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Sepsis, causing multiple organ failure, is the most frequent cause of death in surgical intensive care. The high incidence of sepsis and the resulting mortality ranging from 40 to 70%, have stimulated an increase in research in this field in recent years [1]. Pathophysiological developments, especially regarding the role of the inflammatory system in sepsis have been achieved. Unfortunately, although these findings may have improved our understanding of sepsis, they have not affected the sepsis mortality rate [2]. Therefore, adequate haemodynamic stabilization remains a crucial component in the treatment of sepsis. When studying the pathophysiological aspects of sepsis, it appears that therapeutic strategies to improve tissue oxygenation are those most beneficial.

HEMODYNAMIC MONITORING

Clear and commonly accepted recommendations about useful hemodynamic endpoints are not available. The question of whether so-called extended monitoring (pulmonary artery catheter, echocardiography, transpulmonary indicator dilution) should be used, has been widely discussed and is still controversial.

Nevertheless standard monitoring, such as blood pressure, heart rate or urine output can be helpful in guiding the hemodynamic therapy. A drop in blood pressure, an increase in heart rate and a decreased urine output are often signs of a hypovolemia. A central-venous O_2-saturation below 60% can indicate a drop in cardiac output (CO).

Whether extended monitoring is necessary for assessing the myocardial preload is not fully proven. However, in situations where volume loading alone is not sufficient to maintain adequate circulation methods for a more precise evaluation of cardiac function and preload seem justified.

The long favored concept of useing global oxygen delivery (DO_2) as a central hemodynamic target and to try to establish a DO_2 as high as possible, is doubtful. There is no question that patients who are able to generate a hyperdynamic circulation have a better survival rate. Treatment of hypovolemia by fluid loading to normalize the myocardial preload and thereby increase the CO and DO_2 is also well accepted. Beyond that, to force a hyperdynamic circulation and an elevated DO_2 by the use of catecholamines in high dosages seems to be associated not only with a lack of beneficial effects but also with harmful ones [3].

There is no generally validated target for arterial pressure in septic patients.

Data from several multicenter trials in sepsis demonstrate that mean arterial pressures between 70 and 90 mmHg are commonly accepted to be adequate perfusion pressures. However it must be accepted that there are really no data, supporting unequivocally such a concept.

In a recently published study from Rivers et al. [4] it has been shown that a hemodynamic strategy of establishing a central venous O_2-saturation ($ScvO_2$) above 70% within the first 6 hours after admission to the hospital is associated with a higher survival rate.

However, this study does not really prove the utility and the need of measuring the $ScvO_2$. It includes only patients in the early phase of sepsis (less than 6 hours) and the use of $ScvO_2$ is not compared to the use of other means of hemodynamic monitoring. The study demonstrates above all, that the rapid and consistent stabilization of the circulation is an essential and survival-determining measure

Fluid therapy

The sepsis patient presents with pronounced fluid requirements. These are due to the pathophysiological changes of sepsis, where peripheral vasodilatation results in relative and an absolute volume deficit. The fluid volume that must be infused during the acute phase may amount to several liters.

Optimizing the cardiac preload is the fundamental principle of fluid therapy. Fluids should be infused until volume therapy can produce no further increase in cardiac output, or until signs of worsening pulmonary gas exchange ensue.

The question as to whether colloid of crystalloid fluids should be administered remains unanswered and the very costly use of human albumin is certainly not justified. It appears that the adequate volume replacement, namely the amount of the administered fluid, is more important than the exact kind of fluid [5].

Assuring an optimal hemoglobin content

Fluid therapy with either crystalloid or colloid leads to a drop in Hb-concentration of about 1-3 g/dl. A Hb value lowered to 8-10 g/dl is tolerated well by many patients, especially as it leads to a decrease in blood viscosity, cardiac afterload and an improvement of the venous return, resulting in an increased cardiac output. A study by Hebert et al. [6] demonstrated a lower mortality rate in critically ill patients, treated according to a restrictive transfusion protocol (Hb 7-9 g/dl), when compared to patients who were managed according to a more liberal transfusion protocol (Hb 10-12 g/dl).

