Vasoplegia after heart failure surgery

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CHAPTER 1

General introduction and thesis outline

Introduction

Heart failure is a clinical syndrome that affects approximately 1-2% of the adult population in developed countries.[1] The syndrome is characterized by the inability of the heart to supply blood in quantities commensurate to the organs needs. It results in typical symptoms and signs of heart failure including breathlessness, reduced exercise tolerance, fatigue, ankle edema and orthopnea. The severity of heart failure symptoms is described according to the New York Heart Association (NYHA) functional classification, ranging from class I (no symptoms and no limitations in ordinary physical exercise) to class IV (symptoms at rest). The natural course of heart failure is unpredictable and different for each patient, but in general the disease progresses over time. The ACC/AHA stages of heart failure comprehensively classify this with stage A indicating patients at high risk for heart failure but without structural heart disease or symptoms of heart failure; stage B indicating patients with structural heart disease without symptoms or signs; stage C indicating patients with structural heart disease with prior or current symptoms of heart failure; and stage D indicating patients with refractory heart failure requiring specialized interventions.[2]

Coronary artery disease is the most common cause of heart failure, but the etiology can be diverse.[1, 3] Other causes are: diseases primarily affecting myocardial tissue (including toxic, immune-mediated, genetic), abnormal loading conditions (including hypertension, valvular and myocardial structural defects, volume overload) and arrhythmias (tachy- and bradyarrhythmia).

The therapeutic options for patients with symptomatic heart failure substantially increased over the last years. Lifestyle changes, such as reducing water and salt intake, can help ease the workload of the heart.[1] Medical management, the mainstay of heart failure treatment, provides the recovery path leading to reverse remodeling in patients with heart failure and a reduced ejection fraction. For these patients, the traditional backbone of medical treatment consists of diuretics combined with an angiotensin converting enzyme (ACE) inhibitor or angiotensin II receptor antagonist and a beta-blocker. Over the last decade, the medical options were extended with mineralocorticoid receptor antagonists and ivabradine. More recently, angiotensin receptor neprilysin inhibitors and inhibitors of the sodium-glucose co-transporter 2 were added.[1] If a patient, despite these novel and effective medical treatment options, remains symptomatic, invasive therapy can be of substantial value.

Invasive treatment for (advanced) heart failure

When optimal medical therapy provides insufficient relief and the disease has progressed to ACC/AHA stage C or D, invasive therapy can be considered. Theoretically, the therapeutic options are wide, but the underlying pathology mainly guides the choice of treatment.[1, 3, 4] In patients with significant coronary artery disease, revascularization (either percutaneous or surgical) can be of added value.[1] In patients with a reduced left ventricular function and significant left ventricle desynchrony, cardiac resynchronization therapy improves symptoms and reduces morbidity and mortality.[1] Further, in patients with severe valvular disease, alleviation of valve insufficiency or valve stenosis (either percutaneous or surgical) can reduce symptoms and enhance cardiac function and prognosis.[1] For patients with arrhythmias, ablation can be considered.[1] If (the chance of developing) ventricular arrhythmias persist, an implantable cardioverter defibrillator improves survival. Furthermore, in patients with a large myocardial scar and an unfavorable left ventricular geometry, surgical left ventricular restoration can be considered. Since in the majority of patients a combined approach is warranted to substantially improve clinical status and prognosis, the multidisciplinary cardiothoracic team discusses the different treatment options. If the above described "conventional" treatment options provide insufficient relief, cardiac transplant or long-term mechanical support should be considered.[1] As an introduction to this thesis, a detailed description of the distinct surgical treatment options is provided below.

Surgical revascularization of ischemic territories: coronary artery bypass grafting

Coronary artery disease is the most frequent cause of heart failure. Myocardial revascularization in heart failure patients is recommended when angina persists despite anti-angina drugs.[1] In addition, it should be considered in patients with heart failure and a reduced ejection fraction and significant coronary artery disease (left main stenosis, proximal left anterior descending or multi-vessel disease), where patients with more than 10% dysfunctional but viable left ventricle myocardium seem to have most benefit. If a percutaneous approach is unfeasible or is associated with a substantial risk of peri-procedural complications, a surgical approach is preferred. Furthermore, if cardiac surgery is performed for another indication (such as mitral valve insufficiency), concomitant revascularization of significantly stenosed proximal coronary arteries is advised.[4]

Functional mitral valve insufficiency and restrictive mitral annuloplasty

Left ventricular dysfunction or dilation (either with an ischemic or non-ischemic origin) can result in functional mitral regurgitation due to downward and outward displacement of papillary muscles.[5] This causes tethering of one or both mitral valve leaflets by traction on

the native chords, resulting in systolic restriction and mal-coaptation of the mitral valve leaflets. This in turn, results in functional mitral regurgitation, characterized as Carpentier Type IIIb. When the mitral regurgitation progresses to severe, surgical restrictive mitral annuloplasty should be considered as a treatment option, especially when accompanied by significant coronary artery disease for which revascularization is indicated. This surgical technique consists of implantation of a complete semi-rigid annuloplasty ring that is sized in order to reduce the annular perimeter and reduce the anteroposterior diameter of the mitral valve.[5] To this end, the ring is sized according to the surface of the anterior mitral valve leaflet. Subsequently, a ring that is 2 ring-sizes smaller than the one that would fit the anterior mitral valve leaflet, will be implanted. In this manner, the anteroposterior diameter is reduced and sufficient coaptation for the restricted mitral valve is obtained. Whether or not the restrictive mitral annuloplasty is indicated, is also depending on the end-diastolic diameter of the left ventricle. When the left ventricle is severely dilated, then the chance of durable reduction or abolishment of functional mitral regurgitation is questionable and the chance of reverse remodeling of the diseased ventricle is slim. The indication for mitral valve replacement in these patients is still a matter of debate in current literature.[5, 6] In patients who are ineligible for mitral valve surgery, due to high surgical risk, then transcatheter Edge to Edge Repair (TEER), using for instance MitraClip or Pascal device could be a valid option,[5] but only when the component of functional mitral regurgitation is severe and the left ventricle not too dilated.[7]

Surgical left ventricular restoration, reshaping the left ventricle

Myocardial infarction leads to scar formation. This can lead to aneurysm formation, especially after a large anterior wall myocardial infarction. Aneurysm formation is characterized by progressive dilation and thinning of the infarcted area of the ventricular wall and adversely affects contractility of the remote myocardium by increasing wall tension. Over time, the left ventricle dilates and the left ventricle loses its geometrically ideal oval shape and becomes more spherical in shape. The loss of contractile myocardium, the depressed function of the remote myocardium and the paradoxical bulging of the scar tissue in systole, may result in severely decreased cardiac output. When a patient has progressed to advanced stages of heart failure, surgical left ventricular restoration could be considered. Over the years, several surgical techniques have been developed to restore shape and function of the infarcted and aneurysmatic left ventricle.[8] The most frequently used procedure has been described by Vincent Dor et al.[9] After cardioplegic arrest, the infarcted area is incised. When the endocardial border-zone of the infarcted area is identified, a Fontan stitch is placed at this border-zone, marking the transition to healthy myocardium. Subsequently, a mannequin, inflated to the volume of 55-60mls/m^2 BSA, is inserted in the remaining left ventricular cavity and the Fontan stitch is tied around the mannequin. The remaining apical defect is closed using a Dacron patch,

herewith excluding the aneurysmatic part of the left ventricle. This reshapes the still functional part of the left ventricle to its ideal oval shape, thereby restoring left ventricular ejection fraction and improving forward flow. Several studies have compared the clinical outcome after surgical left ventricular restoration with concomitant surgical revascularization with coronary artery bypass surgery alone. These studies demonstrated a significant improvement in clinical symptoms and left ventricular systolic function that improves survival and symptoms.[8, 10] In contrast, the results of a large multicenter randomized controlled STICH trial failed to demonstrate a significant improvement in survival after surgical ventricular restoration.[11] However, the results of this study are debated in literature, because many of the included patients did not have a significant apical aneurysm to start with.[12] Although the numbers of patients have plummeted after publication of this study, we still encounter patients that benefit from this procedure. Patient selection seems to play an important role in the outcome after surgery. Patients should have enough viable myocardium to generate cardiac output (mainly reflected by the validated Wall Motion Score Index). Furthermore, preoperative right ventricular systolic dysfunction[13] and a postoperative end-systolic volume index greater than 70 mL/m(2)[14] are associated with unfavorable outcome.

Non-ischemic dilated cardiomyopathy, implantation of CorCap cardiac support device

In patients with idiopathic or non-ischemic cardiomyopathy, the left ventricle is globally dilated and in many of these patients, also the right ventricle is involved. The combination of left sided or biventricular dilation may result in functional mitral and tricuspid regurgitation for which there may be an indication for surgical intervention when patient enters the more advanced stages of heart failure. While in surgical left ventricular restoration, a ventricular component is added to the treatment strategy to prevent further left ventricular dilation and induce cardiac reverse remodeling, for idiopathic cardiomyopathy, this is not a valid option. Therefore, from 2008-2012 the Corcap cardiac support device ((Acorn CV, St Paul, Minnesota, USA) was implanted in these patients. The Corcap consists of a polyester mesh that was tailored around the heart in order to support the ventricle during diastole, thereby preventing further ventricular dilation and induce remodeling.[15] Despite encouraging results by our own group, penetrance in the cardiosurgical community was low and due this underusage, in 2008 the FDA disapproved further device trials due to the disappointing clinical outcomes of the support device with regard to NYHA functional class, survival and severe adhesions and fibrosis.[16]

Heart transplantation and left ventricular assist device implantation

When the patients' condition further deteriorates despite optimal medical treatment and cardiac resynchronization therapy and, after careful consideration of the heart failure team, catheter intervention and surgical options have been exhausted, then the question rises whether or not the patients could be amenable for cardiac replacement therapy. Although mechanical circulatory support has developed in the past decades to a reasonable alternative to cardiac transplantation, to date, heart transplantation is still the gold standard in the combat of end-stage chronic heart failure.[1] However, donor shortage is still the Achilles heel of this treatment modality and a significant proportion of patients perishes while awaiting cardiac transplantation. A substantial portion of these patients receive a left ventricular assist device while waiting for cardiac transplantation as a so-called bridge to transplant (LVAD-BTT). Many of the patients receiving an LVAD as a bridge to transplant, will never reach their heart transplantation and effectively these LVAD's are implanted as permanent long-term solution. Heart transplantation is, and will be, for the happy few.

A much larger group of patients with end-stage chronic heart failure is not amenable for cardiac transplantation due to comorbid conditions.[1] In 2010, our departments of Cardiothoracic surgery and Cardiology launched a LVAD program for patients with advanced heart failure that are not amenable for cardiac transplantation, so called Destination Therapy (LVAD-DT). The Leiden University Medical Center was the first center with a LVAD destination program in the Netherlands and one of the first in Europe. Haeck et al demonstrated that LVAD destination therapy is a promising treatment for patients with end-stage heart failure and meanwhile, LVAD-DT has been deemed refundable care by the Dutch healthcare system.[17] This year our department will implant the 100th LVAD as destination therapy.

Impact of heart failure surgery on post-operative course

Although the benefits of surgical intervention for heart failure are well established,[1, 3, 4] surgical procedures in this fragile patient population are not without risks. Even with a specialized team of heart failure cardiologists, heart failure surgeons, cardiac anesthesiologists and a dedicated intensive care team, the postoperative course of these patients is not frequently uneventful. Postoperative complications like bleeding, infections, renal failure, and especially, low cardiac output, are far less well tolerated in this vulnerable patient population. Remarkably, it seems that these patients are more susceptible to the combination of surgical trauma and the use of extracorporeal circulation than non-heart failure patients. With the use of cardiac inotropes and careful monitoring, the intensivists manage to maintain cardiac output well above a cardiac index which, in normal physiological conditions, should be sufficient to maintain an adequate

perfusion pressure. However, in a significant number of patients, we observe a profound hypotension after surgery that responds poorly to the administration of exogenous catecholamines. In previous research by our group,[18] we demonstrate that heart failure patients respond differently to the combination of surgical trauma and exposure to extracorporeal circulation when compared to non-heart failure patients. While Kortekaas and co-workers demonstrated that cardiac ischemia and reperfusion injury cannot be accounted for these marked differences, we hypothesize that the reactivity of the vascular system, or at least the resistance arterioles responsible for maintenance of vascular tone, may be altered in heart failure patients. The result is therapy-resistant systemic hypotension which jeopardizes end-organ perfusion. This condition is known as vasoplegia.

Vasoplegia

Definitions of vasoplegic syndrome, shock and systemic inflammatory response

Vasoplegia, also known as vasoplegic syndrome, is a form of distributive shock.[19] Shock is a life-threatening condition of acute circulatory failure. It can be categorized in four groups: cardiogenic, hypovolemic, distributive and obstructive (see Table 1). However, in many patients the shock type is multifactorial.

Table 1. Different shock types.

Shock types	Causes	MAP	CO	SVR
Cardiogenic	Heart failure Myocardial infarction Arrhythmia	↓	↓	↑
Hypovolemic	Hemorrhagic Non-hemorrhagic (eg, diarrhea)	↓	↓	↑
Distributive	Septic Anaphylaxis Neurogenic Systemic inflammatory response syndrome	↓	↑↓	↓
Obstructive	Tamponade Pneumothorax Pulmonary embolism	↓	↓	↑

MAP: mean aterial pressure; CO: cardiac output; SVR: systemic vascular resistance.

Systemic inflammatory response syndrome (SIRS) is an inflammatory response induced by trigger which can either be infectious or non-infectious. In the case of postoperative vasoplegia, surgery is the trigger of SIRS. Vasoplegia is characterized by the combination of low systemic vascular resistance, and a normal or high cardiac output. The prolonged hypotension and the associated decrease in organ perfusion caused by vasoplegia, lead to increased morbidity and mortality.[20, 21] The most common cause of vasoplegia is sepsis, but it is also seen after major non-cardiac surgery, burns, multiple trauma and pancreatitis.[22] The used definition for vasoplegia after cardiac surgery varies widely between studies.[23] Commonly used parameters are systemic vascular resistance, mean arterial pressure, cardiac index and vasopressor use, but the used combination and cut-off points of these parameters differ. Table 2 provides an overview of the used definitions for vasoplegia in studies on vasoplegia after heart failure surgery.

Epidemiology and risk factors

The incidence of vasoplegia after cardiac surgery ranges from 5 to 54%.[24, 25] On pump cardiac surgery[26] and a reduced left ventricular ejection fraction[27, 28] are related to an increased risk on vasoplegia. Dayan et al. conducted a meta-analysis for the risk factors for vasoplegia after cardiac surgery on cardiopulmonary bypass.[23] They excluded studies on congenital and heart transplant patients and small studies (less than 10 patients in either group). They were able to include 30.035 patients from 10 different studies, of whom 1524 develop postoperative vasoplegia. They identified preoperative renal failure as risk factor. Patients undergoing isolated coronary artery bypass grafting had a lower risk on post-operative vasoplegia, whereas previous cardiac surgery and combined procedures were associated with an increased risk. Furthermore, higher use of red blood cells, longer aortic cross-clamp and cardiopulmonary bypass time increased the risk on vasoplegia.

The epidemiology of vasoplegia after cardiac surgery in heart failure patients is only studied in patients undergoing heart transplantation or left ventricular assist device implantation (see Table 3). In this population the incidence of vasoplegia ranges from 11-54%.[20, 25, 29-34] The risk factors for vasoplegia after heart failure surgery differ between studies. This is caused by the variation in used definition for vasoplegia and study population. Higher preoperative creatinine levels,[25, 30-40] higher weight[20, 25, 29] and longer cardiopulmonary bypass times[29, 31, 32, 34] were found to be associated with an increased risk on vasoplegia in several studies. The results on the effect of the use of a ventricular assist device pre-transplant were inconclusive[25, 29, 31].

Table 2. Overview of the used definition of vasoplegia in studies on vasoplegia after heart failure surgery.

Study	MAP (mmHg)	SVR (dynes/s/cm^5)	CI (L/min/m^2)	Vasopressors	LVEF (%)	Serum bicarbonate (mEq/l)	Timing
Chemma-Iakuzhy 2001 [25]		≤800				≤20	A single reading postoperative
Byrne 2004 [20]		≤800				≤20	A single reading, within 4 days postoperative
Patarroyo 2012 [29]		<800	>2.5	≥2 vasopressors (epinephrine ≥4 µg/min; norepinephrine ≥4 µg/min; dopamine ≥5 µg/kg/min; vasopressin ≥1 U/h)			2 consecutive readings, within 6-48 hours post-surgery
Chan 2017 [31]			≥2.0	Vasopressin; norepinephrine; or epinephrine [>5 µg/min]) to maintain MAP >70 mmHg	≥55%		For >24 hours, within 48 hours postoperative
Chan 2018 [30]			>2.0	Vasopressin; norepinephrine; or epinephrine [>5 µg/min]) to maintain MAP >70 mmHg	≥55%		For >24 hours, within 48 hours postoperative
Tecson 2018 [32]			Normal	Vasopressors to maintain MAP >70 mmHg. Mild: 1 vasopressor (vasopressin, norepinephrine, or epinephrine [>5 µg/min]). Moderate/severe: ≥2 vasopressors.	Normal		For >24 hours, within 48 hours postoperative
De Waal 2018 [33]	≤50	≤800	>2.5	Norepinephrine ≥200 ng·kg^{-1}·min^{-1}; epinephrine ≥200 ng·kg^{-1}·min^{-1}; dopamine ≥30 µg·kg^{-1}·min^{-1}; phenylephrine ≥2 µg·kg^{-1}·min^{-1}; or vasopressin ≥0.08 U·min^{-1})			For ≥3 hours, within 48 hours postoperative
Asleh 2019 [34]		<800	>2.5	≥2 vasopressors (vasopressin; norepinephrine; or epinephrine [>5 µg/min]) to maintain MAP >70 mmHg			For >24 hours, within 48 hours postoperative

MAP: mean arterial pressure; SVR: systemic vascular resistance; CI: cardiac index; LVEF: left ventricular function.

Table 3. Overview of studies on vasoplegia after heart failure surgery.

Study	Study population	Incidence of vasoplegia	Factors associated with vasoplegia	Early post-operative outcome after vasoplegia	Long term outcome after vasoplegia
Chemmalakuzhy 2001 [25]	Heart transplantation (N=70)	54% (N=38)	Preoperative Univariate: Caucasian; height; weight; beta-blockers; waiting time; creatinine. No African-American; no mechanical circulatory assistance. Multivariate: weight. Intraoperative Univariate: ischemic time. Multivariate: ischemic time.	Higher: 30-day mortality.	Not reported.
Byrne 2004 [20]	Orthotopic heart transplantation (N=147)	19% (N=28)	Preoperative Univariate: BSA Multivariate: intravenous heparin; no inotropica.	Higher: ECMO; hospital mortality; reoperation for bleeding; ICU stay. No difference: IABP; LVAD; RVAD; cardiac arrest; deep sternal wound infection; open chest; myocardial infarction; pneumonia, stroke; dialysis; hospital stay.	Not reported.
Patarroyo 2012 [29]	Orthotopic heart transplantation (N=311)	11% (N=35)	Preoperative Univariate: UNOS status 1A; BSA; history of thyroid disease; previous cardiac surgery; aspirin; calcium channel blocker; ventricular assist device; total artificial heart; TSH. no milrinone, lower albumin. Multivariate: history of thyroid disease; ventricular assist device. Intra-operative Univariate: CPB time; donor heart ischemic time	Higher: ICU and hospital stay; intubation time; 30-day mortality; ECMO; IABP; reoperation for bleeding; open chest; mediastinitis.	Not reported.

Chan 201731	Orthotopic heart transplantation (N=347)	30.8% (N=107)	Preoperative univariate: blood transfusion; long-term mechanical circulatory support device; creatinine; aspartate aminotransferase. Intraoperative univariate: CPB time; ischemic time; total blood products.	Higher: reoperation for bleeding; mechanical ventilation time; ICU and hospital stay.	After 1 year: Higher: CVVH; hemodialysis. No difference: non-fatal major adverse cardiac events; cardiac allograft vasculopathy; infection; survival; rejection.
Chan 2018 [30]	Orthotopic heart transplantation (N=244)	34.8% (N=85) Mild: 74.1% (N=63) Moderate/severe: 25.9% (N=22)	Preoperative univariate: prior cardiothoracic surgery; creatinine. Intraoperative univariate: CPB time.	Higher: vasopressor use; intubation time; ICU and hospital stay. No difference: 30-day survival.	No difference: rejection; renal replacement therapy; liver cirrhosis; infection; survival at 1 year.
Tecson 2018 [32]	Left ventricular assist device implantation (N=252)	49.2% (N=124) Mild: 26.6% (N=67) Moderate/severe: 22.6% (N=57)	Preoperative Univariate: MELD score; HeartMate II score; creatinine; vasopressor dependent; length of stay. Multivariate: INTERMACS Intraoperative Univariate: volume ultrafiltrated; concomitant procedure CPB time; cross-clamp use. Multivariate: CPB time.	Higher: major bleed; right heart failure; respiratory failure; hospital stay; 30-day mortality. Lower: driveline infection. No difference: gastrointestinal bleed; pump thrombosis; stroke.	No difference: 1 year mortality.
De Waal 2018 [33]	Short-term (N=19) and long-term (N=99) continuous flow left ventricular assist device implantation implantation (total N=118)	33.1% (N=39) Short-term: 52.6% (N=10) Long-term: 29.3% (N=29)	Preoperative univariate: dopamine use; VIS; bilirubin; creatinine.	Higher: VIS; resternotomy; renal failure; CVVH; ICU mortality; ICU and hospital stay; 30-day mortality. No difference: open chest; mediastinitis; stroke; right ventricular failure; RVAD, gastrointestinal bleeding; pneumonia; pump thrombosis; lactate acidosis; delirium.	Higher: 1 year mortality.

Asleh 2019 [34]	Heart transplantation after bridging with LVAD (N=94)	46.8% (N=44)	Preoperative Univariate: age; duration of LVAD support; Charlson comorbidity index; creatinine. Multivariate: age; duration of LVAD support; creatinine. Intraoperative Univariate: combined organ transplantation. Multivariate: CPB time.	Higher: ICU and hospital stay; duration of vasopressors, inotropes and mechanical ventilation. No difference in mechanical support; 30-day mortality.	Higher: 1 year mortality; all-cause mortality (mean follow-up: 4 years). Lower: eGFR after 1 year. No difference: rejection; infection; allograft LVEF.

BSA: *body surface area; CPB: cardiopulmonary bypass; CVVH: continuous veno-venous hemofiltration; ECMO: extracorporeal membrane oxygenation; eGFR: estimated glomerular filtration rate; IABP: intra-aortic balloon pump; ICU: intensive care unit; INTERMACS: interagency Registry of mechanically assisted circulatory support; LVAD: left ventricular assist device; LVEF: left ventricular ejection fraction; MELD: model for end-stage liver disease; RVAD: right ventricular assist device; TSH: thyroid stimulating hormone; UNOS: united network for organ sharing; VIS: vasoactive inotropic score.*

The pathophysiology of vasoplegia is thought to be multifactorial and depends on both patient and surgical/procedural characteristics.[19] Vasoplegia after on-pump cardiac surgery is the result of inactivation of vasoconstriction and activation of vasodilation as shown in the mechanism proposed by Busse et al (see Figure 1).[19] Vasoconstriction occurs when vascular smooth muscle cells contract. This contraction is induced after binding of a ligand (e.g. norepinephrine, antidiuretic hormone, angiotensin II) to their receptor on the vascular smooth muscle cell. This induces an influx of calcium in the cytosol and leads eventually to phosphorylation of myosin, which causes contraction of the vascular smooth muscle cell. Vasodilatation occurs when vasodilators (e.g. nitric oxide) increase cyclic guanosine monophosphate (cGMP) concentrations in the vascular smooth muscle cell, which leads to dephosphorylation of myosin light chain. As shown in Figure 1, inflammatory mediators released during cardiopulmonary influence these pathways, leading to vasodilation.

The pathophysiological mechanism behind the increased risk of vasoplegia after heart failure surgery is currently unknown. We hypothesize that the fragile balance of vasoconstrictor and vasodilatory abilities of the vascular system in heart failure patients could be easily disturbed, making them more prone to develop vasoplegia. Several mechanisms that are characteristic for heart failure patients could contribute to this risk. For example, the levels of norepinephrine, antidiuretic hormone and angiotensin II are already elevated in heart failure patients before surgery.[35] The systemic inflammatory response reaction initiated by the cardiopulmonary bypass and the surgical trauma, could further deplete the stocks, leading to inactivation of these vasoconstriction pathways.[19,36] Furthermore, the chronic endogenous adrenergic stimulation in heart failure patients seems to result in downregulation and/or desensitization of vascular α1-adrenoreceptors which alternates the responsiveness of the vascular system to vasoconstrictors.[37] In addition, the medication that is used to support heart failure patients (e.g. angiotensin-converting enzyme (ACE) inhibitors, beta-blockers, angiotensin receptor blockers, diuretics) influence the hemodynamics and the ability of the vascular system to respond to alterations (see Table 4).

Figure 1. Pathophysiology of vasoplegia after on-pump cardiac surgery. Inflammatory mediators released during cardiopulmonary, e.g. interleukin 1 (IL-1), interleukin 6 (IL-6) and tumor necrosis factor alpha (TNFα) can lead to: 1) downregulation of alpha-1 adrenergic receptor (α1) and angiotensin type-1 receptor (AT1); 2) increase of vasoconstrictive mediators with subsequent depletion; 3) activation of inducible nitric oxide synthase (iNOS) which leads to production of nitric oxide (NO). Nitric oxide increases cyclic guanosine monophosphate (cGMP) and activation of ATP-sensitive potassium channels (KATP), leading to inhibition of vasoconstriction. Depletion of norepinephrine (NE), antiduretic hormone (ADH) and angiotensin II (ATII) results in decreased activation of the alpha-1 adrenergic receptor, vasopressin-1 receptor (V1) and angiotensin type-1 receptor. Source: Busse et al.[19]

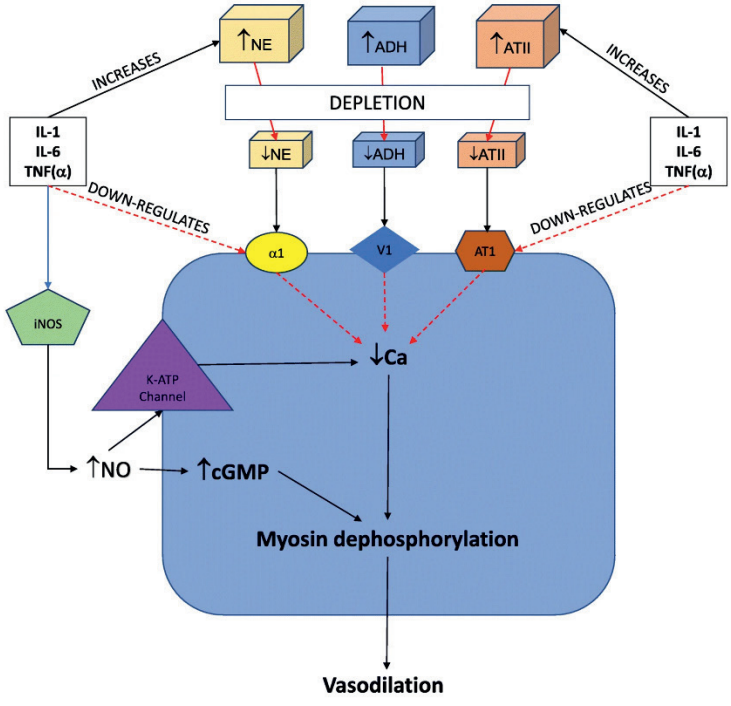

Table 4. Drugs commonly used in heart failure patients and their effects

Drugs		Mechanism	Hemodynamic effects
Beta-blockers		Receptor antagonists that block β1 (selective) β1 and β2 (non-selective) adrenoceptors, thereby preventing binding of (nor)epinephrine.	Cardiac effects: decrease contractility, relaxation state, heart rate and conduction velocity. Vascular effects: mild vasoconstriction.
Angiotensin-converting enzyme inhibitors		Inhibition of the renin–angiotensin-aldosterone system (RAAS) by inhibiting the formation angiotensin II from angiotensin I.	Vasodilation, which reduces the pre- and afterload. Promote diuresis and natriuresis. Downregulates sympathetic adrenergic activity.
Angiotensin receptor blockers		Receptor antagonists that block type 1 angiotensin II receptors on bloods vessels and other tissues (e.g. heart, kidney) thereby preventing angiotensin II from binding. Sometimes used in combination with a neprilysin inhibitor (prevents the breakdown of natriuretic peptides).	Vasodilation, which reduces the pre- and afterload. Downregulates sympathetic adrenergic activity. Promote diuresis and natriuresis.
Diuretics	Loop diuretics	Inhibit the sodium-potassium-chloride cotransporter in the thick ascending limb of the glomerulus.	Promote diuresis and natriuresis. Thereby decreasing the preload, ventricular stroke volume, cardiac ouput en blood pressure.
	Thiazides	Inhibit the sodium-chloride transporter in the distal tubule of the glomerulus.	
	Potassium-sparing diuretics	E.g. aldosterone receptor antagonists: inhibit the aldosterone receptor at the distal tubule of the glomerulus.	

Treatment

Treatment strategies of vasoplegia are focused on fluid resuscitation and activation of vasoconstriction by stimulation of the sympathetic nervous system (norepinephrine, epinephrine, phenylephrine, dopamine), the arginine-vasopressin system (vasopressin), and the renin-angiotensin-aldosterone system (angiotensin II). Other options aim at the inhibition of vasodilatation by influencing the nitric oxide pathway and inflammation (methylene blue, hydroxocobalamin, vitamin C, thiamine and corticosteroids).[19] Norepinephrine is considered the first-line agent for treatment of vasoplegia.[38] Second-line agents include other catecholamines or vasopressin.[19] If the first- and second-line agents fail to improve hemodynamics,

one of the other options may be considered, but further research to validate these protocols is necessary.

Outcome

Vasoplegia is associated with and increased risk on morbidity and mortality in the early post-operative period after heart transplantation and left ventricular assist device implantation (see Table 3). Vasoplegic patients were intubated longer[29-31, 34] and received more frequently extracorporeal membrane oxygenation,[20, 29] reoperation for bleeding[20, 29, 31] and resternotomy[33]. Furthermore, respiratory failure[32] and major bleeding[32] were more often seen in vasoplegic patients. Vasoplegia seemed not to effect the rate of left ventricular assist device[20] and right ventricular assist device[20, 33] implantation, pneumonia, [20, 33] gastrointestinal bleed,[32, 33] pump thrombosis[32, 33] and stroke[20, 32, 33] in the early post-operative period. Results on the occurrence of mediastinitis,[29, 33] right ventricular failure,[32-34] IABP use,[20, 29] dialysis,[20, 33] and open chest treatment[20, 29, 33] were inconclusive. Vasoplegic patients were admitted longer to the intensive care unit[20, 29-31, 33, 34] and the total hospital stay was prolonged as well.[29-34] Most studies showed a higher 30-day mortality rate in vasoplegic patients [25, 29, 32, 33] and a higher hospital mortality[20]. However, two studies did not find a difference in 30-day mortality.[30, 34]

The studies in patients undergoing heart transplantation and left ventricular assist device implantation were inconclusive on the effect of vasoplegia on 1 year mortality rates. Three studies did not find a difference between vasoplegic and non vasoplegic patients,[30-32] whereas two research groups found a higher 1-year mortality rate in vasoplegic patients[33, 34]. After a mean follow-up of 4 years, a higher all-cause mortality was found in vasoplegic patients.[34] Asleh et al. showed that vasoplegic patients had a lower eGFR after 1 year, but the results on renal replacement therapy were inconclusive.[30, 31] Vasoplegia had no effect on the risk of rejection,[30, 31, 34] treated infection,[30, 31, 34] non-fatal major adverse cardiac events,[31] cardiac allograft vasculopathy,[31] liver cirrhosis[30] and allograft left ventricular ejection fraction[34]. The outcomes after heart failure surgery, other than heart transplantation and left ventricular assist device implantation, are currently unknown.

Aim and outline of this thesis

The aim of this thesis is to gain more knowledge on the incidence and risk factors of vasoplegia after heart failure surgery and the consequence this complication has on the affected patients. Furthermore, we intended to unravel the mechanisms responsible for the increased risk on vasoplegia in this patient population. In *chapter 2* the incidence, early survival and predictors of vasoplegia in patients undergoing surgical left ventricular restoration, CorCap implantation or left ventricular assist device implantation was assessed. Furthermore, a risk model is proposed to assess the risk on post-operative vasoplegia pre-operatively. *Chapter 3* focuses on incidence, early survival and predictors of vasoplegia in heart failure patients undergoing restrictive mitral annuloplasty for functional mitral regurgitation. Furthermore, it evaluates the effect of ischemic versus non-ischemic etiology on vasoplegia. In *chapter 4* the effect of vasoplegia on survival, cardiac function, and renal function was assessed 2 years after surgical left ventricular restoration. In *chapter 5*, the rationale and design of a prospective observational study on the vasoresponsiveness in heart failure patients (the VASOR study) is described. The aim of this study is to objectify and characterize the altered vasoresponsiveness in patients undergoing heart failure surgery perioperatively and to identify the etiological factors involved. The results of the in vivo vascular response test of this study are discussed in *chapter 6*. Finally, in *chapter 7*, a summary of the findings of this thesis is presented and directions for future research are proposed.

