Resuscitation, 18, Suppl. (1989) S51 – S61
Elsevier Scientific Publishers Ireland Ltd.

MICROCIRCULATORY THERAPY IN SHOCK

K. MESSMER and U. KREIMEIER*

Department of Experimental Surgery, Surgical Clinic, University of Heidelberg, 6900 Heidelberg 1 (F.R.G.)

SUMMARY

The normal microvascular perfusion pattern is characterized by temporal and spatial variations of capillary flow. Local driving pressure, arteriolar vasomotion and endothelial cells are key-factors for local regulation of hydraulic resistance and fluid balance between the blood and tissue compartments. In shock, both the central and particularly the local mechanisms controlling microvascular perfusion are impaired. The microvascular perfusion pattern becomes permanently inhomogeneous due to lack of arteriolar vasomotion, changes of flow properties of blood, endothelial cell swelling and blood cell-endothelium interaction. Hence the objectives of primary shock therapy are to reestablish precapillary pressure, arteriolar vasomotion and to open the occluded microvascular pathways in order to reestablish the surface area needed for exchange of nutrients and drainage of waste product. These effects can not be achieved by vasoactive drugs, unless blood volume has been restored and blood fluidity improved by hemodilution. Whereas the necessary hemodilution can be achieved by conventional volume substitutes (colloids, crystalloids) restoration of vasomotion and reopening of narrowed capillaries can be obtained by small volume resuscitation using hyperosmotic/hyperoncotic salt dextan solution. The potential of this new concept for primary resuscitation and treatment of tissue ischemia is presently explored.

Key words: Microvascular failure – Arteriolar vasomotion – Endothelial swelling – Hyperosmotic/hyperoncotic solutions – Small volume resuscitation

INTRODUCTION

Primary resuscitation in shock from hemorrhage, trauma or septicemia consists of rapid restoration of the circulating blood volume. Despite the

*Address for correspondence: Prof. Dr. med. Konrad Messmer, Dept. of Experimental Surgery, Surgical Clinic, University of Heidelberg, Im Neuenheimer Feld 347, 6900 Heidelberg 1, F.R.G.

0300-9572/89/$03.50

controversy being entertained for about two decades, whether colloids or crystalloids are preferable for primary resuscitation there is general agreement that the time during which the patient remains hypovolemic and in shock is decisive for his final outcome. While primary resuscitation results in a normalization of the macrohemodynamics, volume therapy might not necessarily abolish the shock-specific impairment of the microcirculation [1]. It is now appreciated that persisting disturbances of nutrional blood flow might lead to local ischemia and local reperfusion damage which in concert with tissue damage — and/or inflammation — induced activation of the complement system and other mediators has the potential to promote multiple organ failure. Microcirculatory failure and local tissue damage has also been demonstrated in the early phase of septic shock, i.e. hyperdynamic endotoxinemia at a time, when cardiac output is normal or above normal values and global organ blood flow seems unimpaired [2]. Of particular importance is the curtailment of nutritional blood flow to the intestine with impairment of the mucosal barrier and subsequent translocation of microorganisms and endotoxins into the systemic circulation promoting the development of bacteremia, endotoxinemia and septic shock.

In the following the shock-specific impairment of the microcirculation will be described and rational approaches to restore normal microcirculatory perfusion are discussed.

I. MICROCIRCULATORY IMPAIRMENT IN SHOCK

Acute volume loss and decrease of venous return is followed by a fall in stroke volume and arterial hypotension whereby the reflex stimulation of the sympathetic system is elicited [3]. Depending upon the availability of adrenergic receptors and depending upon the degree of activation, regional vasoconstriction, local vasodilatation and increased cardiac performance are encountered. The expression of these features is directly correlated to the prevailing type of adrenergic innervation. Vasoconstriction is most pronounced in the splanchnic organs followed by the kidney, skin and skeletal muscle. Due to the mere absence of alpha-adrenergic receptors the coronary and cerebral vessels escape from the vasoconstriction and remain perfused over all but at very low arterial pressures. The redistribution of cardiac output is at the expense of the organs whose vasculature is rich in alpha-receptors, consequently, the most severe vasoconstriction though clinically undetected, but decisive for the progression of shock occurs in the splanchnic organs.