Therapy with vasoactive substances

Dobutamine

It is reasonable to use a primary beta-1-mimetic substance for therapy of a frequently present septic cardiomyopathy and for maintaining of a hyperdynamic circulation. Dobutamine is recommended as the catecholamine of choice [5].

Noradrenaline

The pronounced vasopressor effect of noradrenaline is the basis for the common therapeutic concept that this medication should only be used as a „last resort“ treatment, when stabilization of the circulation cannot be achieved with any other drug. At present this concept is no loner maintained.

It has been possible to demonstrate in several studies, involving patients with sepsis, that the urine output and creatinine clearance increase with noradrenalin therapy [7]. Indeed, the patients without noradrenaline therapy in these studies clearly had lower arterial blood pressure, so the underlying mechanism of improved renal function is the effect of sufficient perfusion pressure. Hence, inadequately low blood pressure should never be tolerated as inadequate perfusion pressure may be more dangerous than the potentially negative effects of the vasopressors. In addition in situations of normovolemia these negative effects of noradrenaline have never been demonstrated. Therefore, in comparison with other vasopressors, such as adrenaline and dopamine, noradrenaline is the vasopressor of first choice.

Adrenaline

Adrenaline is recommended by several authors for the treatment of severe septic shock, because it can increase the CO through its positive inotropic β_1-adrenoreceptor effect while supporting sufficient perfusion pressure through its vasopressor α-adrenoreceptor effect. Several study groups have shown that adrenaline use results in circulatory stabilization in septic shock patients who could not be stabilized either with dopamine nor with noradrenaline.

Nevertheless, adrenaline is not the first-choice catecholamine in sepsis as it leads to selective splanchnic hypoperfusion [8].

5.4. Dopamine

Dopamine is often used as an adjuvant low-dose therapy (1-3 µg/kg/min) in order to improve the renal function and the splanchnic perfusion. However the effectiveness of this strategy has not been demonstrated yet, so it is no longer included in more recent therapeutic recommendations [5]. Even more impressive are the

findings of unfavorable effects on the splanchnic perfusion and oxygen supply, caused by dopamine. It was already shown in animal studies, that worsening of the oxygen supply to the especially vulnerable intestinal mucosa might be expected, based on redistribution of blood flow [9]. Beside these potentially unfavorable effects, it is also known that dopamine is capable of decreasing the concentration of various hormones of the neurohypophyseal axis, possibly the cause of a catabolic state that cannot be controlled therapeutically [10]. Furthermore, dopamine may impair cardiac and vascular function by influencing thyroid hormones. All these unfavorable effects are to be expected and have been also demonstrated with higher dopamine doses (used to increase the cardiac output and the perfusion pressure). Therefore, today dopamine is only to be used in intensive care medicine with restrictions.

Dopexamine

Dopexamine leads to cardiac output increase in septic patients. Regarding the commonly postulated increase in renal and splanchnic blood flow with dopexamine, it must be pointed out that these findings were described for non-septic patients. The potentially beneficial effects of dopexamine are not the result of a selective effect on the regional circulation but due to increase in the regional blood flow in the context of the global cardiac output increase [11]. Furthermore, even worsening of the intestinal mucosa perfusion with dopexamine have been observed both in septic [12] and cardiac surgery patients [13]. Consequently, the effects of dopexamine on the regional circulation and especially on the splanchnic area are still relatively controversial. Clinical trials justifying the administration of dopexamine to selectively improve the splanchnic perfusion, are not available.

Phospodiesteraseinhibitors

Through their positive inotropic and vasodilating effects phosphodiesterase inhibitors produce an increase in cardiac output with reduction of cardiac filling pressures and pulmonary and systemic vascular resistance. Therefore phosphodiesterase inhibitors are suitable for the treatment of severe heart failure, especially when catecholamine therapy is no longer effective, due to decreased catecholamine receptor responsiveness.