References

1. McDonagh TA, Metra M, Adamo M, Gardner RS, Baumbach A, Böhm M, et al. 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. Eur Heart J. 2021.
2. Yancy CW, Jessup M, Bozkurt B, Butler J, Casey DE, Jr., Drazner MH, et al. 2013 ACCF/AHA guideline for the management of heart failure: executive summary: a report of the American College of Cardiology Foundation/American Heart Association Task Force on practice guidelines. Circulation. 2013;128(16):1810-52.
3. Windecker S, Kolh P, Alfonso F, Collet JP, Cremer J, Falk V, et al. 2014 ESC/EACTS Guidelines on myocardial revascularization: The Task Force on Myocardial Revascularization of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS)Developed with the special contribution of the European Association of Percutaneous Cardiovascular Interventions (EAPCI). Eur Heart J. 2014;35(37):2541-619.
4. Baumgartner H, Falk V, Bax JJ, De Bonis M, Hamm C, Holm PJ, et al. 2017 ESC/EACTS Guidelines for the management of valvular heart disease. Eur Heart J. 2017;38(36):2739-91.
5. Petrus AHJ, Klautz RJM, De Bonis M, Langer F, Schäfers HJ, Wakasa S, et al. The optimal treatment strategy for secondary mitral regurgitation: a subject of ongoing debate. Eur J Cardiothorac Surg. 2019;56(4):631-42.
6. Acker MA, Parides MK, Perrault LP, Moskowitz AJ, Gelijns AC, Voisine P, et al. Mitral-valve repair versus replacement for severe ischemic mitral regurgitation. N Engl J Med. 2014;370(1):23-32.
7. Pibarot P, Delgado V, Bax JJ. MITRA-FR vs. COAPT: lessons from two trials with diametrically opposed results. Eur Heart J Cardiovasc Imaging. 2019;20(6):620-4.
8. Klein P, Bax JJ, Shaw LJ, Feringa HH, Versteegh MI, Dion RA, et al. Early and late outcome of left ventricular reconstruction surgery in ischemic heart disease. Eur J Cardiothorac Surg. 2008;34(6):1149-57.
9. Dor V, Saab M, Coste P, Kornaszewska M, Montiglio F. Left ventricular aneurysm: a new surgical approach. Thorac Cardiovasc Surg. 1989;37(1):11-9.
10. Witkowski TG, ten Brinke EA, Delgado V, Ng AC, Bertini M, Marsan NA, et al. Surgical ventricular restoration for patients with ischemic heart failure: determinants of two-year survival. Ann Thorac Surg. 2011;91(2):491-8.
11. Jones RH, Velazquez EJ, Michler RE, Sopko G, Oh JK, O'Connor CM, et al. Coronary bypass surgery with or without surgical ventricular reconstruction. N Engl J Med. 2009;360(17):1705-17.
12. Doenst T, Velazquez EJ, Michler RE. Restoring ventricular restoration: A call to re-evaluate a surgical therapy considered ineffective. J Card Surg. 2021;36(2):693-5.
13. Couperus LE, Delgado V, Palmen M, van Vessem ME, Braun J, Fiocco M, et al. Right ventricular dysfunction affects survival after surgical left ventricular restoration. J Thorac Cardiovasc Surg. 2017;153(4):845-52.
14. Michler RE, Rouleau JL, Al-Khalidi HR, Bonow RO, Pellikka PA, Pohost GM, et al. Insights from the STICH trial: change in left ventricular size after coronary artery bypass grafting with and without surgical ventricular reconstruction. J Thorac Cardiovasc Surg. 2013;146(5):1139-45.e6.
15. Braun J, Ciarka A, Versteegh MI, Delgado V, Boersma E, Verwey HF, et al. Cardiac support device, restrictive mitral valve annuloplasty, and optimized medical treatment: a multimodality approach to nonischemic cardiomyopathy. J Thorac Cardiovasc Surg. 2011;142(3):e93-100.
16. Hetzer R, Javier M, Wagner F, Loebe M, Javier Delmo EM. Organ-saving surgical alternatives to treatment of heart failure. Cardiovasc Diagn Ther. 2021;11(1):213-25.

17. Haeck ML, Beeres SL, Höke U, Palmen M, Couperus LE, Delgado V, et al. Left ventricular assist device for end-stage heart failure: results of the first LVAD destination program in the Netherlands. Neth Heart J. 2015;23(2):102-8.
18. Kortekaas KA, Lindeman JH, Versteegh MI, van Beelen E, Kleemann R, Klautz RJ. Heart failure determines the myocardial inflammatory response to injury. Eur J Heart Fail. 2013;15(4):400-7.
19. Busse LW, Barker N, Petersen C. Vasoplegic syndrome following cardiothoracic surgery-review of pathophysiology and update of treatment options. Crit Care. 2020;24(1):36.
20. Byrne JG, Leacche M, Paul S, Mihaljevic T, Rawn JD, Shernan SK, et al. Risk factors and outcomes for 'vasoplegia syndrome' following cardiac transplantation. Eur J Cardiothorac Surg. 2004;25(3):327-32.
21. Levin MA, Lin HM, Castillo JG, Adams DH, Reich DL, Fischer GW. Early on-cardiopulmonary bypass hypotension and other factors associated with vasoplegic syndrome. Circulation. 2009;120(17):1664-71.
22. Lambden S, Creagh-Brown BC, Hunt J, Summers C, Forni LG. Definitions and pathophysiology of vasoplegic shock. Crit Care. 2018;22(1):174.
23. Dayan V, Cal R, Giangrossi F. Risk factors for vasoplegia after cardiac surgery: a meta-analysis. Interact Cardiovasc Thorac Surg. 2019;28(6):838-44.
24. Fischer GW, Levin MA. Vasoplegia during cardiac surgery: current concepts and management. Semin Thorac Cardiovasc Surg. 2010;22(2):140-4.
25. Chemmalakuzhy J, Costanzo MR, Meyer P, Piccione W, Kao W, Winkel E, et al. Hypotension, acidosis, and vasodilatation syndrome post-heart transplant: prognostic variables and outcomes. J Heart Lung Transplant. 2001;20(10):1075-83.
26. Sun X, Zhang L, Hill PC, Lowery R, Lee AT, Molyneaux RE, et al. Is incidence of postoperative vasoplegic syndrome different between off-pump and on-pump coronary artery bypass grafting surgery? Eur J Cardiothorac Surg. 2008;34(4):820-5.
27. Argenziano M, Chen JM, Choudhri AF, Cullinane S, Garfein E, Weinberg AD, et al. Management of vasodilatory shock after cardiac surgery: identification of predisposing factors and use of a novel pressor agent. J Thorac Cardiovasc Surg. 1998;116(6):973-80.
28. Alfirevic A, Xu M, Johnston D, Figueroa P, Koch CG. Transfusion increases the risk for vasoplegia after cardiac operations. Ann Thorac Surg. 2011;92(3):812-9.
29. Patarroyo M, Simbaqueba C, Shrestha K, Starling RC, Smedira N, Tang WH, et al. Pre-operative risk factors and clinical outcomes associated with vasoplegia in recipients of orthotopic heart transplantation in the contemporary era. J Heart Lung Transplant. 2012;31(3):282-7.
30. Chan JL, Kobashigawa JA, Aintablian TL, Dimbil SJ, Perry PA, Patel JK, et al. Characterizing Predictors and Severity of Vasoplegia Syndrome After Heart Transplantation. Ann Thorac Surg. 2018;105(3):770-7.
31. Chan JL, Kobashigawa JA, Aintablian TL, Li Y, Perry PA, Patel JK, et al. Vasoplegia after heart transplantation: outcomes at 1 year. Interact Cardiovasc Thorac Surg. 2017;25(2):212-7.
32. Tecson KM, Lima B, Lee AY, Raza FS, Ching G, Lee CH, et al. Determinants and Outcomes of Vasoplegia Following Left Ventricular Assist Device Implantation. J Am Heart Assoc. 2018;7(11).
33. de Waal EEC, van Zaane B, van der Schoot MM, Huisman A, Ramjankhan F, van Klei WA, et al. Vasoplegia after implantation of a continuous flow left ventricular assist device: incidence, outcomes and predictors. BMC Anesthesiol. 2018;18(1):185.
34. Asleh R, Alnsasra H, Daly RC, Schettle SD, Briasoulis A, Taher R, et al. Predictors and Clinical Outcomes of Vasoplegia in Patients Bridged to Heart Transplantation With Continuous-Flow Left Ventricular Assist Devices. J Am Heart Assoc. 2019;8(22):e013108.
35. Hartupee J, Mann DL. Neurohormonal activation in heart failure with reduced ejection fraction. Nat Rev Cardiol. 2017;14(1):30-8.

36. Day JR, Taylor KM. The systemic inflammatory response syndrome and cardiopulmonary bypass. Int J Surg. 2005;3(2):129-40.
37. Schwinn DA, McIntyre RW, Hawkins ED, Kates RA, Reves JG. alpha 1-Adrenergic responsiveness during coronary artery bypass surgery: effect of preoperative ejection fraction. Anesthesiology. 1988;69(2):206-17.
38. Papazisi O, Palmen M, Danser AHJ. The Use of Angiotensin II for the Treatment of Post-cardiopulmonary Bypass Vasoplegia. Cardiovasc Drugs Ther. 2020.

CHAPTER 2

Incidence and predictors of vasoplegia after heart failure surgery

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Abstract

Objectives: Vasoplegia has been described as a complication after cardiac surgery, particularly in patients with a poor left ventricular ejection fraction. The aim of the current study was to assess the incidence, survival and predictors of vasoplegia in patients undergoing heart failure surgery and to propose a risk model.

Methods: A retrospective study including heart failure patients who underwent surgical left ventricular restoration, CorCap implantation or left ventricular assist device implantation between 2006-2015. Patients were classified by the presence or absence of vasoplegia.

Results: 225 patients were included. The incidence of vasoplegia was 29%. The 90-day survival rate in vasoplegic patients was lower compared to non-vasoplegic patients (71% versus 91%, *P*<0.001). After adjusting for age, sex and surgical procedure, anaemia (OR 2.195; 95%CI 1.146, 4.204; *P*=0.018) and a higher thyroxine level (OR 1.140; 95%CI 1.033, 1.259; *P*=0.009) increased the risk of vasoplegia; a higher creatinine clearance (OR 0.980; 95%CI 0.965, 0.994; *P*=0.006) and beta-blocker use (OR 0.257; 95%CI 0.112, 0.589; *P*=0.001) decreased the risk. The risk model consisted of the same variables and could adequately identify patients at risk for vasoplegia.

Conclusions: Vasoplegia after heart failure surgery is common and results in a lower survival rate. Anaemia and a higher thyroxine level are associated with an increased risk on vasoplegia. In contrast, a higher creatinine clearance and beta-blocker use decrease the risk on vasoplegia. These factors are used in the risk model that may guide treatment strategy.

Introduction

In recent years, surgical options for patients with severe heart failure have expanded and improved clinical outcome.[1-3] However, a striking observation is the low systemic vascular resistance and need for vasopressor therapy during the first days postoperatively in a substantial proportion of heart failure patients.[4] This state, called vasoplegia, is defined by hypotension and the continuous need of vasopressors, despite a normal or high cardiac output.[5] Vasoplegia results from the activation of several vasodilator mechanisms and the resistance to vasopressors, but the precise aetiology still remains unclear.

Previous observational studies reported that 5-25% of the patients undergoing cardiac surgery on cardiopulmonary bypass develop vasoplegia.[5] Several studies showed that patients with a reduced left ventricular ejection fraction (LVEF) were at increased risk.[6,7] Accordingly, patients with a poor LVEF undergoing heart failure surgery are expected to be particularly at risk. So far, only limited data are available on the development of vasoplegia in this patient population.[8, 9] The purpose of the present study was to provide more insight in the incidence, survival and preoperative factors associated with the occurrence of vasoplegia after heart failure surgery and to develop a risk model.

Materials and methods

Study design

For this retrospective cohort study all heart failure patients with a LVEF ≤35% who underwent surgical left ventricular restoration, CorCap implantation, or left ventricular assist device (LVAD) implantation at the Leiden University Medical Center between 2006-2015 were eligible for inclusion. Heart failure was defined in accordance with the European Society of Cardiology guidelines.[10] Patients were excluded if the diagnosis of vasoplegia could not be confirmed or ruled out, due to the absence of continuous cardiac index registration during postoperative admission at the intensive care unit. This study was conducted in accordance with the declaration of Helsinki. The institutional ethical committee approved the study and waived the need for individual written patient consent.

Endpoints and data collection

The primary endpoint was the occurrence of vasoplegia, defined as the continuous need of vasopressors (norepinephrine ≥0.2 μg/kg/min and/or terlipressin (any dose)) combined with a cardiac index ≥2.2 l/min/m^2 for at least 12 consecutive hours, starting within the first 3 days postoperatively. Norepinephrine 0.04-0.2 μg/kg/min was started if the mean arterial pressure was ≤65 mmHg and the cardiac index was normal (after adequate administration of intravascular fluids if necessary), aiming for a mean arterial pressure >65mmHg and adequate end-organ perfusion. When a norepinephrine dosage >1 μg/kg/min was required, terlipressin was started. The vasoactive medication was reduced when the mean arterial pressure was >65 mmHg in combination with adequate end-organ perfusion. At first terlipressin was reduced and thereafter norepinephrine.

Haemodynamic, laboratory, clinical and survival data were collected prospectively in the patient information systems (EPD-Vision, Leiden University Medical Center, Leiden, the Netherlands; Metavision, Itémedical B.V., Tiel, The Netherlands; CS-PDMS, Chipsoft, Amsterdam, The Netherlands) and analysed retrospectively. Anaemia was defined as a haemoglobin concentration <8.1 mmol/l for men and <7.4 mmol/l for women.[11] Creatinine clearance was estimated with the Cockroft-Gault formula.[12] The dosage of angiotensin-converting enzyme (ACE) inhibitor and/or angiotensin receptor blocker (ARB) use was expressed as a percentage of the target dose.[10]

All patients underwent transthoracic echocardiographic evaluation prior to surgery. The images were digitally stored in cine-loop format and analysed using commercially available software (GE Vingmed Ultrasound AS, Horten, Norway; EchoPAC version 112.0.1). The LVEF was determined from the apical 2- and 4-chamber views using Simpson's biplane method.[13] Pulmonary hypertension was defined as an estimated peak tricuspid regurgitation velocity >3.4 m/s,[14] measured with continuous wave Doppler.[15]

Surgical procedures

The indication for surgery was assessed by the multi-disciplinary heart team and was consisted with the institutional MISSION! heart failure protocol.[2] Surgical left ventricular restoration according to the technique described by Dor,[3] CorCap (Acorn Cardiovascular Inc, St Paul, Minnesota) implantation[1] and LVAD (HeartWare Inc, Framingham, Massachusetts) implantation[16] were performed as previously

described. All operations were performed using cardiopulmonary bypass, aortic cross-clamping and intermittent warm blood cardioplegia, except for the majority of LVAD patients. In those LVAD patients aortic cross-clamping was not necessary and implantation was performed on the beating heart with the use of cardiopulmonary bypass. Patients received an arterial line and a pulmonary artery catheter for intra- and postoperative monitoring of blood pressure, cardiac output and pulmonary pressure. These data were used to calculate the cardiac index and systemic vascular resistance. Patients did not receive ACE inhibitors, ARBs and diuretics on the day of surgery.

Statistical analysis

Continuous variables are expressed as mean ± standard deviation (SD) when normally distributed, or otherwise as median and interquartile range (IQR). Categorical variables are presented as numbers and percentages. Missing values for N-terminal fragment of pro-hormone of brain natriuretic peptide (NT-ProBNP) (N=66, 29%) and thyroxine (N=69, 31%) were replaced using multiple imputation (R package MICE, version 2.22), which was repeated a hundred times. Vasoplegic and non-vasoplegic patients were compared. Comparison of continuous data was performed using two-tailed unpaired Student t test for normally distributed variables or otherwise the Mann-Whitney U test. The Kaplan Meier method was used to assess 90-day survival in vasoplegic and non-vasoplegic patients. The survival distributions were compared using the log-rank test.

To explore the association of variables with the occurrence of vasoplegia, univariable logistic regression analysis was performed. Odds ratios (OR) with 95% confidence intervals (CI) were reported. Next, all variables were entered one by one in a multivariable logistic regression, to assess their independent association with vasoplegia after adjusting for clinically relevant variables (age, sex and surgical procedure). Furthermore, to assess whether thyroxine levels were influenced by amiodarone use and/or thyroid hormonal replacement, these were entered in a separate multivariable logistic regression analysis.

Subsequently, Least Absolute Shrinkage and Selection Operator (LASSO) logistic regression with leave-one-out cross-validation was used to identify and to calibrate the best risk prediction model.[17] This is a state-of-the-art model fitting and variable selection methodology which can jointly select candidate predictors and optimise the resulting model for prediction. Age, sex and surgical procedure were forced

into the model. The model fitting procedure was repeated for each of the hundred imputations. For the final model, a single model was selected from the imputations containing all variables which were used in >85% of the models. The imputation linked to this model was used to re-place the missing values for NT-ProBNP and thyroxine. The performance of the final model was assessed by computing the area under the receiver operating characteristic (ROC) curve. Next, patients were divided into 3 risk categories: low (predicted probability of <25%), intermediate (25-50%) and high risk (≥50%), after which the observed incidence per risk group was calculated. *P-values* <0.05 were considered statistically significant. Statistical analysis was performed using SPSS for Windows (version 20.0, Chicago, Illinois) and R (version 3.2.1, Vienna, Austria).

The preliminary data of this study were presented at the American College of Cardiology 2015 scientific session.[18]

Results

Study population

Between 2006 and 2015, 260 heart failure patients with a LVEF ≤35% underwent surgical left ventricular restoration, CorCap device implantation, or LVAD implantation. A total of 35 patients (22 left ventricular restoration and 13 CorCap patients) were excluded. Accordingly, the final study population consisted of 225 patients (166 (74%) men, age 62±10 years, LVEF 24±6%). Baseline data are summarised in Table 1. A total of 178 (79%) patients were admitted for elective surgery. The remaining 47 patients (21%) required surgery during an ongoing admission for heart failure.

Surgical left ventricular restoration, CorCap implantation or LVAD implantation was performed in 121 (54%), 71 (32%) and 33 (15%) patients respectively. Concomitant cardiac procedures were coronary artery bypass grafting in 82 (36%), mitral valve surgery in 137 (61%), triscuspid valve surgery in 115 (51%) and aortic valve surgery in 15 (7%) patients. Mean cross clamp and cardiopulmonary bypass duration were 127±50 and 193±69 minutes, respectively.

Table 1. Characteristics of the study population.

	Total (N=225)	LV restoration (N=121, 54%)	CorCap (N=71, 32%)	LVAD implantation (N=33, 15%)
Age (years)	62±10	62±10	63±9	59±10
Male sex	166 (74%)	96 (79%)	44 (62%)	26 (79%)
Body mass index (kg/m^2)	27±4	27±4	26±4	26±4
Diabetes	64 (28%)	33 (27%)	24 (34%)	7 (21%)
Prior CVA or TIA	26 (12%)	11 (9%)	11 (16%)	4 (12%)
Prior hypertension	91 (40%)	57 (47%)	27 (38%)	7 (21%)
Left ventricular ejection fraction (%)	24±6	25±6	23±6	23±5
Ischaemic heart failure	164 (73%)	121 (100%)	19 (27%)	24 (73%)
NYHA class 3 or 4	151 (67%)	70 (58%)	49 (69%)	32 (97%)
Pulmonary hypertension	36 (16%)	17 (14%)	10 (14%)	9 (27%)
Previous cardiac surgery	38 (17%)	14 (12%)	6 (9%)	18 (55%)
EuroSCORE II (%)	9 (5, 16)	6 (3, 12)	10 (6, 13)	25 (13, 42)
Preoperative laboratory assessment				
Anaemia	70 (31%)	35 (29%)	16 (23%)	19 (58%)
Creatinine clearance (ml/min)	74±30	78±31	72±32	66±21
NT-ProBNP (ng/l)	1736 (849, 3951)*	1140 (575, 2053)	2558 (1199, 5548)	3863 (2159, 6372)
Thyroxine (pmol/l)	19±3**	18±3	19±4	19±3
Medication				
Beta-blocker	190 (84%)	110 (91%)	54 (76%)	26 (79%)
ACE inhibitor/ARB	193 (86%)	113 (93%)	64 (90%)	16 (49%)
MRA	151 (67%)	76 (63%)	51 (72%)	24 (73%)
Diuretics	195 (87%)	96 (79%)	69 (97%)	30 (91%)
Inotropes	29 (13%)	5 (4%)	3 (4%)	21 (64%)

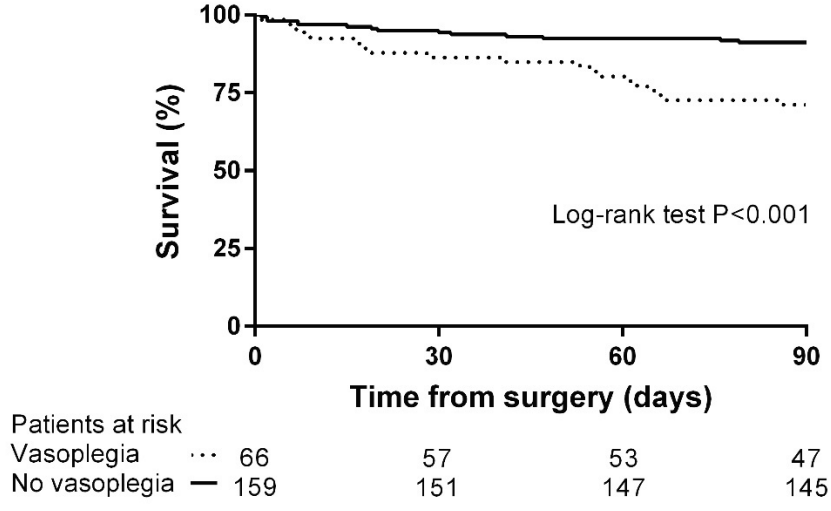
** Data based on 159 patients. ** Data based on 156 patients. Continuous data are presented as mean ± SD or median (IQR). Categorical data are presented as numbers (%). ACE: Angiotensin-converting enzyme; ARB: angiotensin receptor blocker; CVA: cerebrovascular accident; IQR: interquartile range; LVAD: Left Ventricular Assist Device; LV restoration: left ventricular restoration; MRA: mineralocorticoid receptor antagonist; NT-ProBNP: N-terminal fragment of prohormone of brain natriuretic peptide; NYHA: New York Heart Association; TIA: transient ischaemic attack.*

Vasoplegia

A total of 66 patients (29%) developed vasoplegia after heart failure surgery. In these patients, during the vasoplegic period, the mean systemic vascular resistance and mean arterial pressure of the 2 lowest consecutive readings were 649 dyn/s/cm^5 and 51 mmHg, respectively.

Of the 66 vasoplegic patients, 28 (42%) underwent surgical left ventricular restoration, 18 (27%) CorCap implantation and 20 (30%) LVAD implantation. Cross-clamp time (130±44 versus 126±52 minutes, *P*=0.623) and cardiopulmonary bypass time (200±60 versus 191±72 minutes, *P*=0.369) were similar in vasoplegic and non-vasoplegic patients. Of note, non-elective surgery was performed at similar rates in vasoplegic compared to non-vasoplegic patients (N=15 (23%) versus N=32 (20%), *P*=0.719). The length of intensive care unit stay was 8 (IQR 5, 15) days in vasoplegic patients and 2 (IQR 1, 5) days in non-vasoplegic patients (*P*<0.001). As shown in Figure 1, the 90-day survival rate was 71% in vasoplegic patients as compared to 91% in non-vasoplegic patients (*P*<0.001).

Figure 1. Kaplan Meier survival curve for patients with vasoplegia (dotted line) and without vasoplegia (solid line).



From the 19 vasoplegic patients that died during the study period, the cause of death was assessed by post-mortem examination in 8 (42%) patients. These examinations revealed that their death was caused by vasoplegia-induced multi-organ failure (N=6) or infection related to the vasoplegia-induced prolonged ICU admission (N=2). Of note, post-mortem induction revealed two undiagnosed findings: one patient had pulmonary embolisms and one patients had a pneumonia. In the remaining 11 patients (58%) there was no permission for post-mortem examination. Based on the clinical data, their death was caused by vasoplegia-induced multi-organ failure (N=2), infection related to the vasoplegia-induced prolonged ICU admission (N=4) or not related to vasoplegia (N=5). To summarise, in 14 deceased vasoplegic patients (74%) death was related to vasoplegia.

Preoperative factors associated with vasoplegia

The results of the univariable analysis are presented in Table 2. The following parameters were associated with an increased risk of vasoplegia: male sex, New York Heart Association (NYHA) class 3 or 4, pulmonary hypertension, previous cardiac surgery, higher EuroSCORE II, anaemia, a higher thyroxine level, preoperative use of inotropes and LVAD implantation. Of note, the association between the use of inotropes and vasoplegia was caused by the use of sympathomimetics (P=0.002) and not by phosphodiesterase inhibitors (P=0.999). The following parameters were associated with a decreased risk of vasoplegia: history of hypertension, higher creatinine clearance, use of beta-blockers, use of ACE inhibitors and/or ARBs and surgical left ventricular restoration. The median dosage of ACE inhibitors and/or ARBs was significantly lower in vasoplegic patients as compared to non-vasoplegic patients (25% (IQR 0, 50%) versus 33% (IQR 25, 50%) P=0.002).

Multivariable analyses identified 4 factors that were independently associated with the development of vasoplegia, after adjusting for age, sex and surgical procedure. As shown in Table 3, anaemia (OR 2.195; 95%CI 1.146, 4.204; P=0.018) and a higher thyroxine level (OR 1.140; 95%CI 1.033, 1.259; P=0.009) were associated with an increased risk of developing vasoplegia. The positive association between thyroxine level and vasoplegia was independent of amiodaron use and thyroid hormonal replacement. A higher creatinine clearance (OR 0.980; 95%CI 0.965, 0.994; P=0.006) and the use of a beta-blocker (OR 0.257; 95%CI 0.112, 0.589; P=0.001) were associated with a lower risk on vasoplegia.

Table 2. Univariable regression analysis.

	Vasoplegia (N=66)	No vasoplegia (N=159)	OR (95%CI)	P-value
Age (years)	62±10	61±10	1.014 (0.983, 1.045)	0.387
Male sex	56 (85%)	110 (69%)	2.495 (1.176, 5.293)	**0.017**
Body mass index (kg/m^2)	26±4	27±4	0.965 (0.891, 1.044)	0.375
Diabetes	17 (26%)	47 (30%)	0.827 (0.432, 1.581)	0.565
Prior CVA or TIA	7 (11%)	19 (12%)	0.874 (0.349, 2.190)	0.774
Prior hypertension	19 (29%)	72 (45%)	0.488 (0.263, 0.906)	**0.023**
LVEF (%)	25±6	24±6	1.015 (0.966, 1.067)	0.544
Ischaemic heart failure	50 (76%)	114 (72%)	1.234 (0.637, 2.387)	0.533
NYHA class 3 or 4	53 (80%)	98 (62%)	2.538 (1.278, 5.038)	**0.008**
Pulmonary hypertension	16 (24%)	20 (13%)	2.224 (1.069, 4.627)	**0.032**
Previous cardiac surgery	19 (29%)	19 (12%)	2.979 (1.455, 6.099)	**0.003**
EuroSCORE II (%)	12 (7, 22)	7 (4, 14)	1.024 (1.003, 1.044)	**0.023**
Preoperative laboratory assessment				
Anaemia	31 (47%)	39 (25%)	2.725 (1.490, 4.983)	**0.001**
Creatinine clearance (ml/min)	65±28	78±30	0.983 (0.971, 0.994)	**0.003**
NT-ProBNP (ng/l)	2351 (1346, 5439)	1613 (809, 3866)	1.000 (1.000, 1.000)	0.220
Thyroxine (pmol/l)	19±3	18±3	1.131 (1.035, 1.235)	**0.006**
Medication				
Beta-blocker	47 (71%)	143 (90%)	0.277 (0.132, 0.581)	**0.001**
ACE inhibitor/ARB	48 (73%)	145 (91%)	0.257 (0.119, 0.557)	**0.001**
MRA	45 (68%)	106 (67%)	1.071 (0.580, 1.980)	0.826
Diuretics	58 (88%)	137 (86%)	1.164 (0.490, 2.766)	0.731
Inotropes	14 (21%)	15 (9%)	2.585 (1.168, 5.720)	**0.019**
Surgical procedures				
LV restoration	28 (42%)	93 (59%)	0.523 (0.292, 0.935)	**0.029**
CorCap	18 (27%)	53 (33%)	0.750 (0.398, 1.414)	0.374
LVAD implantation	20 (30%)	13 (8%)	4.883 (2.254, 10.577)	**<0.001**

Continuous data are presented as mean ± SD or median (IQR). Categorical data are presented as numbers (%). ACE: Angiotensin-converting enzyme; ARB: angiotensin receptor blocker; CI: confidence interval; CVA: cerebrovascular accident; IQR: interquartile range; LVAD: Left Ventricular Assist Device; LVEF: left ventricular ejection fraction; LV restoration: left ventricular restoration; MRA: mineralocorticoid receptor antagonist; NT-ProBNP: N-terminal fragment of prohormone of brain natriuretic peptide; NYHA: New York Heart Association; OR: odds ratio; TIA: transient ischaemic attack.

Table 3. Multivariable regression analyses.

	OR (95%CI)	P-value
Body mass index (kg/m^2)	0.961 (0.882, 1.048)	0.373
Diabetes	0.854 (0.429, 1.702)	0.654
Prior CVA or TIA	0.795 (0.297, 2.129)	0.647
Prior hypertension	0.550 (0.287, 1.057)	0.073
Left ventricular ejection fraction (%)	1.033 (0.978, 1.092)	0.248
Ischaemic heart failure	1.499 (0.572, 3.930)	0.411
NYHA class 3 or 4	1.951 (0.940, 4.048)	0.073
Pulmonary hypertension	1.867 (0.851, 4.093)	0.119
Previous cardiac surgery	1.696 (0.745, 3.861)	0.208
EuroSCORE II (%)	1.005 (0.980, 1.032)	0.674
Preoperative laboratory assessment		
Anaemia	2.195 (1.146, 4.204)	**0.018**
Creatinine clearance (ml/min)	0.980 (0.965, 0.994)	**0.006**
NT-ProBNP (ng/l)	1.000 (1.000, 1.000)	0.256
Thyroxine (pmol/l)	1.140 (1.033, 1.259)	**0.009**
Medication		
Beta-blocker	0.257 (0.112, 0.589)	**0.001**
ACE inhibitor/ARB	0.412 (0.169, 1.003)	0.051
MRA	1.188 (0.608, 2.325)	0.614
Diuretics	1.027 (0.400, 2.638)	0.956
Inotropes	0.772 (0.244, 2.447)	0.660

A multivariable regression model was fit for each variable separately, containing only that variable and also correcting for the effects of age, sex and surgical procedure (left ventricular restoration, CorCap implantation or left ventricular assist device implantation). ACE: Angiotensin-converting enzyme; ARB: angiotensin receptor blocker; CI: confidence interval; CVA: cerebrovascular accident; MRA: mineralocorticoid receptor antagonist; NT-ProBNP: N-terminal fragment of prohormone of brain natriuretic peptide; NYHA: New York Heart Association; OR: odds ratio; TIA: transient ischaemic attack.

Derivation of risk model

In the current patient population, the LASSO logistic regression method revealed that the risk to develop vasoplegia after heart failure surgery can be calculated using the following formula: Predicted probability = $e^{(\text{prediction score})}$ / (1 + $e^{(\text{prediction score})}$). The prediction score is calculated as follows: -0.500 - $1.533_{\text{left ventricular restoration}}$ - 1.454_{CorCap} + 0.007 x (age) + $0.986_{\text{male sex}}$ + 0.063_{anaemia} - 0.005 x (creatinine clearance) + 0.029 x (thyroxine) - $0.610_{\text{beta-blocker}}$. An online interactive calculator has been developed to allow convenient calculation of the estimated risk of vasoplegia (https://hartlongcentrum.nl/vasoplegia_calculator) (Figure 2). The area under the

ROC curve was 0.759 (95%CI 0.690, 0.829), indicating a fair discriminatory power of the model. As shown in Figure 3, the median predicted probability was 33% (IQR 26, 57%) in vasoplegic patients compared with 23% (IQR 17, 29%) non-vasoplegic patients (*P*<0.001).

