidence interval for the differences.

Parameter	Group A (6 pigs)	Group B (6 pigs)	*p*
Preinjury weight (kg)	24.083±2.672	25.583±3.904	0.455
Temperature (°C)	36.067±0.811	36.737±1.065	0.251
SAP (mmHg)	117.5±12.534	117±27.033	0.968
DAP (mmHg)	89.17±16.857	82.17±17.36	0.495
MAP (mmHg)	98.166±15.091	93.5±19.532	0.653
HR (beats/min)	123.83±17.256	121.5±21.662	0.840
CO (L/min)	3.317±0.354	3.45±0.811	0.720
PH	7.426±0.068	7.476±0.028	0.145
PaO_2 (mmHg)	224±45.25	236.83±24.895	0.556
$PaCO_2$ (mmHg)	40.65±7.202	39.667±1.732	0.757
Arterial lactate (mEq/L)	2.22±0.622	1.620±0.638	0.171
Haemoglobin (g/dl)	11.167±1.671	10.217±1.862	0.374
SBE (mEq/L)	2±3.49	5.883±2.91	0.063
CaO_2 (ml/dl)	14.90±2.089	13.86±2.779	0.522
SvO_2 (%)	66.68±13.7	75.2±14.48	0.320
MPAP (mmHg)	20.67±3.141	19.17±5.672	0.583
PCWP (mmHg)	12.50±2.665	10.17±2.639	0.159
SjO_2 (%)	66.13±21.892	64.77±17.924	0.908
rCBF (ml/100 g/min)	35.5±9.19	35.72±8	0.992

Results

Baseline physiological measurements before brain injury are shown in Table I. No significant differences between the two groups were detected.

Mortality rates

All animals from Group A (goal SAP >80 mmHg) and three animals from Group B (permissive hypotension) died before surgical control of hemorrhage. The three animals from Group B that survived the hemorrhagic phase and surgical haemostasis were further resuscitated for one hour. Survival appears to be more favourable for Group A during the first 45min of uncontrolled hemorrhage (100%, $p<0.05$). However, overall survival is prolonged for animals in Group B (50%, $p=0.033$) (Figure 2).

Systemic hemodynamics and blood oxygenation parameters

Since only animals from Group B survived the hemorrhagic phase, statistical significance for selected parameters prior to surgical haemostasis was defined between the two groups (Table II). Following surgical haemostasis, statistical analysis of selected parameters in Group B was in respect to group baseline values (Table III). Despite aggressive fluid management animals in Group A failed to reach the target SAP >80 mmHg (Figure 3A). Animals in Group B, had significantly higher SAP 45 min after the beginning of hemorrhage (62.5 ± 13.4 *vs.* 33.4 ± 6.58 mmHg, $p<0.01$) and its levels returned gradually to normotensive values following surgical haemostasis. In the same line, measured MAP was lower for animals in

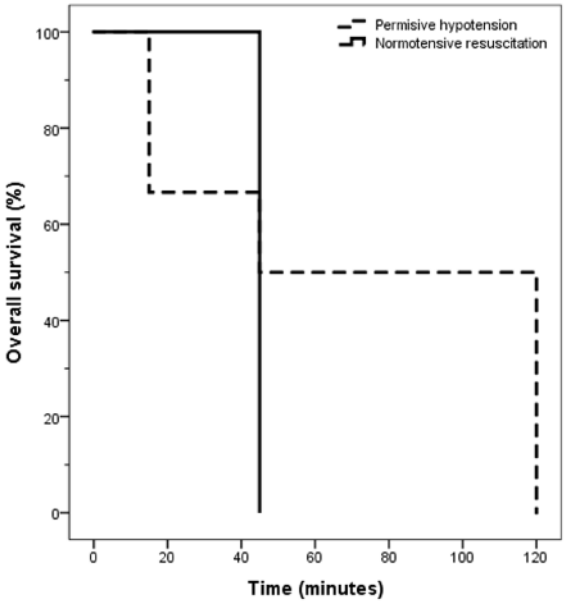

Figure 2. Kaplan-Meier survival curves for the two groups of animals (n=12). Group A (goal MAP = 80 mmHg, n=6) is represented with solid lines and Group B (permissive hypotension) is represented with dashed lines.

