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Rationale of Extra-Corporeal Removal in Sepsis and SIRS

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1. Rationale "Revisited" Based Upon Recent Publications

It has been advocated since the early nineties [1,2] that the reduction of cytokines in the blood compartment could in theory lead to a reduction of mortality but this has been a naive thinking as we do not exactly know the pharmacodynamics and pharmacokinetics of cytokines throughout the body which is probably much more complicated of what we thought before.

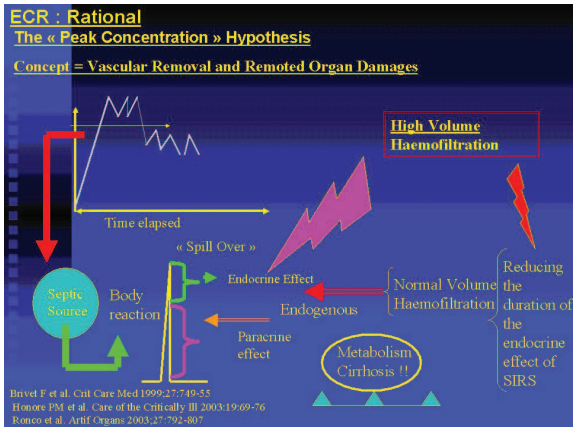

Fig. 1. The "Peak Concentration" Hypothesis.

This had led up to now to three leading theories and concepts. The Ronco and Bellomo concept of "Peak concentration hypothesis"[Fig.1]; In this theory, clinicians are concentrating their efforts to remove from the "blood compartment" mediators and cytokines at the pro-inflammatory phase of sepsis[3, 4, 5]. They hope that, by reducing the amount of "free" cytokines, they can decrease dramatically the level of "remote organ (associated) damages" and automatically as a consequence, the overall "associated"death rate.

In this regard, we do not know already

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what will happen at the interstitial and tissue level concerning mediators and cytokines which are obviously the most important "part" in term of consequences at tissue level. In this setting, techniques that can remove more rapidly and more substantially great amounts of cytokines or mediators are privileged. Amongst those, a large place has been given to high volume and very high volume haemofiltration and quite a lot "hybrid" therapies encompassing from high permeability haemofiltration (HPHF)[6], super high flux haemofiltration (SHFHF) [7], hemo-adsorption [8] or coupled filtration and adsorption (CPFA) [9] and any other types of adsorption using physical or chemical forces rather than driving forces as used normally in haemofiltration derived techniques.

Regarding also this issue, "semantics" is very crucial. Indeed, it can be argued that the term "aDsorption" is probably not the right term because blood is not flooding through a semi-permeable membrane and it is not the "net effect" of convection forces plus oncotic forces that result in the passage of mediators through this kind of device. In that type of device, it is more appropriated to use the term "aBsorption" as chemical and physical forces are really engaged in that setting. So, we should be very careful about the use of the appropriate terms when describing this kind of techniques [10]. Indeed, through membrane separation is only occurring with "aDsorption".

The second concept is called the "Threshold immunomodulation hypothesis" [Fig.2] and has been called by anglo-saxons authors the "Honore concept" [11,12]. In this concept the view of the system is much more dynamic. Indeed, when removal is occurring at the blood compartment side, we can see in some experiments that the level at the interstitial side (and also at the tissue side) is also changed and, because we are removing not only mediators but also pro-mediators, some pathways are really "stopped" when enough pro-mediators have been removed by this technique. At this point, the cascade is blocked and when reached, is called the "threshold point". Indeed at this level, the cascade is lost and no further harm can be done to the tissue of the organism. But obviously, it is difficult to know when this point is reached once we do apply high volume haemofiltration at the clinical level. But what we do know, is that we can improve haemodynamics and survival in some patients and this is shown by various studies using high volume haemofiltration without any significant drop of mediators inside the blood compartment itself [13,14,15]. This effect is obtained without any dramatic fall in plasma cytokine level because where the cytokine or mediators level should fall, is at the tissue level (where they do harm) and not specifically at the blood compartment level.