Within the entire vascular bed the alpha-receptor mediated constriction is most pronounced in the precapillary arterioles, but also present in postcapillary venules. Due to precapillary constriction, the local driving pressures, local flow velocities and the number of perfused capillaries are reduced [4]. At the same time the spontaneous arteriolar vasomotion by which spatial and temporal distribution of flow is achieved in all parts of a given tissue [5] is abolished. Loss of arteriolar vasomotion changes the microangiodynamics

with impact on the fluidity of the blood contained in the microvessels as well as on transcapillary fluid exchange. As a consequence tissue perfusion becomes permanently heterogeneous [6] and the relationship between blood flow and the capillary surface area available for exchange of nutrients and metabolites (Ps, Permeability Surface Area Product) is greatly reduced [4,7].

The dissociation of capillary perfusion into areas of stagnant flow and areas preferentially perfused by plasma compromises the tissue supply of nutrients, but equally important diminishes the drainage of cellular metabolites leading to accumulation of mainly acid metabolites from anaerobic cell metabolism. Tissue acidosis changes the microvascular reactivity to endogenous catecholamines allowing dilatation of the precapillary resistance vessels, while constriction of the postcapillary venules is maintained. In addition outflow from postcapillary vessels is severely compromised by the excessive deteriotation of blood fluidity originating from red cell aggregation at low flow velocities. The net result of the shock-specific vasomotion are forcible shifts of ions and fluids into the interstitium and into the tissue cells, further impairment of the flow conditions and of the flow properties of the blood within the microvessels. Edema develops in the extravascular tissues with increase of intravascular hematocrit, whereby a vicious circle is established at the level of the microcirculation. The exclusion of microvessels from flow by red cell aggregates is reinforced by granulocytes adhering to the surface of the endothelial cells thereby blocking the microvascular lumen [8]. The adherence of leukocytes to the endothelial surface of capillaries and preferably of postcapillary venules is followed by release of oxygen free radicals. Tissue damage is therefore not exclusively due to lack of oxygen but also to incomplete reperfusion and reoxygenation of ischemic tissues. During this phase the oxygen free radicals formed by lipoperoxydation denature cellular proteins and irreversibly damage the tissue cells. Reperfusion injury is characterized by endothelial lesions, intracellular edema and finally by deleterious influx of calcium into the cells [8].

The efficacy of primary resuscitation and shock treatment depends upon whether reversal of microcirculation failure and inhomogeneous tissue perfusion can be achieved with the final goal to prevent progression from shock into multiple organ failure [1].

II. AIMS OF VOLUME REPLACEMENT THERAPY IN SHOCK

Since the detrimental and potentially fatal feedback mechanisms in the microcirculation are elicited by volume loss and reinforced by the vicious circles established in the microvasculature system the microcirculatory therapy of shock has to start with volume replacement [9].

The aim of primary resuscitation and volume replacement is the reversal of the maldistribution of blood flow in the macro- and the microcirculation. The fluidity of the blood is crucial for the persistence of the shock-specific impairment of the nutritional perfusion and for oxygen delivery to the tissues: microcirculatory failure results from both the loss of driving forces

(hypotension, low flow) and from loss of blood fluidity. Cell free fluids, preferentially colloid solutions allow to improve the fluidity of the blood in a short time by virtue of inducing hemodilution preferentially in the postcapillary segments of the microcirculation [10]. The hemodilution achieved by infusion of colloid solutions is instrumental for the efficacy of shock treatment: blood with low hematocrit requires less forces to reverse stasis and to restore flow. By decreasing the viscous component of the peripheral vascular resistance, hemodilution reduces afterload and improves the flow conditions for the blood in all segments of the circulation.

It is important to note that unless volume has been restored and the blood rheology has been normalized by means of intentional hemodilution, vasoactive substances will remain inefficient, because they can not overcome the rheological obstacles. In contrast cell free fluids enhance the blood fluidity and allow resolution of rheological problems. The hematocrit, which is the most important single determinant of blood fluidity can be decreased during initial resuscitation to values of approximately 30%. This hematocrit value reflects an optimum compromise between blood fluidity and oxygen carrying capacity and oxygen delivery to the tissues is preserved [11]. Only when coronary circulation is compromised or oxygen demands are elevated (sepsis) a higher oxygen content of the blood is required to maintain adequate oxygen delivery [11].