Table II. Physiological parameters before surgical haemostasis. Values are expressed as the mean ± SD. Asterisks denote statistical difference between the two groups for the given time point *$p<0.05$, **$p<0.01$, ***$p<0.001$.

Group and parameter	Baseline	5 min	15 min	45 min
Group A (goal SAP >80 mmHg)				
Temperature (°C)	36.06±0.81	36.72±0.44	36.27±0.547	35.88±1.01
DAP (mmHg)	89.17±16.85	20.67±13.29	26.5±9.75	19.40±0.89
pH	7.42±0.06	7.55±0.11	7.42±0.11	7.52±0.05
PaO_2 (mmHg)	224±45.25	233±44.07	170±94.31	172.78±71.82
$PaCO_2$ (mmHg)	40.65±7.2	25.8±6.28	30.1±7.41	19.26±3.11***
Arterial lactate (mEq/L)	2.22±0.62	4.7±2.49	8.02±1.11	10.22±2.11
Haemoglobin(g/dl)	11.16±1.67	7.65±1.92	5.83±2.51*	4.22±2.67
SBE (mEq/L)	2±3.49	0.233±2.97	-4.9±3.16	-6.26±3.75
CaO_2 (ml/dl)	14.90±2.08	10.32±2.77	7.1±3.12	4.74±2.64
SvO_2 (%)	66.68±13.7	21.06±9.76	20.9±9.36	18.517±9.76
MPAP (mmHg)	20.67±3.14	20.17±3.25	19.83±3.97	17±7.41
PCWP (mmHg)	12.50±2.66	13.33±3.2**	13.83±3.97**	11±5
Group B (permissive hypotension)				
Temperature (°C)	36.73±1.06	36.75±1.08	36.68±1.12	36.65±0.73
DAP (mmHg)	82.17±17.36	22.83±8.63	33.50±15.04	42.4±15.61
pH	7.47±0.02	7.60±0.09	7.41±0.15	7.31±0.14
PaO_2 (mmHg)	236.83±24.89	235.33±67.18	173.37±111.85	224.5±76.27
$PaCO_2$ (mmHg)	39.667±1.732	24.78±8.54	35.28±12.18	41.87±2.79
Arterial lactate (mEq/L)	1.620±0.638	3.62±1.84	6.02±1.93	6.5±2.94
Haemoglobin (g/dl)	10.217±1.862	9.65±1.55	9.083±1.70	8.72±3.38
SBE (mEq/L)	5.883±2.91	4.01±3.38	-0.933±3.24	-3.52±8.03
CaO_2 (ml/dl)	13.86±2.77	13.02±2.21	10.84±4.33	11.067±4.21
SvO_2 (%)	75.20±14.48	16.36±15.29	23.43±20.69	31.2±15.26
MPAP (mmHg)	19.17±5.672	15.17±6.76	15.83±7.16	14.25±5.9
PCWP (mmHg)	10.17±2.639	8.67±1.36	8±2	7.5±2.51

Group A throughout the hemorrhagic phase, whereas in Group B the parameter progressively improved and did not differ to baseline values after surgical haemostasis (Figure 3B). HR was significantly higher in animals in Group B during late hemorrhagic and post-surgical phase (Figure 4A). During hemorrhage, CO (Figure 4B) remained below baseline values but didn't differ significantly between the two groups. In animals in Group B the parameter was gradually restored to baseline values 45 min after surgical haemostasis. Reductions in Hb and CaO_2 levels were less pronounced in animals in Group B, but lower than baseline values throughout the experiment

Table III. Physiological parameters for Group B (permissive hypotension) after surgical haemostasis. Values are expressed as mean ± SD. Asterisks denote statistical difference from group baseline values, **$p<0.05$, **$p<0.01$, ***$p<0.001$.