For simplicity, patients were divided in 3 risk categories based on the derived risk score: 1. low risk (<25%), 2. intermediate risk (25-50%) and 3. high risk (>50%). The low risk group consisted of 108 patients of which 14 (13%) patients developed vasoplegia. In the intermediate risk group (N=91) 35 (39%) patients developed vasoplegia and in the high risk group (N=26) 17 (65%) patients developed vasoplegia.

Figure 2. Vasoplegia risk score calculator.

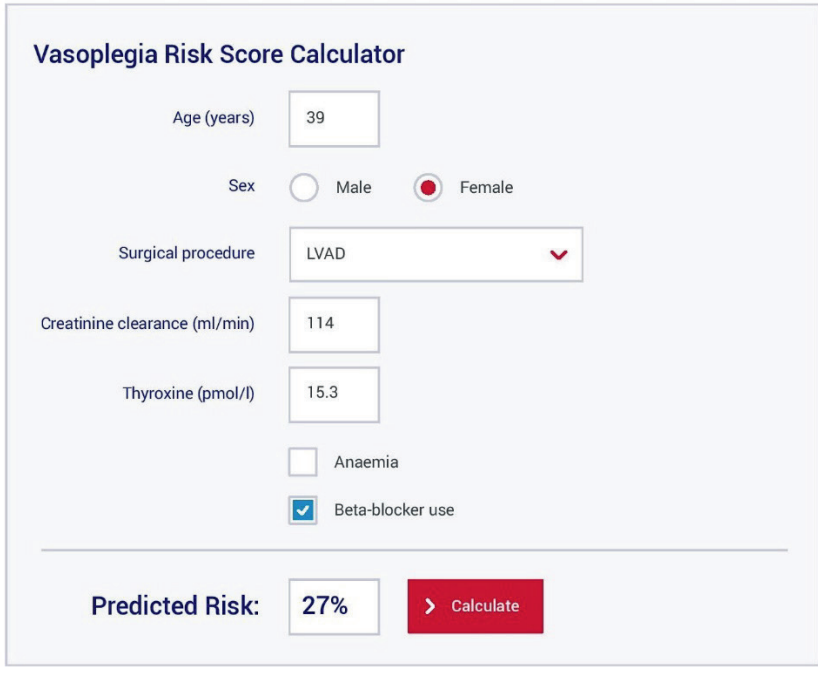
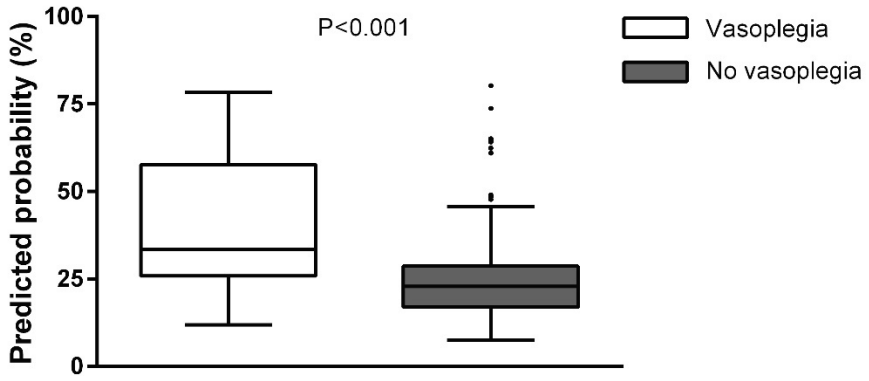


Figure 3. Predicted probability for patients with vasoplegia and without vasoplegia.



Discussion

The main finding of the current study is that vasoplegia frequently occurs after heart failure surgery and results in an impaired 90-day survival. Furthermore, anaemia and a higher thyroxine level were associated with an increased risk of developing vasoplegia whereas a higher creatinine clearance and the use of a beta-blocker were associated with a reduced risk on vasoplegia.

Previous studies reported that vasoplegia is common after cardiac surgery on cardiopulmonary bypass with an incidence ranging between 5% and 25%.[5] In several studies, patients with a reduced LVEF were found to be at increased risk. For instance, in a study of 145 cardiac surgical patients, Argenziano et al. reported an 8% incidence of vasoplegia in the entire study population, as compared to 27% in patients with a reduced LVEF.[19] The incidence of vasoplegia of 29% in the current study including severe heart failure patients with a reduced LVEF seems to be in line with these prior observations. The 90-day survival rate was decreased in vasoplegic patients as compared to non-vasoplegic patients. In most cases (74%) the death of vasoplegic patients was caused by vasoplegia-induced multi-organ failure or infection related to the vasoplegia-induced prolonged ICU admission.

To date, 2 previous studies assessed factors associated with postoperative vasoplegia in heart failure patients. Byrne et al. studied 147 heart transplant patients. Hospital mortality (death within 30 days or during the same

hospitalisation) was higher in vasoplegic patients (25%) compared to non-vasoplegic patients (9%) (P=0.031).[8] The preoperative use of intravenous heparin (OR 2.8; 95%CI 1, 7.4; P=0.039) and preoperative inotropic support (OR 0.25; 95%CI 0.08, 0.79; P=0.018) were independent predictors for the development of vasoplegia. Preoperative use of beta-blockers, creatinine levels and haemoglobin levels did not differ significantly between vasoplegic and non-vasoplegic patients. Thyroxine levels were not reported. In another study, Patarroyo et al. reviewed peri-operative data in 311 heart transplant patients. Patients with vasoplegia had a higher 30-day mortality (17 versus 3%, P=0.0003).[9] In this study, ventricular assist device prior to transplant (OR 2.8; 95%CI 1.07, 7.4; P=0.03), preoperative use of milrinone (OR 0.29; 95%CI 0.07, 0.87; P=0.027) and thyroid hormonal replacement at the time of transplant (OR 2.7; 95%CI 1.0, 7.0; P=0.04) were independently associated with the development of vasoplegia. Preoperative beta-blocker use, thyroxine level, haemoglobin level and creatinine level did not differ between vasoplegic and non-vasoplegic patients.

Although the decreased survival rate after vasoplegia in the current study is in line with the observations of the above described heart transplantation studies, the present study found different factors to be associated with vasoplegia. In the present study, a higher thyroxine level was associated with an increased risk of vasoplegia. Conceptually, the increased risk of vasoplegia due to higher thyroxine levels could be related to the previous observation that a higher thyroxine level is associated with a decreased systemic vascular resistance, as described by Klein et al.[20] Anaemia was another predictor for vasoplegia in the current study. Haemoglobin is known to be a nitric oxide scavenger. Previous studies demonstrated that nitric oxide is an endothelium-derived relaxation factor that acts on the vascular smooth muscle cells and plays an important role in the pathophysiology of vasoplegia.[5] When anaemia results in a reduced level of captured nitric oxide, this may consequently enhance vasodilation.[21] Another potential explanation for the association between anaemia and poor postoperative outcome could be that anaemia simply is a marker of chronic disease, as recently suggested by Fowler based on a meta-analysis of the association between preoperative anaemia and mortality after non-cardiac surgery.[22] The present study identified beta-blocker use to decrease the risk of vasoplegia. It may be hypothesised that the disturbance induced by the surgical trauma and the cardiopulmonary bypass causes a release of vasoactive factors. Conceptually, the ability to still tolerate a beta-blocker, may indicate patients with more reserves to compensate for these disturbances, thereby preventing them to develop

vasoplegia. Also a higher creatinine clearance decreases the risk of vasoplegia. This finding may support the hypothesis that patients with more reserves have a reduced risk of vasoplegia.

An important aspect that may have contributed to the disagreement between the factors associated with vasoplegia in the current study as compared to the previous 2 studies, is the difference in study population. Whereas the 2 previous studies only included orthotopic heart transplant patients, the current study included severe heart failure patients with a reduced LVEF undergoing non-transplant heart failure surgery. The differences in patient characteristics, surgery type, postoperative cardiac function and medication, may have resulted in different findings.

Limitations

There are potential limitations to the present study that should be considered when interpreting the results. At first, as this was a single-centre retrospective study, future prospective studies are warranted to confirm the present findings and to validate the proposed risk model. Second, due to the relatively long inclusion period, expanding guidelines for the pharmacological and surgical treatment of heart failure could have created a heterogeneous study population. Nevertheless, this would have affected both study groups in a similar way. Finally, the inclusion of heart failure patients undergoing 3 types of heart failure surgery may have yielded different results from what could be obtained if only patients undergoing 1 type of surgery would have been included. This limitation was partially overcome by correcting for surgery type in the multivariable analysis and risk model.

Clinical implications

The present study emphasises the major clinical impact of vasoplegia in heart failure patients in whom cardiac surgery is considered. In particular, the prolonged intensive care unit stay and the impaired survival of patients with vasoplegia should be taken into account when deciding to perform heart failure surgery. Furthermore, patients with an increased risk of vasoplegia could potentially benefit from additional preoperative measures such as optimization of the haemodynamic situation and renal function. In addition, in patients with an increased risk of vasoplegia, early initiation of a vasopressor regime (vasopressin or methylene blue) in the perioperative phase could be considered.[5] However, it should be stipulated

that more research is needed to understand the mechanism which links heart failure to the development of vasoplegia after cardiac surgery. Understanding these mechanisms can guide the development of better-targeted preventive strategies.

Conclusion

In conclusion, this study indicates that vasoplegia in heart failure patients undergoing cardiac surgery is common and results in a lower survival rate. Anaemia and a higher thyroxine level are associated with an increased risk of vasoplegia. In contrast, a higher creatinine clearance end the use of beta-blockers decrease the risk on vasoplegia. These factors are incorporated in the proposed risk model that may guide treatment strategy.

References

1. Braun J, Ciarka A, Versteegh MI, Delgado V, Boersma E, Verwey HF, et al. Cardiac support device, restrictive mitral valve annuloplasty, and optimized medical treatment: a multimodality approach to nonischemic cardiomyopathy. J Thorac Cardiovasc Surg 2011;142:e93-100.
2. Haeck ML, Hoogslag GE, Rodrigo SF, Atsma DE, Klautz RJ, van der Wall EE, et al. Treatment options in end-stage heart failure: where to go from here? Neth Heart J 2012;20:167-75.
3. Klein P, Holman ER, Versteegh MI, Boersma E, Verwey HF, Bax JJ, et al. Wall motion score index predicts mortality and functional result after surgical ventricular restoration for advanced ischemic heart failure. Eur J Cardiothorac Surg 2009;35:847-52.
4. Kortekaas KA, Lindeman JH, Versteegh MI, Stijnen T, Dion RA, Klautz RJ. Preexisting heart failure is an underestimated risk factor in cardiac surgery. Neth Heart J 2012;20:202-7.
5. Fischer GW, Levin MA. Vasoplegia during cardiac surgery: current concepts and management. Semin Thorac Cardiovasc Surg 2010;22:140-4.
6. Alfirevic A, Xu M, Johnston D, Figueroa P, Koch CG. Transfusion increases the risk for vasoplegia after cardiac operations. Ann Thorac Surg 2011;92:812-9.
7. Levin MA, Lin HM, Castillo JG, Adams DH, Reich DL, Fischer GW. Early on-cardiopulmonary bypass hypotension and other factors associated with vasoplegic syndrome. Circulation 2009;120:1664-71.
8. Byrne JG, Leacche M, Paul S, Mihaljevic T, Rawn JD, Shernan SK, et al. Risk factors and outcomes for 'vasoplegia syndrome' following cardiac transplantation. Eur J Cardiothorac Surg 2004;25:327-32.
9. Patarroyo M, Simbaqueba C, Shrestha K, Starling RC, Smedira N, Tang WH, et al. Pre-operative risk factors and clinical outcomes associated with vasoplegia in recipients of orthotopic heart transplantation in the contemporary era. J Heart Lung Transplant 2012;31:282-7.
10. Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JG, Coats AJ, et al. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. Eur J Heart Fail 2016; doi:10.1002/ejhf.592.
11. Benoist B, McLean E, Egli I, Cogswell M. Worldwide prevalence of anaemia 1993-2005. World Health Organization [published 2008, accessed 1 October 2015]. Available from: http://apps.who.int/iris/bitstream/10665/43894/1/9789241596657_eng.pdf
12. Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. Nephron 1976;16:31-41.
13. Lang RM, Badano LP, Mor-Avi V, Afilalo J, Armstrong A, Ernande L, et al. Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. Eur Heart J Cardiovasc Imaging 2015;16:233-70.
14. Galiè N, Humbert M, Vachiery JL, Gibbs S, Lang I, Torbicki A, et al. 2015 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension: The Joint Task Force for the Diagnosis and Treatment of Pulmonary Hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS): Endorsed by: Association for European Paediatric and Congenital Cardiology (AEPC), International Society for Heart and Lung Transplantation (ISHLT). Eur Heart J 2016;37:67-119.
15. Rudski LG, Lai WW, Afilalo J, Hua L, Handschumacher MD, Chandrasekaran K, et al. Guidelines for the echocardiographic assessment of the right heart in adults: a report from the American Society of Echocardiography endorsed by the European Association of Echocardiography, a registered

branch of the European Society of Cardiology, and the Canadian Society of Echocardiography. J Am Soc Echocardiogr 2010;23:685-713.
16. Haeck ML, Beeres SL, Höke U, Palmen M, Couperus LE, Delgado V, et al. Left ventricular assist device for end-stage heart failure: results of the first LVAD destination program in the Netherlands. Neth Heart J 2015;23:102-8.
17. Hastie T, Tibshirani R, Wainwright M. Statistical Learning with Sparsity: The Lasso and Generalizations. Boca Raton: CRC press, 2015.
18. van Vessem M, Palmen M, Couperus L, Mertens B, Tops L, Verwey H, et al. Preoperative anemia, thyroxine levels, creatinine clearance and beta-blocker use are associated with the development of vasoplegia after heart failure surgery. J Am Coll Cardiol 2016;67:1385.
19. Argenziano M, Chen JM, Choudhri AF, Cullinane S, Garfein E, Weinberg AD, et al. Management of vasodilatory shock after cardiac surgery: identification of predisposing factors and use of a novel pressor agent. J Thorac Cardiovasc Surg 1998;116:973-80.
20. Klein I, Ojamaa K. Thyroid hormone and the cardiovascular system. N Engl J Med 2001;344:501-9.
21. Anand IS. Anemia and chronic heart failure implications and treatment options. J Am Coll Cardiol 2008;52:501-11.
22. Fowler AJ, Ahmad T, Phull MK, Allard S, Gillies MA, Pearse RM. Meta-analysis of the association between preoperative anaemia and mortality after surgery. Br J Surg 2015;102:1314-24.

CHAPTER 3

Vasoplegia after restrictive mitral annuloplasty for functional mitral regurgitation in patients with heart failure

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Abstract

Objectives: Patients undergoing heart failure surgery are at risk for developing postoperative vasoplegia. The aim of this study was to determine the incidence, survival and predictors of vasoplegia in heart failure patients undergoing mitral valve repair for functional mitral regurgitation and to evaluate the effect of ischemic versus non-ischemic etiology.

Design: Retrospective.

Setting: University medical center, single institutional.

Participants: Heart failure patients with functional mitral regurgitation, who underwent restrictive mitral annuloplasty (2006-2015).

Measurements and main results: 122 patients were included (48% ischemic etiology). The incidence of vasoplegia was 19% and was not influenced by mitral regurgitation etiology. 90-day survival rate was decreased in vasoplegic compared to non-vasoplegic patients (65% versus 93%, P<0.001). After adjusting for age, gender and heart failure etiology, prior hypertension (OR 0.28; 95%CI 0.08-0.91; P=0.034), higher creatinine clearance (OR 0.97; 95%CI 0.95-0.99; P=0.009) and beta-blocker use (OR 0.25; 95%CI 0.09-0.73; P=0.011) decreased the risk of vasoplegia. Anemia (OR 3.00; 95%CI 1.10-8.20; P=0.032) and longer cross clamp (OR 1.03; 95% CI 1.01-1.04; P=0.001), cardiopulmonary bypass (OR 1.01; 95%CI 1.00-1.02; P=0.003) and procedure times (OR 1.01; 95%CI 1.00-1.02, P=0.002) increased the risk of vasoplegia.

Conclusions: Vasoplegia occurs in 19% of heart failure patients undergoing mitral valve repair for functional mitral regurgitation. It is associated with a poor early outcome. Prior hypertension, a higher creatinine clearance and beta-blocker use were associated with a decreased risk of vasoplegia, whereas anemia and longer procedure times were associated with an increased risk of vasoplegia, independent of heart failure etiology.

Introduction

Functional mitral regurgitation (MR) is frequently observed in patients with ischemic and non-ischemic heart failure and results from a combination of increased systolic leaflet tethering and decreased closing forces secondary to left ventricular remodeling (Carpentier classification IIIb).[1, 2] Presence of functional MR is independently associated with poor prognosis.[3, 4] Surgical mitral valve repair – generally by implantation of a restrictive mitral annuloplasty (RMA) ring – may be considered in patients with moderate to severe MR and persisting symptoms of heart failure, despite optimal medical and device therapy.[5-9] Mitral valve repair may result in durable correction of MR, left ventricular (LV) reverse remodeling and beneficial clinical outcomes.[10-13] However, each cardiac operation carries associated perioperative risks, which should be taken into account when considering a surgical intervention.

Vasoplegia is an important determinant for adverse postoperative outcome and is observed in 5 – 54% of patients undergoing cardiac surgery using cardiopulmonary bypass (CPB). [14-17] Postoperative vasoplegia is defined as a state with low systemic vascular resistance despite a normal or high cardiac output, and the need for vasopressor therapy, due to an imbalance of vasodilator and vasopressor mechanisms.[14] Previous studies demonstrated that patients with heart failure with reduced ejection fraction and patients undergoing valvular procedures are at increased risk for developing vasoplegia after cardiac surgery, independent of surgical procedure times.[18-20] Therefore we hypothesized that patients undergoing mitral valve repair for functional MR, may be at substantial risk of postoperative vasoplegia, with potential deleterious outcomes.[21]

The aim of this study was (1) to determine the incidence of postoperative vasoplegia in patients with functional MR due to ischemic or non-ischemic heart failure, (2) to assess the prognostic impact of vasoplegia on early clinical outcome and (3) to identify its baseline predictors.

Methods

Study design and study population

For this retrospective cohort study, consecutive heart failure patients with reduced left ventricular ejection fraction (LVEF ≤35%) and functional MR, who underwent RMA (as a single procedure or with concomitant tricuspid valve annuloplasty, cardiac support device (CSD) implantation, and/or coronary artery bypass grafting) at our institution between 2006-2015, were included. Patients were excluded if the diagnosis of vasoplegia could not be confirmed or ruled out, due to the absence of continuous cardiac index registration during postoperative admission at the intensive care unit. This study was conducted in accordance with the declaration of Helsinki. The institutional ethical committee approved the study and waived the need for individual written informed consent.

Study outcomes and data collection

Hemodynamic, laboratory, clinical and survival data were collected prospectively in the patient information systems (EPD-Vision, Leiden, the Netherlands; Metavision, Itémedical B.V., Tiel, The Netherlands; CS-PDMS, Chipsoft, Amsterdam, The Netherlands) and analyzed retrospectively. In line with the WHO definition, anemia was defined as a hemoglobin concentration <8.1 mmol/l for men and <7.4 mmol/l for women.[22] Creatinine clearance was estimated with the Cockroft-Gault formula.[23] For both variables, the last preoperative assessment was used. All patients underwent transthoracic echocardiographic evaluation prior to surgery. The images were digitally stored and analyzed using commercially available software (GE Vingmed Ultrasound AS, Horten, Norway; EchoPAC version 112.0.1). The LVEF was determined from the apical 2- and 4-chamber views using Simpson's biplane method.[24] MR severity was graded qualitatively and semi-quantitatively.[6] Pulmonary hypertension was defined as an estimated peak tricuspid regurgitation velocity >2.9 m/s, measured with continuous wave Doppler.

Vasoplegia was defined as previously described: the continuous need for vasopressors (norepinephrine ≥0.2 µg/kg/min and/or any dose of terlipressin) combined with a cardiac index ≥2.2 l/min/m^2 for at least 12 consecutive hours, starting within the first 3 days postoperatively.[16]

Surgical procedures

The indication for surgery was assessed by the multidisciplinary Heart Team, consisting of cardiologists, cardiothoracic surgeons, imaging specialists, heart failure specialists and anesthesiologists.[26] All operations were performed through midline sternotomy using CPB, aortic cross-clamping and intermittent antegrade warm blood cardioplegia. RMA was performed for moderate to severe functional MR in all patients. Ring size was determined by measuring the anterior leaflet height and then downsizing by two ring sizes, using a semi-rigid annuloplasty ring (Physio ring, Edwards Life Sciences, Irvine, California). RMA was considered successful in case no or mild MR and a leaflet coaptation height of ≥8 mm were observed on transesophageal echocardiography. Tricuspid valve repair was performed with an annuloplasty ring (Edwards Life Sciences MC3 ring or Edwards Physio Tricuspid) in patients with tricuspid regurgitation ≥grade 3 and/or a tricuspid annular diameter ≥40 mm (or >21mm/m^2 body surface area). Concomitant implantation of a CorCap CSD (Acorn Cardiovascular, St. Paul, Minnesota) was performed in patients with non-ischemic heart failure and a preoperative left ventricular end-diastolic diameter (LVEDD) ≥65 mm or indexed LVEDD ≥30 mm/m^2. The CSD is a passive external fabric mesh containment device that is implanted to reduce LV wall stress by providing circumferential diastolic support, in order to prevent further LV remodeling. Concomitant myocardial revascularization was performed when indicated. Patients did not receive ACE inhibitors, ARBs or diuretics on the day of surgery.

Anesthetics and hemodynamic monitoring

Before induction all patients received an arterial catheter for invasive monitoring of blood pressure. A central venous catheter was inserted in the internal jugular vein and a flow-directed balloon-tipped pulmonary artery catheter (Edwards LifeSciences, Irvine, CA, USA) was introduced after induction for continuous monitoring of cardiac output and pulmonary pressure. These data were used to calculate the cardiac index and systemic vascular resistance. Norepinephrine 0.04–0.2 µg/kg/min was started when the mean arterial pressure was <65 mmHg and the cardiac index was normal (after adequate administration of intravascular fluids if necessary). Aim was a mean arterial pressure >65 mmHg and adequate end-organ perfusion. When a norepinephrine dosage >1 µg/kg/min was required, terlipressin was started. Both norepinephrine and terlipressin were reduced when the mean arterial pressure was >65mmHg and end-organ perfusion was restored.

Statistical analysis

Continuous variables are expressed as mean ± standard deviation (SD) when normally distributed, or otherwise as median and interquartile range (IQR). The normality of data distribution was determined graphically using the Q-Q plot and tested with the Shapiro-Wilk Test of Normality. Categorical variables are presented as numbers and percentages. Missing values for cross clamp time (N=2, 2%) were replaced using multiple imputation with predictive mean matching, which was repeated a hundred times. Baseline age, gender, EuroSCORE, NYHA class, creatinine clearance, cross clamp time and procedure time were used as predictors in the model. The pooled data was used for analysis. Heart failure patients with ischemic and non-ischemic MR, and vasoplegic and non-vasoplegic patients were compared. Comparison of continuous data was performed using two-tailed unpaired Student's t-test for normally distributed variables or otherwise the Mann-Whitney U test. The Kaplan-Meier method was used to assess 30-day and 90-day survival in vasoplegic and non-vasoplegic patients; the analysis was repeated for heart failure patients with ischemic and non-ischemic MR. The survival distributions were compared using the log-rank test.

To explore the association of variables with the occurrence of vasoplegia, univariable logistic regression analysis was performed. Odds ratios (OR) with 95% confidence intervals (CI) were reported. For each variable with a P-value <0.100 during univariable analysis, a multivariable logistic regression analysis was performed to assess their independent association with vasoplegia after adjusting for age, sex and ischemic heart failure.

Results

Study population

A total of 127 patients with LVEF ≤35% and moderate to severe functional MR underwent RMA (as a single procedure or with concomitant tricuspid valve annuloplasty, CSD implantation, and/or coronary artery bypass grafting) at our institution between 2006 and 2015. Since 5 patients in whom the presence of vasoplegia could not be assessed due to absence of cardiac index measurements were excluded, the final population consisted of 122 patients. The baseline characteristics are described in Table 1. Mean age was 65±9 years and the majority of patients were male (66%). Mean LVEF was 27±6%. Concomitant procedures

were tricuspid valve annuloplasty (66%), CSD implantation (43%) and coronary artery bypass grafting (51%).

In total, 64 patients (52%) had functional MR due to non-ischemic heart failure and 58 patients (48%) due to ischemic heart failure. As expected, baseline characteristics were different between these patient groups (Table 1). Patients with non-ischemic MR were on average 7 years younger (P <0.001), had a 5% lower mean LVEF (P <0.001), and had more often NYHA-class 3 and 4 symptoms (73% versus 50%, P=0.009). In addition, patients with non-ischemic MR had less often a history of previous cardiac surgery and more often used mineralocorticoid receptor antagonists and diuretics. Furthermore, patients with non-ischemic MR received more often concomitant tricuspid valve annuloplasty and CSD implantation. Coronary artery bypass grafting was performed in 91% of patients with ischemic MR. 14% of patients with non-ischemic MR received concomitant coronary artery bypass grafting for single vessel coronary artery disease. Since coronary artery disease could not account for the degree of LV dysfunction on echocardiography in these patients, etiology of MR was classified as non-ischemic. A longer mean procedure time was observed in ischemic compared to non-ischemic MR patients (median 336 minutes [IQR 293-407] versus 267 minutes [IQR 235-314], P <0.001). The same was seen for cross clamp time (median 127 minutes [IQR 110-164] versus 80 [IQR 63-100], P <0.001) and CPB time (median 186 minutes [IQR 154-227] versus 135 [IQR 118-167], P <0.001).

Table 1. Characteristics of the study population.

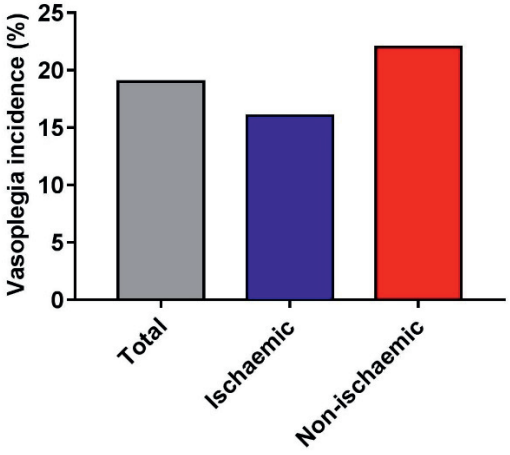
	Overall (N=122)	RMA non-ischemic (N=64, 52%)	RMA ischemic (N=58, 48%)	P-value
Age (years)	65±9	62±9	69±9	**<0.001**
Male sex	66%	61%	72%	0.249
Body mass index (kg/m^2)	26±4	26±3	27±4	0.093
Diabetes	28%	27%	29%	0.840
Prior CVA or TIA	10%	11%	9%	0.766
Prior hypertension	38%	30%	47%	0.063
LVEF (%)	27±6	25±5	30±5	**<0.001**
NYHA class 3 or 4	62%	73%	50%	**0.009**
Pulmonary hypertension	57%	64%	50%	0.144
Previous cardiac surgery	7%	2%	12%	**0.027**
EuroSCORE II (%)	9 (5-13)	9 (6-13)	8 (5-15)	0.693
Preoperative laboratory assessment				
Anemia	23%	19%	28%	0.285
Creatinine clearance (ml/min)	62 (49-80)	62 (54-83)	60 (44-78)	0.222
Medication				
Beta-blocker	80%	78%	81%	0.823
ACE inhibitor/ARB	83%	86%	79%	0.349
MRA	56%	67%	43%	**0.010**
Diuretics	91%	98%	83%	**0.003**
Inotropes	4%	6%	2%	0.368
Concomitant procedures				
Tricuspid valve annuloplasty	66%	81%	48%	**<0.001**
CSD	43%	81%	0%	**<0.001**
CABG	51%	14%	91%	**<0.001**
Cross clamp time (min) *	104 (74-133)	80 (63-100)	127 (110-164)	**<0.001**
CPB time (min)	155 (131-205)	135 (118-167)	186 (154-227)	**<0.001**
Procedure time (min)	296 (255-360)	267 (235-314)	336 (293-407)	**<0.001**
ICU time (days)	3 (1-5)	3 (2-6)	3 (1-5)	0.654

** Data based on 120 patients. P-values for comparison of patients with ischaemic and non-ischaemic MR. Continuous data are presented as mean ± SD or median (IQR). Categorical data are presented as numbers (%). ACE: Angiotensin-converting enzyme; ARB: angiotensin receptor blocker; CABG: Coronary artery bypass grafting; CPB: Cardiopulmonary bypass; CSD: cardiac support device; CVA: cerebrovascular accident; IQR: interquartile range; LVEF: Left ventricular ejection fraction; MRA: mineralocorticoid receptor antagonist; NYHA: New York Heart Association; RMA: restrictive mitral annuloplasty; TIA: transient ischaemic attack.*

Incidence and clinical impact of vasoplegia

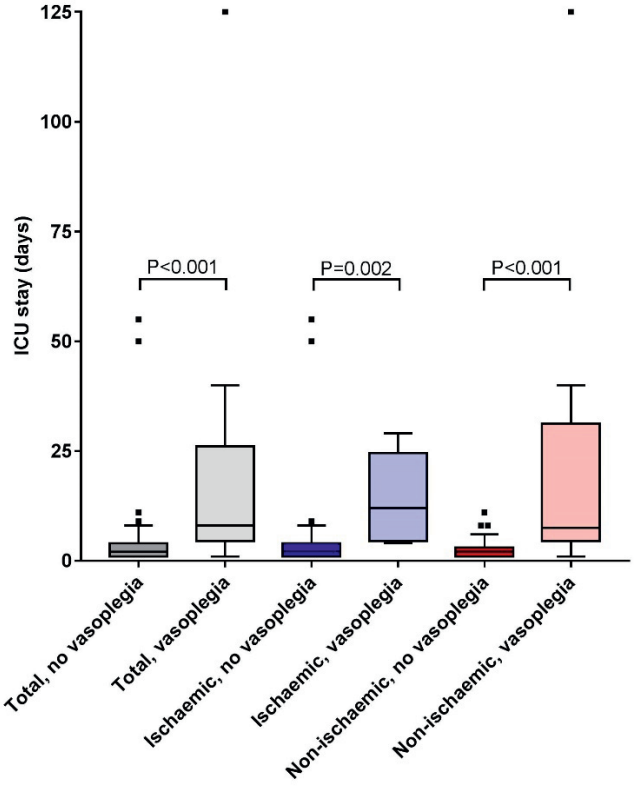
The incidence of vasoplegia in heart failure patients with functional MR was 19% (Figure 1). The incidence of vasoplegia was not significantly different between ischemic and non-ischemic MR patients (16% versus 22%, P=0.488).

Figure 1. Incidence of vasoplegia in the total study population and in the subgroups (ischemic and non-ischemic heart failure patients).



As shown in Figure 2, the duration of ICU admission was longer in patients with vasoplegia (median 8 days [IQR 5-26]) compared to patients without vasoplegia (2 days [IQR 1-4], P <0.001). In addition, renal failure occurred more often in patients with vasoplegia (48% versus 8%, P <0.001). Accordingly, patients with vasoplegia received more often continuous veno-venous hemofiltration (44% versus 4%, P <0.001). Furthermore, both 30-day (78% versus 98%, P <0.001) and 90-day survival rate (65% versus 93%, P <0.001) were lower in patients with vasoplegia compared to patients without vasoplegia (Figure 3A). The same applies when the population is stratified for ischemic (56% versus 90%, P=0.002) and non-ischemic MR patients (71% versus 96%, P=0.004, Figure 3B). There was no significant difference in survival when vasoplegic patients with ischemic MR were compared to vasoplegic patients with non-ischemic MR (P=0.458). The same applies to non-vasoplegic patients (P=0.234).

Figure 2. Duration of ICU stay in vasoplegic compared to non-vasoplegic patients. Box plot of the IQR and median, with minimum and maximum indicated with whiskers. Outliers are plotted as individual points.



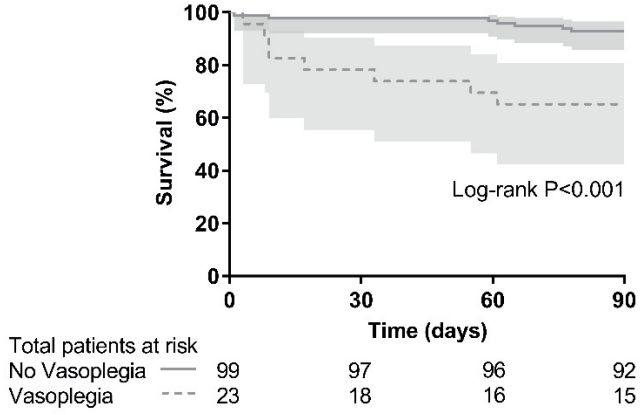
Predictors of vasoplegia

Univariable analysis showed that prior hypertension and beta-blocker use were associated with a decreased risk of vasoplegia, whereas anemia, longer cross clamp time, CPB time and total procedure time were associated with an increased risk of vasoplegia (Table 2).

