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ANALYSIS OF THE LINK BETWEEN CLINICAL OUTCOME AND HEMOADSORPTION APPLIED DURING MECHANICAL CIRCULATORY SUPPORT IN HIGH–RISK CARDIAC AND CARDIAC SURGICAL PATIENTS

PhD thesis

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List of Abbreviations

Abbreviation	Definition
ACC	aortic cross clamp
ACEI	angiotensin–converting enzyme inhibitor
AKI	acute kidney injury
AMI	acute myocardial infarction
APACHE II	Acute Physiology and Chronic Health Evaluation II
ARB	angiotensin–receptor blocker
ARNI	angiotensin receptor–neprilysin inhibitor
ATG	anti–thymocyte globulin
BMI	body mass index
BRB	beta receptor blocker
CAD	coronary artery disease
CHF	congestive heart failure
CI	confidence interval
CKD	chronic kidney disease
CLD	chronic liver disease
CM	cardiomyopathy
COPD	chronic obstructive pulmonary disease
COVID–19	coronavirus disease 2019
CPB	cardiopulmonary bypass
CRP	C–reactive protein
CS	cardiogenic shock

dLVAD	durable left ventricular assist device
DM	diabetes mellitus
ECMO	extracorporeal membrane oxygenation
ECPR	extracorporeal cardiopulmonary resuscitation
eGFR	estimated glomerular filtration rate
EMB	endomyocardial biopsy
FFP	fresh frozen plasma
fHb	free haemoglobin
HCM	hypertrophic cardiomyopathy
HF	heart failure
ICU	intensive care unit
IDCM	ischaemic cardiomyopathy
IMPACT	Index for Mortality Prediction After Cardiac Transplantation
LCOS	low–cardiac–output–syndrome
MAP	mean arterial pressure
MCS	mechanical circulatory support
MMF	mycophenolate mofetil
MP	methylprednisolone
MPA	mycophenolic acid
MV	mechanical ventilation
NYHA	New York Heart Association
OHT	orthotopic heart transplantation

OR	odds ratio
PCB	per cent change in bilirubin level
PCT	procalcitonin
PLT	platelet transfusion
PRC	packed red cell
PS	propensity score
PSM	propensity score matching
PVD	peripheral vascular disease
PVR	pulmonary vascular resistance
RCT	randomized controlled trial
RO	reoperation
RRT	renal replacement therapy
SAVE	survival after venoarterial extracorporeal membrane oxygenation
SCAI	Society for Cardiovascular Angiography & Interventions
SOFA	sequential organ failure assessment
TAC	tacrolimus
TIA	transient ischemic attack
TIT	total ischaemic time
UNOS	United Network for Organ Sharing
VA–ECMO	venoarterial extracorporeal membrane oxygenation
VIS	vasoactive–inotropic score
VS	vasoplegic syndrome

1 Introduction

Since its first introduction to medical practice approximately 70 years ago, the extracorporeal mechanical circulatory support (MCS) has undergone significant progress both in the technical and the management aspects (1). These developments have contributed to the establishment of MCS as a key component (i.e. cardiopulmonary bypass, CPB) of complex cardiac surgical procedures (1). Conversely, MCS has also been integrated into multilevel treatment strategies for cardiogenic shock through various temporary paracorporeal modalities in recent years (2). Despite the significant accumulation of clinical experience and research–based knowledge regarding MCS application in the past period, there are still uncontrolled, ongoing pathophysiological issues induced by patient–device interactions (3, 4). These may act as negative contributing factors in patients' outcomes, thereby hindering the theoretically possible benefits of these modalities (3, 4). Recognising the crucial roles of the MCS modalities in patient care, the exploration of effective modulatory mechanisms / therapeutic options for these pathophysiological processes is a pivotal area of clinical research in this field.

1.1 Modalities of paracorporeal mechanical circulatory support systems – operates with membrane oxygenator

1.1.1 Cardiopulmonary bypass

Cardiopulmonary bypass (CPB) is an established extracorporeal technology that temporarily replaces the basic functions of the heart and lung, thereby maintaining systemic perfusion and gas exchange (1, 5). The technology comprises several fundamental components, including venous cannula(s) and drainage systems, a reservoir, an oxygenator, an arterial pump, an arterial line and cannula, a cardioplegia line, and at least two additional suction systems (i.e. pericardial suction and vent). (5). During CPB, the patient's right–side venous blood is completely drained into the reservoir, resulting in non–perfused pulmonary circulation (5). The volume of the drained venous blood provides the preload of the CPB, which is returned to the patient's systemic circulation by the arterial pump through the CPB membrane oxygenator (5). In terms of technical structure, the arterial pumps are predominantly roller pumps; nevertheless, new generation centrifugal pumps are also available for this purpose, providing improved hemocompatibility during CPB (5). The arterial pump is responsible for maintaining

systemic perfusion, which is defined as a non–pulsatile flow of 2.4 L/min/m^2 in accordance with international standards (5, 6). The hollow fibre–based membrane oxygenator is the dedicated biological surface for gas exchange (i.e. primarily for oxygen and CO_2) (5). Concurrently, the membrane oxygenator serves as the conventional location for blood temperature regulation during CPB, employing an external heater–cooler system (5). From a physiological standpoint, it means a close temperature control of the central compartment of the global blood flow over a short time interval (5). The most prevalent target temperature range is 32.0–35.0 C° (5). During CPB, the homeostatic environment is maintained by goal–directed perfusion strategy including mean arterial pressure– (MAP), DO_2– and alpha–stat pH management (6–8).

1.1.2 Extracorporeal membrane oxygenation

In recent decades, extracorporeal membrane oxygenation (ECMO), particularly its venoarterial modality (VA–ECMO), has become an integral component of the treatment of refractory cardiogenic shock, with a broad spectrum of cardiac and cardiac surgical applications (9–11). Theoretically, VA–ECMO is a short–term, temporary extracorporeal MCS system that provides complete or partial cardiopulmonary support, thereby restoring macrocirculation, oxygenation and gas exchange in cases of cardiorespiratory failure that is refractory to conventional pharmacotherapy (9–11). The technical structure of the VA–ECMO circuit comprises a venous cannula for inflow, a centrifugal pump that functions by generating active venous suction and delivering blood flow, a polymethylpentene fiber membrane oxygenator, and connecting tube systems (10, 12, 13). In terms of configuration, VA–ECMO support can be performed by central cannulation (i.e. direct cannulation of the right atrium for inflow and aorta for outflow via sternotomy) or peripheral cannulation (i.e. cannulation of the right atrium for inflow and aorta for outflow via the femoral vein and artery, respectively) (10, 13). VA–ECMO operates with non–pulsatile flow characteristics providing a flow support in range of 2.0 L/min – 6.0 L/min (10, 13). Currently, there is no universally accepted guideline for the management of VA–ECMO, particularly with regard to the optimal level of haemodynamic support (10, 13). However, maintaining MAP ≥ 60 mmHg, SvO_2 ≥ 60%, and adequate tissue oxygen delivery are common goals during its application and the initial VA–ECMO flow rate recommended is typically in the range of 3.0 – 4.0 L/min (10, 13). In light of the most prevalent complications associated with VA–ECMO support,

including left ventricle overdistension, haematologic complications, peripheral vascular complications, neurological injuries, Harlequin–syndrome, and immunological complications, it is recommended to limit VA–ECMO support to a duration of 5–7 days in order to minimise adverse events and the risk of negative outcomes (10, 11, 13, 14). Within the time frame of this type of temporary MCS support (i.e. VA–ECMO), three different exit strategies can be defined clinically: i) bridge–to–recovery and VA–ECMO weaning; ii) bridge–to–bridge (i.e. durable MCS) or bridge–to–heart transplantation; iii) palliate and terminate (15).

1.2 The complex pathophysiology induced by extracorporeal mechanical circulatory support

1.2.1 Microcirculatory alterations in the context of end–organ perfusion and tissue oxygenation

Irrespective of the patients' actual haemodynamic conditions, extracorporeal MCS has been shown to be able to directly induce dysregulation in the haemodynamic coherence between the macro– and microcirculation (16). Both experimental and human clinical data confirm a significant reduction in functional capillary density during extracorporeal MCS support (16). The combined effects of non–pulsatile flow characteristics, hypothermia (even in the mild range of 34.0–35.0°C in the case of CPB), haemodilution, hyperoxemia and the amplified dysregulated inflammatory response induced by the extracorporeal circuit has been demonstrated to result in a reduction in the dimension of the endothelial glycocalyx and deterioration of endothelial regulation of the microcirculation, progressing to vasoconstrictive predominance, capillary leakage and a marked reduction in functional capillary density (16–20). Additionally, the elevated plasma free haemoglobin levels due to extravascular haemolysis (particularly in cases of longer CPB/VA–ECMO run), the consecutively depleted soluble guanylyl cyclase activity and augmented platelet aggregation within the capillary bed can further exacerbate the microcirculatory dysfunction (16). The aforementioned pathophysiological processes lead to a persistent imbalance between tissue oxygen delivery and demand, thereby facilitating the development of severe end–organ failure. (16–20). In addition, these processes exert a negative influence on the normalisation of microcirculatory function subsequent to cardiogenic shock (16).

1.2.2 Maladaptive inflammatory response to extracorporeal system

The extracorporeal MCS is proven to be a strong inductor of a dysregulated inflammatory response based on the non–physiological effects of the large endothelium–free inner surface of the extracorporeal device, the non–pulsatile flow pattern and direct blood–air contact (CPB), which interact with further pathophysiological processes such as hypothermia, surgical trauma, ischemia–reperfusion injury of end–organs (during post–CPB or post–VA–ECMO initiation period) and endotoxemia originated from visceral hypoperfusion (21–24). This complex maladaptive mechanism can be characterized by early and late phases involving the overactivation of the humoral–(kinin–, complement– and cytokine cascade) and cellular (platelets, neutrophils, monocytes, dendritic cells, lymphocytes) immune response, and the endothelial system (21–24). Considering the dominant pathophysiological component and the magnitude of the consecutive endothelial injury, the extracorporeal MCS induced maladaptive inflammatory response is an independent trigger factor of the MCS associated multiorgan– and immune dysfunction as well as the development of major complications, and the adverse outcomes (23, 24).

1.2.3 Extracorporeal mechanical circulatory support induced coagulopathy

In addition to the maladaptive inflammatory response, the extracorporeal MCS also interacts with the patient's haemostasis system through complex mechanisms (25). Interestingly, the pathophysiological characteristics of the MCS associated coagulopathy can vary considerably depending on the extracorporeal MCS modality (i.e. CPB or VA–ECMO) (25). Nevertheless, it remains a significant factor in the occurrence of adverse clinical outcomes (25).

Despite of the systemic anticoagulation, the residual low–grade contact activation, CPB–related haemodilution and blood loss from the surgical field result in a combined four–domain–based impairment of the haemostasis system such as thrombocytopenia and platelet dysfunction, hypofibrinogenemia and fibrinogen dysfunction, impaired thrombin generation and hyperfibrinolysis (25–28). Of the four main pathomechanisms under consideration, hypofibrinogenemia and fibrinogen dysfunction, in addition to impaired thrombin generation, have been identified as the key factors most affected by CPB–associated coagulopathy (26, 27). In the context of post–CPB coagulopathy, it is

important to consider the adverse anticoagulant properties of protamine when present in excess to heparin, which has been demonstrated to facilitate the inhibition of platelet function, down–regulation of thrombin generation, and reduction of activation of coagulation factors V, X, and VII (29, 30). Finally, the CPB–associated coagulopathy can be further aggravated by the preexisting pharmacological effects of antiplatelet or anticoagulant agents (25).

On the other hand, VA–ECMO is characterized by longer duration of MCS, lower dose of heparin anticoagulation requirement and direct interaction with progressive amplified inflammatory processes compared to CPB (31, 32). Therefore, the effects of the ECMO circuit generated shear–stress on the blood components and the ECMO–blood interaction will be more pronounced resulting in the dominant impairment of the primary haemostasis accompanied by severe thrombocytopenia and platelet dysfunction and acquired von Willebrand syndrome extended by severe hyperfibrinolysis (31, 32). Moreover, coagulation factor XIII deficiency is present in approximately ¾ part of ECMO–supported patients (32). While the exact pathophysiological background of the acquired coagulation factor XIII deficiency of the ECMO–supported patients has not been revealed yet, it is typically linked with low fibrinogen levels and an important cofactor of severe ECMO associated coagulopathy (32). Additionally, due to the longstanding exposure to contact activation of the ECMO circuit, and the locally missing endothelial regulatory mechanisms on the extracorporeal surface, a significant complement system dysregulation can develop, which contributes to the induction of immunothrombotic processes (31, 32). Accordingly, the ECMO associated complex coagulopathy can be presented with dual simultaneous dysfunction of the haemostasis system such as haemorrhagic and prothrombotic impairments (31, 32).

1.3 Hemoadsorption as a blood purification technology and its potential targets

The extracorporeal hemoadsorption is a blood purification technology with confirmed adsorption capacity for cytokines, chemokines, bilirubin, myoglobin, plasma free haemoglobin, endo– and exotoxins and various pharmacological agents up to approximately 60 kDa (33–35). The hemoadsorption therapy is typically performed by a 300 mL biocompatible polystyrene divinylbenzene copolymer beads containing cartridge (34–36). The size range of the beads is between 300 and 800 μm and their pores and

channels form a composite surface of 40,000 m^2 for the size exclusion– and hydrophobic interaction–based adsorption (34, 36). The hemoadsorption treatment can be applied as a stand–alone or as an integrated modality (34–36). With regard to the integrated modality, the hemoadsorption cartridge is integrated into the circuit of an extracorporeal system such as continuous renal replacement therapy, CPB or ECMO (34–36).

As demonstrated in previous studies, hemoadsorption treatment has been shown to have positive effects on the haemodynamic stability and the outcome of severe sepsis in both animal studies and clinical investigations (37–39). Moreover, a most recent systematic review and meta–analysis suggested that the hemoadsorption treatment may be associated with improved short–term survival in patients with septic shock compared to standard care (40). Additionally, recent clinical investigations in the field of cardiac surgery have reported reduced sepsis related mortality, less bleeding complications related to adsorption of direct acting oral anticoagulants or P2Y12 inhibitors, and faster recovery of haemodynamics and organ function in patients undergoing complex cardiac surgeries when the hemoadsorption treatment has been applied intraoperatively (36, 41–45). Despite the increase in the number of randomized and observational studies for the evaluation of hemoadsorption in cardiac surgery over the past decade, published results remain controversial regarding clarifying the clinical utility of this intervention in terms of post–operative morbidity and mortality (35, 46).