III. THE CHOICE OF FLUID FOR INITIAL VOLUME THERAPY SHOCK

Depending on the cause of shock and the length of time, the patient has been in shock the intravascular volume deficit is accompanied by depletion of interstitial and intracellular fluid volumes. Loss of extravascular fluid occurs in all types of shock due to influx of interstitial fluid into the intravascular space and fluid uptake into tissue cells, including endothelial cells. Comparing identical volumes of colloids and crystalloids reaching the circulation, colloids prove superior for primary resuscitation on the basis of their oncotic power and capacity to retain water in the intravascular space [10].

Crystalloids have to be given in amounts equivalent to 3—4 times the volume loss resulting in a fall rather than maintenance of colloid osmotic pressure, consequently fluid is accumulated in tissues with high compliance. It is fair to state, that both resuscitation modalities, namely crystalloids and colloids in association with electrolytes have proven suitable in clinical practice. Nevertheless the controversial discussion concerning potential advantages and disadvantages both forms of shock treatment modalities continues [9,10].

IV. HYPERTONIC SALINE AS PRIMARY RESUSCITATION FLUID

The requirements for an optimal solution for primary resuscitation are efficiency, practicability and safety. Considering the new information on the importance of local ischemia and reperfusion injury and their importance for the development of multiple organ failure, one has to reconsider, whether

primary resuscitation with conventional colloid and crystalloid solutions is efficient in restoring microcirculatory perfusion at the earliest time of therapy. In this context the observations of Roche e Silva and coworkers [12–14] are of particular importance. These authors have demonstrated in dogs and humans that the infusion of hypertonic sodium chloride solution with an osmolarity of 2400 mOsm/l can restore the cardiovascular function within a few minutes when given in volumes of only 4 ml/kg body wt. From these initial studies the concept of small volume resuscitation by means of hypertonic/hyperoncotic solutions has evolved. Velasco et al. [14] have demonstrated that 4 ml/kg body wt. of 7.5% sodium chloride when given without any further volume substitution restore the macrohemodynamics and allowed definite survival from hemorrhagic hypotension, whereas the control animals receiving identical amounts of isotonic saline died. The most striking effect of small volume resuscitation are an instantaneous increase of cardiac output to values above control and release of vasoconstriction [1,15–18]. Since only a small volume is needed to obtain this effect, it is now possible to markedly improve cardiovascular function from the very beginning of shock treatment, i.e. more rapidly and efficiently as compared to present resuscitation techniques which require much higher volumes of fluid, particularly when isotonic crystalloids are used.

V. HYPERTONIC/HYPERONCOTIC DEXTRAN SALT SOLUTIONS

With the aim to improve and to prolong its hemodynamic effect the colloid dextran has been added to the hypertonic salt solution. Smith et al. [19] demonstrated that animals subjected to standardized hemorrhagic shock were best resuscitated when they had received a single bolus infusion of 7.5% sodium chloride/6% Dextran 70. The cardiac output of animals treated with this solution remained at significantly higher values during the 3-h observation period; this finding was confirmed by Kramer et al. [17]. The cardiovascular and metabolic function of these authors' animals was fully restored after initial resuscitation from severe hemorrhage and total volume requirements were significantly lower as compared to primary resuscitation with normal saline. From the studies on hypertonic saline/colloid solutions one can conclude that the colloid Dextran 60/70 appears superior to 6% hetastarch, probably due to the higher oncotic power and the slower extravasation of dextran from the intravascular space [20].

VI. EFFECT OF HYPERTONIC/HYPERONCOTIC SALINE DEXTRAN ON NUTRITIONAL BLOOD FLOW

While all studies on small volume resuscitation have demonstrated a beneficial effect of hypertonic salt and salt/colloid solution on the macrohemodynamics, the metabolic status and, eventually, survival of the animals, few studies have addressed the effect of these solutions on the nutritional perfusion. We have therefore analyzed the effect of the hypertonic saline

(7.2%), hyperoncotic Dextran solution (10% Dextran 60) and the hypertonic saline/Dextran solution (7.2% saline, 10% Dextran 60) on the macrohemodynamic parameters and on nutritional blood flow as measured by the radioactive microspheres technique [1,18,20]. In a first series all dogs undergoing hemorrhagic hypotension 40 mmMg for 45 min) we have been able to demonstrate that both the macro- and microhemodynamics are instantaneously restored when 4 ml/kg body wt. hypertonic saline Dextran was given over a 2-min period; this infusion volume was equivalent to 10% of the volume loss. Within 5 min nutrional blood flow of most of the organs was normalized. While blood flow to brain, myocardium (Fig. 1), adrenal glands and to colon increased above control values, it reached control values in the other organs with exception of pancreas and gastric mucosa, where blood flow remained slightly below the initial control values. The high myocardial blood flow (Fig. 1) was homogeneously distributed to all layers and regions of the heart. In a second