Subsequent multivariable analysis showed that all characteristics mentioned above were associated with vasoplegia independent of age, gender and ischemic heart failure (Table 3). In addition, a higher creatinine clearance proved to be associated with a decreased risk of vasoplegia, when corrected for age, gender and ischemic heart failure.

Figure 3.

A. Kaplan-Meier survival curve of the total study population. Patients with (dotted line) and without (solid line) vasoplegia were compared. The shaded areas represent the 95% confidence intervals.



B. Kaplan-Meier survival curve of ischemic heart failure (blue) and non-ischemic heart failure patients (red). Patients with (dotted line) and without (solid line) vasoplegia were compared. Survival rates were lower in vasoplegic patients for both ischemic (P = 0.002) and non-ischemic etiology (P = 0.004).

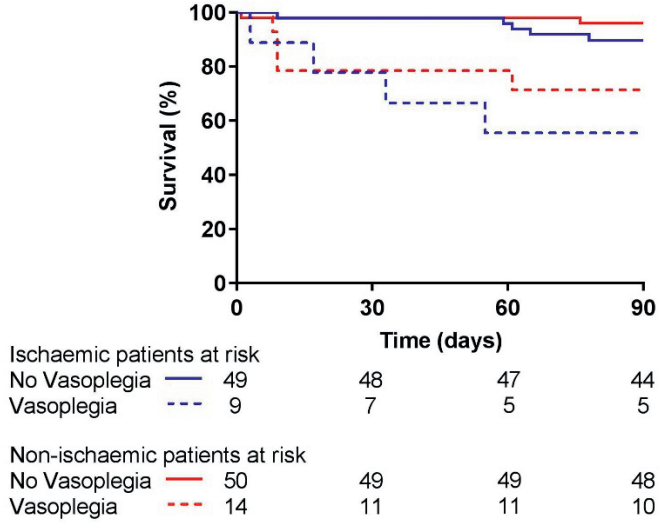


Table 2. Univariable analysis for vasoplegia.

	Vasoplegia (N=23)	No vasoplegia (N=99)	Univariable OR (95% CI)	P-value
Age (years)	65±8	65±10	0.99 (0.95-1.04)	0.714
Male sex	74%	65%	1.55 (0.56-4.29)	0.399
Body mass index (kg/m^2)	25±3	26±4	0.90 (0.78-1.04)	0.146
Diabetes	26%	28%	0.90 (0.32-2.50)	0.832
Prior CVA or TIA	9%	10%	0.85 (0.17-4.16)	0.839
Prior hypertension	17%	42%	0.29 (0.09-0.90)	**0.033**
Left ventricular ejection fraction (%)	27±6	27±6	1.00 (0.92-1.09)	0.958
Ischemic heart failure	39%	50%	0.66 (0.26-1.66)	0.372
NYHA class 3 or 4	70%	61%	1.49 (0.56-3.94)	0.426
Pulmonary hypertension	70%	55%	1.91 (0.72-5.04)	0.194
Previous cardiac surgery	4%	7%	0.60 (0.07-5.11)	0.638
EuroSCORE II (%)	12 (7-14)	8 (5-13)	1.02 (0.96-1.08)	0.479
Preoperative laboratory assessment				
Anemia	39%	19%	2.71 (1.02-7.18)	**0.045**
Creatinine clearance (ml/min)	57 (40-77)	62 (52-81)	0.98 (0.96-1.00)	0.058
Medication				
Beta-blocker	61%	84%	0.30 (0.11-0.81)	**0.018**
ACE inhibitor/ARB	83%	83%	0.99 (0.30-3.26)	0.980
MRA	48%	58%	0.68 (0.27-1.68)	0.398
Diuretics	100%	89%		0.999
Inotropes	4%	4%	1.08 (0.12-10.14)	0.947
Procedure type				
Tricuspid valve annuloplasty	65%	66%	0.98 (0.38-2.54)	0.968
CSD	52%	40%	1.61 (0.65-4.00)	0.306
Coronary artery bypass grafting	61%	49%	1.65 (0.66-4.17)	0.287
Cross clamp time (min)	112 (96-154)	98 (72-123)	1.01 (1.00-1.02)	**0.009**
Cardiopulmonary bypass time (min)	197 (140-262)	150 (128-195)	1.01 (1.00-1.02)	**0.008**
Procedure time (min)	334 (296-465)	285 (250-340)	1.01 (1.00-1.01)	**0.003**

ACE: Angiotensin-converting enzyme; ARB: angiotensin receptor blocker; CSD: cardiac support device; CVA: cerebrovascular accident; IQR: interquartile range; MRA: mineralocorticoid receptor antagonist; NYHA: New York Heart Association; RMA: restrictive mitral annuloplasty; TIA: transient ischaemic attack.

Table 3. Multivariable analysis assessing preoperative predictors for vasoplegia. Each variable is corrected for age, gender and ischemic heart failure.

	Multivariable OR (95% CI)	P-value
Prior hypertension	0.28 (0.08-0.91)	**0.034**
Anemia	3.00 (1.10-8.20)	**0.032**
Creatinine clearance (ml/min)	0.97 (0.95-0.99)	**0.009**
Beta-blocker	0.25 (0.09-0.73)	**0.011**
Cross clamp time (min)	1.03 (1.01-1.04)	**0.001**
Cardiopulmonary bypass time (min)	1.01 (1.00-1.02)	**0.003**
Procedure time (min)	1.01 (1.00-1.02)	**0.002**

Discussion

The main findings of this study can be summarized as follows: (1) the incidence of vasoplegia in heart failure patients undergoing mitral valve repair for functional MR was 19%; (2) vasoplegia was associated with a prolonged ICU admission and an increased 30- and 90-day mortality rate; (3) prior hypertension, a higher creatinine clearance and beta-blocker use were associated with a decreased risk of vasoplegia, whereas anemia and longer procedure times were associated with an increased risk of vasoplegia; (4) the results were independent of ischemic or non-ischemic functional MR etiology.

Incidence of vasoplegia

In the present study, vasoplegia was observed in 19% of patients who underwent a mitral valve repair for functional MR. The incidence of vasoplegia in this study is higher compared to the incidence observed after isolated coronary artery bypass grafting (6.9%) in patients with and without heart failure.[27] However, the incidence of vasoplegia in this study is lower compared to the incidence observed after surgical left ventricular restoration (23%), CSD implantation (25%), LVAD implantation (33-61%) or orthotopic heart transplantation (11-54%) in patients with heart failure.[15-17, 28-30] The wide range of reported vasoplegia incidences may be explained by differences in definitions of vasoplegia,[28] although differences in patient and surgical characteristics play a role as well. In line with previous studies, the incidence of vasoplegia was not significantly different between patients with ischemic and non-ischemic MR.[15-17, 29]

Clinical impact of vasoplegia

In literature, early postoperative (30-day and in-hospital) mortality after RMA for functional MR ranges from 2.6-8% in ischemic [11, 12, 31] and 5-5.8% in non-ischemic patients.[32-34] The overall 30-day mortality rate after RMA in this study (6%; 5% in ischemic and 6% in non-ischemic MR patients) is comparable to these reports. However, 30-day mortality proved to be much higher in patients who developed postoperative vasoplegia (22%) compared to non-vasoplegic patients (2%, P <0.001) - independent of etiology of functional MR.

Pathophysiology and predictors of vasoplegia

Several mechanisms have been proposed in the pathophysiology of vasoplegia. Landry and Oliver suggested three mechanisms: 1. Activation of adenosine triphosphate (ATP) dependent potassium channels (KATP) on the vascular smooth muscle cell; 2. Activation of inducible nitric oxide synthase (iNOS); 3. Deficiency of arginine vasopressin (AVP).[35] The latter was confirmed by Colson et al., showing that vasoplegic patients have higher preoperative copeptin (a precursor of AVP) plasma concentrations, but lower AVP concentrations postoperatively.[36] Furthermore, Kortekaas et. al showed that pre-existing endothelial cell activation (reflected by higher baseline von Willebrand Factor propeptide and sP-selectin levels, both markers for heart failure) is associated with vasoplegia in patients undergoing mitral valve surgery.[37, 38] Further, the systemic inflammatory response caused by CPB and surgical trauma, plays a major role in vasoplegia.[39] Although the exact pathophysiology of vasoplegia has not yet been elucidated, its etiology is multifactorial and results from activation of vasodilator mechanisms and inactivation of vasoconstrictor mechanisms.

In the present study, preoperative predictors of vasoplegia were assessed in heart failure patients undergoing mitral valve repair for functional MR. Heart failure patients proved to be at an increased risk of vasoplegia after cardiac surgery in several studies.[18-20] This might be explained by the fragile balance of the vascular system in patients with heart failure, since all systems perform on maximal capacity to assure adequate perfusion pressure. This fragile balance can easily be disturbed by CPB and surgical trauma.

Several preoperative patient characteristics – no beta-blocker use, no hypertension, a lower creatinine clearance and anemia – proved to be associated

with an increased risk of postoperative vasoplegia, Furthermore, prolonged CPB time was related to an increased risk of vasoplegia as well.

We hypothesize that these patient characteristics influence activation of vasodilation mechanisms and/or inactivation of vasoconstriction mechanisms (e.g. drug use, anemia), and are a marker of the fragile balance of the vascular systems. Heart failure patients who tolerate a beta-blocker and are able to maintain an adequate hemoglobin level and renal function, may simply represent a subgroup of patients better able to compensate for hemodynamic disturbances caused by surgical trauma and CPB. In contrast, studies in heart transplantation patients did not find a difference in beta-blocker use between vasoplegic and non-vasoplegic patients.[15, 29, 30] Interestingly, the overall use of beta-blockers in these studies was much lower (22-61%)[15, 29, 30] compared to studies which found betablocker use to be protective (80-84%)[16], indicating an important difference in study population.

In line with previous studies in heart failure patients,[29, 30] prolonged CPB time proved to be associated with an increased risk of vasoplegia (median 197 minutes in vasoplegic patients versus 150 in non-vasoplegic patients, P=0.008). This might be explained by the systemic inflammatory response induced by CPB and surgical trauma, which disturbs the balance of the cardiovascular system. A longer CPB time and larger surgical trauma may induce a more severe systemic inflammatory response and consequently increase the risk of vasoplegia. However, a study with much longer CPB times (van Vessem et al., mean 193±69 minutes[16]) did not observe an association between CPB time and vasoplegia after heart failure surgery. Therefore, we hypothesize that prolonged CPB time increases the risk of vasoplegia in heart failure patients until a certain duration threshold; when this threshold is reached, the risk of vasoplegia does not further increase. However, since a longer CPB time represents more extensive surgery, duration of CPB could simply be a marker of disease progression, although in this study left ventricular ejection fraction, NYHA class, and EuroSCORE II were not associated with an increased risk of vasoplegia.

Limitations

When interpreting the results of the current study, several study limitations should be taken into account. Firstly, this was a retrospective observational study, bearing associated biases. Secondly, this was a single centre study. Further research is necessary to verify whether these results can be extrapolated to other centres.

Clinical implications

Vasoplegia is a hazardous complication in heart failure patients undergoing mitral valve repair for functional MR and is related to a prolonged ICU admission and increased early mortality. Therefore, the likelihood of developing postoperative vasoplegia should be taken into account by the Heart Team when deciding on whether or not to perform surgery. Furthermore, preoperative optimization of hemodynamics and renal function could potentially reduce the risk of vasoplegia. Finally, vasopressin and methylene blue may be considered as treatment option in patients with vasoplegia resistant to fluid and vasopressor therapy.[40-43] However, further research is warranted to unravel the pathophysiologic mechanisms of vasoplegia after cardiac surgery, in order to improve therapeutic and preventive treatment options.

Conclusion

Vasoplegia occurs in 19% of heart failure patients undergoing mitral valve repair for functional MR. It is associated with an impaired early outcome. Prior hypertension, a higher creatinine clearance and beta-blocker use were associated with a decreased risk of vasoplegia, whereas anemia and longer procedure times were associated with an increased risk of vasoplegia, independent of MR etiology.

References

1. Levine RA, Hung J, Otsuji Y, et al. Mechanistic insights into functional mitral regurgitation. Curr Cardiol Rep 2002;4:125-9.
2. Enriquez-Sarano M, Akins CW, Vahanian A. Mitral regurgitation. Lancet 2009;373:1382-94.
3. Bursi F, Enriquez-Sarano M, Jacobsen SJ, et al. Mitral regurgitation after myocardial infarction: a review. Am J Med 2006;119:103-12.
4. Rossi A, Dini FL, Faggiano P, et al. Independent prognostic value of functional mitral regurgitation in patients with heart failure. A quantitative analysis of 1256 patients with ischaemic and non-ischaemic dilated cardiomyopathy. Heart 2011;97:1675-80.
5. Ponikowski P, Voors AA, Anker SD, et al. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC). Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. Eur J Heart Fail 2016;18:891-975.
6. Baumgartner H, Falk V, Bax JJ, et al. 2017 ESC/EACTS Guidelines for the management of valvular heart disease. Eur Heart J 2017;38:2739-91.
7. Nishimura RA, Otto CM, Bonow RO, et al. 2017 AHA/ACC Focused Update of the 2014 AHA/ACC Guideline for the Management of Patients With Valvular Heart Disease: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. J Am Coll Cardiol 2017;70:252-89.
8. Nishimura RA, Otto CM, Bonow RO, et al. 2014 AHA/ACC guideline for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol 2014;63:e57-185.
9. Lavall D, Hagendorff A, Schirmer SH, et al. Mitral valve interventions in heart failure. ESC heart failure 2018.
10. Chan KM, Punjabi PP, Flather M, et al. Coronary artery bypass surgery with or without mitral valve annuloplasty in moderate functional ischemic mitral regurgitation: final results of the Randomized Ischemic Mitral Evaluation (RIME) trial. Circulation 2012;126:2502-10.
11. Braun J, van de Veire NR, Klautz RJ, et al. Restrictive mitral annuloplasty cures ischemic mitral regurgitation and heart failure. Ann Thorac Surg 2008;85:430-6; discussion 6-7.
12. Geidel S, Lass M, Schneider C, et al. Downsizing of the mitral valve and coronary revascularization in severe ischemic mitral regurgitation results in reverse left ventricular and left atrial remodeling. Eur J Cardiothorac Surg 2005;27:1011-6.
13. Grossi EA, Woo YJ, Patel N, et al. Outcomes of coronary artery bypass grafting and reduction annuloplasty for functional ischemic mitral regurgitation: a prospective multicenter study (Randomized Evaluation of a Surgical Treatment for Off-Pump Repair of the Mitral Valve). J Thorac Cardiovasc Surg 2011;141:91-7.
14. Fischer GW, Levin MA. Vasoplegia during cardiac surgery: current concepts and management. Semin Thorac Cardiovasc Surg 2010;22:140-4.
15. Byrne JG, Leacche M, Paul S, et al. Risk factors and outcomes for 'vasoplegia syndrome' following cardiac transplantation. Eur J Cardiothorac Surg 2004;25:327-32.
16. van Vessem ME, Palmen M, Couperus LE, et al. Incidence and predictors of vasoplegia after heart failure surgery. Eur J Cardiothorac Surg 2017;51:532-8.
17. Chemmalakuzhy J, Costanzo MR, Meyer P, et al. Hypotension, acidosis, and vasodilatation syndrome post-heart transplant: prognostic variables and outcomes. J Heart Lung Transplant 2001;20:1075-83.

18. Argenziano M, Chen JM, Choudhri AF, et al. Management of vasodilatory shock after cardiac surgery: identification of predisposing factors and use of a novel pressor agent. J Thorac Cardiovasc Surg 1998;116:973-80.
19. Alfirevic A, Xu M, Johnston D, et al. Transfusion increases the risk for vasoplegia after cardiac operations. Ann Thorac Surg 2011;92:812-9.
20. Levin MA, Lin HM, Castillo JG, et al. Early on-cardiopulmonary bypass hypotension and other factors associated with vasoplegic syndrome. Circulation 2009;120:1664-71.
21. Lip GY, Pearce LA, Chin BS, et al. Effects of congestive heart failure on plasma von Willebrand factor and soluble P-selectin concentrations in patients with non-valvar atrial fibrillation. Heart 2005;91:759-63.
22. Benoist B, McLean E, Egli I, et al. Worldwide Prevalence of Anaemia 1993–2005: World Health Organization [Available from: http://apps.who.int/iris/bitstream/10665/43894/1/9789241596657_eng.pdf.
23. Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. Nephron 1976;16:31-41.
24. Lang RM, Badano LP, Mor-Avi V, et al. Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. Eur Heart J Cardiovasc Imaging 2015;16:233-70.
25. Galie N, Humbert M, Vachiery JL, et al. 2015 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension: The Joint Task Force for the Diagnosis and Treatment of Pulmonary Hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS): Endorsed by: Association for European Paediatric and Congenital Cardiology (AEPC), International Society for Heart and Lung Transplantation (ISHLT). Eur Heart J 2016;37:67-119.
26. Haeck ML, Hoogslag GE, Rodrigo SF, et al. Treatment options in end-stage heart failure: where to go from here? Neth Heart J 2012;20:167-75.
27. Sun X, Zhang L, Hill PC, et al. Is incidence of postoperative vasoplegic syndrome different between off-pump and on-pump coronary artery bypass grafting surgery? Eur J Cardiothorac Surg 2008;34:820-5.
28. de Waal EEC, van Zaane B, van der Schoot MM, et al. Vasoplegia after implantation of a continuous flow left ventricular assist device: incidence, outcomes and predictors. BMC Anesthesiol 2018;18:185.
29. Patarroyo M, Simbaqueba C, Shrestha K, et al. Pre-operative risk factors and clinical outcomes associated with vasoplegia in recipients of orthotopic heart transplantation in the contemporary era. J Heart Lung Transplant 2012;31:282-7.
30. Chan JL, Kobashigawa JA, Aintablian TL, et al. Vasoplegia after heart transplantation: outcomes at 1 year. Interact Cardiovasc Thorac Surg 2017;25:212-7.
31. Bax JJ, Braun J, Somer ST, et al. Restrictive annuloplasty and coronary revascularization in ischemic mitral regurgitation results in reverse left ventricular remodeling. Circulation 2004;110:Ii103-8.
32. Westenberg JJ, van der Geest RJ, Lamb HJ, et al. MRI to evaluate left atrial and ventricular reverse remodeling after restrictive mitral annuloplasty in dilated cardiomyopathy. Circulation 2005;112:I437-42.
33. Braun J, Ciarka A, Versteegh MI, et al. Cardiac support device, restrictive mitral valve annuloplasty, and optimized medical treatment: a multimodality approach to nonischemic cardiomyopathy. J Thorac Cardiovasc Surg 2011;142:e93-100.
34. De Bonis M, Taramasso M, Verzini A, et al. Long-term results of mitral repair for functional mitral regurgitation in idiopathic dilated cardiomyopathy. Eur J Cardiothorac Surg 2012;42:640-6.
35. Landry DW, Oliver JA. The pathogenesis of vasodilatory shock. N Engl J Med 2001;345:588-95.

36. Colson PH, Bernard C, Struck J, et al. Post cardiac surgery vasoplegia is associated with high preoperative copeptin plasma concentration. Crit Care 2011;15:R255.
37. Kortekaas KA, Lindeman JH, Reinders ME, et al. Pre-existing endothelial cell activation predicts vasoplegia after mitral valve surgery. Interact Cardiovasc Thorac Surg 2013;17:523-30.
38. Chong AY, Blann AD, Patel J, et al. Endothelial dysfunction and damage in congestive heart failure: relation of flow-mediated dilation to circulating endothelial cells, plasma indexes of endothelial damage, and brain natriuretic peptide. Circulation 2004;110:1794-8.
39. Day JR, Taylor KM. The systemic inflammatory response syndrome and cardiopulmonary bypass. Int J Surg 2005;3:129-40.
40. Noto A, Lentini S, Versaci A, et al. A retrospective analysis of terlipressin in bolus for the management of refractory vasoplegic hypotension after cardiac surgery. Interact Cardiovasc Thorac Surg 2009;9:588-92.
41. Hajjar LA, Vincent JL, Barbosa Gomes Galas FR, et al. Vasopressin versus Norepinephrine in Patients with Vasoplegic Shock after Cardiac Surgery: The VANCS Randomized Controlled Trial. Anesthesiology 2017;126:85-93.
42. Leite EG, Ronald A, Rodrigues AJ, et al. Is methylene blue of benefit in treating adult patients who develop catecholamine-resistant vasoplegic syndrome during cardiac surgery? Interact Cardiovasc Thorac Surg 2006;5:774-8.
43. Liu H, Yu L, Yang L, et al. Vasoplegic syndrome: An update on perioperative considerations. J Clin Anesth 2017;40:63-71.

CHAPTER 4

Vasoplegia after surgical left ventricular restoration: two year follow-up

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Abstract

Background: Vasoplegia is a severe complication which can develop after heart failure surgery. The aim of the current study was to evaluate the effect of vasoplegia on survival, cardiac function and renal function 2 years after surgical left ventricular restoration (SVR).

Methods: Heart failure patients with a left ventricular ejection fraction (LVEF) ≤35% who underwent SVR in 2006-2014 were included. Vasoplegia was defined as the continuous need of vasopressors (norepinephrine ≥0.2 μg/kg/min and/or terlipressin (any dose)) combined with a cardiac index ≥2.2 l/min/m^2 for at least 12 consecutive hours, starting within the first 3 days postoperatively. The effect of vasoplegia on mortality, NYHA class, LVEF and creatinine clearance was assessed up to 2-year follow-up.

Results: 113 patients (80% male, age 62±10 years, LVEF 25±6%) underwent SVR. Postoperative vasoplegia developed in 23%. Both 6-month and 2-year survival were lower in patients with vasoplegia compared to patients without vasoplegia (62% versus 90%, P=0.001 and 50% versus 84%, P<0.001). At 2-year follow-up, NYHA class and LVEF had improved and were similar in both groups (respectively, P=0.319 and P=0.444). Creatinine clearance was lower in patients with vasoplegia compared to patients without vasoplegia 2 years postoperatively (P<0.001), even after correcting for baseline creatinine clearance (P=0.009).

Conclusions: Vasoplegia after SVR is associated with decreased survival. Despite an improved and similar cardiac function, renal function was compromised in vasoplegic patients at 2-year follow-up.

Introduction

In recent years the treatment options for patients with heart failure have expanded significantly. Apart from pharmacological therapy, a number of surgical treatment options are available nowadays. Unfortunately, however, a technically uncomplicated procedure with good surgical result does not guarantee a good clinical result. Postoperative complications, including the occurrence of vasoplegia, may impair clinical outcome. Vasoplegia is a syndrome defined by hypotension and the continuous need of vasopressors, despite a normal or high cardiac output.[1] Earlier studies revealed that patients with a poor left ventricular ejection fraction (LVEF) undergoing cardiothoracic surgery are particularly at risk for developing vasoplegia.[2] The incidence of vasoplegia ranges from 11-31% in patients with a poor LVEF undergoing heart failure surgery.[2-6] In our previous study we showed that anemia, a higher thyroxine level, a lower creatinine clearance and beta-blocker intolerance were associated with an increased risk on vasoplegia.[4] Prolonged hypotension and the accompanying hypoperfusion may lead to end-organ dysfunction in these patients. In previous studies, vasoplegia has been associated with a prolonged intensive care unit (ICU) stay.[4-6] Furthermore, vasoplegia results in increased mortality in the early postoperative phase.[3-5]

Although previous studies reported on the short-term effects of vasoplegia after heart failure surgery, the effects of vasoplegia 2 years after heart failure surgery have not been investigated to date. Therefore, the aim of the current study was to evaluate the effects of vasoplegia on survival, cardiac function and renal function 2 years after surgical left ventricular restoration (SVR).

Patients and methods

Study design

Heart failure patients (defined according to the ESC guidelines[7]) with a LVEF ≤35% who underwent SVR at the Leiden University Medical Center between 2006-2014 were eligible for inclusion in this retrospective study. This is a subpopulation of a cohort that has been described previously.[4] The whole cohort concerned patients undergoing three different types of heart failure surgery, which resulted in a heterogeneous population. Therefore we only included the largest subpopulation. To ensure complete 2-year follow-up, we only included the cohort of 2006-2014. We screened all patients that underwent cardiothoracic surgery at our institution

in the given period. Patients in whom the diagnosis of vasoplegia could not be established due to the absence of continuous cardiac index (CI) registration postoperatively were excluded. This study was conducted in accordance with the declaration of Helsinki. The institutional ethical committee approved the study. Written informed consent was obtained to collect follow-up data from referral centers.

Data collection and analysis

Hemodynamic, laboratory, clinical and survival data were collected prospectively in the patient information systems (EPD-Vision, Leiden University Medical Center, Leiden, the Netherlands; Metavision, Itémedical, Tiel, The Netherlands; CS-PDMS, Chipsoft, Amsterdam, The Netherlands) and analyzed retrospectively. Additional follow-up data was retrieved from referral centers. Three researchers (MV, RB and SB) assessed the causes of death independently using the post-mortem examinations when available and the clinical letters. Disagreements were resolved by the three researchers after discussing the patient record in more detail.

Vasoplegia was defined as previously: the continuous need of vasopressors (norepinephrine ≥0.2 μg/kg/min and/or terlipressin (any dose)) combined with a cardiac index (CI) ≥2.2 l/min/m^2 for at least 12 consecutive hours, starting within the first 3 days postoperatively.[4] Anemia was defined as a hemoglobin concentration <8.1 mmol/l for men and <7.4 mmol/l for women.[8] Creatinine clearance was estimated with the Cockroft-Gault formula.[9] All patients underwent transthoracic echocardiographic evaluation pre- and postoperatively according to the institutional heart failure protocol.[10] The images were digitally stored in cine-loop format and analyzed (GE Vingmed Ultrasound AS, Horten, Norway; EchoPAC version 112.0.1) by a researcher blinded to the clinical status of the patient. The LVEF was determined from the apical 4- and 2-chamber views using Simpson's biplane method.[11] Right ventricular function was assessed using tricuspid annular plane systolic excursion (TAPSE). This was calculated on M-mode recordings of the lateral tricuspid annulus in the right ventricular apical view. TAPSE <16 mm was considered as impaired right ventricular function.[12] Pulmonary hypertension was defined as an estimated peak tricuspid regurgitation velocity >3.4 m/s,[13] measured with continuous wave Doppler.[12]

Surgical procedure

The multi-disciplinary heart team decided on the indication and timing of surgery. SVR was performed if it was likely that a postoperative end-systolic volume index of 70 ml/m^2 or less was achieved in a heart failure patient with a postinfarction left ventricular aneurysm.[14] The procedure was performed according to the technique described by Dor.[15] All operations were performed using cardiopulmonary bypass, aortic cross-clamping and intermittent warm blood cardioplegia. Patients received an arterial line and a pulmonary artery catheter for intra- and postoperative monitoring. These data were used to calculate CI. Intraoperatively, a mean arterial pressure (MAP) ≤65 mmHg was corrected using norepinephrine. Postoperatively, norepinephrine was started if the MAP was ≤65 mmHg and the CI was normal (after adequate administration of intravascular fluids if necessary), aiming for a MAP >65mmHg and adequate end-organ perfusion. When a norepinephrine dosage >1 µg/kg/min was required, terlipressin was started.

Statistical analysis

Continuous variables are expressed as mean ± standard deviation (SD) when normally distributed, or otherwise as median and interquartile range (IQR). Categorical variables are presented percentages. Missing values (NT-ProBNP baseline (N=37); thyroxine baseline (N=36); creatinine clearance 6 months (N=18), 12 months (N=19) and 24 months (N=12) follow up; NYHA 24 months (N=3) follow up; LVEF 24 months (N=3)), were replaced using multiple imputation with predictive mean matching, which was repeated a hundred times. Baseline age, gender, EuroSCORE, NYHA class, creatinine clearance and follow up data of NYHA and creatinine clearance were used as predictors in the model. The pooled data was used for analysis. Vasoplegic and non-vasoplegic patients were compared. Comparison of continuous data was performed using two-tailed unpaired Student t test for normally distributed variables or otherwise the Mann-Whitney U test. Comparison of categorical variables was performed using the Fisher's exact test. The Kaplan Meier method was used to assess 6-month and 2-year mortality in vasoplegic and non-vasoplegic patients. Landmark analysis was used to assess the late effect of vasoplegia on mortality between 6 months and 2-years postoperative.

Survival distributions were compared using the log-rank test. Univariable Cox regression analysis was used to investigate the association between perioperative characteristics and 2-year mortality. The proportional hazards assumption was tested using time-dependent variables. Subsequently, all significant associations,

which were not related to each other, were entered in a multivariable Cox regression analysis to investigate the unique effect of vasoplegia on mortality after adjusting for all other relevant characteristics.

To explore the effects of vasoplegia on NYHA class and LVEF at 2-year follow-up, generalized estimating equations (GEE) was performed, utilizing an independent working correlation structure. Further GEE was used to assess the effect of vasoplegia on creatinine clearance, with and without correction for baseline renal function, during 2-year follow-up.

P-values <0.05 were considered statistically significant. Statistical analysis was performed using SPSS for Windows (version 21.0, Chicago, Illinois) and R (version 3.2.1, Vienna, Austria).

Results

Study population

Of the 135 screened patients, 22 patients were excluded due to the absence of continuous CI registration postoperatively. Therefore, we included 113 patients (80% male, age 62±10 years). Perioperative data are summarized in Table 1 and 2. 60% had NYHA class 3 and 4 symptoms, and the mean baseline LVEF was 25±6%.Postoperative vasoplegia occurred in 26 patients (23%). The median duration of vasoplegia was 42 (IQR 19-106) hours. Prior hypertension and beta-blocker use was less frequent in vasoplegic patients and these patients had lower creatinine clearance and higher thyroxine levels on average. There was no difference in milrinone and enoximone use between vasoplegic and non-vasoplegic patients pre-, intra- (P=1.000) and postoperatively (P=0.588). Of note, there was no significant difference between surgeons in the occurrence of vasoplegia (P=0.063). Patients with vasoplegia received more often an IABP and renal replacement therapy postoperatively. Furthermore, the ICU admission time was prolonged in vasoplegic patients (2 (IQR 1-5) versus 14 (IQR 7-27) days, P<0.001).

Table 1. Baseline characteristics.

	Total (N=113)	No vasoplegia (N=87, 77%)	Vasoplegia (N=26, 23%)	P-value
Age (years)	62±10	61±10	64±9	0.303
Male sex	(80%	77%	88%	0.272
Body mass index (kg/m^2)	27±4	27±3	26±4	0.534
Diabetes	28%	26%	35%	0.461
Prior CVA or TIA	10%	11%	4%	0.452
Prior hypertension	50%	55%	31%	**0.043**
Left ventricular ejection fraction (%)	25±6	25±6	26±6	0.413
TAPSE <16 mm*	24%	20%	38%	0.067
NYHA class 3 or 4	60%	56%	73%	0.171
Pulmonary hypertension	14%	11%	23%	0.196
Previous cardiac surgery	12%	11%	15%	0.734
EuroSCORE II (%)	6 (4-13)	5 (3-13)	10 (5-13)	0.070
Preoperative laboratory assessment				
Anemia	30%	25%	46%	0.053
Creatinine clearance (ml/min)	77±30	81±31	64±25	**0.012**
NT-ProBNP (ng/l)**	1256 (573-2205)	1140 (578-1915)	1392 (486-4076)	0.630
Thyroxine (pmol/l)***	18±3	18±3	19±3	**0.038**
Medication				
Beta-blocker	91%	94%	81%	0.049
ACE inhibitor/ARB	94%	95%	88%	0.198
Antiarrhythmics	29%	30%	27%	1.000
MRA	63%	63%	62%	1.000
Diuretics	80%	79%	81%	1.000
Inotropes	4%	3%	8%	0.324

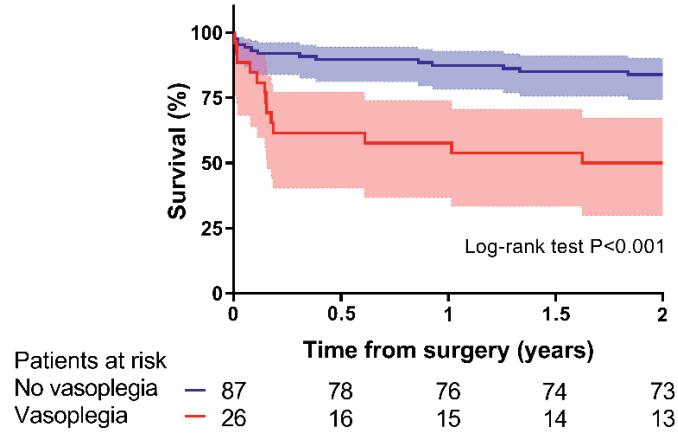
**112, **76, ***77 patients. Continuous data are presented as mean ± SD or median (IQR). Categorical data are presented as %. CVA: cerebrovascular accident; ECMO: extracorporeal membrane oxygenation; IABP: intra-aortic balloon pump; ICU: intensive care unit; IQR: interquartile range; TAPSE: tricuspid annular plane systolic excursion; TIA: transient ischemic attack*

Table 2. Intra- and postoperative characteristics.

