Protocol for the Use of Hemoperfusion in Cardiac Surgery

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1. Introduction:

Hemoperfusion is a therapeutic method in which a large volume of the patient's blood is passed over an adsorbent material to remove toxins from the blood. Adsorption is a process where molecules or particles of one substance adhere to the surface of a solid material, which is called an adsorbent. Hemoperfusion is described as an extracorporeal treatment because the blood is pumped through a device outside the patient's body, and after being purified from removable toxins, it is returned to the patient's body (1).

The adsorbents used in hemoperfusion are resins and various forms of activated carbon or charcoal. Resin adsorbents are currently used in Europe but are not utilized in the United States. Since 1999, all hemoperfusion systems manufactured in the United States have used cartridges or columns containing carbon adsorbents. A newer type of cartridge containing an adsorbent polymer has also been undergoing clinical trials in the United States since the summer of 2002 (2-4).

Cardiopulmonary bypass (CPB) is a technique used in cardiac surgery to divert the patient's heart and lungs from the circulatory system, and it is widely employed in such surgeries. Despite its numerous benefits, this technology also causes issues, one of which is the increased activity of the inflammatory system. This phenomenon leads to many postoperative complications. Therefore, minimizing the systemic inflammatory response during CPB is crucial for improving surgical outcomes in cardiac patients, and various measures have been undertaken in recent years to address this issue (5).

Currently, numerous studies have demonstrated the effectiveness of hemoperfusion during cardiac surgery, claiming that this method can reduce the levels of inflammatory factors such as interleukins and cytokines during and after cardiac surgery, thereby decreasing surgical complications. Additionally, the recent application of this technique in patients taking anticoagulant medications and undergoing emergency surgery has been associated with reduced postoperative bleeding and improved surgical outcomes.

The aim of this paper is to review the benefits of using hemoperfusion in cardiac surgeries and to explore its applications in this field.

2. Applications of hemoperfusion

Currently, hemoperfusion has several major applications (7, 8).

- Removal of drugs or toxins from the blood in emergency situations
- Elimination of nephrotoxic substances from the blood in patients with kidney disease to improve renal function
- Extraction of harmful substances and bilirubin in patients with liver failure
- Providing supportive treatment before and after transplant and cardiac surgery by reducing levels of inflammatory markers and interfering drugs

Hemoperfusion is more effective than other treatment methods for removing certain specific toxins from the blood, especially those that bind to body proteins or are poorly soluble in water. This method is used to treat poisoning or overdose with barbiturates, meprobamate, glutethimide, theophylline, digitalis, carbamazepine, methotrexate, ethchlorvynol, and acetaminophen, as well as paraquat poisoning, and more recently, to remove anticoagulants used before treatment (9).

3. Evolution and development of hemoperfusion (10)

1850	The first mineral aluminosilicates (zeolites) were used for the exchange of NH4 and Ca++ ions.
1910	Water softeners using zeolites demonstrate instability in the presence of mineral acids.
1935	Adams and Holmes synthesized the first organic polymeric ion-exchange resin.
1948	The first application of hemoperfusion using ion-exchange resin for treating uremia in dogs was published.
1950	The experimental use of porous artificial polymers for blood purification.
1958	The use of ion exchange resin for the treatment of patients suffering from barbiturate poisoning.
1960	The clinical use of hemoperfusion with ion exchange resins for the elimination of salicylates and phenobarbital in dogs.
1970	The widespread application of charcoal and resin-coated membranes for the treatment of poisoning.
1980	The use of charcoal and resin-coated membranes for treating various conditions.
1990	Decreased interest in hemoperfusion with charcoal and resin, due to the emergence of side effects associated with its use.
2000	Continuous decline in the use of hemoperfusion as dialysis membranes.
2010	Improvements in coverage, construction, and positive experimental results have rekindled interest in hemoperfusion, as evidenced by an increasing number of reports.
2020	**Use of Hemoperfusion for Managing Increased Incidence of Inflammatory and/or Septic Conditions**

4. Preparation:

The hemoperfusion system can be utilized through the use of hemodialysis machines, continuous renal replacement therapy (CRRT), via arteriovenous fistulas, cardiopulmonary bypass (CPB) pumps, or ECMO (extracorporeal membrane oxygenation). Essentially, to perform this task, blood must be withdrawn from the body, which in most cases is achieved by incorporating a shunt and utilizing dialysis systems. However, in cases where other devices such as CPB are installed during cardiac surgeries or when the patient is on ECMO, it is also possible to connect the hemoperfusion cartridge to these systems and perform the process (11).