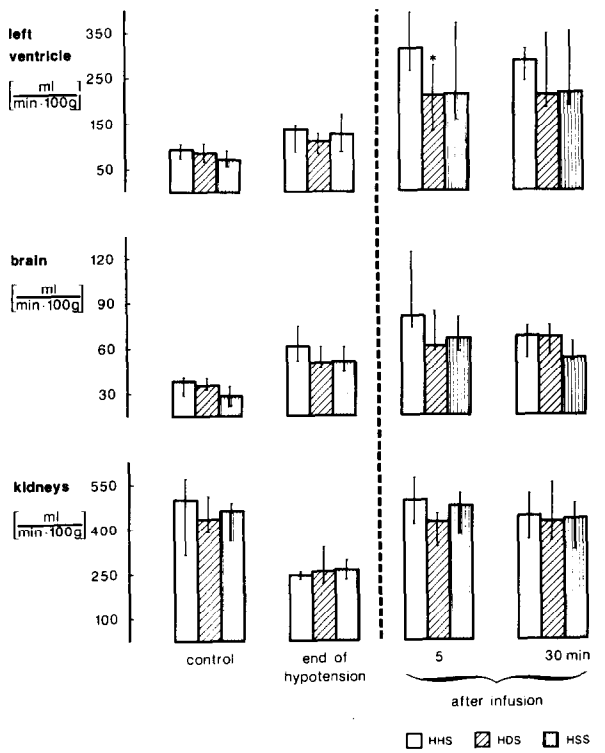

Fig. 1. Effect of hypertonic and hyperoncotic solution on nutrional blood flow of dogs undergoing hemorrhagic hypotension (MAP, 40 mmMg for 45 min). Blood flow in left ventricle, brain and kidneys was measured by radioactive microspheres. 4 ml/kg of the test solutions were given as a bolus infusion over a period of 2 min. Blood flow measurements were performed at control, end of hypotension and 5 and 30 min, respectively after the bolus infusion. HHS (7.2% sodium chloride/10% Dextran 60), HDS (10% Dextran 60), HSS (7.2% sodium chloride).

series using a more severe shock model, namely traumatic-hemorrhagic hypotension, we have demonstrated that bolus infusion of 4 ml/kg body wt. of 7.2% saline/10% Dextran 60 resulted in an instantaneous normalization of blood flow to most organs, including gastric mucosa and pancreas while blood flow to the brain and myocardium again reached the highest values [20].

These data indicate that by means of small volume resuscitation, nutritional blood flow can be improved not only in hemorrhagic hypotension but also in traumatic-hemorrhagic shock and furthermore that 7.2% saline/10% Dextran 60 is particularly effective [20].

VII. MECHANISMS OF ACTION OF SMALL VOLUME RESUSCITATION

The basic mechanism of action of small volume resuscitation consists in the induction of an osmotic gradient across vascular and cell membranes by bolus infusion of the concentrated salt solution. Whether the sodium ion is superior to non-electrolyte osmotic molecules has not been elucidated clearly [20]. The mechanism of action of small volume resuscitation includes rapid mobilization of endogenous fluid and expansion of the plasma volume; furthermore, a positive inotropic effect on the myocardium, vasodilatation, reestablishment of arteriolar-vasomotion, improvement of the blood fluidity by hemodilution and, finally, stimulation of the vasomotor center [20]. The dynamics of the fluid redistribution during hyperosmotic resuscitation have been analyzed in great detail by Mazzoni and Intaglietta [21,22]. These authors have demonstrated by means of model analysis and experiments in rabbits, that immediately after hyperosomotic infusion water shifts into the plasma, first from the red blood cells and the endothelial cells, followed by a fluid shift from the interstitium and from tissue cells (Fig. 2). This fluid redistribution occurs within a few seconds and is transient, however, the volume expansion can be sustained by addition of 6% Dextran 70 to the salt solution. These authors concluded that concurrent hemodilution and shrinkage of endothelial cells lead to a decrease of capillary hydraulic resistance and that this effect should become even more significant when the endothelial cells are edematous. In their most recent study on skeletal muscle of rabbits in hemorrhagic shock, Mazzoni [23] has demonstrated by means of intravital microscopy that indeed the capillary lumina are narrowed due to swelling of the endothelial cells and that this effect can be counteracted most efficiently with hypertonic salt/ Dextran solution, while treatment with isotonic Ringers Lactate solution remains completely inefficient, i.e. does not reverse endothelium swelling (Fig. 3).

