



Universiteit  
Leiden  
The Netherlands

## Vasoplegia after heart failure surgery

Vessem, M.E. van

### Citation

Vessem, M. E. van. (2022, September 20). *Vasoplegia after heart failure surgery*. Retrieved from <https://hdl.handle.net/1887/3464203>

Version: Publisher's Version

License: [Licence agreement concerning inclusion of doctoral thesis in the Institutional Repository of the University of Leiden](#)

Downloaded from: <https://hdl.handle.net/1887/3464203>

**Note:** To cite this publication please use the final published version (if applicable).

# **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.<sup>1</sup> 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.<sup>2</sup>

Coronary artery disease is the most common cause of heart failure, but the etiology can be diverse.<sup>1, 3</sup> 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.<sup>1</sup> 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.<sup>1</sup> 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.<sup>1, 3, 4</sup> In patients with significant coronary artery disease, revascularization (either percutaneous or surgical) can be of added value.<sup>1</sup> In patients with a reduced left ventricular function and significant left ventricle desynchrony, cardiac resynchronization therapy improves symptoms and reduces morbidity and mortality.<sup>1</sup> 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.<sup>1</sup> For patients with arrhythmias, ablation can be considered.<sup>1</sup> 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.<sup>1</sup> 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.<sup>1</sup> 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.<sup>4</sup>

### **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.<sup>5</sup> 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.<sup>5</sup> 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.<sup>5, 6</sup> 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,<sup>5</sup> but only when the component of functional mitral regurgitation is severe and the left ventricle not too dilated.<sup>7</sup>

### **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.<sup>8</sup> The most frequently used procedure has been described by Vincent Dor et al.<sup>9</sup> 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<sup>2</sup> 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.<sup>8, 10</sup> In contrast, the results of a large multicenter randomized controlled STICH trial failed to demonstrate a significant improvement in survival after surgical ventricular restoration.<sup>11</sup> 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.<sup>12</sup> 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<sup>13</sup> and a postoperative end-systolic volume index greater than 70 mL/m<sup>2</sup><sup>14</sup> 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.<sup>15</sup> 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.<sup>16</sup>

### **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.<sup>1</sup> 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.<sup>1</sup> 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. Haec 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.<sup>17</sup> This year our department will implant the 100<sup>th</sup> 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,<sup>1, 3, 4</sup> 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,<sup>18</sup> 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.<sup>19</sup> 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 arterial 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.<sup>20, 21</sup> The most common cause of vasoplegia is sepsis, but it is also seen after major non-cardiac surgery, burns, multiple trauma and pancreatitis.<sup>22</sup> The used definition for vasoplegia after cardiac surgery varies widely between studies.<sup>23</sup> 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%.<sup>24, 25</sup> On pump cardiac surgery<sup>26</sup> and a reduced left ventricular ejection fraction<sup>27, 28</sup> 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.<sup>23</sup> 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%.<sup>20, 25, 29-34</sup> 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,<sup>25, 30-40</sup> higher weight<sup>20, 25, 29</sup> and longer cardiopulmonary bypass times<sup>29, 31, 32, 34</sup> 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<sup>25, 29, 31</sup>.

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

Study	MAP (mmHg)	SVR (dynes/s/cm <sup>2</sup> )	CI (L/min/m <sup>2</sup> )	Vasopressors	LVEF (%)	Serum bicarbonate (mEq/l)	Timing
Chemma-lakuzhy 2001 <sup>25</sup>		≤800				≤20	A single reading postoperative
Byrne 2004 <sup>20</sup>		≤800				≤20	A single reading, within 4 days postoperative
Patarroyo 2012 <sup>29</sup>		<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 <sup>31</sup>			≥2.0	Vasopressin; norepinephrine; or epinephrine (>5 µg/min) to maintain MAP >70 mmHg	≥55%		For >24 hours, within 48 hours postoperative
Chan 2018 <sup>30</sup>			>2.0	Vasopressin; norepinephrine; or epinephrine (>5 µg/min) to maintain MAP >70 mmHg	≥55%		For >24 hours, within 48 hours postoperative
Tecson 2018 <sup>32</sup>			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 <sup>33</sup>	≤50	≤800	>2.5	Norepinephrine ≥200 ng·kg <sup>-1</sup> ·min <sup>-1</sup> ; epinephrine ≥200 ng·kg <sup>-1</sup> ·min <sup>-1</sup> ; dopamine ≥30 µg·kg <sup>-1</sup> ·min <sup>-1</sup> ; phenylephrine ≥2 µg·kg <sup>-1</sup> ·min <sup>-1</sup> ; or vasopressin ≥0.08 U·min <sup>-1</sup>			For ≥3 hours, within 48 hours postoperative
Asleh 2019 <sup>34</sup>		<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 <sup>25</sup>	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 <sup>20</sup>	Orthotopic heart transplantation (N=147)	19% (N=28)	Preoperative Univariate: BSA Multivariate: intravenous heparin; no inotropics.	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 <sup>29</sup>	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 2017 <sup>31</sup>	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. Preoperative univariate: prior cardiotoracic surgery; creatinine. Intraoperative univariate: CPB time.	Higher: reoperation for bleeding; mechanical ventilation time; ICU and hospital stay. