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The Promise of Adsorption for Chronic Dialysis Patients

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In the last months, *Blood Purification* has seen a remarkable increase in submissions and publications related to hemoperfusion and new sorbent materials. Such trend highlights the worldwide interest in this relatively new method of solute removal and alternative blood cleansing techniques. Adsorption is a mass separation process by a solid agent. It differs significantly from the classic mechanisms of convection and diffusion based on separation by a barrier (dialysis membrane) (Fig. 1). This modality of solute removal goes beyond membrane characteristics and permeability and explores the complex phenomena of molecular interaction between adsorbent (material where adsorption takes place) and adsorbate (molecule adsorbed onto the surface of the adsorbent). Due to its specific blood cleansing mechanism, hemoperfusion can overcome the limitations imposed by dialysis membranes and achieve effective removal of a wider spectrum of solutes [1]. This opportunity opens a completely new perspective in the field of blood purification by extracorporeal techniques but requires the generation of new literature and evidence. Both end-stage kidney disease (ESKD) and acute kidney injury associated to sepsis and other critical illness represent possible areas of application of hemoperfusion. In critically ill patients, sorbents have mostly been applied for endotoxin and cytokine removal in conditions such as infection, intoxication, immune-dysregulation, sepsis, and cytokine release syndromes. In spite of an early interest in the 80s, the use of hemoperfusion in ESKD has been mostly overlooked due to inadequate sorbent materials and often neglected because of overwhelming side effects. Nevertheless, there is a clear rationale to consider adsorption in this clinical setting, especially in light of the new hemo-compatible sorbent materials recently made available for hemoperfusion. Several molecules accumulate in uremic patients due to reduced kidney function and their increased blood levels are associated with specific clinical outcomes [2]. Improved dialysis adequacy based on urea kinetics and Kt/V contributed to reduce the risk of treatment failure. However, general morbidity, hospitalization, cardiovascular, and skeletal complications remain substantially elevated [3]. The pathophysiological foundation of this problem seems to be related to the retention of solutes other than urea and low molecular weight proteins (size range 5 to 45 kDa) supporting the previously described theory of middle molecules [4]. For example, plasma concentration of β2-microglobulin has been correlated with formation of amyloid deposits in bone, tendons, and joints [5]. Other low molecular weight proteins (such as free light chains) retained or modified (glycosylation, oxidation) in uremia, cause inflammation and cardiovascular adverse events [6]. These observations have spurred new interest in increasing removal of solutes in the medium-large molecular weight spectrum well beyond what classic dialysis techniques can achieve [7].

Cellulosic membranes were mostly utilized in hemodialysis (HD) to remove small solutes by diffusion. Improved removal of middle molecular weight solutes (500–

