CHAPTER 194

Plasmafiltration-Adsorption-Dialysis System

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OBJECTIVES

This chapter will:
1. Describe the possibility of combining convection, diffusion, and adsorption to improve the efficiency of extracorporeal depurative techniques.
2. Discuss the role of plasma as a substrate and a medium of blood purification.
3. Describe the use of the patient's plasma as "dialysate" to perform a new type of high-permeability-cutoff plasma dialysis.

Molecules are present in the plasma dissolved in plasmatic water or bound to specific and unspecific proteic carriers. Albumin is the most important proteic carrier in the plasma. Consequently, according to their characteristics of solubility, plasma molecules are present as solutes in the plasmatic water, if water soluble, or bound to carriers, if hydrophobic.

Extracorporeal blood purification techniques such as hemodialysis (HD), hemofiltration (HF), and their combination, hemodiafiltration (HDF) and high-flux dialysis (HFD), are able to remove small molecules (urea and creatinine) and medium-sized molecules, such as the β_2-microglobulin, depending on the membrane cutoff value (HD/HDF/HFD) and the volume of reinfusion (HF/HDF). To improve the efficiency and the specificity of molecule removal, convective and/or diffusive techniques may be combined with adsorption. Adsorption allows removal of a wide range of hydrophobic and higher-molecular-weight substances, such as bilirubin, salt acids, cytokines, and myoglobin. The possibility of using specific physical interactions in some resin adsorbers (ion exchange, chemical affinity, van der Waals forces) allows the removal of specific molecule targets, such as cytokines in the patient with sepsis, and bile acids and bilirubin in the patient with acute or chronic liver failure. The adsorption process acts on protein-bound substances (bilirubin, toxins, drugs) and high-molecular-weight toxins present as solutes in the plasma (cytokines and proteins). Convection and diffusion cannot achieve good clinical clearances for high-molecular-weight and hydrophobic molecules owing to their theoretical and practical limitations related to the limited volume of infusion in convection and limited membrane permeability/cutoff in diffusion.

According to all these elements we can identify a central role of plasma as transporter of toxic molecules and its potential role as medium of purification in the extracorporeal blood purification techniques. Through its intrinsic capacity to bind and transport molecules, plasma is the best fluid to perform a purification process. In physiologic and pathologic conditions, molecules are present and transported by the plasma or in plasmatic water or bound to selective/unselective proteic carriers. In this view, it seems useful to combine diffusion, convection, and adsorption in the same technique to improve and obtain the best removal of substances with a broad spectrum of molecular weight.

According to this concept, coupled plasmafiltration-adsorption, an innovative technique, combines plasma adsorption with hemofiltration. In general, the adsorption process is specific to removal cytokines while the convective process is able to reestablish fluid balance, acid-base status, and electrolytes balance. Clinical applications of coupled plasmafiltration-adsorption are sepsis, septic shock, and systemic inflammatory response syndrome (SIRS). Further evolution of a combined system is Molecular Adsorbent Recycling System (MARS; Gambro AG, Lund, Sweden). This technique bases its mechanism on the transporter role of albumin. The closed loop of albumin is used as a medium to transport albumin-bound toxins from whole blood to the sites of purification (cartridges and a dialyzer with a low-permeability-cutoff membrane, where hemofiltration or hemodialysis of albumin is performed). Albumin from donors in the closed loop is regenerated and reused continuously. The clinical application of the MARS is liver failure and hepatorenal syndrome.

In these two techniques, plasma is viewed as a substrate of purification and the albumin, one of its components, is used as a medium of purification (MARS). The combination of more purification principles allows coupled plasmafiltration-adsorption and MARS to improve the clearance and the total removal of the substances implicated in the pathophysiology of the treated disease. This new concept of plasma as medium and substrate of purification at the same time opens a new view of purification for an innovative technique.

