**Hemofiltration and left ventricular function in sepsis**

**Mechanisms and clinical implications**

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Over the last decade, it became clear that left ventricular (LV) dysfunction is typical of animal and human septic shock [1]. Circulating myocardial depressant substances [2] and local release of mediators [3], rather than global myocardial hypoperfusion [4,5], seem responsible for this phenomenon. Indeed, a series of reports [3] by Parrillo et al. in the 1980s were able to conclusively link left ventricular systolic dysfunction in septic patients to the effects of a myocardial depressant substance in the patient's own serum. Moreover, immunoabsorption of both tumor necrosis factor (TNF)-alpha and interleukin (IL)-1 beta from the sera of patients with septic shock completely eliminated its cardiac myocyte depressant activity, suggesting that TNF-alpha and IL-1 beta contribute to septic myocardial depression [2].

Removing various proinflammatory substances by hemofiltration became consequently very attractive, especially as several studies showed that the left ventricular systolic function of septic animals was improved by hemofiltration and confirmed the presence of a depressive substance in the plasma and ultrafiltrate of septic animals [6,7].

In this issue of Critical Care Medicine, Dr. Kline and colleagues [8] not only have confirmed the previous reports showing that large-pore membrane hemodiafiltration was able to increase left ventricular systolic function of endotoxemic dogs, but have also evidenced other potentially salutary effects of this technique on left ventricular function (i.e., a trend toward improved myocardial efficiency and an increase in myocardial glucose uptake). They postulated that large-pore membrane hemodiafiltration improved left ventricular systolic function in endotoxemic dogs by successfully removing soluble negative inotropic mediators, although no assay was performed in this study. Observations from often retrospective and uncontrolled clinical studies, comprising only a small number of patients, support the thesis that hemofiltration may exert beneficial effects on left ventricular systolic function [9].

However, the mechanism by which hemofiltration acts is not as simple as was previously expected. To be eliminated by convection-the physical principle on which hemofiltration relies-a substance has to be present in the plasma water in an unbound form. Its molecular size has to allow passage through the pores of the membrane, although adsorption to the membrane could represent an alternative route of elimination [9]. In addition, the detection of substantial amounts of a substance in the ultrafiltrate does not imply a clinically relevant elimination, the contribution to total body clearance must exceed 25% to 30%. Table 1 describes the characteristics of substances that are likely able to directly or indirectly trigger left ventricular dysfunction in sepsis. The "endotoxin-TNF-alpha-NO pathway" clearly plays a
substantial part of myocardial depression in sepsis \cite{2}. However, the critical review \cite{9} of existing literature on cytokine removal with renal replacement therapy leads to the conclusion that their characteristics are not compatible with clinically relevant removal. Indeed, the variable detection of TNF-alpha in the circulation of septic patients, the high molecular weight of the biologically active trimer, its binding to tissue and circulating soluble receptors, and its high endogenous clearance represent important limitations to the filtration of large amounts. Although the molecular weight of IL-1 beta allows its passage through the hemofiltration membrane, the low incidence of IL-1 beta detection in the plasma of septic patients, the presence of naturally occurring binding antagonists, and the high endogenous clearance also preclude clinically important elimination. Consequently, no clinical study has shown a reduction in cytokine levels with these techniques. Moreover, studying plasma cytokines profiles during the intense inflammatory reaction induced by cardiopulmonary bypass in small children, Journois et al. \cite{10} reported that the reduced IL-1 beta plasma concentrations observed at 24 hrs after high volume zero-balanced hemofiltration was not due to removal of IL-1 beta during this procedure (IL-1 beta was not detected in the plasma and ultrafiltrate), but probably was related to removal of one (or several) other substance(s). Indeed, it is possible that hemofiltration removes some other mediators, as arachidonic acid metabolites (0.6 kD), beta-endorphin (4 kD), bradykinin (1 kD), or complement factors (10 to 12 kD), but their role in sepsis-induced left ventricular dysfunction seems relatively weak \cite{3}.

| Table 1. Characteristics of myocardial depressant substances (see \cite{2} for review) |

In fact, convective transport creates many modifications other than removing inflammatory mediators. Convection is no more than a physical principle and molecules are removed from plasma depending only on their physical properties, without any specificity. Because of its physical characteristics, the main "toxin" most removed by hemofiltration is water. There is no diuretic more powerful than hemofiltration and some spectacular effects observed with this therapy are likely to be only due to its ability to rapidly remove water from plasma \cite{11}. Zero-balanced hemofiltration, performed to isolate the effect of water removal from other properties of hemofiltration, must be considered with caution. "Zero-balanced" usually means "zero-fluid-volume-balance." However, water distribution between intra- and extracellular compartments is essentially affected by the changes in plasma osmolarity. Consequently, when Dr. Kline and colleagues \cite{8} readministered 0.9% NaCl to "volume balance" ultrafiltration, they achieved their goal in terms of volume but overloaded the animals with NaCl. This phenomenon may have lead to alterations in plasma osmolarity. The increased plasma osmolarity is then responsible for a reduction in myocardial edema, improving left ventricular diastolic function, as well as systolic function via, at least, the Frank-Starling mechanism. Similarly, hypothermia, altered glucose concentration, acidosis correction, and many other metabolic events can occur and may play a more important role in myocardial function improvement in sepsis than any mediator removal.

Even if the evidence that high-volume hemofiltration/hemodiafiltration with large-pore membrane is able
to improve the left ventricular systolic function in septic shock is compelling, the effect of global hemodynamic and oxygenation conditions remains to be proven, although a study [12] in endotoxemic dogs reported an improved cardiac output, a reduced pulmonary hypertension, an increased hepatic blood flow, and an attenuated lactic acidosis using this technique early after endotoxin challenge. Finally, Lee et al. [13] showed that the use of high permeability membranes, with a cutoff close to albumin molecular weight, was able to reduce the mortality rates of induced septicemia in swine. The question of whether this technique should be used in patients with septic shock before the appearance of renal failure can only be answered with a prospective controlled clinical trial evaluating its effect on survival.

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