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High Volume Haemofiltration in ICU: Where are we in 2006

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1. Introduction

Since the last decade, haemofiltration and especially high volume haemofiltration has rapidly evolved from a somewhat experimental treatment towards a potentially effective "adjunctive" therapy in severe septic shock and especially refractory or catecholamine resistant (hypodynamic) septic shock (CRSS). Nevertheless, this approach lacks prospective randomized studies (PRT'S) evaluating the critical role of early haemofiltration in sepsis.

An important step forward which could be called the "big bang" in term of haemofiltration [1] was the publication of a PRT in patients with acute renal failure (ARF) [2]. Before this study [2], nobody believed that haemofiltration could change the survival rate in intensive care. Since that "big bang", many physicians consider that a "correctly dosed" haemofiltration has the potential to change the survival rate in intensive care. So the world of haemofiltration in ICU is not a definitive world, it is still in expansion ! Indeed, right now, we have to try to define what will be the exact dose needed in septic ARF. This dose might well be "higher" than 35 ml/kg/h in the septic ARF group as suggested by many studies [2-5].

In order to challenge this hypothesis, continuous dose rather than pulse dose of high volume haemofiltration(HVHF) will be tested in ongoing or future randomized studies. Since the "Vicenza" study [2] has shown that 35 ml/kg/h was the best dose in term of survival, while dealing with non septic ARF in ICU, several studies from different groups have shown that, in septic ARF, a higher dose might correlate with better

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survival [3-5]. This has also been shown in some way by the study of the "Vicenza" group but unfortunately not with a statistically significant value [2].

New PRT'S have just started in Europe like the IVOIRE (hIgh VOlume in Intensive Care) study [6] and the RENAL study, another large study looking more basically at dose in non septic ARF in Australasia and is led by the group of Rinaldo Bellomo in Melbourne [7] as well as the ATN study led by Paul Palevsky and colleagues in the USA, also testing the importance of dose in the treatment of ARF. Nevertheless, "early goal-directed haemofiltration therapy" like early goal directed therapy [8] has to be studied in our critically ill patients. Regarding this issue, fewer studies mainly retrospective studies do exist, but again the IVOIRE study [6] will address this issue by studying septic patients with acute renal injury according to the RIFLE classification [9] rather than ARF which is already late in the process anyway.

So, this review will focuse on the early application and on the adequate dosing of continuous HVHF in septic shock in order to improve not only haemodynamics, but also survival in this very severely ill cohort of patients.

This could be called the "big bang of haemofiltration" as one could never anticipated the fact that an adequate dose of haemofiltration could markedly influence the survival rate in ICU while treating septic ARF patients.

On top of the use of early and adequate dose of haemofiltration in sepsis, an higher dose could also provide a better renal recovery rate and reduce the risk of chronic dialysis dependency in these patients.

2. The "Big Bang" of Haemofiltration

The "big bang" of clinical haemofiltration occured when the study of Claudio Ronco was published in the Lancet in 2000 [2]. This study was looking at 425 patients and prospectively assessing three types of doses, respectively 20, 35 and 45 ml/kg/h. Exchange was exclusively realized in post-dilution in order to maximize convection. The membrane was also changed every 24 hours. This study demonstrates that in non-septic ARF, a dose of 35 ml/kg/h was correlated with the best survival rate.This difference was statistically significant. This can be expressed as a "big bang" in term of haemofiltration [10]. Indeed, before that study, nobody was really thinking "realistically" that the world of haemofiltration could ever change survival in intensive care. Since that "big bang", it is now believed by many that the use of a "correctly dosed" haemofiltration has the potential to change the survival rate in intensive care patients. So the world of haemofiltration in ICU is not a definitive world, it is still in expansion ! Indeed, we have to try to define now what is going to be the exact dose that we do need in septic ARF. This dose will probably be "higher" than 35 ml/kg/h in the septic ARF group as suggested by many studies [4,5,11-16].

This has been also put in perspective in an interesting review paper recently published [17] highlighting all the potential of extra-corporeal therapy regarding the wide spectrum of molecules that could be removed, ranging in theory from 500 up to 900,000 daltons when for instance using plasmafiltration. Other outcome-dose studies will also participate in the expansion of this

initial "big bang". Amongst those, IVOIRE [6], RENAL [7] and ATN will take the lead. The IVOIRE study [6] will try to expand the findings of the initial Ronco study [2] to the septic ICU world. Indeed, we will include more than 480 patients with septic shock plus acute renal injury defined by the RIFLE classification in ICU[9]. Allocation into the two arms will be determined by computerized randomization. One group will receive 35 ml/kg/h versus 70 ml/kg/h in the other group. This study will try to demonstrate that "higher" dose (like 70 ml/kg/h) will further improve the survival rate of septic ARF in ICU respectively at 28,60 and 90 days after ICU admission.

3. Animal models

Animal models have shown benefits in term of survival when "early" and "strong" haemofiltration dose was applied in septic animal models.