Nevertheless we do not know the exact mechanism by which high volume haemofiltration can increase the flow of mediators and cytokines between the interstitial compartment and the blood compartment (and back to the blood side). Before the end of the year 2005, we do know whether this "missing step" is perhaps well explained by the last theory and/or concept.

The third theory and concept is called the "Mediator delivery hypothesis" [Fig.3] and has been called the "Alexander concept" by several authors[16]. In this theory, the use of high volume haemofiltration and especially

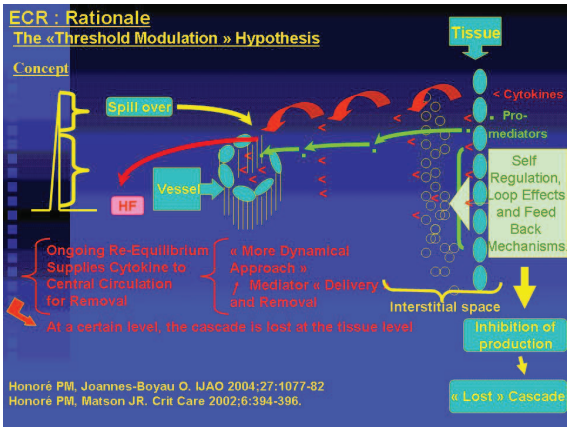

Fig. 2. The "Threshold Modulation" Hypothesis.

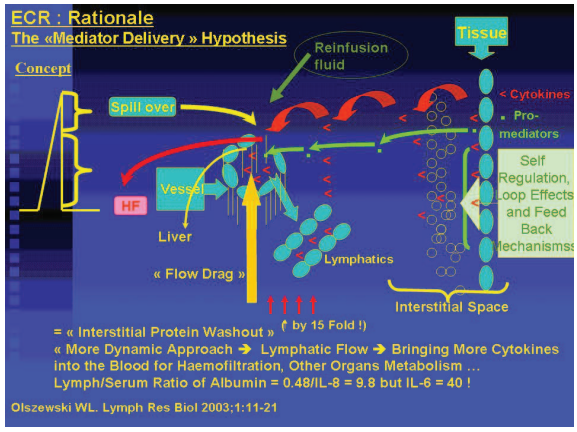

Fig. 3. The " Mediator Delivery" Hypothesis.

high intakes of incoming fluids (3 to 5 litters/hour) is able to increase the lymphatic flow by 20 to 40 folds even more especially for mediators and cytokines lymphatic flow (drag). This has been demonstrated in several papers [17,18,19] and is obviously extremely important. Thus, the use of exchange fluid might be very important (and not only extraction) in order to increase the flow of lymphatic transport between the interstitial tissue and the blood compartment.

We can now understand why high flow haemofiltration is able to increase dramatically the lymphatic transport from tissue and interstitial space including cytokines and mediators back to the blood compartment in order to be potentially removed afterwards.

So in comparison, high permeability haemofiltration is able to remove maybe "larger" amounts of mediators and cytokines in the blood compartment but is not able to increase lymphatic flow and, as a consequence, is not able to remove some very crucial cytokines and mediators at the interstitial and at the tissue level side (where they do harm). Therefore, this can explain that some very recent studies using high permeability haemofiltration in sepsis have been shown not to be effective to improve haemodynamics and survival in septic acute animal models like in the last Rogiers' study recently presented [20].

As a consequence, clinicians should be aware of this new insights regarding rationale of extra-corporeal removal in severe septic shock in order to choose the best option regarding the use of an adjunctive treatment for severe septic shock at the bedside.