The hemoperfusion system with cartridge washing is prepared by priming a sterile cartridge containing an adsorbent with heparinized saline solution. Prior to connection to the patient, the system undergoes a pressure test.

The function of hemoperfusion commences as blood is introduced via the arterial catheter pathway into a column or cartridge containing absorbent materials. As the blood traverses the carbon or resin particles within the column, toxic molecules or particles are attracted to the surface of the absorbent particles and sequestered within the column. Subsequently, blood exits from the opposite end of the column and is returned to the patient through a venous catheter pathway. Depending on the available cartridges, this technique can be continuously employed for up to 8 hours and is capable of purifying toxins from a larger volume of blood compared to hemodialysis or other filtration methods, processing over 300 milliliters of blood per minute (12).

To prevent clotting, infusion of anticoagulant drugs can be utilized, while in patients at high risk of bleeding, this procedure can be performed without anticoagulation (14,15).

5. Technical aspects of hemoperfusion:

The absorption stages in hemoperfusion are as follows (13):

-External mass transfer (interfacial) of salts from the bulk fluid to the outer surface of the adsorbent through diffusion through a thin layer or boundary layer.

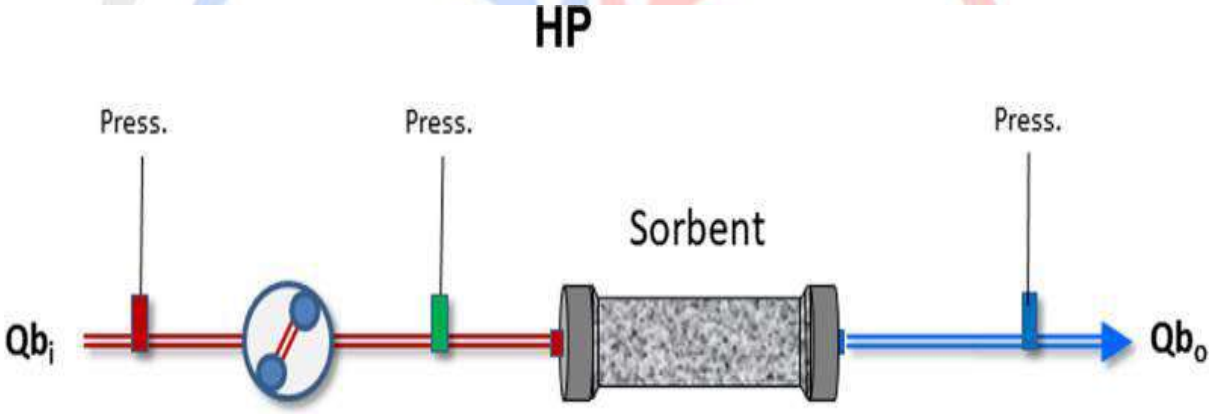
-Internal mass transfer (intrafacial) of salts by diffusion through pores from the outer surface of the adsorbent to the inner surface of the internal porous structure.

-Surface diffusion along the porous surface.

- Adsorption of salts on the porous surface.