The plasmafiltration-adsorption-dialysis (PFAD) system combines a process of high-volume hemofiltration directly on plasma with a process of plasma adsorption on specific adsorber. The regenerated patient's plasma can be reinfused to the patient through the venous line or used as a dialysate in a process of "plasma dialysis" through a membrane with a very high cutoff (HCO).

PROCESS OF PLASMAFILTRATION-ADSORPTION-DIALYSIS

PFAD technology is based on new principles of purification that use a tricompartmental dialyzer (TD) to purify the patient's blood through a combination of three sequential techniques:
1. Convective process on plasma
2. Adsorption process on plasma
3. Diffusive process on whole blood provided by patient's regenerated plasma as dialysate (diffusive process through a very high cutoff membrane)

This process of purification is depicted in Figs. 194.1 and 194.2.[1]

The tricompartmental dialyzer is the core of this technology (Fig. 194.3). It is composed by hollow fibers, like those in a regular hemodialyzer. The compartments are located in different areas, each with a particular function, as explained

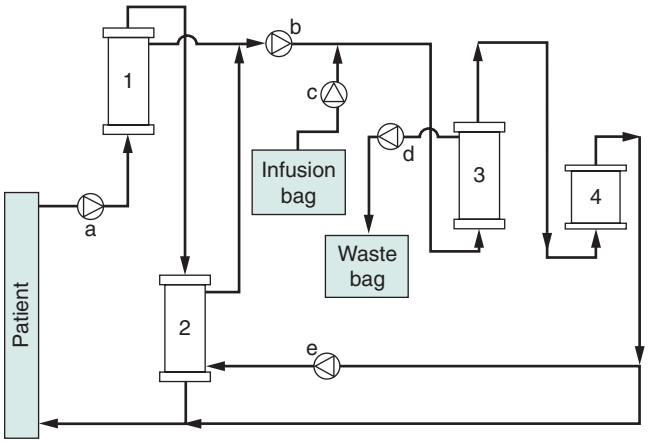
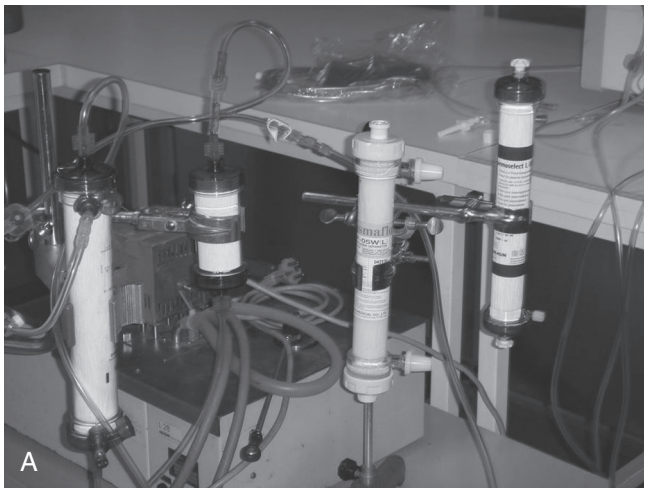


FIGURE 194.1 Schematic representation of the plasmafiltration-adsorption-dialysis system: *a,* Blood pump (blood flow = Q_B); *b,* plasma (plasma flow = Q_P); *c,* infusion pump (reinfusion flow = Q_R); *d,* ultrafiltration pump; *e,* plasma dialysate pump (dialysate flow = Q_D); *1,* plasma separator (second compartment); *2,* dialyzer (third compartment); *3,* filter to perform convection on plasma; *4,* adsorber. The second and third compartments are described as separate devices to simplify the explanation of a single process.



