Are the synergistic effects of high-volume haemofiltration and enhanced adsorption the missing key in sepsis modulation?*

Olivier Joannes-Boyau1, Patrick M. Honore2, Willem Boer3 and Vincent Collin4

1Anaesthesia and Intensive Care Department II, University Hospital of Bordeaux, University of Bordeaux II, Pessac, France,
2St-Pierre Para-Universitary Hospital, Ottignies-Louvain-La-Neuve, Belgium, 3Atrium Medical Center, Heerlen, The Netherlands and 4Clinique de L’Europe, Brussels, Belgium

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Introduction

Despite major recent therapeutic improvements, septic shock remains a leading cause of mortality in intensive care patients [1]. For more than a decade, it has been advocated [2,3] that the reduction of blood cytokine levels could, at least theoretically, lead to reduced mortality. However, in view of the complexity of the pharmacodynamics and pharmacokinetics of cytokines, this concept seems too oversimplified to apply. In this issue of the journal, Rimmelé and co-authors attempt to demonstrate that high-volume haemofiltration (HVHF) with enhanced adsorption (EA) can modulate and ameliorate sepsis-induced haemodynamical instability [4]. It is suggested in this paper that membranes with EA are key and that increased extraction from the central circulation is sufficient to obtain a beneficial clinical effect. It seems at least theoretically reasonable that effective removal of mediators from the tissue, where they are harmful, and transporting them to the central circulation must work synergistically in this model. In order to consolidate this hypothesis, it seems fruitful to discuss the three...
separate theories that in recent years have been put forward as possible explanation for the clinical findings observed in septic patients who underwent a number of different blood purification techniques. The HVHF and hybrid techniques that at present are available to the clinician are diverse and deserve a brief description.

In the peak concentration hypothesis [5–7] of Ronco and Bellomo, efforts are concentrated on removing mediators and cytokines from the blood compartment in the pro-inflammatory phase of sepsis. It is hoped that by reducing the amount of free cytokines, remote organ (associated) damage can be limited, thereby improving patient survival. In this theory, changes in mediators and cytokines at interstitial and tissue levels are not taken into account although it seems logical that they are of clinical importance. In this setting, techniques that facilitate rapid and substantial removal of mediators should be preferred.

After an extensive literature review, a second model was developed coupling mediator removal from the blood compartment to changes in interstitial and blood compartment. This model, the threshold immunomodulation hypothesis, sometimes referred to as the Honoré concept [8,9], takes a more dynamic view of the system. Pro-mediators as well as mediators are removed at interstitial and tissue levels, following removal from the blood compartment, until a so-called threshold point is reached at which some pathways and cascades are stopped. At this level, the cascades are interrupted and no further harm can be done to the tissues. However, when applying HVHF in clinical practice, determination of this threshold point is difficult as there might still be significant changes taking place at the interstitial and tissue level, while no changes in the blood compartment can be observed. A number of observational studies using HVHF demonstrated improved haemodynamics and survival in some patients without a significant drop in mediator blood levels [10–12]. One could therefore postulate that substantial biological effects of HVHF can be obtained without any dramatic fall in plasma cytokine levels, while still the harmful tissue levels fall. It remains unclear in this model how HVHF promotes mediator and cytokine flow from the tissue and interstitium to the blood compartment.

In the mediator delivery hypothesis [13], otherwise known as the Alexander concept, the beneficial use of HVHF and especially of high replacement volumes (3–5 l/h) has been emphasized. With this technique, a 20- to 40-fold increase in lymphatic flow has been demonstrated in several papers [14–16] that could result in a concomitant substantial drag and displacement of mediators and cytokines to the blood compartment where they become available for removal. Thus, the use of high volumes of replacement fluid might be of great importance, not only for extraction but also to stimulate lymphatic transport between the interstitium and tissue compartments and the blood compartment. It seems thus plausible that HVHF enhances the transfer of mediators to the blood stream and that EA plays a role in the efficient removal of those mediators from the blood circulation, thereby acting synergistically.