	Total (N=113)	No vasoplegia (N=87, 77%)	Vasoplegia (N=26, 23%)	P-value
Intraoperatively				
Concomitant procedures				
CABG	52%	54%	46%	0.510
Mitral valve surgery	59%	55%	73%	0.117
Tricuspid valve surgery	28%	28%	31%	0.806
Aortic valve surgery	6%	6%	8%	0.660
Cross clamp time (min)	148±47	148±50	149±39	0.904
Cardiopulmonary bypass time (min)	212 (168-254)	212 (158-249)	212 (180-267)	0.284
Procedure time (min)	349 (289-424)	341 (280-415)	356 (309-469)	0.126
Postoperatively				
Tamponade	7%	5%	15%	0.080
IABP	28%	23%	46%	**0.027**
ECMO	6%	6%	8%	0.660
CVA or TIA	2%	2%	0%	1.000
Renal replacement therapy	11%	2%	38%	**<0.001**
ICU admission time*	3 (1-7)	2 (1-5)	14 (7-27)	**<0.001**

** Data based on 96 patients, due to mortality. Continuous data are presented as mean ± SD or median (IQR). Categorical data are presented as %. CABG: coronary artery bypass grafting; CVA: cerebrovascular accident; ECMO: extracorporeal membrane oxygenation; IABP: intra-aortic balloon pump; ICU: intensive care unit; TIA: transient ischemic attack*

Figure 1. Kaplan Meier survival curve for patients with vasoplegia (red) and without vasoplegia (blue) with 95% confidence intervals.



Mortality

As shown in Figure 1, both 6-month and 2-year survival were lower in patients with vasoplegia compared to patients without vasoplegia (62% versus 90% at 6-month follow-up, *P*=0.001 and 50% versus 84% at 2-year follow-up, *P*<0.001). When excluding patients who deceased in the first 6 months, the difference in 2-year mortality between both groups did not persist (*P*=0.097). Of interest, 2-year mortality was higher in patients in whom vasoplegia persisted >24 hours (67%) compared to patients in whom vasoplegia was corrected within 24 hours (13%, *P*=0.030).

Tables 3-5 illustrate the results of the uni- and multivariable cox regression analysis investigating the association between vasoplegia and 2-year mortality. Univariable cox regression analysis revealed that vasoplegia was associated with increased mortality. Subsequent multivariable analysis demonstrated that vasoplegia was still associated with increased mortality after adjusting for baseline, intraoperative and postoperative variables.

The causes of death are shown in Figure 2. The risk on multiple organ failure-related death was 8% in vasoplegic patients. All died within the first 6 months after surgery, while no patients without vasoplegia died from multiple organ failure (*P*=0.051). The risk of death due to infection related to ICU admission was 15% in vasoplegic patients, compared to 1% in non-vasoplegic patients (*P*=0.010), all within the first 6 months after surgery. The 2-year risk on cardiac related death was similar in vasoplegic (23%) and non-vasoplegic patients (13%, *P*=0.216). Of note, death due to heart failure accounted for most of the cardiac deaths. The 2-year risk of death caused by heart failure was 19% for vasoplegic and 11% for non-vasoplegic patients (*P*=0.330). Furthermore, there was no significant difference between surgeons in 6 month (*P*=0.281) or 2 year mortality (*P*=0.451).

Figure 2. 2-year mortality risk per cause of death in vasoplegic (red) and non-vasoplegic patients (blue).

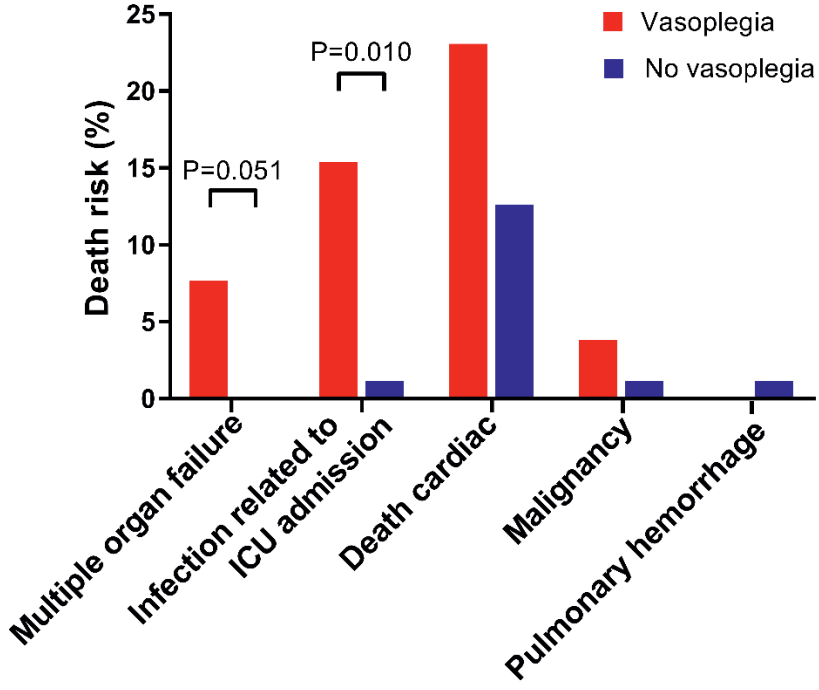


Table 3. Crude risk of death preoperatively.

	HR (95%CI)	P-value
Age (years)	1.03 (0.99-1.08)	0.120
Male sex	7.45 (1.01-54.95)	**0.049**
Body mass index (kg/m^2)	1.05 (0.95-1.17)	0.357
Diabetes	2.70 (1.27-5.74)	0.010
Prior CVA or TIA	2.70 (1.02-7.14)	**0.045**
Prior hypertension	0.79 (0.37-1.68)	0.537
Left ventricular ejection fraction (%)	1.00 (0.94-1.06)	1.000
TAPSE << 16	2.61 (1.21-5.62)	**0.015**
NYHA class 3 or 4	2.58 (1.04-6.39)	**0.041**
Pulmonary hypertension	1.83 (0.74-4.55)	0.190
Previous cardiac surgery	2.89 (1.22-6.86)	**0.016**
EuroSCORE II (%)	1.04 (1.01-1.06)	**0.001**
Preoperative laboratory assessment		
Anemia	2.85 (1.34-6.08)	**0.007**
Creatinine clearance (ml/min)	1.00 (0.98-1.01)	0.406
NT-ProBNP (ng/l)	1.00 (1.00-1.00)	0.895
Thyroxine (pmol/l)	0.97 (0.83-1.14)	0.705
Medication		
Beta-blocker	0.49 (0.17-1.40)	0.182
ACE inhibitor/ARB	0.39 (0.12-1.31)	0.129
Antiarrhythmics	1.33 (0.60-2.96)	0.488
MRA	1.14 (0.51-2.55)	0.743
Diuretics	3.48 (0.82-14.70)	0.090
Inotropes	2.29 (0.54-9.66)	0.261

CVA: cerebrovascular accident; HR: hazard ratio; TAPSE: tricuspid annular plane systolic excursion; TIA: transient ischemic attack.

Table 4. Crude risk of death intra- and postoperatively.

	HR (95%CI)	P-value
Intraoperatively		
Concomitant procedures		
CABG	3.04 (1.28-7.19)	**0.011**
Mitral valve surgery	2.04 (0.86-4.82)	0.105
Tricuspid valve surgery	1.85 (0.86-3.98)	0.118
Aortic valve surgery	2.30 (0.69-7.66)	0.174
Cross clamp time (min)	1.01 (1.00-1.02)	**0.001**
Cardiopulmonary bypass time (min)	1.01 (1.01-1.02)	**<0.001**
Procedure time (min)	1.01 (1.00-1.01)	**<0.001**
Postoperatively		
Vasoplegia	3.93 (1.84-8.39)	**<0.001**
Tamponade	2.91 (1.01-8.42)	**0.049**
IABP	7.09 (3.18-15.84)	**<0.001**
ECMO	10.99 (4.29-28.16)	**<0.001**
CVA or TIA	0.05 (0.00-7814.37)	0.620
ICU admission time	1.08 (1.04-1.11)	**<0.001**

CABG: coronary artery bypass grafting; CVA: cerebrovascular accident; ECMO: extracorporeal membrane oxygenation; HR: hazard ratio; IABP: intra-aortic balloon pump; ICU: intensive care unit; TIA: transient ischemic attack

Table 5. Adjusted risk of death. Multivariable survival analysis of the effect of vasoplegia, adjusted for preoperative (model 1), intraoperative (model 2) and postoperative (model 3) variables.

	Model 1		Model 2		Model 3	
	HR (95%CI)	P-value	HR (95%CI)	P-value	HR (95%CI)	P-value
Vasoplegia	3.34 (1.54-7.23)	**0.002**	4.59 (2.03-10.37)	**<0.001**	3.34 (1.49-7.48)	**0.003**
TAPSE <16 mm	1.80 (0.82-3.96)	0.142				
EuroSCORE II (%)	1.03 (1.00-1.06)	0.054				
Anemia	1.70 (0.74-3.87)	0.209				
Concomitant CABG			2.11 (0.83-5.32)	0.115		
Cross clamp time (min)			1.00 (0.99-1.01)	0.491		
CPB time (min)			1.01 (1.01-1.02)	**<0.001**		
Tamponade					2.06 (0.66-6.39)	0.212
IABP					3.54 (1.43-8.78)	**0.006**
ECMO					7.17 (2.39-21.51)	**<0.001**

CABG: coronary artery bypass grafting; CPB: Cardiopulmonary bypass; ECMO: extracorporeal membrane oxygenation; IABP: intra-aortic balloon pump; TAPSE: tricuspid annular plane systolic excursion

Clinical outcome

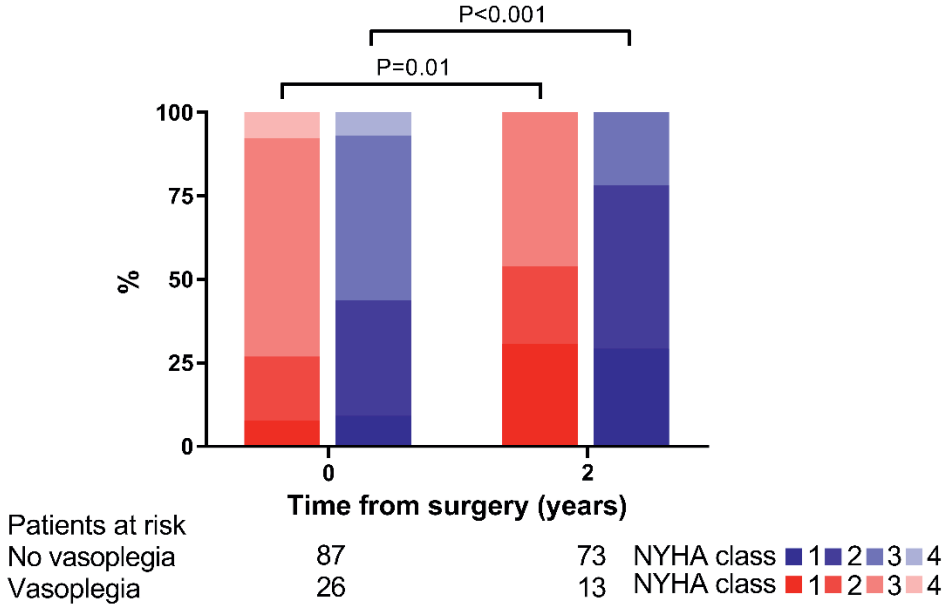
Clinical and echocardiographic findings at baseline and 2-year follow-up are depicted in Figure 3. At 2-year follow-up, there was an improvement in NYHA class and LVEF, in both vasoplegic and non-vasoplegic patients. Of importance, at 2-year follow-up, NYHA class (*P*=0.319) and LVEF (*P*=0.444) were similar in vasoplegic and non-vasoplegic patients. The same accounted for left ventricular function measured 5-7 days postoperatively (*P*=0.826).

The course of creatinine clearance from baseline to 2-year follow-up is shown in Figure 4A. Baseline creatinine clearance was lower in vasoplegic patients compared to non-vasoplegic patients, *P*=0.003). Despite a non-significant difference between both groups 30 days postoperatively, creatinine clearance was significantly lower in vasoplegic as compared to non-vasoplegic patients at 6 months, 1 year and 2 years postoperatively (*P*<0.001).

Figure 4B shows the course of creatinine clearance after adjusting for baseline creatinine clearance. Even after correction, creatinine clearance at 2-year follow-up remained significantly (*P*=0.009) lower in the vasoplegic patients compared to the non-vasoplegic patients. Of note, 39% of the vasoplegic patients received renal replacement therapy postoperatively compared to 2% in the non-vasoplegic patients (P<0.001). Median time from start of vasoplegia to renal replacement therapy was 63 (IQR 48-325) hours. Both non-vasoplegic patients received renal replacement therapy until their death at the ICU. 8% of the vasoplegic patients received chronic renal replacement therapy, 15%received temporarily therapy during their ICU admission and 15% until their death at the ICU.

Figure 3. Follow up of NYHA class (A) and LVEF (B) for vasoplegic (red) and non-vasoplegic patients (blue) with 95% confidence intervals.

A.



B.

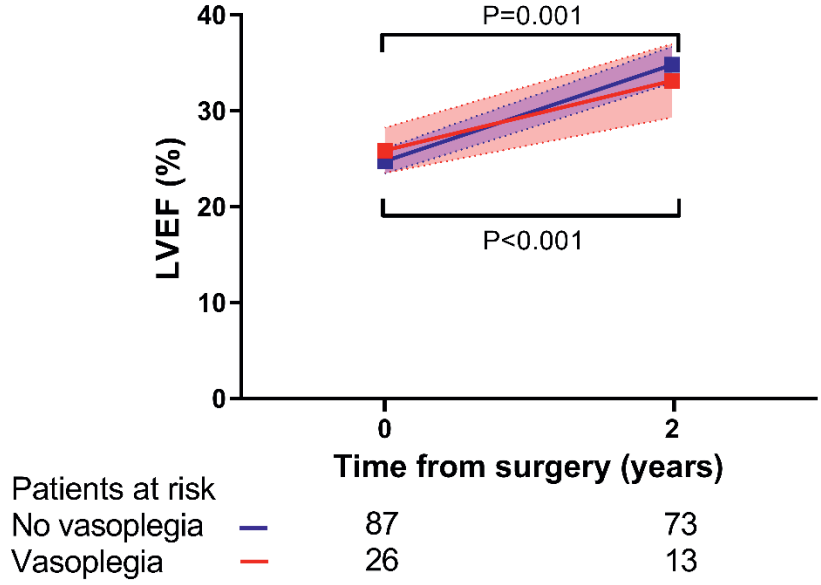
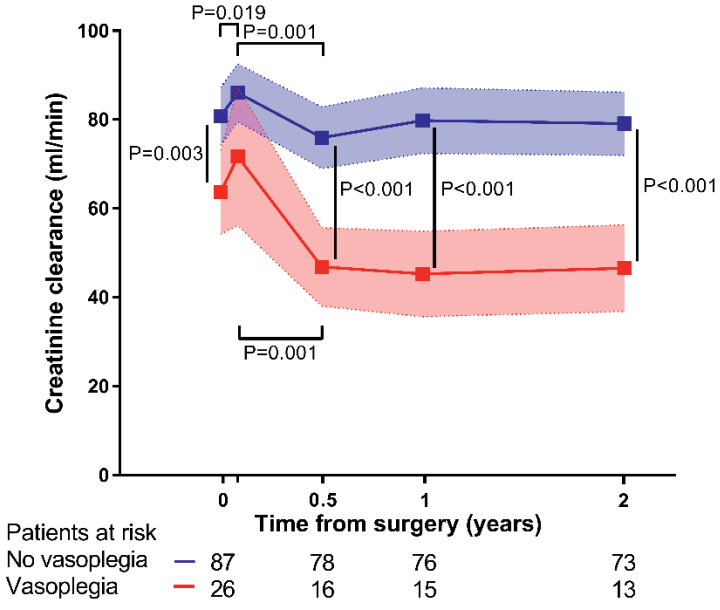
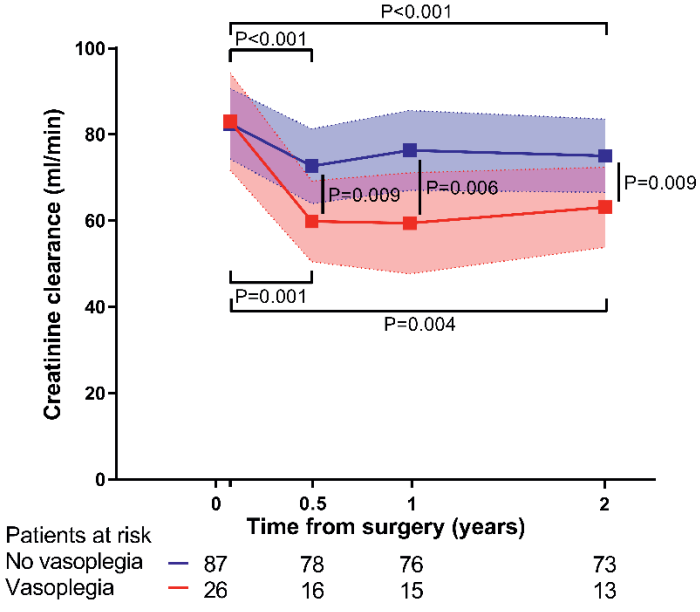


Figure 4. Follow up of creatinine clearance (A) and creatinine clearance, corrected for baseline creatinine clearance (B) for vasoplegic (red) and non-vasoplegic patients (blue) with 95% confidence intervals.

A.



B.



Discussion

The main finding of this study is that vasoplegia is associated with an increased mortality rate after SVR. Furthermore, despite a similar and improved cardiac function at 2-year follow-up, vasoplegic patients had a compromised renal function even when correcting for the lower creatinine clearance at baseline.

Vasoplegia is associated with an increased mortality rate

Previous studies demonstrated that vasoplegia after heart failure surgery is associated with an early mortality.[3-5] The current study extends this observation by demonstrating that also 2-year mortality rate is higher after vasoplegia. Chan et al. studied 347 patients undergoing a heart transplantation of whom 30.8% developed vasoplegia.[6] This study did not find a significant difference in 1-year mortality in vasoplegic compared to non-vasoplegic patients (11.4% versus 8.0%, P=0.338). Importantly, 27 (25.2%) vasoplegic patients and 41 (17.1%) non-vasoplegic patients were lost to follow-up in the study by Chan et al.

The current study demonstrated that vasoplegia was associated with increased mortality even after adjusting for significant perioperative characteristics. Accordingly, it may be presumed that vasoplegia was an important contributor to mortality. Most vasoplegic patients died during the first 6 months postoperatively, mainly due to infection related to the ICU admission, multiple organ failure or heart failure. Several other studies showed that vasoplegia is associated with a longer ICU admission, thereby increasing the risk of hospital-acquired infections that could explain the high infection related mortality rate.[4, 5]

Vasoplegia related renal dysfunction

Four previous studies evaluated perioperative creatinine plasma levels in vasoplegic and non-vasoplegic patients after cardiothoracic surgery. Creatinine levels increased in vasoplegic patients in the early postoperative phase in three studies.[5, 6, 16] In the first study, Patarroyo et al. studied 311 patients undergoing heart transplantation, of whom 11% developed vasoplegia.[5] Creatinine levels were 1.5 ± 0.6 mg/dl in vasoplegic patients, compared to 1.3 ± 0.57 mg/dl in non-vasoplegic patients (P=0.0046) in the first 48 hours postoperatively. In the second study, Chan et al. showed that creatinine levels were 1.7 ± 1.4 in vasoplegic patients compared to 1.4±1.1 in non-vasoplegic patients (P=0.037) post-transplant.[6] Furthermore, vasoplegic patients received more often continuous replacement therapy and hemodialysis in the first year postoperatively. In the third study, Weis et al. studied 1158 patients undergoing cardiac surgery and compared outcome of patients with and without vasopressor dependence (>0.1 µg/kg/hour norepinephrine for

>3 hours to maintain a MAP >70 mmHg during normvolemia).[16] The incidence of vasopressor dependence was 27%. Creatinine level was 114.9 mmol/l (IQR 88.4-167.9) in vasopressor dependent patients, compared to 97.24 mmol/l (IQR 88.4-123.67) in non-vasopressor dependent patients (P<0.01) in the first 48 hours postoperatively. Furthermore, Weis et al. showed that vasopressor dependent patients required renal replacement therapy more often in the early postoperative phase compared to non-vasopressor dependent patients. Our findings on the effects of vasoplegia on creatinine clearance 2 years after surgery are in line with these three studies. In a fourth study, Byrne et al. studied 147 patients undergoing orthotopic heart transplantation, of whom 19% developed vasoplegia.[3] Unlike the present study Byrne et al. found no difference in median early postoperative creatinine plasma levels in vasoplegic patients (1.4 mg/dl) compared to non-vasoplegic patients (1.5 mg/dl, P=0.544). Of note, the above mentioned studies are performed in a different study population compared to the present study and focus on short-term follow-up.

Several hypotheses could be considered to explain the negative effect of vasoplegia on renal function 2 years postoperatively. Firstly, it could be hypothesized that the currently observed impaired renal function after vasoplegia is merely a reflection of cardiac function. However, previously we showed that the risk of vasoplegia is not related to baseline NYHA class and LVEF in this population.[4] Furthermore, the current study showed that both NYHA class and LVEF at 2-year follow-up were similar in vasoplegic and non-vasoplegic patients. A second explanation for the impaired renal function could be the lower baseline renal function in patients with vasoplegia. Therefore, the analysis was repeated whilst adjusting for baseline creatinine clearance. This analysis revealed that the difference between vasoplegic and non-vasoplegic patients at 2-year follow-up was partly explained by the baseline renal function and partly independent of baseline renal function. Therefore, we assume that the prolonged hypoperfusion caused by vasoplegia has a lasting detrimental effect on renal function. However, since the difference between vasoplegic and non-vasoplegic patients in baseline-corrected creatinine clearance is greater at 1 year compared to 2 years postoperatively, it seems that the effect of vasoplegia on renal function decreases in the years after surgery.

Limitations

A number of limitations merit consideration when interpreting the results. At first, due to the retrospective study design, there are some missing data. However, analysis revealed that the incidence of vasoplegia did not differ between patients with and without missing data, therefore it can be assumed that both groups are affected equally. Secondly, we only included patients who underwent SVR. Therefore it remains to be investigated whether our results can be extrapolated to all patients undergoing heart failure surgery.

Clinical implications

The current study emphasizes that vasoplegia is a severe clinical condition which occurs frequently after SVR. In particular, the increased mortality and the negative effect on renal function should be taken into account when considering SVR. On the other hand, NYHA class and cardiac function improved in both vasoplegic and non-vasoplegic patients, underlining the benefits of surgery for both groups. Accordingly, the development of strategies preventing vasoplegia are an important clinical need. Until preventive measures become available, patients could potentially benefit from preoperative hemodynamic optimization, early-onset and aggressive treatment of vasoplegia and perioperative renoprotection strategies.

Conclusion

In conclusion, this study indicates that vasoplegia after SVR is associated with decreased survival rate. Despite a similar and improved clinical and cardiac function at 2-year follow-up, patients with vasoplegia had a compromised renal function even when correcting for the lower creatinine clearance at baseline.

References

1. Fischer GW, Levin MA. Vasoplegia during cardiac surgery: current concepts and management. Semin Thorac Cardiovasc Surg. 2010;22(2):140-4.
2. Argenziano M, Chen JM, Choudhri AF, Cullinane S, Garfein E, Weinberg AD, et al. Management of vasodilatory shock after cardiac surgery: identification of predisposing factors and use of a novel pressor agent. J Thorac Cardiovasc Surg. 1998;116(6):973-80.
3. Byrne JG, Leacche M, Paul S, Mihaljevic T, Rawn JD, Shernan SK, et al. Risk factors and outcomes for 'vasoplegia syndrome' following cardiac transplantation. Eur J Cardiothorac Surg. 2004;25(3):327-32.
4. van Vessem ME, Palmen M, Couperus LE, Mertens B, Berendsen RR, Tops LF, et al. Incidence and predictors of vasoplegia after heart failure surgery. Eur J Cardiothorac Surg. 2017;51(3):532-8.
5. Patarroyo M, Simbaqueba C, Shrestha K, Starling RC, Smedira N, Tang WH, et al. Pre-operative risk factors and clinical outcomes associated with vasoplegia in recipients of orthotopic heart transplantation in the contemporary era. J Heart Lung Transplant. 2012;31(3):282-7.
6. Chan JL, Kobashigawa JA, Aintablian TL, Li Y, Perry PA, Patel JK, et al. Vasoplegia after heart transplantation: outcomes at 1 year. Interact Cardiovasc Thorac Surg. 2017;25(2):212-7.
7. Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JG, Coats AJ, et al. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC). Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. Eur J Heart Fail. 2016;18(8):891-975.
8. Benoist B, McLean E, Egli I, Cogswell M. Worldwide Prevalence of Anaemia 1993–2005: World Health Organization. http://apps.who.int/iris/bitstream/10665/43894/1/9789241596657_ eng.pdf.
9. Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. Nephron. 1976;16(1):31-41.
10. Haeck ML, Hoogslag GE, Rodrigo SF, Atsma DE, Klautz RJ, van der Wall EE, et al. Treatment options in end-stage heart failure: where to go from here? Neth Heart J. 2012;20(4):167-75.
11. Lang RM, Badano LP, Mor-Avi V, Afilalo J, Armstrong A, Ernande L, et al. Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. Eur Heart J Cardiovasc Imaging. 2015;16(3):233-70.
12. Rudski LG, Lai WW, Afilalo J, Hua L, Handschumacher MD, Chandrasekaran K, et al. Guidelines for the echocardiographic assessment of the right heart in adults: a report from the American Society of Echocardiography endorsed by the European Association of Echocardiography, a registered branch of the European Society of Cardiology, and the Canadian Society of Echocardiography. J Am Soc Echocardiogr. 2010;23(7):685-713; quiz 86-8.
13. Galie N, Humbert M, Vachiery JL, Gibbs S, Lang I, Torbicki A, et al. 2015 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension: The Joint Task Force for the Diagnosis and Treatment of Pulmonary Hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS): Endorsed by: Association for European Paediatric and Congenital Cardiology (AEPC), International Society for Heart and Lung Transplantation (ISHLT). Eur Heart J. 2016;37(1):67-119.
14. Couperus LE, Delgado V, Palmen M, van Vessem ME, Braun J, Fiocco M, et al. Right ventricular affects survival after surgical left ventricular restoration. J Thorac Cardiovasc Surg. 2017;153(4):845-52.
15. Klein P, Holman ER, Versteegh MI, Boersma E, Verwey HF, Bax JJ, et al. Wall motion score index predicts mortality and functional result after surgical ventricular restoration for advanced ischemic heart failure. Eur J Cardiothorac Surg. 2009;35(5):847-52; discussion 52-3.
16. Weis F, Kilger E, Beiras-Fernandez A, Nassau K, Reuter D, Goetz A, et al. Association between vasopressor dependence and early outcome in patients after cardiac surgery. Anaesthesia. 2006;61(10):938-42.

CHAPTER 5

Vasoresponsiveness in patients with heart failure (VASOR): protocol for a prospective observational study

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Abstract

Introduction: Vasoplegia is a severe complication which may occur after cardiac surgery, particularly in patients with heart failure. It is a result of activation of vasodilator pathways, inactivation of vasoconstrictor pathways and the resistance to vasopressors. However, the precise etiology remains unclear. The aim of the Vasoresponsiveness in patients with heart failure (VASOR) study is to objectify and characterize the altered vasoresponsiveness in patients with heart failure, before, during and after heart failure surgery and to identify the etiological factors involved.

Methods: This is a prospective, observational study conducted at Leiden University Medical Center. Patients with and patients without heart failure undergoing cardiac surgery on cardiopulmonary bypass are enrolled. The study is divided in two inclusion phases. During phase 1, 18 patients with and 18 patients without heart failure are enrolled. The vascular reactivity in response to a vasoconstrictor (phenylephrine) and a vasodilator (nitroglycerin) is assessed in vivo on different timepoints. The response to phenylephrine is assessed on t1 (before induction), t2 (before induction, after start of cardiotropic drugs and/or vasopressors), t3 (after induction), t4 (15 minutes after cessation of cardiopulmonary bypass) and t5 (1 day post-operatively). The response to nitroglycerin is assessed on t1 and t5. Furthermore, a sample of pre-pericardial fat tissue, containing resistance arteries, is collected intraoperatively. The ex vivo vascular reactivity is assessed by constructing concentrations response curves to various vasoactive substances using isolated resistance arteries. Next, expression of signaling proteins and receptors is assessed using immunohistochemistry and mRNA analysis. Furthermore, the groups are compared with respect to levels of organic compounds that can influence the cardiovascular system (e.g. copeptin, (nor)epinephrine, ANP, BNP, NTproBNP, angiotensin II, cortisol, aldosterone, renin and VMA levels). During inclusion phase 2, only the ex vivo vascular reactivity test is performed in patients with (N=12) and without heart failure (N=12).

Discussion: Understanding the difference in vascular responsiveness between patients with and without heart failure in detail, might yield therapeutic options or development of preventive strategies for vasoplegia, leading to safer surgical interventions and improvement in outcome.

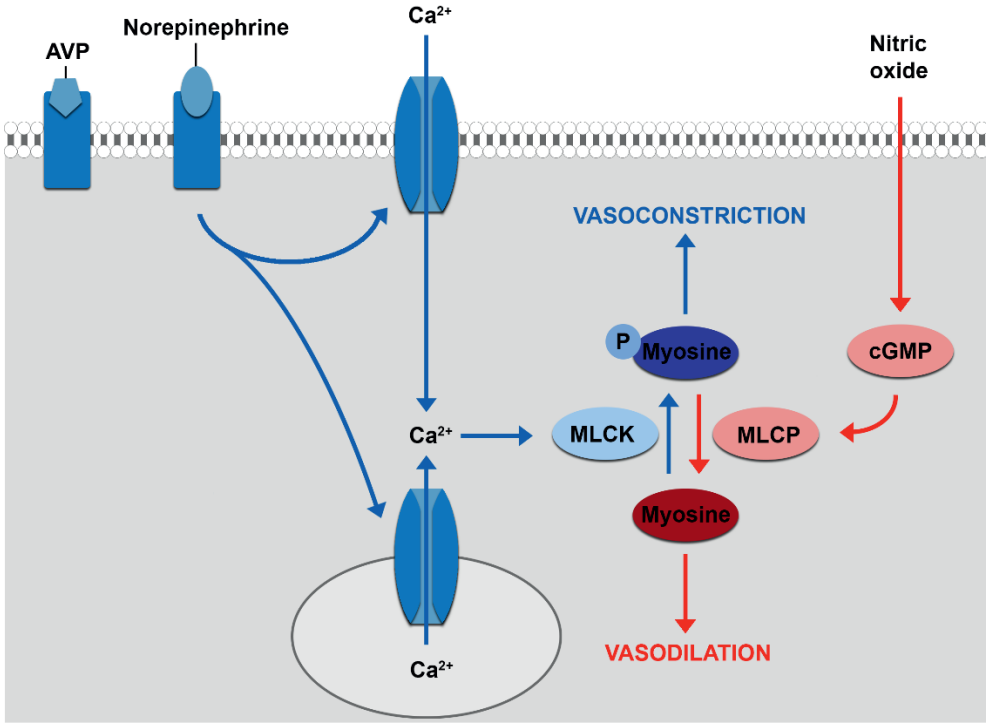
Trial registration: The Netherlands Trial Register (NTR), NTR5647. Registered 26 January 2016.

