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Permissive hypotension¹

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Summary

In trauma patients restoration of intravascular volume in an attempt to achieve normal systemic pressure faces the risk of increasing blood loss and thereby potentially affecting mortality. Due to the lack of controlled clinical trials in this field, the growing evidence that hypotensive resuscitation results in improved long-term survival mainly stems from experimental studies in animals. The main differences between concepts for the reduction of blood loss in systemic hypotension are between “deliberate hypotension” (synonym “controlled hypotension”, used intraoperatively), “delayed resuscitation” (where the hypotensive

period is intentionally prolonged until operative intervention) and “permissive hypotension” (where restrictive fluid therapy increases systemic pressure without reaching normotension). In this review the concept of “permissive hypotension” is delineated on the basis of macro- and microcirculatory changes secondary to hypovolaemia and low driving pressure, and the potential indications and limitations are discussed.

Keywords: permissive hypotension; hypotensive resuscitation; primary resuscitation; trauma care; fluid therapy; brain injury

Zusammenfassung

Bei Patienten nach Trauma und Schock ist die Steigerung des Intravasalvolumens zwecks Erzielung einer Normotension mit dem Risiko eines erhöhten Blutverlusts und damit möglicherweise mit einem (negativen) Einfluss auf die Überlebensrate verbunden. In Ermangelung kontrollierter klinischer Studien zu diesem Thema legen bislang vor allem die Ergebnisse tierexperimenteller Untersuchungen einen positiven Effekt auf die Überlebensrate mittels «hypotensive resuscitation» nahe. Bei den Konzepten zur Verminderung des Blutverlusts in Anwesenheit einer systemischen Hypotension ist zu unterscheiden zwischen «deliberate hypotension» (Synonym: «controlled hypotension», die intraoperativ angewandt wird), «delayed resuscitation» (wobei das hy-

potensive Intervall bewusst bis zur operativen Versorgung verlängert wird) und «permissive hypotension» (wobei mittels restriktiver Flüssigkeitstherapie zwar der systemische Druck erhöht wird, ohne allerdings normotensive Werte zu erreichen). In dieser Übersicht wird das Konzept der permissiven Hypotension auf der Grundlage der infolge Hypovolämie und niedrigem Perfusionsdruck eingetretenen Veränderungen von Makro- und Mikrozirkulation erläutert und mögliche Indikationen und Limitierungen dieser Methode diskutiert.

Keywords: permissive Hypotension; hypotensive Reanimation; primäre Reanimation; Traumabehandlung; Flüssigkeitstherapie; Gehirnverletzung

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Introduction

The present review focusses on the management of the polytraumatised patient in view of pathophysiologic alterations induced by trauma and shock. Restoration of intravascular volume in an attempt to achieve normal systemic pressure faces the risk of increasing blood loss and thereby potentially affecting

mortality. The concept of permissive hypotension is delineated on the basis of macro- and microcirculatory changes secondary to hypovolaemia and low driving pressure, and the potential indications and limitations are discussed.

Defining the problem

In recent years there have been increased activities in the prehospital management of trauma and shock and a trend towards early and aggressive intervention. While logistics have been improved and therefore the time interval until arrival of the emergency team at the accident site has been shortened, issues of debate have been prehospital airway management and fluid resuscitation.

Many trauma victims show signs of hypovolaemia and shock in conjunction with tissue injury, and there has been an ongoing controversy whether or not to perform early aggressive fluid replacement therapy. While restoration of intravascular volume and pressure is intuitively logical, attempts to achieve normal arterial pressure during uncontrolled bleeding will increase blood loss. In contrast, from experimental studies there is growing evidence

that hypotensive resuscitation results in improved long-term survival [1–4]. To date, the only published study in humans, in victims of penetrating torso trauma, has demonstrated a significant reduction in mortality when fluid resuscitation was restricted in the prehospital period [5]. However, it is important to note that the objective of that study was the comparison between standard prehospital and trauma centre fluid resuscitation versus delayed onset of fluid resuscitation, i.e. having vascular catheters placed but i.v. fluid not administered until patients reached the operating room. Moreover, the mean length of time from injury to arrival in the operating room was remarkably short in both groups. Thus, clinical data from well controlled, prospective trials applying the concept of permissive hypotension in trauma patients are still missing.