1.4 Characteristics of the end–stage heart failure patients in terms of heart transplantation

Approximately 5% of patients who suffering from chronic heart failure (HF) will progress to advanced stage of their condition (47). Based on the most recent criteria established by the Heart Failure Association of the European Society of Cardiology for defining advanced stage HF, these patients can be characterized by the constant symptoms of severe HF (i.e. NYHA class III/IV), severely decreased exercise capacity (peak VO_2 < 12–14 mL/kg/min) and the presence of extra–cardiac organ dysfunction(s) such as renal and/or hepatic dysfunction and/or type 2 pulmonary hypertension and cardiac cachexia (47, 48). In case of further progression of the HF, the patients' haemodynamic imbalance becomes refractory to optimized HF treatment presenting hypotension, end–organ failure (i.e. type 2 cardiorenal syndrome; cardiohepatic syndrome) and intermittent or continuous

dependency on inotropic support (47–49). Additionally, the severe low–cardiac–output–syndrome (LCOS) has been identified as a significant trigger for the development of a chronic pro–inflammatory predominance (i.e. immune priming of the end–stage HF) (50). The persistent LCOS in conjunction with the pro–inflammatory priming and the consecutive extra–cardiac organ dysfunctions definitely will position the end–stage HF patients to among the 'high risk' candidates for orthotopic heart transplantation (OHT) or durable left ventricular assist device (dLVAD) implantation obviously influencing both the short– and long–term outcomes of these procedures (47, 51). It is important to note that in the case of a critical decline in CO and change in the LCOS associated multiorgan failure and type 2 pulmonary hypertension to irreversible/refractory phase, the end–stage HF patients may drop out from the window of a rational and successful OHT or dLVAD procedure (47).

While there has been an expansion in candidate acceptance criteria for OHT, including the 'high–risk' end–stage HF patients, over recent years, the multiple organ failure has been confirmed as the second most frequent cause of death in the first 30 days after OHT (52).

1.5 Characteristics of the patient presented with refractory cardiogenic shock

Cardiogenic shock (CS) is defined as a complex acute hemodynamic syndrome characterised by significant hypotension (i.e. systolic blood pressure <90 mmHg for ≥30 minutes or need for haemodynamic support to maintain systolic blood pressure ≥90 mmHg), clinical and laboratory signs of end–organ and tissue hypoperfusion and confirmed critical LCOS (i.e. cardiac index ≤2.2 L/min/m2 and pulmonary capillary wedge pressure ≥15 mmHg) (53). The CS related early mortality rate as high as 40–90% depending on its aetiology and resistance to conventional pharmacotherapy (53–56). The dynamic process of CS has been refined and structured according to its severity, phenotype and aetiology, and risk modifiers (i.e. SCAI SHOCK Stage Classification) in order to facilitate the early prognostication of the ongoing CS as well as the optimized clinical decision making (57). Furthermore, the SCAI SHOCK Stage Classification may have a significant impact on the early recognition of CS refractory to conventional pharmacotherapy (i.e. SCAI SHOCK Stage D–E) (57).

The major causes of CS can be classified into acute ischaemic (i.e. AMI–related) and non–AMI–related aetiologies (i. acute–on–chronic heart failure–related cardiogenic shock; ii. post–cardiotomy cardiogenic shock; iii. non–myocardial cardiogenic shock) (53, 58). In accordance with the data published previously, a changing trend can be observed in the epidemiology of the leading CS aetiologies (58). These findings indicate the non–AMI–related aetiologies as larger group compared to the acute ischaemic aetiology (58). The predominant component of the non–AMI–related CS causes is the post–cardiotomy CS, a specific subtype among the CS aetiologies (58, 59). While the post–cardiotomy CS sharply differs from the other forms of CS with regards to its pathophysiology, the exact pathomechanisms of the post–cardiotomy CS remain poorly understood (59). In fact, the development of the post–cardiotomy CS is presumed to be the consequence of multiple interacting factors, including myocardial hibernation and stunning, dysregulated inflammatory response to CPB and ischaemia-reperfusion injury, manifesting clinically as severe left ventricle–, right ventricle– or biventricular failure (59). Acute–on–chronic heart failure–related cardiogenic shock is also a relevant subtype of the non–AMI–related CS aetiologies, accounting for almost 1/3 of CS cases (58). Finally, less frequent subtypes of CS are the pericardial disease–, valvular heart disease–, arrhythmia–, inflammatory cardiomyopathy–, peripartum cardiomyopathy–, and cor pulmonale associated cardiogenic shocks (58).

In the refractory CS stage, the persistent critical LCOS and tissue hypoperfusion accelerate the progression of multiorgan dysfunction, which will be further aggravated by microcirculatory dysfunction linked to dysregulated activation of proinflammatory cytokines, complements, and excessive release of nitric oxide (60–63). It has been established that these complex processes result in severe multiorgan failure, which has been confirmed as the primary cause of death related to refractory CS (60, 61). Over the last two decades, temporary MCS technology has become a pivotal tool in the acute care of refractory CS aiming to restore the macro– and micro–haemodynamics within a short time interval and prevent the emerging multiorgan dysfunction from progressing to an irreversible phase, whilst simultaneously reducing the mortality risk (61, 64).

2 Objectives

As outlined above, the microcirculatory dysfunction linked to interrelated complex pathomechanisms, is presumed to be the key factor of both the OHT related– and the refractory CS related multiple organ failure. Because of the complexity of the pathophysiological pathways, to date, there are no specific pharmacological treatments which have been shown to be effective for the control or prevention of severe vasoregulatory dysfunction. Consequently, experimental and human clinical research has recently focused on extracorporeal blood purification treatments as a potential tool for effectively controlling the pathophysiological environment associated with OHT– and CS.

Therefore, the aims of this thesis were the following:

i. To assess the clinical effectiveness of the hemoadsorption treatment in controlling vasoregulatory dysfunction linked to OHT surgery applying in an intraoperative CPB setting.
ii. To assess the clinical effectiveness of the hemoadsorption treatment in controlling multiorgan dysfunction linked to refractory CS applying in a VA–ECMO support setting.
iii. To assess the clinical safety of the hemoadsorption treatment in terms of adverse effects such as increased risks of bleeding/thromboembolic– and immunological events.
iv. To evaluate the link between hemoadsorption treatment and clinical outcomes in relation to high risk cardiac– and cardiac surgical patients.

2.1 Intraoperative hemoadsorption treatment and its impact on the outcome of patients undergoing orthotopic heart transplantation

The predominant component of post–transplant multiorgan dysfunction is severe vasoplegia and consecutive haemodynamic instability, which substantially increases the risk of developing extended multiple organ dysfunctions (65, 66). The complex pathophysiology of vasoplegic syndrome (VS) involves coexisting pathways of endogenous vasopressin depletion, dysregulated inflammatory response, and endothelial dysfunction resulting in excessive nitric oxide production and loss of vascular tone (65, 67).

Our previous observational study showed that OHT recipients who were treated with hemoadsorption intraoperatively experienced significantly reduced post–operative vasopressor requirements and favourable trends in clinical outcome (68). While the number of randomized and observational studies for the evaluation of hemoadsorption in cardiac surgery has increased in the last 10 years, published results remain controversial regarding clarifying the clinical utility of this intervention in terms of post–operative morbidity and mortality (46). Considering the unique pathophysiological environment of OHT, the presumed benefit of intraoperative hemoadsorption during CPB could be based on control of the immune system dysregulation along with endogenous vasoactive substance overproduction. To date, there have been no published randomized controlled trial (RCT) in field of OHT, which have analysed the relationship between intraoperative hemoadsorption and clinical outcome.

The aim of our proof–of–concept RCT was to compare the effects of intraoperative hemoadsorption versus standard medical care on the severity of early postoperative haemodynamic instability, frequency of postoperative organ dysfunctions, early graft rejection, and length of hospital stay in patients undergoing OHT (69).

2.2 Influence of VA–ECMO integrated hemoadsorption on the early reversal of multiorgan and microcirculatory dysfunction and outcome of refractory cardiogenic shock

Despite the application of MCS in the complex therapy of refractory CS, the survival to discharge remains 45% according to 2021 data from the Extracorporeal Life Support Registry Report summary (16). VA–ECMO is among the MCS modalities most frequently used in the acute care of refractory CS (53, 64). While VA–ECMO is effective in supporting macrocirculatory haemodynamics to rapidly normalize, the same benefit on CS–associated microcirculatory dysfunction and impaired tissue oxygen delivery remains controversial (16, 19, 70). Additionally, recent investigations have demonstrated that ineffective recruitment of functional capillary density during the early phase of VA–ECMO support can be associated with worse outcomes in refractory CS (19, 70, 71). The mechanisms that contribute to rapid recovery of persisting microcirculatory dysfunction after VA–ECMO initiation have not yet been discovered (16). However, adverse interactions of pathophysiological factors such as elevated plasma free haemoglobin

(fHb) levels, depleted soluble guanylyl cyclase activity, and concomitant increased platelet aggregation and amplified dysregulated proinflammatory response linked to the application of extracorporeal MCS can negatively influence the normalization of the microcirculatory function (16).

The aim of our retrospective observational study was to analyse the clinical impact of VA–ECMO integrated hemoadsorption in terms of early reversal of multiorgan– and microcirculatory dysfunction, and short–term clinical outcomes in patients undergoing VA–ECMO support for refractory CS (72).

3 Methods

3.1 Intraoperative hemoadsorption treatment and its impact on the outcome of patients undergoing orthotopic heart transplantation

3.1.1 Study design and patients

Our prospective, single–centred, open–label RCT was approved by the Semmelweis University Regional and Institutional Committee of Science and Research Ethics (approval number: 246/2016) and was registered at ClinicalTrials.gov (identifier: NCT03145441). To establish a homogenous study cohort, adult OHT candidates registered on the waiting list (age ≥18 years) with United Network for Organ Sharing (UNOS) Status 6 at the time of OHT were eligible for inclusion during the study period between April 2018 and December 2021. UNOS 6 status represents the most stable and active subgroup of OHT candidates who are treated at home within a 6–tiered risk–stratification system (73). In consideration of the clinical condition and medical urgency for OHT, UNOS 6 patients form the most homogenous low-risk OHT subgroup in the aspects to test the hypotheses of our RCT. Consequently, we excluded OHT recipients from the RCT with 'high urgency' status, re-transplantation, long-standing hospitalization, inotrope dependence, mechanical circulatory support, and progressive end-organ failure prior to OHT. The exclusion criteria summarize the diverse high-risk OHT recipient population with the meaning of higher risk for patient group heterogeneity and patient selection bias, particularly in case of smaller sample size. Patients who met the inclusion criteria were randomly allocated to either the control group or the hemoadsorption group according to the randomization scheme of 60 subjects (69).

3.1.2 Perioperative patient management

All patients involved in our proof–of–concept randomized trial received standardized anaesthetic, surgical and post–operative intensive care in accordance with the institutional protocol. Non–pulsatile, mild hypothermic CPB was applied for all participants using a roller–pump (SORIN C5 Perfusion System, Sorin Group Deutschland GmbH, Munich, Germany) and a membrane oxygenator (SORIN Inspire P8, Sorin Group Italia Srl, Mirandola, Italy). The clinical management of unfractionated heparin anticoagulation, haemodynamic, temperature, and metabolic targets during CPB was based on institutional standards. The basic pharmacological components of

haemodynamic management were noradrenaline as first–line and argipressin as second–line vasopressors, and dobutamine and milrinone as inotropic agents. Argipressin was indicated in cases where noradrenaline requirements were ≥0.3 μg/kg/min. Inhalational nitric oxide was given routinely from the beginning of CPB weaning and extended for the subsequent post–CPB/post–operative period depending on actual pulmonary vascular resistance and right ventricular function. Invasive pulmonary arterial pressure monitoring was regularly continued over the first post–operative 48 hours. Cardiac allograft function follow–up was performed with echocardiography (transthoracic or transoesophageal) 24 hourly during the first 5 post–transplant days, and on a weekly basis thereafter. Immunosuppression therapy consisted of mycophenolate mofetil (MMF), methylprednisolone, anti–thymocyte globulin and tacrolimus. The institutional protocol for perioperative immunosuppression of OHT used in our trial is summarized in **Table 1**. Cardiac allograft rejection was followed up with endomyocardial biopsy (EMB) weekly during the first month after the OHT (74).

3.1.3 Intraoperative hemoadsorption treatment

In relation to patients who were randomised into the hemoadsorption group, the intraoperative hemoadsorption procedure was conducted using a CytoSorb™ 300 mL cartridge (CytoSorbents™, Monmouth Junction, NJ, USA) for a one–cycle treatment during the entire period of CPB. The hemoadsorption cartridge was integrated into the CPB circuit (see **Figure 1**) (69).

Table 1. *Applied immunosuppression protocol of orthotopic heart transplantation during the perioperative period and the first month postoperatively.* MMF, mycophenolate mofetil; MP, methylprednisolone; CPB, cardiopulmonary bypass; ATG, anti–thymocyte globulin; TAC, tacrolimus (69).

