CHAPTER 171

High-Volume Hemofiltration in the Intensive Care Unit

Olivier Joannes-Boyau, A. Dewitte, and Patrick M. Honoré

OBJECTIVES

This chapter will:
1. Explain the rationale to use high-volume hemofiltration in the intensive care setting.
2. Provide the latest definition of high-volume hemofiltration.
3. Describe the related studies performed in the last 15 years and the recommendations based on the latest randomized controlled trials.

High-volume hemofiltration (HVHF) still is used in the intensive care unit (ICU) for various pathologies despite some recent negative randomized controlled trials (RCTs). The definition, practice, and rationale for HVHF have changed in the last 15 years with increasing volume of treatment. Despite promising initial studies, the most recent RCTs and subsequent recommendations are clearly against the use of HVHF in clinical practice. The purpose of this chapter is to provide advice and recommendations, because the technique still is used routinely in numerous healthcare centers.

DEFINITION OF HIGH VOLUME

Twenty years ago, standard hemofiltration often was given at 1 or 2 L/hr of ultrafiltration treatment and only in predilution mode. Practices began to change with the Ronco et al. study in 2001, which proved the beneficial effect on outcome of increasing the ultrafiltration rate to 35 mL/kg/hr in patients with acute kidney injury (AKI).[1] At that time, the old definition of HVHF became the standard of care, and volumes used for high volume increased dramatically from 35 mL/kg/hr to 100 mL/kg/hr.[2–4] Two latest large RCTs, the VA/NIH study and the RENAL study,[5,6] demonstrated that high intensity of hemofiltration was not beneficial compared with 25 mL/kg/hr, the dose currently recommended. Furthermore, two different HVHF methods became common: continuous high-volume treatment providing 50 to 70 mL/kg/hr 24 hours a day and intermittent HVHF with brief, very high-volume treatment at 100 to 120 mL/kg/hr for 4 to 8 hours, which used to be called "pulse" HVHF. Both came under the heading HVHF despite their concepts, and the results are somewhat different, as described later in this chapter. In the 2015 Vicenza Nomenclature Standardization Initiative

(NSI),[7] they defined HVHF as a continuous convective treatment with a (prescribed) target dosage greater than 35 mL/kg/hr. A dosage exceeding 45 mL/kg/hr represents very HVHF (VHVHF). Intermittent procedures using brief VHVHF episodes (100–120 mL/kg/hr for 4–8 hr), followed by conventional continuous venovenous hemofiltration (CVVH), are identified as "pulse" HVHF.

Rationale

The first idea to justify the outbreak of hemofiltration is the recognition of AKI as an independent factor of severity and is associated with a poor outcome in the ICU. Numerous studies indeed have shown that mortality of patients requiring renal replacement therapy (RRT) for AKI in the ICU is dramatically higher than those without AKI.[8] This suggests that AKI is independently responsible for an increased mortality, even if RRT is used. In fact, although standard RRT significantly reduced mortality in patients with AKI in comparison with no use of dialysis, it did not achieve a mortality rate comparable with patients without AKI.

Then, new ideas arose to try to improve the outcome of patients, particularly in case of sepsis, entitled "the blood purification challenge." Inflammation and sepsis are known to be the leading causes of AKI in the ICU by creating immunologic disturbances and a cytokine storm. Sepsis is a life-threatening organ dysfunction caused by a dysregulated host response to infection, meaning that the host response to infection is overwhelming, going beyond its adaptive role of restoring homeostasis, and drives organ dysfunction. The activation of the innate immune system realizes a systemic hyperinflammatory condition that parallels a compensatory antiinflammatory response. The inflammatory phase is characterized by the generation of soluble proinflammatory mediators and immune cell activation, and sepsis prognosis is linked to the magnitude and duration of the early inflammatory response, high circulating cytokine levels being associated with poor outcome. In the past, many attempts were made to block parts of the inflammatory cascade or to target specific components of the immune response. Some results were obtained in animal models but without any clinical benefit.[9] Some studies indeed demonstrated beneficial effects of unspecific removal of cytokines, even if most of them failed to demonstrate survival benefit.[10–13] However, this approach is complicated by the fact that the pharmacodynamics, the pharmacokinetics of cytokines and immune effectors, nor even their exact function are known exactly.