Thrombocytopenia is an important side effect of phosphodiesterase inhibitor therapy.

In the context of the treatment of septic patients with circulatory instability, Enoximon leads to an increase in O_2-suppy and demand. At present there is no clear answer as to whether these agents have selective effects on the regional perfusion. Together with the increase in the pulmonary shunt and the pronounced vasodilatation, often requiring the administration of catecholamines, the significant disadvantages of the phosphodiesterase inhibitors include their long half-life (20-45 min for milrinone) and difficulties in their titration. Therefore the use of phosphodiesterase inhibitors should be reserved for situations in which heart failure is the leading problem. These include, for example, patients with significant coexisting cardiac disease, or when the conventional treatment is no longer effective, due to prolonged therapy, causing „down-regulation“ of the catecholamine receptors.

Vasopressin

Vasopressin leads to a V1-receptor-mediated elevation of the intracellular calcium concentration. A number of studies have demonstrated that vasopressin can be used to achieve hemodynamic stability in patients with septic shock, especially when noradrenaline therapy had been unsuccessful. However, these impressive effects, which were achieved typically with the synthetic vasopressin-analogue terlipressin, should not lead to unregulated use of this substance. With regard to the long-term administration of vasopressin, there remain a lot of unanswered questions. One important question is, whether in the treatment of hypotension, vasopressin should be used as a vasopressor or as substitution therapy in the setting of absolute or relative vasopressin deficit. It is well proven that such a vasopressin deficit exists frequently in septic patients [14]. Whether substitution therapy is justified and whether there is a qualitative difference between a low dose substitution therapy and a high dose vasopressor therapy remains speculative as long as appropriate studies are still unavailable. Although a number of data demonstrate that vasopressin can bring about stabilization of the global hemodynamics in the most severe shock states, it is unclear whether this is achieved at the expense of a worsening perfusion status at the level of the microcirculation, as recently suggested [15]. Due to lack of knowledge concerning the effects of vasopressin on the microcirculation and the effects which could cause organ failure, thus influencing patient survival, vasopressin should only be used with major restrictions as a longer-term treatment within the frame of the hemodynamic sepsis therapy.

Other therapeutic approaches

Other therapeutic approaches that target the hemodynamics, especially at the level of the microcirculation, include the use of hypertonic solutions (HTS), prostacyclin, N-acetylcystein (NAC), L-N-methylarginine (LMNA), or methylene blue. All these approaches have in common is that so far no clinical usefulness has been shown and their use is not justified.

Corticosteroid substitution

The high-dose administration of corticosteroids for sepsis therapy is not justified. Large studies have shown no useful and one unfavorable effect of such a therapy [16]. However so-called steroid substitution therapy appears different. In critically ill patients the serum cortisol concentration is initially elevated as a part of the stress response. Later comes a disturbance in the hypothalamus-pituitary-adrenal axis. That leads to a stage in the later phases of septic shock when appropriate cortisol release is often not possible. It can be shown that the hydrocortisone substitution in septic shock patients leads to shorter duration vasopressor therapy, shorter treatment times and a lower incidence of organ failure. A multicenter study of 299 patients provides justification for such therapy [17]. This study demonstrated a 30 % higher survival rate in patients who had a negative corticotropin test and were treated with 200 mg hydrocortisone. Currently, a second European multicenter study (CORTICUS-Study) should test the effectiveness of hydrocortison therapy. In a therapy recommendation from the "European Sepsis Forum" – 2001, the use of low dose hydrocortisone was recommended [5].

