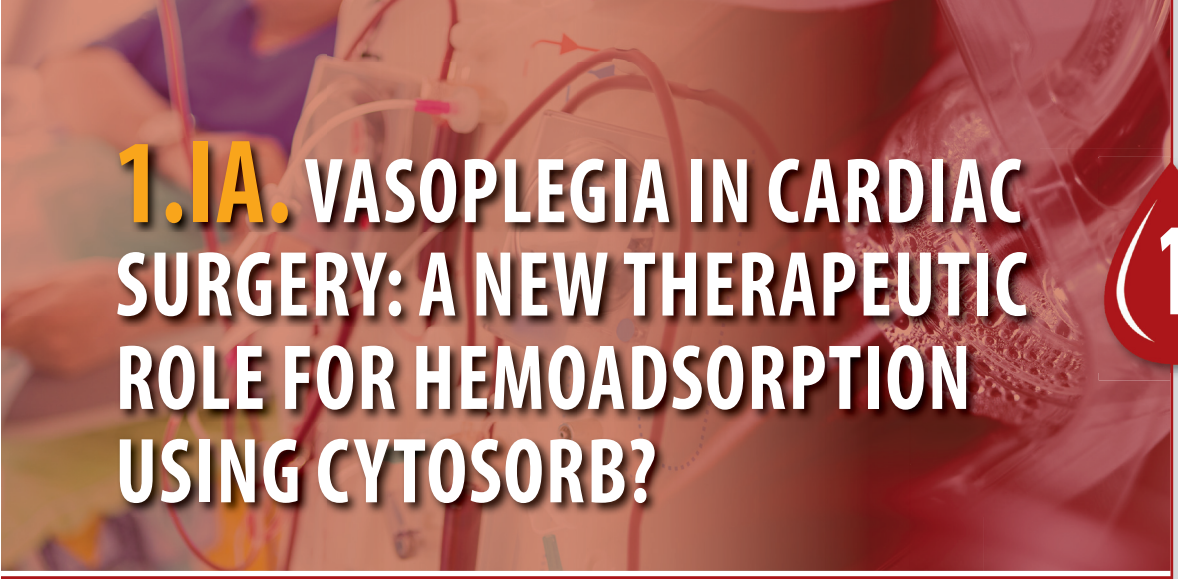

1.IA. VASOPLEGIA IN CARDIAC SURGERY: A NEW THERAPEUTIC ROLE FOR HEMOADSORPTION USING CYTOSORB?

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CARDIAC SURGERY, SURGICAL INFLAMMATORY RESPONSE, AND VASOPLEGIA

Open-heart surgery remains the cornerstone of treating structural and functional heart diseases; it provides increased survival, improvements in symptoms of acquired cardiac disease, and better quality of life for a large volume of patients. However, cardiac surgery remains associated with a substantial risk of major adverse events including death, postoperative organ failure, and persistent postoperative disability.[1,2]

Cardiac surgical operations, especially those involving long cardiopulmonary bypass (CPB) times, initiate a whole body inflammatory reaction termed systemic inflammatory response syndrome (SIRS). This condition is believed to be at least partially due to blood contact with a foreign surface and resultant activation of blood leukocytes and plasma cascades of coagulation and complement.[3] Hemodynamic alterations – including reduction in systemic vascular resistance, lung mechanics, and gas exchange – as well as hematological alterations together with several specific biological markers contribute to form this systemic inflammatory reaction after surgery and bypass. The magnitude of SIRS varies among cardiac patients, but the persistence of severe inflammation is considered harmful and appears to significantly influence the postoperative patient journey. Activation of a large number of potentially important mediators has been identified; among these, pro-inflammatory cytokines have been proposed to be responsible for many deleterious effects of CPB.[4]

Vasoplegia is characterized by severe hypotension due to lack of vasomotor tone refractory to catecholamine therapy. It occurs frequently after routine cardiac surgery (up to 27%)[5,6] and is associated with severe postoperative complications and increased mortality. Vasoplegia is even more prevalent after advanced surgical treatment of heart failure. The incidence of vasoplegia after heart transplantation (HTx) ranged between 8.8% and 54%, depending on the definition used.[7] It was reported to affect more than 40% of patients after pulsatile left ventricular assist device (pLVAD) implantation[8] and about one third of patients after insertion of the newer generation of continuous flow left ventricular assist device (cfLVAD).[9]