Parameter	Baseline (n=6)	5 min (n=3)	15 min (n=3)	45 min (n=3)
Temperature (°C)	36.73±1.06	35.6±1.28	35.4±0.98	35.6±1.6
DAP (mmHg)	82.17±17.36	52.33±2.51**	48.33±2.88**	68.66±7.09
pH	7.47±0.02	7.29±0.1**	7.26±0.07***	7.24±0.01***
PaO_2 (mmHg)	236.83±24.89	198±37.5	214±64.5	220.3±66.57
$PaCO_2$ (mmHg)	39.667±1.732	43.8±12.77	45.43±6.47	47.96±2.62*
Arterial lactate (mEq/L)	1.620±0.638	9.9±0.79***	9.13±0.3***	8.43±0.37***
Haemoglobin (g/dl)	10.217±1.862	6.93±1.51**	6.71±2.02**	5.53±1.82***
SBE (mEq/L)	5.883±2.91	-5.23±0.92**	-6.2±3.5***	-6±2.57***
SvO_2 (%)	75.20±14.48	31.4±18.83***	39.86±11.22***	52±7.18***
MPAP (mmHg)	19.17±5.672	15±8.8***	32.±10.58***	20±9.53***
PCWP (mmHg)	10.17±2.639	9.33±3.21***	10.66±3.05***	13±3.46***

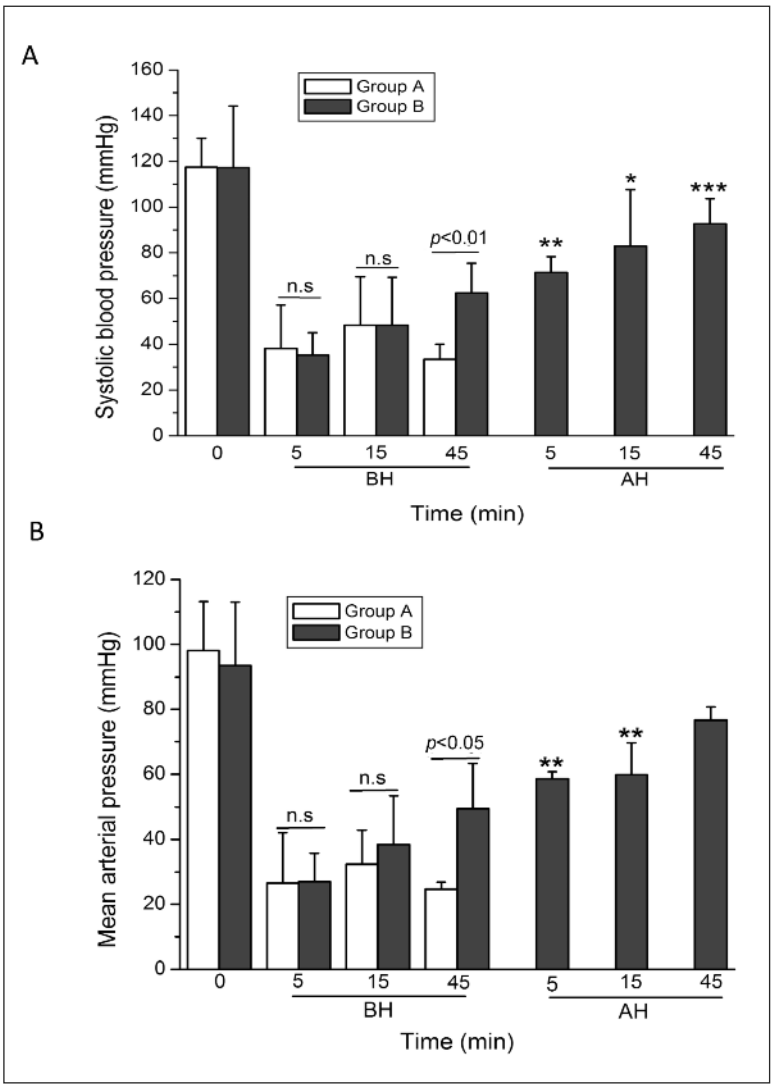

Figure 3. Graph showing SAP **(A)** and MAP **(B)** at different time points before (BH) and after surgical haemostasis (AH). Results are expressed as mean ± SD. Asterisks denote statistical difference from the corresponding baseline values, *p<0.05, **p<0.01, ***p <0.001.