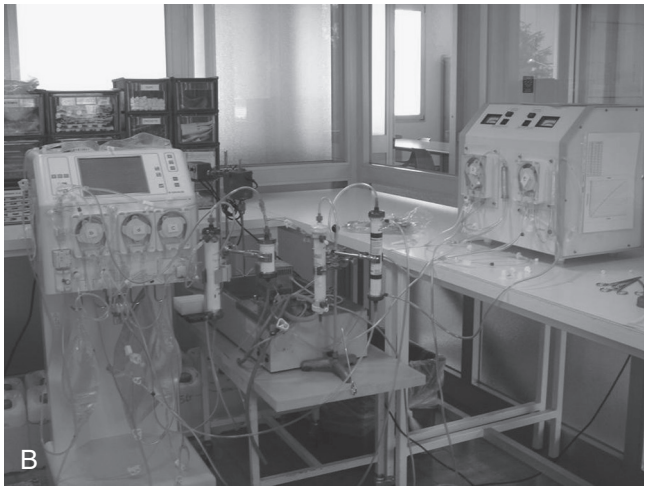


FIGURE 194.2 A, The three compartments of the tricompartmental dialyzer, the filter for the convective process, and the adsorber. B, The prototype plasmafiltration-adsorption-dialysis system.

below. The hollow fibers form three compartments along the extension of the dialyzer (see Fig. 194.3). The first compartment is formed by the inner space of hollow fibers in which the blood goes through the whole fibers' length thanks to a roller pump (blood pump). The internal compartment of the dialyzer is divided into two more compartments separated by a wall along the extension of the hollow fibers; the second compartment forms a stage for filtering plasma (Plasma Filtration Compartment, PFC), and the third compartment forms a stage for dialysis (Dialysis Compartment, DC). The second compartment is the space where patient's plasma can be filtered from whole blood across the hollow-fiber membrane (see Fig. 194.1, 1). The third compartment is the space where the patient's regenerated plasma undergoes purification based on a "diffusive and binding process"; in this way, the regenerated patient's plasma is used as a dialysate in countercurrent to purify the blood flowing in the first compartment (see Figs. 194.1 and 194.2). The membranes of second and third compartments have specific permeability cutoff values according to their specific function, and their area is able to ensure the processes that occur (filtration and dialysis). The second and the third compartments communicate through a particular opening in the arterial end of dialyzer (see Fig. 194.3; not shown in Fig. 194.1 or 194.4). In the first human prototype of this system, the second and the third compartments are separated and formed by two different devices, as shown in the figures.

The first step of the technique separates the plasma from whole blood (see Fig. 194.1; Table 194.1). This process determines the plasmafiltration from the inner space of hollow fibers to the space of the second compartment (Plasma Filtration Compartment). This plasma, obtained from the patient, enters the plasma purification circuit, where it is purified in series by convection (see Figs. 194.1 and 194.3) and adsorption (see Figs. 194.1 and 194.4). The plasma flow in this circuit is performed by a roller pump (see Fig. 194.1B).

The plasma purification circuit is designed by two separate processes to remove water-soluble toxic molecules (dialyzable molecules) by convection and hydrophobic molecules (not dialyzable) by adsorption on specific adsorber/s (see Figs. 194.1, 194.3, and 194.4). Convection is obtained through high-volume hemofiltration on plasma. It is known that high-volume ultrafiltration using a super-high-flux filter has achieved better cytokine clearances than those currently achieved by urea during standard continuous renal replacement therapy.[2] The convective process is also able to reestablish electrolyte balance, acid-base equilibrium, and fluid balance by acting directly on plasmatic water.

After the convective purification, the plasma is adsorbed by a specific adsorber/s to remove hydrophobic or not dialyzable molecules (very high molecular weight molecules) (see Figs. 194.1 and 194.4). The adsorber is specific for the patient's disease (e.g., sepsis, hepatorenal syndrome, acute and chronic liver failure). The cartridge for adsorption has to present good pressure-flow performance and excellent mechanical and chemical stability to perform the best plasma adsorption.

