High-flow Hemofiltration as an Adjunctive Therapy in Sepsis

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Introduction

Almost ten years ago, standard hemofiltration was often provided at 1 or 2 l/h of ultrafiltration and only in pre-dilution mode. However, practice began to change as results from new studies were published in the early 2000s demonstrating a beneficial effect on outcome of increasing the ultrafiltration rate to 35 ml/kg/h in patients with acute kidney injury (AKI). Two methods of high volume hemofiltration (HVHF), with different underlying concepts and results, became prevalent: Continuous high volume hemofiltration (CHVH) providing 50 to 70 ml/kg/h 24 hours a day, and intermittent high volume hemofiltration (IHVH) with brief, very high volume treatment at 100 to 120 ml/kg/h for 4 to 8 hours (previously called 'pulse' HVHF). Two recently published studies [1, 2] highlight the crucial role of adequate dosage of continuous venovenous hemofiltration (CVVH), demonstrating that, in critically ill patients with renal failure, a dose of 35 ml/kg/hour was associated with dramatic improvement in survival of nearly 20%. The incorporation of the results from these studies into daily clinical practice can now be deemed to be urgent, although the results of other ongoing confirmatory (or not) studies are awaited. In a world increasingly guided by evidence based medicine, two level I studies lead to a Grade A recommendation, and this intervention should, therefore, be applied by every intensivist instigating continuous hemofiltration, while awaiting the results of the ongoing studies. Nevertheless, the implementation process is exposed to a number of potential difficulties. These encompass items such as blood flow requirements, vascular access problems, pre-and post-dilution policy, type of membranes used, as well as restitution fluid and the possible need for associated dialysis. Implementation of these findings will necessitate a collaborative network between medical staff members and the entire nursing staff.

Mechanism of Action: Hemofiltration as a New Shield against the ‘Chaos Theory’ and ‘Complex Non-linear Systems’ in Sepsis

Hemofiltration was first used in AKI, which is an independent factor for increased severity of illness and poor outcome in critically ill patients. Early studies had shown that the mortality rate of patients requiring renal replacement therapy (RRT) for AKI in the ICU was nearly twice as high compared to those without AKI (62.8 vs 38.5%) [3, 4]. This suggests, therefore, that AKI is independently responsible for increased mortality, even if RRT is used. In fact, while standard RRT significantly reduced mortality in patients with AKI in comparison with mortality rates before
RRT was used, mortality rates were still not as low as in patients without AKI. The new concept of ‘purification plasma challenge’ was then developed to try to decrease mortality. Systemic inflammatory response syndrome (SIRS), sepsis and septic shock, and acute pancreatitis are known to be the leading causes of AKI in ICU patients, creating an immunologic disturbance with a cytokine storm. Sepsis and inflammatory pathologies disrupt homeostasis with a cellular and humoral response, generating secretion of cytokines such as interleukins and tumor necrosis factor (TNF)-α. Over the years, many attempts have been made to block some parts of the inflammatory cascade or to destroy specific components; some positive results were obtained in animal models but were not translated into clinical benefit [5]. It has been suggested that a large and non-specific reduction in cytokines in the blood compartment could in theory reduce mortality more than simply concentrating on removing or blocking one specific element [6]. However, this approach is complicated by the fact that neither the pharmacodynamics nor the pharmacokinetics of cytokines and other immune components are well known, not even their precise functions. Some of the leading theories in this field are provided by current experts in hemofiltration. First, the ‘peak concentration hypothesis’ of Ronco and Bellomo postulates that removing the peak cytokine concentration from the blood circulation during the early phase of sepsis could stop the inflammatory cascade and the accumulation of free cytokines, which are the leading cause of organ damage and homeostasis disruption [7, 8].

The second concept is called the ‘threshold immunomodulation hypothesis’, also called the ‘Honore’ concept [9, 10]. In this concept, the removal of cytokines does not only affect the cytokine concentration in the blood stream but also in the tissues. Indeed, when cytokine concentrations are reduced in the blood, blood and tissue concentrations may equilibrate to remove the immune components trapped in the organs. This could explain why no crucial reduction in cytokine concentration is observed in the blood stream during hemofiltration, because cytokines from the organs permanently replace those lost in the blood. The third theory, which has been proposed by Di Carlo, sheds new light on the mediator delivery hypothesis, in which the use of HVHF with a high volume of crystalloid fluids (3 to 5 l/hour) is able to increase the lymphatic flow by 20 to 40 fold [11, 12]. Indeed, this increase is correlated with the infusion of a high dose of fluids. Since cytokines and other immune components are transported by the lymphatic stream, this could explain their removal even though large amounts of cytokines were not found in ultrafiltration fluid [13]. Thus, the use of high volumes of exchange fluid might be the principal motor of cytokine removal.

To achieve a wider view of these theories, we need to explore the new paradigm of chaos and ‘complex non-linear systems’ in sepsis and SIRS [14]. The principal goal underlying these theories is not only removal of cytokines but also immunomodulation and control of the inflammatory response, which becomes deleterious when it surpasses its designed purpose. Indeed, the immune response of the host against septic aggression could be compared to a complex non-linear system which is defined by the infinite number of possible actions in response to a lone stimulus. In a complex non-linear system, e.g., the situation by which a flight of butterflies in China can change the weather in Boston three days later, a bacterial attack or cytokine secretion will have repercussions in the whole body. This explains why homeostasis is not a state of stability per se but rather the ability to stay stable while the status is permanently changing. Yet this incredible adaptability is halted when the system is drowned by an excess of information and when the ‘endocrine effect’ of