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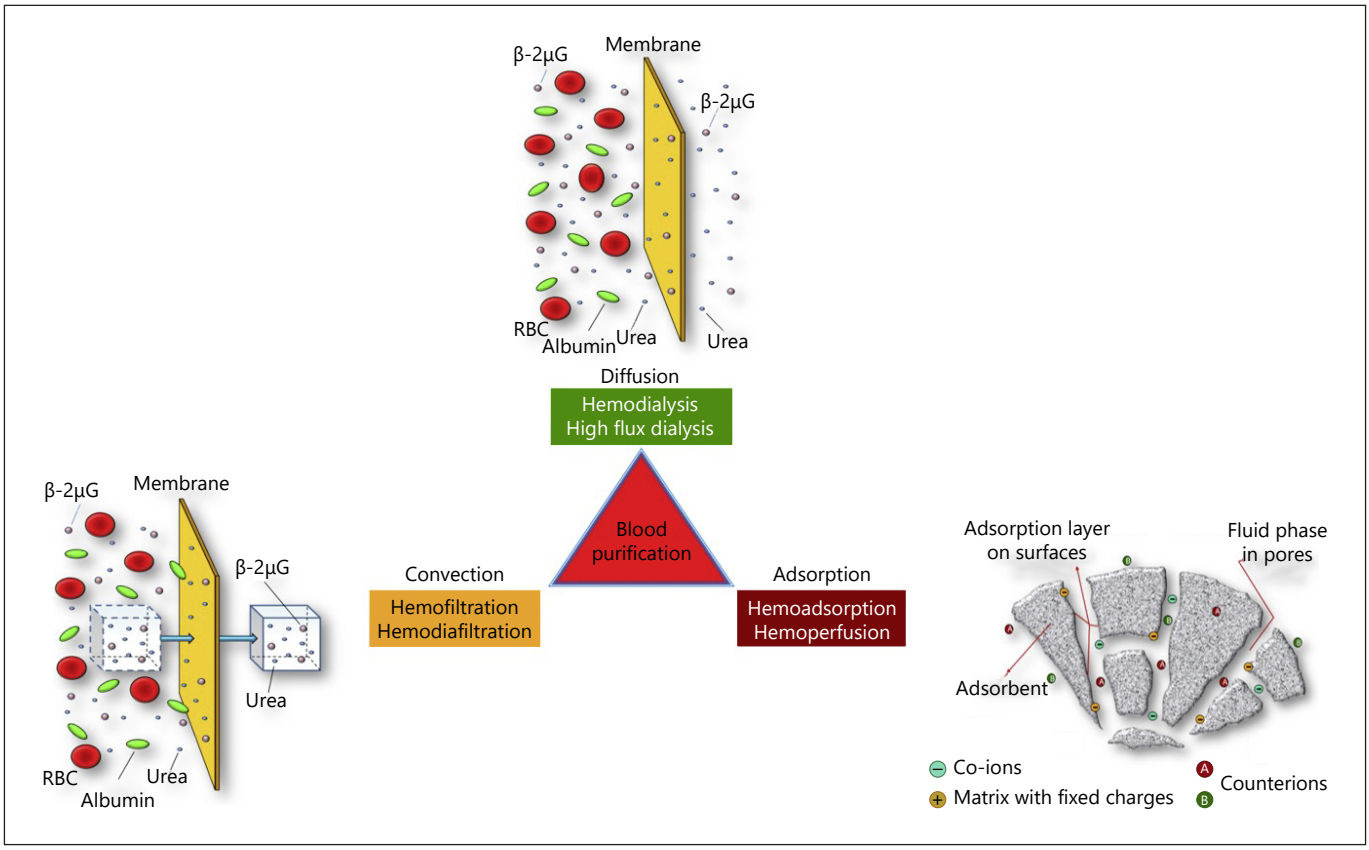

Fig. 1. A triad of mechanisms can be applied today for blood purification purposes in extracorporeal therapies: (**a**) Diffusion: a mass separation process by a barrier (membrane) based on difference in solute concentration gradients between blood and dialyzate. This mechanism is mostly used in HD and it is efficient in removing small solutes such as urea. **b** Convection: a mass separation process by a barrier (membrane) based on application of a transmembrane pressure gradient leading to augmented ultrafiltration. The solvent drag carries solutes of various molecular weights across the membrane that sieves solutes in relation to molecular weight and molecular radius. This mechanism is mostly utilized in hemofiltration and hemodiafiltration techniques where part of the ultrafiltrate must be replaced by a fresh solution. **c** Adsorption: a mass separation process by a solid agent where the solute is trapped inside the tridimensional structure of the sorbent thanks to ionic bonds, van der Waals forces and hydrophobic bonds. This mechanism is utilized in techniques defined as hemoperfusion and allows for removal of solutes in a molecular weight spectrum that goes beyond that normally removed by dialysis membranes.

5,000 Da) was subsequently obtained with synthetic high flux membranes and the application of convective therapies such as high flux dialysis (HFD), expanded HD, and hemodiafiltration (HDF) [7–10]. Despite this evolution, cardiovascular complications and high mortality rates are still a major concern in chronic dialysis where a significant degree of inflammation and solute retention is observed. Based on this, new options should be explored to provide adequate middle-large solute removal in ESKD and improve patients' outcomes.

The history of sorbents started almost two centuries ago with inorganic allumo-silicates (zeolites), carbons, and organic polymer ion exchange resins [11]. Only recently however, biocompatible synthetic porous polymers (styrene or acrylic acid based) have been applied for blood purification purposes [12]. In fact, while original hemoperfusion techniques presented significant side effects and adverse reactions, highly biocompatible new sorbent materials, represent today a possibility for incremental application of adsorption in acute and chronic blood purification therapies [13–19]. In the last domain, initial reports of application of hemoperfusion combined with HD in chronic patients with pruritus and other middle molecule-related symptoms have provided encouraging results [20]. In a prospective randomized controlled trial on more than 400 chronic HD patients, Zhao et al. [21] made an important observation supporting the use of hemoperfusion combined with HD (HP + HD). Pa-