Published definitions for vasoplegia post-cardiac surgery vary markedly and include different hemodynamic parameters, vasoactive drugs, patient groups, and variable observation time periods. Each measure may lead to variations in reported incidence[1,3] and associations with relevant clinical outcomes.[1,3] For instance, careful analysis of these definitions reveals that their application to the cfLVAD population is limited, especially if low central venous pressure (CVP) is included in the definition. To overcome this issue, we have proposed a new and unified definition for this specific patient population, considering high vasopressor requirements to maintain normal systemic vascular resistance (SVR) during the first 48 postoperative hours.[9]

PLAUSIBLE EFFECT OR MECHANISMS OF CARDIAC SURGICAL INFLAMMATION AND VASOPLEGIA

Cytokines

Cytokines play a critical role as signaling molecules that set off, intensify, and terminate local and systemic inflammatory responses. Among these proteins, tumor necrosis factor α (TNFα) and interleukin (IL)-1β are particularly important because they can be stimulated by a broad spectrum of stimuli, and they can act on a large number of effectors, making them ideal candidates for the negative inotropic state, systemic vasodilation, and pulmonary dysfunction following systemic inflammation.[10]

Leukocyte activation, oxidative stress, and endothelial dysfunction

Beyond classical proinflammatory cytokines, leukocytes play a major role in organ dysfunction and have been strongly implicated in SIRS and CPB-induced postoperative organ dysfunction.[3] Neutrophils are equipped with multiple effector mechanisms that include proteolytic enzymes such as elastase, permeability-increasing substances such as heparin binding protein, and release of various reactive oxygen and nitrogen species upon their activation and during their respiratory burst. In addition, they release myeloperoxidase, a potent oxidant-generating enzyme. These factors may impact tissue matrices and endothelial glycocalyx and may cause tissue damage by limiting microvascular perfusion via tissue edema and direct endothelial dysfunction.[11] Indeed, various components of the protective endothelial glycocalyx are released to the circulation during SIRS in various forms of cardiac surgery, suggesting destruction and remodeling of the endothelial glycocalyx.[11] The role of such a leukocyte-dependent mechanism in perioperative complications of cfLVAD insertion is demonstrated by the fact that white blood cells (WBCs) appear to feature in various prediction models of right ventricular dysfunction and perioperative morbidity.

Metabolic alterations

Inflammation and metabolism are closely linked, and it is conceivable that cytokines and associated inflammatory mediators elicit organ dysfunction predominantly through metabolic alterations. Global and untargeted metabolic profiling has recently provided a convincing picture of the extent and details of metabolic derangement associated with systemic inflammatory states.

For instance, Mickiewicz and colleagues identified characteristic metabonomic profiles among critically ill septic shock patients and their controls.[12] They found 31 significant variables that were responsible for the separation between septic shock

patients and intensive care unit (ICU) controls, with 14 metabolites increased and 17 metabolites reduced. A representative pathway network indicated changes in small molecule and lipid metabolism and molecular transport. Such a metabolic pattern was consistent with molecular signatures of organ dysfunction and energy requirements of the human body during septic shock. Interestingly, combining a metabolic profiling dataset with inflammatory cytokine data enhanced prediction of adverse clinical events.

Regarding cardiac surgery, investigators at Imperial College recently identified a group of metabolites whose concentrations and trajectory appeared to be associated with clinical outcomes following cardiac surgery in children.[13] The strength of pro-inflammatory response, particularly IL-8 and IL-6 concentrations, also appeared to correlate with the ICU stay duration. Such observations strongly suggest a link between cytokines, metabolism, and clinical outcomes.

Despite major past efforts and large clinical trials, clinical attempts to interfere with the SIRS response, for instance, using high dose corticosteroids, have not provided major therapeutic benefits and remain controversial.[14] As an alternative therapeutic potential, the use of hemoadsorption with cytokine absorption technology is gaining momentum.