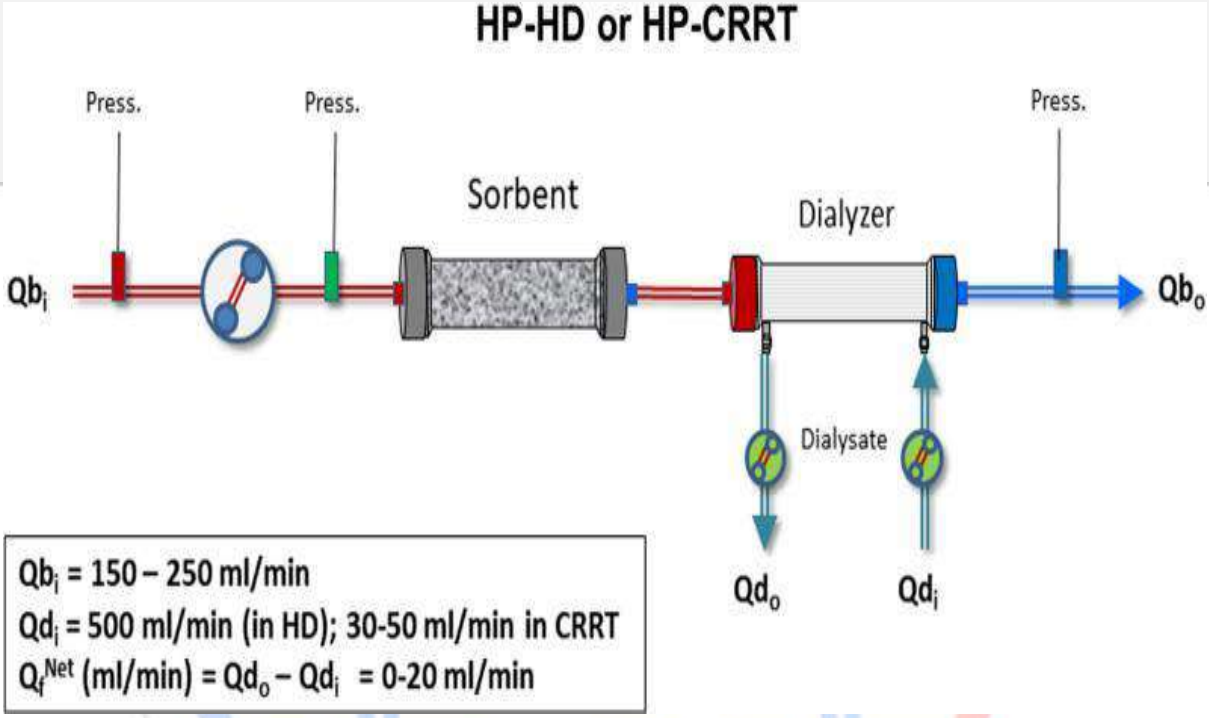
Due to the nature of adsorbent cartridges, the extracorporeal circuit may undergo changes leading to various techniques.

5.1.Hemoperfusion (direct adsorption): Blood is pumped through an adsorbent unit (cartridge) and comes into direct contact with the adsorbent particles. The blood flow rate may vary depending on the size of the cartridge (100-250 milliliters per minute). The extracorporeal circuit is anticoagulated with heparin or citrate(16).