Introduction

The incidence and prevalence of chronic heart failure is increasing. Despite the expansion of therapeutic options, including the development of new pharmacological therapies and cardiological interventions, overall survival and quality-of-life remains poor.[1] When optimal medical therapy and cardiological interventions have failed to improve a patient's condition, surgical intervention may be a valid option in order to improve cardiac function. Surgical treatment of end-stage chronic heart failure encompasses different treatment modalities like surgical revascularization of ischemic territories using coronary artery bypass grafting (CABG), alleviating functional mitral valve insufficiency (using restrictive mitral annuloplasty) and reconstructing left ventricular geometry and thereby improving contractility in patients that suffered from a large myocardial infarction resulting in a scarred and dilated left ventricle. Ultimately, left ventricular function can be replaced by performing orthotopic heart transplantation or by implantation of a left ventricular assist device (LVAD). These surgical options have improved clinical outcome.[2-4] Unfortunately, heart failure surgery is associated with an increased risk on vasoplegia, also named vasodilatory shock.[5] This syndrome is characterized by hypotension and the continuous need of vasopressors, despite a normal or high cardiac index. The incidence of vasoplegia ranges from 11-31% in patients undergoing heart failure surgery.[5-9] The prognosis of vasoplegia is poor. Prolonged hypotension and the accompanying hypoperfusion lead to end-organ dysfunction and is associated with an increased morbidity. An earlier study showed that the 90-day survival rate after heart failure surgery is decreased in vasoplegic patients compared with non-vasoplegic patients (71% vs 91%, $P < 0.001$).[8]

Vasoplegia is a result of failure of the vascular smooth muscle cells to constrict to normal endogenous and exogenous stimuli. Normally, a vascular smooth muscle cell constricts due to binding of a ligand (e.g. arginine vasopressin or norepinephrine) to a receptor on the vascular smooth muscle cell surface (Figure 1). This activates a signal transduction pathway, resulting in an increase of the calcium concentration in the cytosol due to release of intracellular calcium and an influx of extracellular calcium through voltage-gated calcium channels. Binding of calcium to calmodulin leads to phosphorylation of myosin light chain kinase, which activates myosin light chain, leading to vasoconstriction. In contrast, vasodilators (e.g. nitric oxide, atrial natriuretic peptide) increase cyclic guanosine monophosphate (cGMP) concentrations in the vascular smooth muscle cell. This leads to the activation of myosin light chain phosphatase, which deactivates myosin light chain, introducing vasodilatation.

Figure 1. Regulation of vascular smooth muscle tone. Binding of arginine vasopressin and norepinephrine to their receptor on the vascular smooth muscle cell surface results in an increase of the calcium concentration in the cytosol, thereby activating myosin light chain, leading to vasoconstriction. Vasodilators (e.g. nitric oxide, atrial natriuretic peptide) deactivate myosin light chain, introducing vasodilatation.



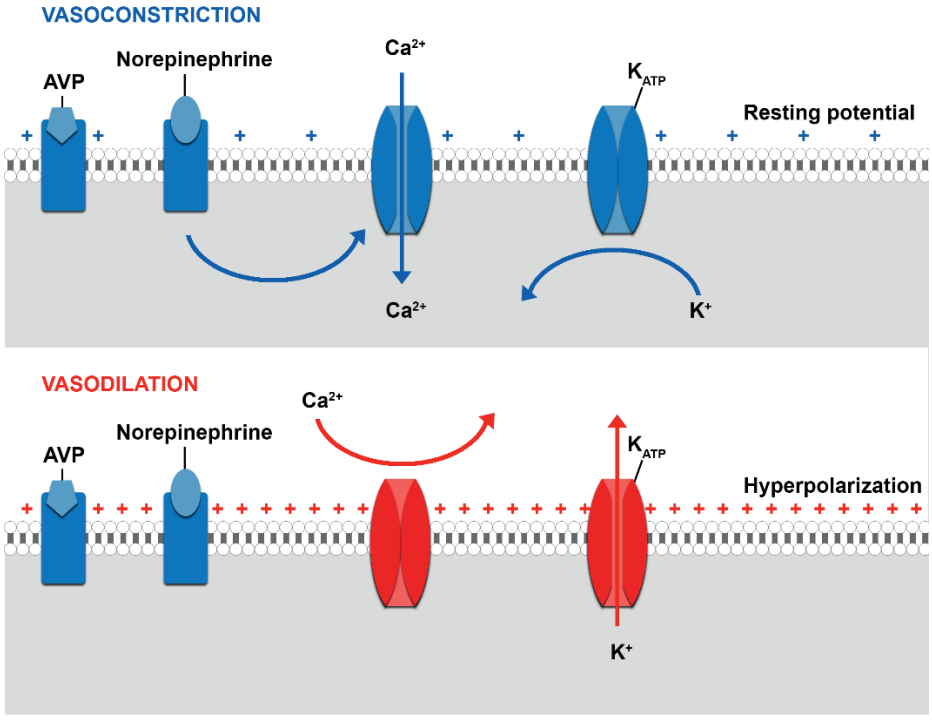
AVP, arginine vasopressin; Ca^{2+}, calcium ion, cGMP, cyclic guanosine monophosphate; MLCK, myosin light chain kinase; MLCP, myosin light chain phosphatase.

The mechanism that causes vasoplegia is thought to be multifactorial. It seems to involve activation of vasodilator pathways and inactivation of vasoconstrictor pathways resulting in a resistance to vasopressors, but the precise etiology remains subject of debate. Vasodilatory shock due to sepsis is the most studied etiology, but it is likely that the pathophysiological mechanisms differ depending on the underlying etiology. However, Landry and Oliver propose three mechanisms that contribute to all types of vasodilatory shock.[10]

1) Activation of adenosine triphosphate (ATP) dependent potassium channels (K_{ATP}) on the vascular smooth muscle cell.

When the vascular smooth muscle cell depolarizes, voltage gated calcium channels open, thereby increasing the calcium concentration in the cytosol, causing vasoconstriction. In contrast, hyperpolarization closes the channel, leading to relaxation. K_{ATP} channels influence the membrane potential (Figure 2 and Figure 3). Opening leads to an efflux of potassium, thereby hyperpolarizing the plasma membrane, causing the voltage gated calcium channels to close. Under normal circumstances K_{ATP} channels are closed, but they open when intracellular ATP concentration is low and when lactate and hydrogen ion concentrations are high, like during hypoxic and increased metabolic states. Atrial natriuretic peptide, calcitonin gene-related peptide, adenosine and increased nitric oxide concentrations (indirectly) may open the channel as well.

Figure 2. Influence of the K_{ATP} channel on the vascular smooth muscle tone. Closing of K_{ATP} channels leads to depolarization of the vascular smooth muscle cell, thereby opening the voltage gated calcium channels and causing vasoconstriction. Opening of the K_{ATP} channels leads to an efflux of potassium, thereby hyperpolarizing the plasma membrane, causing the voltage gated calcium channels to close, which results in vasodilation.



AVP, arginine vasopressin; Ca^{2+}, calcium ion; K^+, potassium ion.

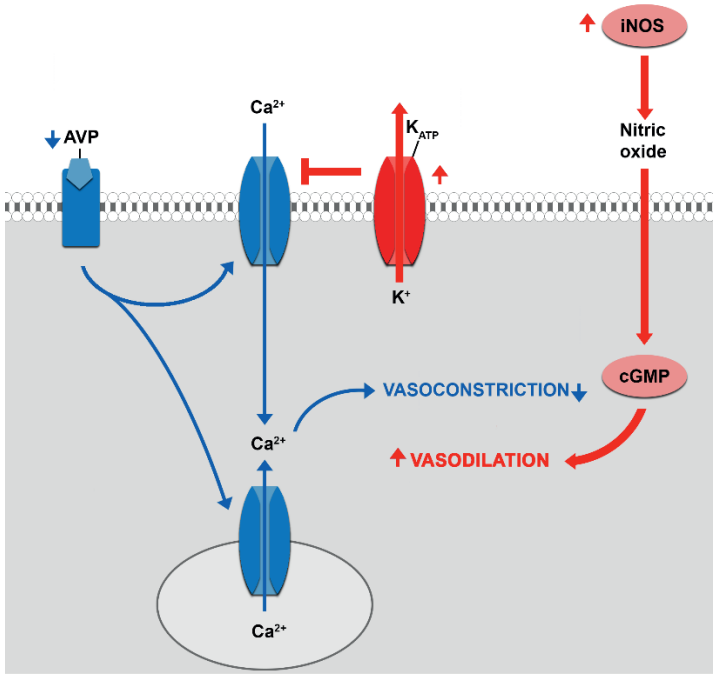
2) Activation of inducible nitric oxide synthase (iNOS).

iNOS (NOS2), is one of the three isoforms of nitric oxide synthase. The other forms are neuronal nitric oxide synthase (nNOS or NOS1) and endothelial nitric oxide synthase (eNOS or NOS3). The synthases are responsible for the production of nitric oxide. Therefore, activation of iNOS leads to increased vasodilatation (see Figure 3). Accordingly, the use of methylene blue, a cGMP inhibitor, seems to be effective for the treatment of vasoplegic syndrome.[11]

3) Deficiency of arginine vasopressin (AVP).

The binding of AVP to the vascular smooth muscle cell leads to vasoconstriction. Accordingly, a deficiency in AVP leads to a reduced ability of the vascular smooth muscle cell to constrict (see Figure 3). The role of AVP in vasoplegic shock is confirmed by Colson et al who showed that vasoplegic patients have higher preoperative copeptin (a precursor of AVP) plasma concentrations, but lower AVP concentration postoperatively.[12]

Figure 3. Summary of the three mechanisms contributing to vasodilatory shock: Activation of adenosine triphosphate (ATP) dependent potassium channels (K_{ATP}), activation of inducible nitric oxide synthase (iNOS) and arginine vasopressin (AVP) deficiency.



Besides these mechanisms, we postulate that other characteristics of heart failure patients make them more prone to develop vasoplegia. For instance, the chronic endogenous adrenergic (over)stimulation leads to downregulation and desensitization of myocardial β_1-adrenergic receptors and desensitization β_2-adrenergic receptors in heart failure.[13] This continuous adrenergic stimulation also seems to result in downregulation and/or desensitization of vascular α_1-adrenoreceptors, leading to an altered responsiveness of the vascular system of heart failure patients.[14] We hypothesize that the balance of the vascular system of patients with heart failure is fragile and therefore could easily be disturbed by the systemic inflammatory response (SIRS) reaction caused by the cardiopulmonary bypass and surgical trauma, making these patients more prone to develop vasoplegia.[15] Furthermore, the sympathetic activation is likely to be related to the proinflammatory state of a heart failure patient.[16] In addition, the medication that is prescribed to heart failure patients (e.g. beta blockers, ACE inhibitors, angiotensin receptor blockers, diuretics) influences the hemodynamics as well and could contribute to the risk on vasoplegia. Most probably all the above described factors may play a role in the development of vasoplegia after heart failure surgery, but this has never been proven in patients.

Methods

The Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) checklist is online provided.

Study design

The aim of the current study is to objectify and characterize the altered vasoresponsiveness in patients with heart failure, before, during and after heart failure surgery and to identify the etiological factors involved. This is a prospective, observational study, conducted at the Leiden University Medical Center. Patients with heart failure will be compared with patients without heart failure. Figure 4 shows a schematic overview of the study (SPIRIT statement). The study is divided in two inclusion phases. The protocol of the patients who are included in phase 1 consists of several in vivo vascular reactivity tests, an ex vivo vascular reactivity test and blood and urine sample analysis. In patients included in phase 2, only the ex vivo vascular reactivity test is performed.

Participants

Two researchers (MV and MP) screen patients scheduled for elective or urgent cardiac surgery on cardiopulmonary bypass for eligibility. Patients are recruited for either the heart failure group or the non-heart failure group. Heart failure is defined according to the European Society of Cardiology guidelines.[17] In order to be eligible for inclusion in the heart failure group, patients must meet all of the following inclusion criteria: 1) Diagnosed with heart failure and 2) LVEF ≤ 35%. Patients that are included in the non-heart failure group are 1) not diagnosed with heart failure and 2) have a LVEF > 50%. In addition, patients are selected according to the expected cardiopulmonary bypass and estimated aortic cross clamp duration.

A patients who meets any of the following criteria is excluded from participation in this study: 1) age <18 years; 2) incapacitated adults; 3) emergency operation; 4) patients in need of moderate of high dosages of intravenous inotropic support (>4 gamma dobutamine or dopamine), vasopressin and/or mechanical support; 5) patients with aortic valve insufficiency > grade 1; 6) patients using a daily dosage of nitrates or 7) α-adrenergic blockers; and 8) patients not willing to sign the consent form. All included patients receive a subject identification code starting at 1001, up to 1060.

Figure 4. Schedule of enrolment and assessments.

	Enrolment		**Post-allocation**							
	Pre visit	Day 0	Day 1					Day 2	Day 4	End ICU admission
			1	2	3	4	5			
Enrolment										
Eligibility screen	X	X								
Informed consent		X								
Enrolment		X								
Assessments										
Baseline characteristics		X								
Perioperative routine blood values		♦	—	—	—	—	—	—	—	♦
Hemodynamic monitoring			♦	—	—	—	—	—	—	♦
Use of drugs			♦	—	—	—	—	—	—	♦
Vasodilation test			X					X		
Vasoconstriction test			X	X	X		X	X		
Harvesting fat tissue*						X				
Ex vivo vascular reactivity test*								X		
Blood sample			X		X		X	X	X	
Urine sample					X					

** During phase 2, only fat tissue will be harvested and the ex vivo vascular reactivity test will be performed. 1, before induction; 2, before induction, after start of cardiotropic drugs and/or vasopressors when necessary; 3, after induction; 4, before the cardiopulmonary bypass is connected; 5, 15 minutes after cessation of cardiopulmonary bypass.*

Clinical parameters

Baseline characteristics (including age, gender, EuroSCORE, comorbidity, medication), perioperative routine blood values, use of (vasoactive) drugs (e.g. phenylephrine, norepinephrine, epinephrine, dopamine, dobutamine, milrinone), hemodynamic parameters and transfusion products are registered in the hospital's electronic patient information system.

Anesthetics and hemodynamic monitoring

Anesthetics are given according to a standard protocol. Patients are anesthetized with target-controlled infusion of propofol and remifentanil or sufentanil. Bispectral index monitoring is used to guide the anesthetic dosing. Ketamine and sevoflurane are not used.

Before induction all patients will receive an arterial line for invasive monitoring of blood pressure and blood sampling. A central venous catheter is inserted in the internal jugular vein and a flow-directed balloon-tipped pulmonary artery catheter is introduced after induction. The pressure transducers of the arterial catheter and central venous catheter are connected to separate M1006A invasive blood pressure modules (Hewlett-Packard-medical-products-group, Andover, MA. USA) for optimal data recording at a frequency of 100Hz and the resolution 0.2mmHg.

Three different systems are used for hemodynamic measurements. 1) The FloTrac-sensor of the radial artery catheter is connected to a Vigileo system (Edwards LifeSciences, Irvine, CA, USA). The system uses the arterial pressure waveform and patient characteristics (height, weight, age and sex) to estimate cardiac output/stroke volume. The value of central venous pressure was entered into the Vigileo-monitor in order to calculate systemic vascular resistance (SVR). 2) The pulmonary artery catheter is connected to a Vigilance-II monitor (Edwards LifeSciences, Irvine, CA, USA). The patient characteristics (height, weight, age) are entered in the monitor and used for the algorithm. 3) PulseCO™ software (LiDCO, London, UK) is used for measurement of hemodynamic variables as arterial blood pressure, cardiac output/stroke volume, pulse pressure variation, stroke volume variation and after entering central venous pressure, SVR. The system uses arterial waveform and patient characteristics (age, height, weight, and value of hemoglobin). The cardiac output derived from the Vigilance-II monitor, is used to calibrate the cardiac

output as measured by PulseCO. Software of the LiDCOplus (LiDCOviewSE, LiDCO Ltd, London, UK) is used for off-line analysis of the vasoreactivity tests. The decision to evaluate hemodynamic variables with pulse contour analysis lay in the character of these monitoring systems. FloTrac/Vigileo and PulseCO, providing a quick response time to medication induced vaso(motor)reactivity by beat to beat analysis of arterial blood pressure.

Surgical procedures

Main procedures that are performed are mitral valve plasty and aorta surgery. In the heart failure group left ventricular reconstruction and left ventricular assist device implantation are performed as well. All surgeries are performed via a midline sternotomy with the use of cardiopulmonary bypass with antegrade warm blood cardioplegia.

In vivo vascular reactivity test

The vascular reactivity in response to a vasoconstrictor (phenylephrine, an α_1-adrenoreceptor agonist) and vasodilator (nitroglycerin) is assessed for all patients in phase 1 of the study. During the vasoconstriction test, a bolus of 2 µg/kg phenylephrine is administered intravenously, after which the effect on SVR and MAP is registered. The test is performed 5 times: t1) before induction; t2) before induction, after start of cardiotropic drugs and/or vasopressors (e.g. dobutamine, milrinone, norepinephrine) when necessary; t3) after induction; t4) 15 minutes after cessation of cardiopulmonary bypass; and t5) on the first postoperative day. The timepoints reflect different stages perioperatively, during which the hemodynamic situation changes and that are present in all procedures that are included in this study.

For the vasodilation test a bolus of 10 µg nitroglycerin is given intravenously. The effect on SVR and MAP are registered. Dosages are increased to 20 µg, 40 µg and 60 µg until a drop of 10% in MAP is reached. The vasodilation test is performed twice: t1) before induction and t5) 1 day post-operatively. The test is only performed at these timepoints since we anticipate that in most heart failure patients the test cannot be performed intraoperatively due to the hemodynamic effect. Before the test is started, the patient needs to be in supine rest for at least 10 minutes.

Both the vasoconstriction and the vasodilation test will only be performed when the clinical condition of the patient allows an increase or drop in MAP.

Ex vivo vascular reactivity tests

This test will be conducted in both phase 1 as phase 2 of the study. A sample of pre-pericardial fat tissue, containing resistance arteries, is collected before the cardiopulmonary bypass is connected. The tissue is directly preserved in Krebs-Henseleit buffer and transferred in a cooled box (± 4°C) to the Erasmus Medical Center. Here, the tissue is stored overnight at 4°C. The next morning, the arterioles are isolated, cut into ring segments of ± 2mm length and mounted in a Mulvany myograph. The 6 ml organ baths contain gassed Krebs-Henseleit buffer at 37ºC. The tension on the segments is normalized to 90% of the estimated diameter at 100 mm Hg of effective transmural pressure. After a 30-minute stabilization period, the maximal contractile response is determined by exposing the vessels to 30 and 100 mmol/L of potassium chloride. The following concentration-response curves (CRCs) are constructed: 1) phenylephrine (1 to 100 nmol/L); 2) vasopressin (0.1 to 300 nmol/L); 3) sodium nitroprusside (SNP) (1 – 100 µmol/L); and 4) bradykinin (0.1 to 1000 nmol/L). bradykinin CRCs are constructed in the absence or presence of 5) 1H-[1,2,4]oxadiazolo[4,3-a]quinoxalin-1-one (ODQ) (10 µmol/L, after concentration response curve 0.1 to 10 µmol/L) and 6) N^G-nitro-L-arginine methyl ester (L-NAME) (100 µmol/L, after CRC 1 to 100 µmol/L). SNP and bradykinin induced relaxation was assessed after preconstriction with U46619 (10 to 30 nmol/L, aiming for 70-100% of the 100 mmol/L potassium chloride contraction).

Another sample of fat tissue is fixed in 4% formaldehyde for 7 days and paraffin-embedded for later determination of activated signaling proteins (e.g. protein kinase C, protein kinase G, protein kinase A) and the expression of receptors (e.g. β_2, α_1 , V_{1a}, AT_1) using immunohistochemistry. Furthermore, a small segment of arterial tissue is snap-frozen in liquid nitrogen and stored at -80ºC for mRNA analysis. Precise analysis will be guided by the findings of the functional tests.

Blood and urine sample

Arterial blood samples (one 10 ml ethylenediaminetetraacetic acid (EDTA) tube and one 8.5 ml serum-separating tube) are collected at 5 time points during phase 1 of the study: 1) before induction; 2) after induction; 3) after cardiopulmonary bypass; 4) on day 1 post-operative and 5) on day 3 post-operative. The samples are centrifuged at 1500g, at 4°C for 10 minutes. Plasma and serum are stored in five 500 µl cups at -80°C to analyse levels of organic compounds that can influence the cardiovascular system (e.g. norepinephrine, epinephrine, ANP, copeptin, NTproBNP, angiotensin II, cortisol, aldosterone, renin, IL-1, IL-6 and TNF-α).

After an urinary catheter is placed, a urine sample is collected. The sample is stored at -80°C until analysis for levels of organic compound that effect the cardiovascular system (e.g. steroids, VMA, angiotensinogen). Precise analysis will be guided by the findings of the functional tests.

Study parameters

The primary outcome is the change in SVR after phenylephrine administration at baseline.

The secondary outcomes are 1) change in MAP after phenylephrine administration; 2) change in MAP and SVR after nitroglycerin administration; 3) vasoplegia (defined as the continuous need of vasopressors (norepinephrine ≥ 0.2 µg/kg/min for at least 12 consecutive hours, terlipressin or methylene blue) in combination with a cardiac index ≥2,2 l/min/m2 for at least 12 consecutive hours, starting within the first 3 days post-operatively); 4) Copeptin, norepinephrine, epinephrine, ANP, BNP, NTproBNP, angiotensin II, cortisol, aldosterone, renin and VMA levels; 5) correlation between change in SVR after phenylephrine administration and clinical parameters (duration, amount and maximal concentration of norepinephrine postoperatively).

Ex vivo secondary outcomes are 1) change in vessel diameter in response to vasoactive drugs; 2) activated signaling proteins which are associated with vasoresponsiveness; and 3) receptors (quantity and function) which are associated with vasoresponsiveness.

Sample size calculation

The primary outcome is change in SVR after phenylephrine administration at baseline. A sample size of 17 in each group will have 90% power to detect a difference in means of 400 dyn·s/cm5 assuming that the common standard deviation is 350 dyn·s/cm5 using a student t-test with a 0.05 two-sided significance level.[14] One extra patient is included in each group to compensate for possible loss of data due to failing of the test, so 36 patients are included in total in phase 1 of the study. In phase 2, 24 extra patients will be included.

Statistical analysis

All data of the in vivo and ex vivo tests are analyzed by a researcher (respectively RW and RV) blinded for the patient group. Baseline patient characteristics are described using summary statistics. Continuous variables are reported as mean with SD when normal distributed, or as median with interquartile range when appropriate. Differences between

groups (heart failure versus no heart failure) are compared using an unpaired Students t-test, or Mann Whitney U-test. Categorical data is reported as numbers and percentages. Fisher's exact test is used to compare the differences between groups. Pairwise deletion is used to handle missing data. The effect of the vasoreactivity tests is adjusted for the level of used vasoactive medication. The significance level is set at $P < 0.05$. The Statistical Package for the Social Sciences (SPSS, version 22) is used for the statistical analyses.

Consent

Participation in the study is voluntary and written informed consent is obtained by the investigators (MV and MP). Participants can withdraw their consent at any time. Study findings will be disseminated through peer-reviewed publications.

Data management

Handling of data complies with the Dutch Personal Data Protection Act (in Dutch: De Wet Bescherming Persoonsgegevens, Wbp). A subject identification code list is used to link data to the patient number of the patient and is stored on a secured computer on the study site. The anonymous dataset is accessible for all investigators of the research team.

Safety monitoring

A data monitoring committee deemed not to be necessary since it concerns a non-randomized, non-blinded study without serious safety concerns and no follow up. All serious adverse events are reported to the medical ethical committee within 7 days after the responsible investigator has first knowledge of the adverse event. All protocol deviations and adverse events are recorded. The investigators will submit a summary of the progress to the medical ethical committee once a year, including information on numbers of patients included, study progress, (serious) adverse events and amendments.

Discussion

The incidence and prevalence of chronic heart failure is increasing. It is therefore to be expected that the number of heart failure surgery procedures will increase. Unfortunately, vasoplegia is frequently seen after these procedures and is associated with a poor prognosis. The mechanism that causes vasoplegia is thought to be multifactorial, but the

precise etiology remains unclear. This study is designed to improve understanding of these mechanisms. There are some issues in our study design that need to be noted. First, since the vasoconstriction and the vasodilation test can only be performed when the clinical condition of the patient allows an increase or drop in MAP, we expect that these tests cannot be conducted in all patients. Secondly, baseline vasoreactivity tests are performed uncalibrated since the central venous catheter and the pulmonary artery catheter are introduced after induction to limit the burden for the study patients. Thirdly, collecting a sample of pre-pericardial fat tissue can be difficult in patients who underwent previous cardiac surgery. Furthermore, this tissue is fragile and it can therefore be expected that we will not be able to perform the ex vivo vascular reactivity test in all included patients.

Conclusion

In summary, this single-center prospective observational study is designed to objectify and characterize the altered vasoresponsiveness in patients with heart failure, before, during and after heart failure surgery and to identify the etiological factors involved. Understanding the difference in vascular responsiveness between patients with and without heart failure in detail, might yield therapeutic options or development of preventive strategies for vasoplegia, leading to safer surgical interventions and improvement in outcome.

Declarations

Ethics approval and consent to participate

This study is being conducted in accordance with the principles of the Declaration of Helsinki and Good Clinical Practice guidelines. The study protocol is approved by the scientific committee of Heart Lung Center Leiden (October, 2015) and the medical ethics committee of the Leiden University Medical Center (May, 2015. Protocol number: P14.298). Written informed consent will is obtained from all participants. The Leiden University Medical Center has a liability insurance for all research projects.

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References

1. McMurray JJ, Pfeffer MA. Heart failure. Lancet. 2005; doi:10.1016/s0140-6736(05)66621-4.
2. Haeck ML, Hoogslag GE, Rodrigo SF, Atsma DE, Klautz RJ, van der Wall EE, et al. Treatment options in end-stage heart failure: where to go from here? Neth Heart J. 2012; doi:10.1007/s12471-011-0211-4.
3. Braun J, Ciarka A, Versteegh MI, Delgado V, Boersma E, Verwey HF, et al. Cardiac support device, restrictive mitral valve annuloplasty, and optimized medical treatment: a multimodality approach to nonischemic cardiomyopathy. J Thorac Cardiovasc Surg. 2011; doi:10.1016/j.jtcvs.2010.12.027.
4. Klein P, Holman ER, Versteegh MI, Boersma E, Verwey HF, Bax JJ, et al. Wall motion score index predicts mortality and functional result after surgical ventricular restoration for advanced ischemic heart failure. Eur J Cardiothorac Surg. 2009; doi:10.1016/j.ejcts.2008.12.046.
5. Argenziano M, Chen JM, Choudhri AF, Cullinane S, Garfein E, Weinberg AD, et al. Management of vasodilatory shock after cardiac surgery: identification of predisposing factors and use of a novel pressor agent. J Thorac Cardiovasc Surg. 1998; doi:10.1016/s0022-5223(98)70049-2.
6. Byrne JG, Leacche M, Paul S, Mihaljevic T, Rawn JD, Shernan SK, et al. Risk factors and outcomes for 'vasoplegia syndrome' following cardiac transplantation. Eur J Cardiothorac Surg. 2004; doi:10.1016/j.ejcts.2003.11.032.
7. Patarroyo M, Simbaqueba C, Shrestha K, Starling RC, Smedira N, Tang WH, et al. Pre-operative risk factors and clinical outcomes associated with vasoplegia in recipients of orthotopic heart transplantation in the contemporary era. J Heart Lung Transplant. 2012; doi:10.1016/j.healun.2011.10.010.
8. van Vessem ME, Palmen M, Couperus LE, Mertens B, Berendsen RR, Tops LF, et al. Incidence and predictors of vasoplegia after heart failure surgery. Eur J Cardiothorac Surg. 2017; doi:10.1093/ejcts/ezw316.
9. Chan JL, Kobashigawa JA, Aintablian TL, Li Y, Perry PA, Patel JK, et al. Vasoplegia after heart transplantation: outcomes at 1 year. Interact Cardiovasc Thorac Surg. 2017; doi:10.1093/icvts/ivx081.
10. Landry DW, Oliver JA. The pathogenesis of vasodilatory shock. N Engl J Med. 2001; doi:10.1056/NEJMra002709.
11. Evora PR, Alves Junior L, Ferreira CA, Menardi AC, Bassetto S, Rodrigues AJ, et al. Twenty years of vasoplegic syndrome treatment in heart surgery. Methylene blue revised. Rev Bras Cir Cardiovasc. 2015; doi:10.5935/1678-9741.20140115.
12. Colson PH, Bernard C, Struck J, Morgenthaler NG, Albat B, Guillon G. Post cardiac surgery vasoplegia is associated with high preoperative copeptin plasma concentration. Crit Care. 2011; doi:10.1186/cc10516.
13. Ruffolo RR, Jr., Kopia GA. Importance of receptor regulation in the pathophysiology and therapy of congestive heart failure. Am J Med. 1986;
14. Schwinn DA, McIntyre RW, Hawkins ED, Kates RA, Reves JG. alpha 1-Adrenergic responsiveness during coronary artery bypass surgery: effect of preoperative ejection fraction. Anesthesiology. 1988;
15. Day JR, Taylor KM. The systemic inflammatory response syndrome and cardiopulmonary bypass. Int J Surg. 2005; doi:10.1016/j.ijsu.2005.04.002.
16. Ng TM, Toews ML. Impaired norepinephrine regulation of monocyte inflammatory cytokine balance in heart failure. World J Cardiol. 2016; doi:10.4330/wjc.v8.i10.584.
17. McMurray JJ, Adamopoulos S, Anker SD, Auricchio A, Bohm M, Dickstein K, et al. ESC guidelines for the diagnosis and treatment of acute and chronic heart failure 2012: The Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2012 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association (HFA) of the ESC. Eur J Heart Fail. 2012; doi:10.1093/eurjhf/hfs105.

CHAPTER 6

Diminished vasoresponsiveness in heart failure patients: an observational study

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Submitted

Abstract

Objectives: Heart failure patients undergoing cardiac surgery have a higher risk of postoperative vasoplegia. We hypothesize that they are more susceptible to vasoplegia due to a diminished vasoresponsiveness. The aim of this study is to objectify this altered vasoresponsiveness perioperatively.

Design: Prospective, observational study.

Setting: Leiden University Medical Center, Leiden, The Netherlands.

Patients: Patients with and without heart failure undergoing cardiac surgery on cardiopulmonary bypass (CPB) were enrolled.

Interventions: None.

Measurements and Results: The vascular reactivity in response to a vasoconstrictor (phenylephrine) and a vasodilator (nitroglycerin) was assessed perioperatively by measuring changes in systemic vascular resistance (SVR). 36 patients were included. 17% of the heart failure patients developed vasoplegia, compared to 6% of controls (P=0.603). At baseline, heart failure patients had an increase of 26% (16-35%) in SVR in response to phenylephrine, compared to 51% (38-64%) in control patients (P=0.002). Delta SVR remained significantly lower in heart failure patients perioperatively The same pattern was found when excluding patients that received norepinephrine. There was no difference in the dosage of nitroglycerin needed to achieve a drop of at least 10% in mean arterial pressure. Delta SVR after CPB is significantly associated with the amount of norepinephrine received during the first postoperative day (P=0.001).

Conclusions: We found that heart failure patients have a diminished response to a vasoconstrictor at baseline compared to control patients. This reduced vasoresponsiveness persists throughout the perioperative period, independent of used norepinephrine. Furthermore, we showed that vasoresponsiveness intra-operatively is associated with the amount of norepinephrine received postoperatively.

Registration: The Netherlands Trial Register, NTR5647. Registered 26 January 2016.
http://www.trialregister.nl/trialreg/admin/rctview.asp?TC=5647

Introduction

When optimal medical therapy and cardiac interventions fail to improve a heart failure (HF) patient's condition, HF surgery may be a valid option.[1-3] Unfortunately, surgical intervention in this vulnerable patient population is associated with increased risk of vasoplegia with a reported incidence of 11-31%.[4-9] Vasoplegia is characterized by hypotension and the excessive need of vasopressors, despite a normal or even high cardiac output (CO) and is shown to be associated with increased morbidity and mortality.[7]

The mechanism responsible for vasoplegia remains to be unraveled. It is thought to be multifactorial in origin, including both activation of vasodilator pathways and inactivation of vasoconstrictor pathways, resulting in resistance to vasopressors. We postulate that the pathophysiological characteristics of HF patients make them more prone to develop postoperative vasoplegia.[10] In particular, the fragile balance of vasoconstrictor and vasodilatory abilities of their vascular system could easily be disturbed by the systemic inflammatory response reaction caused by cardiopulmonary bypass (CPB) and surgical trauma.[11] This results in an impaired responsiveness to exogenous vasopressors and leads to a downward spiral of end-organ hypoperfusion resulting in multiple-organ failure.

Understanding the mechanisms leading to vasoplegia in HF patients could contribute to the development of preventive measures and treatment strategies, thereby reducing morbidity and mortality in this vulnerable patient group. The aim of the current study is to objectify the altered vasoresponsiveness in HF patients undergoing cardiac surgery.

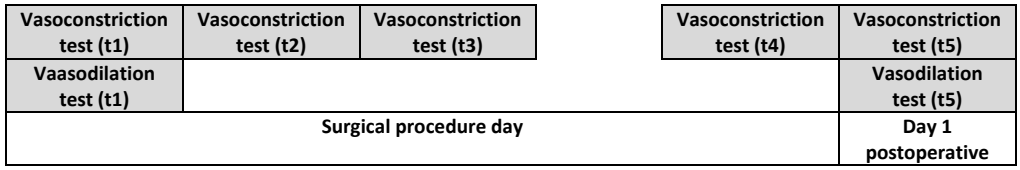
Materials and methods

A more extensive description of the study methods was recently published online.[10]

Study design

VASOR is a prospective, observational study, conducted at Leiden University Medical Center. Patients with and without HF undergoing cardiac surgery on CPB were compared. The study protocol was executed intraoperatively and on the first postoperative day (Figure 1). The study is registered at The Netherlands Trial Register (NTR5647). The Medical Ethical Committee of Leiden The Hague Delft approved the protocol (P14.298) which was performed in line with the Declaration of Helsinki.