Consequences of trauma and blood loss

Hypovolaemia affects myocardial performance predominantly through the decrease in cardiac output via the Frank-Starling mechanism. Minor losses up to 10% of blood volume are generally compensated by a slight increase in heart rate leaving cardiac output and systemic blood pressure unaffected. With increasing volume loss and a concomitant decrease of venous return, a fall in cardiac output occurs. If hypovolaemia exceeds 20% of normal intravascular volume, the heart rate substantially increases, and peripheral vasoconstriction and a decrease in systolic pressure develop [6]. Blood flow to the skin and peripheral tissues is reduced in an effort to preserve perfusion of vital organs.

Even in organs with autoregulatory response to a variation in blood pressure shifts of intra-organ blood flow occur, which are relevant for organ function particularly in case of underlying disease. With regard to the kidney, e.g. glomerular filtration rate is maintained until

MAP falls below 75 mm Hg. At this level, perfusion is still sufficient to meet the metabolic needs of the kidneys cells, although oliguria may ensue. These data, however, stem from experiments in which blood pressure was lowered pharmacologically, i.e. normovolaemia was maintained (see below: “deliberate hypotension”). When challenging the autoregulatory threshold, one has to take into account potentially preexisting alterations relevant for blood flow in organs, for example diabetes, atherosclerosis, or other vascular abnormalities compromising total inflow under normal circulatory conditions (e.g. renal or carotid artery stenosis).

In response to hypovolaemia the distribution of cardiac output to the organs is rearranged depending on their α - and β -adrenergic innervation [7]. Due to the high α -adrenergic innervation of the splanchnic vascular bed, blood flow to the intestine and to the gut mucosa in particular are curtailed, and early failure of in-

testinal barrier function further contributes to the process of protracted shock states. Even short phases of low flow as result of trauma and shock can induce lesions of the gut mucosa [8], and represent one of the key factors for the

loss of intestinal mucosal barrier function with ensuing translocation of bacteria and endotoxins with the release of cytokines (TNF α , IL-1, IL-6) and postanoids (PGE₂) [9].

Alterations at the microcirculatory level secondary to low perfusion pressure and shock

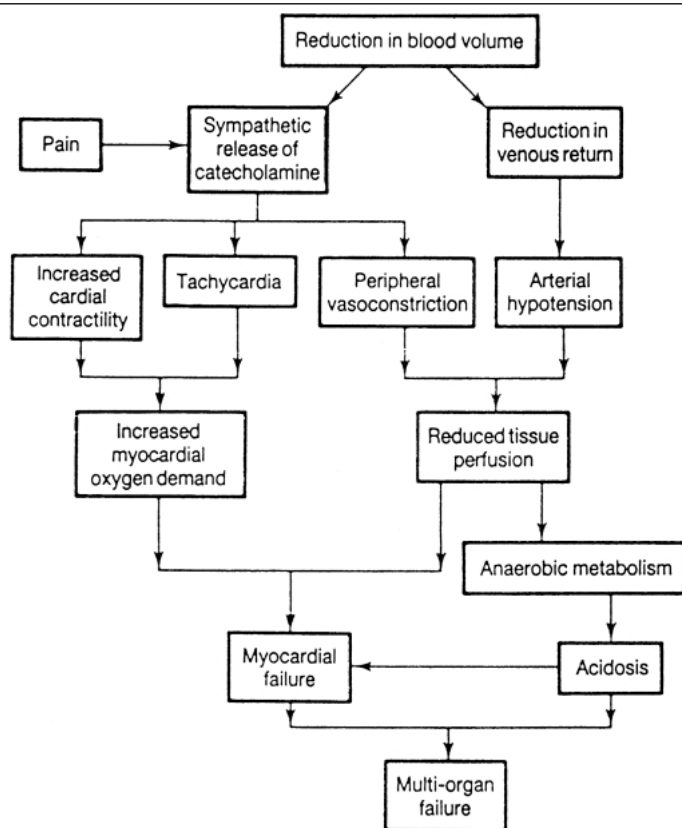
The two major factors responsible for the decrease in nutritional blood flow following trauma and shock are hypovolaemia and low perfusion (driving) pressure. The balance between total oxygen delivery and oxygen demand is maintained as long as tissue oxygen extraction can be enhanced while nutritional blood flow decreases as result of blood loss. However, beyond a critical point tissue perfusion can no longer meet the local oxygen needs. The consequences are anaerobic metabolism, cellular acidosis, and impairment of specific organ function favouring the development of multiple organ failure (fig. 1) [10].

