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Summary, general discussion and future perspectives

Septic shock is a complex clinical syndrome which results from a systemic response to infection that involves proinflammatory and anti-inflammatory processes, the innate immune response, procoagulant and antifibrinolytic pathways and alterations in metabolism.[1-6] In this thesis, circulating markers and mediators in the course of human septic shock are described and their relation with cardiac function and hemodynamics is studied. Coagulation and fibrinolysis are affected by circulating proinflammatory cytokines and complement activation products and the relation with lactate production and outcome is addressed. Since the acute inflammatory response in sepsis might be modulated by treatment with vasopressors/inotropics, the relation between vasopressor/inotropic treatment and the innate immune response is studied.

Circulating markers and mediators of cardiovascular dysfunction in acute illness are described in **Chapter 2**, with some reflecting mediator action on hemodynamics (e.g. asymmetric dimethylarginine (ADMA), endothelin, nitric oxide (NO) and adrenomedullin) and others reflecting action on heart function (e.g. natriuretic peptides, vasopressin).[7-19] Some factors may be both markers as well as mediators of cardiovascular dysfunction in acutely ill patients and they seem to have prognostic significance.[8,9,12,14,20] Assessing circulating plasma levels of these factors, together with measuring hemodynamic variables and other clinical signs encountered at the bedside, is suggested to help in refining clinical judgment of the cardiovascular derangements in these patients. Future studies aligning hemodynamic abnormalities with patterns of circulating cardiovascular markers and mediators may help to stratify patients for inclusion in studies to assess the causes, response to therapy and prognosis of cardiovascular derangements in acutely ill patients.

In human septic shock, the role of innate immunity, i.e. complement activation and cytokine release, in relation to hemodynamic alterations in the course of disease is largely unknown. We therefore studied hemodynamic variables and plasma levels of C3a, a product of complement activation, interleukin (IL)-6, and tumor necrosis factor alpha (TNF-α) in 14 septic shock patients (**Chapter 3**). Our results showed that in human septic shock, peripheral vasodilation is associated with IL-6 release, independently of other inflammatory factors, which might be explained by IL-6 being involved in upregulation of inducible NO synthase or other vasodilating factors.[21-24] Since complement activation inversely related to systemic vascular resistance index (SVRI), it is suggested that vasodilation and resultant hypotension in the development of shock might partly be accounted for by complement activation during sepsis.[25,26] However, in our study, complement activation was associated with, but did not independently relate to, vasodilation. Previous studies showed elevated plasma levels of either IL-6 or TNF-α to play a role in the myocardial depression in sepsis,[27-30] although these relations could not be confirmed in our study. Suggested negative effects on the heart might have been offset, at least in part,

by complement activation, since we found a positive relation between complement activation and cardiac function, which is in accordance with previous reports showing a positive inotropic response of complement activation products.[31,32] The relations between complement activation, release of cytokines and hemodynamic abnormalities and cardiac function in our relatively small number of patients may not allow definite conclusions on cause-effect relations between innate immunity factors and hemodynamic alterations in human septic shock. However, it can be concluded that innate immunity factors may differ in their contribution to hemodynamic abnormalities in the course of septic shock. Moreover, complement activation partly offsets the myocardial depression of the syndrome but does not aggravate the vasodilation which is mainly associated with IL-6 release.