Regarding animal models, early use of haemofiltration has been really well applied in many animal models. Indeed, most of the earlier experimentations led by the so called "godfather" of HVHF, Albert Grootendorst [18-21] have most of the time used haemofiltration before or just after the injection of bolus or even infusion of endotoxin.

It has been only in the late nineties with the studies of Rogiers [22,23] and others, that the investigators start to wait about 6 to 12 hours before using HVHF and so "allowing" the animal models to become extremely ill, haemodynamically unstable and with early multiple organ dysfunction syndrome(MODS). By this way, the animal model could "mimic" in some ways the clinical situation. Only animal models that have been submitted to the early application of HVHF have shown to be very beneficial (and in some ways with very impressive results) mainly by the fact that additionally to early use, the investigators have applied a very "stronger" dose of HVHF. Indeed a recent study by Honore and co-workers [24] has shown that the "aggregation" of the last twelve studies in the last ten years or so regarding animal models revealed that the "mean dose" used in those experimentations was about 100 ml/kg/h whereas for humans (last thirteen human studies or so) only 40 ml/kg/h was effectively given. The most beneficial effects of HVHF have been shown in these animal models whereas the maximum delay between the septic insult and the intervention was less than 12 hours. This is totally different from the clinical situation whereas the delay can be rarely below 24 hours and/or even below 48 hours. The literature unravel that the animal models have shown that not only a stronger application of dose was very important but also that early application was the second important condition as well to make the use of haemofiltration in sepsis beneficial in terms of haemodynamics and survival [25] (Table 1). It has also been advocated that the best response seen in the animal model was obtained when the sepsis was intravascular as opposed to extravascular or when sepsis was "restricted" in an other more "confined" compartment as for instance peritonitis. This might explain why the use of high permeability haemofiltration (HPHF) in a sheep model of peritonitis described by Rogiers [26] was not able to show any

beneficial effect. Indeed, if we believe into the "Mediator Delivery" hypothesis [27], we can see that the absence of large intakes of fluids in high permeability haemofiltration has a major consequence : no increase of the lymphatic flow. Indeed,this increased lymphatic flow is in charge of "retrieving" massive amounts of cytokines and mediators from the interstitium and the tissue level back to the blood compartment level making them available for extra-renal removal.

In that setting, it makes more sense to think that HVHF could be efficient in an acute model of peritonitis as demonstrated by the group of Rogiers et al [27] as well whereas HPHF remains ineffective in that specific setting of this particular study. It is also known that, in this kind of animal model, the cytokine pattern is very different from the human situation because the pro-inflammatory phase "duration" is much longer in the animal setting and is not always followed by an "immunoparalysis" secondary phase. But more recently, what the animal model has "brought to light", is the use of HVHF as a "prophylactic measure" in the second phase of sepsis (the so-called "immunoparalysis" phase or the CARS [Compensatory Anti-inflammatory Response Syndrome] phase as explained by Roger Bone) [28]. The group of Yekebas [29-31] and the group of Lee [32] have worked to modelize this "immunoparalysis" post-SIRS (Systemic Inflammatory Response Syndrome).

Therefore, they induced traumatic pancreatitis in healthy pigs. Haemofiltration started 12 hours after pancreatic trauma but before sepsis and shock state did occurred. They waited about twelve hours and, after this time, bacterial translocation occurred and very fulminant peritonitis and intravascular sepsis occurred inducing a shock state in these pigs. By comparing different settings of haemofiltration, especially low dose(20 ml/kg/h) plus adsorption and HVHF at the rate of 100 ml/kg/hours, the authors were able to demonstrate that the "prophylactic use" of HVHF (100 ml/kg/h) was able to reduce the immunoparalysis "level" and the subsequent risk of secondary infection and, ultimately, the death rate. So, for the first time, HVHF was able to show that it could work not only on the pro-inflammatory phase but also on the secondary "immunoparalysis" phase *per se* as a prophylactic measure.

Still after all this, transposition of these findings to the human setting is even more difficult because most of the animal models used a so-called "hypodynamic" septic shock [33]. It is only in the last few years that researchers are really challenging the so-called hyperdynamic septic shock concept, which is much closer to the human situation. Researchers like Rogiers [34] or other groups [35] have nicely shown that this option was really feasible.

4. Human studies

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" resulting from the high cost of the technique. What is important in these human studies, is to understand that HVHF applied at a continuous dose of 96 hours can be compared in some ways to Activated Protein C (APC) [36, 37]. Obviously, we can not rely on the same