Figure 1. Flowchart study.



Study population

Patients scheduled for elective or urgent cardiac surgery with CPB were screened for eligibility. In order to yield comparable study groups, patients were selected according to the expected CPB duration and level of surgical trauma. Patients were assigned to either the HF or the non-HF group. HF was defined according to the European Society of Cardiology guidelines.[12] Inclusion criteria for the HF group were: 1) diagnosed with HF and 2) left ventricular ejection fraction (LVEF) ≤ 35%. Patients that were included in the non-HF group were 1) not diagnosed with HF and 2) had a LVEF > 50%. Exclusion criteria were: 1) age <18 years; 2) incapacitated adults; 3) emergency operation; 5) patients in preoperative need of moderate or high dosages of intravenous inotropic support (>4 gamma dobutamine or dopamine), vasopression and/or mechanical support; 6) patients with aortic valve insufficiency > grade 1; 7) patients using a daily dosage of nitrates and 8) α-adrenergic blockers or 9) phosphodiesterase type 5 inhibitors; 10) patients with endocarditis; and 11) patients with acute heart failure. Factors named in exclusion criteria 5-11 would influence the primary outcome. All patients gave written informed consent for study participation.

Surgical procedures

All patients undergoing cardiac surgery with comparable durations of CPB and similar level of surgical trauma were eligible. The indication and timing for surgery was assessed by the multidisciplinary Heart Team. In the HF group patients underwent mitral valve plasty (mainly treatment of functional mitral regurgitation with the use of restrictive mitral annuloplasty),[9] surgical left ventricular restoration (Dor technique),[3] left ventricular assist device (HeartWare Inc, Framingham, MA) implantation[1] and aorta surgery. Tricuspid valve annuloplasty, aortic valve replacement and coronary revascularization were performed concomitant if indicated. In the control group, mainly patients undergoing mitral valve plasty were included. Tricuspid valve annuloplasty and coronary revascularization were performed concomitant if indicated. All surgeries were performed via conventional midline sternotomy using CPB and (when cardioplegic arrest was indicated) with intermittent antegrade warm blood cardioplegia. Patients did not receive angiotensin-

converting-enzyme inhibitors, angiotensin receptor blockers and diuretics on the day of surgery.

Anesthetics and hemodynamics

All patients received anesthesia according to a standardized protocol, using target-controlled infusion of propofol and remifentanil or sufentanil. Cannulation of the radial artery was performed in all patients before induction for invasive hemodynamic blood pressure monitoring. A central venous catheter was inserted in the internal jugular vein and a flow-directed balloon-tipped pulmonary artery catheter was introduced after induction. PulseCO™ software (LiDCO, London, UK) was used for measurement of cardiac output and systemic vascular resistance. The cardiac output derived from the Vigilance-II monitor (Edwards LifeSciences, Irvine, CA, USA), connected to the pulmonary artery catheter, was used to calibrate the cardiac output as measured by PulseCO. Software of the LiDCOplus (LiDCOviewSE, LiDCO Ltd, London, UK) was used for off-line analysis of the vasoreactivity tests.

Intra- and postoperatively, norepinephrine 0.04–0.2 µg/kg/min was started if the mean arterial pressure was ≤ 65 mmHg and the cardiac index was normal (after adequate administration of intravascular fluids if necessary), aiming for a mean arterial pressure > 65 mmHg and adequate end-organ perfusion. When a norepinephrine dosage >0,5 µg/kg/min was required, terlipressin was started. The vasoactive medication was reduced when the mean arterial pressure was > 65 mmHg in combination with adequate end-organ perfusion. In this situation, terlipressin was reduced first.

Patients did not receive angiotensin-converting-enzyme (ACE) inhibitors, angiotensin receptor blockers and diuretics on the day of surgery.

Study outcomes

The objective of VASOR study was to determine the peri-operative vasoresponsiveness to an exogenous vasoconstrictor in patients with and without HF. We hypothesized that HF patients would demonstrate a reduced response. The primary end-point was the change in systemic vascular resistance (SVR) after phenylephrine administration at baseline. Secondary end points included: 1) change in SVR after phenylephrine administration intra- and postoperatively; 2) dosage nitroglycerin needed for a 10% decrease in mean arterial pressure (MAP) pre- and postoperatively; 3) correlation between change in SVR after phenylephrine administration pre- and intraoperatively and the amount of norepinephrine used postoperatively; 4) the occurrence of vasoplegia (defined as the continuous need of

vasopressors (norepinephrine ≥ 0.2 μg/kg/min for at least 12 consecutive hours or terlipressin) in combination with a cardiac index ≥2,2 l/min/m2 for at least 12 consecutive hours, starting within the first 3 days postoperatively).

Vascular reactivity test

The vasoreactivity in response to a vasoconstrictor (phenylephrine, an α_1-adrenoreceptor agonist) and vasodilator (nitroglycerin) was assessed in all patients. During the vasoconstriction test, a bolus of 2 μg/kg phenylephrine was administered intravenously and the effect on SVR was registered. The vasoconstrictor test was performed 5 times: t1) at baseline (before induction); t2) before induction, after start of cardiotropic drugs and/or vasopressors (e.g. dobutamine, milrinone, norepinephrine) when necessary; t3) after induction; t4) 15 minutes after cessation of CPB; and t5) on the first postoperative day.

For the vasodilation test a bolus of 10 μg nitroglycerin was administered using peripheral intravenous access. The effect on MAP was registered. Dosages were increased to 20, 40 and 60 μg until a drop of 10% in MAP was reached. The vasodilation test was performed twice: t1) at baseline (before induction) and t5) 1 day postoperatively.

Both the vasoconstriction and the vasodilation test were only performed when the patient's clinical condition allowed an increase or decrease in MAP.

Statistical analysis

The study was designed to achieve 90% power to detect a difference in means of 400 dyn·s/cm^5 in SVR assuming that the common standard deviation (SD) was 350 dyn·s/cm^5 using a student t-test with a 0.05 two-sided significance level.[13]

Baseline patient characteristics were described using summary statistics. Continuous variables were reported as mean ± SD or as median with interquartile range. Differences between groups (HF versus non-HF) were compared using an unpaired Student's t-test, or Mann-Whitney U-test. Categorical data were reported as numbers and percentages. Fisher's exact test was used to compare differences between groups. Pairwise deletion was used to handle missing data.

To explore the effects of HF on vasoreactivity, generalized estimating equations (GEE) was performed, utilizing an independent working correlation structure. The analysis was

repeated including only patients that did not receive norepinephrine to exclude its effect on vasoreactivity.

Univariable linear regression analysis was used to assess whether vasoreactivity could predict the amount of norepinephrine used in the first 24 hours postoperatively. Subsequently, this analysis was repeated in a multivariable linear regression whilst adjusting for HF and norepinephrine use.

The significance level was set at $P < 0.05$. Statistical analysis was performed using SPSS (version 25.0).

Results

Study population

Among 1864 adult patients who underwent cardiac surgery in our center during the study period (2016-2018), 347 patients were eligible for inclusion. Of these patients 36 patients were enrolled (Figure 2). Overall, median age was 67 (IQR 61-71) years and 78% were male. At baseline, HF and control patients were comparable with respect to age, sex and co-morbidities. HF patients had a significantly higher Body Mass Index (27±4 vs 24±3, P=0.024) and, as expected, a higher EuroSCORE II (9.76 (IQR 6.59-15.49) vs 1.45 (IQR 1.07-2.71), P<0.001). Furthermore, the use of betablockers (89% vs 33%, P=0.002) and diuretics (89% vs 28%, <0.001) was more prevalent in the HF group (Table 1).

In both groups CPB times, aortic cross clamp times and procedural durations (Table 2) were comparable. HF patients were more likely to receive inotropic support intra- and postoperatively, compared to control patients. During the first 24 hours postoperatively, the MAP was significantly lower in HF patients (72±8 vs 77±5, P=0.037), despite more inotropic and vasopressor support (Table 3). Postoperative vasoplegia occurred in 17% of the HF patients as compared to 6% in the control group (P=0.603).

Figure 2. Patient selection flow diagram.

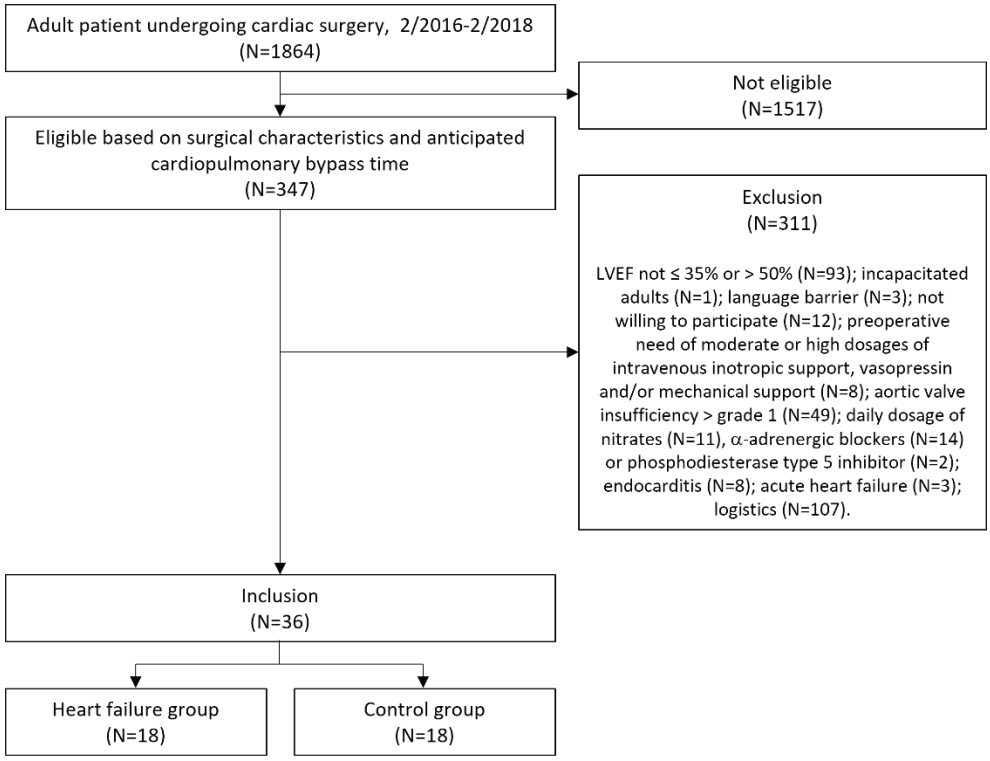


Table 1. Baseline characteristics.

	Heart failure (N=18)	Control (N=18)	P-value
Age (years)	68 (62-71)	64 (59-69)	0.279
Male sex (%)	67	89	0.228
Body mass index (kg/m2)	27±4	24±3	**0.024**
Diabetes (%)	28	6	0.177
Prior hypertension (%)	39	17	0.264
Pulmonary hypertension (%)	28	11	0.402
Previous cardiac surgery (%)	22	6	0.338
Hemoglobin (mmol/l)	8.5±1.0	9.1±1.0	0.093
Creatinine clearance (ml/min/1,73m2)	67±20	78±16	0.090
EuroSCORE II (%)	9.76 (6.59-15.49)	1.45 (1.07-2.71)	**<0.001**
Left ventricular ejection fraction (%)			
Normal, >60%	0	94	**<0.001**
Mildly abnormal, 45-60%	0	6	
Moderately abnormal, 30-45%	11	0	
Poor, <30%	89	0	
Medication use			
Betablocker (%)	89	33	**0.002**
ACE-inhibitor/ARB (%)	61	50	0.738
Antiarrhythmics (%)	28	11	0.402
MRA (%)	44	11	0.060
Diuretics (%)	89	28	**<0.001**
Inotropes (%)	11	0	0.486

Numbers are mean±SD, median (IQR) or %. ACE: Angiotensin-converting-enzyme; ARB: angiotensin receptor blockers; MRA: Mineralocorticoid receptor antagonists

Table 2 Intraoperative characteristics

	Heart failure (N=18)	Control (N=18)	P-value
Procedure type			
Mitral valve plasty (%)	56	94	**0.018**
Tricuspid valve plasty (%)	33	50	0.500
Surgical left ventricular restoration (%)	39	0	**0.008**
Left ventricular assist device implantation (%)	22	0	0.104
Coronary artery bypass grafting (%)	39	6	**0.041**
Aortic valve replacement (%)	17	0	0.229
Aorta surgery (%)	11	6	1.000
Medication use			
Epinephrine (%)	28	0	**0.045**
Norepinephrine (%)	94	44	**0.003**
Dobutamine (%)	83	33	**0.006**
Milrinone (%)	94	17	**<0.001**
Procedure characteristics			
Hypothermia during CPB (°C)	32 (32-37)	32 (30-33)	0.265
CPB time (min)	174 (120-214)	143 (103-225)	0.696
Cross clamp time (min)	135±37	132±52	0.854
Procedure time (min)	300 (254-388)	243 (188-326)	0.064

Numbers are mean±SD, median (IQR) or %. CPB: cardiopulmonary bypass.

Table 3 Postoperative characteristics

	Heart failure (N=18)	Control (N=18)	P-value
SVR 0-24 hours	1132 (929-1283)	1189 (952-1472)	0.377
MAP 0-24 hours	72±8	77±5	0.037
CI 0-24 hours	2.3±0.4	2.5±0.6	0.217
Medication use			
Epinephrine (%)	28	0	**0.045**
Norepinephrine (%)	94	56	**0.018**
Dobutamine (%)	94	28	**<0.001**
Milrinone (%)	94	17	**<0.001**
Terlipressin (%)	17	0	0.229
Max dose Nor on ICU (ug/kg/min)	0.18 (0.08-0.6)	0.03 (0-0.13)	**0.002**
Total duration Nor on ICU (min)	1281 (215-1615)	177 (0-882)	**0.009**
Total Nor on ICU (ug/kg)	186.51 (14.77-345.03)	3.61 (0-41.60)	**0.003**
Nor on ICU 0-24 hours (ug/kg)	169.80 (14.77-318.97)	3.61 (0-41.60)	**0.003**
Vasoplegia (%)	17	6	0.603
ICU time (days)	2 (1-3)	1 (1-2)	0.133

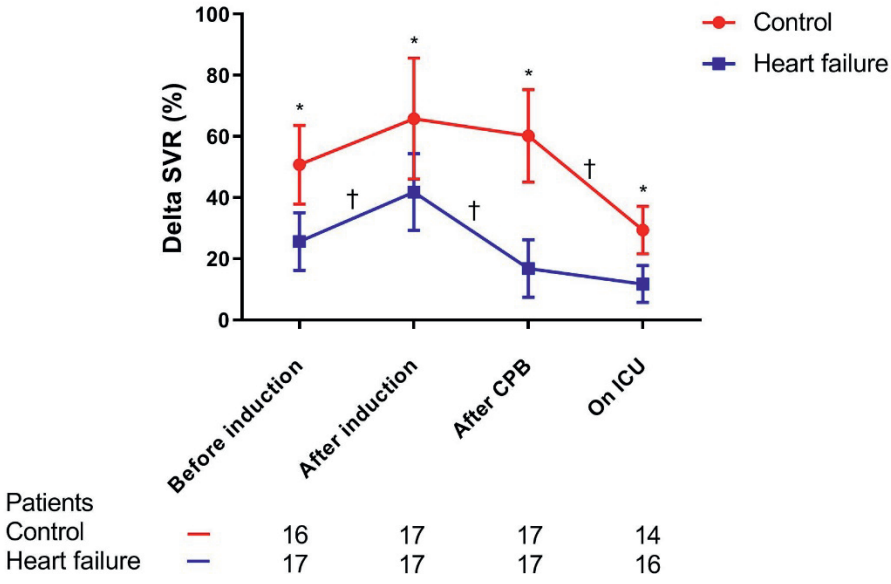
Numbers are mean±SD, median (IQR) or %. CI: cardiac index; ICU: Intensive Care Unit; MAP: mean arterial pressure; Nor: norepinephrine; SVR: systemic vascular resistance.

Vasoresponsiveness at baseline

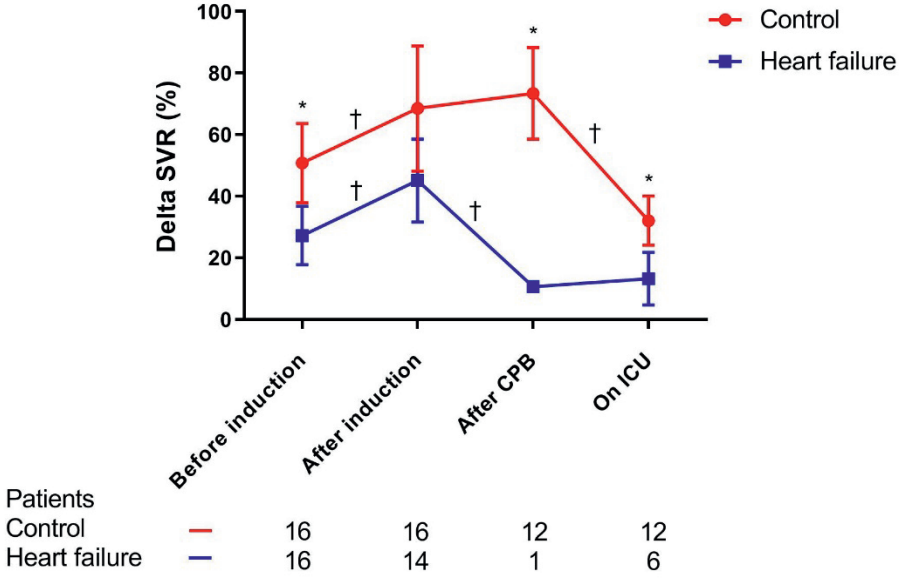
The increase in SVR in response to phenylephrine at baseline was significantly diminished in HF patients as compared to controls (Figure 3A). On average, the increase in SVR in HF patients was 26% (95%CI 16-35) compared to 51% (95%CI 38-64) in controls (P=0.002). The change in cardiac index and MAP after administration of a standardized dosage of phenylephrine at baseline are depicted in Figure 4. Of note, in none of the patients was it necessary to start cardiotropic drugs and/or vasopressors before induction, therefore vasoconstriction test 2 (t2) was not performed.

Figure 3. Vasoconstriction test

A. Total population.



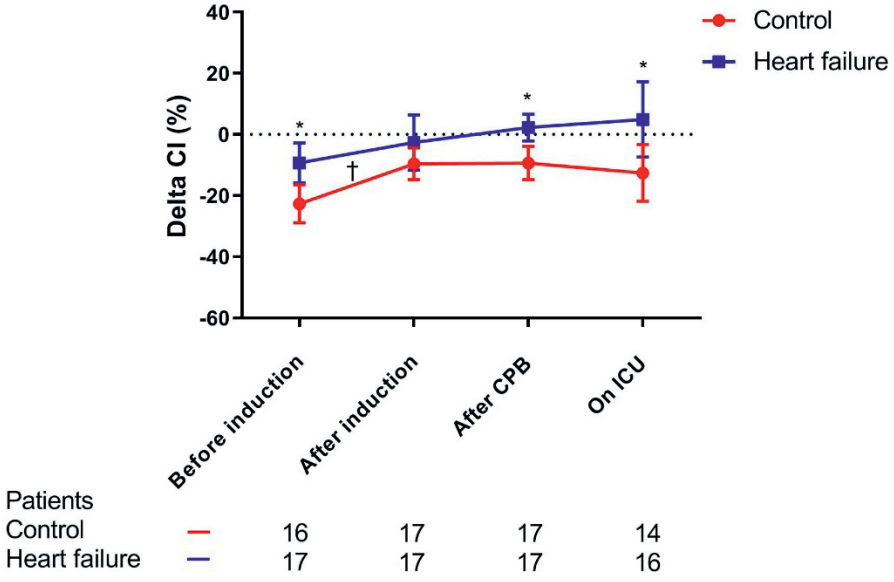
B. Patients not receiving norepinephrine.



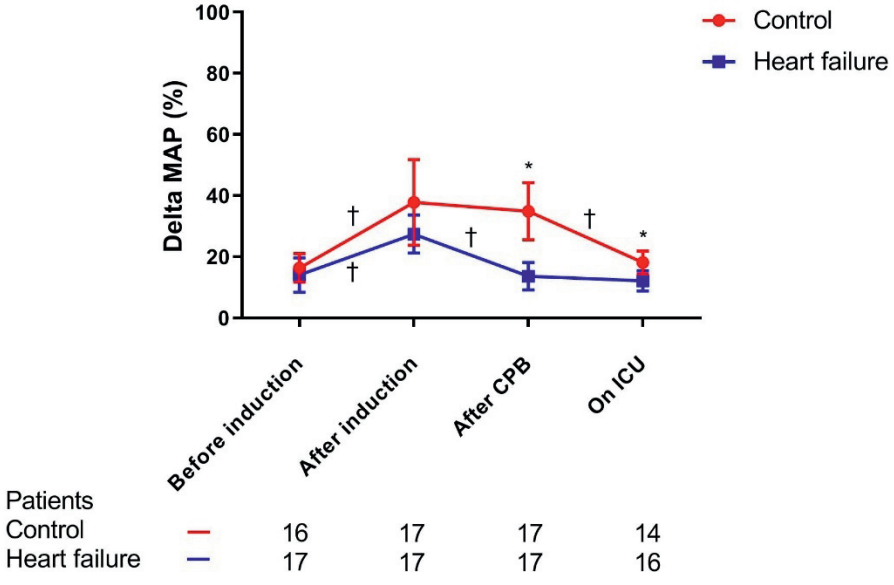
*Delta systemic vascular resistance (SVR, %) with 95%CI. * Significant difference (P<0.05) between groups; † significant difference between timepoints.*

Figure 4. Vasoconstriction test

A. Change in cardiac index



B. Change in mean arterial pressure



*Delta systemic cardiac index (CI, %) and mean arterial pressure (MAP, %) with 95%CI. * Significant difference (P<0.05) between groups; † significant difference between timepoints.*

Vasoresponsiveness after induction and during cardiac surgery

As shown in Figure 3A, delta SVR increased in both groups after induction, indicating an increased vasoresponsiveness. However, delta SVR remained significantly lower in HF patients on all timepoints. Interestingly, vasoresponsiveness was almost abolished after cessation of CPB in HF patients (decline from 42% (95%CI 29-54) to 17% (95%CI 7-26) after cessation, P=0.002). In contrast, the response to phenylephrine did not significantly change in control patients after cessation of CPB (66% (95%CI 46-86) to 60% (95%CI 45-75), P=0.623).

Both intra-operatively and post-operatively, significantly more HF patients received norepinephrine when compared to controls (Table 2 and 3). Conceptually, the higher use of norepinephrine in HF patients in the intra- and post-operative phase could have interfered with the response to phenylephrine. Accordingly, the analyses were repeated in the subgroup of patients who did not receive norepinephrine. As shown in Figure 3B, roughly the same pattern was found. This indicates that HF patients have a decreased vasoconstrictor response compared to control patients which is independent from the effect of norepinephrine.

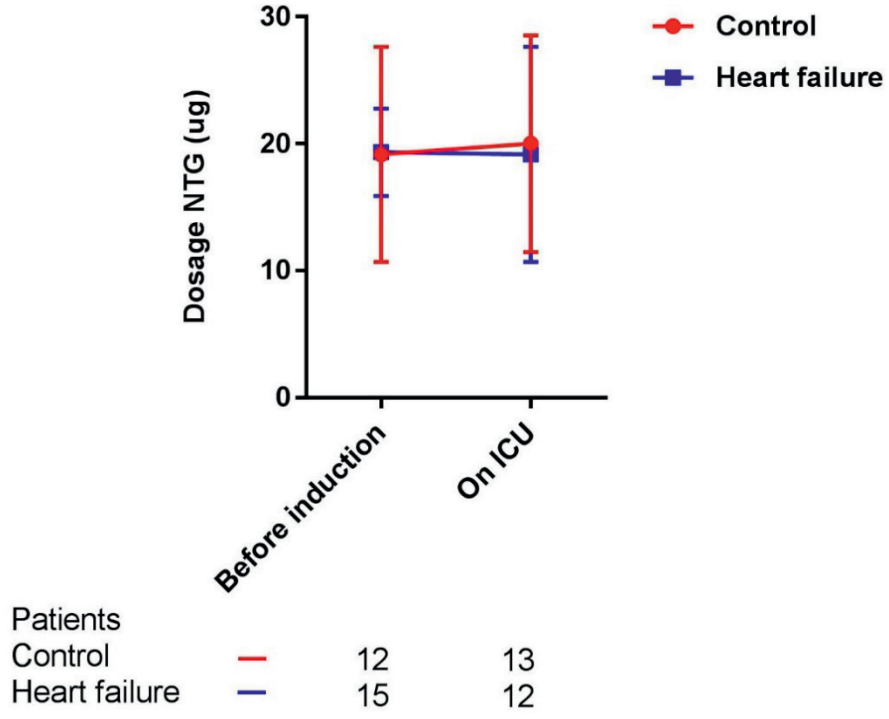
Vasoresponsiveness in the early postoperative period

The almost abolished vasoresponsiveness to phenylephrine continued to persist in HF patients on day 1 postoperatively. In particular, delta SVR was 12% (95%CI 6-18) in the HF group as compared to 29% (95%CI 22-37) in the control group (P<0.001). Remarkably, there was a significant decrease in SVR in control patients at the ICU compared to intraoperatively (60% (45-75%) to 29 (22-37%), P<0.001).

Vasoresponsiveness to a vasodilator

Both at baseline and at the first postoperative day there was no difference in the dosage of nitroglycerin needed to achieve a decrease of at least 10% in MAP between both groups (Figure. 5).

Figure 5. Vasodilation test: Dosage nitroglycerin (with 95% CI) needed for 10% decrease in MAP.

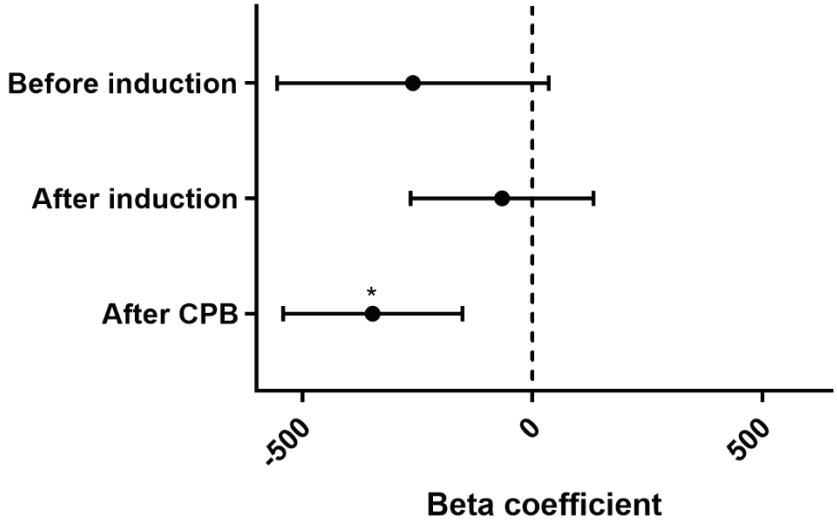


Predicting vasoplegia

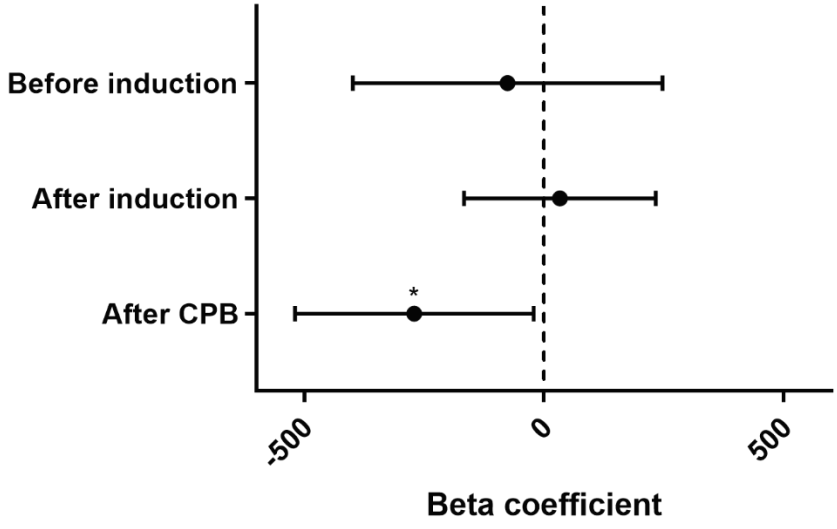
As shown in Figure 6, the change in SVR upon phenylephrine administration after CPB significantly associates with the total amount of norepinephrine received during the first 24 hours on the intensive care unit (P=0.001). This association persists after adjusting for HF and the norepinephrine dosage at this time point (P=0.034).

Figure 6. Predicting the total amount of norepinephrine given during the first 24 hours on the ICU, using the % SVR at baseline, after induction and after cessation of the cardiopulmonary bypass.

A. Univariate.



B. Multivariate, adjusted for heart failure and norepinephrine dosage at that time point.



*Beta coefficient with 95%CI. * Significant association (P<0.05)*

Discussion

We found that HF patients have a diminished response to a vasoconstrictor compared to control patients during the pre-, intra- and postoperative phase, independent of norepinephrine use. Furthermore, we showed that vasoresponsiveness intraoperatively is associated with the amount of norepinephrine received postoperatively.

Diminished vasoresponsiveness in HF patients at baseline

Chronic endogenous adrenergic (over)stimulation is known to lead to downregulation and desensitization of myocardial β1-adrenergic receptors and desensitization β2-adrenergic receptors in HF.[14] Our study shows that the response to phenylephrine, an α_1-adrenoreceptor agonist, is diminished in HF patients at baseline. This support our hypothesis that continuous adrenergic stimulation also results in downregulation and/or desensitization of vascular α_1-adrenoreceptors, leading to an altered responsiveness of the vascular system of HF patients.

Recently, Kaykı-Mutlu et al. performed a systematic meta-analysis examining the role of both cardiac and vascular α_1-adrenoreceptors.[15] They concluded that there is no consistent evidence for down-regulation or desensitization of vascular α_1-adrenoreceptors in HF. The heterogenous results might be due to interspecies differences, variations in expression levels of the three subtypes of α_1-adrenoreceptors in specific cell and tissue types, the effects of the pathophysiological mechanism underlying HF (e.g. ischemic versus non-ischemic) or due to poorly reproducible results.

Two of the presented studies measured the effect of α_1-adrenoreceptor agonists on SVR in HF patients. Goldsmith et al. concluded that HF patients have a diminished vasoresponsiveness to norepinephrine, since exogenous norepinephrine infusion did not had an significant effect on SVR.[16] In contrast to our study, Schwinn et al. failed to demonstrate a significant difference in a_1-adrenergic responsiveness between patients with LVEF ≤40% undergoing CABG on CPB versus controls when measured pre-induction.[13] However, patients with impaired ventricular function had reduced vasoresponsiveness after induction before CPB started. They explained their inability to demonstrate reduced vasoresponsiveness pre-induction by patient selection: all patients were in good condition and none of the patients had end-stage HF. This is an important contrast to our study. Other differences in patient population included: 1) patients with impaired ventricular function used less often betablockers compared to control patients; 2) patients using nitrates were included in the study; 3) the control group also included one patient with congestive HF and 4) use of norepinephrine was not documented.

A reduced response to an α_1-adrenoreceptor agonist in HF might derive from lower expression levels of the receptor or from alterations in signal transduction and could be influenced by disease progression.[15] More research is required to understand the changes in α_1 adrenergic function in HF and to identify the specific mechanisms that are involved.

Reduced vasoresponsiveness in HF patients intra- and postoperatively

We showed that the diminished response to phenylephrine in HF patients continues to exist throughout the study period, independent of the received norepinephrine dosage. Interestingly, vasoresponsiveness was almost abolished after cessation of CPB in HF patients, which persisted on day 1 postoperatively. The use of CPB is a known risk factor for vasoplegia.[17] The combination of surgical trauma and the use of CPB induces a systemic inflammatory response.[11] Our results support the hypothesis that the fragile balance of the vascular system of HF patients is easily disturbed by this response. This leads to the severely impaired vasoresponsiveness after cessation of CPB and contributes to the high risk for postoperative vasoplegia in HF patients.[6]

The response to nitroglycerin is not affected by HF

It is suggested that activation of inducible nitric oxide synthase (iNOS) plays a role in the pathogenesis of vasoplegia.[18-20] Activation of iNOS results in nitric oxide (NO) production which stimulates the production of cyclic guanosine monophosphate (cGMP), leading to smooth muscle relaxation and thereby vasodilation. Inhibition of cGMP by methylene blue is used to prevent and treat postoperative vasoplegia, however there is a limited level of evidence at this time.[21]

We found no difference in the response to nitroglycerin between our study groups. We postulate that this is a result of the endothelium-independent mechanism of nitroglycerin, which is accomplished by its conversion into NO.[22] This suggests that the vascular responsiveness to NO is comparable between HF patients and controls and that this does not influence the risk of vasoplegia. Considering that endothelial dysfunction is usually present in HF, endothelium-dependent mechanisms should be further investigated in relation to vasoplegia.[23]

Predicting vasoplegia

We showed that the change in SVR after CPB is significantly associated with the amount of norepinephrine received during the 24 hours on the intensive care unit. Unfortunately, due to the small sample size we were not able to find a direct association with vasoplegia. However, this finding indicates a link between reduced vasoresponsiveness intra-

operatively and vasoplegia. When confirmed in a larger cohort, this could provide a screening tool that could be used for a strategy to prevent vasoplegia or to start early treatment.

