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Opinion

Dysregulated Inflammatory Response. From Hemofiltration to Hyperfiltration. There is No "Divine Particle"

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Received: August 26, 2019; **Published:** September 27, 2019

There is no critical care unit that has started using the technique and it has stopped using it for lack of results in its patients. Continuous hemofiltration has revolutionized multiorgan support strategies in critically ill patients with a dysregulated inflammatory response (DIR) and multiorgan dysfunction.

We have been studying for decades how to improve results, but the reality that we must assume, is that we are stuck debating aspects as elementary as continuous or intermittent mode and the depurative mechanism (dissemination, convection, adsorption), always based on the paradigm of acute kidney failure. It remains controversial whether hemofiltration improves the mortality of our patients because there is not yet a definitive study to prove it clearly. However, in terms of mortality or improved scores in the SOFA scale, these multicentre clinical trials do not describe the reality that other professionals see daily in their patients. The current failure to reduce mortality by increasing ultrafiltration has led to novel efforts in purification protocols that achieve elimination by adsorption with specific and non-specific membranes.

In our opinion, we overlooked something as essential as focusing on the type of patients and their pathophysiology. Although we assume that this it´s due immunomodulation mechanism, the truth is that we do not know exactly how or where we are interacting in the inflammatory cascade.

It's time to rethink the theoretical approach to the problem and recognize that we're really using a "black box" method to move forward. That is, we study inputs (hemofiltration machine, dysregulated inflammatory response, organic failures…) and outputs (clinical improvement, technical variables, time…). We have not made any progress by studying the inside of the "black box", that is, how we act exactly on the inflammatory response. From modifications in the inputs and observing their effect on the outputs is how we have defined some variables such as the convection dose that Ronco., *et al*. [1] established in the septic patient.

There is currently a need to improve the hemofiltration protocols offered to patients that develop a DIR, in which kidney function is evaluated as a non-specific and limited indicator of the onset, adaptation and completion of the technique. Indeed, it may be necessary to extend the parameters considered to renal and extra-renal events, both in the presence or absence of sepsis. In this way, it is important to distinguish isolated renal processes from systemic inflammatory events, given that an incorrect therapeutic focus could bias the results of the studies and raise questions about their validity. Therefore, our approach to the problem should consider the DIR a global dysfunction of the whole organism, not just renal.

Clinical trials are complicated experiments that have not allowed us to move forward on these issues. The Paired Availability Design for Historical Controls are a valid alternative, which could from the experience of a few hospitals being reproduced in others and achieve an

adequate level of evidence and sufficient external validity. Once focused on a well-defined study population, we would use measurement tools based on the final pathophysiological consequences. That is, parameters that measure organic dysfunction in line with the current definition of dysregulated inflammatory response. In addition, we should add basic analyses that measure the cellular components that are compromised in the process in order to try to associate an explanation with the observed improvement. For now, interleukins do not serve us to answer key questions. There is no "divine particle" that can explain everything.

DIR can be triggered by several events, including infection and ischemia-reperfusion injury, and they can have different systemic effects on the endothelial glycocalyx, not only renal consequences, these including: vasodilation, fluid extravasation, platelet micro-aggregation, etc. In fact, when patients respond poorly to treatment (measured on the SOFA scale), immunomodulation strategies involving the non-specific elimination of inflammatory mediators should be performed as some groups have shown in one-centered studies. Therefore, an improvement in hemofiltration-related variables (lower SOFA score) would suggest the presence of a DIR-related pathophysiology, and we can therefore assume that the inflammatory response is being modulated.

We have seen the benefits of a continuous convective hemofiltration protocol based on the use of high doses of citrate as an anticoagulant and pre-filter substitution liquid, and non-specific adsorption with an AN69-ST-Heparin Grafted membrane (AN69-ST-HG). The pathophysiological consequences of this protocol on the DIR were measured by monitoring multiorgan dysfunction. Indeed, we define the clinical phases in which the technique can be employed, how to adapt and optimize it, and when to terminate the process. Using simple tools, we can achieve clear, well-defined objectives through multimodal monitoring. We refer to this protocol as CONVEHY - Continuous Venous Hyperfiltration [2], a protocol that can be applied in more critical-clinical situations and that integrates the objective-guided recommendations for critical patients with an adequate/adapted and dynamic depuration strategy in order to avoid dialysis secondary effects.

We distinguish an "anti-inflammatory phase" (AIP, phase 1) and a "dehydration phase" (DP, phase 2), and these phases are monitored. The withdrawal of vasoactive drugs, lactate normalization, the absence of acidosis, the absence of severe heart dysfunction, and correct purification/cleansing mark the end of the AIP. The aim of the DP is to restore normovolemia and to correct the interstitial oedemas that impair both oxygen diffusion, as well as the distribution of nutrients and antibiotics.

The use of high doses of citrate could be better than the use of heparin with the AN69-ST-HG membrane due to:

- The membrane maintaining its maximal efficiency for more time, coupled to a weaker activation of leukocytes and platelets that saturate less the membrane [3].
- The PEI (polyethylenimine, the high adsorption cationic polymer) not becoming saturated by heparin, thereby remaining more readily accessible.
- The unpredictable effect of heparin on patients in septic shock or IRI, which could provoke inflammation and micro-thrombosis in the microcirculation [4].
- Citrate, as a substrate of the respiratory cycle, may act at the mitochondrial level, enhancing the metabolic alterations and maintaining the respiratory complexes in a latent state, thereby avoiding apoptosis [5].

In the coming years the clinical approach to the indication of the technique based on the degree of organic dysfunctions will define the methodology of the studies. The extension of their indications beyond sepsis and renal failure will be consistent with the pathophysiology of other processes that also carry on a dysregulated inflammatory response, such as ischemia reperfusion. The "purifying" strategy that combines non-specific adsorption and convection to control the systemic inflammatory response without doing any further harm to the patient, and the use of substances that improve damaged cellular components with citrate or other energy substrates, are in our opinion the approach that has given us the best results and whose potential development is very high.

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Volume 5 Issue 10 October 2019