Undoubtedly, the strength of the experimental study presented by Rimmelé et al. [4] lies in the randomization of septic animals over two membranes with different adsorption capacities together with an in vitro study. However, some drawbacks of this study should be pointed out. In focusing on effective adsorption, changing the membranes is frequently essential and herein lies a potential hurdle for implementation in daily medical practice, because of increasing costs and the nursing workload during the haemofiltration sessions [17]. To counter this, the authors instigated frequent changes only in the very early phase of septic shock, when modulation of serum endotoxins and cytokines levels seems most critical. Furthermore, the phenomenon of adsorption might be transient not only because of the saturation of the membrane but also due to the de-adsorption process which takes place after only a few hours [18]. Last but not least, it would have been desirable to assess the survival of the experimental animals, as showing a correlation of improved haemodynamics by a plasma separation technique (PST) with improved survival would answer the question most relevant to the clinician [19], whether there is a link between improved haemodynamics and eventual improvement in mortality [20]. Some evidence was provided by the experiments done by Yekebas et al. [21], who demonstrated that the early application of HVHF in a pig model of pancreatogenic sepsis could lower secondary infection of ascites and blood and was associated with lower mortality. This was the first time that early application of HVHF could demonstrate reversal of the ‘immunoparalysis’ induced by sepsis. In other words, HVHF restored late immunohomeostasis and down-regulated back to normal the (over)-compensatory anti-inflammatory response syndrome [22]. Kellum et al. added some additional evidence [23]. Sepsis was induced in a rat model and the animals were randomly assigned to PST in order to assess the effect on liver production of mediators through nuclear factor (NF)-kappa-B production. Application of PST improved not only haemodynamics but also survival. These experiments also demonstrated for the first time that PST was able not only to reduce mediator blood levels but also mediator production into the liver. The exact mechanism of this upstream down-regulated effect remains to be elucidated. Finally, Li et al. [24] investigated the role of HVHF directly in a pig model of sepsis. In some of the animals the activity of the mitochondrial respiratory chain was measured in the myocardium. It was demonstrated that sepsis induced a dramatic reduction of this activity that was however fully restored by HVHF. Altogether, these three series of experiments were able to demonstrate the link between improved haemodynamics and improved survival [25]. While all these studies were promising, it is now time for larger studies and randomized controlled clinical trials. The results from one such study, the so-called VA/NIH study, were published in 2008 [26]. This was a very large and well-conducted randomized study comparing two different doses of CRRT (20 versus 35 ml/kg/h) and two different intensities of intermittent renal replacement therapy (RRT) depending on the haemodynamic status of the patient. This study was not able to show that intensive renal support in critically ill patients with acute kidney injury resulted in decreased mortality, improved recovery of kidney function or reduced rate of non-renal organ failure as compared with less-intensive therapy. Several criticisms have been
formulated against this study [27,28], notably on the supposed 35 ml/kg dose of CVVH in the intensive treated group. This group was split into an 18 ml/kg/h dose of dialysis (1500 ml/h) and a 17 ml/kg/h of convection rate, giving an actual dose of roughly 15 ml/kg/h (when taking into account the pre-dilution modality instead of full post-dilution). Additionally, the patients were enrolled in the study and treated relatively late in the course of the illness, as compared to other studies (after a mean of 7 days in the ICU and 10 days in hospital). Of note also is the fact that >65% of the patients received either intermittent haemodialysis or sustained low-efficiency dialysis (SLED) treatment within 24 h prior to the randomization. Needless to say that the results of the ANZICS clinical trials group renal study [29] comparing augmented with normal RRT in severe acute renal failure are eagerly awaited. While several large randomized trials are currently in progress investigating haemofiltration doses in AKI patients, only one is comparing HVHF with standard CVVH in septic AKI. The so-called IVOIRE (High VolVume in Intensive Care) study [30] will try to expand on the findings of the initial study by Ronco and colleagues [31] in septic patients. This large randomized study will include patients with septic shock plus AKI, as defined by the RIFLE classification [32], with patients receiving HVHF at either 35 or 70 ml/kg/h. The first interim analysis will be performed when 150 patients have been included, sometime in 2009.