Time	Agent	Dose	Route of administration
60 minutes prior to surgery (premedication)			
	MMF	1.5 g	oral
Induction of anaesthesia			
	MP	500 mg	Intravenous
30 minutes after the aortic declamp (on–CPB)			

	MP	500 mg	Intravenous
Postoperative day 0			
	MP	125 mg	Intravenous
	ATG	1.5 mg/kg	Intravenous
	MMF	1.5 g	Intravenous
Postoperative day 1 – 2			
	MP	125 mg	Intravenous
	ATG	1.5 mg/kg	Intravenous
	MMF	2 x 1.5 g	Intravenous / oral
Postoperative day 3 – 4			
	MP	16 mg	oral
	MMF	2 x 1.5 g	oral
Postoperative day 5 – 9			
	MP	16 mg	oral
	MMF	2 x 1.5 g	oral
	TAC	2 x 0.05–0.1 mg/kg	oral
Postoperative day 10 – 16			
	MP	12 mg	oral
	MMF	2 x 1.0 g	oral
	TAC	2 x 0.05–0.1 mg/kg	oral
Postoperative day 17 – 30			
	MP	8 mg	oral
	MMF	2 x 1.0 g	oral
	TAC	2 x 0.05–0.1 mg/kg	oral

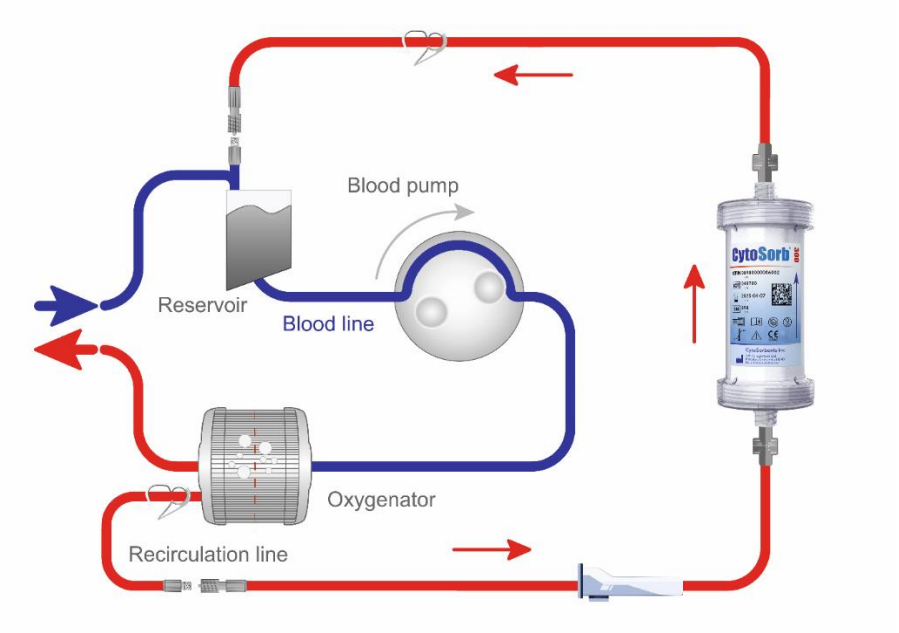


Figure 1. *Integration method of the hemoadsorption cartridge (CytoSorb^{TM}) into the cardiopulmonary bypass* (69).

3.1.4 Outcome parameters and measurements

The primary outcome of our randomised trial was early post–operative haemodynamic instability quantified by the vasoactive inotropic score (VIS), frequency of VS and length of vasopressor need. VIS was calculated according to the formula: VIS = dopamine dose (μg/kg/min) + dobutamine dose (μg/ kg/min) + 100× adrenaline dose (μg/kg/min) + 10× phosphodiesterase inhibitor dose (μg/kg/min) + 100× noradrenaline dose (μg/kg/min) + 10 000× vasopressin dose (U/kg/min) (75) based on the mean doses in the post–operative first 24 h for each agent. VIS was considered as 'high' if values ≥30 points, representing a higher risk for unfavourable outcomes (76). Quantitative criteria of VS were mean noradrenaline requirements ≥0.3 μg/kg/min and need for argipressin supplementation at any dose to achieve a MAP >60 mmHg assessed over the first 24 h (69).

Secondary outcome parameters were defined as the inflammatory response characterized by a 72–hour change in procalcitonin (PCT) and C–reactive protein (CRP) levels; duration of mechanical ventilation (MV); surgery associated bleeding and reoperation for bleeding; frequency and severity of acute kidney injury (AKI) classified by applying the KDIGO creatinine–based definition criteria for the first 5 post–operative

days (77); 24–h per cent change in bilirubin level using the equation: PCB = ([post–CPB 24–hour bilirubin level (mg/dL)] – [pre–operative bilirubin level (mg/dL)]/[pre–operative bilirubin level (mg/dL)]) × 100, frequency of early sepsis screened for in the first 5 post–operative days; length of ICU and hospital stay; intraoperative change in mycophenolic acid (MPA) plasma concentration; early allograft rejection; 30–day mortality rate and 1–year survival. Biomarkers of inflammatory response and creatinine clearance as well as the total bilirubin serum concentration were quantified using standard validated laboratory measurements. MPA (active metabolite of MMF) was quantified by particle–enhanced turbidimetric inhibition immunoassay (PETINA, Siemens Dimension® System MPAT, Siemens Healthcare GmbH, Erlangen, Germany; detection limit <0.1 μg/mL) (69).

3.1.5 Statistical analysis

Because of the lack of published RCTs performed in OHT patients with a similar primary outcome, no formal sample size calculation was performed. Based on our regular OHT activity we assumed that including 60 patients (30 per group) in a study over 3 years would be feasible.

All statistical tests were performed using IBM SPSS Statistics for Windows, version 28.0.1.0 (IBM Corp., Armonk, NY, USA). Continuous variables were tested with the Shapiro–Wilk test for normality. Descriptive statistics of data were displayed as median [interquartile range], mean ± standard deviation, and number of patients and frequency where appropriate. Mann–Whitney U test, two–sample t–test, χ^2 test or Fisher's exact test were performed for the univariate analysis of group comparisons. The comparative analyses of within–subjects changes in the cohort were accomplished with the Wilcoxon signed–rank test. To evaluate the impact of intraoperative hemoadsorption on the early post–operative VS a multivariate, logistic regression, backward elimination, likelihood–ratio method was performed. One year follow–up was completed for all participants and included an estimated one–year survival using the Kaplan–Meier method. Equality testing of survival curves was accomplished with a log–rank test applying the Mantel–Cox method. Statistical significance was defined as a *P* value of 0.05 in all tests (69).

3.2 Influence of VA–ECMO integrated hemoadsorption on the early reversal of multiorgan and microcirculatory dysfunction and outcome of refractory cardiogenic shock

3.2.1 Patients and data collection

Our observational study was approved by the Regional and Institutional Committee of Science and Research Ethics (approval number: 72/2022) (72).

This study analysed retrospectively collected clinical data of adult patients supported with VA–ECMO due to refractory cardiogenic shock between 1 January 2012 and 31 December 2020. Clinical characteristics, follow–up, and outcome data, along with acute physiology and chronic health evaluation II (APACHE II) (78), sequential organ failure assessment (SOFA) (79), and survival after venoarterial extracorporeal membrane oxygenation (SAVE) scores (80), arterial and venous blood gas variables obtained from the digital databases of the Cardiovascular Critical Care Unit and the Hospital Healthcare System, as well as data from individual treatment charts (intensive care observational charts) were collated. Patients who died within 72 h or did not develop vasoplegic syndrome were excluded from the extended analyses. Over the screened period there were no relevant changes in the indication criteria for VA–ECMO support and all patients received standardized intensive care of VA–ECMO management (72).

3.2.2 Venoarterial extracorporeal membrane oxygenation management

VA–ECMO support was provided using the Medos Deltastream System (Medos Medizintechnik AG, Stolberg, Germany). Patients received peripheral (i.e., femoral) or central cannulation for the VA–ECMO circuit according to the aetiology of the refractory CS. Peripheral VA–ECMO circuit was extended by a femoral distal perfusion catheter in all cases. Initial VA–ECMO support was adjusted to achieve blood flow rates of 3.0–4.0 L/min, which was supplemented by an additional 500 mL/min if hemoadsorption treatment was also introduced. After the completion of 3–5 days of optimized VA–ECMO support, all patients received standardized stepwise VA–ECMO weaning (200–300 rate/minute decrease 12–24 hourly up to 2.0 L/minute flow support depending on cardiac performance and hemodynamic response) for the subsequent days in accordance with the institutional protocol. Patients were candidates for VA–ECMO explanation after successful weaning, including a 24–hour period on low flow support (2.0 L/minute). In

case of persistent MCS dependence, patients were converted to a mid–term MCS device (72).

3.2.3 VA–ECMO integrated hemoadsorption treatment

Patients were candidates for hemoadsorption treatment if they presented with vasoplegia syndrome, defined as a norepinephrine requirement ≥0.3 μg/kg/min and the need for argipressin at any dose, 4–6 hours after VA–ECMO initiation, despite combined haemodynamic resuscitation. Hemoadsorption was performed using CytoSorb^{TM} 300 mL cartridge (Cytosorbents^{TM}, Monmouth Junction, NJ, USA) incorporated into the VA–ECMO circuit for a 72–hour continuous treatment in total (**Figure 2**) (72).

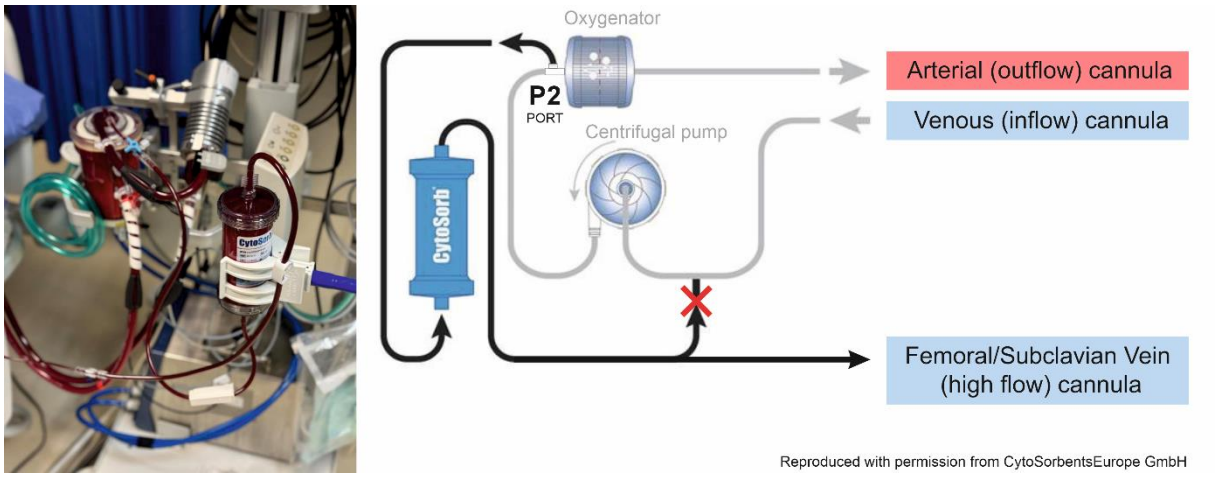


Figure 2. *Integration method of the hemoadsorption cartridge (CytoSorb^{TM}) into the VA–ECMO system; "Semmelweis method"* The inflow line of the hemoadsorber cartridge is connected pre-membrane to the P2 port of the oxygenator, while the outflow line is attached to a high flow femoral/subclavian vein cannula. This approach of the hemoadsorber cartridge integration promotes to minimize the hemoadsorption shunt and to achieve the highest volume of clearance. (72, 81).

3.2.4 Outcome parameters

The primary outcomes of this study were the change in SOFA score after 72 hours of VA–ECMO run and in–hospital mortality.

Secondary outcome parameters were defined as early metabolic stability, change in microcirculatory function described by the $P_{(v-a)}CO_2$ gap ($P_{(v-a)}CO_2$ gap = P_vCO_2 – P_aCO_2), inflammatory activity characterized by C–reactive protein (CRP) and white

blood cell (WBC) count, hemodynamic stability described by VIS (75) based on the actual doses of each adjusted agent in a time frame of the first 72–hour VA–ECMO support, major complications associated with refractory CS and VA–ECMO support, intensive care unit and hospital stay, and 90–day survival (72).

3.2.5 Statistical analysis

The statistical analyses of this study were performed with IBM SPSS Statistics for Windows, version 27.0 (IBM Corp., Armonk, NY, USA) and R–statistics for Windows, version 3.6.0 (R Foundation for Statistical Computing, Vienna, Austria). Descriptive statistics of data were presented as mean ± standard deviation, while categorical variables were displayed as the number of patients and frequency. We performed a 1:1 match, nearest neighbour method propensity score matching (PSM) with a calliper width of 0.2 (82) using the logistic regression estimation algorithm with adjusted covariates from the APACHE II and SOFA scores, average ECMO flow, and postcardiotomy aetiology of refractory CS. The comparative analyses of continuous and categorical variables, including within–subjects changes in the matched cohort, were accomplished with the paired t–test and McNemar test, where appropriate. We completed 90–day follow–up for all included patients and estimated the 90–day survival for the two matched groups using the Kaplan–Meier method. The equality testing of survival curves was performed with the stratified log–rank test involving the quintiles of the estimated propensity scores as strata (83, 84). Statistical significance was defined at the 0.05 level in all tests (72).

4 Results

4.1 Intraoperative hemoadsorption treatment and its impact on the outcome of patients undergoing orthotopic heart transplantation

4.1.1 Study population

During the study period, 165 patients were assessed for eligibility. Sixty patients were randomized to the control (N = 30) and hemoadsorption (N = 30) groups, but five patients from the control group had to be excluded. The reasons for exclusion and details of the study flowchart are summarized in **Figure 3**. Baseline clinical characteristics and intraoperative factors were similar in both groups (**Table 2**); however, the pre–transplant use of amiodarone was less frequent in the control group than in the hemoadsorption group. The demographic and baseline characteristics are depicted in **Table 2** (69).

