Cytokine Adsorption in Lung Transplantation and Heart Transplantation

Subjects: Surgery

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Cytokine adsorption can resolve different complications characteristic of transplantation medicine, such as cytokine storm activation and blood ABO and immune incompatibilities. Cytokine adsorption is also performed for the treatment of various life-threatening conditions, such as endotoxic septic shock, acute respiratory distress syndrome, and cardiogenic shock, all potentially leading to adverse clinical outcomes during transplantation. After surgery, dysmetabolism and stress response limit successful graft survival and can lead to primary or secondary graft dysfunction. In this clinical context, and given that a major problem in transplant medicine is that the demand for organs far exceeds the supply, a technological innovation such as a hemoadsorption system could greatly contribute to increasing the number of usable organ donors.

Keywords: cytokine adsorption ; lung transplantation ; heart transplantation ; experimental studies ; clinical studies

1. Introduction

Cytokine adsorption (CA) is the basis of a promising therapy to resolve different complications characteristic of transplantation medicine, such as the activation of a cytokine storm, rapid immunological responses to blood incompatibilities, and immunological obstacles such as ABO blood group incompatibilities and pre-existing donor-specific antibodies. CA is performed for the treatment of various life-threatening conditions, like sepsis, acute respiratory distress syndrome (ARDS), and cardiogenic shock, all potentially worsening the transplantation clinical outcomes. After transplantation surgery, frequent dysmetabolism and stress response limit successful graft survival and can lead to primary (PGD) or secondary graft dysfunction. In this clinical context, and given that a major problem in transplant medicine is that the demand for organs far exceeds the supply, a technological innovation such as a CA system could greatly contribute to increasing the number of usable organ donors.

2. Therapeutic Applications in Lung Transplantation

2.1. Experimental Studies

In 2008, Kellum determined the practicability of cytokine removal with a hemoadsorption (HA) device in a study conducted in brain-dead subjects considered unfit for organ donation [1]. The authors established that the feasibility of CA therapy did not differ from 1 h to 4 h, and the elimination fluctuated across the CA device from 4% to 30%. The study found that CA could reduce plasma concentrations of IL-6 and TNF-α, but not IL-10, in the first hour of therapy, and the effect was unsustained over time. In 2017, Iskender reported a randomized, controlled animal study in which pigs were subjected to prolonged EVLP with and without perfusate CA, [2]; see also **Table 1**. The experimental animals underwent evaluation of the pulmonary function and the measurement of the cytokine levels in the bronchoalveolar lavage fluid. The control group was subjected to EVLP without cytokine filtration, while the experimental group was subjected to EVLP with CA. The results of the study showed that the experimental group had significantly better lung function versus the control group, with lower levels of cytokines in the bronchoalveolar lavage fluid. This suggests that perfusate CA during prolonged EVLP is safe and effective at improving pulmonary function and reducing inflammation. In another follow-up study, in a large animal model, Iskender observed with 6 h of CA a sharp decrease of perfusate cytokine concentrations that correlated with better EVLP physiology and biochemistry [3][4][5]. This protocol improved both transplanted lung dynamic compliance and oxygenation function in the treated group after 4 h of reperfusion and decreased local inflammatory response. These findings suggest that the EVLP protocol was improved after implementing a CA in the circuit. This study provides evidence that perfusate CA during EVLP can improve short-term graft function after LuTx and may be an effective strategy to recondition the allograft after ischemia reperfusion-induced injury (IRI) and may improve patient outcomes following LuTx.

In a large animal model, Frick uses a porcine-LuTx model and finds that continuous CA results in a significant improvement in lung graft function, as assessed by the degree of allograft injury, post-transplant survival, and blood