MULTIPLE CYTOKINE ABSORPTION TECHNOLOGY

Over the past few years, there has been a significant paradigm shift in medical management of the inflammatory response associated with sepsis, critical illness, and multiple organ failure. This shift comprises a trend away from a single cytokine concept toward treatment modalities targeting multiple cytokines. In particular, several experimental and clinical studies have reported that adsorption of cytokines using cytokine-adsorbing columns is beneficial during endotoxemia and sepsis. Among these columns, CytoSorb®, the first-in-class, CE-approved cytokine removal filter manufactured using synthetic porous microbeads, has excellent adsorption rates for multiple inflammatory cytokines such as TNFa, IL-1b, IL-6, and IL8. Many studies have demonstrated that treatment with cytokine-adsorbing columns has beneficial effects on the survival rate and inflammatory responses in sepsis animal models. The National Institute for Health and Care Excellence (NICE) recently issued a favorable MedTech Innovation Briefing about CytoSorb for the treatment of sepsis.

Building on progress with CytoSorb use in sepsis and extracorporeal life support applications, studies addressing the influence of HA in patients undergoing cardiac surgery with CPB have begun to emerge. Some of the initial studies have focused on safety and cytokine removal as biological efficacy evaluation, but there is increasing activity to show clinical benefits in both more routine or higher risk cardiac surgeries.

CYTOSORB THERAPY IN CARDIAC SURGERY

There seems to be contradiction regarding cytokine removal in more routine cardiac surgery, with retrospective and prospective studies reporting either alleviation of inflammation or no significant benefits. In the earliest report, Pichlmaier *et al.*[15] reported that intraoperative application of CytoSorb during CPB had lasting benefits for the postoperative period, with both IL-6 and procalcitonin (PCT) showing decreased postoperative levels. However, a group from Vienna did not find a reduction of the pro-inflammatory response and no changes in the perioperative course. IL-10 was elevated by CytoSorb treatment, a

finding that suggests a longer-lasting anti-inflammatory effect.[16] They also evaluated the microvesicle response and found no changes in microvesicle numbers of phenotypes. By contrast, the retrospective clinical study by Born *et al.* investigated 40 patients who underwent surgery of the ascending aorta and aortic arch; they showed positive effects of hemadsorption on inflammatory mediators after CPB. This effect may relate to the different type of cardiac surgery, which featured a nearly four-hour CPB duration.[15] The prospective study of Garau and colleagues also showed a significant reduction in pro-inflammatory cytokines (IL-8 and TNFα) with hemadsorption. Of note, the differences in cytokine levels and cardiac output between patients treated with and without hemadsorption were minor and of a short duration.[17]

Contrary to the above-mentioned data is a report from a group in Ljubljana who compared CytoSorb to methylprednisolone on the inflammatory response; they provided detailed characterization of the cytokine response and flow cytometry assessment of the cellular inflammatory response. They found that intraoperative use of methylprednisolone during CPB was more effective in ameliorating the systemic inflammatory responses in adults undergoing cardiac surgery. This effect was seen by reductions in proinflammatory molecules and increases in anti-inflammatory mediators, when compared with CytoSorb or standard routine clinical treatment. Hemadsorption increased CD64 expression on monocytes and CD163 expression on granulocytes during surgery. However, short-term clinical outcomes were similar. In particular, there was no significant difference with regard to vasoactive/inotropic drug consumption between groups at any time point.[18]

By contrast, Saller *et al.* reported some clinical benefits; they studied hemadsorption during aortic surgery with hypothermic circulatory arrest. They showed a reduced requirement for norepinephrine (0.102 *vs.* 0.113 µg/kg/minute; P=0.043). Severe disturbances of acid-base balance, maximum lactate concentrations, and the need for tris(hydroxymethyl)aminomethane buffer were less frequent with HA.[19]

The REFRESH I study from the United States Food and Drug Administration (FDA) was a prospective, randomized controlled trial involving high-risk cardiac surgery patients.[20] The results demonstrated device safety with a statistically significant reduction in postoperative inflammatory markers such as IL-6 and PCT, plasma-free hemoglobin, and activated complement. While the study was not powered to evaluate organ dysfunction, *post hoc* analysis showed an odds ratio of 0.260 for the development of acute kidney injury in high-risk patients. Such therapeutic potential is currently being evaluated in the REFRESH II trial in the United States.[20] A pilot study in heart transplantation in Budapest also demonstrated improvement in hemodynamic status with reduced inotropic and vasopressor requirement and a significant reduction in the need for renal replacement therapy.[21] This study has now been extended to a prospective single center randomized controlled trial.