These findings are of particular importance for the microcirculatory therapy of shock. There is evidence that endothelial swelling due to metabolic inhibition of cell volume control is a prominent feature not only in hemorrhagic shock [22], ischemia and reperfusion [8], but also in hyperdynamic endotoxinemia [2]. shock therapy must therefore include volume restoration, hemodilution and reduction of the hydraulic resistance of the capillaries. With implementation of the hyperosmotic principle conventional shock treatment has attained a new

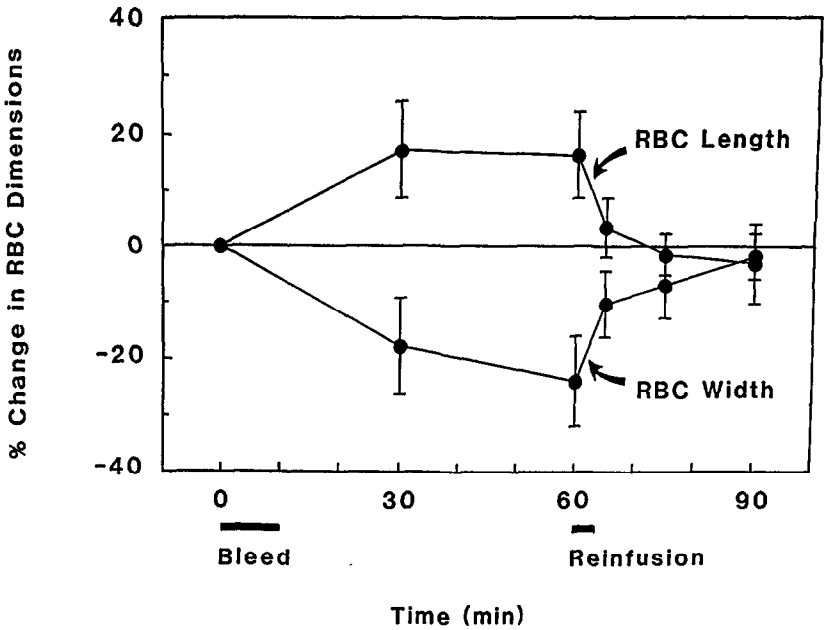

Fig. 2. Model calculations for compartmental volume changes in the first minute after small volume resuscitation (replacement of 1/7 total blood loss) by means of 7.5% NaCl/ 6% Dextran 70. Volumes changes in extracellular compartment (plasma and interstitium, combined intracellular compartment and blood). The volume is restored to nearly control value after 1 min due to influx of fluid from the interstitium and the intracellular compartments. The intracellular fluid is first withdrawn from the red blood cells, the endothelium cells and then from the tissue cells (From Ref. 21 with permission).

dimension. The efficiency of small volume resuscitation in terms of restoration of nutritrional flow and reversal of maldistribution of flow is due to the fact that this new concept includes improvement of the flow properties and flow conditions of the blood, but in addition affects the geometry of the microvascular bed by increasing the capillary lumina and therefore reducing their hydraulic resistance.

At present the concept of small volume resuscitation is under scrutiny of various groups involved in experimental and clinical shock research. Promising results have been reported from hemorrhagic, traumatic and endotoxic shock [24]. The first clinical studies employing hypertonic salt and hypertonic dextran salt solutions appear to confirm the experimental results. It was reported that resuscitation can be achieved rapidly with better restoration of central hemodynamics and higher survival rates, while significantly less volumes of conventional fluids are needed [24,25]. The concept of small volume resuscitation offers several advantages: (1) Practicability — for initial treatment only small infusion volumes (4 ml/kg body wt.) are needed and the total