The current experts in hemofiltration provided some of the leading theories. 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 circulating cytokines, which are the leading causes of organ damage and homeostasis disruption.[14]

The second concept is called the "threshold immunomodulation hypothesis" and has been developed by Honore.[15,16] In this concept, the removal of cytokines affects not only the cytokine concentration in the bloodstream but also their level in tissues. Indeed, when the cytokine concentration is reduced in blood, both concentrations may be equilibrated to extract the immune components trapped in the organs. This could explain why no crucial reduction in cytokine concentration is observed in the bloodstream during hemofiltration, because cytokines from the organs permanently compensate for their loss in the blood.

The third theory, which has been advanced by Di Carlo, sheds new light on the mediator delivery hypothesis: the use of HVHF with a high volume of crystalloid fluids given to the patient (3 to 5 L/hr) could increase the lymphatic flow by 20- to 40-fold.[17] Because the cytokines and other immune effectors are transported by the lymphatic system, this could explain their removal, even though high quantities of cytokines were not found in the ultrafiltration fluid.[18,19] Thus the use of high volumes of exchange fluid may be the principal motor for cytokine removal.

To gain a wider view of these theories, we have to explore the new paradigm of chaos and complex nonlinear systems in sepsis.[20,21] The principal goal underlying these theories is not only the removal of cytokines but also the immunomodulation and the control of the inflammatory response, which becomes deleterious when it supersedes its role. Indeed, the immune response of the host against septic aggression could be compared with a complex nonlinear system, which is defined by the infinity of solutions in response to a lone stimulus. In a complex nonlinear system, like in the chaos theory in which a flight of butterflies in China can change the weather in Boston 3 days later, a bacterial attack or cytokine secretion will have repercussions on the whole body. This explains why homeostasis is not a state of stability but rather the capability to stay stable while the status is changing permanently. However, this incredible adaptability is halted when an excess of information drowns the system and when the "endocrine effect" of cytokines and other immune messages are lost in the storm. The resources of the body system become depleted, and the complex nonlinear system becomes a linear system, with only one course of action to follow. This heralds the onset of multiple organ dysfunction syndrome (MODS). Hemofiltration could play a role at this point by decreasing the cytokine storm through different modes and by allowing the efficacy of the immune messages to be recovered, conducting to a return from this complex nonlinear system to homeostasis. However, no study has demonstrated this clearly until now.

Practical Aspects

New treatment volumes imply changes in hemofiltration practice to guarantee the efficacy and safety of the technique. Indeed, to reach 60 or 100 mL/kg/hr of treatment volume, important principles must be respected. First, a high blood flow is necessary to maintain a filtration fraction (FF) below 25%:

$$FF = (\text{Predilution} + \text{Postdilution} + \text{Fluid removal}) / (\text{Predilution} + \text{Blood flow})$$

a level above which "protein cake" clogging in the membrane becomes a major concern.[22] However, to attain such a blood flow, excellent vascular access is required, with a large catheter (13.5 or 14 French), adequate location (right jugular and femoral are the best), and good structure (double-lumen kidney-shaped design with shotgun tip).[23] Second, the best restitution fluid is probably buffered bicarbonate and should be administered one third in predilution and two thirds in postdilution (i.e., the best compromise between loss of treatment efficacy and optimization of blood rheology).[24] The choice of the membrane is also primordial, and a highly biocompatible synthetic filter with a high exchange surface is recommended (1.7 to 2.1 m^2). Temperature control is not important with low fluid exchange volumes but becomes essential when the volume increases dramatically. Two systems are possible: heating the fluid before restitution

or heating the blood directly. Empirically heating the replacement fluid seems preferable to heating the blood, owing to possible deleterious effects of high heat on the blood. However, no problems have been recorded, and the two systems have demonstrated their safety and efficacy.