A prospective, multicenter, international registry was established in 2015 with the objective of documenting the use of the CytoSorb device under real-world conditions. This ongoing registry, developed by Jena University in Germany, aims to capture relevant information in the course of the use of the CytoSorb device, including diagnosis, comorbidities, clinical course, treatment with the device, concomitant medication use, clinical laboratory parameters, and the clinical outcome of mortality during treatment, at ICU or at hospital discharge. The primary endpoint of the study is in-hospital mortality compared

with the mortality predicted by the Acute Physiology and Chronic Health Evaluation (APACHE) II and Simplified Acute Physiology Score (SAPS) II scores. Secondary endpoints include Sequential Organ Failure Assessment (SOFA) scores and biomarkers, including C-reactive protein (CRP), platelet count, IL-6, myoglobin, and plasma-free hemoglobin. Its first report showed marked reduction in IL-6 levels in a predominantly sepsis population. The observed mortality (65%) was significantly lower than the predicted risk of death (78%). The registry has a significant but relatively low number of cardiac surgical patient population. The mortality rate for the cardiac surgery patients undergoing intra-operative CytoSorb hemoadsorption appears numerically lower than predicted by their EuroSCOREs.[22]

Taken together, the early evaluation of CytoSorb for routine cardiac surgery appears feasible, with an excellent safety profile with respect to device-related adverse events and the clinical course. There is indication that hemoadsorption confers biological benefit on some measures of inflammation, but clinical benefits in routine cardiac surgery is minimal. Some benefits appear when CPD is of a very long duration and/or with complex surgery; these aspects are being evaluated in some ongoing larger clinical trials. The reduction of vasoconstrictor requirement in some of the studies is promising, but a clinically significant effect on those patients who exhibit severe intraoperative vasoplegia needs to be established.

The inflammatory response in end-stage heart failure and vasoplegia during LVAD implantation.

We have investigated the inflammatory status of rapidly deteriorating heart failure patients requiring LVAD implantation and compared them to a more stable population awaiting heart transplantation[23] (Figure 1.1.). We have observed significantly higher IL-6 levels in the LVAD patients than patients on the transplant waiting list. This was accompanied by increases in various early response pro-inflammatory cytokines as well as their anti-inflammatory counterparts. A striking feature of the inflammatory status was the wide variation and individual differences (on a logarithmic scale) in patients' pro-inflammatory cytokines, anti-inflammatory cytokines, their cytokine balance, and variance in the ability of patients' plasma to trigger inflammatory signaling in resting target vascular cells (a bioassay of net inflammatory potential).[24] For instance, the level of pro-inflammatory IL-6 varied between 6.3 pg/mL and 129.8 pg/mL and TNFα ranged from 4.1 pg/mL to 32.9 pg/mL. There was nearly eightyfold variability in the anti-inflammatory IL-10 levels and 20-fold variability in the molar ratio of TNF and soluble TNF receptors, indicative of a wide spectrum in cytokine balance.

These data clearly demonstrate that the markedly variable inflammatory status of individual patients prior to surgery provides a strong foundation for the possibility of differential and patient-specific inflammatory responses to surgery, LVAD implantation, and cardiopulmonary bypass. Literature data strongly support such a possibility.

Regarding the preoperative IL-6 levels, Caruso *et al.*[25] identified a plasma concentration cut-off of 8.3 pg/mL and showed that patients with higher levels were more susceptible to a poor early outcome and longer ICU stay and hospitalization. As a mechanistic explanation, they showed that the IL-6 response remained higher throughout the perioperative period in patients with higher preoperative IL-6, and those patients exhibited more pronounced neopterin (a marker of monocyte activation) and IL-8 release. These phenomena link IL-6 to additional cytokine and leuko-