The normal microvascular perfusion is characterised by temporal and local variations of capillary flow, which in general is determined by local driving pressure, the dimensions of the capillary network and the rheologic properties of the blood [11]. All three factors are compromised in patients after trauma and haemorrhagic shock. Recent experimental data from haemorrhagic shock and resuscitation in a con-

scious hamster model indicate that response of the small arteries is the crucial determinant of blood flow at the microcirculatory level, and constriction of these vessels may help sustain arterial pressure, while constriction of small veins may enhance blood redistribution from the skin to the vital organs under the hypotensive condition. The recovery of blood flow, oxygenation, and functional capillary density (the latter describing the number of capillaries with RBC flow stemming from a small arteriole) following haemorrhagic shock and resuscitation depends not only on blood oxygen content, but also on the viscosity of the circulating blood and the heterogenous shear stress-dependent production of endothelium-derived relaxing factor (EDRF) [12, 13].

Rapid restoration of intravascular volume may lead to restitution of cardiac preload. However, the changes of microvascular permeability through the activation of cascade systems and activated leukocytes (whole body inflammatory response) may lead to pathologic shifts of

Figure 1
Pathophysiology of hypovolaemic shock (from [10]).



fluid and plasmatic macromolecules resulting in tissue oedema formation or third space fluid losses. Early in the course of hypovolaemia and shock, the lumen of the capillaries becomes narrowed due to the swelling of hypoxic endothelial cells and the adhesion of activated polymorphonuclear leukocytes (PMNL) to the endothelium of postcapillary venules. This phenomenon causes exclusion of microvessels from perfusion and leads to a highly heterogeneous perfusion pattern within the microcirculatory network [14]. Moreover, occlusion of microvessels either by swollen endothelial cells or capillary plugging through uncontrolled activation of coagulation may completely abolish nutritional blood flow.

In addition, the interaction of PMNL with the venular endothelium impedes outflow from the capillaries and is followed by the release of vasoactive mediators and toxic oxygen species, promoting redistribution of tissue perfusion, macromolecular leakage, interstitial oedema, and further impediment of nutritional flow and delivery of oxygen to the tissues [11].

Recent interest focusses on the cell-cell interactions in the blood stream and platelet-endothelial cell interaction in particular [15]. It has been shown in experimental studies in the

mouse that during ischaemia/reperfusion (I/R) a strong activation of platelets occurs leading to local accumulation of platelets reaching a maximum within minutes after the onset of reperfusion, indicating that platelets are among the first cells recruited to the site of injury. The data from this group provide strong evidence that P-selectin expressed by the endothelium is the molecular determinant of I/R-induced platelet-endothelial cell interaction [15]. Under conditions of low pressure-induced low flow these alterations may occur in the small arterioles and thus perfusion may already be redirected at this early point bypassing the microcirculatory network and resulting in reduced nutritional blood flow.

In the polytraumatised patient an episode of hypotension with decreasing driving pressure in the microcirculation and thus compromised nutritional blood flow may early produce local, hence clinically undetectable, or global ischaemia with reperfusion injury in more severe cases. Any subsequent insult will amplify the tissue response as manifested by increased cytokine production of macrophages, neutrophil oxidant release and microcirculatory disturbance [16].