The new machines specially dedicated to high volumes have extremely sensitive and precise pressure control and volume balance functions. Furthermore, it is important to stay in the normal pressure range for optimal use of hemofiltration. Indeed, staying below –120 mm Hg of arterial pressure is indicative of a catheter problem and likely early machine failure. The same is true with a venous line, in which high pressure indicates catheter or bubble trap clotting. The transmembrane pressure reflects the state of clogging in the filter, whereas a high pressure indicates that many fibers are clogged. To alleviate the pressure problem, it is recommended to stop the treatment when the patient is being nursed or moved, especially with high volumes. HVHF also requires adequate management and control of fluid exchange and small solutes. In fact, the small molecules are removed mainly during hemofiltration, and strict monitoring of sodium, glucose, and acid-base balance is mandatory.[22]

Clinical Results

Animal models have shown benefits in terms of survival when "early" and "strong" hemofiltration doses were applied in septic animals. Regarding animal models, early use of hemofiltration has been investigated thoroughly.[25,26] Most of the earlier studies used hemofiltration before or just after the injection of bolus or even infusion of endotoxin. It was only in the late 1990s that investigators started to wait about 6 to 12 hours before using HVHF, thereby "allowing" the animals to become extremely ill and hemodynamically unstable and to develop early multiple organ dysfunction syndrome.[27] In this way, animal models were closer to the human clinical situation usually encountered. Only animal models in which HVHF was applied early proved to be very beneficial (some with a dramatic improvement), mainly because of the fact that in addition to early application, the investigators administered a much "stronger" dose of HVHF.[28–31] However, the differences between human and animal models do not allow these results to be extrapolated to humans. Even on the contrary, latest animal studies have shown opposite results with HVHF, although teams continue to show that HVHF improves clinical parameters and survival, others failed to find beneficial effects.[32,33]

One of the greatest remaining problems with human studies (and especially the mechanistic studies) is the fact that the number of patients is very limited because the technique is so expensive. Moreover, clinical studies have failed far beyond short of the mean 100 mL/kg/hr exchange obtained in initial animal models. As a consequence, many anticipated effects seen in animal models never have been reproduced in human settings owing to the use of inadequate doses of HVHF. On the other hand, there is huge variability between clinical trials concerning the range of doses applied, ranging from 1 to 15-fold in the recent studies.

The foundations of the high-volume technique were laid by Ronco et al., who showed that in their subgroup of septic patients, increasing the volume of treatment from 35 mL/kg/hr to 45 mL/kg/hr could improve outcome.[34] That study effectively demonstrated that hemofiltration could be considered as a viable medication in ICUs. The volume of treatment has to be adapted not only to body weight but also to the severity of illness of ICU patients. However, about 10 years later, two large multicenter RCTs demonstrated that a lower-volume exchange of hemofiltration (25 mL/kg/hr) may be sufficient for ICU patients.[5,6] If a nonseptic AKI patient is being treated, then a lower dose may be optimal. On the contrary, a septic AKI may require a higher dosage, close to 50 or 70 mL/kg/hr, and perhaps even higher or with different modalities for catecholamine-resistant septic shock (CRSS) (or refractory hypodynamic septic shock), acute pancreatitis, or post–cardiac arrest.

At the end of the 1990s, Journois et al. applied HVHF in 20 children during cardiac surgery (100 mL/kg/hr) and found a reduction in postoperative blood loss, earlier extubation time, and reduced cytokine plasma levels.[35]

The first cohort study using pulse HVHF was performed by Honoré et al. in 20 septic patients with refractory hypodynamic shock, running at about 100 mL/kg/hr for 4 consecutive hours (and then back at 35 mL/kg/hr) as an important adjunctive treatment. They found that a large number of patients improved, and the mortality rate (55%) was lower than expected by severity score (79%) in this very ill population.[36] However, some patients were hemodynamic nonresponders (9/20) with disastrous mortality.