The hemodynamic changes of septic shock are characterized by an elevated cardiac output, hypotension, peripheral vasodilation, and myocardial depression.[33,34] The latter is already seen early in the course of disease and is suggested to contribute to death by limiting oxygen supply to the tissues.[5,34,35] During congestive heart failure and following myocardial infarction, alpha-atrial nariuretic peptide (α-ANP), cyclic guanosine monophosphate (cGMP), and endothelin are released and plasma levels of these factors are elevated.[36-39] Both α-ANP and cGMP are used as markers of congestive heart failure,[40,41] and α-ANP, cGMP and endothelin are associated with a poor outcome.[36-39] Since plasma levels of α-ANP, cGMP and endothelin are elevated in septic shock,[42-45] we measured hemodynamic variables and cardiac function indices, outcome, and plasma levels of these factors in 14 septic shock patients to assess their value as markers of myocardial depression and mortality in human septic shock (**Chapter 4**). Our results showed impaired left ventricular function in nonsurvivors compared to survivors. Moreover, it was shown that elevated plasma levels of α-ANP, cGMP and endothelin related to impaired left ventricular function and were predictive of myocardial depression. Previous reports suggested that acute lung injury and an increased afterload following pulmonary hypertension in sepsis might contribute to cardiac dilatation and production and release of α-ANP and its second messenger cGMP.[43,44,46,47] However, our results showed comparable relations with right and left ventricular function indices and no relation with pulmonary hemodynamic variables. Thus, myocardial depression seems to be independent of right ventricular afterload and resultant cardiac dilatation, even though endothelin plasma levels were elevated and may have contributed to pulmonary vasoconstriction and increased right ventricular afterload.[38,39] Moreover, it was shown that plasma levels of α-ANP, cGMP and endothelin were higher in nonsurvivors compared to survivors and high levels were predictive of mortality. In conclusion, it was suggested that circulating α-ANP, endothelin, and particularly cGMP, may be markers of the myocardial depression early in the course of human septic shock and elevated plasma levels are associated with mortality. These circulating markers may facilitate recognition of myocardial

depression in septic shock, and may help to predict and monitor the response to treatment of the syndrome.[37-40]

In primary cardiac disease, the N-terminal pro-B-type natriuretic peptide (NT-proBNP), which is released by ventricular myocytes in response to increased wall stress, has diagnostic and therapeutic monitoring value.[48,49] The value of NT-proBNP in septic patients is unclear, with reports showing associations between NT-proBNP plasma levels and measures of cardiac filling and function,[50-53] and poor relations and predictive values for cardiac output responses to fluid loading (fluid responsiveness), described by others.[51,53-59] Several confounding factors have been identified,[48-51,56,58,60-62] and in sepsis, proinflammatory stimuli may have a greater impact on cardiac release of NT-proBNP than alterations in cardiac filling and function.[63,64] Since sepsis has rarely been compared with nonsepsis for NT-proBNP release and hemodynamic associations in critically ill patients,[50,53,54,57,65] we evaluated NT-proBNP as a marker of cardiac function and fluid responsiveness by measuring plasma levels of NT-proBNP and hemodynamic variables in 18 septic and 68 nonseptic, critically ill patients, before and after fluid administration (**Chapter 5**). The transpulmonary dilution technique for measurement of cardiac output and filling volumes was used, because this technique correlates with indices obtained by echocardiography but obviates operator dependency of the latter, and allows for evaluation of (systolic) cardiac function and of fluid responsiveness.[63,66,67] Results showed higher NT-proBNP plasma levels and lower systolic cardiac function indices in patients with sepsis, compared with nonseptic patients. These higher NT-proBNP plasma levels can, at least in part, be explained by greater systolic cardiac dysfunction, characteristic for myocardial depression during severe sepsis and septic shock.[52,65] From all hemodynamic parameters, plasma levels of NT-proBNP best (inversely) related to systolic (rather than diastolic) cardiac function indices, before and after fluid loading, and independently of confounders such as renal function. This might be explained by an increased wall stress upon acute systolic dysfunction with insufficient ability of the heart to dilate, as reported before to occur in sepsis.[64,68,69] According to previous reports, our data suggest a primary role of myocardial depression in the release of natriuretic peptides during sepsis, as judged by concomitant release of troponins and global hemodynamic or echocardiographic indices,[52,59,62,65,70,71] arguing against the suggestion that the proinflammatory response in sepsis is the main cause of cardiac NT-proBNP release, independent of hemodynamics or cardiac function.[53,54,57-59,61,70] In sepsis, elevated plasma levels of NT-proBNP were predictive of fluid nonresponsiveness, defined as an increase in cardiac index of less than 15%,[56,72] and the predictive value of NT-proBNP was greater than that of the diastolic filling pressure and volume, central venous pressure and global end-diastolic volume, respectively. This can be explained by the idea that NT-proBNP might be a better indicator of increased wall stress and exhausted preload reserve than either a filling pressure or volume indicator in septic myocardial depression. Moreover, elevated

plasma levels of NT-proBNP were predictive of mortality. In conclusion, this study showed that, independently of confounding factors, an increased NT-proBNP plasma level is a marker of systolic cardiac dysfunction and a better predictor of fluid nonresponsiveness in septic versus nonseptic, critically ill patients.