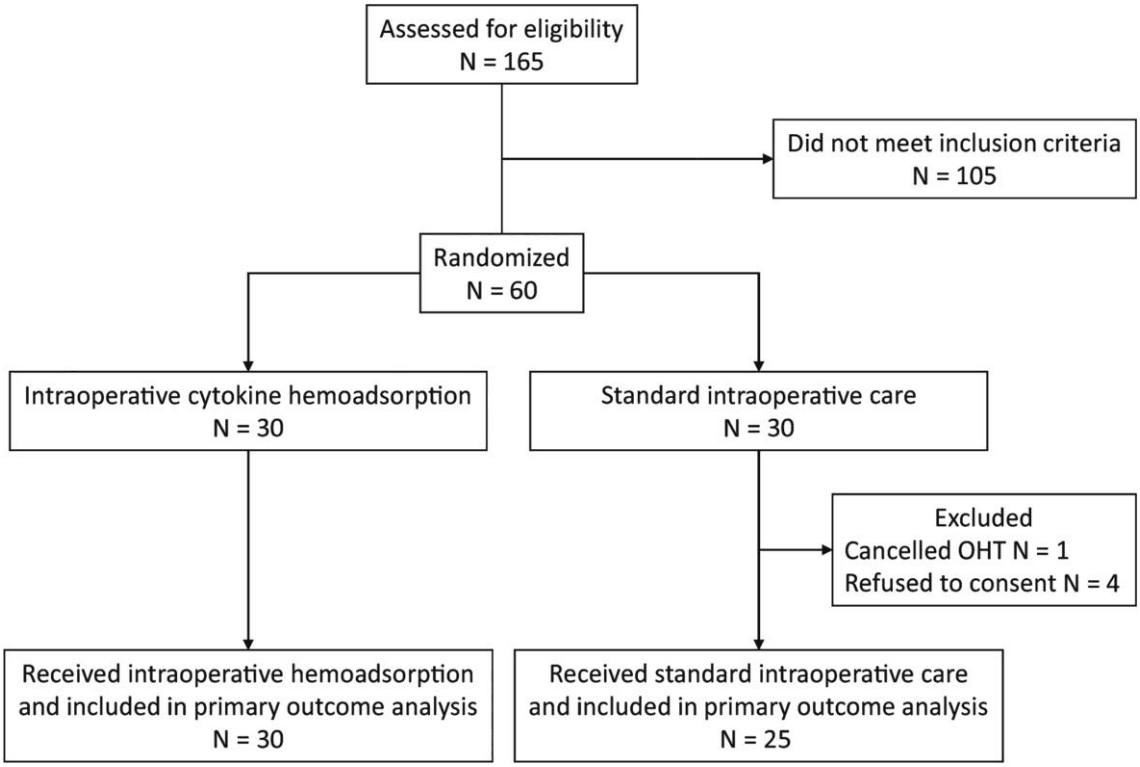


Figure 3. *Patient selection flowchart.* OHT, orthotopic heart transplantation (69).

Table 2. *Demographic and baseline characteristics of the study population.* Data are presented as median [interquartile range], mean ± standard deviation and number of patients (frequency). N=55. [a]CKD was defined as estimated glomerular filtration rate <60 ml/min/1.73 m^2. [b]TIT corresponds the ischaemic time of the donor heart. BMI, body mass index; DM, diabetes mellitus; CKD, chronic kidney disease; ACEI, angiotensin–converting enzyme inhibitor; ARB, angiotensin–receptor blocker; ARNI, angiotensin receptor–neprilysin inhibitor; BRB, beta receptor blocker; PVR, pulmonary vascular resistance; IMPACT, Index for Mortality Prediction After Cardiac Transplantation; eGFR, estimated glomerular filtration rate; CRP, C–reactive protein; PCT, procalcitonin; IDCM, ischaemic cardiomyopathy; HCM, hypertrophic cardiomyopathy; CM, cardiomyopathy; ACC, Aortic cross–clamp; CPB, cardiopulmonary bypass; TIT, total ischaemic time (69).

	Control group N=25	**Hemoadsorption group N=30**	***P***
Preoperative variables			
Recipient age, year	56 [48–60]	56 [47–61]	0.839
Donor age, year	46 ± 9	41 ± 11	0.355
BMI, kg/m^2	26.9 ± 4.8	25.4 ± 3.3	0.084
Female sex, n	10 (40.0%)	15 (50.0%)	0.458
DM, n	6 (24.0%)	5 (16.7%)	0.521
CKD, n[a]	10 (40.0%)	13 (43.3%)	0.803
Chronic anaemia, n	10 (40.0%)	9 (30.0%)	0.437
ACEI / ARB, n	10 (40.0%)	18 (60.0%)	0.140
ARNI, n	9 (36.0%)	12 (40.0%)	0.761
BRB, n	21 (84.0%)	28 (93.3%)	0.394
Amiodarone, n	3 (12.0%)	11 (36.7%)	0.061
PVR, Wood unit	2.4 [1.2–3.5]	2.7 [1.9–4.4]	0.257
IMPACT score, point	4 [2.5–5.0]	4 [2.0–7.0]	0.892
Creatinine, µmol/L	104.0 [82.5–149.5]	105.5 [80.3–132.8]	0.742
eGFR, ml/min/1.73 m^2	64.2 [42.4–73.6]	61.5 [46.9–76.5]	0.813
Haemoglobin, g/dL	13.4 ± 1.9	13.0 ± 1.3	0.068
Bilirubin, mg/dL	0.56 [0.34–0.98]	0.69 [0.37–0.83]	0.919

CRP, mg/L	3.3 [1.8–7.3]	2.3 [0.9–4.8]	0.151
PCT, µg/L	0.04 [0.03–0.09]	0.04 [0.02–0.07]	0.463
White cell count, G/L	8.2 [6.2–9.7]	8.0 [7.0–9.2]	0.980
Aetiology of end–stage heart failure			
IDCM, n	8 (32.0%)	8 (26.7%)	0.665
HCM, n	1 (4.0%)	3 (10.0%)	0.617
Idiopathic CM, n	12 (48.0%)	15 (50.0%)	0.883
Other, n	4 (16.0%)	4 (13.3%)	1.00
Intraoperative factors			
ACC time, min	50 [41–79]	72 [43–86]	0.375
CPB time, min	129 [104–169]	133 [116–154]	0.819
TIT, min[b]	173 ± 41	152 ± 45	0.484

4.1.2 Severity of the hemodynamic stability and vasoregulatory dysfunction

Patients in the hemoadsorption group had significantly lower VIS than patients in the control group during the first post–operative 24 h (median VIS: 27.2 [14.6–47.7] vs. 41.9 [22.4–63.2], P = 0.046, respectively). Among the dominant components of VIS, there was a tendency of lower dose of vasopressors in the hemoadsorption group compared to controls, which reached a statistically significant difference in the case of argipressin (**Figure 4**). However, the median dose of inotropes did not differ between the groups (**Figure 4**). According to the a priori definition, the observed rate of VS was 48.0% (12 patients) in the control group versus 20.0% (6 patients) in the hemoadsorption group, P = 0.028. Additionally, the frequency of extreme noradrenaline demand (i.e. ≥0.5 µg/kg/min) during the first post–transplant 24 h was significantly lower in patients from the hemoadsorption rather than the control group: 3.3% (1 patient) versus 24.0% (6 patients), P = 0.039, respectively. Similarly, patients in the control group experienced a longer median length of vasopressor support compared to subjects in the hemoadsorption group: 3.0 [1.5–5.0] days versus 2.0 [1.0–4.0] days, P = 0.046, respectively. In a multivariate logistic regression model, patients who received intraoperative hemoadsorption had a 6.4–fold lower odds ratio for developing early post–operative VS

(P = 0.029) than those who received standard intraoperative care. The independent predictors of the early post–operative VS are presented in **Table 3** (69).

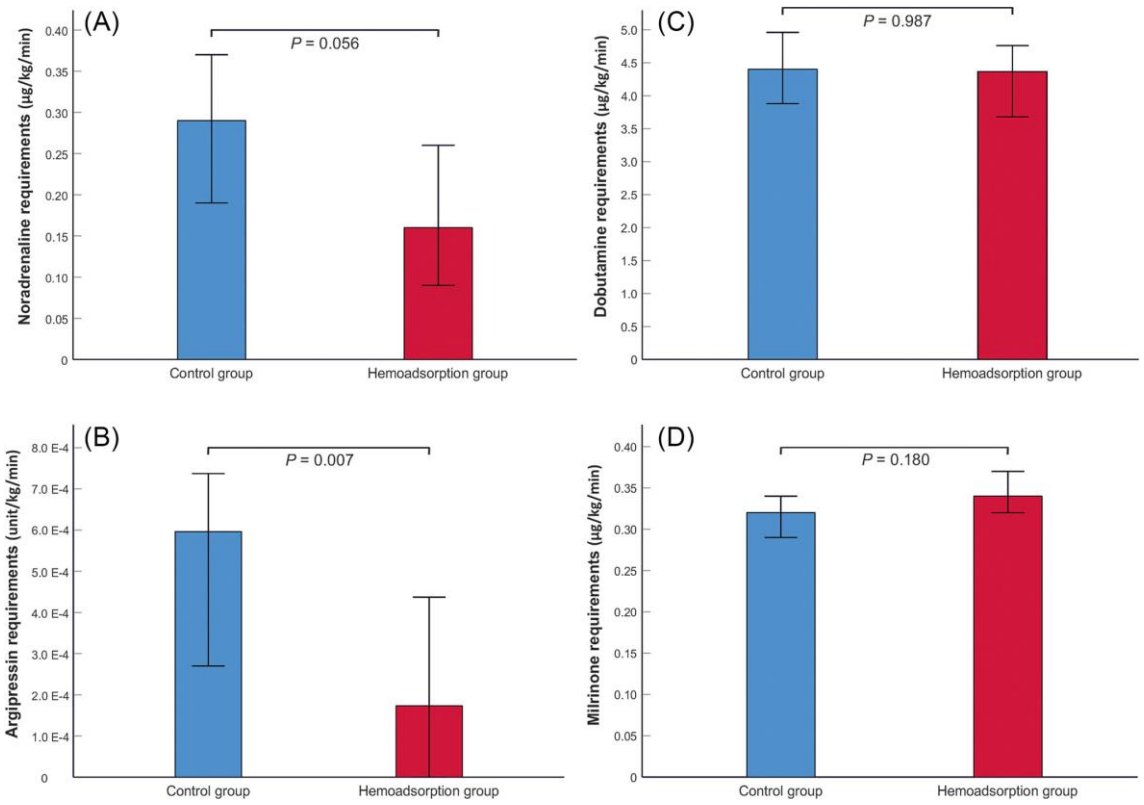


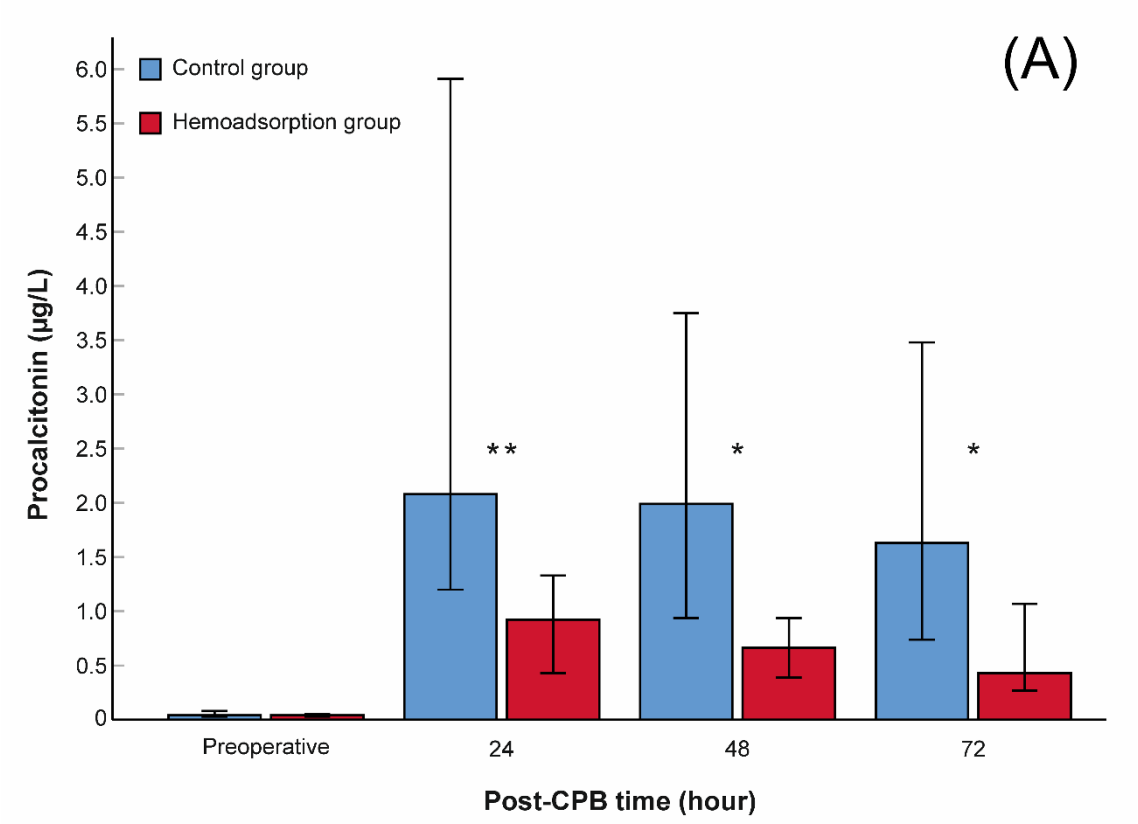
Figure 4. *Major components of vasoactive inotropic score during the first 24 h after orthotopic heart transplantation.* Noradrenaline (A); Argipressin (B); Dobutamine (C); Milrinone (D). N=55. Data are presented as medians and 95% confidence intervals (69).

Table 3. *Independent predictors of early postoperative vasoplegic syndrome*. Multivariable logistic regression, backward elimination likelihood–ratio, N=55. Adjusted covariates in the regression model: intraoperative hemoadsorption treatment; female sex; chronic kidney disease; angiotensin–converting enzyme inhibitor/angiotensin II receptor blocker treatment pre–transplant; amiodarone treatment pre–transplant; preoperative pulmonary vascular resistance > 3.0 Wood units; CPB ≥ 180 minutes. OR, odds ratio; CI, confidence interval; CPB, cardiopulmonary bypass (69).

Variable	OR	95% CI	*P*
Intraoperative hemoadsorption	0.156	0.029–0.830	0.029
Preoperative amiodarone therapy	6.315	1.032–38.630	0.046
CPB ≥ 180 minutes	25.776	2.089–318.016	0.011

4.1.3 Secondary outcomes

PCT and CRP levels showed a marked increase post–operatively with their peaks at 24 hours and 48 hours, respectively (**Figure 5**). Interestingly, PCT concentrations were significantly lower at each time point of the 72–h observation period in the hemoadsorption group compared to controls (**Figure 5**). However, CRP concentrations did not differ between the groups (**Figure 5**) (69).