(Tables II and III). $PaCO_2$ in carotid arterial blood was significantly lower for animals in Group A 45 min after the beginning of hemorrhage (19.26 ± 3.11 *vs.* 41.87 ± 2.79 mmHg, p<0.001) (Table II). SvO_2 in both animal groups was below baseline values prior to surgical haemostasis, although higher in animals in Group B compared to animals in Group A (Table II). After surgical haemostasis, SvO_2 did not return to baseline values but remained in the normal physiological range for animals in Group B (Table III).

Cerebrovascular Response

Statistical analysis was performed as mentioned in the previous paragraph. In animals in Group A, rCBF declined in a time-dependent manner despite aggressive resuscitation and at 45 min of hemorrhage reached its lower levels (Figure 5A). Animals in Group B showed initially a sharp decrease in rCBF that was improved at 45 min post-hemorrhage and returned to baseline values soon after surgical haemostasis. In the same line, SjO_2 decreased to similar levels for both groups during hemorrhage and in animals in Group B the parameter returned to baseline levels after surgical intervention (Figure 5B). $AVDO_2$ during the hemorrhagic phase was higher in animals in Group A, reaching significance at 5 min (10.68 ± 1.15 *vs.* 6.78 ± 0.95 ml/dl) and remained otherwise in normal physiological range (Figure 6). In animals in Group B, $AVDO_2$ decreased below physiological values at 45 min of haemorrhage but eventually returned to baseline levels after surgical haemostasis.