Table 1. HVHF in animal studies : survival

Authors	Material	Membrane surface	Hemofiltration technique	UF/hour	Timing	Animal weight (kg)	LD (%)	UF indexed to body size	Survival (%)	Survival (time)	Effect
Freeman *et al* (1)	Dog	PS	HVHF	600	61h After	10	100	60 ml/kg/h	142 (T)	7 days (T)	N
	Peritonitis	S : NA	(CAVH)		peritoneal clot				14.2 (C)	7 days (C)	
Rogiers *et al* (2)	Sheep	PS	VHVHF	NA	4 h after	NA	100	100 ml/kg/h	100 (T)	14 H (T)	P
	Peritonitis, Caecostomy	S : NA	(CVVH)		surgery				0 (C)	14 H (C)	
Yekebas *et al* (3)	Pig	CA-SMS	VHVHF	NA	Immediately	NA	100	100 ml/kg/h	67 (T)	60 H (S)	P
	pancreatitis + sepsis	S : 0.6 m^2	(CVVH)		after induction			20 ml/kg/h	0 (C)	60 H (C)	
	+ MODS				of pancreatitis						
Lee *et al* (4)	Pig staph	PS :	VHVHF	1000	Immediately after	7.5	100	133 ml/kg/h	38.5 (T)	7 days (T)	P
	Staph. aureus infusion	S : NA	(CAVH)		staph aureus infusion				0 (C)	7 days (C)	
Grootendorst	Pig SMA clamping	CP	VHVHF	6000	before	37	100	150 ml/kg/h	66 (T)	24 H (T)	P
et al (5)		S :2.3 m^2	(CVVH)		clamping				0 (C)	24 H (C)	

PS = polysulphone; NA non available; N = no; Y = yes; CP = cuprophane; P = positive; N = negative; C = control; S=surface, CA−SMS = Copolymer Acrylonitrile and Sodium Methal Sulfate (AN69); T = treated; LD; low dose, UF; ultrafiltration SMA; superior mesentenc artery, PA=polyacrylonitrile

(1) Freeman *et al.* J Am Coll Surg 1995;180:286−92.
(2) Rogiers *et al* 21st symposium on ICU Brussels March 2001.
(3) Yekebas *et al* Crit Care Med 2001;29:1423−30.
(4) Lee *et al.* Crit Care Med 1993;21:14−24.
(5) Grootendorst *et al.* Shock 1994;2:72−8.

Table 2. HVHF in human studies : surviva

Authors	Patients Number	Diagnosis and Severity	Design	CRRT technique	Mb+ S	Ultrafiltrate (E) ml/h	Observed effect	Survival	Timing	Weight	UF volume indexed to body
Sander *et al* 1997 (1)	26	SIRS	R	13 CVVH 13 Control	CA-SMS SA:0.6m^2	1000	No effect	NA	NA	NA-75 Kg(E)	13 ml/kg/h (E)
Matamis *et al* 1994 (2)	20	Sepsis MODS	P, UNC	LVCVVH LVHF	PS SA:0.7m^2	1500	↗ MAP ↗ SVR	NA	NA	NA-75 Kg(E)	20 ml/kg/h
Ronco *et al* 2000 (3)	425	USI-ARF	R	LV-CVVH MV-CVVH LVHF	PS S:0.7-1.3m^2	-1500 -2700 -3400	ND	↗ survival with ↗ doses	NA	NA-75 Kg (E)	20 ml/kg/h 35 ml/kg/h 45 ml/kg/h
John *et al* 1998 (4)	30	Sepsis	R	20 CVVH 10 IHD	NA	NA	↗ SVR	NA ↗ survival without	NA	NA	NA
Grootendorst *et al* 1996 (5)	26	Sepsis MODS	P, UNC	HV-CVVH HVHF	PA SA:NA	4500	↗ MAP CI ?	relationship with hemodynamics	NA	NS-75 Kg(E)	60 ml/kg/h (E)
Oudemans-van straaten *et al* 1999 (6)	306	USI-ARF Septic shock+	P, cohort	Intermittent HV-CVVH HVHF	Cell tri SA:1.9 m^2	5000	NA	↗ survival	NA	NA-75 Kg(E)	65 ml/kg/h (E)
Cole *et al* 2001 (7)	11	MODS	R Cross	HV-CVVH HVHF	CA-SMS SA:1.6 m^2	6000	↘ Vaso ↗ MAP + SVR	NA	NA	NA-75	80 ml/kg/h (E)
Honore *et al* 2000 (8)	20	Refractory septic shock	P, inter, UNC	Short-term HV-CVVH VHVHF	PS SA:1.6 m^2	9000	↗ CI ↗ LVSWI	↗ survival with relationship to hemodynamics	S = 6.5 h NS=14h	S=66.2 kg NS=82.5 kg	140 ml/kg/h 110 ml/kg/h

P = Prospective, UNC = uncontrolled, C = Controlled, R = Randomised, Cross = Cross over study, ARF = ARF, NA = Non Available, E = Estimed, Inter = Interventional, Cell Tri = cellulose triacetate, Vaso = vasopressor; S = survivors, NS = non survivors; PS = Polysulfone, PA: Polyamide, CA-SMS: Copolymer Acrylonitrile and Sodium Methal Sulfate (AN 69), Mb: membrane, SA: surface area, MAP: mean arterial pressure, SVR: systemic vascular resistance, LVSWI: left ventricular stroke work index, CI: cardiac index.