Fluid resuscitation and sympathomimetic agents (norepinephrine, epinephrine, and phenylephrine) are first-line treatment for vasoplegia. When catecholamines fail to restore hemodynamics, arginine vasopressin or angiotensin II could be used.[19, 20] Other treatment options are non-vasopressors, including methylene blue, ascorbic acid, hydroxocobalamin and corticosteroids. Thus far, few studies have focused on the prevention of vasoplegia. Future studies should focus on pre- and intraoperative strategies like early intervention with vasopressin.[24, 25]

Study strengths and limitations

Due to broad inclusion criteria, our study population properly represents the real-world population undergoing HF surgery. Of importance, factors that were previously reported to influence the risk of vasoplegia (prior hypertension, creatinine clearance, hemoglobin level, previous cardiac surgery, CPB time, aortic cross clamp time and procedural duration),[7, 9, 26] were comparable in both groups. Only the use of betablockers, which has earlier been suggested to be a protective factor for vasoplegia,[7, 9] was more prevalent in HF patients as advised by the HF guidelines.[12, 27]

There are limitations that should be taken into account while interpreting these results. As expected in this study population, there were some missing data (9% of the phenylephrine and 14% of the nitroglycerin measurements) since the patients' clinical condition did not always allow the tests to be performed. Importantly, however, the baseline data were complete. Moreover, this study was not powered to detect differences in vasodilation. Another limitation is that the central venous catheter and the pulmonary artery catheter were introduced post-induction for measurement of CO and SVR. These data were used to calibrate CO as measured by PulseCO. Due to the absence of catheters before induction, calibration was not possible at that timepoint. Therefore, SVR at baseline was not directly comparable with the other timepoints, so we had to use relative numbers for the change in SVR.

Conclusions

We found that HF patients have a diminished response to phenylephrine compared to control patients perioperatively. The reduced vasoresponsiveness is already present at baseline and persists throughout the entire perioperative period, independent of norepinephrine use. After cessation of CPB, vasoresponsiveness is almost abolished in HF patients. Furthermore, we showed that intraoperative vasoresponsiveness is associated with the amount of norepinephrine received postoperatively, suggesting a link between reduced vasoresponsiveness and the occurrence of vasoplegia. The diminished vasoresponsiveness in HF patients might explain the increased risk of developing postoperative vasoplegia. The current results provide insight in the mechanisms underlying vasoplegia. This could yield therapeutic options or preventive strategies for vasoplegia, leading to safer surgical interventions and improvement in outcome.

References

1. Haeck ML, Hoogslag GE, Rodrigo SF, et al. Treatment options in end-stage heart failure: where to go from here? Neth Heart J. 2012;20:167-75.
2. Braun J, Ciarka A, Versteegh MI, et al. Cardiac support device, restrictive mitral valve annuloplasty, and optimized medical treatment: a multimodality approach to nonischemic cardiomyopathy. J Thorac Cardiovasc Surg. 2011;142:e93-100.
3. Klein P, Holman ER, Versteegh MI, et al. Wall motion score index predicts mortality and functional result after surgical ventricular restoration for advanced ischemic heart failure. Eur J Cardiothorac Surg. 2009;35:847-52; discussion 52-3.
4. Byrne JG, Leacche M, Paul S, et al. Risk factors and outcomes for 'vasoplegia syndrome' following cardiac transplantation. Eur J Cardiothorac Surg. 2004;25:327-32.
5. Patarroyo M, Simbaqueba C, Shrestha K, et al. Pre-operative risk factors and clinical outcomes associated with vasoplegia in recipients of orthotopic heart transplantation in the contemporary era. J Heart Lung Transplant. 2012;31:282-7.
6. Argenziano M, Chen JM, Choudhri AF, et al. Management of vasodilatory shock after cardiac surgery: identification of predisposing factors and use of a novel pressor agent. J Thorac Cardiovasc Surg. 1998;116:973-80.
7. van Vessem ME, Palmen M, Couperus LE, et al. Incidence and predictors of vasoplegia after heart failure surgery. Eur J Cardiothorac Surg. 2017;51:532-8.
8. Chan JL, Kobashigawa JA, Aintablian TL, et al. Vasoplegia after heart transplantation: outcomes at 1 year. Interact Cardiovasc Thorac Surg. 2017;25:212-7.
9. van Vessem ME, Petrus AHJ, Palmen M, et al. Vasoplegia After Restrictive Mitral Annuloplasty for Functional Mitral Regurgitation in Patients With Heart Failure. J Cardiothorac Vasc Anesth. 2019;33:3273-80.
10. van Vessem ME, Beeres S, de Wilde RBP, et al. Vasoresponsiveness in patients with heart failure (VASOR): protocol for a prospective observational study. J Cardiothorac Surg. 2019;14:200.
11. Day JR, Taylor KM. The systemic inflammatory response syndrome and cardiopulmonary bypass. Int J Surg. 2005;3:129-40.
12. Ponikowski P, Voors AA, Anker SD, et al. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC). Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. Eur J Heart Fail. 2016;18:891-975.
13. Schwinn DA, McIntyre RW, Hawkins ED, et al. alpha 1-Adrenergic responsiveness during coronary artery bypass surgery: effect of preoperative ejection fraction. Anesthesiology. 1988;69:206-17.
14. Ruffolo RR, Jr., Kopia GA. Importance of receptor regulation in the pathophysiology and therapy of congestive heart failure. Am J Med. 1986;80:67-72.
15. Kaykı-Mutlu G, Papazisi O, Palmen M, et al. Cardiac and Vascular α(1)-Adrenoceptors in Congestive Heart Failure: A Systematic Review. Cells. 2020;9.
16. Goldsmith SR, Francis GS, Cohn JN. Norepinephrine infusions in congestive heart failure. Am J Cardiol. 1985;56:802-4.
17. Sun X, Zhang L, Hill PC, et al. Is incidence of postoperative vasoplegic syndrome different between off-pump and on-pump coronary artery bypass grafting surgery? Eur J Cardiothorac Surg. 2008;34:820-5.
18. Landry DW, Oliver JA. The pathogenesis of vasodilatory shock. N Engl J Med. 2001;345:588-95.
19. Papazisi O, Palmen M, Danser AHJ. The Use of Angiotensin II for the Treatment of Post-cardiopulmonary Bypass Vasoplegia. Cardiovasc Drugs Ther. 2020.
20. Barnes TJ, Hockstein MA, Jabaley CS. Vasoplegia after cardiopulmonary bypass: A narrative review of pathophysiology and emerging targeted therapies. SAGE Open Med. 2020;8:2050312120935466.
21. Evora PR, Alves Junior L, Ferreira CA, et al. Twenty years of vasoplegic syndrome treatment in heart surgery. Methylene blue revised. Rev Bras Cir Cardiovasc. 2015;30:84-92.

22. Zhou K, Parker JD. The role of vascular endothelium in nitroglycerin-mediated vasodilation. Br J Clin Pharmacol. 2019;85:377-84.
23. Drexler H, Hornig B. Endothelial Dysfunction in Human Disease. J Mol Cell Cardiol. 1999;31:51-60.
24. Hasija S, Makhija N, Choudhury M, et al. Prophylactic vasopressin in patients receiving the angiotensin-converting enzyme inhibitor ramipril undergoing coronary artery bypass graft surgery. J Cardiothorac Vasc Anesth. 2010;24:230-8.
25. Morales DL, Garrido MJ, Madigan JD, et al. A double-blind randomized trial: prophylactic vasopressin reduces hypotension after cardiopulmonary bypass. Ann Thorac Surg. 2003;75:926-30.
26. Dayan V, Cal R, Giangrossi F. Risk factors for vasoplegia after cardiac surgery: a meta-analysis. Interact Cardiovasc Thorac Surg. 2019;28:838-44.
27. Yancy CW, Jessup M, Bozkurt B, et al. 2017 ACC/AHA/HFSA Focused Update of the 2013 ACCF/AHA Guideline for the Management of Heart Failure: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Failure Society of America. Circulation. 2017;136:e137-e61.

CHAPTER 7

Summary, conclusions and future perspectives

Samenvatting, conclusie en toekomstperspectieven

Summary, conclusions and future perspectives

Heart failure is a chronic syndrome for which surgical treatment is proven to be beneficial in selected patients in stage C and D. However, surgical treatment is not without risks. Vasoplegia, a subtype of vasodilatory shock, is a severe complication which may occur after cardiac surgery, particularly in patients with heart failure. It is caused by inactivation of vasoconstriction and activation of vasodilation mechanisms. The aim of this thesis was to gain more knowledge on the incidence and risk factors of vasoplegia after heart failure surgery and the consequence this complication has on the affected patients, early and after surgery and during follow-up. Furthermore, we intended to unravel the mechanisms responsible for the increased risk on vasoplegia in this patient population.

The general introduction of this thesis (*chapter 1*) provided an overview of the definition, epidemiology, pathophysiology and treatment of vasoplegia after heart failure surgery. We proposed that the characteristics of heart failure patients make them more prone to develop vasoplegia. In the past, vasoplegia after heart failure surgery was only studied after heart transplantation and left ventricular assist device implantation. In these populations vasoplegia was associated with an impaired clinical outcome.

In *chapter 2* the incidence, survival and predictors of vasoplegia in patients undergoing heart failure surgery was assessed. Vasoplegia was defined as the continuous need of vasopressors (norepinephrine ≥0.2 μg/kg/min and/or terlipressin (any dose)) combined with a cardiac index ≥2.2 l/min/m2 for at least 12 consecutive hours, starting within the first 3 days post-operatively. In total 225 heart failure patients with a left ventricular ejection fraction (LVEF) ≤35%, undergoing surgical left ventricular restoration, CorCap implantation or left ventricular assist device implantation were included. The incidence of vasoplegia was 29%. Only 71% of the vasoplegic patients survived the first 90 days post-operative, compared to 91% of the non-vasoplegic patients. Preoperative anemia and a higher thyroxine level were associated with an increased risk on vasoplegia. In contrast, a higher creatinine clearance and beta-blocker use decreased the risk on vasoplegia. A risk model to assess the risk on post-operative vasoplegia was proposed which had a fair discriminatory power to identify patients at risk for vasoplegia, dividing them over 3 risk categories: 1) low risk (<25%), 2). intermediate risk (25-50%) and 3 high risk (>50%).

The aim of the study described in *chapter 3* was to determine the incidence and predictors of vasoplegia in heart failure patients undergoing mitral valve repair for functional mitral regurgitation and to evaluate the effect of ischemic versus non-ischemic etiology. Furthermore, the prognostic impact of vasoplegia on early clinical outcome was assessed. In total 122 heart failure patients with a LVEF ≤35% were included. The mitral regurgitation etiology was ischemic in 48%. The incidence of vasoplegia was 19% and was not influenced by mitral regurgitation etiology. Within 90 days after surgery, only 65% of

the vasoplegic patients survived, compared to 93% of the non-vasoplegic patients. Prior hypertension, a higher creatinine clearance and beta-blocker use were associated with a decreased risk of vasoplegia, whereas anemia and longer cross clamp -, cardiopulmonary bypass - and procedure times were associated with an increased risk of vasoplegia, independent of mitral regurgitation etiology, age and gender.

The objective of the study described in *chapter 4* was to assess the effects of vasoplegia on survival, cardiac function, and renal function 2 years after surgical left ventricular restoration. A total of 113 heart failure patients with a LVEF <35% were included. Cardiac function was assessed using the New York Heart Association Functional Classification (NYHA) and LVEF. The incidence of post-operative vasoplegia was 23%. After 6 months the survival rate was 62% in the vasoplegic patients, compared to 90% in the non-vasoplegic patients. 2 years after the procedure, only 50% of the vasoplegic patients survived, compared to 84% of the non-vasoplegic patients. At 2 year follow-up, cardiac function had improved and was similar in both groups. Despite an improved and similar cardiac function in both groups, renal function was compromised in vasoplegic patients at the 2-year follow-up. Even after correcting for baseline creatinine clearance.

The rationale and design of a prospective observational study on the vasoresponsiveness in heart failure patients was described in *chapter 5*. It was proposed that vasoplegia is the result of activation of vasodilator pathways, inactivation of vasoconstrictor pathways and the resistance to vasopressors. However, the precise etiology remained unclear. The aim of the Vasoresponsiveness in patients with heart failure (VASOR) study was to objectify and characterize the altered vasoresponsiveness in patients with heart failure, before, during and after heart failure surgery and to identify the etiological factors involved. This single-center prospective observational study included patients undergoing cardiac surgery on cardiopulmonary bypass. In phase one, a total of 36 patients were enrolled. Heart failure and control patients were compared with respect to the vascular response, measured by a change in systemic vascular resistance after administration of a vasoconstrictor (phenylephrine) and a vasodilator (nitroglycerin) pre-, intra- and post-operatively. Furthermore, blood and urine samples were collected and evaluated for levels of organic compounds related to the cardiovascular system (e.g. copeptin, angiotensin II). In addition, ex vivo vascular reactivity was assessed using isolated resistance arteries collected from fat tissue intraoperatively. mRNA analysis and immunohistochemistry was used to assess the expression of signaling proteins and receptors in the vascular bed. During phase 2, only the ex vivo vascular reactivity tests were performed in 12 heart failure and 12 control patients.

The results of the in vivo vascular response test of the VASOR study were discussed in *chapter 6*. The vascular reactivity in response phenylephrine and nitroglycerin was assessed perioperatively by measuring changes in systemic vascular resistance in heart

failure (N=18) and control patients (N=18). The incidence of post-operative vasoplegia was 17% in the heart failure group, compared to 6% in the control group. We found that heart failure patients have a diminished response to a vasoconstrictor perioperatively compared to control patients. The reduced vasoresponsiveness is present at baseline and persists throughout the perioperatively period, independent of used norepinephrine. After cessation of cardiopulmonary bypass, vasoresponsiveness is almost abolished in heart failure patients. There was no difference in the dosage of nitroglycerine needed to achieve a drop of at least 10% in mean arterial pressure between both groups. Vasoresponsiveness intra-operatively was associated with the amount of norepinephrine received post-operatively, indicating a link between reduced vasoresponsiveness and vasoplegia.

Conclusion and future perspectives

Vasoplegia is a common complication after heart failure surgery, although the incidence differs for each surgical procedure type. It is associated with poor early and late survival rates. In the vasoplegic survivors, renal function is compromised compared to non-vasoplegic patients even though the cardiac function is similar. Preoperative factors associated with an increased risk on vasoplegia (e.g. anemia and a higher thyroxine levels) and factors associated with an decreased risk (e.g. higher creatinine clearance, beta-blocker use, prior hypertension) could be used to assess the risk on vasoplegia preoperatively for specific heart failure procedures. Also, intraoperative factors that are associated with an increased risk of vasoplegia (intraoperative vasoresponsiveness, longer cross clamp -, cardiopulmonary bypass - and procedure times) could be used to estimate the risk on vasoplegia. Further research is necessary to verify whether these results can be extrapolated to other hospitals and to validate the proposed risk model.

Thus far, few studies have focused on the prevention of vasoplegia. Until preventive measures become available, patients could potentially benefit from preoperative hemodynamic optimization, early-onset and aggressive treatment of vasoplegia and perioperative renal protection strategies. Current treatment strategies of vasoplegia should be further evaluated with respect to the used (combination of) drugs, dosage and timing. In addition, future studies should focus on (non)-pharmacological preventive strategies. For example, the use of blood purification techniques to minimize the effects of the inflammatory mediators that are released during cardiopulmonary (e.g. CytoSorb, CytoSorbents Corporation, New Jersey, USA).

In this thesis the rationale and design of the VASOR study is described. Inclusion of phase 2 is ongoing and is thought to be complete in 2021. Furthermore, the blood, urine and tissue samples are currently evaluated. The diminished vasoresponsiveness in heart failure

patients might explain the increased risk of developing post-operative vasoplegia. More research is required to understand these changes and to identify the specific mechanisms that are involved. This could yield better-targeted therapeutic options or preventive strategies for vasoplegia, leading to safer surgical interventions and improvement in outcome after heart failure surgery.

Samenvatting, conclusie en toekomstperspectieven

Hartfalen is een chronisch ziekte met hoge mortaliteit en morbiditeit. Voor geselecteerde patiënten met hartfalen in stadium C en D is operatieve behandeling bewezen effectief. Een chirurgische ingreep is echter niet zonder risico's. Vasoplegie, een subtype van vasodilatoire shock, is een ernstige complicatie die kan optreden na een hartoperatie. Deze complicatie wordt vaker gezien bij patiënten met dan bij patiënten zonder hartfalen. Het wordt veroorzaakt door inactivering van vasoconstrictie- en activering van vasodilatatiemechanismen. Het doel van het onderzoek zoals beschreven in dit proefschrift was om meer inzicht te krijgen in de incidentie en risicofactoren van vasoplegie na hartfalenchirurgie. Daarnaast werden de gevolgen van deze complicatie, zowel in de eerste fase na de operatie als tijdens de lange termijn follow-up bestudeerd. Tot slot werden de mechanismen die verantwoordelijk zijn voor het verhoogde risico op vasoplegie in deze patiëntenpopulatie onderzocht.

In de algemene inleiding van dit proefschrift (hoofdstuk 1) werd een overzicht gegeven van de definitie, epidemiologie, pathofysiologie en behandeling van vasoplegie na hartfalenchirurgie. We stelden dat de kenmerken van hartfalenpatiënten hen vatbaarder maken voor het ontwikkelen van vasoplegie. Eerder werd vasoplegie na hartfalenchirurgie alleen bestudeerd na harttransplantatie en implantatie van een left ventricular assist device (LVAD, ook wel steunhart genoemd). In deze populaties werd vasoplegie geassocieerd met een slechtere klinische uitkomst.

In hoofdstuk 2 werd de incidentie, overleving en voorspellers van vasoplegie bij patiënten die hartfalenchirurgie ondergingen onderzocht. Vasoplegie werd gedefinieerd als de continue behoefte aan vasopressoren (noradrenaline ≥0,2 µg/kg/min en/of terlipressine (elke dosis)) in combinatie met een cardiac index ≥2,2 l/min/m^2 gedurende tenminste 12 opeenvolgende uren, beginnend tijdens de eerste 3 dagen postoperatief. In totaal werden 225 hartfalenpatiënten met een linker ventrikel ejectiefractie (LVEF) ≤35% geïncludeerd, die chirurgisch een linker ventrikel reconstructie, CorCap of LVAD implantatie ondergingen. De incidentie van vasoplegie was 29%. Slechts 71% van de vasoplege patiënten overleefden de eerste 90 dagen na de operatie, vergeleken met 91% van de niet-vasoplege patiënten. Preoperatieve anemie en een hogere thyroxinespiegel waren geassocieerd met een verhoogd risico op vasoplegie. Daarentegen verminderden een hogere creatinineklaring en het gebruik van bètablokkers het risico op vasoplegie. Er werd een risicomodel voorgesteld om het risico op postoperatieve vasoplegie te beoordelen. Dit model had een redelijk onderscheidend vermogen om patiënten met een risico op vasoplegie te identificeren, door ze te verdelen in 3 risicocategorieën: 1) laag risico (<25%), 2) intermediair risico (25-50%) en 3) hoog risico (>50%).

Het doel van de studie beschreven in hoofdstuk 3 was het bepalen van de incidentie en de voorspellers van vasoplegie bij hartfalenpatiënten die een mitralisklep reparatie ondergingen vanwege een functionele mitralisklepinsufficiëntie en het evalueren van het effect van ischemische versus niet-ischemische etiologie op het voorkomen van vasoplegie. Bovendien werd de prognostische impact van vasoplegie op de vroege klinische uitkomst onderzocht. In totaal werden 122 hartfalenpatiënten met een LVEF ≤35% geïncludeerd. De etiologie van de mitralisklepinsufficiëntie was in 48% van de gevallen ischemisch. De incidentie van vasoplegie was 19% en werd niet beïnvloed door etiologie. Binnen 90 dagen na de operatie overleefde slechts 65% van de vasoplege patiënten, vergeleken met 93% van de niet-vasoplege patiënten. Pre-existente hypertensie, een hogere creatinineklaring en het gebruik van bètablokkers waren geassocieerd met een verminderd risico op vasoplegie, terwijl bloedarmoede en langere klem-, cardiopulmonale bypass - en proceduretijden geassocieerd waren met een verhoogd risico op vasoplegie, onafhankelijk van de etiologie van de mitralisklepinsufficiëntie, leeftijd en geslacht.

Het doel van de studie beschreven in hoofdstuk 4 was het bepalen van de effecten van vasoplegie op overleving, hartfunctie en nierfunctie, 2 jaar na chirurgische linkerventrikel reconstructie. In totaal werden 113 hartfalenpatiënten met een LVEF ≤35% geïncludeerd. De hartfunctie werd beoordeeld met behulp van de New York Heart Association Functional Classification (NYHA) en LVEF. De incidentie van postoperatieve vasoplegie was 23%. Na 6 maanden was het overlevingspercentage 62% bij de vasoplege patiënten, vergeleken met 90% bij de niet-vasoplege patiënten. 2 jaar na de procedure was slechts 50% van de vasoplege patiënten nog in leven, vergeleken met 84% van de niet-vasoplege patiënten. Na 2 jaar follow-up was de hartfunctie verbeterd en vergelijkbaar in beide groepen. Ondanks een verbeterde en vergelijkbare hartfunctie in beide groepen, was de nierfunctie verminderd in vasoplege patiënten bij de 2-jaar follow-up, ook na correctie voor creatinineklaring op baseline.

De rationale en opzet van een prospectieve observationele studie naar de vasoresponsiviteit bij patiënten met hartfalen werd beschreven in hoofdstuk 5. Voorgesteld werd dat vasoplegie het resultaat is van activatie van vasodilatie, inactivatie van vasoconstrictie en verminderde gevoeligheid voor vasopressoren, maar de precieze etiologie was nog onduidelijk. Het doel van de Vasoresponsiveness in patients with heart failure (VASOR) studie was het objectiveren en karakteriseren van de veranderde vasoresponsiviteit bij patiënten met hartfalen, voor, tijdens en na hartfalenchirurgie en het identificeren van de etiologische factoren die hierbij betrokken zijn. In deze single-center prospectieve observationele studie werden patiënten geïncludeerd die een hartoperatie ondergingen aan de hartlongmachine. In fase één werden in totaal 36 patiënten geïncludeerd. Hartfalen- en controlepatiënten werden vergeleken met betrekking tot de vasoresponsiviteit, gemeten door een verandering in de systemische

vasculaire weerstand na toediening van een vasoconstrictor (fenylefrine) en een vasodilator (nitroglycerine) pre-, intra- en post-operatief. Bovendien werden bloed- en urinemonsters verzameld en geëvalueerd op het gehalte aan organische stoffen die een rol spelen in het cardiovasculaire systeem (bv. copeptine, angiotensine II). Daarnaast werd de ex vivo vasoreactiviteit beoordeeld door gebruik te maken van geïsoleerde arteriolen die intraoperatief uit vetweefsel werden gehaald. mRNA-analyse en immunohistochemie werden gebruikt om de expressie van signaalproteïnen en receptoren in het vaatbed te beoordelen. Tijdens fase 2 werden alleen de ex vivo vasoreactiviteit testen uitgevoerd bij 12 hartfalers en 12 controlepatiënten.

De resultaten van de in vivo vasculaire reactiviteitstest van de VASOR studie werden besproken in hoofdstuk 6. De vasoreactiviteit na een bolus fenylefrine en nitroglycerine werd perioperatief beoordeeld door het meten van veranderingen in de systemische vasculaire weerstand bij hartfalers (N=18) en controlepatiënten (N=18). De incidentie van postoperatieve vasoplegie was 17% in de hartfalengroep, vergeleken met 6% in de controlegroep. Hartfalers reageerden perioperatief verminderd op een vasoconstrictor in vergelijking met controlepatiënten. De verminderde vasoresponsiviteit was aanwezig op baseline en hield gedurende de gehele perioperatieve periode aan, onafhankelijk van de gebruikte noradrenaline dosering. Na het afkoppelen van de hartlongmachine daalde de vasoresponsiviteit na toediening van een vasoconstrictor nog verder bij patiënten met hartfalen. Er was geen verschil in de dosering nitroglycerine die nodig was om een daling van tenminste 10% van de gemiddelde arteriële druk te bereiken tussen beide groepen. Vasoresponsiviteit intra-operatief was geassocieerd met de hoeveelheid noradrenaline die postoperatief werd toegediend, wat wijst op een verband tussen verminderde vasoresponsiviteit en vasoplegie.

Conclusie en toekomstperspectieven

Vasoplegie is een veel voorkomende complicatie na hartfalenchirurgie, hoewel de incidentie verschilt per type chirurgische ingreep. Het is geassocieerd met slechte vroege en late overlevingskansen. Bij patiënten die vasoplegie hebben doorgemaakt, is de nierfunctie slechter dan bij niet-vasoplege patiënten, ook al is de hartfunctie vergelijkbaar. Preoperatieve factoren die geassocieerd zijn met een verhoogd risico op vasoplegie (bv. anemie en een hoger thyroxinegehalte) en factoren die geassocieerd zijn met een verlaagd risico (bv. hogere creatinineklaring, gebruik van bètablokkers, pre-existente hypertensie) zouden kunnen worden gebruikt om het risico op vasoplegie preoperatief te beoordelen voor specifieke ingrepen in hartfalers. Ook intra-operatieve factoren die geassocieerd zijn met een verhoogd risico op vasoplegie (intraoperatieve vasoresponsiviteit, langere klem-, cardiopulmonaire bypass - en proceduretijden) zouden kunnen worden gebruikt om het risico op vasoplegie in te schatten. Verder onderzoek is

nodig om na te gaan of deze resultaten kunnen worden geëxtrapoleerd naar andere ziekenhuizen en om het voorgestelde risicomodel te valideren.

Tot nu toe hebben weinig studies zich gericht op de preventie van vasoplegie. Totdat directe preventieve maatregelen beschikbaar komen, zouden patiënten mogelijk baat kunnen hebben bij indirecte maatregelen als preoperatieve hemodynamische optimalisatie, vroegtijdige en agressieve behandeling van vasoplegie en perioperatieve strategieën om de nieren te beschermen. De huidige behandelingsstrategieën van vasoplegie moeten verder worden geëvalueerd met betrekking tot de gebruikte (combinatie van) geneesmiddelen, dosering en timing. Daarnaast moeten toekomstige studies zich richten op (niet)-farmacologische preventieve strategieën. Bijvoorbeeld het gebruik van bloedzuiveringstechnieken om de effecten van de inflammatoire mediatoren die vrijkomen tijdens cardiopulmonale interventies te minimaliseren (bv. CytoSorb, CytoSorbents Corporation, New Jersey, USA).

In dit proefschrift werden de rationale en opzet van de VASOR-studie beschreven. De inclusie van fase 2 loopt en zal naar verwachting in 2022 voltooid zijn. Verder worden momenteel de bloed-, urine- en weefselmonsters geëvalueerd. De verminderde vasoresponsiviteit bij patiënten met hartfalen zou het verhoogde risico op het ontwikkelen van postoperatieve vasoplegie kunnen verklaren. Er is meer onderzoek nodig om deze veranderingen te begrijpen en om de specifieke mechanismen die hierbij betrokken zijn te identificeren. Dit zou kunnen leiden tot beter gerichte therapeutische opties of preventieve strategieën voor vasoplegie, wat zou kunnen leiden tot veiligere chirurgische ingrepen en een verbetering van het resultaat na hartfalenchirurgie.

LIST OF PUBLICATIONS

Diminished vasoresponsiveness in heart failure patients: an observational study. M.E. van Vessem, O. Papazisi, S.L.M.A. Beeres, R.B.P. de Wilde, R.R. Berendsen, E. de Jonge, L.P.H.J. Aarts, M.J. Schalij, R.J.M. Klautz, M. Palmen. Submitted

van Keeken SM, Dijkstra JW, Vreugdenhil A, **van Vessem ME**, Schep G. Medisch specialistische beweegzorg binnen de oncologie. Sport en geneeskunde. 2021;4:10-25.

Rozenberg R, Schep G, **van Vessem ME**, Dijkstra JW. Sportgeneeskunde Advies Nazorg COVID-19: herstel fysieke fitheid. Sport en geneeskunde. 2020;3:32-35.

Berendsen RR, **van Vessem ME**, Bruins M, Teppema LJSM, Aarts LPHJ, Kayser B. Electronic Nose Technology Fails to Sniff Out Acute Mountain Sickness. High Alt Med Biol. 2018;19(3):232-236.

van Vessem ME, Palmen M, Couperus LE, Stijnen T, Berendsen RR, Aarts LPHJ, de Jonge E, Klautz RJM, Schalij MJ, Beeres SLMA. Vasoplegia After Surgical Left Ventricular Restoration: 2-Year Follow-Up. Ann Thorac Surg. 2018;106(5):1371-1378.

van Vessem ME, Beeres SLMA, de Wilde RBP, de Vries R, Berendsen RR, de Jonge E, Danser AHJ, Klautz RJM, Schalij MJ, Palmen M. Vasoresponsiveness in patients with heart failure (VASOR): protocol for a prospective observational study. J Cardiothorac Surg. 2019;14(1):200.

van Vessem ME, Palmen M, Couperus LE, Mertens B, Berendsen RR, Tops LF, Verwey HF, de Jonge E, Klautz RJ, Schalij MJ, Beeres SL. Incidence and predictors of vasoplegia after heart failure surgery. Eur J Cardiothorac Surg. 2017;51(3):532-538.

van Vessem ME, Petrus AHJ, Palmen M, Braun J, Schalij MJ, Klautz RJM, Beeres SLMA. Vasoplegia After Restrictive Mitral Annuloplasty for Functional Mitral Regurgitation in Patients With Heart Failure. J Cardiothorac Vasc Anesth. 2019;33(12):3273-3280.

Couperus LE, Delgado V, Palmen M, **van Vessem ME**, Braun J, Fiocco M, Tops LF, Verwey HF, Klautz RJ, Schalij MJ, Beeres SL. Right ventricular dysfunction affects survival after surgical left ventricular restoration. J Thorac Cardiovasc Surg. 2017;153(4):845-852.

Couperus LE, Delgado V, **van Vessem ME**, Tops LF, Palmen M, Braun J, Verwey HF, Klautz RJM, Schalij MJ, Beeres SLMA. Right ventricular dysfunction after surgical left ventricular restoration: prevalence, risk factors and clinical implications. Eur J Cardiothorac Surg. 2017;52(6):1161-1167.

van Vessem ME, Kayser B, Stijnen T, Berendsen RR. Preventie van acute hoogteziekte met acetazolamide. Huisarts en wetenschap. 2013;12:610-615.

Beekman JM, Vervoort SJ, Dekkers F, **van Vessem ME**, Vendelbosch S, Brugulat-Panès A, van Loosdregt J, Braat AK, Coffer PJ. Syntenin-mediated regulation of Sox4 proteasomal degradation modulates transcriptional output. Oncogene. 2012;31(21):2668-79

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CURRICULUM VITAE

Marieke Evelien van Vessem werd geboren op 25 februari 1988 te Utrecht. In 2006 haalde zij haar VWO diploma aan het St. Bonifatiuscollege te Utrecht. Van 2006-2009 studeerde zij Biomedische Wetenschappen aan de Universiteit van Utrecht, alwaar zij in 2009 haar bachelordiploma behaalde. Van 2009-2014 studeerde zij Geneeskunde (Selective Utrecht Medical Master, SUMMA). In 2014 begon zij aan haar promotieonderzoek op de afdeling Cardiologie en Cardiothoracale Chirurgie van het Leids Universitair Medisch Centrum onder leiding van prof. dr. R.J.M. Klautz, dr. M. Palmen en dr. S.L.M.A. Beeres, waarvan de resultaten in dit proefschrift staan beschreven. Tevens volgde zij in deze periode de master Clinical Science in Mountain Medicine aan de Universiteit van Leicester (Verenigd Koninkrijk) en werkte zij als arts-assistent sportgeneeskunde niet in opleiding bij Sport Medisch Adviescentrum Midden Nederland. In 2019 startte zij met haar opleiding tot sportarts in het Máxima Medisch Centrum te Veldhoven (opleider: dr. G. Schep en M. van der Cruijsen).