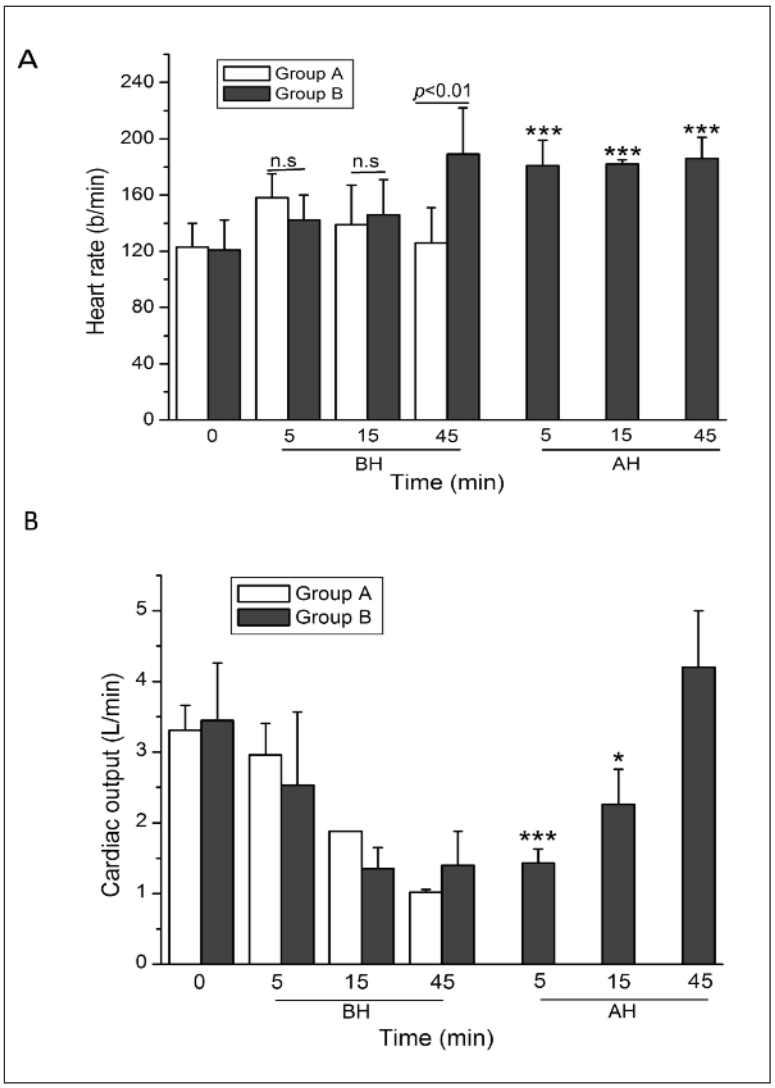

Figure 4. Graphs showing HR ***(A)*** and CO ***(B)*** at different time points before (BH) and after surgical haemostasis (AH). Results are expressed as mean ± SD. Asterisks denote statistical difference from group baseline values, *$p<0.05$, ***$p<0.001$.

Discussion

The cornerstone of emergency and prehospital resuscitation in the traumatic brain injury patient is to support brain oxygenation and restore cerebral perfusion. Since blood loss is the most common cause of hypotension in TBI patients, current Brain Trauma Foundation guidelines recommend resuscitation with isotonic fluids to target a SAP > 90 mmHg with ultimate goal to maintain a CPP greater than 70 mmHg[7]. Hypotension has been shown to be an independent factor associated with increased mortality rates and worse outcomes after TBI[1]. Mechanisms involved include impairment of cerebral autoregulation and altered cerebrovascular resistance. However, data supporting this notion were collected several hours or days after primary injury and predominant pathophysiological processes may vary from those of the period immediately following injury. It is also shown that high resuscitation speed in order to maintain the proposed SAP in severe hypotensive shock is associated with higher levels of fluid extravasation which is detrimental when combined to TBI[16]. Withholding fluid resuscitation during uncontrolled hemorrhage at the early acute phase of brain injury to conduct prospective randomized controlled trials would not be humane or ethically responsible. In this pilot animal study, we found that withholding fluid resuscitation in combined TBI and near fatal hemorrhage prior to definite surgical haemostasis resulted in increased survival. We also showed that normotensive resuscitation resulted in increased survival only during