(1) Sander *et al.* Intensive Care Med 23;878-84/1997
(2) Matamis *et al.* Intensive Care Med 20 ;431-6.1994
(3) Ronco *et al.* Lancet 356 ;S26-30.2000
(4) John *et al.* Intensive Care Med S75.1998
(5) Grootendorst *et al.* Am J Kidney Dis 28;90-7.1996.
(6) Oudemans-van straaten *et al.* Intensive Care Med 25:814-21.1999
(7) Cole *et al.* Intensive Care Med 2001;27:978-86
(8) Honore *et al.* Critical Care Med,28 ;3581-7. 2000.

"level" of evidence as we can for APC.

Anyway, HVHF like APC can have a "pleiotropic" action on sepsis in the human setting. Indeed, it can interfere with the pro-inflammatory phase and by decreasing the so-called pro-inflammatory phase, it can potentially reduce the "unbound" part of cytokines and reducing the so-called corresponding "remote organ associated" damages [38,39].

As a second point, it can also alter and reduce some cardiovascular compounds (in the blood compartment) that are responsible for the "shock state" in the human situation. Indeed, endothelin-I can be removed and is held responsible for the early pulmonary hypertension in sepsis, where as endocannabinoids are responsible for the vasoplegia and myodepressant factor responsible for the cardiodepression seen in sepsis [40, 41, 42]. All these factors can be easily removed by HVHF.

At as a third point, HVHF can also alter the clotting system in the way that it can decrease PAI (Platelet activating Inhibitor) -1 and by this way eventually reduce the level of diffuse intravascular coagulopathy (DIC) [43]. It is effectively well known that the level of PAI-1 is correlated in sepsis with a increased APACHE II score and as well an higher mortality rate [44].

As a fourth type of action, it has been shown many times in animals that HVHF can reduce the risk of "immunoparalysis" post-sepsis and the subsequent risk of nosocomial or secondary infection [29-32].

As a fifth type of action, it has been shown also that HVHF can reduce the level of "inflammatory cell apoptosis" occurring during sepsis as it can extract caspase-3 products range within a molecular weight of about 35,000 daltons and some products as well of the caspase-8 pathways which are heavily involved in the setting of inflammatory cell apoptosis especially in macrophages and neutrophils [45].

Also, we do know that the clinical studies are not reproducing by far the mean 100 ml/kg/h amount of exchange that has been realized in animal models (only 40 ml/kg/h versus 100 ml/kg/h in human studies) [24].

As a consequence, many anticipated effects seen in animal models can never been reproduced in human settings related to the use of inadequate low doses of HVHF.(Fig.1)

What we do know is that, there is a huge variability between clinical trials concerning the range of doses applied. It can vary for 1 to 15 in term of dose [24] when we aggregate all the recent studies.

If we decided to show that haemofiltration can be considered as a medication in ICU, it has to be adapted to the body weight but it has also to be adapted to the severity of illness of ICU patients. Indeed, if we have to deal with a non-septic ARF, perhaps a lower dose will be optimal. On the contrary, if we do have to deal with septic ARF than we might need a higher dose as close to to 50 or 70 ml/kg/h. From the data that we have right now, we can say that in CRSS-(or refractory hypodynamic septic shock), the use of pulse HVHF (PHVHF) running at about 100 ml/kg/h during 4 consecutive hours (and then back at 35 ml/kg/h) is an important adjunctive treatment that can really increase dramatically the survival (Table 2) on these severely ill patients as compared with classical treatment [4,5,14,15]. The monocentric study of Oudemans Van Straaten

[3] which was realized with a cohort design of mainly cardiac surgery patients with oliguria at the time of inclusion did show us that the patient subgroup which had the best improvement (in term of observed versus expected mortality) was the septic subgroup of patients in this specific study. The technique used at the time was intermittent haemofiltration at a dose of 60 ml/kg/h. Since several "positive" trials dealing with CRSS have been published [4,5, 14,15], it is almost accepted now in the "haemofiltration ICU world" that when dealing with catecholamine resistant septic shock (CRSS), a short-term procedure applying a very "high dose" should be the preferred procedure whereas in comparison, for classical hyperdynamic septic shock with acute renal injury, a continuous moderate high dose(during 96 hours) might be the ideal choice in order to achieve a dose of 50 up 70 ml/kg/h(for 96 hours). Indeed, in this setting we do need to work upon the "pleiotropical background" and mainly against the immunoparalysis "post-septic insult" showed by many papers and especially by Yekebas and Lee [29-32].

Pulse high volume has been shown to be still very effective in septic shock as recently outlined in the literature [46,47]. Those studies confirmed the initial findings of Honore and co-workers [4,5,14,15].

They also showed that the threshold dose needed to improve patients with septic ARF was about 45 ml/kg/h as suggested by Ronco [2] and Piccinni [47]. At last, recent studies have also shown that in CRSS but this time hyperdynamic, HVHF might be a salvage therapy if a protocol guided approache is used [48].