tients were randomized to four groups: (1) low flux HD (LFHD), (2) high flux HD (HFHD), (3) once-weekly hemoperfusion combined with low flux HD (HP + LFHD), and 4) once-weekly hemoperfusion combined with high flux HD (HP + HFHD). Patients were followed for 12 months and the main endpoints were predialytic blood levels of β2-microglobulin and PTH and uremic pruritus score (UP). The results reported in the special focus of this issue [21] indicate that the addition of hemoperfusion once a week to both LFHD and HFHD significantly improved all target endpoints compared to HD alone (LF or HF). Further analysis demonstrates that positive results depend on the addition of HP, independently on the membrane flux. This study has important implications and may open interesting treatment opportunities for chronic patients. The positive effect of a single session per week of HP + HD can be explained by the slow kinetic turnover of medium-large molecules between compartments in the body compared to small solutes such as urea. β2 microglobulin progressively accumulates in the body, while kidney function declines and reaches a steady state level that can be determined by generation, volume of distribution, and elimination by dialysis. However, when levels reach a threshold value, deposition in tissues occur to a rate that observed predialytic concentrations in blood are maintained fairly stable. The volume of distribution accessible for clearance during a dialysis session is close to 20% of body weight (intravascular and extravascular) [22]. Treatments such as HFD or HDF that are capable to remove higher amounts of β2 microglobulin compared to LFHD still present reduction ratios not greater than 50–60% at the end of each session. This maintains a significant amount of the solute in the body and leads to tissue deposition if predialytic blood levels overcome the critical threshold. Dialytic removal is related to convective clearance which is dependent on the technique and the blood flow. High convective rates can only be achieved with high blood flows and a significant number of patients may not present a vascular access adequate for that. Furthermore, in different geographical areas HFD or HDF may not be available for technical or economical reasons. In those conditions, the addition of hemoperfusion once weekly may represent an interesting solution. The HA 130 cartridge utilized by the authors allows for high adsorption clearances even at blood flows of 250 mL/min or even lower. The reduction of predialysis levels of β2 microglobulin in both groups (HP + LFHD and HP + HFHD) suggest that the intercompartimental kinetics of the solute in the body can be modified thanks to an increased removal. The treatment could in fact promote an improved mass transport of the solute among different compartments and facilitate the contact with the sorbent for a better blood purification.

A better understanding of the basic aspects of the adsorption process and of the pathophysiological foundations of clinical effects of hemoadsorption, will certainly expand the potential for clinical application of sorbent devices. We need to identify meaningful target molecules and measure their intracorporeal and extracorporeal kinetics, possibly utilizing in vitro studies with creation of appropriate isotherms. We need to understand what conditions should trigger the application of hemoadsorption and how long such technique should be applied. We need to discover what the adequate dose of hemoadsorption for different disorders is, how to measure efficiency/efficacy, and how many sessions should be prescribed. We need to understand the potential of adsorption of each single device in order to define the best timing of application, the duration of the session and the timing of device change. We finally need to understand the basic properties of each sorbent material, the mechanisms of adsorption and the potential side effects including the unwanted removal of solutes such as antibiotics or nutrients. Last but not least, we need to understand the financial implications for this new approach although interesting economic analysis have already been published [23]. In the present issue, we have published the results of a consensus group of experts that tried to establish a common ground for research design and data analysis in studies utilizing hemoperfusion combined with HD [24]. Recommendations are made in terms of treatment modalities, operational parameters, and minimum set of data collection. This may help to homogenize and harmonize the nomenclature in future studies and trials.

In conclusion, we have a well-defined pathway towards acquisition of newer and stronger evidence but the basis and rationale are well identified. We have a remarkable research agenda, but this is the basis of scientific progress and the rigorous methodology for technological advancement. The final target remains the possibility to offer our patients a chance of a better quality of life in dialysis.

Conflict of Interest Statement

In the last 3 years, Claudio Ronco has received fees for lectures, advisory boards, consultation, and speaker bureau from ASAHI, ASTUTE, BAXTER, B.BRAUN, Biomerieux, CYTOSORBENTS, FMC, GE, JAFRON, Medtronic, Ortho, ESTOR, and TORAY.

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Claudio Ronco is the sole author.

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