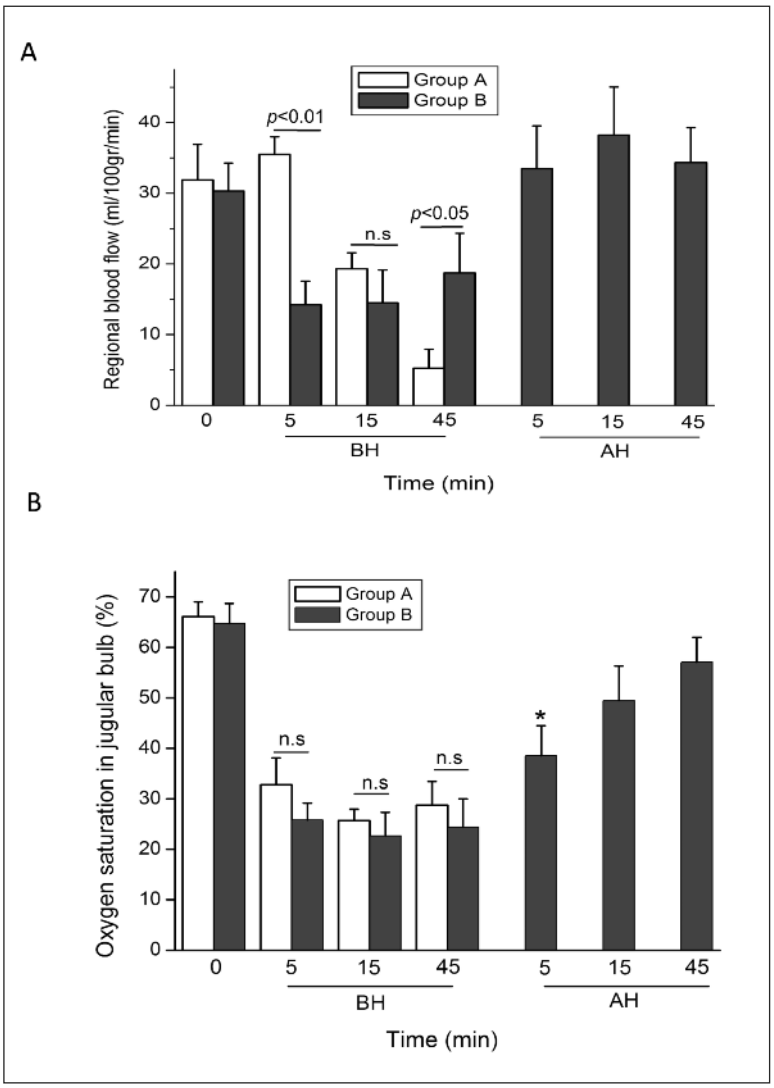

Figure 5. Graphs showing rCBF **(A)** and SjO_2 **(B)** at different time points before (BH) and after surgical haemostasis (AH). Results are expressed as mean ± SD, n.s non significant. Asterisks denote statistical difference from group baseline values, *p<0.05.

the first 45min of hemorrhagic shock. This is in line with other published animal and laboratory studies showing that survival outcomes from different resuscitation strategies depend on whether or when bleeding is controlled[9,10]. In modern urban trauma systems this time frame is sufficient for definite management of haemorrhage, but it can't be encountered in rural areas or military settings. Since all animals from the resuscitation group died before surgical haemostasis we cannot directly compare physiological parameters between the two groups following this time point. We showed however that hemodynamic and cerebral oxygenation profile were restored to baseline values in non resuscitated animals, suggesting that definite management of hemorrhage is of great importance.

As described previously by others[11] and shown in this study, the proposed SAP goal of 80 mmHg was never achieved despite aggressive delivery of fluids. We also showed that SAP and MAP were significantly higher during the late haemorrhagic phase in the permissive hypotension group. In addition, CO decreased to a plateau in the permissive hypotension group but declined in a time-dependent manner and showed a trend towards lower values in aggressively resuscitated animals. The latter is known to carry a greater risk for cardiac arrest. At the same time, S_vO_2 was higher in the permissive hypotension group and oxygen delivery could better meet tissue oxygen needs during hemorrhage. After surgical haemostasis, all the parameters above returned to normal physiological values suggesting

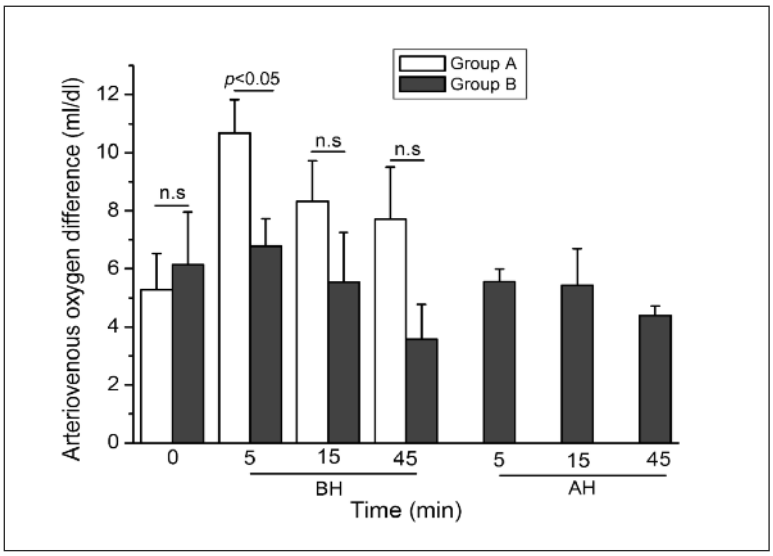

Figure 6. Graph showing AVDO2 at different time points before (BH) and after surgical haemostasis (AH). Results are expressed as mean ± SD, n.s non significant.

that withholding fluid resuscitation leads to stable hemodynamics during ongoing hemorrhage and safely prolongs the time for intervention.