5. Recommendations for Clinical Practice, Future Research, HVHF Evolving Technology and Drug Adaptation during Haemofiltration

Regarding recommendations for clinical practice : CRSS either hypodynamic [4,5,14,15] or hyperdynamic [48] could be seen as an indication (Level V evidence and Grade E Recommendation) for experienced clinicians in the field of HVHF.

Septic shock with ARF should receive a renal replacement dose of at least 35 ml/kg/h(Level II evidence and Grade C Recommendation). Despite the numerous studies published and the ongoing IVOIRE study [6], there are no sufficient "hard data on board" yet to support a "higher" extended dose in this condition. This is true for other potential indications, such as septic shock with or without renal failure or injury or even sepsis and SIRS (with or without failure or injury). in the case of SIRS induced by out-of-hospital cardiac arrests [49], the existing data are to scarce to allow guidelines yet.

Regarding recommendations for future research concerning CRSS, it will be very difficult in this case to apply a PRT'S and we should stick to available data or perform small bi-centric randomized studies.

Evaluating hyperdynamic septic shock patients, more numerous larger prospective randomized studies are needed, to detect potential interference with APC. Indeed, this potential interference should deserve more attention since the molecular weight of the APC (55,000 daltons) creates the theoretical possibility that the membrane during HVHF can adsorb the drug. Yet the risk is really minimal.

Table 3. Studies for renal recovery and renal vs. septic dose: Higher dose vs. lower dose

Study First author	Year	Design	No of patients	Interventions	Groups	Main Outcome	Survival	Level of evidence
Jackamy *et al.*	2005	Retrospective Study	116	Renal Recovery	CRRT=87% Recovery IHD=37.5% Recovery	Better Recovery in CRRT	Not Affected	Ⅳ
Manns B *et al.*	2003	Retrospective Cohort Study	261	Cost of Acute Renal Failure	CRRT=Non Renal Recovery	Better Renal Recovery CRRT	Not Affected	Ⅳ
Best Ⅲ Study	2005	Data Collection Epidemiological Study	1260	Type of CRRT	CRRT>75% Recovery IHD=60%	Better Renal Recovery CRRT	Not Affected	Ⅲ
Schiffl *et al.*	2002	Prospective Randomized Study	74 74	DHD AHD	DHD = 9 days of Renal Recovery	Quicker Recovery of Renal Function	DHD = 76% AHD = 22%	Ⅱ

(1) Jacka My *et al.* Can J Anesth 2005;52:327-332
(2) Manns B *et al.* Crit Care Med 2003;31:644-646
(3) Best III Study. Unpublished Data 2004.
(4) Schiffl *et al.* N Engl J Med 2002;34:305-310

Nevertheless we have to think also about possible synergy between HVHF and APC as shown by experimental work completed by the group of Rogiers [50]. Regarding Sepsis and SIRS, the aim is still to reduce immunoparalysis showed by various animal studies (Level II evidence). For this type of patient, who do need more mechanistic studies evaluating the potential risk of the technique that has to be balanced with anticipated beneficial effects. In many cases, short-term procedure will not be the ideal technique in those patients because to reduce "immunoparalysis" as we do know , a "long standing" technique like for instance 96 hours will be required.

What should be the best "environment" for future researches? A first condition should be to develop a "safer" technique which should be more efficient in order to increase the "clinical" operability, a "safer" applicability and as well a better "clinical" effectiveness. A second condition should be to develop a greater understanding of mechanisms of sepsis and SIRS in order to identify the "molecular" as well the "proteinomics" targets for HVHF.

We have to ensure better design of new HVHF technology rather than modification of already existing technology, in order to meet the specific "needs" of controlling and restoring the immune homeostasis in sepsis and SIRS. The third condition is to appropriately design (and with a suitable

power), a trial of HVHF that can be conducted to test the clinical effectiveness of this therapy in patients with SIRS and/or sepsis. And the very last condition should be to ensure that this trial should be conducted with indexing the dose to body size and paying more attention to controlling (and analyzing) the effects of time delay between the onset of SIRS or sepsis and HVHF initiation in order to better define the duration of treatment as well the appropriate initiation window.

6. Conclusions

The so-called "big bang" of haemofiltration has taught us that haemofiltration was not a definitive world. It was demonstrated by the Lancet trial in 2000 [2] that it is a world in expansion. Since we are aware of this "big bang phenomenon" concerning non-septic ARF in ICU, we are now trying to define what should be the exact dose for continuous haemofiltration in septic ARF.

HVHF can still be seen as a potent immunomodulatory treatment in sepsis or SIRS. Since the Mediator Delivery Hypothesis has been unravel [27], we do know, that not only the extraction is important but also the exchanged amount of fluids and so the intake of fluids *per se* that can increase dramatically the lymphatic flow up to 20 to 40 folds. As a consequence, circulatory cytokines are no longer valuable players perhaps except for very severe CRSS[51,52] and now, what is important is the crucial relationship between immunological changes at the tissue level (where mediators do harm), haemodynamic modifications and survival. A last point is obviously the possible synergism in term of therapy between APC and HVHF as both treatments do have a lot of similarities in terms of pleiotropical effects and so, indeed recent research work has shown that synergy is possible between these two therapies. Nevertheless, we still need many more studies to define very well what is it the exact role (and the exact impact on survival) of HVHF and especially in hyperdynamic septic shock without acute renal injury.