Proinflammatory cytokines (e.g. TNF-α and IL-6) and production of vasodilating and vasoconstricting factors in the vessel wall, such as NO and endothelin, are thought to be, at least in part, responsible for the hemodynamic changes seen in septic shock.[73-75] The vasodilation is thought to be associated with maldistribution of blood flow with regional overperfusion at the cost of hypoperfusion, relative to demand, with low O_2 extraction, which results in anaerobic metabolism and lactic acidemia.[5,6,76] In fact, a cytokine-induced increase in NO production from L-arginine in vascular endothelium and smooth muscle by upregulated inducible NO synthase stimulates guanylate cyclase to produce vasorelaxing cGMP,[73,74] and elevated circulating levels of nitrate-nitrite (NN) levels, the end products of NO, in sepsis and septic shock are reported.[6,77-80] Circulating NN and cGMP plasma levels seem to relate to circulating cytokine levels and seem to be higher in septic than in nonseptic patients.[78-81] Increased production of NO over that of endothelin, may partly account for the hypotension associated with vasodilation, diminished catecholamine sensitiveness and O_2 extraction, and lactic acidemia in human septic shock.[73,82,83] To examine whether cytokine-induced activation of the NO pathway over that of endothelin in the vessel wall can account for the early peripheral hemodynamic abnormalities of human septic shock, we measured hemodynamic and metabolic (e.g. O_2 extraction and lactate plasma levels) variables and plasma levels of cytokines, endothelin, and NN in 14 septic shock patients, and studied relations between these variables (**Chapter 6**). Our results showed that except for a higher final lactate plasma level and more vasopressor treatment in nonsurvivors, as compared with survivors, hemodynamic and O_2-related variables did not differ between outcome groups. Endothelin and NN plasma levels were elevated and related to elevated plasma levels of TNF-α and IL-6, early in the course of disease, which is in agreement with previous studies, suggesting that cytokines (e.g. TNF-α, IL-1, and IL-6) influence endothelin release and activate inducible NO synthase.[73-79,81,84] However, the correlation between IL-6, NN and endothelin plasma levels, and the correlation between endothelin plasma levels and doses of infused catecholamines, may indicate a common origin, i.e. endothelial activation, but it cannot be excluded that release of endothelin was induced by catecholamines.[75,85] Plasma levels of endothelin increased in time in nonsurvivors, as compared with survivors, and NN plasma levels declined in survivors but not in nonsurvivors. Endothelin and NN plasma levels and the ratio between them, did not relate to creatinine plasma levels, which suggests increased production, rather than decreased excretion by the kidneys. The SVRI, the O_2 extraction ratio, and lactate plasma levels directly related to endothelin levels, and SVRI and O_2 extraction ratio inversely, and lactate plasma levels directly, related to NN levels.

In conclusion, it is suggested that the peripheral hemodynamic and metabolic abnormalities of human septic shock are partly mediated by endothelin and NO, and a cytokine-induced activation of the L-arginine/NO pathway over endothelin, at least partly, accounts for the inappropriate systemic vasodilation, which is associated with impaired O_2 extraction and lactic acidemia. Moreover, it is suggested that increased production rather than diminished renal clearance accounts for elevated plasma levels of NN and endothelin, and that the latter are associated with a poor outcome.