Adjuvant therapies

Anti Tumor Necrose Factor Strategies

Tumor Necrosis Factor alpha (TNFα) plays a central role in the septic mediator cascade. High TNFα plasma concentrations are associated with a poor prognosis. It was possible to show in animal experiments that anti-TNFα antibodies dramatically decrease mortality in the respective sepsis model. These findings are the reason why anti-TNFα strategies are the most widely tested in big clinical trials. Nevertheless most of these trials have not yet been able to demonstrate that the use of a certain anti-TNFα antibody or soluble TNFα-receptors is associated with a better survival rate of the septic patient. The MONARCS-study alone, which tested the effectiveness of a particular antibody fragment (Afelinomab) on 2634 septic patients, showed a beneficil effect in the Afelinomab group [18]. Out of all studied patients, the mortality rate could be decreased from 6,9% to 3,6% in a subgroup of patients with elevated interleukin-6 (IL-6) plasma levels (998 patients). However, it is not yet clear whether Afelinomab will be clinically available in the near future.

Antithrombin III, activated Protein C, Tissue Factor Pathway Inhibitor

The sepsis-associated cytokines produce a pathologically increased activity of the plasma coagulation and fibrinolytic systems. This increased activity leads to disseminated fibrin deposition, which is one of the causative factors for the sepsis-associated multiorgan failure and to consumption of coagulation factors, resulting from the increased coagulation tendency. Physiologic coagulation inhibitors, such as Antithrombin III (AT III), activated Protein C and Tissue Factor Pathway Inhibitor (TFPI), inactivate the procoagulant factors as well as the fibrin formation and can by that limit the consequences of the above mentioned activation of the coagulation system. All three strategies have demonstrated potentially beneficial effects in small studies. In large studies however only the effectiveness of activated Protein C could be demonstrated.

In a study of 2300 patients, no differences were shown between high-dose AT III and a placebo, with regard to the 28-day mortality rate. Only a subgroup of patients who received no low-dose heparin therapy seemed to benefit from treatment with AT III [19]

One big multicenter study on the effectiveness of TFPI has just been completed. Even though the results are not yet published it has been said that this study also failed to show any mortality-lowering effect associated with TFPI.

The recently published study on the effectiveness of the recombinant human activated Protein C (Drotecogin-α) in 1690 patients, showed a clear effect on the survival rate (PROWESS-Study) [20]. The patients treated with Protein C had mortality rate that was 6.1% lower in comparison to that of the placebo group patients. However, the fact that the incidence of heavy bleeding in patients treated with activated Protein C was 3,5%, which was higher than that in the placebo group – 2%, also demonstrates that this substance should be critically evaluated and used with utmost care. Drotecogin-α is approved for use both in the USA and Europe.

Patients, who met the criteria for severe sepsis or septic shock were enrolled in the primary trials. Regarding the actual definition, three of the so-called Systemic-Inflammatory-Response-Syndrome (SIRS)-criteria had to be fulfilled. Furthermore, the time from the onset of organ failure, leading to the diagnosis to the first treatment with Drotecogin-α, had to be no more than 48 hours. A number of coexisting diseases and all conditions associated with increased risk of bleeding are exclusion criteria. These relatively narrow inclusion criteria of the PROWESS-study have lead to the fact that relatively few postoperative patients were included (patients with pneumonia > 50%). Therefore the results of the PROWESS-study cannot be representative for all sepsis patients. A post-hoc analysis of the study data has shown, that the effectiveness of Drotecogin-α in patients with only one organ failure is questionable. As a result the use of this substance in Europe is presently approved only for patients with at least two-organ failure. Therefore, Drotecogin-α must be used very cautiously and critically, and in stricter compliance with its contraindications, in order to prevent causing more harm than benefit to certain patients.

Other immunomodulator therapy approaches

In addition to the anti-TNFα strategies and the activated Protein C therapy, there is a number of other immunomodulator therapy approaches. Such approaches, such as the use of anti-endotoxin antibodies, antibodies to different interleukins, platelet-activating factor or granulocyte-colony-stimulating factor (G-CSF) have to be tested in appropriate designed studies in the future and therefore are far from being even discussed as a standard approach in sepsis.