Indeed, "Higher doses" of treatment may be also important whatever the choice of the initial therapy could be as it is able to influence the rate of secondary chronic dialysis "dependency" or conversely the rate of renal recovery [53,54] as shown also by the work of Schiffl [55] and a somewhat recent study of Ronco [56] (Table 3).

So, in other words, the "costeffectiveness" for continuous haemofiltration therapy when compared to intemittent techniques may be changing very quickly as time goes on. The expansion and the odyssey of the haemofiltration universe continues.

Abbreviations

APC: Activated protein C
ARF: Acute renal failure
CARS: Compensatory anti-inflammatory response syndrome
CAVH: Continuous arteriovenous haemofiltration
CRSS: Catecholamine resistant septic shock
CVVH: Continuous venovenous haemofiltration
HPHF: High permeability haemofiltration
HVHF: High volume haemofiltration
IHD: intermittent haemodialysis
LVCVVH: Low volume continuous venovenous

haemofiltration
MODS: Multiple organ dysfunction syndrome
MVCVVH: Moerate volume continuous venovenous haemofiltration
PHVHF: Pulse high volume haemofiltration
PRT: Prospective randomized trial
SIRS: Systemic inflammatory response syndrome
VHVHF: Very high volume haemofiltration

References

1. Lemaitre Georges Henri (Eddington's Translation) The Big Bang Theory. The Royal Astronomical Society . Monthly Notices of March 1931.
2. Ronco C, Bellomo R, Homel P, Brendolon A, Dan M, Piccini P, *et al*. Effects of different doses in continuous veno-venous haemofiltration. *Lancet* 2000;**356**:26-30.
3. Oudemans-van Straaten HM, Bosman RJ, Van der Spoel JL, Zanstra DF. Outcome of critically ill patients treated with intermittent high-volume haemofiltration : a prospective cohort analysis. *Intensive Care Med* 1999;**25**:814-21.
4. Honoré PM, Jamez J, Wauthier M, Lee P, Dugernier T, Pirenne B, Hanique G, Matson JR. 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**:3581-7.
5. Joannes-Boyau O, Rapaport S, Bazin R, Fleureau C, Janvier G. Impact of high volume hemofiltration on hemodynamic disturbance and outcome during septic shock. *ASAIO J* 2004;**50**:102-9.
6. Honoré PM, Joannes-Boyau O. The IVOIRE (hIgh VOlume in Itensive caRE) study : impact of HVHF in early septic shock with acute renal injury. A prospective multicentric randomized study. Design presented for the Stoutenbeek award of the 18th annual Congress of ESICM Society. Berlin 10-13 October 2004. Principal investigator : O. Joannes-Boyau and co-principal investigator P. Honore - Ongoing study.
7. Bellomo R.Http//clinical trials.gov/show/NCT221013.
8. Rivers E, Nguyen B, Havstad S, Ressler J, Muzzin A, Knoblich B, Peterson E,Tomlanovitch M. Early goal-directed therapy in the treatment of severe sepsis and Septic Shock . *N Engl J Med* 2001;**345**:1368-77.
9. Bellomo R, Kellum JA, Mehta R, Palevsky PM, Ronco C. The acute dialysis II : The Vicenza Conference. *Adv Ren Replace Ther* 2002;**9**:290-3.
10. Lemaitre Georges Henri. La theorie Cosmologique du "Big Bang". Cosmologie dynamique et theorie de l'atome primitif. Annales de la Societe Scientifique de Bruxelles, BXL 1927.
11. Bellomo'R, Honore PM, Matson JR, Ronco C, Winchester J. Extracorporeal blood treatment (EBT) methods in SIRS/Sepsis. Consensus statement. ADQI III Conference. *Int J Artif Organs* 2005;**28**:450-8.
12. Honoré 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**:1077-82.
13. Honoré 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**:896-7.
14. Honoré PM, Jamez J, Wauthier M, Dugernier T. Prospective evaluation of short-time high volume isovolemic hemofiltration on the haemodynamic course and outcome of patients with refractory septic shock. *Crit Care Nephrol* 1998;**90**:87-99.
15. Honoré PM, Jamez J, Wittebole X, Wauthier M. Influence of HVHF on the haemodynamic course and outcome of patients with refractory septic shock. Retrospective study of 15 consecutives cases. *Blood Purif* 1997;**15**:135-6.