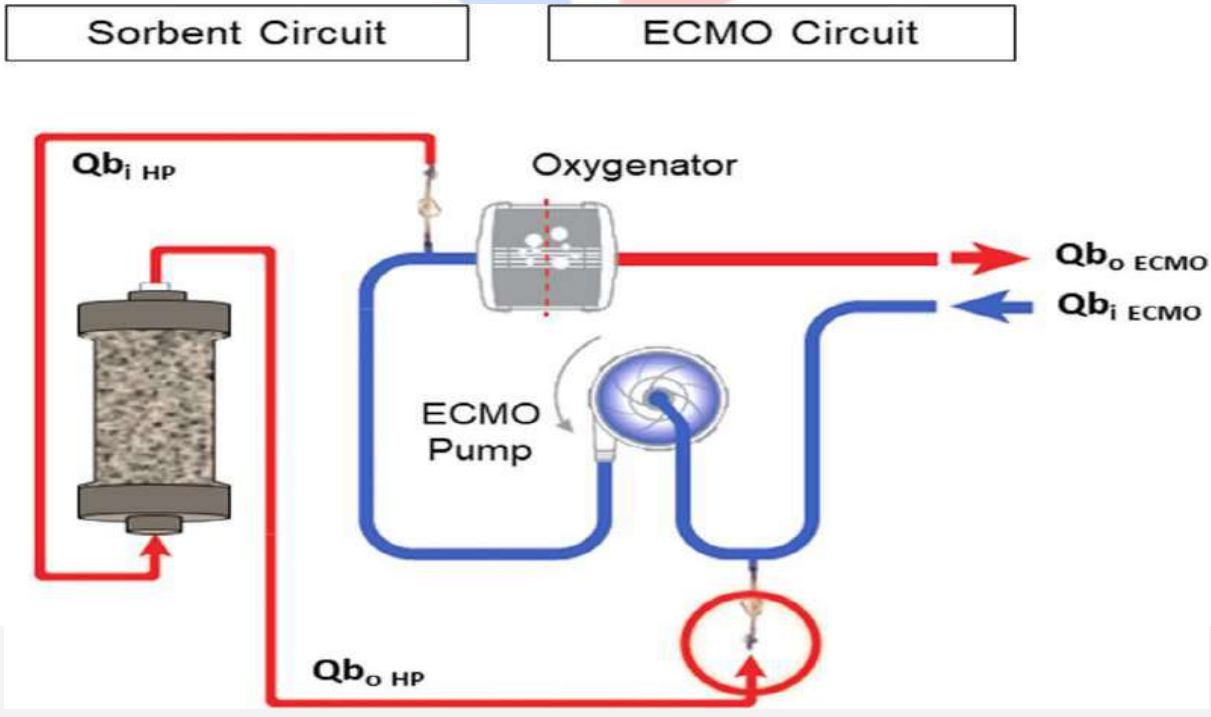


$Qb_i = 100 - 250$ ml/min
Q_f^{Net} (ml/min) = 0 ml/min

5.2.Hemoperfusion combined with dialysis/CRRT: The adsorbent is used in combination with hemodialysis (HP-HD) or with CRRT (HP-CRRT). The adsorbent can be placed before or after dialysis(17).



5.3.Hemoperfusion in combination with ECMO: In patients undergoing veno-venous or veno-arterial oxygenation (VV-ECMO or VA-ECMO), hemoperfusion may be connected to the ECMO circuit. However, adsorbent gradients and pressures must be adjusted to achieve sufficient flows while avoiding disruptions to the main circuit. Similar circuits can be created during post-cardiac pulmonary bypass(18,19).



All of these approaches have been used successfully without any major adverse events. However, several aspects still require technical and clinical studies. Firstly, it is necessary to define the kinetics and isotherms of salts for specific salts and various devices. Secondly, further work is needed to define the optimal treatment duration in relation to blood volume, cartridge saturation, and risk of clotting. Thirdly, in the clinical setting, we need to examine patients, identify criteria for starting and stopping hemoperfusion, define the optimal "absorption dose" for a specific patient, and finally identify molecular markers and clinical parameters to determine effectiveness (20_22).

6. When should hemoperfusion be considered?

6.1.Poisoning

There are indications regarding the effective use of hemoperfusion in various types of poisoning. For example, this technique has been used effectively in the treatment of drug poisoning (e.g., valproate, carbamazepine, digitalis toxins, etc.), toxic chemical substances (such as paraquat or organophosphates), or poisonous natural products (e.g., mushroom toxins). In the past decade, hemoperfusion devices primarily used for such treatment have been commercial cartridges like Cytosorb® or the HA series by Jafron Biomedical, with extraction rates ranging from 20 to 90 percent(23_25). Considering the mentioned points, it appears that the use of this method in cardiac patients who require drug removal from the blood for any reason and lowering the blood levels of medications can be effective.