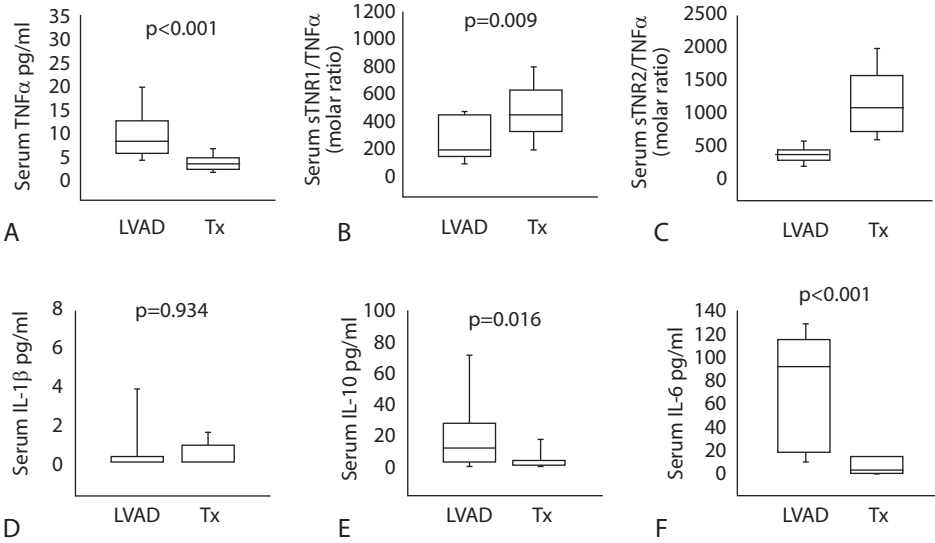

FIGURE 1.1. Serum cytokine concentrations in deteriorating patients with heart failure undergoing emergency LVAD implantation compared with patients with stable advanced heart failure undergoing elective Tx. A, TNF-α; B, molar ratio of type 1 soluble TNF-α receptor (sTNFR1)/TNF-α; C, molar ratio of sTNFR2/TNF-α; D, IL-1β; E, IL-10; F, IL-6 Box plots depict median values with 10tb, 25th, 75th, and 90th percentiles. (Mean plasma cytokine concentrations in healthy controls (data from R%D systems ELISA handbooks); TNF-α 1.98 pg/ml, IL-1b <3.9 pg/ml, sTNFR1 914 pg/ml; sTNFR2 1,500 pg/ml, IL-10 <7.8 pg/ml, IL-6 1.49 pg/ml.

cyte responses and the severity of multiple organ failure.

Regarding the postoperative cytokine response, Masai[26] reported that LVAD recipients who presented deceased multiple organ failure syndrome (MOFS) during the first three postoperative months, had higher postoperative CRP, IL-6, and IL-8 levels than survivors. Other groups have observed release of pro-inflammatory mediators even in event-free LVAD recipients during the first postoperative hours. Moreover, the findings of a group from Milan suggest that an activated inflammatory system soon after LVAD implant is implicated in the development of MOFS and non-survival.[27]

Despite such insights, there is little information available on the cytokine response in the setting of cardiac surgery with the newest generation of cfLVADs and contemporary surgical approaches that tend toward minimally invasive thoracotomy approaches and utilizing only a shorter CPB run or performing the operation without the use of CPB. Moreover, there is no information on serious efforts attempting to modulate directly the cytokine response. The current pilot study will explore these important aspects for the first time.

Recent analysis of patients in the University Medical Centre in Utrecht, the Netherlands, has indicated a third of patients undergoing LVAD insertion with the newest generation of devices developed significant vasoplegia. This phenomenon was associated with a 3-4 fold higher risk of developing renal failure, as well as increased mortality in the ICU and at 1-year follow-up.[9] These data highlight the urgent need to modulate and eliminate vasoplegia in heart failure patients undergoing LVAD implantation and heart transplantation (see the chapter on transplants).