16. Klouche K, Cavadore P, Portales P, Clot J, Canaud B, Beraud JJ. Continuous veno-venous hemofiltration improves hemodynamic in septic shock with ARF without modifying TNF-*α* and IL-6 plasma concentrations. *J Nephrol* 2002;**15**:150-7.
17. Matson JR, Zydney RL, Honoré PM. Blood filtration : New opportunities and the implications on system biology. *Crit Care Resusc* 2004;**6**:209-18.
18. Grootendorst AF, van Bommel AF, van der Hoeven B, van Leengoed LA, Van Oosta AL. HVHF improves right ventricular function in endotoxin induced shock in the pig. *Intensive Care Med* 1992;**18**:235-240.
19. Grootendorst AF, van Bommel AF, van der Hoeven B. HVHF improves haemodynamics in endotoxin induced shock in the pigs. *J Crit Care* 1992;**7**:67-75.
20. Grootendorst AF, van Bommel AF, van Leengoed LA, van Zande AR, Huygens HJ, Groenefeld ABJ. Infusion of ultrafiltrate from endotoxemic pigs depressed myocardial performance in normal pigs. *J Crit Care* 1993;**8**:61-9.
21. Grootendorst AF, van Bommel AF, van Leengoed LA, Nabuurs M, Boumans CS, Groenefeld ABJ. HVHF improves haemodynamics and survival of pigs exposed to gut ischemia reperfusion. *Shock* 1994;**2**:72-8.
22. Rogiers P, Zhang H, Smail N, Pauwels D, Vincent JL. Continuous veno-venoushaemofiltration improves right cardiac performance by mechanisms other than tumor necrosis factor alpha attenuation during endotoxin shock. *Crit Care Med* 1999;**27**:1848-55.
23. Rogiers P, Zhang H, Pauwels D, Vincent JL. Comparison of polyacrylonitrile (AN69) and polysulfone membrane doing haemofiltration in canine endotoxic shock. *Crit Care Med* 2003;**31**:19-1225.
24. Honoré PM, Zydney AL, Matson JR. High volume and high permeability haemofiltration in sepsis. The evidences and the key issues. *Care Crit III* 2003;**3**:69-76. Review.
25. Matson JA, Lee PA. Evolving concepts of therapy for sepsis and septic shock and the use of hyperpermeable membranes. *Curr Opin Crit Care* 2000;**6**:431-6.
26. Rogiers P. Hemofiltration treatment for sepsis: is it time for controlled trials? *Kidney Int* 1999;**72**:99-103.
27. Di Carlo JV, Alexander SR. Hemofiltration for cytokine-driven illness : the mediator delivery hypothesis. Review. *Int J Artifi Organs* 2005;**28**:777-86.
28. Bone RC, Sir Isaac Newton. Sepsis, SIRS and CARS. *Crit Care Med* 1996;**24**:1125-8.
29. Yekebas EF, Treede H, Knoefel WT, Bloechle C, Fink E, Isbicki JR. Influence of zero balanced haemofiltration on the course of severe experimental pancreatitis in pigs. *Ann Surg* 1999;**229**:514-22.
30. Yekebas EF, Eisenberger CF, Ohnnesorge H, Saalmuller, Elsmer HA, Engelhardt *et al*. Attenuation of sepsis-immunoparalysis with continuous veno-venous haemofiltration in experimental porcine pancreatitis. *Crit Care Med* 2001;**29**:1423-30.
31. Yekebas EF, Strate T, Zolmajd S, Eisenberger CE, Erbesdobler A, Saalmuller, *et al.* Impact of different modalities of continuous veno-venous hemofiltration on sepsis-induced alterations in experimental pancreatitis. *Kidney Int* 2002;**62**:1806-18.
32. Wang H, Zhang ZH, Yan XW, Li WQ, Ji DX, Quan ZF, Gong DH, Li N, Li JS. Amelioration of haemodynamics an oxygen metabolism by continuous veno venous hemofiltration in experimental pancreatitis. *Word J Gastroenterol* 2005;**11**:127-31.
33. Piper RD, Cook DJ, Bone RC, Sibbald WJ Introducing Critical Appraisal to studies of animal models investigating novel therapies in sepsis. *Crit Care Med* 1996;**24**:2059-70. Review.