After these two processes, the purified plasma can go either of two ways (see Fig. 194.1):

1. The purified plasma returns to the patient through the venous line, as regenerated plasma.
2. The patient's purified plasma is used as dialysate in the third compartment. This regenerated plasma is used as dialysate in the third compartment in countercurrent to perform a diffusive process through a very high cutoff membrane. Thanks to this characteristic, molecules from

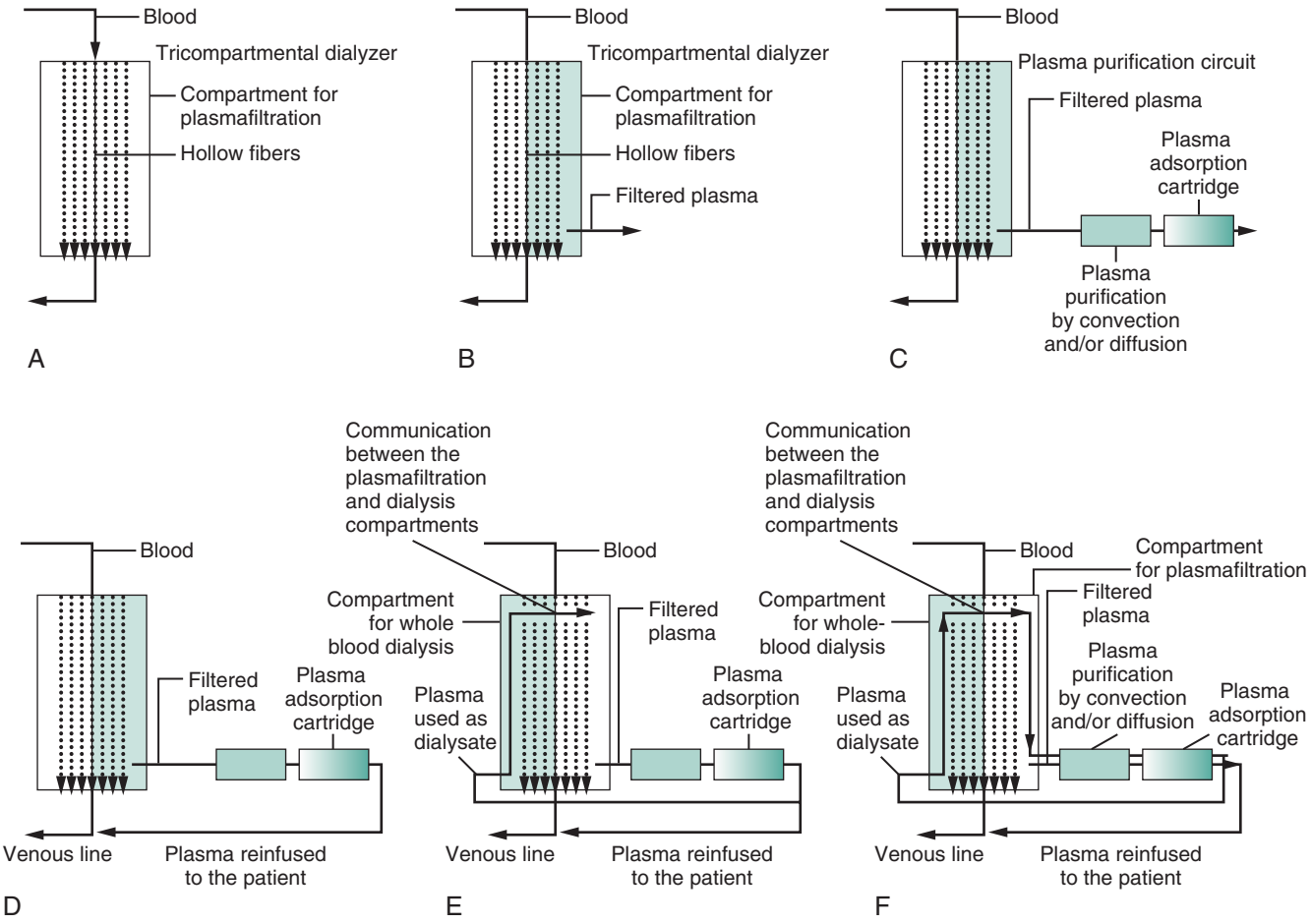


FIGURE 194.3 The tricompartmental dialyzer and the purification processes. A, First compartment; B, second compartment; C, plasma purification; D, plasma reinfusion; E, plasma dialysis; F, recycling virtual system. The second and third compartments are described as separate devices to simplify the explanation of a single process.