Deliberate hypotension in surgery

The main purpose of deliberately inducing hypotension intraoperatively is to decrease blood loss, thereby improving operating conditions or decreasing the need for blood transfusions [17]. This concept of intentionally decreasing arterial blood pressure to hypotensive levels during surgery was first proposed by Cushing [18] in 1917 for intracranial surgery. Eckenhoff and Rich [19] supplied objective data that deliberate hypotension can indeed decrease blood loss. Blood loss was compared for patients undergoing rhinoplasty, porto-caval shunt, or craniotomy for aneurysm or suspected tumour with or without deliberate hypotension. For each of these procedures blood loss decreased by 50% or more with hypotension. For some patients, however, the correlation between decrease in arterial blood pressure and blood loss is not linear, and it has been suggested that depression of cardiac output correlated better with a dry operation field than did (mean) systemic pressure.

Reviewing the literature indicates that most

studies define deliberate hypotension as a reduction in systolic blood pressure to 80–90 mm Hg, or decreasing MAP to 50–65 mm Hg in normotensive patients. Because deliberate hypotension is clearly designed to decrease arterial blood pressure but still preserve organ blood flow and function, it must be emphasised that this procedure requires constant assessment of intravascular volume by invasive haemodynamic monitoring throughout surgery, to ensure optimal organ function.

Possible need for deliberate hypotension is in neurosurgery, large orthopaedic procedures, surgery on large tumours, or even when religious beliefs preclude blood transfusion [17]. A history of cerebrovascular disease, renal dysfunction, liver dysfunction, or severe peripheral claudication suggests that the patient is less likely to have good organ perfusion during hypotension. Also, patients with hypovolaemia or severe anaemia, who have diminished reserves for adequate organ perfusion, are generally not regarded as suitable candidates [17].

Permissive hypotension versus delayed resuscitation in trauma care

Systemic hypotension may reflect myocardial pump failure, intravascular volume depletion, or vasodilation. Posttraumatic hypotension is generally caused by haemorrhagic shock, and current guidelines include rapid infusion of crystalloid solutions with the goal of normalising blood pressure as rapidly as possible. However, attempts to normalise blood pressure in case of uncontrolled bleeding as in victims with penetrating trauma, may result in increased blood loss and worse outcomes. In this context, restriction of fluid resuscitation may actually improve outcome. This particularly holds true for the prehospital scenario in metropolises, where trauma centres may be reached within few minutes. Optimal therapy can be initiated after ER admission and in view of the results obtained from radiodiagnostics (chest X-ray, computer tomography), ultrasonography of the abdomen and even echocardiography (excluding pathologic pump function secondary to myocardial infarction or valve abnormalities).

The study of Bickell and coworkers [5], published in 1994, addressed the point that intravenous volume infusion may be detrimental in the clinical setting, if administered before haemorrhage is surgically controlled. At that time, major concerns focussed on the fact that aggressive administration of fluids may disrupt the formation of thrombus, increase bleeding and decrease survival. The authors included 598 patients with penetrating injuries to the torso and a prehospital systolic blood pressure of ≤ 90 mm Hg. Patients assigned to the immediate-resuscitation group received standard fluid resuscitation before they reached the hospital and in the trauma centre, and those assigned to the delayed-resuscitation group received i.v. cannulation but no fluid resuscita-

tion until they reached the operating room. Despite the criticism against major points in the protocol and the realisation of this study published in subsequent issues of the New England Journal of Medicine, the data suggest that restriction of volume therapy in hypotensive patients with penetrating torso injuries may be associated with lower mortality, fewer post-operative complications and a shorter hospital stay.