Thereafter, some studies in the early 20th century concentrated on hemodynamic response and cytokine removal, such as that by Cole et al., who showed interesting hemodynamic improvement in septic patients treated by HVHF.[37] A few years later, an Argentinean team headed by Cornejo designed a study similar to the one by Honoré and obtained comparable results. They created an algorithm based on the international recommendations for sepsis treatment and incorporated the rescue intermittent HVHF therapy (100 mL/kg/hr for a single 12-hour period) as a salvage therapy for patients in refractory septic shock.[38] However, as in the Honoré study, although the observed mortality (40%) was lower than the expected one (60%), there was also a responder and a nonresponder group. In comparison, Joannes-Boyau et al. studied the effect of HVHF at 50 mL/kg/hr maintained for 96 hours in patients with septic shock with MODS.[39] Results in terms of mortality were comparable to those in previous studies (45% observed vs. 70% predicted by three severity scores), but all the patients were hemodynamic responders. All these studies were only single-center, nonrandomized, and uncontrolled, but they all showed the same results and proved that HVHF can be delivered safely.

The first randomized study was a single-center study that compared HVHF with standard CVVH and was conducted by Bouman et al.; 106 patients were randomized in three groups: early HVHF (within the first 12 hours from acute renal failure [ARF]), early standard CVVH, and late standard CVVH.[40] No difference was found in terms of mortality at 28 days or recovery of renal function, but no statistical conclusions could be drawn owing to the lack of power with only 35 patients in each group. Therefore the specific patient population, most coming from cardiac surgery, explains the low rate of mortality, so the possibility of finding any statistical differences between the groups was even more remote. The first positive randomized controlled study on HVHF was performed by Laurent et al. in post–cardiac arrest patients, with clear positive results in favor of the experimental arm,[41] but this study never has been reproduced or confirmed. It recently was challenged by an animal study that did not show any beneficial impact of HVHF on post–cardiac arrest in the rat population.[32] After these preliminary observational studies, the first positive RCT in septic patients was performed by Boussekey: 20 patients randomized in two groups (65 vs. 35 mL/kg/hr), with beneficial impact of HVHF on hemodynamic parameters.[42]

Several studies, in particular in Asia, also have explored the effects of HVHF on severe acute pancreatitis: Wang et al. on animal models[43] and human patients[44] and Jiang et al. proved its clinical benefit in humans[45]. They studied HVHF alone or in comparison with standard CVVH on mortality and organ function recovery and showed a clear benefit in using high volumes with early initiation. However, recent studies have had opposite results, and there is always a lack of large randomized controlled trials in this specific population.[46,47]

END OF THE STORY?

Regarding recommendations for clinical practice, patients with AKI should receive a renal replacement dosage of 25 mL/kg/hr delivered (level I evidence and grade A recommendation).[22] A higher dose when they suffer from sepsis remains questionable.

The first large RCT on HVHF came from China by Zhang et al., who randomized 280 septic patients with AKI in a single center into two groups, one treated by HVHF at 50 mL/kg/hr and the other by VHVHF at 80 mL/kg/hr.[48] They did not find any difference in terms of mortality or hemodynamic improvement. In 2013 a large multicenter RCT, the IVOIRE study, conducted by Joannes-Boyau et al., included 140 patients with AKI and septic shock randomized in two groups: 35 mL/kg/hr versus 70 mL/kg/hr. The authors definitely demonstrated that HVHF had no beneficial effect in terms of hemodynamic parameters improvement or mortality at 28 or 90 days.[49] They also found that a large amount of antibiotics is removed by hemofiltration, which may be an explanation of the negative results of the HVHF studies, because the benefit of high volume may be counteracted by the harmful effect of drugs removal. However, a recent study using a specific technique,[50] the cascade HVHF, which allows VHVHF (120 mL/kg/hr) with removal of only middle-size molecules, contradicts this argument. This technique uses a large-pore–size filter (40 kDa) upstream of a low-pore–size membrane (15 kDa) refiltrating the ultrafiltrate. The majority of the ultrafiltrate containing small molecules (e.g., antibiotics, drugs, vitamins) then is readministered to the patient while a little part of the ultrafiltrate containing middle-size molecules (and cytokines) is retained in the effluent bag. In this multicenter RCT, Quenot et al.[50] included 60 septic shock patients randomized in two groups: cascade HVHF versus standard care. The authors failed to demonstrate any beneficial effect in terms of catecholamine drug requirement, mortality, or even the cytokines removal except for IL-8.