The duration and severity of hypotension is a critical parameter in the neurologic outcome following TBI. In a study in swines even a 2 hour of severe hemorrhagic shock (MAP = 35 mmHg) could produce large but still reversible brain lesions[17]. Moderate hypotension (MAP = 60 mmHg) prior to surgical haemostasis did not compromise cerebrovascular hemodynamics in a combined model of TBI and extra- and intraperitoneal hemorrhage in swines[11]. In our work, we showed that during hemorrhage rCBF was below normal values for both animal groups but was better maintained at the later stages of hemorrhage in non-resuscitated animals. We also showed that rCBF could be restored to baseline values following surgical haemostasis although we can't conclude about the neurological outcome. We speculate that the more stable hemodynamic profile and the higher $PaCO_2$ in the permissive hypotension group favors cerebral arterioles to dilate and sustain blood flow. In their study, Carrillo et al[14] observed that in severe haemorrhagic shock controlling MAP 40 mm Hg for 60 minutes or MAP 30 mm Hg for 45 minutes did not cause functional or brain damage as defined by neurologic deficit scores and histological analysis in 10 d-surviving rats. In our animal model, median MAP was about 28 mmHg for resuscitated animals and 42 mmHg for non-resuscitated animals (data non shown). We also showed that SjO_2 remained below the ischemic threshold for both animal groups throughout the haemorrhagic phase and in animals in Group B returned within normal physiological values after surgical intervention. $AVDO_2$ which is a better indicator of global ischemia than SjO_2 or CBF alone remained almost within normal physiological range and didn't differ between groups during hemorrhage. Furthermore, in animals in Group B the parameter didn't differ with baseline values after surgical haemostasis. All the above suggest that brain oxygen delivery in the permissive hypotension group could finally meet the brain metabolic demands.

Limitations of our study: In this study we used a well established animal model of TBI that has been shown to offer several advantages over others used previously[18]. However it is also subjected to certain limitations and can't be generalized to all TBI patients. Since we measured certain cerebrovascular parameters representing the time before medical intervention and during surgical haemostasis in the operation theater, we can't conclude about the long-term neurological outcome. In the same line, we can't exclude subsequent complications of the multi-trauma patient that pose a high risk of mortality after surgical intervention and transfer to the ICU; unfortunately we were not able to include histopathological data to evaluate end-organ damage triggered among others by hemorrhage and/or tissue hypoperfusion. The risk of development of multiple organ dysfunction syndrome (MODS) post-surgery is always present but can usually be managed especially upon delayed presentation. In our study

SvO_2 and lactic acid changes that reflect anaerobic metabolism and tissue perfusion were minor after surgical haemostasis and we can speculate that tissue damage if any, is reversible. In favour to the later an experimental study in swines showed that the kidney can tolerate 90 minutes of warm ischemia without impairment of its function[19] which is well above the time used in our study. All the above imply that it would be premature to recommend withhold of fluid resuscitation based only on the present study. Finally, we used propofol anesthesia which has been shown to decrease CBF in humans and experimental brain injury[20,21] and we address that our results would be more representative in a non-anesthetized model. On the other hand, a multi-injured patient with severe TBI will probably be intubated prior to his admission at the emergency room and propofol is the most commonly used anesthetic under these conditions.

Conclusions

This study compared the effect of permissive hypotension in a combined animal model of traumatic brain injury and uncontrolled hemorrhage. Our data demonstrate that permissive hypotension by withholding fluid resuscitation prior to definite surgical haemostasis results in increased survival, more stable and reversible hemodynamics and brain function parameters. Collectively, even extreme hypotension may not be harmful or increase the potential for secondary brain insult at least for a limited time period.

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Conflict of Interest

The Authors declare that there are no conflicts of interest.

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