It is important, however, to focus on two issues: first, this was a clinical study in which hypotensive patients immediately received either fluid therapy or not, i.e. normalisation of blood pressure was not the primary objective. Second, the interpretation of the results is restricted to penetrating trauma, in which significant and ongoing blood loss occurs during a phase, in which medical personnel is able to resuscitate the trauma victim, insert an i.v. cannula and infuse any i.v. solution (crystalloids, colloids) or drug (dopamine, epinephrine). In contrast, the concept of "permissive hypotension" does not exclude therapy by means of i.v. fluids, inotropes or vasopressors, the only restriction is to avoid completely normalising blood pressure in a context where blood loss may be enhanced (table 1).

It is interesting to note that in an animal model of pressure-driven haemorrhage in dogs fluid resuscitation indeed improved haemodynamic performance and oxygen delivery in the presence of increased blood loss [20]. The model dictates that all forms of treatment which improve systemic pressure will also induce increased blood removal. But, despite this, cardiac output and oxygen delivery were significantly improved with respect to untreated controls [20].

Table 1

Main differences between concepts for reducing blood loss involving systemic hypotension.

	deliberate hypotension	delayed resuscitation	permissive hypotension
indication/scenario	intraoperatively	trauma care	trauma care
systemic pressure	intentionally reduced pharmacologically or by means of positioning	hypotensive period intentionally prolonged until operative intervention	increased by primary therapy without reaching normotension
intravascular volume	unaffected	left reduced	increased during restrictive primary fluid therapy (hypovolaemic state will persist)
blood haemoglobin concentration	unaffected	left reduced	left reduced

"deliberate hypotension" is a synonym for "controlled hypotension", "induced hypotension" and "hypotensive anaesthesia".

"delayed resuscitation" is a synonym for "delayed fluid resuscitation".

"permissive hypotension" is a synonym for "hypotensive resuscitation".

Determining the optimum target blood pressure

Kowalenko et al. [1] investigated progressive haemorrhage to a MAP = 30 mm Hg followed by free intraperitoneal haemorrhage (aortotomy) in pigs in an attempt to mimic uncontrolled haemorrhagic shock. Resuscitation consisted of saline infusion to reach a MAP of 40 mm Hg (group 1) or 80 mm Hg (group 2), or no resuscitation (group 3). After a maximum saline infusion of 90 ml/kg, the infusate was changed to shed blood at 2 ml/kg/minute. One-hour survival was 87.5%, 37.5% and 12.5% for groups 1, 2 and 3, respectively. Intraperitoneal haemorrhage in the same groups was 8.2 ml/kg, 39.9 ml/kg and 6.7 ml/kg. The authors concluded that the attempt to restore normotension with aggressive saline infusion markedly increases haemorrhage volumes and fails to improve survival in the setting of severe uncontrolled haemorrhage. Maintenance of the hypotensive state with judicious saline administration causes less blood loss and may be preferable before definitive surgical repair of the bleeding site [1].

Similar results have been reported by Stern and coworkers [2] in an experimental model of uncontrolled intraabdominal bleeding in pigs. These authors investigated the effect of volume therapy by means of 0.9% saline administered over 30 minutes, followed by the animals' own blood (shed blood). Resuscitation endpoints were a MAP of 40 (group 1), 60 (group 2) or 80 mm Hg (group 3). Animals were observed for 60 minutes or until death. Mortality was highest in the group resuscitated to a MAP of 80 mm Hg, and mean survival time amounted to 44 minutes. The average intraperitoneal haemorrhage volumes were 13 ± 14 , 20 ± 25 and 46 ± 11 ml/kg for the animals in the groups with MAP of 40, 60 or 80 mm Hg, respectively, showing significance at the 0.001 level between groups 1 and 3. The authors stated that attempts to restore blood pressure with crystalloid result in increased haemorrhage volume and markedly higher mortality [2].