chemistries [6]. The study also reports a significant reduction in pro-inflammatory cytokine and chemokine levels in the systemic circulation of the animals. These results suggest that CA may attenuate IRI in the allograft after LuTx. Furthermore, the findings suggest that the inflammatory cytokines and chemokines play an important role in the pathogenesis of IRI. In a large animal model, Niroomand investigates how CA affects lung function both during EVLP and post-transplant. The study hypothesis states that the inflammatory and immunomodulatory differences in lungs treated with or without CA contribute by modulating the molecular mechanisms and signaling pathways that impact lung function [7]. The results show that, after CA treatment, both inflammatory and immune processes and coagulation pathways are affected significantly. Moreover, Niroomand also reviews the EVLP technology that was developed as a therapeutic platform to improve donor lung quality prior to lung transplantation (LuTx) [8]. The application of EVLP as a therapeutic intervention has led to significant improvements in donor lung quality and has allowed for the successful transplantation of organs previously considered too damaged or too marginal to be used. EVLP reduces inflammation, ameliorates lung function, and avoids post-transplant complication risk. Additionally, EVLP has been used to evaluate the efficacy of various cell therapies and cell product therapies, as well as to test the effectiveness of CA. In a large animal model, Ghaidan shows that the two-step treatment with CA is effective in improving lung function in ARDS, as indicated by a significant increase in the PaO_2/FiO_2 ratio [9]. Furthermore, this treatment was associated with a reduction in the incidence of PGD, a common severe complication associated with LuTx that affects up to 50% of recipients and increases the risk of chronic rejection and mortality. Molecular outcomes showed that the two-step treatment resulted in decreased systemic inflammation and oxidative stress in the lungs and other organs. The treatment was accompanied by improved tissue oxygenation and reduced cellular damage. In addition, the two-step treatment was associated with a decrease in the expression of inflammatory genes and a decrease in the number of inflammatory cells. Taken together, these results suggest that the two-step treatment with the CA is effective in improving lung function and reducing the incidence of PGD with ARDS after LuTx. In the same context, Ehrsam reports the applicability of CA during and after reperfusion as a viable approach to reduce post-transplant inflammation following LuTx [10]. The study was conducted on pig left LuTx previously exposed to 24 h of cold ischemic storage. The control group did not receive extracorporeal CA, whereas the treatment group received adsorption for 6 h post- and 30 min pre-reperfusion. A significant reduction in plasma pro-inflammatory IL-2 was noticed during CA, along with trends of lower pro-inflammatory TNFα, IL-1α, and GM-CSF and significantly fewer systemic neutrophils. The study found that CA during and after reperfusion is effective in reducing post-transplant inflammation following LuTx. Compared to the control group, the treatment group exhibited significant improvement in CO_2 elimination, in lessening of acidosis, and in the PaO_2/FiO_2 ratio. The research concludes that CA during and after reperfusion is a feasible technique to lessen post-transplant inflammation following LuTx.

2.2. Clinical Studies

In human patients, Peyneau performed a small-sample-size study with a single-arm pilot design that was limited by the absence of a control group, making it difficult to draw conclusions about the efficacy of CA therapy compared to standard treatment [11]. The research also had a short follow-up period, and the long-term effects of CA therapy remain unchartered. Despite these limitations, the results of this research provide important preliminary evidence regarding the potential of CA therapy to reduce inflammation and improve clinical outcomes in LuTx. Moreover, Boffini describes the value of EVLP to remove cytokines from lungs prior to transplantation [12]. Among the 54 EVLPs performed, 21 were handled with and 33 without CA therapy. At the end of the process, the researchers observed a significant decrease in IL-10 and GCSF in the CA-treated group. After the EVLP performed with CA, they recorded a significant decrease in the amount of IL-6 and GCSF, but also IL-10 and MCP1, as determined from the transplanted patients. This transplanted group also had lower in-hospital mortality ($p = 0.03$) and a lower 1-year death rate ($p = 0.01$). The results of this human study suggest the value of CA and EVLP to effectively decrease the concentration of inflammatory mediators, indicating both the safety and effectiveness of this procedure. Even if more research is needed to fully understand the clinical impact of cytokine reduction during EVLP, this research found that EVLP with cytokine removal was safe and feasible and that it could be used to improve the quality of lungs for transplantation. Lindstedt discusses the applicability of CA during LuTx to reduce or remove elevated levels of neutrophil extracellular traps (NETs) [13]. NETs are composed of a network of neutrophil DNA associated with microorganisms and form an important antimicrobial mechanism of neutrophilic granulocytes. NETs modulate both inflammatory and autoimmune diseases and are involved in organ transplantation. NETs can induce tissue damage, activate the complement system, promote thrombosis, and trigger adaptive immune responses. In LuTx, NETs have been associated with PGD. NETs can impair alveolar gas exchange, increase vascular permeability, and induce inflammation and fibrosis in the transplanted lung. The study found that using a CA adsorber during LuTx may diminish the systemic inflammatory state by filtering out NETs and consequently reinforcing graft acceptance. The CA-treated group of patients had fewer circulating nucleosomes and at 30 and 90 days post-LuTx remained clear of PGD and indications of acute rejection in comparison to the patient group without CA. The research's findings suggest that CA could be a method for clearing NETs. Lindstedt describes a Swedish national interventional