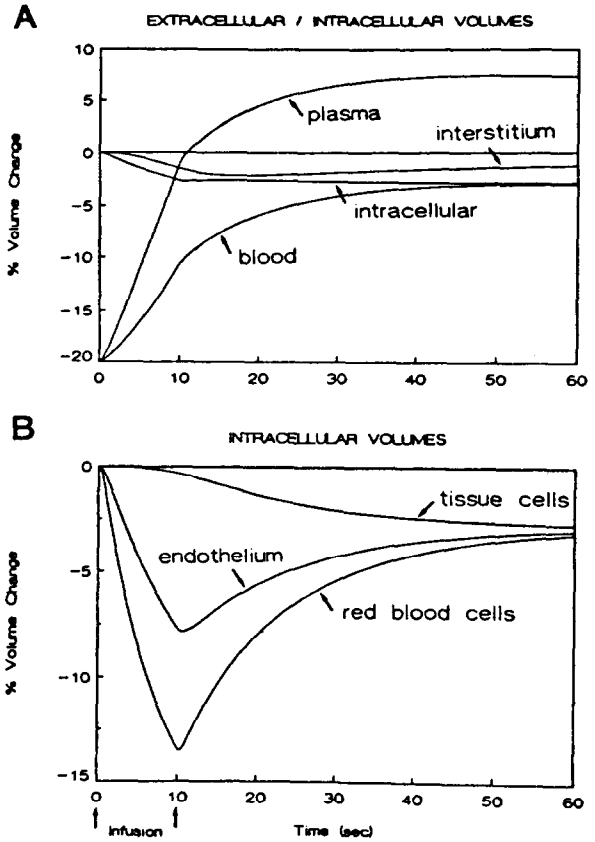

Fig. 3. Effect of hemorrhagic hypotension and small volume resuscitation (7.5% NaCl/6% Dextran 70) on RBC-length and RBC-width in capillaries of rabbit skeletal muscle. The increase in length and the decrease in width of the red blood cells traversing the capillaries reflects narrowing of the capillary lumen during hemorrhagic hypotension due to swelling of the endothelial cells. On small volume resuscitation (1/7 of the shed blood volume) there was a rapid normalization of the RBC-dimensions to control values indicating shrinkage of the endothelium cells. The initial opening of the capillary lumen has to be attributed to osmotic shrinkage of the endothelium, while further improvement occurring much later than the peak in plasma osmalality suggests recovery of cell volume regulation (From Ref. 22 with permission).

fluid requirements are reduced. (2) The cardiovascular response including the improvement of nutrional flow is obtained almost instantaneously. This should be advantageous with regard to prevent focal ischemia and its sequelae and potentially the development of multiple organ failure. (3) It is unlikely that side-effects will occur when small volumes of the hypertonic solutions are administered; the circulatory effect of hypertonic solutions is clearly controlled by the osmotic gradient achieved. Hypernatremia and hyperosmolarity should not become a problem when using small volumes [20].

VIII. CONCLUSIONS

The novelty of hypertonic/hyperoncotic solutions for the treatment of microcirculatory failure is that they directly affect the endothelial cell, rather than the smooth muscle of the microvascular segments. It is conceivable that swollen endothelial cells do modify the effect of vasoactive drugs at the level of the microcirculation and that the vasoactive drugs presently used for shock treatment (adrenergic agents, calcium agonists, vasodilators) would influence the microcirculation more efficiently when encountering volume controlled endothelial cells. The use of hypertonic/hyperoncotic solutions does not preclude application of vasoactive drugs necessary to improve cardiac contractility and to maintain sufficient perfusion pressure [26].

REFERENCES

1 U. Kreimeier and K. Messmer, New perspectives in resuscitation and prevention of multiple organ system failure. In: Surgical Research: Recent Concepts and Results. Editors: A. Baethmann and K. Messmer, Springer-Verlag, Berlin-Heidelberg-New York, 1987, pp. 38–50.

2 K. Messmer, U. Kreimeier and F. Hammersen. Changes in the microcirculation in sepsis and septic shock. In: sepsis: An interdisciplinary challenge. Editors: K. Reinhart and K. Eyrich, Springer-Verlag, 1989, pp. 148–160.

3 S. Chien, Role of the sympathetic nervous system in hemorrhage, Physiol. Rev., 47 (1967) 214–288.

4 K.L. Appelgren, Perfusion and diffusion in shock. Acta Physiol. Scand. Suppl., 378 (1972).

5 W. Funk and M. Intaglietta, Spontaneous arteriolar vasomotion. In: Progress in Applied Microcirculation, Vol. 3, Karger, Basel-New York, 1983, pp. 66–82.

6 M. Intaglietta. Reactivation of the microcirculation in ischemia. In: Ischemia and Reperfusion. Editors: K. Messmer, F. Hammersen, Karger, Basel-New York, 1989, pp. 27–37.