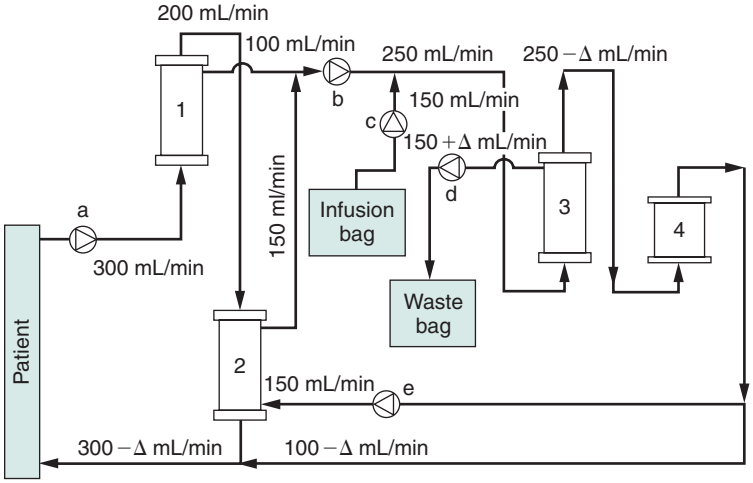


FIGURE 194.4 Standard flows during a plasmafiltration-adsorption-dialysis treatment. *a,* Blood pump (blood flow = Q_B); *b,* plasma (plasma flow = Q_P); *c,* infusion pump (reinfusion flow = Q_R); *d,* ultrafiltration pump; *e,* plasma dialysate pump (dialysate flow = Q_D); *1,* plasma separator (second compartment); *2,* dialyzer (third compartment); *3,* filter to perform convection on plasma; *4,* adsorber. The second and third compartments are described as separate devices to simplify the explanation of a single process. Δ, weight loss during treatment.

whole blood can diffuse in the compartment or can be bound to regenerated albumin, used as a carrier.

The filtrated patient's plasma from the whole blood (second compartment) and the exhausted dialysate from the third compartment can be purified again in the plasma circuit (see Fig. 194.1). In fact, there is a connection between the second and the third compartment at the arterial end of the TD; thus the exhausted dialysate can go to the plasma circuit through the second compartment (see Fig. 194.3), generating a virtual open loop. In the human prototype of this system, the separation between the second and the third compartment ensures the same plasma amount in the open loop. Because the plasma circuit is an open circuit, the dialysis system is not working in closed recycling modality, as in MARS system, but receiving fresh regenerated plasma from the plasma circuit every time (see Fig.