randomized controlled study (NCT05242289) involving 116 patients [14]. The research investigates the potential benefits of a cytokine filtration administered for 12 h in the first 24 h following LuTx that may improve graft outcomes. The clinical trial objectives were to demonstrate the advantage of CA in improving LuTx success, as a consequence of its effects on oxygenation index, plasma levels of inflammatory markers, PGD incidence and severity, lung function, kidney function, survival, and quality of life compared with standard treatment without cytokine filtration. Previous research [9] found that cytokine filtration can modulate pulmonary metabolism and edema formation during EVLP. The process involved exposure of the graft to a 24 h ischemic time at 4 °C, followed by an EVLP of 12 h, where the perfusate of the treated group was continuously run through CA. This procedure resulted in significant improvement in airway pressure and dynamic compliance, with reduced glucose utilization and lactate accumulation in the CA group. This suggests that CA could potentially improve outcomes in LuTx.

In conclusion, and also listed in **Table 1** (see column “Effects of CA therapy”), much experimental and clinical evidence at different interventional steps (pre-, during, post-) of lung transplantation support the notion that CA therapy indeed improves the functional graft outcomes (↑ oxygenation, ↑ compliance, ↓ pharmacotherapy, ↑ CO_2 removal, ↓ neutrophil extracellular traps, ↓ coagulation and complement pathways, ↓ humoral immune response pathways) and tends to lessen early pathological complications (↓ in-hospital mortality, ↓ PGD, ↓ AR).

Table 1. Effect of CA therapy on different models involving large, solid organs and transplantations.

Organ Targeted	Model and Treatment	Effects of CA Therapy	References
Lung	Porcine EVLP + CA, then LuTx.	↓ cytokines, ↑ oxygenation, ↑ compliance, ↓ pharmacotherapy.	[3][4][5]
	Porcine EVLP + CA, then LuTx.	↓ coagulation and complement pathways, ↓ humoral immune response pathways.	[7]
	Porcine EVLP + CA.	↓ pulmonary oedema, ↓ electrolytes imbalance.	[2]
	Porcine EVLP + CA, then LuTx + CA.	↓ cytokines, ↓ immune cells, ↓ PGD.	[9]
	Porcine post LuTx and CA.	↓ cytokines, ↑ CO_2 removal.	[10]
	Human LuTx and CA.	↓ neutrophil and monocyte activation markers.	[11]
	Human EVLP + CA, then LuTx.	↓ cytokines, ↓ in-hospital mortality.	[12]
	Human intraoperative LuTx and CA.	↓ neutrophil extracellular traps, ↓ AR and PGD.	[13]
Heart	Human CPB + CA.	↓ hemodynamic and metabolic and organ instability.	[15][16]
	Human CPB + CA.	↓ plasma-free hemoglobin and complement C3a and C5a.	[17]
	Human CPB + CA.	↑ IL-10 anti-inflammatory long-lasting effects.	[18]
	Human CPB for infective endocarditis + CA.	↓ cytokines but without resolution of hemodynamic instability and in-hospital mortality.	[19]
	Human CBP for acute endocarditis + CA.	↓ in vasopressor use but not significant.	[20]
	Human intraoperative HTx and CA.	↓ CRRT frequency.	[21]
	Human donor heart resuscitation for HTx and CA.	Donor heart implantation after 7 h cold ischemia.	[22]
	Human HTx and CPB and CA.	Control of heparin-induced thrombocytopenia in HTx.	[23]
	Human VA-ECMO for giant-cell myocarditis and CA.	↓ hemodynamic and metabolic and organ instability.	[24]
	Human VA-ECMO for cardiogenic shock and CA.	↓ lactate, ↑ urine output, ↓ in-hospital mortality.	[25]
	Porcine DCD heart ex vivo perfusion and CA.	↓ cytokines, ↓ markers of endothelial injury.	[26]