In conclusion, in recent years, a number of different techniques have been studied and developed in the field of RRT in the septic patient. Manipulation of ultrafiltrate dose, membrane porosity, mode of clearance and combinations of techniques have yielded promising findings including the study of Rimméle and co-workers, published in this issue [4]. However, at present, conclusive evidence based on well-designed randomized controlled trials remains scarce, limiting the practical implementation of many techniques in daily practice outside the context of a study. From the few well-designed and documented studies that we have so far, it is safe to say that optimization of delivered dose in RRT has a proven positive effect. An ultrafiltration rate between 35 and 45 ml/kg/h, with adjustment for predilution and down time, can be recommended for the septic patient with AKI until other data become available. If continuous haemofiltration is not available, daily dialysis should be recommended in septic AKI [33]. The results of further dose outcome studies with higher ultrafiltration rates will likely be the stepping stone to further improvements in daily clinical practice. Hybrid techniques will also likely have a role in the expanding field of RRT in the septic patient in the near future.

Conflict of interest statements. None declared.

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Is altruistic-directed living unrelated organ donation a legal fiction?

Miran Epstein¹ and Gabriel Danovitch²

¹Academic Unit for Human Science and Medical Ethics, Barts and The London School of Medicine and Dentistry, Queen Mary, University of London, London and ²Department of Medicine, David Geffen School of Medicine at UCLA, Los Angeles, CA, USA

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Introduction

The majority of pertinent political and professional bodies now regard ‘altruism’ and ‘solidarity’ as the sole foundations of any acceptable donor–recipient interaction. The European Directive, for example, makes an unequivocal statement in this respect.

As a matter of principle, tissue and cell application programmes should be founded on the philosophy of voluntary and unpaid donation, anonymity of both donor and recipient, altruism of the donor and solidarity between donor and recipient. [1]

Similar views have equally been endorsed inter alia by American law, the World Health Organization (WHO), and, most recently, The Transplantation Society (TTS) [2–4]. Whatever the dictionary definition of ‘altruism’ and ‘solidarity’, in the legal transplant jargon they have come to be understood as any motivation for organ donation other than such that are formed under consent-invalidating coercion. In fact, unless otherwise specified, the term ‘altruistic donation’ has come to mean ‘non-commercial donation’.

The market, however, constantly challenges these conceptions. By offering an apparently unlimited supply of organs, it gives patients who are facing a long wait for an organ, primarily a kidney, from a deceased donor the option of buying one from a living donor, instead of putting their relatives and loved ones to the test. By putting a price tag on body parts, it lures strangers, who would not give their organs for free anyway, into considering selling them. Finally, it promises parsimonious payers of health care a quick and cheap relief—one that does not need to rely on social solidarity or the good will of individuals. Success of the market comes at the expense of the altruistic sphere, and a bigger market is likely to intensify the pressure on the latter even further [5,6]. Ironically, claims suggesting that altruism and solidarity are unable to meet the demand for organs, which are often invoked by proponents of the market in their attempts to promote their own solution to the global shortage of organs, ignore the fact that the problem has been caused, at least on part, by pervasive commercialization.

At any rate, within the altruistic sphere, different categories of living donation are more or less resistant to market pressures. For example, non-directed anonymous living donation may seem uncommercializable, but it is not. There is always some contact, whether direct or via intermediaries, between donor and recipient, which makes this category

Correspondence and offprint requests to: Miran Epstein, Senior Lecturer in Medical Ethics and Law, Academic Unit for Human Science and Medical Ethics, Barts and The London School of Medicine and Dentistry, Queen Mary, University of London, 2 Newark Street, London E1 2AT, UK. Tel: +402-7882-7086; Fax: +402-7882-2552; E-mail: m.epstein@qmul.ac.uk

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