TABLE 194.1

Process of Plasmafiltration-Adsorption-Dialysis

STEPS	CHARACTERISTICS OF PROCESS	INNOVATION	SUBSTANCES REMOVED
Plasmafiltration	Filtration through the hollow fibers of the plasma separator (second compartment of tricompartmental dialyzer)	High volume of plasma filtration	Not applicable (production of plasma)
Plasma purification by high-volume hemofiltration	Plasma is processed by convection of a very high volume in predilution The device used is a super-high-flux filter	Application of convection directly on plasma instead of whole blood	All molecules removed by convective process A little quota of unselective adsorption on membrane surface
Plasma purification by adsorption	Adsorption as a specific adsorber The adsorber is specific to remove the target molecules	The absorber is chosen according to the molecules implicated in the pathophysiology of patient's disease The new design of cartridge allows obtaining high plasma flow	Depending on the specific adsorber: cytokines, myoglobin, lipopolysaccharide, bilirubin, salt acids, immune complex, autoantibodies, specific high-molecular-weight proteins
Plasma reinfusion into the patient	Reinfusion of purified plasma into the patient through the venous line The purification of the patient's body is obtained by the whole blood toxin dilution as a result of the regenerated plasma reinfusion and by the shifting and binding of toxins from the tissues because of the regenerated carriers in the reinfused plasma	Plasma regenerated by two different sequential processes, convection and adsorption	The same molecules as in the previous two processes
Plasma dialysis	Use of a very high-permeability-cutoff membrane to obtain the diffusion of very high-molecular-weight molecules through the membrane Driving force of regenerated plasma to shift and bind toxins from whole blood	The membrane allows diffusion of molecules with high molecular weight such as immunoglobulins M, G, and more Plasma used as dialysate in a diffusive process Driving force of plasma carrier used as a medium of purification	According to the combination of several factors: diffusive process through the membrane, plasma driving force, and previous plasma purification by specific adsorption
Recycling of plasma in the plasma purification system	The system is recycling a virtual amount of plasma because the plasma circuit is open at the venous line	The possibility of obtaining patient's plasma avoids the use of donor albumin The virtual amount of patient's plasma recycling enables high dialysate flows in the system for the plasma dialysis	It allows the plasma dialysis process described previously to be obtained

194.1). The plasma circuit peculiarity is that to obtain the dialysate from the third compartment thus the plasma flow in this circuit is a virtual flow inside the open plasma loop and can exceed the plasma filtration flow from the second compartment, being a recycling flow, as shown in the figures.

PFAD can be performed continuously or intermittently, through 8 hours' sessions (or longer) on a daily basis. During the first prototype application, the standard blood flow (Q_B) was 300 mL/min and the plasma flow (Q_P) from the second compartment was 100 mL/min (6 L/hr); the dialysate flow (Q_D) was 150 mL/min (9 L/hr), and the flow of reinfusion fluid (Q_R) for convection was 150 mL/min (see Fig. 194.4). Plasma purification by convection was achieved through predilution by a standard solution for hemodiafiltration at the same flow as Q_D. The circuit heparinization was mandatory and required at least 300 to 800 U/hr, depending on the patient's clinical condition. Thermal balance was maintained or modified through changes in fluids temperature used in the plasma purification circuit.

It is also possible to consider the use of citrate as anticoagulant. In this configuration, the regional anticoagulation can be useful in patients with bleeding risk who cannot be exposed to systemic heparinization. Also, the antiinflammatory role of citrate during sepsis and SIRS to improve purification can be used: as a matter of fact, heparin owns proinflammatory effects because of the release of mediators from leukocytes and platelets. On the other hand, local hypocalcemia at the membrane level during anticoagulation with citrate may reduce inflammatory mediator release from cells adhered to the membrane.[3,4] Citrate can be used safely in patients with significant liver disease,[5] provided that monitoring is intensified and the dose is carefully adjusted. The use of citrate also may be associated with less inflammation because of hypocalcemia-induced suppression of intracellular signaling at the membrane and avoidance of heparin, which may have proinflammatory properties.

PRELIMINARY DATA FROM IN VITRO STUDIES

The special geometry of the sorbent used in the prototype allowed very high plasma flows (up to 250 mL/min). We measured single-pass clearances of urea, creatinine, inulin, and myoglobin (Table 194.2). The specific solution was as follows: urea 100 mg/dL, creatinine 10 mg/dL, inulin

TABLE 194.2

Clearance and Removal Rates Achieved by the Plasmafiltration-Adsorption-Dialysis System

SUBSTANCES	REMOVAL RATE
Substances Cleared	
Urea	89 mL/min
Creatinine	96 mL/min
Inulin	118 mL/min
Myoglobin	84 mL/min
Substances Removed	
Lipopolysaccharide	84%
Potassium	34%