Immunoglobulines

The immunoglobulins are used both in the prophylaxis and the therapy of sepsis. The data on the effectiveness of immunoglobulin prophylaxis and therapy have always been controversial. However, a recently published metaanalysis of the Cochrane library showed a reduction in the mortality rate in septic patients, treated with immunoglobulin [21]. Of note is that 11 studies with a total of only 492 patients were included in the analysis. Taking into consideration the fact, that especially with small studies, the likelihood of being published is higher when the findings are positive [22], the results of the Cochrane analysis cannot be viewed as a basis for therapy recommendations. Furthermore, the Cochrane analysis did not consider an essential study, which to this day has been published only as an abstract [23]. This study (SBITS-study) included 653 patients who were treated either with immunoglobulins or with placebo. This is the largest to date of immunoglobulin therapy effectiveness in septic patients and could show no benefits from treatment with immunoglobulins. Therefore, based on the current scientific data, the use of immunoglobulins cannot be recommended for the therapy of sepsis. In the recommendations for sepsis therapy from the "European Sepsis Forum – 2001", the use of immunoglobulins was also omitted [5].

Summary

The most important measures in the course of sepsis and multiorgan failure therapy can be summarized as follows:

I. Causal therapy

Search for septic focus, surgical removal/cleaning of the septic focus, removal of infected foreign body/material, antibiotic therapy

II. Assuring adequate volume status

Optimizing of the cardiac preload, type of volume replacement fluid is secondary, attention to the markers of peripheral perfusion and organ function (urine output, lactate)

III. Assuring adequate oxygen supply and correction of decreased cardiac pump function

The concept of maximizing the DO_2 by high-dose catecholamine is not appropriate. The optimal DO_2 is to be titrated individually for each patient. In order to decide whether further increase of DO_2 is beneficial, one must pay attention to the markers of peripheral perfusion and organ function (i.e. urine output, lactate). For treatment of decreased contractility/pump function, dobutamine is the drug of choice

IV. Assuring adequate perfusion pressure

Noradrenaline is the catecholamine of choice. The optimal perfusion pressure should also be individually titrated by following the parameters of peripheral perfusion and organ function (i.e. urine output, lactate). Inadequate perfusion pressure should never be tolerated. Potentially adverse effects of noradrenaline are unlikely, provided that an adequate volume status is maintained. In patients with negative corticotropin-test, substitution therapy with hydrocortison (200-300 mg/d) is justified.

V. Adjuvant therapy

The treatment with activated Protein C (Drotecogin-α) can be described as a proven strategy. The indications and contraindications should be strictly observed.