Finally, Capone et al. [3] examined the long-term effects of deliberate hypotension using an experimental design which takes into account the different phases of therapeutic intervention. Uncontrolled haemorrhagic shock was produced in rats by a preliminary bleed followed by tail amputation. The experimental design consisted of three phases: a "prehospital phase" (90 minutes of uncontrolled bleeding with or without treatment with lactated Ring-

er's solution), followed by a "hospital phase" of 60 minutes, including control of haemorrhage and fluid resuscitation including blood), and a 3-day "observation phase". Four groups of animals were investigated, including one group without fluid therapy during the prehospital phase, one group having prehospital resuscitation to a MAP of 40 mm Hg with lactated Ringer's solution and a further group receiving prehospital fluid resuscitation to a MAP of 80 mm Hg. A fourth group consisted of untreated controls (without any resuscitation). At the end of the observation period none of the animals of the untreated controls had survived, and only one animal in the group with no prehospital fluid resuscitation had survived (10% survival rate). Most strikingly, however, was the fact that in the group resuscitated to MAP of 80 mm Hg by prehospital fluid resuscitation 8 of the 10 animals died within 90 minutes and none survived long-term. In contrast, hypotensive fluid resuscitation to MAP of 40 mm Hg resulted in a survival rate of 60%. Hypotensive resuscitation resulted in less acidaemia and improved long-term survival in this scenario, whereas attempts to achieve normal MAP during uncontrolled bleeding increased blood loss and mortality [3]. A different entity was addressed in an experimental rat model of closed head trauma combined with uncontrolled haemorrhage [4]. The study examined whether using phenylephrine or large volumes of saline i.v. to increase MAP to 70, 80 or 90 mm Hg during the combination of head trauma and uncontrolled haemorrhage improved neurologic outcome. In groups that received saline to maintain MAP at 70, 80, or 90 mm Hg, survival rate at 2 and 24 hours was inversely related to MAP, volume of blood lost, and volume of saline given, and was directly related to head trauma. However, as the authors stated themselves, there were multiple factors that may have contributed to mortality in these groups, including hypovolaemic circulatory failure, hypoxic brain and cardiac damage secondary to decreased oxygen-carrying capacity, and brain damage and negative circulatory effects resulting from head trauma. The results in the groups receiving pharmacological support by means of phenylephrine to maintain MAP ≥ 70 mm Hg during 2 hours of haemorrhage after head trauma showed similar unfavourable results [4].

When “permissive hypotension” should best be avoided

The shift in the autoregulatory curve to the right for hypertensive patients puts these patients at higher risk of death and morbidity during permissive hypotension. Also angina pectoris or preexistence of cardiovascular disease limits the use of this concept: myocardial infarction with compromised cardiac function, where lowered systemic pressure reduces afterload but at the same time coronary perfusion pressure; cerebrovascular disease and carotid artery stenosis; compromised renal function due to A. renalis stenosis; intermittent claudication stage III/IV, where low blood pressure may induce sludge and lead to occlusion of the vessel lumen.

In a high percentage of polytraumatised patients also the brain is affected. The results from the Traumatic Coma Data Bank show the influence of the presence or absence of hypotension (defined as one or more recordings of a systolic blood pressure ≤ 90 mm Hg) or hypoxia ($\text{PaO}_2 < 60$ mm Hg) at the time of admission on the outcome of patients expressed by the Glasgow Outcome Scale (GOS) measured at 6 months after injury [21]. Most notably was the markedly detrimental effect of admission hypotension on outcome. Patients who were hypotensive at the time of admission had twice the mortality and a significant increase in morbidity when compared with patients who were normotensive. The concomitant presence of hypoxia and hypotension upon admission resulted in a 75% mortality. Evidence strongly suggests that the avoidance or mini-

misation of hypotensive insults during the entire acute, postinjury period has the highest likelihood of improving outcome of any one single therapeutic manoeuvre [22].

In addition, because hypotensive patients with traumatic brain injury will usually be victims of blunt vehicular trauma and have associated non-penetrating injuries, the data from the Bickell study [5] are not directly relevant. Owing to impaired cerebral autoregulation after trauma, hypovolaemic hypotension that would not otherwise reduce cerebral blood flow may lead to brain ischaemia. Thus, prompt application of life support, i.e. tracheal intubation and mechanical ventilation as well as i.v. fluid resuscitation may limit secondary hypoxic brain damage, and concerns that adequate fluid resuscitation results in increased intracranial pressure (ICP) after head injury appear to be unfounded [23].