20 mg/dL, potassium 6 mEq/L, and myoglobin 10.000 ng/mL; lipopolysaccharide removal (2.5 UI/mL solution). The treatment settings were Q_B 300 mL/min, Q_P 100 mL/min, Q_R 150 mL/min, and Q_D 150 mL/min. According to our preliminary data, the adsorber was able to adsorb the 84% of lipopolysaccharide. This mechanism of purification is improved by the whole-blood dialysis performed by the regenerated plasma, used as a dialysate, which is able to shift and bind lipopolysaccharide and cytokines from the whole blood. The same mechanism acts in the tissues in the human body, when the regenerated plasma is reinfused into the patient. The plasma hemofiltration in predilution and the plasma dialysis are also able to substitute the renal function. Therefore the plasma is a substrate for and a medium of purification and can improve the total purification by the plasma dialysis process. The results highlight the importance of this device as continuous renal replacement therapy for the critically ill patient in the intensive care unit affected by sepsis, SIRS, or multiple-organ failure syndrome.

POTENTIAL CLINICAL EFFECTS OF PLASMAFILTRATION-ADSORPTION-DIALYSIS

In the specific case of sepsis and septic shock, PFAD can support or substitute the renal function and remove the high levels of proinflammatory and antiinflammatory cytokines responsible for the pathophysiology of organ injury and failure.[6] This is possible by means of the association of convective purification and specific adsorption for cytokines and lipopolysaccharide, improved by the plasma dialysis.

Another extremely important clinical problem relates to patients affected by liver failure, in whom, as the pathology progresses, kidney failure (hepatorenal syndrome) inevitably develops along with all the complications caused by retention of liver toxins. The accumulation of albumin-bound toxins has been demonstrated during liver failure; these toxins are responsible, to variable extents, for multiple-organ dysfunction (e.g., kidney, cardiovascular instability).[7] The functions of albumin as transporter and as possible purification vector have been described in albumin dialysis; the removal of these molecules through the process improves the clinical condition of the patient. The best-known and most widely used extracorporeal device for liver function support is the MARS,[8] which uses albumin only to perform purification by adsorption and by a classic high-flux dialysis. The current literature demonstrates that this approach is capable of improving patient survival.[9] Moreover, this type of approach is useful for intoxications caused by exogenous pathogens that are scarcely water soluble but are plasma protein bound.

In all of these conditions (sepsis, hepatorenal syndrome, SIRS) cytokines are involved in the pathophysiology of organs injury and damage. The damage that affects the various organs is determined by cytokines and other molecular factors that circulate in the blood or either dissolved in the plasma water or bound to albumin. Summarizing, PFAD system is able to reestablish electrolyte balance and acid-base equilibrium acting directly on plasmatic water in the plasma circuit; the specificity of the adsorber used for the plasma adsorption is important to remove toxic molecules retained or produced during sepsis, SIRS, acute-on-chronic liver failure, chronic liver failure, primary liver dysfunction, and hepatorenal syndrome. In theese diseases, one or more adsorbers with high selectivity for cytokines, unconjugated and conjugated bilirubin, phenols, and other retained molecules can be used.

PFAD is a technology that can combine more processes of blood/plasma purification to determine a selective and effective purification of molecules implicated in disease, such as sepsis, SIRS, and liver failure.

Key Points

1. The combination of convection with adsorption improves the total removal of toxic molecules implicated in the pathophysiology of diseases that are treated by extracorporeal therapy.
2. All toxic molecules are transported by the plasma, in the plasmatic water, or bound to some carriers.
3. Plasma is the medium of transportation of toxins, and acting directly on it can improve total purification.
4. Purified plasma is the best fluid to perform purification of the whole blood or pathologic plasma.
5. The combination of one or more principles of purification (convection, adsorption, diffusion) with use of regenerated plasma as purification fluid (plasma dialysis) can achieve the best results in the purification process.

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