34. Sun Q, Rogiers P, Pauwels D, Vincent JL. Comparison of continuous thermodilution and bolus cardiac output measurements in septic shock. *Intensive Care Med* 2002;**28**:1276-80.
35. Natanson C, Hoffman WD, Suffredini AF, Eichacker PQ, Danner RL. Selected treatment strategies for septic shock based on proposed mechanisms of pathogenesis. *Ann Intern Med* 1994;**120**:771-83. Review.
36. Bernard GR, Vincent JL, Laterre PF, LaRosa SP, Dhainaut JF, Lopez-Rodriguez A, Steingrub JS, Garber GE, Helterbrand JD, Ely EW, Fischer CJ Jr. Recombinanyt human protein C Worldwide Evaluation in Severe Sepsis (PROWESS) Study group. Efficacy and safety of recombinant human activated protein C for severe sepsis. *N Engl J Med* 2001;**344**:699-709.
37. Bernard GR, Margolis BD, Shanies HM, Ely EW, Wheeler AP, Levy H, Wong K. Wright TJ for the US investigators. Extended evaluation of recombinant human activated protein C United States Trial (ENHANCE US): a single-arm, phase 3, multicenter study of drotrecogin alfa (activated) in severe sepsis. *Chest* 2004;**125**:2206-16.
38. Tetta C, Bellomo R, Kellum J, Ricci Z, Pohlmeiere R, Passlick-Deetjen J, Ronco C. High volume hemofiltration in critically ill patients: why, when and how ? *Contrib Nephrol* 2004;**144**:362-75.
39. Brendolan A, D'Intini V, Ricci Z, Bonello M, Ratanarat R, Salvatori G, Bordoni V, De Cal M, Andrikos E, Ronco C. Pulse high volume hemofiltration. *Int J Artif Organs* 2004;**27**:398-403. Review.
40. Bellomo R, Kellum JA, Gandhi CR, Pinsky MR, Ondulik B. The effect of intensive plasma water exchange by hemofiltration on hemodynamics and soluble mediators in canine endotoxemia. *Am J Respir Crit Care Med* 2000;**161**:1429-36.
41. Kohro S, Imaizumi H, Yamakage M, Masuda Y, Namiki A, Asai Y. Reductions in levels of bacterial superantigens/cannabinoids by plasma exchange in a patient with severe toxic shock syndrome. *Anaesth Intensive Care* 2004;**32**(4):588-91.
42. Court O, Kumar A, Parrillo JE, Kumar A. Clinical review: Myocardial depression in sepsis and septic shock. *Crit Care* 2002;**6**:500-8.
43. Garcia Fernandez N, Lavilla FJ, Rocha E, Purroy A. Haemostatic changes in systemic inflammatory response syndrome during continuous renal replacement therapy. *J Nephrol* 2000;**13**:282-9.
44. Zouaoui Boudjeltia KZ, Piagnerilli M, Broheé D, Guillaume M, Cauchie P, Vincent JL, Remacle C, Bouchaert Y, Vanhaverbeck M. Relationship between CRP and hypofibrinolysis : is this a possible mechanism to explain the association between CRP and outcome in critically ill patients *Thromb J* 2004;**2**:7-12.
45. Bordoni V, Balgon I, Brendolan A, Crepaldi C, Gastoldon F, D'intini V, *et al*. Caspase 3 and 8 activation and cytokine removal with a novel cellulose tracetate super-permeable membrane in vitro sepsis model. *Int J Artif Organs* 2003;**26**:897-905.
46. Ratanarat R, Brendolan A, Piccinni P, Dan M, Salvatory G, Ricci Z, Ronco C. Pulse high-volume haemofiltration for treatment of severe sepsis: effects on hemodynamics and survival. *Crit Care* 2005 ;**9**:294-302.
47. Piccinni P, Dan M, Barbacini S, Carraro R, Lieta E, Marafon S, *et al.* Early isovolaemic haemofiltration in oliguric patients with septic shock. *Intensive Care Med* 2006;**32**(1):80-6.
48. Cornejo R, Downey P, Castro R, *et al.* High-Volume Hemofiltration as salvage therapy in severe hyperdynamic septic shock. *Intensive Care Med* 2006;**42**:713-22.
49. Laurent I, Adrie C, Vinsonneau C, *et al*. High-Volume Hemofiltration after out-of-hospital cardiac arrest: a prospective randomized study. *J Am Coll Cardiol* 2005;**46**:432-7.

50. Heylen A, Bervoets K, Smet M, Alexan der JP, Rogiers P. Combination of Drotecogin *α* and early hemofiltration can improve outcome in severe septic patients with ARF. Abstract presented at the spring meeting of the Belgium Society of ICM − 2 June 2005.
51. Tetta C, Bellomo R, D'Intini V, *et al.* Do circulating cytokines really matter in Sepsis? *Kidney Int* 2003;**63**:69-71.
52. Honoré PM, Ernst Y, Jamez J, Lemaire M, Pirenne B, Lebaupin C, *et al.* VHVHF is accompagnied by a significant drop in cytokines only in survivors during early refractory septic shock. *Crit Care* 2003;**7**:106-7.
53. Jacka MY, Ivancinova X,Gibney RT. Continuous renal replacement therapy improves renal recovery from ARF. *Can J Anesth* 2005;**52**:327-32.
54. Manns B, Doig CJ, Lee H, Dean S, Tonelli M, Johnson D, Donalson C. Cost of ARF requiring dialysis in the intensive care unit: clinical and resource implications of renal recovery. *Crit Care Med* 2003;**31**:644-6.
55. Schiffl H., Lang SM, Fischer R. Daily hemodialysis and the outcome of ARF. *N Engl J Med* 2002;**34**:305-10.
56. Ronco C, Belomo R, Homel P, Brendolan A, Dan M, Piccinni P, La Greca G. Effects of different doses in continuous veno-venous haemofiltration on outcomes of ARF: a prospective randomised trial. *EDTNA ERCA J* 2002;**2**:7-12.