In cardiogenic and distributive shock post–cardiac surgery, Combes et al. published the HEROICS trial, which studied the effect on mortality of HVHF (80 mL/kg/hr) in post–cardiac surgery patients; 224 patients were included and randomized in two groups: HVHF versus standard treatment.[51] Again, the authors did not find differences in terms of mortality between groups; HVHF patients only experienced faster correction of metabolic acidosis and tended to be more rapidly weaned from catecholamines despite more frequent hypophosphatemia, metabolic alkalosis, and thrombocytopenia.

Notwithstanding all these negative results, some research groups continue to provide new HVHF data on animals and humans, with some interesting beneficial effects but often on a small contingent of subjects and therefore underpowered.[10,47,52–54]

CONCLUSION

The indications of hemofiltration have been extended considerably in the last decade, from the simple treatment of AKI to the adjunctive therapy for SIRS or sepsis. After 15 years of active research and some large, multicentric, well-conducted RCTs, we now can conclude that HVHF has not demonstrated sufficient benefit to be recommended in routine practice. For the time being, the standard hemofiltration dosage must remain 25 mL/kg/hr for every ICU patient, whereas HVHF may be reserved for research only.

Key Points

1. High-volume hemofiltration (HVHF) is a hemofiltration with a dosage of more than 35 mL/kg/hr.
2. Animal and small single-center human studies have shown positive results for HVHF in sepsis.
3. Large randomized controlled trials did not demonstrate any beneficial effect of HVHF in the intensive care unit.
4. HVHF must not be used outside clinical research.

Key References

7. Neri M, Villa G, Garzotto F, et al. Nomenclature for renal replacement therapy in acute kidney injury: basic principles. *Crit Care Lond Engl*. 2016;20(1):318.
48. Zhang P, Yang Y, Lv R, et al. Effect of the intensity of continuous renal replacement therapy in patients with sepsis and acute kidney injury: a single-center randomized clinical trial. *Nephrol Dial Transpl*. 2012;27(3):967-973.
49. Joannes-Boyau O, Honoré PM, Perez P, et al. High-volume versus standard-volume haemofiltration for septic shock patients with acute kidney injury (IVOIRE study): a multicentre randomized controlled trial. *Intensive Care Med*. 2013;39(9):1535-1546.
50. Quenot J-P, Binquet C, Vinsonneau C, et al. Very high volume hemofiltration with the Cascade system in septic shock patients. *Intensive Care Med*. 2015;41(12):2111-2120.
51. Combes A, Bréchot N, Amour J, et al. Early High-Volume Hemofiltration versus Standard Care for Post-Cardiac Surgery Shock. The HEROICS Study. *Am J Respir Crit Care Med*. 2015;192(10):1179-1190.

A complete reference list can be found online at ExpertConsult.com.