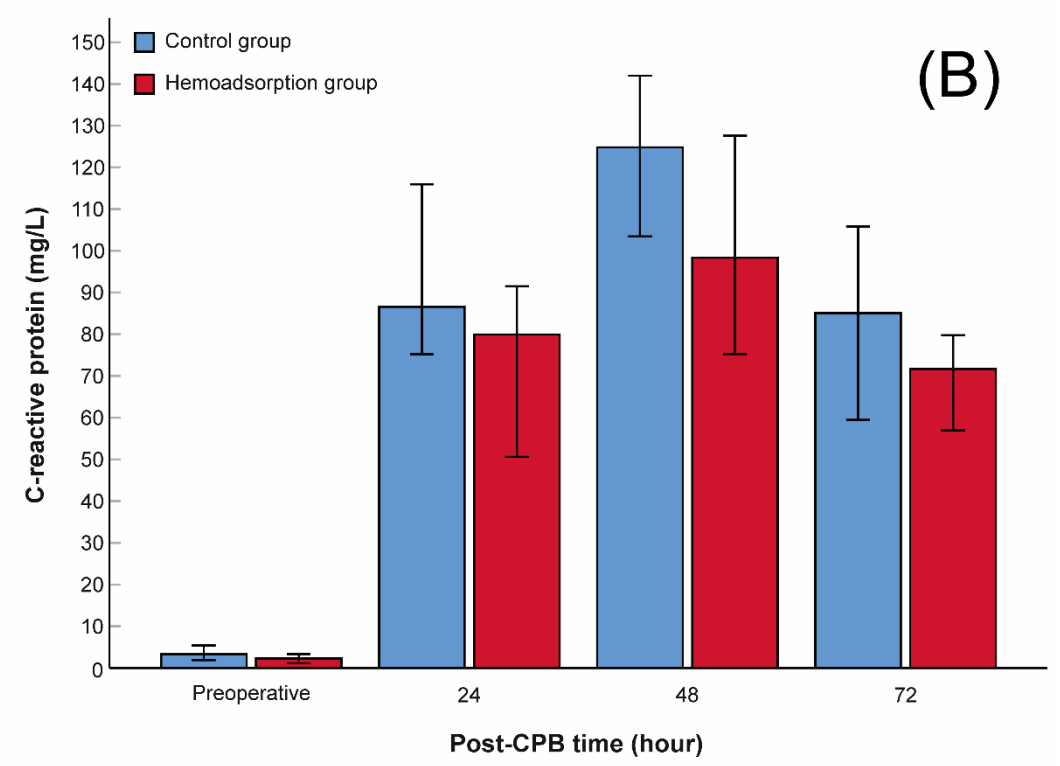


Figure 5. *Post–transplant changes in procalcitonin (A) and C–reactive protein (B).* N=55. Data are presented as medians and 95% confidence interval. **P* < 0.05; ***P* < 0.01 (69).

MPA plasma concentrations decreased considerably after 2 hours of CPB compared to pre–CPB levels in both groups, but its median level was comparable to controls in the hemoadsorption group at each measurement point (**Figure 6**). The time interval between MMF pre–operative administration and CPB start was 123 ± 48 min in the control group versus 226 ± 44 min in the hemoadsorption group, *P* = 0.302 (69).

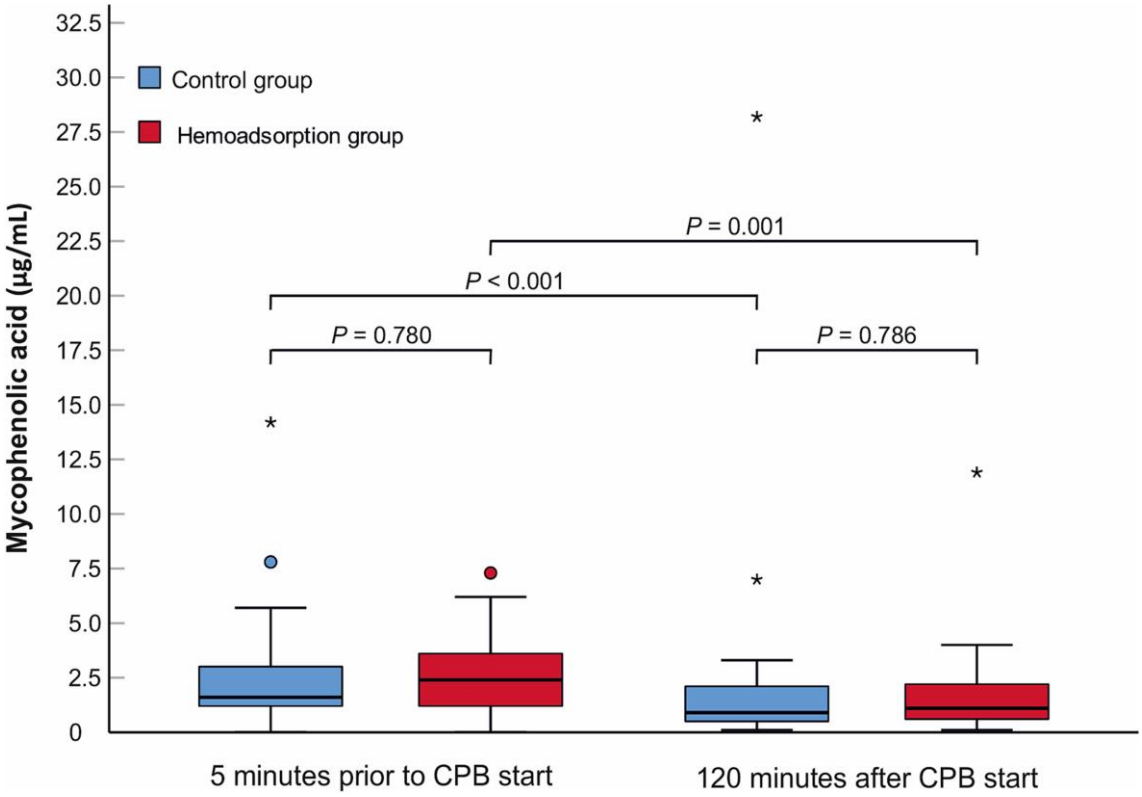


Figure 6. *Intraoperative change in mycophenolic acid.* N=55. Filled circle indicates outlier, while asterisk represents extreme value (69).

As shown in **Table 4**, shorter durations of MV and ICU stay were registered in the hemoadsorption than in the control group. Similarly, patients who had intraoperative hemoadsorption experienced significantly lower rates of post–operative AKI and renal replacement therapy (RRT) versus subjects in the control group (**Table 4**). In addition, the PCB was significant in the controls, while it was found to be <3.0% in the hemoadsorption group over a 24–h time frame (**Table 4**). Nevertheless, only one patient from the control group developed post–operative hyperbilirubinaemia (bilirubin ≥3.0 mg/dL). There was a low rate of 30–day mortality for the total study cohort (3.6%) which did not show difference between the groups (**Table 4**). Importantly, the follow up EMB examinations did not confirm any grade of cardiac allograft rejection on post–operative day 7 and the frequency of low–grade allograft rejections were similar in the groups over the subsequent weeks (**Table 4**). The secondary outcome parameters are described in **Table 4**. The analysis of cumulative post–transplant 1–year survival did not reveal any statistically significant difference between the groups (control group: 88.0% vs.

hemoadsorption group: 96.7%, *P* = 0.210, **Figure 7**). There were no reported hemoadsorption device–related adverse events over the study period (69).

Table 4. *Comparative analysis of secondary outcome parameters.* Data are presented as number of patients (frequency) and median [interquartile range]. N=55. [a]AKI was classified according to Kidney Disease Improving Global Outcomes creatinine–based definition criteria over the first 5 postoperative days. [b]Early sepsis was screened over the first 5 postoperative days. ECMO, extracorporeal membrane oxygenation; PRC, packed red cell; FFP, fresh frozen plasma; PLT, platelet transfusion; MV, mechanical ventilation; AKI, acute kidney injury; RRT, renal replacement therapy; ICU, intensive care unit; EMB, endomyocardial biopsy (69).

Parameters	Control group N=25	Hemoadsorption group N=30	*P*
Postcardiotomy ECMO, n	3 (12.0%)	0 (0%)	0.088
Postoperative bleeding, mL	570 [385–1305]	565 [350–1130]	0.543
Reoperation for bleeding, n	2 (8.0%)	0 (0%)	0.202
PRC/post–CPB 24 h, unit	4.0 [0–5.5]	2.0 [0–4.0]	0.243
FFP/post–CPB 24 h, unit	2.0 [0–3.0]	2.0 [0–3.0]	0.571
PLT/post–CPB 24 h, unit	12.0 [0–16.0]	12.0 [8.0–16.0]	0.597
Postoperative MV, hour	65 [23–287]	25 [19–68.8]	0.025
AKI stage 1, n[a]	15 (60.0%)	9 (30.0%)	0.025
AKI stage 2, n[a]	0 (0%)	1 (3.3%)	1.00
AKI stage 3, n[a]	4 (16.0%)	1 (3.3%)	0.104
AKI_{total}, n	19 (76.0%)	11 (36.7%)	0.004
Postoperative RRT, n	4 (16.0%)	0 (0%)	0.037
Percent change in bilirubin, %	72.1 [11.2–191.4]	2.5 [–24.6–71.1]	0.009
Early sepsis, n[b]	1 (4.0%)	0 (0%)	0.455
Length–of–ICU–stay, day	12 [8.5–18.0]	8.5 [8.0–10.3]	0.022
Length–of–hospital stay, day	28 [24–38.5]	25 [22–34.3]	0.232
30–day mortality, n	2 (8.0%)	0 (0%)	0.202
EMB cellular rejection			
Post–transplant day 7., n	0 (0%)	0 (0%)	

Post–transplant day 14., n	5 (20.0%)	5 (16.7%)	1.00
Post–transplant day 21., n	5 (20.0%)	5 (16.7%)	1.00
Post–transplant day 28., n	6 (24.0%)	10 (33.3%)	0.448
EMB antibody–mediated rejection			
Post–transplant day 7., n	1 (4.0%)	0 (0%)	0.455
Post–transplant day 14., n	1 (4.0%)	2 (6.7%)	1.00
Post–transplant day 21., n	1 (4.0%)	3 (10.0%)	0.617
Post–transplant day 28., n	2 (8.0%)	1 (3.3%)	0.585

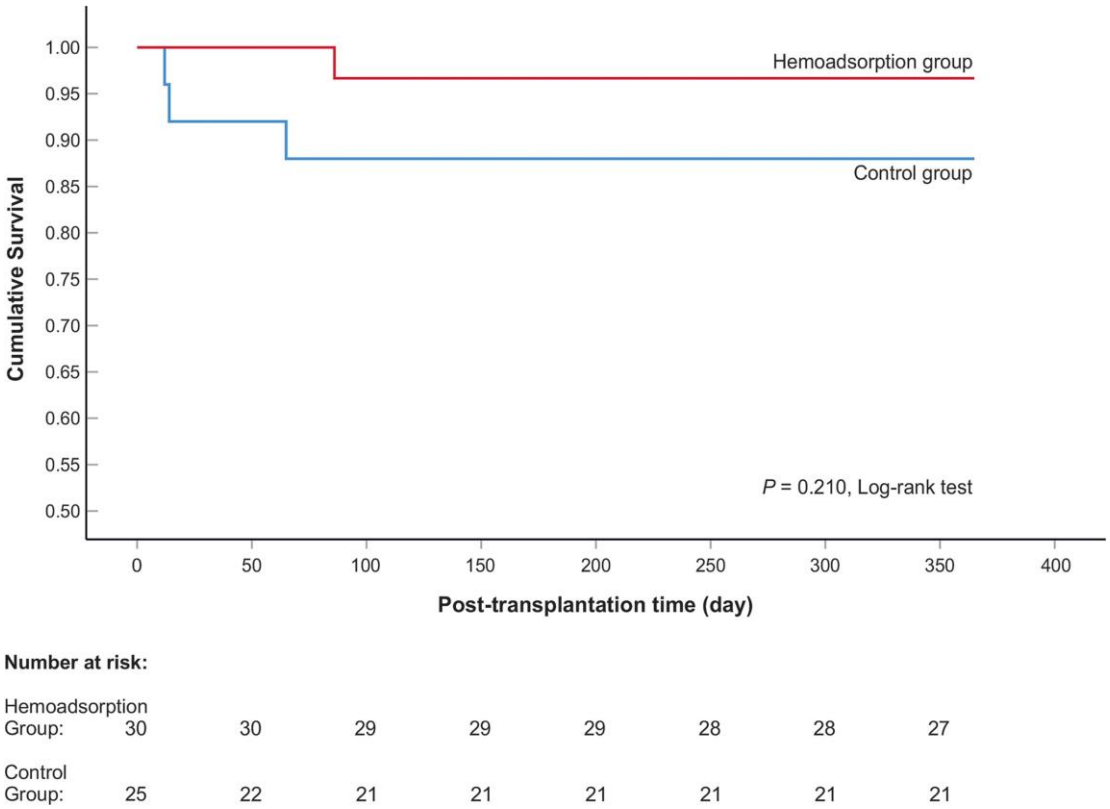


Figure 7. *Kaplan–Meier estimates of cumulative 1–year survival, according to the intraoperative treatment.* Red line represents the hemoadsorption group, while blue line illustrates the control group. *P* value (log–rank test) shows the difference in survival (69).

4.2 Influence of VA–ECMO integrated hemoadsorption on the early reversal of multiorgan and microcirculatory dysfunction and outcome of refractory cardiogenic shock

4.2.1 Clinical characteristics

Overall, 268 patients were treated with refractory CS and VA–ECMO support in the investigated period at our institution. After the exclusions, the PSM procedure involving 150 patients resulted in 29 matched pairs (**Figure 8**). The absolute values of standardized mean differences were found to be less than 0.225 for all adjusted covariates. APACHE II and SOFA scores achieved balance by PSM, which indicated similar risks for early mortality in both groups prior to VA–ECMO implantation. The univariate analyses of the baseline parameters did not reveal relevant differences between the two groups in terms of patient characteristics (**Table 5**). However, the peripheral VA–ECMO support was less frequent in patients of the hemoadsorption group than the control group. The patient selection process and the clinical characteristics in the unmatched and matched cohorts are summarized in **Figure 8** and **Table 5**, respectively.