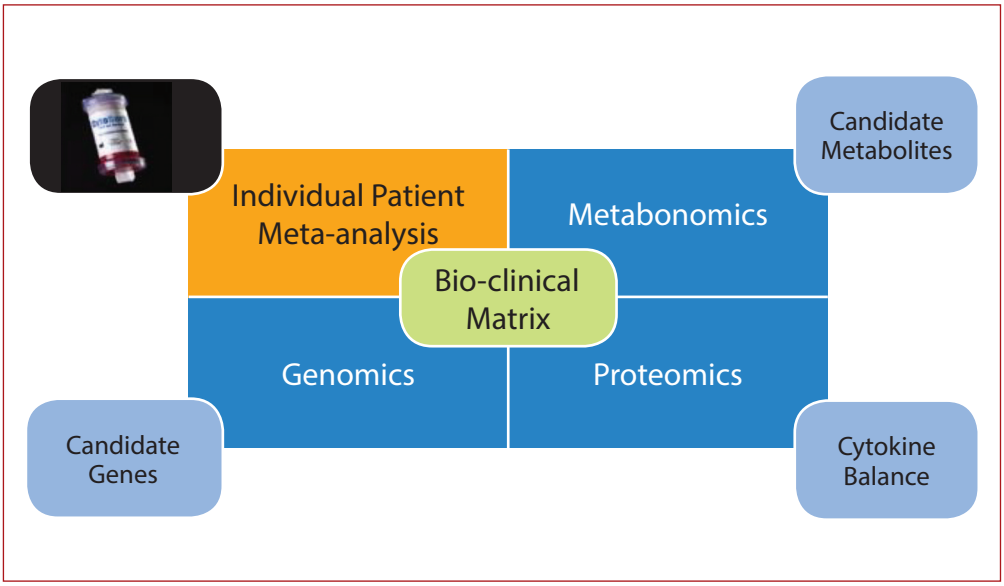

FIGURE 1.2. CU-BioSORB: Consortium for Unbiased Biological evaluation of Cytosorb Therapy.

FUTURE DIRECTIONS

This short review indicates some promising aspect of CytoSorb therapy for perioperative inflammation and vasoplegic states in high-risk cardiac patients. All studies have so far indicated feasibility and a favorable safety profile of single device application during CPB in cardiothoracic surgery patients. The remaining challenge is to identify high-risk patient groups that are prone to perioperative inflammatory response, vasoplegia, and organ dysfunction. While we predict that CytoSorb will have very limited roles in routine cardiac surgery, the suggestion of reduced vasopressor requirements and reduced kidney injury are important aspects if confirmed in larger, high-quality clinical trials. It is likely that patients at risk for vasoplegia need to be identified intraoperatively and the influence of hemoadsorption investigated in this special group.

There is much more promise for CytoSorb use in advanced heart failure patients who require LVAD insertion and subsequent heart transplantation. The former is being investigated in a two-center pilot study in London and Utrecht (CYCLONE-LVAD study). We have also mobilized all efforts in the United Kingdom for a potential study in heart transplantation (CYCLONE-heart transplant) involving all United Kingdom transplant centers. However, assessing clinically relevant outcomes such as primary graft dysfunction, survival, and economic aspects will require a large international and definite randomized controlled trial.

We have also expanded our international collaboration regarding basic translational science and founded CU-BioSORB, a biological and molecular mechanistic study consortium of the CYTOSORB Network.[28] This international and multidisciplinary consortium has been developed to recruit and organize leading biological expertise to provide a molecular and cellular translational domain to the major clinical trials related to CytoSorb therapy. Thus, the overarching objective of this research network is to provide mechanistic insights and explanations for the outcomes of current and future clinical trials, es-

pecially in the field of high-risk cardiac surgery and mechanical support. While the clinical trials will deliver the well-defined clinical endpoints, and the established international registry will provide exciting novel outcomes, we envision that the basic translational domain will validate emerging biological markers and discover new and better signatures of postoperative complications with the CytoSorb therapeutic angle (Figure 1.2). We anticipate that these outcomes could then be exploited as innovative diagnostic and therapeutic targets and tested in future clinical trials to improve intraoperative patient outcomes, to reduce postoperative complications, and to facilitate full recovery via improved and optimized clinical applications of the CytoSorb therapy.

Our vision is to better integrate basic science with human physiology and clinical outcomes during the CytoSorb trials. Based on leading theories of innate immunity, surgical inflammatory response, and metabolic determinants of perioperative organ injury, we propose inflammation and metabolism as the two overarching themes of the consortium. To this end, we have recruited and shall continue to recruit a multidisciplinary group of investigators, including clinical trialists, leading academic clinicals, and basic scientists representing these themes.

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