References

1. Ronco C, Bellomo R, Homel P, et al. Effects of different doses in continuous veno-venous haemofiltration on outcomes of acute renal failure: a prospective randomised trial. *Lancet*. 2000;356(9223):26-30.
2. Honore PM, Joannes-Boyau O. High volume hemofiltration (HVHF) in sepsis: a comprehensive review of rationale, clinical applicability, potential indications and recommendations for future research. *Int J Artif Organs*. 2004;27(12):1077-1082.
3. Bellomo R, Honore PM, Matson J, et al. Extracorporeal blood treatment (EBT) methods in SIRS/Sepsis. *Int J Artif Organs*. 2005;28(5):450-458.
4. Tetta C, Bellomo R, Kellum J, et al. High volume hemofiltration in critically ill patients: why, when and how? *Contrib Nephrol*. 2004;144:362-375.
5. Palevsky PM, Zhang JH, O'Connor TZ, et al. Intensity of renal support in critically ill patients with acute kidney injury. *N Engl J Med*. 2008;359(1):7-20.
6. Bellomo R, Cass A, Cole L, et al. Intensity of continuous renal-replacement therapy in critically ill patients. *N Engl J Med*. 2009;361(17):1627-1638.
7. Neri M, Villa G, Garzotto F, et al. Nomenclature for renal replacement therapy in acute kidney injury: basic principles. *Crit Care Lond Engl*. 2016;20(1):318.
8. De Corte W, Dhondt A, Vanholder R, et al. Long-term outcome in ICU patients with acute kidney injury treated with renal replacement therapy: a prospective cohort study. *Crit Care Lond Engl*. 2016;20(1):256.
9. Hotchkiss RS, Karl IE. The pathophysiology and treatment of sepsis. *N Engl J Med*. 2003;348(2):138-150.
10. Park JT, Lee H, Kee YK, et al. High-Dose Versus Conventional-Dose Continuous Venovenous Hemodiafiltration and Patient and Kidney Survival and Cytokine Removal in Sepsis-Associated Acute Kidney Injury: A Randomized Controlled Trial. *Am J Kidney Dis Off J Natl Kidney Found*. 2016;68(4):599-608.
11. Honore PM, Jacobs R, Boer W, et al. New insights regarding rationale, therapeutic target and dose of hemofiltration and hybrid therapies in septic acute kidney injury. *Blood Purif*. 2012;33(1-3):44-51.
12. Joannes-Boyau O, Honore PM, Boer W, et al. Are the synergistic effects of high-volume haemofiltration and enhanced adsorption the missing key in sepsis modulation? *Nephrol Dial Transpl*. 2009;24(2):354-357.
13. Joannes-Boyau O, Honore PM, Boer W. Hemofiltration: The case for removal of sepsis mediators from where they do harm. *Crit Care Med*. 2006;34(8):2244-2246.
14. Ronco C, Ricci Z, Bellomo R. Importance of increased ultrafiltration volume and impact on mortality: sepsis and cytokine story and the role of continuous veno-venous haemofiltration. *Curr Opin Nephrol Hypertens*. 2001;10(6):755-761.
15. Honore PM, Joannes-Boyau O. High volume hemofiltration (HVHF) in sepsis: a comprehensive review of rationale, clinical applicability, potential indications and recommendations for future research. *Int J Artif Organs*. 2004;27(12):1077-1082.
16. Honore PM, Matson JR. Extracorporeal removal for sepsis: Acting at the tissue level–the beginning of a new era for this treatment modality in septic shock. *Crit Care Med*. 2004;32(3): 896-897.
17. Di Carlo JV, Alexander SR. Hemofiltration for cytokine-driven illnesses: the mediator delivery hypothesis. *Int J Artif Organs*. 2005;28(8):777-786.
18. Wasserman K, Mayerson HS. Dynamics of lymph and plasma protein exchange. *Cardiologia*. 1952;21(4):296-307.
19. Olszewski WL. The lymphatic system in body homeostasis: physiological conditions. *Lymphat Res Biol*. 2003;1(1):11-21.
20. Zitelli G, Djouadi SM, Day JD. Combining robust state estimation with nonlinear model predictive control to regulate the acute inflammatory response to pathogen. *Math Biosci Eng MBE*. 2015;12(5):1127-1139.
21. Day J, Rubin J, Clermont G. Using nonlinear model predictive control to find optimal therapeutic strategies to modulate inflammation. *Math Biosci Eng MBE*. 2010;7(4):739-763.
22. Vinsonneau C, Allain-Launay E, Blayau C, et al. Renal replacement therapy in adult and pediatric intensive care : Recommendations by an expert panel from the French Intensive Care Society (SRLF) with the French Society of Anesthesia Intensive Care (SFAR) French Group for Pediatric Intensive Care Emergencies (GFRUP) the French Dialysis Society (SFD). *Ann Intensive Care*. 2015;5(1):58.