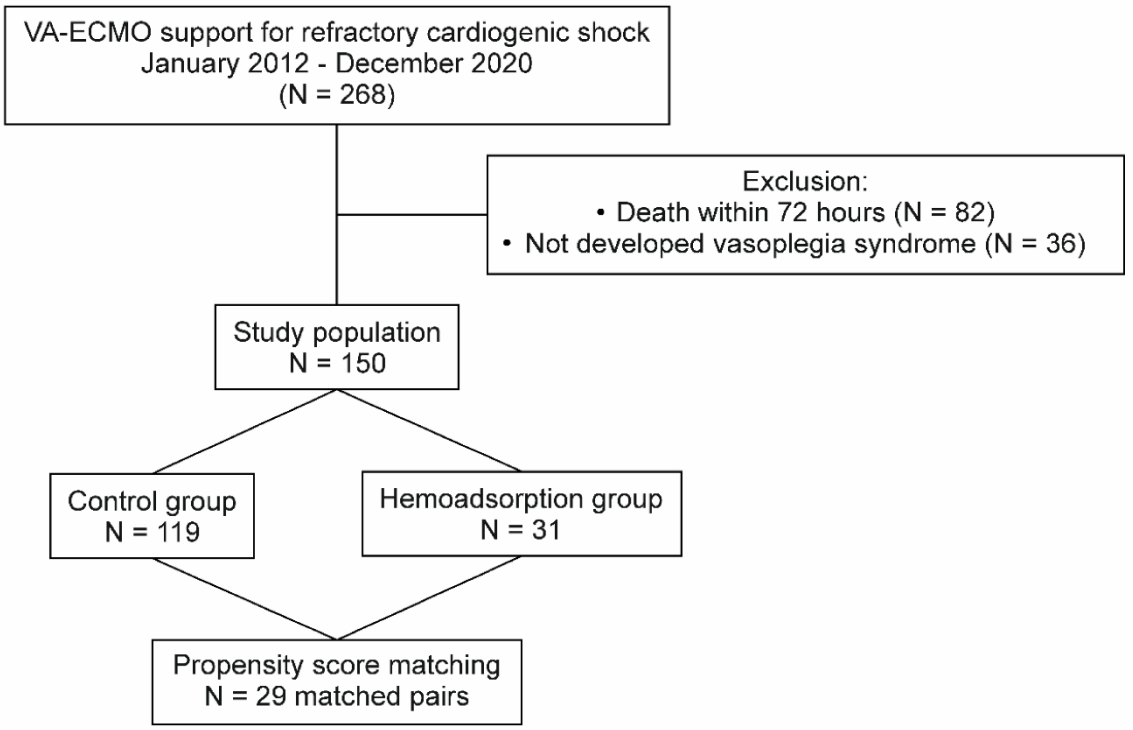


Figure 8. *Patient selection flowchart.* VA–ECMO: venoarterial extracorporeal membrane oxygenation (72).

Table 5. *Patient characteristics and clinical data in the unmatched and matched cohorts.* Data are presented as mean ± standard deviation and number of patients (frequency). [a]CKD was defined as estimated glomerular filtration rate < 60 mL/min/1.73 m^2. [b]$P_{(v-a)}CO_2$ gap = $P_vCO_2 - P_aCO_2$; Normal range: 2–6 mmHg (85). *P*–value shows the difference between the control group and hemoadsorption group (propensity score matched cohort). PS: propensity score; BMI, body mass index; CAD, coronary artery disease; CHF, congestive heart failure; COPD: chronic obstructive pulmonary disease; CLD, chronic liver disease; CKD, chronic kidney disease; DM, diabetes mellitus; PVD, peripheral vascular disease; TIA: transient ischemic attack; AMI: acute myocardial infarction; CHF: congestive heart failure; OHT: orthotopic heart transplantation; ECMO: extracorporeal membrane oxygenation; APACHE II: Acute Physiology and Chronic Health Evaluation II; SOFA: Sequential Organ Failure Assessment; SAVE: Survival after Veno–Arterial ECMO (72).

	Study Population N = 150	**Control Group N = 29**	**Hemoadsorption Group N = 29**	***P***
	PS matched cohort N = 58			
Age, year	53 ± 16	55 ± 14	51 ± 15	0.291
Age > 70 years, n	17 (11.3%)	2 (6.9%)	1 (3.4%)	1.00
Female sex, n	38 (25.3%)	8 (27.6%)	6 (27.0%)	0.774
BMI, kg/m^2	27.8 ± 5.1	28.2 ± 5.5	27.8 ± 4.6	0.717
Hypertension, n	69 (46.0%)	13 (44.8%)	10 (34.5%)	0.581
CAD, n	60 (40.0%)	14 (48.3%)	11 (37.9%)	0.549
CHF, n	67 (44.7%)	14 (48.3%)	16 (55.2%)	0.791
COPD, n	20 (13.3%)	3 (10.3%)	6 (20.7%)	0.453
CLD, n	7 (4.7%)	3 (10.3%)	0 (0%)	0.250
CKD, n [a]	72 (48.0%)	12 (41.4%)	14 (48.3%)	0.804
DM, n	35 (23.3%)	7 (24.1%)	8 (27.6%)	1.00
PVD, n	8 (5.3%)	0 (0%)	3 (10.3%)	0.250
Previous stroke, TIA, n	8 (5.3%)	2 (6.9%)	3 (10.3%)	1.00

Aetiology of refractory cardiogenic shock				
AMI, n	40 (26.7%)	5 (17.2%)	3 (10.3%)	0.687
Acute–on–CHF, n	21 (14.0%)	4 (13.8%)	5 (17.2%)	1.00
Acute myocarditis, n	7 (4.7%)	0 (0%)	3 (10.3%)	0.250
Intoxication, n	3 (2.0%)	1 (3.4%)	0 (0%)	1.00 –
Severe septic shock, n	2 (1.3%)	1 (3.4%)	0 (0%)	1.00
Postcardiotomy, n	77 (51.3%)	18 (62.1%)	18 (62.1%)	1.00
OHT graft failure, n	43 (28.7%)	10 (34.5%)	12 (41.4%)	0.774
Pre–ECMO parameters				
pH	7.33 ± 0.10	7.33 ± 0.09	7.36 ± 0.09	0.439
Lactate, mmol/L	7.52 ± 5.35	6.90 ± 4.12	6.56 ± 4.96	0.769
$P_{(v-a)}CO_2$ gap, mmHg[b]	8.83 ± 3.40	9.19 ± 3.03	8.47 ± 3.76	0.388
White blood cell, G/L	13.04 ± 7.48	11.64 ± 4.28	14.45 ± 9.57	0.146
C–reactive protein, mg/L	49.06 ± 67.46	31.57 ± 43.25	66.57 ± 82.23	0.054
APACHE II score	30.4 ± 5.3	30.0 ± 5.5	31.1 ± 5.1	0.413
SOFA score	11.3 ± 2.3	12.2 ± 1.8	12.1 ± 2.8	0.789
SAVE score	–6.9 ± 6.1	–7.2 ± 5.6	–6.5 ± 6.7	0.668
VA–ECMO support				
Peripheral ECMO support, n	45 (30.0%)	11 (37.9%)	3 (10.3%)	0.039
Average ECMO flow, L/min	3.3 ± 0.5	3.5 ± 0.4	3.5 ± 0.5	0.366
ECMO support duration, hour	159 ± 67	154 ± 59	183 ± 73	0.106
Hemoadsorption treatment, hour	70.6 ± 8.7	0	70.5 ± 8.9	–

4.2.2 Primary outcomes

Subjects from the hemoadsorption group experienced a significant reduction in the follow–up 72–hour SOFA score from 12.1 ± 2.8 to 10.1 ± 3.3 ($P < 0.001$), with no difference detected in the control group (12.2 ± 1.8 versus 12.1 ± 3.7, $P = 0.815$, respectively; **Figure 9**). Additionally, the 72–hour SOFA score was also significantly lower in the hemoadsorption than in the control group (**Table 6**). We registered a higher frequency of in–hospital mortality in the control compared to the hemoadsorption groups (62.1% vs. 44.8%, respectively), however, this difference was not statistically significant (**Table 6**). Interestingly, the observed in–hospital mortality was also lower than the mean predicted value calculated according to the APACHE II and SOFA scores prior to VA–ECMO initiation in patients from the hemoadsorption group (44.8% vs. 63.1% and 73.2%, respectively), while there were no relevant differences in the controls (62.1% vs. 59.3% and 74.4%, respectively, **Figure 10**).

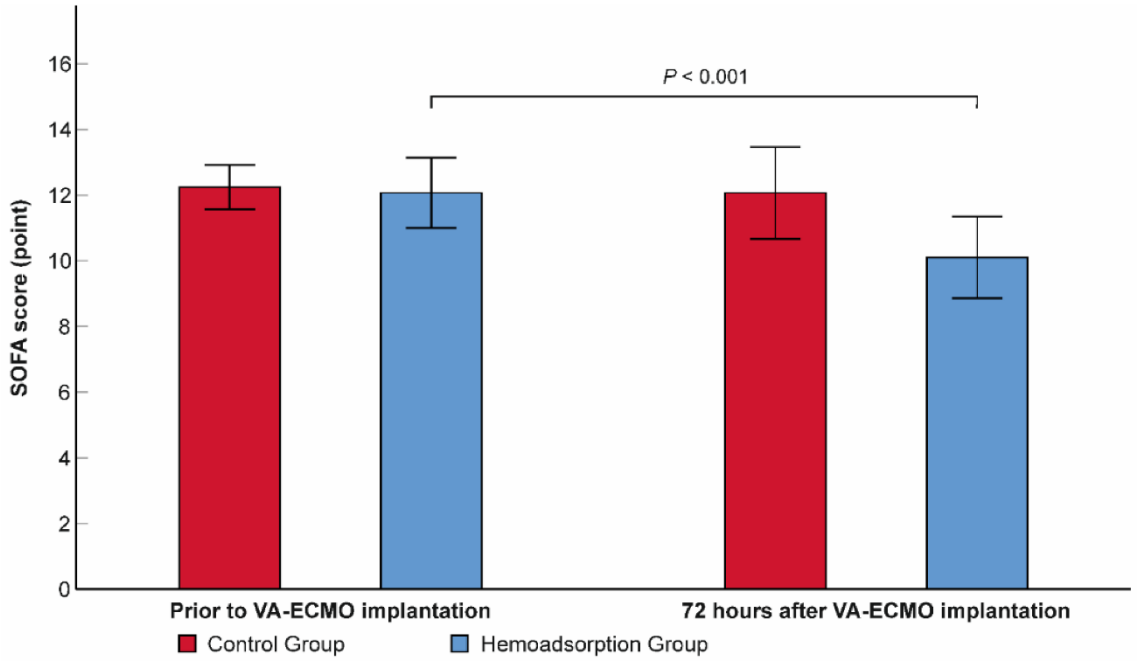


Figure 9. *Within–subjects change in sequential organ failure assessment score over the first 72 hours of venoarterial extracorporeal membrane oxygenation support.* N=58. Data are presented as means. Error bars show 95% confidence intervals. SOFA: sequential organ failure assessment; VA–ECMO, venoarterial extracorporeal membrane oxygenation (72).

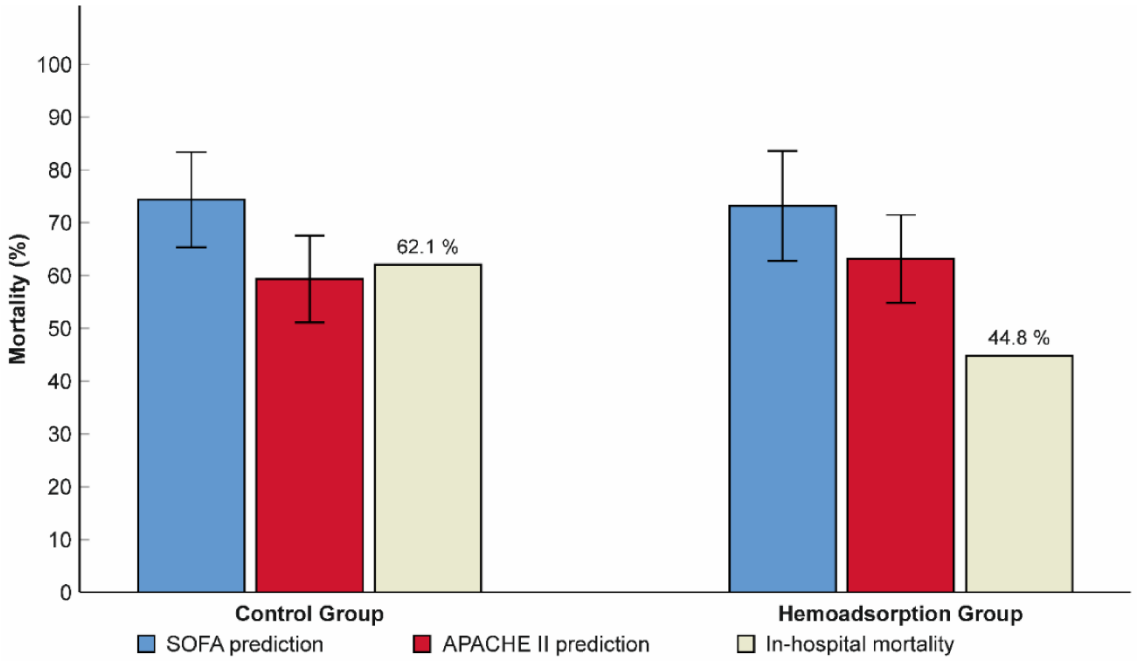


Figure 10. *Relationship between predicted and observed in–hospital mortality rates in patients from the hemoadsorption and control groups.* N=58. Data are presented as means and frequency (%). Error bars show 95% confidence intervals. SOFA: sequential organ failure assessment; APACHE II, acute physiology and chronic health evaluation II (72).

4.2.3 Secondary outcomes

The mean lactate level decreased significantly in both the control and hemoadsorption groups 72 hours after VA–ECMO initiation (2.11 vs. 6.90 mmol/L, $P < 0.001$, 1.57 vs. 6.56 mmol/L, $P < 0.001$, respectively). Nevertheless, the mean lactate was found to be in the normal range and significantly lower in the hemoadsorption than the control group, which persisted outside the lactate upper limit in the latter group at the 72–hour follow–up time point (**Table 6**). Similarly, the $P_{(v-a)}CO_2$ gap declined significantly and normalized after 72 hours of VA–ECMO support in subjects from the hemoadsorption group (4.47 vs. 8.47 mmHg, $P < 0.001$), while the $P_{(v-a)}CO_2$ gap remained elevated and in the pre–ECMO range in the controls (8.13 vs. 9.19 mmHg, $P = 0.109$). We observed a significant reduction in VIS in the two groups during the first 72–hour time frame of VA–ECMO run (control group: 79.2 ± 51.0 vs. 35.2 ± 36.1 points, $P < 0.001$ and hemoadsorption group: 90.0 ± 61.7 vs. 13.8 ± 19.5 points, $P < 0.001$). Additionally, the VIS of the hemoadsorption group was significantly lower comparing to that of the control group (P = 0.007, **Table 6**). The mean CRP showed an increase up to similar ranges in

both the control and hemoadsorption groups (140.05 mg/L vs. 116.69 mg/L, $P = 0.159$, respectively, **Table 6**) after 72 hours of VA–ECMO support. However, the magnitude of the CRP change (delta CRP) was significantly smaller in the hemoadsorption than in the control group (50.13 ± 85.29 mg/L vs. 108.47 ± 87.20 mg/L, $P = 0.005$, respectively, **Figure 11**). The length of mechanical ventilation, intensive care unit, and hospital stays were comparable in the two groups. Early major complications, registered for the first 72 hours of the VA–ECMO support, did not show relevant differences, except for clinically relevant bleeding related to the VA–ECMO application. While this complication had a significantly lower frequency in the hemoadsorption versus control group, the rate of reoperation for bleeding was similar in both groups (**Table 6**). Detailed analyses of the primary and secondary outcome parameters from the hemoadsorption and control groups are shown in **Table 6**. Analysis of cumulative 90–day survival did not reveal a statistically significant difference between the groups; however, there was a trend towards improved mortality in the hemoadsorption group compared to the control group for the complete observational period (**Figure 12**).