Septic shock is often complicated by disseminated intravascular coagulation (DIC), which is associated with organ failure and mortality.[86,87] DIC is thought to result from release of proinflammatory cytokines and the activated complement cascade,[88,89] and is thought to contribute to microvascular obstruction and tissue hypoxygenation.[90-92] During DIC, circulating thrombin-antithrombin (TAT) complexes are considered a measure of coagulation, and plasminogen activator inhibitor (PAI) is considered a measure of (inhibition of) fibrinolysis.[90,93-95] Inhibition of fibrinolysis activation by PAI is an important predictor of organ failure and poor outcome in sepsis and DIC.[96-98] In septic shock, elevated plasma levels of lactate are the result of lactate production following tissue hypoxygenation and anaerobic metabolism, and are of prognostic value, even independently of presence of organ failure or shock.[99-101] It is suggested there might be a direct pathogenic role of a coagulation/fibrinolysis imbalance in tissue hypoxygenation and resultant lactic acidosis in septic shock, although release of proinflammatory variables could also contribute to tissue hypoxygenation. However, lactate concentrations seem of greater prognostic value than circulating proinflammatory variables.[99,100,102] To further elucidate the role of a coagulation/fibrinolysis imbalance leading to DIC and lactic acidosis in human septic shock, we measured proinflammatory mediators, coagulation and fibrinolysis variables, lactate plasma levels, hemodynamics and outcome in 14 septic shock patients and studied relations in the course of disease (**Chapter 7**). All patients had a hyperdynamic circulation with an increased cardiac index and mild hyperlactatemia. They had prolonged prothrombin time (PT), thrombocytopenia, and raised proinflammatory mediators and coagulation and fibrinolysis variables. TAT complexes were associated with IL-6 plasma levels and PAI was directly associated with TNF-α, which agrees with previous reports showing differential effects of cytokines on activation of coagulation and inhibition of fibrinolysis, with TNF-α, rather than IL-6, being involved in the control of fibrinolysis and coagulation.[88,96,103,104] The course of PAI best predicted the time course of lactate, independently of hemodynamics, proinflammatory mediators, PT, fibrinogen and platelet counts. Elevated plasma levels of lactate, PAI and PT concentrations persisted in nonsurvivors compared with survivors. Both activation of coagulation and inhibition of activated fibrinolysis were associated with hyperlactatemia, independent of confounding factors, which argues in favor of tissue hypoxygenation caused, at least in part, by a coagulation/fibrinolysis imbalance

leading to DIC and helping to explain organ failure and mortality in human septic shock.[92,98,102,105,106] Moreover, our results showed that coagulation/fibrinolysis variables were more closely related to lactate concentrations than inflammatory variables, which supports a direct role for the former in the hyperlactatemia of human septic shock. It was concluded that in the course of human septic shock and DIC, particularly inhibition of activated fibrinolysis may be independently associated with hyperlactatemia, and it is therefore suggested that a coagulation/fibrinolysis imbalance may contribute to tissue hypoxygenation, anaerobic metabolism and ultimate demise.

In experimental settings, vasopressor and inotropic drugs, commonly used in the treatment of septic shock to increase arterial blood pressure and ameliorate cardiac function and organ perfusion, have been suggested to modulate immune responses and thereby contributing to their effects on outcome, with several reports showing conflicting results.[107-109] Cathecholamine-induced modulation of the immune response, by augmenting the acute inflammatory response, is suggested to play a role in the host defense in sepsis,[110] however, the significance hereof in the treatment of human septic shock is largely unknown.[111-114] To elucidate the role of drug treatment in modulating innate immunity in septic shock, we studied longitudinal relations between vasopressor/inotropic doses and proinflammatory mediators during treatment in 20 septic shock patients in the course of disease (**Chapter 8**). Compared to survivors, nonsurvivors had more vasopressor drugs administered, and had persistent lactic acidosis. Proinflammatory mediators did not differ between survivors and nonsurvivors. The 7 patients receiving dobutamine had higher TNF-α plasma levels, than those not receiving dobutamine. In multivariable analysis, dobutamine doses were positively related to TNF-α plasma levels, independently of confounding factors. It is suggested that dobutamine-induced secretion of TNF-α, which has been demonstrated in isolated hepatocytes and the hepatosplanchnic region, accounts for this relation in septic shock patients,[115,116] and this proinflammatory effect might partly explain the detrimental effects of high-dose dobutamine used previously.[112] Dopamine doses were positively associated with IL-6 plasma levels, as reported before.[108,111,115] In some multivariable models, norepinephrine doses were inversely associated with IL-8 and TNF-α plasma levels, which might explain, in part, reported better outcome of use of norepinephrine, compared to dopamine and dobutamine in the treatment of shock.[114] Since our analyses were adjusted for confounding factors, the positive relation between dobutamine doses and TNF-α plasma levels early in the course of disease may reflect cause effect relations, rather than a common origin. To our knowledge, this is the first study to address the in vivo immune-modulating effect of various catecholamines used early in the management of human septic shock, independently of disease severity, hemodynamics, and outcome. Our results argue in favor of immunosurveillance in future studies on the hemodynamic management of human septic shock with help of vasopressor/inotropic drugs. In