7 U. Bagge and M. Braide, Microcirculatory effects of white blood cells in shock. In: Progress in Applied Microcirculation, Vol. 7, Karger, Basel/New York, 1985, pp. 43–50.

8 M.D. Menger, F.Hammersen, J.H. Barker, G. Feifel and K. Messmer, Ischemia and reperfusion in skeletal muscle: experiments with tourniquet ischemia in the awake syrian golden hamster. In: Ischemia and Reperfusion. Editors: K. Messmer and F. Hammersen, Karger, Basel-New York, 1989, pp. 93–108.

9 K. Messmer, Blood substitutes in shock therapy. In: Shock and related problems. Editor: G.T. Shires, Churchill Livingston, Edinburgh, 1984, pp. 192–205.

10 K. Messmer, Characteristics, effects and side-effects of plasma substitutes. In: Blood Substitutes. Editor: K.C. Lowe, Ellis, Horwood, 1988, pp. 51–69.

11 K. Messmer, Acceptable hematocrit levels in surgical patients, World J. Surg., 11 (1987) 41–46.

12 M. Rocha e Silva, G.A. Negraes, A.M. Soares et al., Hypertonic resuscitation from severe hemorrhagic shock: patterns of regional circulation, Circ. Shock, 19 (1986) 165–175.

13 J. De Felippe, J. Timoner, I.T. Velasco et al., Treatment of refractory hypovolemic shock by 7.5% sodium chloride injections, Lancet, i (1980) 1002–1004.

14 I.T. Velasco, V. Pontieri, M. Rocha e Silva et al., Hyperosmotic NaCl and severe hemorrhagic shock, Am. J. Physiol., 239 (1980) H664–H673.

15 S. Nakayama, L. Sibley, R.A. Gunther et al., Small-volume resuscitation with hypertonic saline (2.400 mosm/liter) during hemorrhagic shock, Circ. Shock, 13 (1984) 149–159.

16 R.D. Hands, R.A. Gunther, P.R. Perron et al., Peripheral injection of hypertonic saline-dextran to resuscitate from hemorrhagic shock, Circ. Shock, 18 (1986) 377–378.

17 G.C. Kramer, P.R. Perron, D.C. Lindey et al., small-volume resuscitation with hypertonic saline dextran solution, Surgery, 100 (1986) 239–247.

18 U. Kreimeier, U.B. Bruckner and K. Messmer, Improvement of nutritional blood flow using hypertonichyperoncotic solutions for primary treatment of hemorrhagic hypotension, Eur. Surg. Res., 20 (1988) 277 – 279.
19 G.J. Smith, G.C. Kramer, P. Perron, S.I. Nakayama, R.A. Gunther and J.W. Holcroft, A comparison of several hypertonic solutions for resuscitation of bled sheep, J. Surg. Res., 39 (1985) 517 – 528.
20 U. Kreimeier and K. Messmer, Small volume resuscitation with hypertonic-hyperoncotic solutions. In: Fluid Resuscitation. Bailliere's Clinical Anaesthesiology. Editors: W. Kox, J. Gamble, 1989, in press.
21 M.C. Mazzoni, P. Borgstroem, K.E. Arfors et al., Dynamic fluid redistribution in hyperosmotic resuscitation of hypovolemic hemorrhage, Am. J. Physiol., 255 (1988) H629 – H637.
22 M.C. Mazzoni, Systemic, capillary and endothelial cell responses in hyperosmotic fluid resuscitation of hemorrhagic shock. Ph.D dissertation, University of California, San Diego, 1989.
23 P. Luypaert, J.L. Vincent and M. Domb, Fluid resuscitation with hypertonic saline in endotoxic shock, Circ. Shock, 20 (1986) 311 – 320.
24 J.W. Holcroft, M.J. Vasar, J.E. Turner et al., 3% NaCl and 7.5% NaCl/Dextran 70 in the resuscitation of severely injured patients, Ann. Surg., 206 (1987) 279 – 288.
25 P.A. Maningas, K.L. Mattox, P.E. Pepe, R.L. Jones, D.V. Feliciano and J.M. Burch, Hypertonic saline-dextran solutions for the prehospital management of traumatic hypotension, Am. J. Surg., 157 (1989) pp. 528 – 533.
26 J.L. Vincent, Choice of fluids and vasoactivce agents. In: Update in Intensive Care and Emergency Medicine. Editors: J.L. Vincent and L.G. Thijs, Springer, 1987, pp. 186 – 196.