23. Parienti J-J, Mégarbane B, Fischer M-O, et al. Catheter dysfunction and dialysis performance according to vascular access among 736 critically ill adults requiring renal replacement therapy: a randomized controlled study. *Crit Care Med*. 2010;38(4):1118-1125.
24. Uchino S, Fealy N, Baldwin I, et al. Pre-dilution vs. post-dilution during continuous veno-venous hemofiltration: impact on filter life and azotemic control. *Nephron Clin Pr*. 2003;94(4):c94-c98.
25. Grootendorst AF, van Bommel EF, van der Hoven B, et al. High volume hemofiltration improves right ventricular function in endotoxin-induced shock in the pig. *Intensive Care Med*. 1992;18(4):235-240.
26. Grootendorst AF, van Bommel EF, van Leengoed LA, et al. High volume hemofiltration improves hemodynamics and survival of pigs exposed to gut ischemia and reperfusion. *Shock*. 1994;2(1):72-78.
27. Rogiers P, Zhang H, Smail N, et al. Continuous venovenous hemofiltration improves cardiac performance by mechanisms other than tumor necrosis factor-alpha attenuation during endotoxic shock. *Crit Care Med*. 1999;27(9):1848-1855.
28. Honore PM, Joannes-Boyau O, Gressens B. Blood and plasma treatments: high-volume hemofiltration–a global view. *Contrib Nephrol*. 2007;156:371-386.
29. Li W, Yan X, Wang H, et al. Effects of continuous high-volume hemofiltration on experimental severe acute pancreatitis in pigs. *Pancreas*. 2007;34(1):112-119.
30. Rimmelé T, Assadi A, Cattenoz M, et al. High-volume haemofiltration with a new haemofiltration membrane having enhanced adsorption properties in septic pigs. *Nephrol Dial Transplant Off Publ Eur Dial Transpl Assoc - Eur Ren Assoc*. 2009;24(2):421-427.
31. Li C, Zhang P, Cheng X, et al. High-volume hemofiltration reduces the expression of myocardial tumor necrosis factor-alpha in septic shock pigs. *Artif Organs*. 2013;37(2):196-202.
32. Shinozaki K, Lampe JW, Kim J, et al. The effects of early high-volume hemofiltration on prolonged cardiac arrest in rats with reperfusion by cardiopulmonary bypass: a randomized controlled animal study. *Intensive Care Med Exp*. 2016; 4(1):25.
33. Zhao P, Zheng R, Xue L, et al. Early Fluid Resuscitation and High Volume Hemofiltration Decrease Septic Shock Progression in Swine. *Biomed Res Int*. 2015;2015:181845.
34. Ronco C, Bellomo R, Homel P, et al. Effects of different doses in continuous veno-venous haemofiltration on outcomes of acute renal failure: a prospective randomised trial. *Lancet*. 2000;356(9223):26-30.
35. Journois D, Israel-Biet D, Pouard P, et al. High-volume, zero-balanced hemofiltration to reduce delayed inflammatory response to cardiopulmonary bypass in children. *Anesthesiology*. 1996;85(5):965-976.
36. Honore PM, Jamez J, Wauthier M, et al. Prospective evaluation of short-term, high-volume isovolemic hemofiltration on the hemodynamic course and outcome in patients with intractable circulatory failure resulting from septic shock. *Crit Care Med*. 2000;28(11):3581-3587.
37. Cole L, Bellomo R, Hart G, et al. A phase II randomized, controlled trial of continuous hemofiltration in sepsis. *Crit Care Med*. 2002;30(1):100-106.
38. Cornejo R, Downey P, Castro R, et al. High-volume hemofiltration as salvage therapy in severe hyperdynamic septic shock. *Intensive Care Med*. 2006;32(5):713-722.
39. Joannes-Boyau O, Rapaport S, Bazin R, et al. Impact of high volume hemofiltration on hemodynamic disturbance and outcome during septic shock. *ASAIO J*. 2004;50(1):102-109.
40. Bouman CS, Oudemans-Van Straaten HM, Tijssen JG, et al. Effects of early high-volume continuous venovenous hemofiltration on survival and recovery of renal function in intensive care patients with acute renal failure: a prospective, randomized trial. *Crit Care Med*. 2002;30(10):2205-2211.
41. Laurent I, Adrie C, Vinsonneau C, et al. High-volume hemofiltration after out-of-hospital cardiac arrest: a randomized study. *J Am Coll Cardiol*. 2005;46(3):432-437.