Organ Targeted	Model and Treatment	Effects of CA Therapy	References
Kidney	Porcine kidney ex vivo perfusion and CA, then KTx.	↑ IL-6 and IL-8 at reperfusion, ↑ mean renal blood flow, ↓ prostaglandin E2 and prostacyclin and thromboxane.	[27]
	Human FSGS + CA.	↓ soluble urokinase plasminogen activator receptor.	[28]
	Human FSGS + lipoprotein apheresis.	↑ complete or partial remission of proteinuria, ↑ response rates to steroid or immunosuppressive therapy.	[29]
	Human kidney ex vivo perfusion and CA, then KTx.	↑ oxidative phosphorylation (OXPHOS), ↓ inflammatory pathway genes.	[30]
	Human FSGS + CA.	↓ proteinuria.	[31]
Liver	Human ALF + CA.	↓ TNFα and CRP and procalcitonin and α1-fetoprotein.	[32]
	Human ACLF + CA.	↓ TNFα, ↑ IL-6.	[33]
	Human LF + CA.	↓ TNFα, ↓ IL-6, ↓ IL-1, ↓ IL-10.	[34]
	Human LF + CA.	↓ bilirubin, ↓ ammonia, ↓ LDH, ↓ platelets.	[35]
	Human LF + CA.	↓ bilirubin.	[36]
	Human hyperbilirubinemia + CA.	↓ bilirubin.	[37]
	Human ALF + CA.	↓ bilirubin.	[38]
	Human septic shock after LiTx + CA.	↓ procalcitonin, ↓ endoxins, ↓ IL-6, ↓ IL-10.	[39]
	Human hyperbilirubinemia + CA.	↓ bilirubin.	[40]
	Human ACLF + CA.	↓ bilirubin.	[41]
	Human ACLF + CA.	↓ bilirubin.	[42]
	Human hyperbilirubinemia + CA.	No change in 30-day hospital mortality.	[43]
	Human pediatric hyperbilirubinemia + CA.	↓ bilirubin.	[44]
	Porcine DCD liver ex vivo perfusion and CA.	↓ cytokines.	[45]

3. Therapeutic Applications in Heart Transplantation

3.1. Experimental Studies

In a large animal model, Saemann used a normothermic donation after circulatory death (DCD) heart model, in which the DCD hearts were perfused with the donor's blood collected before and after CA [26]. The study found that CA during blood perfusion (BP) of DCD hearts significantly reduced coronary microvascular dysfunction, oxidative stress, and IRI of the coronary microvascular endothelium compared to hearts perfused without CA. The author also observed that CA during BP was associated with a reduction in the expression of the proinflammatory genes TNF-α, IL-1β, IL-6, and IL-8 and a significant overexpression of the anti-inflammatory genes IL-10 and TGF-β. The results suggest that CA during BP of DCD hearts may be beneficial in reducing coronary microvascular dysfunction, oxidative stress, and IRI of the coronary microvascular endothelium.

3.2. Clinical Studies

Early application of CA in the management of heart diseases was investigated by Trager [15]; see also **Table 1**. The researcher used a CA device in order to control hyperinflammatory systemic reactions in patients undergoing cardiothoracic surgery with cardiopulmonary bypass (CPB). This retrospective case series involved 16 cardiac surgery patients who developed severe inflammatory response syndrome (SIRS) and subsequent AKI following prolonged CPB. The treatment reduced cytokine concentrations, and this reduction was associated with a rectification of disturbed hemodynamic, metabolic, and heart function variables. The safety and tolerance of the treatment was high, without showing any CA-related adverse complications. Moreover, Trager also used CA during CPB as a way to reduce the pro-inflammatory response and improve postoperative organ function [16]. The reduction in the severity of postoperative organ dysfunction was explored in a clinical trial investigating the value of CA during surgery. The usefulness of CA for patients