Table 6. *Comparative analysis of the primary and secondary outcome parameters in the propensity score matched cohort.* Data are presented as mean ± standard deviation and number of patients (frequency). [a]$P_{(v-a)}CO_2$ gap = $P_vCO_2 - P_aCO_2$; Normal range: 2–6 mmHg (85). [b]Clinically relevant blood loss required conservative (i.e. blood products and factor concentrates) and/or surgical therapy (registered for the post–VA–ECMO implantation period). PS: propensity score; SOFA: Sequential Organ Failure Assessment; VIS, vasoactive–inotropic score; RO: reoperation; PRC: packed red cell; AKI: acute kidney injury; RRT: renal replacement therapy; ICU: intensive care unit (72).

Outcome Measures	**Control Group N = 29**	**Hemoadsorption Group N = 29**	***P***
	PS matched cohort N = 58		
Primary outcome parameters			
72–hour SOFA score, point	12.1 ± 3.7	10.1 ± 3.3	0.040
In–hospital mortality, n	18 (62.1%)	13 (44.8%)	0.180
Secondary outcome parameters			

72–hour pH	7.40 ± 0.04	7.43 ± 0.04	0.048
72–hour lactate, mmol/L	2.11 ± 0.77	1.57 ± 0.96	0.015
72–hour $P_{(v-a)}CO_2$ gap, mmHg[a]	8.13 ± 1.26	4.47 ± 1.69	<0.001
72–hour white blood cell, G/L	11.95 ± 4.32	11.35 ± 6.16	0.650
72–hour C–reactive protein, mg/L	140.05 ± 86.72	116.69 ± 55.33	0.159
72–hour VIS, point	35.2 ± 36.1	13.8 ± 19.5	0.007
Bleeding /72 hours, n[b]	22 (75.9%)	13 (44.8%)	0.049
RO for bleeding /72 hours, n	9 (31.0%)	7 (24.1%)	0.754
PRC transfusion /72 hours, unit	9 ± 9	10 ± 6	0.461
AKI_{total} within 72 hours, n	21 (72.4%)	21 (72.4%)	1.00
RRT within 72 hours, n	15 (51.7%)	19 (65.5%)	0.481
Mechanical ventilation, day	30.3 ± 39.2	34.6 ± 30.3	0.673
Length–of–ICU stay, day	37 ± 45	37 ± 23	0.962
Length–of–Hospital stay, day	49 ± 59	45 ± 33	0.707

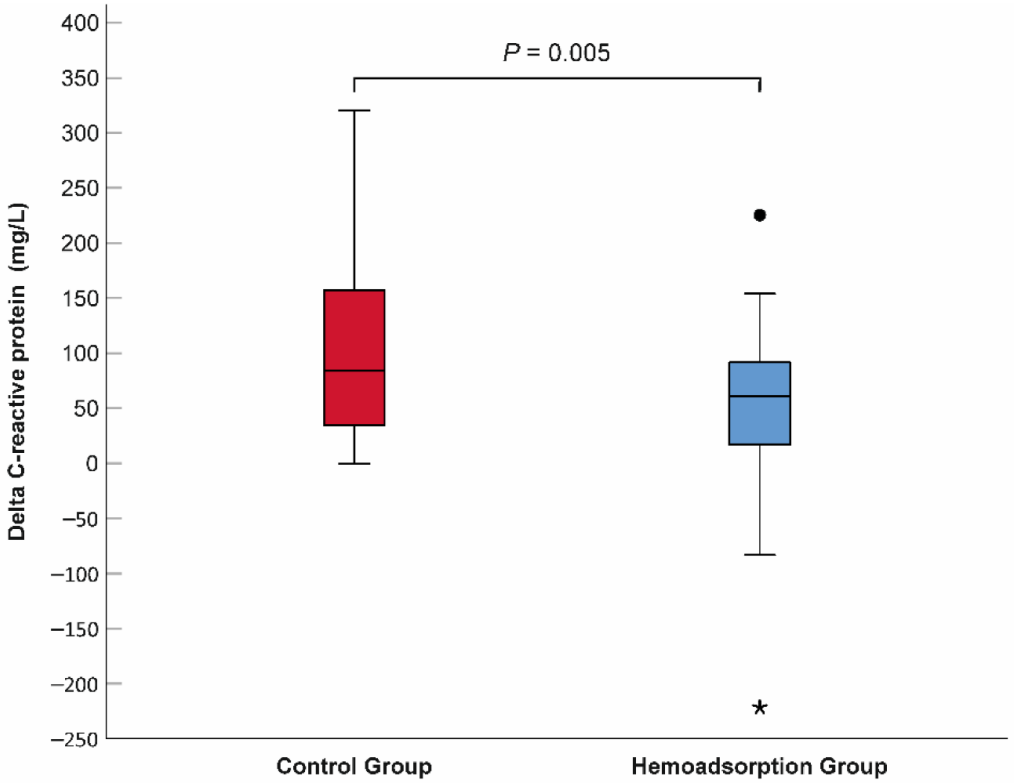


Figure 11. *Comparison of delta C–reactive protein between the hemoadsorption and control groups.* N=58. Delta C–reactive protein = 72–hour CRP – baseline CRP. Filled circle indicates outlier, while asterisk represents extreme value (72).

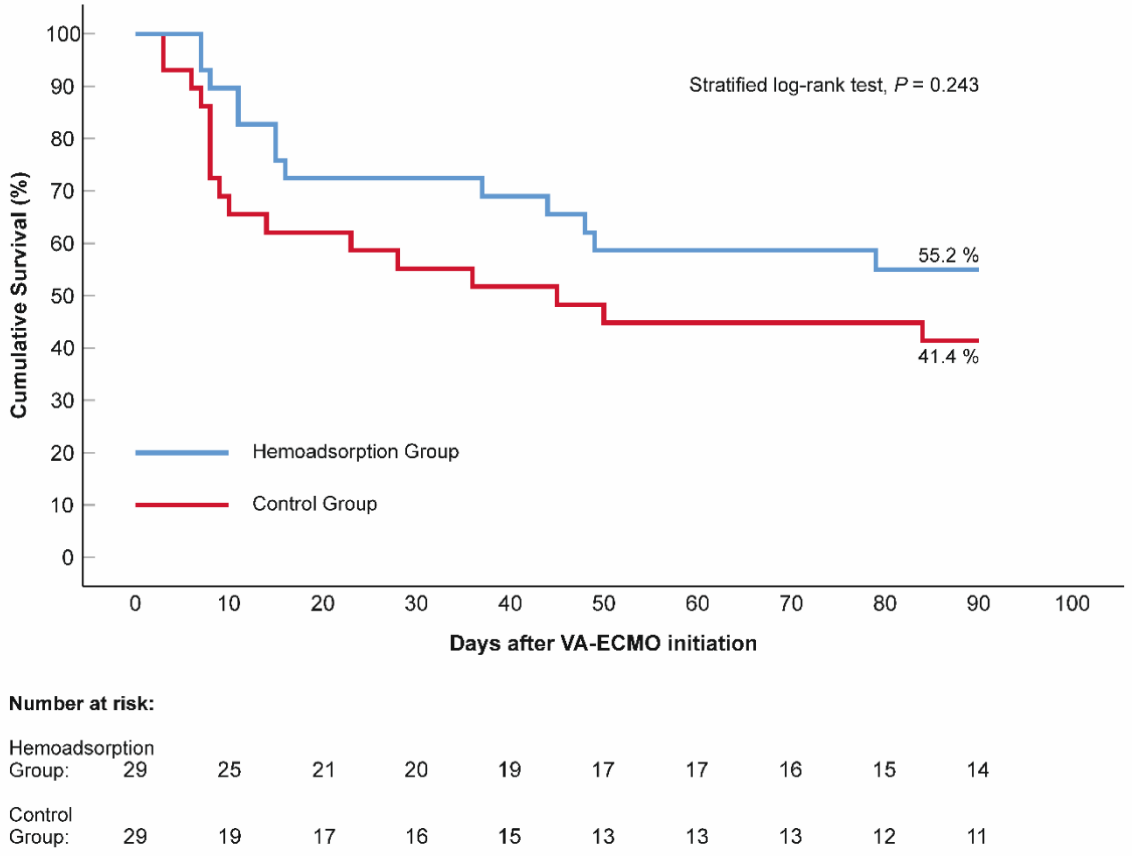


Figure 12. *Kaplan–Meier estimates of cumulative 90–day survival, according to the applied venoarterial extracorporeal membrane oxygenation management.* N=58. The blue line represents the hemoadsorption group, while the red line illustrates the control group. *P* value (stratified log–rank test) indicates the difference in survival. VA–ECMO, venoarterial extracorporeal membrane oxygenation (72).

5 Discussion

5.1 Intraoperative hemoadsorption treatment and its impact on the outcome of patients undergoing orthotopic heart transplantation

5.1.1 Control on development of the severe post–CPB vasoregulatory dysfunction and haemodynamic instability

Patients undergoing OHT are reported to be at a remarkably higher risk for developing severe vasoplegia with an incidence ranging from 11% to 66% based on previous analyses (86–89). Playing a dominant role in post–transplant haemodynamic instability, VS can substantially contribute to the development of post–operative multiple organ dysfunction, resulting in prolonged duration of MV and increased ICU and hospital stays (89). Considering the most relevant predisposing factors for post–transplant VS such as advancing age, elevated body mass index, chronic kidney disease, and expanded CPB time, the two groups were found to be homogenous (87, 89). In this RCT, intraoperative hemoadsorption showed significant associations with reduced post–operative VIS. The median VIS was significantly higher in the control than in the hemoadsorption group, where it was in the range of ≥30 indicating a higher risk for unfavourable outcomes. Among the four major VIS components, decreased vasopressor requirements were the main determinant of the reduced VIS in the hemoadsorption group; however, the doses of inotropes did not differ between the groups (**Figure 4**). These results are indicative of the less severe vasoplegia that developed in the hemoadsorption group, and they are also consistent with the less frequent VS and extreme noradrenaline demand, shortened vasopressor need and decrease in the odds of VS found in the same group. To date, only one observational study performed by our workgroup has investigated the effect of intraoperative hemoadsorption on post–operative vasopressor need and outcome among OHT patients (68). Interestingly, we observed significantly reduced vasopressor requirements linked to hemoadsorption use (68). Similarly, in a propensity score matched analysis of high–risk infective endocarditis patients, the median vasopressor dose on post–operative day 1 was found to be significantly lower in the hemoadsorption group than in controls (36). On the other hand, several recent RCTs including intraoperative hemoadsorption in medium– to high–risk cardiac surgical patients reported controversial data on the post–operative need for vasoactive support (42,

90–93). The results of our RCT are in line with earlier observational studies confirming a clear relationship between intraoperative hemoadsorption and the moderate manifestation of post–operative vasoplegia. Most likely, the discrepancies among these results can be explained by the inhomogeneity of the examined patient populations in terms of perioperative risk for severe vasoplegia.

5.1.2 Modulating the dysregulated post–CPB inflammatory response

One of the theoretical aims for introducing intraoperative hemoadsorption in OHT recipients is to modulate the dysregulated inflammatory response related to OHT surgery. This trial demonstrated a mitigated post–operative PCT response at all pre–defined time points in the hemoadsorption group compared to controls (**Figure 5**) emphasizing a clear modulating effect on the post–CPB inflammatory response. Our previous observational study in OHT patients showed similar kinetics in post–operative PCT in both the hemoadsorption and control groups (68). However, an arbitrary criterion was used to indicate intraoperative hemoadsorption in this previous investigation, definitely influencing patient selection bias in terms of pre–operative immune priming level and increasing the chance of highly diverse post–CPB immune response including PCT kinetics (68).

5.1.3 Clinical effects on post–transplant complications and immunological adverse events

Consistently with the finding of mitigated post–operative PCT response in patients receiving intraoperative hemoadsorption, these patients also exhibited reduced incidence of post–operative organ dysfunction such as severe vasoplegia, respiratory failure and AKI. Additionally, our data indicate a well–preserved hepatic bilirubin excretion in the interventional (PCB < 3.0%) versus control group, in which a significant post–operative decline of this hepatic function was observed (PCB > 70.0%). It has recently been shown that bilirubin can be removed directly by hemoadsorption treatment integrated into extracorporeal devices (94–97). In line with these results, a degree of direct bilirubin removal by intraoperative hemoadsorption can be supposed. The preserved hepatic bilirubin excretion in the interventional group correlated with less manifested post–operative organ dysfunction, associated with reduced VIS and mitigated PCT response as represented in our study group versus controls. The previous observational study in OHT

patients showed only favourable trends in the length of MV, ICU stay, and rate of AKI (68). But the presumably inhomogeneous patient population resulted in different risk and reversibility of post–operative organ dysfunction (68). Our RCT aimed to analyse homogeneous patient groups selecting low risk recipient (i.e. UNOS status 6 patients), which underlines the relative power of the better post–operative complication profile of the hemoadsorption group (69).