conclusion, our observations suggest that catecholamines used in the treatment of human septic shock differ in their potential modulation of the innate immune response in septic shock, by differing adrenergic and dopaminergic receptor stimulation. Dobutamine treatment may contribute to circulating TNF-α and dopamine to IL-6. Conversely, norepinephrine may lack proinflammatory actions.

CONCLUSIONS

The studies in this thesis show that septic shock is a highly complex clinical syndrome which results from a systemic response to infection that involves proinflammatory and anti-inflammatory processes, the innate immune response, procoagulant and antifibrinolytic pathways and alterations in metabolism. Circulating markers and mediators in the course of human septic shock are described and their relation with cardiac function and hemodynamic alterations is studied, showing innate immunity factors to differ in their contribution to hemodynamic abnormalities in the course of disease, with complement activation that partly offsets the myocardial depression and IL-6 release being associated with vasodilation. Circulating plasma levels of α-ANP, cGMP and endothelin were shown to facilitate recognition of myocardial depression, and were suggested to help in predicting and monitoring the response to treatment of the syndrome. An increased NT-proBNP plasma level was shown to be a marker of systolic cardiac dysfunction and to better predict fluid nonresponsiveness in septic, than in nonseptic, critically ill patients. It was shown that the inappropriate systemic vasodilation, which is associated with impaired O_2 extraction and lactic academia in human septic shock is, at least partly, accounted for by a cytokine-induced activation of the L-arginine/NO pathway over endothelin. In human septic shock, coagulation and fibrinolysis are affected by released proinflammatory cytokines and complement activation products. It was shown that inhibition of activated fibrinolysis might be associated with hyperlactatemia and it is suggested that a coagulation/fibrinolysis imbalance may contribute to tissue hypoxygenation, anaerobic metabolism and ultimate demise. The in vivo immune-modulating effect of treatment with vasopressor/inotropic drugs used early in the management of human septic shock is described, showing that catecholamines differ in their potential modulation of the innate immune response, with dobutamine being associated with circulating TNF-α, dopamine with IL-6, and norepinephrine lacking proinflammatory actions.

FUTURE PERSPECTIVES

Although our understanding of the pathogenesis of sepsis and septic shock has progressed, attempts to affect clinical outcome by modulating these pathogenetic pathways have been disappointing. More research is needed to elucidate the complex pathophysiology of the sepsis syndrome and concomitant processes and to establish the value of different circulating markers and mediators during the course of disease. During the past decade, many more factors have been identified and knowledge increases rapidly, however, there might be no single marker for clinical use, and future measurements of a combination of specific factors might provide insight in the syndrome and guide treatment. Further evaluation is required to identify this combination of factors.

Future studies aligning hemodynamic abnormalities with patterns of circulating cardiovascular markers and mediators may help to stratify patients for inclusion in studies to assess the causes, response to therapy, and prognosis of cardiovascular derangements in critically ill patients. Since the immune response in sepsis appears to be biphasic, serial measurements of circulating markers and mediators of the immune response should be done and studied in relation to the time course of cardiac function and hemodynamic alterations, evaluating the different stages of sepsis and thereby contributing in directing therapy. For this reason also, longitudinal relations between NT-proBNP plasma levels and cardiac function parameters should be studied by doing serial measurements in the course of disease.

In this thesis, the immune-modulating effect of treatment with vasopressors/inotropes is addressed, and therefore, immunosurveillance is advised in studies on the hemodynamic management of human septic shock with help of vasopressor/inotropic drugs.

Future management of septic shock may be directed at immune modulation, depending on genetic polymorphisms, the characteristics of the pathogen, and the stage and duration of disease.

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