during CPB surgery due to infective endocarditis was also investigated, showing a decline of pro-inflammatory cytokines. Furthermore, the assistance of CA in DCD hearts during BP has been suggested to reduce the pro-inflammatory response, vascular damage, and IRI of the coronary microvascular endothelium, which may ultimately improve graft survival. In 2018, Nemeth proposed a CA treatment in the course of HTx surgery that reduced the need for (1) vasopressor requirement, (2) continuous renal replacement therapy (CRRT), and (3) lengthy mechanical ventilation and ICU stay [21]. This suggests that CA may be a useful adjunct to improve outcomes in patients undergoing orthotopic HTx. Dogan describes the successful use of CA in combination with extracorporeal life support therapy in a patient with giant-cell myocarditis [24]. Large and sustained improvements were recorded in both hemodynamic and inflammatory parameters with the resolution of metabolic acidosis to normal values and improved liver function. This case report highlights the potential of CA to improve organ function and inflammation following the extracorporeal support of a patient with giant-cell myocarditis and may represent an additional therapeutic option for patients with a severe form of this disease. In the context of prolonged cardiovascular bypass, Gleason reports the results on the safety and potentiality of CA therapy in a prospective, multicenter REFRESH (REduction in FREe Hemoglobin) clinical trial that assesses the reduction of plasma-free hemoglobin and activated complements during prolonged CPB in patients undergoing elective, nonemergency complex cardiac surgery [17]. Enrolled patients were allocated to either obtain CA therapy or standard medical therapy (SMT). The pilot study found that CA therapy during complex cardiac surgery was safe and achievable. This CA pilot study recorded significant decreases in both plasma-free hemoglobin and C3a and C5a levels. Bernardi also investigated the effect of CA therapy during CPB surgery and hypothesized that the CA of cytokines may suppress inflammatory responses and improve patients' perioperative course [18]. Of the 37 patients undergoing elective CPB surgery, a total of 19 were randomly assigned to CA therapy and 18 to the control group. The researchers found that there were no differences in cytokine concentrations of IL-1β, IL-6, IL-18, TNF-α, and IL-10 as primary outcomes immediately following the CA treatment. Nonetheless, they observed a long-lasting anti-inflammatory effect of IL-10. In a case report, Kaliyev describes the clinical data of an HTx performed after 7 h in cold Custodiol solution and paracorporeal donor heart resuscitation [22]. The researchers used controlled warm reperfusion, medical treatment, and CA to resuscitate the donor organ. The report also mentions that "suboptimal" organs are transplanted more often, and this approach could potentially increase the viability of organs for transplantation and improve patient outcomes. Diab conducted a trial in two phases [19]. In the run-in phase, all patients underwent conventional cardiac surgery for infective endocarditis, and intraoperative CA was performed in a subset of patients. Patients in the CA group had significantly lower plasma levels of inflammatory mediators than those in the control group. In the randomized phase, patients were assigned to the CA or control group and were assessed for changes in Sequential Organ Failure Assessment (SOFA) score from postoperative day 0 to day 3. Secondary outcomes included postoperative infection, extent of stay in the ICU, and mortality. The results showed that patients in the CA group had significantly lower SOFA scores at postoperative day 3 than those in the control group, but no significant differences in the matter of postoperative infection, extent of stay in the intensive care unit, or mortality were found. As measured by changes in the SOFA score, these findings suggest that intraoperative CA may be beneficial for patients experiencing cardiac surgery for infective endocarditis. In a single-center pilot study, Poli studied CA therapy in patients undergoing elective cardiac surgery [46]. The patients were randomly distributed in two groups of 15 and treated either with or without CA therapy. The researchers concluded that CA therapy did not improve clinical outcome and did not ameliorate the levels of pro- or anti-inflammatory cytokines. In 2022, Holmen reported that CA during cardiac surgery may reduce the need for vasopressors after surgery for endocarditis, but despite a decrease both in the need for red blood cell transfusion and in the dosage of norepinephrine in the treated group, at all time points, those differences did not reach statistical significance [20]. Overall, these results indicate that CA during cardiac surgery may reduce the need for vasopressors after surgery for endocarditis. In 2023, Lovric presented several findings related to the applicability of CA in patients with signs of cardiogenic shock and treated with veno-arterial extracorporeal membrane oxygenation (VA-ECMO) [25]. From the 16 patients included in the study, and stratified based on CA application in the first 24 h of treatment, the patients treated with CA required significantly lower doses of vasopressors at the start and before weaning from VA-ECMO, with significantly greater urine output ahead of weaning and lower lactate levels during VA-ECMO. The mortality rate was lower among the group that received CA therapy (22.2% vs. 57.1%). This study suggests that CA can lead to improved urinary output and a tendency for better survival among VA ECMO patients. In conclusion, and also listed in **Table 1** (see column "Effects of CA therapy"), many clinical and some experimental results at different interventional steps (pre-, during, post-) of heart transplantation support the notion that CA therapy may improve, in some cases, the functional graft outcome (↓ hemodynamic and metabolic and organ instability) and may tend to lessen early pathological complications (↓ in-hospital mortality, ↓ markers of endothelial injury).

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