6.2.Liver Disease

There is information or research regarding the use of hemoperfusion to control severe liver failure (both acute and acute-on-chronic), and in cases where the blood bilirubin level reaches a critical stage and poses a threat to the body, it has been able to reduce the level of this toxic substance in the blood. Additionally, by removing inflammatory substances and other damaging agents from the liver, it has led to improved liver function and reduced liver enzymes (26). Considering this fact, the consideration of this method can be beneficial for candidates for heart surgery who experience liver dysfunction around the time of surgery.

6.3. Kidney Disease

In some cases, various toxins associated with end-stage kidney failure are not adequately removed during dialysis, which justifies the combined use of resins in selected patients for the removal of these substances, as well as issues such as removing beta-2 microglobulin, parathyroid hormone, or controlling uremic syndrome. In situations where there is a risk of kidney damage due to an increase in inflammatory factors, this technique can also be accompanied by improved kidney function(27). Therefore, the use of hemoperfusion in patients with kidney failure or individuals at risk of kidney injury during or after heart surgery can be promising.

6.4. Sepsis

Direct hemoperfusion using polymyxin-B has been associated with improvement in hemodynamic conditions and mortality in patients with septic shock. Hemoperfusion with CytoSorb cartridges represents an anti-inflammatory strategy in cases of severe sepsis. On the other hand, hemoperfusion with JAFRON HA cartridge series has also been used in sepsis, reducing levels of TNF and IL-1 and proving effective in controlling sepsis and associated acute lung or kidney injury, but has shown no impact on mortality (28-30).

Given this information, controlling the overall condition of patients with infective endocarditis or sepsis during and after cardiac surgery can be considered among the beneficial applications of hemoperfusion.

6.5.Cardiac Surgery

The reasons for performing hemoperfusion in patients undergoing cardiac surgery are as follows (31).

6.5.1. Modulation of inflammatory and immunological indices:

1. IL-6, IL-8, IL-10, TNF-α

2. Plasma-free hemoglobin

3.Circulating fragments of the endothelial glycocalyx

4. CRP, PCT, WBC levels

6.5.2. Removal or reduction of blood levels of medications

Removal or reduction of blood levels of anticoagulants (Rivaroxaban, Apixaban, Ticagrelor, Clopidogrel)

Results from some studies have shown that the use of hemoperfusion leads to a decrease in plasma levels of anticoagulant drugs (Rivaroxaban, Apixaban, Ticagrelor, Clopidogrel) in patients undergoing cardiac surgery(32).

7. Timing of hemoperfusion in cardiac surgery patients (33):

1. Before and during surgery,

2. During surgery only,

3.During and after surgery,

4. Continuous use from before surgery to after surgery.

8. Indications for the use of hemoperfusion in cardiac surgery:

1.Endocarditis (34).

2.Emergency surgery in patients on anticoagulant drugs such as Ticagrelor, Rivaroxaban, or Clopidogrel (35,36).

3. Infection or septic shock after cardiac surgery (37,42).

4. Complex surgeries with longer bypass times exceeding 90 minutes and especially 120 minutes, such as aortic arch surgery, double valve surgery, concurrent coronary and valve surgery(38).

5. Coronary artery surgery in patients with familial hypercholesterolemia (39).

6. Cardiac surgery in patients with liver disorders (41).

7. Cardiac surgery in patients with kidney disorders (33).

8. Heart transplantation (10).

9) Vasoplegia and post-operative cardiac shock in children with congenital heart surgery (10).

9. Positive outcomes and benefits of implementing hemoperfusion in cardiac surgery patients (31, 10):

1. Hemodynamic stability
2. Reduced mechanical ventilation time
3. Decreased length of ICU stay
4. Reduced risk of kidney failure
5. Reduced risk of liver dysfunction
6. Decreased mortality

10. Risks of using hemoperfusion in cardiac surgery patients (31).

Most studies have shown that the use of hemoperfusion, even in patients at high risk of bleeding and undergoing emergency cardiac surgery, is safe. However, conducting further studies on the safety of this new adsorptive blood purification device can be beneficial.

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