2. Future of HPHF and Increased Filter Porosity: "Increase" may not be (always) equal to "Improvement"

Regarding mediators and despite the increased complexity of the rationale, one should think that increasing the filter porosity could be a good option [21]. Indeed, many mediators have a greater molecular weight and could be eliminated by using more sophisticated techniques as HPHF, SHFHF

and hemo-adsorption. Those techniques are able to remove more substantial amounts and perhaps greater mediators but the question remains: to remove in the " right compartment" obviously. Also, the risk is to loose many important nutrients, hormones, drugs and especially antibiotics and many unknown metabolites. So, investigators have tried to use hybrid techniques that can utilize at the same time the advantages of different techniques without having to support their drawbacks. Indeed, CPFA and Cascade Haemofiltration (CCHF) [22] are able to retrieve large amounts and large molecules without taking the risk of loosing important nutrients because part of the so-called "purified" blood is going back to the patient.

Concerning filter porosity, if we "stick" to hybrid techniques as CCHF and CPFA and, if a significant part of this so-called "purified" blood is going back to the patients, they would be no really "theoretical limits" as nothing important should be losted and only target molecules should be adsorbed. Along these lines, we can see, that a complete neglected domain exist right now as HVHF and derived techniques are seeking molecules below 45 kDa and plasmafiltration is seeking molecules around 900 kDa[23].

As a consequence, the entire world of molecules between these two limits is really neglected and clinicians (and as well investigators) should pay much more attention to it. So, we need to extend the limits widely of our targets if we can guarantee that all the "purified" blood will go back to the patient "eluding" the potential risk of loosing many important blood components.

3. Clinical implications for the intensivist in 2006 regarding the use of ECT in Sepsis as Adjunctive Therapy

Regarding the use of ECT in sepsis as an adjunctive therapy in intensive care nowadays, we can say that we need to apply widely the 35 ml/kg/h "rule" in our respective intensive care units as recent unpublished surveys have shown that less than 20% of the units (at least in continental Europe) are applying those.

A recent "position" paper published by an ADQI (Acute Dialysis Quality Initiative) group has underlined that HVHF could be used by clinicians in catecholamine resistant septic shock (CRSS) (Level V Evidence and Grade E Recommendation) [24]. The same position paper of the ADQI did also widely support the extended use of the 35 ml/kg/h 'rule" with a Level II Evidence and a Grade C Recommendation[24].

In classical hyperdynamic septic shock and especially ICU acute septic renal failure or ICU acute septic renal injury (according to the RIFLE classification), we are eagerly waiting the results of several "outcome dose" studies in ICU.

Amongst those ongoing studies regarding appropriate dose of haemofiltration in critically ill septic acute renal failure, we need to underline the IVOIRE study (IVOIRE Stand for hIgh VOlume in Intensive caRE) [25] This ongoing study will potentially give us very important insights for the future, regarding the exact dose to use in subgroups of septic patients with acute renal injury. The IVOIRE study will include more than 480 patients with septic shock plus acute renal injury defined by the RIFLE classification in ICU. Allocation

into the two groups 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 acute renal failure in ICU. As the Ronco study [5] has already allude to with the 45 ml/kg/h subgroup whereas the septic sub-population had a better survival although the non septic one did not improve further.

4. Conclusions

Clinicians should be aware of this new insights regarding rationale of extra-corporeal removal in severe septic shock in order to choose the best option regarding the use of an adjunctive treatment for severe septic shock at the clinical level. Indeed, exchange volume is not only important for removal of mediators but also for displacement of mediators throughout the body [26,27,28]. Membrane porosity or system complexity can never replace systems that are just using high exchange rates of volume with simple membrane separation technology.

As a final note, we can see that the world of haemofiltration and associated hybrid therapies is still evolving rapidly. Not only the investigator but also the clinician should be aware about the recent advances as several ongoing "dose outcome" studies may change profoundly our daily practice. The expansion and the odyssey of the haemofiltration universe continues.

Abbreviation

ADQI: Acute dialysis quality initiative
CCHF: Cascade haemofiltration
CPFA: Coupled filtration and adsorption
CRSS: Catecholamine resistant septic shock
ECR: Extra-corporeal removal
ECT: Extra-corporeal therapy
HPHF: High permeability haemofiltration
HVHF: High volume haemofiltration
SHFHF: Super high flux haemofiltration

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