Cardiac allograft rejection early after OHT is among the most severe complications which can negatively affect recipients' long–term outcomes (98). High variability in the immunosuppressive drug concentrations is confirmed to be linked to increased risk for acute allograft rejection (99). To date, no data exist on interactions between intraoperative hemoadsorption and immunosuppressive drug concentrations in terms of OHT. Interestingly, Lindstedt et al. did not find histopathological signs of acute rejection at 1– and 3–month posttransplant in patients who received cytokine adsorption during lung transplantation, compared to patients managed without the adsorber (100). Also, a very recently published large animal study reported on an adsorption rate of less than 5% for immunosuppressive agents such as tacrolimus, cyclosporin A, mycophenolate mofetil, everolimus, and methylprednisolone during 6 h of in vivo extracorporeal hemoadsorption treatment (101). Data presented in our RCT strongly substantiate these previous investigations. Similar MPA concentrations were measured pre–CPB and at 2 h of CPB run in the study groups (**Figure 6**), and there were no differences in the frequencies of cardiac allograft rejection over the 1–month follow–up period between the groups (**Table 4**). These results demonstrate significant safety information regarding the interaction between intraoperative hemoadsorption treatment and perioperative immunosuppressive therapy of OHT (69).

5.1.4 Relationship with 1–year survival

In our RCT we involved low risk OHT recipients (median IMPACT score was 4 in both groups, see **Table 2**) with identical pre–operative inflammatory activity and risk profile for post–operative organ dysfunctions (**Table 2**). Accordingly, the registered 30–day mortality rate was 8.0% and 0%, and 1–year survival was 88.0% and 96.7% in the control versus hemoadsorption groups, respectively. In the light of these favourable survival numbers in both groups, a positive impact of hemoadsorption on mortality was

not to be expected. However, our results in terms of proximal endpoints suggest the effectiveness of intraoperative hemoadsorption in controlling the dysregulated inflammatory processes and reducing post–operative organ dysfunctions. In addition, this method of intraoperative immune modulation of OHT surgery did not show a relationship with an increased rate of adverse immunological events, and the use of intraoperative hemoadsorption was not linked to any complications in our study (69).

5.1.5 Limitations of the trial

Our proof–of–concept RCT has strengths and limitations. To the best of our knowledge, our investigation is the first RCT to assess the clinical effects of intraoperative hemoadsorption among OHT patients focusing on proximal primary endpoints. Despite the small sample size, a homogeneous cohort of patients were randomized into two similar arms in terms of clinical characteristics and risk profile. However, due to a lack of any previous RCT in this field based on similar primary outcomes, we did not perform a formal sample size calculation. It is a single–centre study; therefore, the presented results are subject to selection bias requiring external validation by other centres. These limitations in part restrict the interpretation of our results.

5.2 Influence of VA–ECMO integrated hemoadsorption on the early reversal of multiorgan and microcirculatory dysfunction and outcome of refractory cardiogenic shock

5.2.1 Early change of the refractory cardiogenic shock associated multiorgan dysfunction

Multiorgan dysfunction is a dominant contributing factor of in–hospital mortality risk associated with refractory CS (61). The SOFA score is a widely employed composite assessment tool in critical care to classify and monitor multiorgan dysfunction over time (102). SOFA score assessed prior to VA–ECMO initiation has been found to have good predictive value for in–hospital mortality in earlier clinical investigations of patients undergoing VA–ECMO support (103–105). Similarly, a decreasing SOFA score at day 3 of VA–ECMO support has been associated with better hospital survival in the same clinical scenario, demonstrating the link between the early improvement of organ function and outcome (104, 106). In our study, we observed significantly reduced mean SOFA scores in the hemoadsorption group after 72 hours of VA–ECMO start compared to the

initial value (**Figure 9**). Despite the identical combined mechanical and pharmacological circulatory support applied in the control group the mean 72–hour SOFA score persisted in the pre–ECMO range in these subjects. Only very few clinical studies and case series have previously examined the significance of ECMO integrated hemoadsorption on patient outcome–among them, two comparative investigations involving VA–ECMO patients (107–109). Of these two studies only the RCT published by Supady et al. used longitudinal SOFA score follow–up (109). They did not find any significant differences in either the longitudinal change or the 72–hour values of the SOFA scores (109). However, 54.5% of patients in the cytokine adsorption group, and 73.7% of patients in the control group compared to baseline survived the 72–hour timepoint in their study, which restricts the interpretation of SOFA score change in the study groups (109). In our analysis, we excluded patients who died on VA–ECMO within 72 hours to mitigate patient selection bias in the advanced analyses, which resulted in the complete comparison of groups in terms of SOFA score change. Interestingly, in a recent RCT including patients with severe COVID–19 pneumonia requiring venovenous ECMO, a marked reduction in SOFA score was seen in the cytokine adsorption group versus controls with a time frame of 72 hours, despite the lower range of initial SOFA scores registered in the groups (110). These results are in line with the findings of our study supporting the assumption that VA–ECMO integrated hemoadsorption can contribute to accelerate the reversal of multiorgan dysfunction induced by refractory CS (69).

5.2.2 Early change of the macro– and microhaemodynamics

Our analysis confirmed significant reduction of VIS in both groups over the first 72 hours of VA–ECMO support demonstrating an obvious stabilization of the macrohemodynamics. This change of VIS was more robust in the hemoadsorption group than the control group (**Table 6**). However, the restoration of macrohemodynamics during adequate VA–ECMO support does not result in instant and simultaneous improvement in microcirculatory dysfunction (16). Moreover, prolonged impairment of microhemodynamics and tissue oxygen delivery can be an independent factor of unfavourable outcome in patients receiving VA–ECMO support (16, 19, 70). Indeed, ECMO associated pathomechanisms involving plasma fHb and dysregulated inflammatory response linked processes can amplify microcirculatory dysfunction and delay its normalization (16). In this context, the integration of the hemoadsorption

treatment into a VA–ECMO system early on in the clinical course can theoretically control the adverse microcirculatory effects of the aforementioned pathophysiological interferences (111). As a surrogate marker of hemodynamic coherence and microcirculatory function, the $P_{(v-a)}CO_2$ gap was monitored in VA–ECMO patients in a recent retrospective cohort study (112). They found that an elevated $P_{(v-a)}CO_2$ gap measured in the initial course of VA–ECMO support was associated with poor outcome (112). Our data show a significantly lower and normalized 72–hour $P_{(v-a)}CO_2$ gap and lactate level in patients from the hemoadsorption group than controls (**Table 6**). Both parameters suggest early reversal of microcirculatory dysfunction and impaired tissue oxygen delivery in the hemoadsorption group, which was delayed in the controls according to their persistently elevated mean $P_{(v-a)}CO_2$ gap and lactate level registered at 72 hours. Considering the results of our investigation it can be supposed that a 72–hour VA–ECMO integrated hemoadsorption treatment can contribute to the rapid reversal of macro– and microcirculatory dysfunction and restoration of hemodynamic coherence, resulting in improved organ function (72).

5.2.3 Early inflammatory response

Previous case reports and case series demonstrated marked reductions in CRP, procalcitonin, and interleukin–6 (IL–6) related to hemoadsorption treatment combined with VA–ECMO support (81, 113, 114). Nevertheless, most recent PSM– and RCT–based analyses of extracorporeal cardiopulmonary resuscitation (ECPR) patients found comparable CRP and IL–6 levels in both the cytokine adsorption and control group after 72 h of VA–ECMO run (108, 109). The results of our study are different from findings of the latter investigations. While the mean 72–hour levels of CRP were in a similar range in the groups, the magnitude of delta CRP was significantly smaller in the patients from the hemoadsorption than the control group (**Figure 11**), suggesting a mitigated inflammatory response. The possible explanation for this discrepancy can be the divergent patient selections used in the investigations. Unlike the former studies that analysed ECPR patients, we investigated unselected refractory cardiogenic shock patients that received VA–ECMO support, with 62.1% of postcardiotomy cases in each group. Additionally, the more significant immune system priming along with higher mortality rate within 72 hours of patients presented in the cytokine versus control group in the CYTER study assume relevant differences in terms of the severity of initial multiorgan

dysfunction as well as the intensity of the inflammatory response between the analysed groups, which can influence the interpretation of the detected levels of the inflammatory markers (109). Furthermore, the significantly smaller mean delta CRP measured in the hemoadsorption group in our study is in line with the findings of the reduced mean SOFA score, lactate level, and $P_{(v-a)}CO_2$ gap at the 72–hour follow–up point compared to controls indicating the role of the inflammatory control provided by the continuous hemoadsorption in the early reversal of the refractory CS associated multiorgan dysfunction (72).

5.2.4 Clinical effects on the outcome of refractory cardiogenic shock

This study analysed cohorts of patients with various aetiologies for refractory CS. However, both the unmatched and matched cohorts presented comparable frequencies of the typical CS aetiologies with previously reported data (**Table 5**) (115). Due to the between group comparison of clinical characteristics including the major CS aetiologies, APACHE II and SOFA composite scores did not reveal any differences in the PSM cohort; we presumed identical risks for complications and early mortality. The frequency of in–hospital mortality was 62.1% in the control group, which is congruent with the mean predicted values of the pre–ECMO APACHE II and SOFA scores (**Figure 10**). Additionally, the observed in–hospital mortality of the control group is in line with recently published data of non–selected and post–cardiotomy VA–ECMO patients, demonstrating an in–hospital survival rate between 34.4% and 43.4% (104, 116–119). On the other hand, we registered lower in–hospital mortality (44.8%) and better 90–day survival in the hemoadsorption group than in controls in our study. Although these marked differences in the mortality and survival outcome did not reach statistical significance, they are indicative of an early mortality risk reduction to ~50% that might be a result of the improvement in microcirculatory and multiorgan dysfunction linked to the VA–ECMO integrated hemoadsorption treatment. Among the major complications, the observed number of ECMO–associated bleeds showed a significant difference between the two groups. The definition of bleeding complications regarding VA–ECMO support shows large diversity in the publications, which makes for limited comparison possible between the observed and registry data (115). Furthermore, none of the published investigations have examined the frequency of bleeding related to VA–ECMO integrated hemoadsorption treatment to date. In our study, we have defined an ECMO associated

bleeding complication as a clinically relevant event requiring conservative therapy (i.e., blood products and factor concentrates) and/or surgical therapy. Considering the differences in the total number of bleeding events and reoperation rates, our data suggest that the dominant component of the between–group discrepancy is the minor bleeding complication, because the reoperation rates were similar in the groups (**Table 6**). This result from our study raises the possibility that the more frequent instability of the haemostatic system during the early phase of the VA–ECMO support in the control versus hemoadsorption group could be a part of the persistent multiorgan dysfunction presented by the significantly higher mean 72–hour SOFA score in the control group (72). On the other hand, the controlled ECMO circuit–induced inflammatory processes achieved by the continuous hemoadsorption treatment could also contribute to stabilize haemostatic system indirectly gaining more restraint in terms of diffuse bleeding at the surgical sites (72).

5.2.5 Limitations of the study

Our observational study has some limitations. Due to the retrospective design applied in this investigation, we performed the PSM modelling approach to minimize the characteristic discrepancy linked bias. Nevertheless, some hidden confounders may be present. The therapeutic utilization of VA–ECMO integrated hemoadsorption was not strictly protocolized in the study period, and the clinical decision whether to start hemoadsorption treatment or not was at the discretion of the treating physician. Considering these limitations and the sample size of the analysed cohort in part restricts the interpretation of our results.

6 Conclusions

i. The intraoperative hemoadsorption during OHT is associated with better haemodynamic stability, as indicated by a 6.4–fold decrease in the odds of developing VS and less frequent VS in the early post–operative period compared to standard care.

ii. Patients in the hemoadsorption versus the control group experienced a mitigated PCT response, lower rates of post–operative AKI and RRT, more stable hepatic bilirubin excretion, and shorter durations of MV and ICU stay.

iii. Our investigations did not confirm any relevant adsorption effect on MPA and more frequent adverse immunological events such as early cardiac allograft rejection and sepsis related to intraoperative hemoadsorption treatment.

iv. The patients who received a 72–hour length VA–ECMO integrated hemoadsorption treatment realized significant reductions in their SOFA score, faster normalization of macrohemodynamics, metabolic state, and $P_{(v-a)}CO_2$ gap over the same time frame than subjects in the control group, suggesting accelerated recovery of CS–associated multiorgan and microcirculatory dysfunction.

v. The VA–ECMO integrated hemoadsorption treatment was associated with mitigated inflammatory response, less bleeding complications, and lower risk for early mortality predicted by the APACHE II and SOFA composite scores in comparison with controls.

vi. The promising outcomes of our proof–of–concept randomised trial and propensity score–matched cohort study support the necessity for adequately powered RCTs in this field to clarify the potential benefits of the intraoperative– or VA–ECMO integrated hemoadsorption treatment.

7 Summary

The microcirculatory dysfunction is presumed to be the key factor of both the orthotopic heart transplantation (OHT) related– and the refractory cardiogenic shock (CS) related multiple organ failure.

In our proof–of–concept randomised controlled trial (RCT) we compared the effects of the pre–emptive, intraoperative hemoadsorption versus standard medical care on the severity of early postoperative haemodynamic instability, frequency of postoperative organ dysfunctions, early graft rejection, and length of hospital stay in patients underwent OHT. Our trial found that OHT patients who received intraoperative hemoadsorption experienced reduced vasoactive–inotropic score and less severe post–operative vasoplegia compared to standard care alone. The use of intraoperative hemoadsorption was associated with a 6.4–fold decrease in the odds of developing early post–operative vasoplegic syndrome, mitigated procalcitonin kinetics, lower rates of post–operative acute kidney injury and renal replacement therapy, preserved post–cardiopulmonary bypass hepatic bilirubin excretion and shorter durations of mechanical ventilation and intensive care unit stay. Our trial did not confirm any relevant adsorption effect on mycophenolic acid, and did not reveal differences in the frequency and severity of early cardiac allograft rejection as well as in mortality between the groups.

The aim of our retrospective observational study was to analyse the clinical impact of VA–ECMO integrated hemoadsorption in terms of early reversal of multiorgan– and microcirculatory dysfunction, and short–term clinical outcomes in patients undergoing VA–ECMO support for refractory CS, using propensity score matching. Our study demonstrated that patients who received a 72–hour period of hemoadsorption treatment showed a significant reduction in SOFA score, faster normalization of macrohemodynamics, metabolic state and $P_{(v-a)}CO_2$ gap, and lower risk for early mortality than patients in the control group. VA–ECMO integrated hemoadsorption treatment was associated with reduced delta CRP and less bleeding complications compared with the controls.

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9 Bibliography of the candidate's publications

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