42. Boussekey N, Chiche A, Faure K, et al. A pilot randomized study comparing high and low volume hemofiltration on vasopressor use in septic shock. *Intensive Care Med*. 2008;34(9):1646-1653.
43. Wang H, Zhang ZH, Yan XW, et al. Amelioration of hemodynamics and oxygen metabolism by continuous venovenous hemofiltration in experimental porcine pancreatitis. *World J Gastroenterol*. 2005;11(1):127-131.
44. Wang H, Li W-Q, Zhou W, et al. Clinical effects of continuous high volume hemofiltration on severe acute pancreatitis complicated with multiple organ dysfunction syndrome. *World J Gastroenterol*. 2003;9(9):2096-2099.
45. Jiang HL, Xue WJ, Li DQ, et al. Influence of continuous venovenous hemofiltration on the course of acute pancreatitis. *World J Gastroenterol*. 2005;11(31):4815-4821.
46. Guo J, Huang W, Yang X-N, et al. Short-term continuous high-volume hemofiltration on clinical outcomes of severe acute pancreatitis. *Pancreas*. 2014;43(2):250-254.
47. He W-H, Yu M, Zhu Y, et al. Emergent Triglyceride-lowering Therapy With Early High-volume Hemofiltration Against Low-Molecular-Weight Heparin Combined With Insulin in Hypertriglyceridemic Pancreatitis: A Prospective Randomized Controlled Trial. *J Clin Gastroenterol*. 2016;50(9):772-778.
48. Zhang P, Yang Y, Lv R, et al. Effect of the intensity of continuous renal replacement therapy in patients with sepsis and acute kidney injury: a single-center randomized clinical trial. *Nephrol Dial Transpl*. 2012;27(3):967-973.
49. Joannes-Boyau O, Honoré PM, Perez P, et al. High-volume versus standard-volume haemofiltration for septic shock patients with acute kidney injury (IVOIRE study): a multicentre randomized controlled trial. *Intensive Care Med*. 2013;39(9):1535-1546.
50. Quenot J-P, Binquet C, Vinsonneau C, et al. Very high volume hemofiltration with the Cascade system in septic shock patients. *Intensive Care Med*. 2015;41(12):2111-2120.
51. Combes A, Bréchot N, Amour J, et al. Early High-Volume Hemofiltration versus Standard Care for Post-Cardiac Surgery Shock. The HEROICS Study. *Am J Respir Crit Care Med*. 2015;192(10):1179-1190.
52. Shinozaki K, Lampe JW, Kim J, et al. The effects of early high-volume hemofiltration on prolonged cardiac arrest in rats with reperfusion by cardiopulmonary bypass: a randomized controlled animal study. *Intensive Care Med Exp*. 2016;4(1):25.
53. Zhang N, Zhang J, Cao Z, et al. Effect of pulse high-volume hemofiltration on Toll-like receptor in patients with severe sepsis. *Exp Ther Med*. 2016;12(3):1377-1382.
54. Ren H-S, Li M, Zhang Y-J, et al. High-volume hemofiltration combined with early goal-directed therapy improves alveolar-arterial oxygen exchange in patients with refractory septic shock. *Eur Rev Med Pharmacol Sci*. 2016;20(2):355-362.