LITERATURE

1. From the Centers for Disease Control. Increase in National Hospital Discharge Survey rates for septicemia--United States, 1979-1987. JAMA 1990; 263:937-938.
2. Zeni F, Freeman B, Natanson C. Anti-inflammatory therapies to treat sepsis and septic shock: a reassessment. Crit Care Med 1997; 25:1095-1100.
3. Heyland DK, Cook DJ, King D, Kernerman P, Brun Buisson C. Maximizing oxygen delivery in critically ill patients: a methodologic appraisal of the evidence. Crit Care Med 1996; 24:517-524.
4. Rivers E, Nguyen B, Havstad S, Ressler J, Muzzin A, Knoblich B, Peterson E, Tomlanovich M. Early goal-directed therapy in the treatment of severe sepsis and septic shock. N Engl J Med 2001; 345:1368-1377.
5. Sprung CL, Bernard GR, Dellinger RP. Guidelines for the management of severe sepsis and septic shock. Intensive Care Med 2001; 27:1-134.
6. Hebert PC, Wells G, Blajchman MA, Marshall J, Martin C, Pagliarello G, Tweeddale M, Schweitzer I, Yetisir E. A multicenter, randomized, controlled clinical trial of transfusion requirements in critical care. Transfusion Requirements in Critical Care Investigators, Canadian Critical Care Trials Group. N Engl J Med 1999; 340:409-417.
7. Desjars P, Pinaud M, Potel G, Tasseau F, Touze MD. A reappraisal of norepinephrine therapy in human septic shock. Crit Care Med 1987; 15:134-137.
8. Meier-Hellmann A, Reinhart K, Bredle DL, Specht M, Spies CD, Hannemann L. Epinephrine impairs splanchnic perfusion in septic shock. Crit Care Med 1997; 25:399-404.
9. Giraud GD, MacCannell KL. Decreased nutrient blood flow during dopamine- and epinephrine- induced intestinal vasodilation. J Pharmacol Exp Ther 1984; 230:214-220.
10. Van den Berghe G, de Zegher F, Lauwers P. Dopamine suppresses pituitary function in infants and children. Crit Care Med 1994; 22:1747-1753.
11. Meier-Hellmann A, Sakka S, Reinhart K. Supportive therapy of the sepsis syndrome. Clin Chem Lab Med 1999; 37:333-339.
12. Meier-Hellmann A, Bredle DL, Specht M, Hannemann L, Reinhart K. Dopexamine increases splanchnic blood flow but decreases gastric mucosal pH in severe septic patients treated with dobutamine. Crit Care Med 1999; 27:2166-2171.
13. Uusaro A, Ruokonen E, Takala J. Gastric mucosal pH does not reflect changes in splanchnic blood flow after cardiac surgery. Br J Anaesth 1995; 74:149-154.
14. Landry DW, Levin HR, Gallant EM, Ashton RC, Jr., Seo S, D'Alessandro D, Oz MC, Oliver JA. Vasopressin deficiency contributes to the vasodilation of septic shock. Circulation 1997; 95:1122-1125.
15. Klinzing S, Simon M, Reinhart K, Bredle DL, Meier-Hellmann A. High-dose vasopressin is not superior to norepinephrine in septic shock. Crit Care Med 2003; 31:2646-2650.
16. Bone RC, Fisher CJ, Jr., Clemmer TP, Slotman GJ, Metz CA, Balk RA. A controlled clinical trial of high-dose methylprednisolone in the treatment of severe sepsis and septic shock. N Engl J Med 1987; 317:653-658.
17. Annane D, Sebille V, Charpentier C, Bollaert PE, Francois B, Korach JM, Capellier G, Cohen Y, Azoulay E, Troche G, Chaumet-Riffaut P, Bellissant E. Effect of treatment with low doses of hydrocortisone and fludrocortisone on mortality in patients with septic shock. JAMA 2002; 288:862-871.
18. Panacek EA, Marshall J, Fischkoff S, Barchuk W, Teoh L. Neutralization of TNF by a monoclonal antibody improves survival and reduces organ dysfunction in human sepsis: Results of the MONARC trial. Chest 2000; 118:88
19. Warren BL, Eid A, Singer P, Pillay SS, Carl P, Novak I, Chalupa P, Atherstone A, Penzes I, Kubler A, Knaub S, Keinecke HO, Heinrichs H, Schindel F, Juers M, Bone RC, Opal SM. Caring for the critically ill patient. High-dose antithrombin III in severe sepsis: a randomized controlled trial. JAMA 2001; 286:1869-1878.
20. Bernard GR, Vincent JL, Laterre PF, LaRosa SP, Dhainaut JF, Lopez-Rodriguez A, Steingrub JS, Garber GE, Helterbrand JD, Ely EW, Fisher CJ. Efficacy and safety of recombinant human activated protein C for severe sepsis. N Engl J Med 2001; 344:699-709.
21. Alejandria MM, Langsang MA, Dans LF. Intravenous immunglobulin for treating sepsis and septic shock. The Cochrane Library 2003; 3/03.
22. Callaham ML, Wears RL, Weber EJ, Barton C, Young G. Positive-outcome bias and other limitations in the outcome of research abstracts submitted to a scientific meeting. JAMA 1998; 280:254-257.
23. Werdan K, Pilz G, and the SBIT Study group. Polyvalent immune globulins. Shock 1997; 7:1918