The concept of maintaining cerebral perfusion pressure, which in case of traumatic brain injury calls for normotensive systemic pressures, has been extended to patients with spinal cord injury. Maintaining spinal cord blood flow reduces the changes of secondary injury and may improve outcome [24]. In a clinical study in which MAP was maintained at 85 mm Hg by volume expansion and use of vasopressor therapy combined with spinal stabilisation and steroid therapy, most patients had improved neurologic function at a 6- to 12-month follow-up [25].

The best “solution” in this dilemma

Hence we have to select the subpopulation of trauma patients, who definitely will benefit from low-volume or hypotensive resuscitation after having analysed data from well controlled clinical trials. Although there is growing evidence from experimental studies, clinical data are in most cases observational or case reports, and do not yet justify to give a general recommendation.

From the practical point of view the debate should no longer focus on whether or not to perform initial fluid resuscitation during the prehospital period, what how much or which fluid should be infused how fast [26]. Permissive hypotension may be appropriate in patients with penetrating trauma or even with blunt trauma in the absence of traumatic brain injury or spinal cord injury, without known

preexisting cardiovascular diseases or compromised organ function. Mostly younger people with good physiological compensatory working mechanism, representing the major part of trauma victims, might fit into this concept. It is, however, important to note the difference between “low systemic pressure” and “low flow” at the microcirculatory level. Although driving pressure is a somewhat crucial determinant for blood flow below a certain pressure range, tissue oxygenation and metabolism also depend on the circulating blood volume, rheologic properties and cell-cell interactions (leukocyte-endothelium, leukocyte-thrombocyte, thrombocyte-endothelium) in different segments of the microcirculatory network. From this point of view it seems attractive to incorporate the concept of “small-volume resuscita-

tion" using hyperosmolar saline colloid solution into the discussion of permissive hypotension [27]. It is a well established fact that by a small amount (4 ml/kg, 250 ml in an adult) of hyperosmolar saline colloid solution nutritional blood flow is substantially enhanced in case of severe trauma and blood loss, although systemic pressure remains reduced. Especially for patients suffering from traumatic brain injury and hypotension it has been shown that the initial i.v. bolus infusion of 250 ml of hyperosmolar saline dextran resulted in a survival rate until discharge of 37.9% compared with 26.9% with standard of care ($p = 0.080$) [28]. The authors concluded that patients who have traumatic brain injuries in the presence of hypotension and receive small-volume hyperosmolar resuscitation are about twice as likely to survive as those who receive SOC.

Another option or improvement of oxygen transport to the tissues is to augment oxygen transport capacity, provided early intubation and ventilation in polytraumatised patients has been established. This aspect has been addressed by different companies presently exploring the applicability of artificial oxygen carriers [24]. In an experimental study Stern and colleagues [29] used supplemental perfluorocarbon for permissive hypotension (hypotensive resuscitation) of severe uncontrolled haemorrhage in pigs. Following severe uncontrolled haemorrhage and resuscitation both oxygen content and delivery were significantly higher in the treatment group receiving the oxygen carrying perfusate. Further clinical trials using such compounds are presently on the way.

Recommendations

- 1) Permissive hypotension is a therapeutical option for victims of penetrating injuries, provided fast evacuation to definite (surgical) intervention.
- 2) Permissive hypotension by means of fluid restriction is not recommended in case of blunt trauma.
- 3) Permissive hypotension is contraindicated in patients with traumatic brain injury (TBI), even in case of penetrating trauma, or in spinal cord injury due to worse neurological outcome.
- 4) Elderly patients or those with preexisting compromised cardiovascular function will probably not benefit from the concept due to fast exhaustion of physiologic compensatory mechanisms.

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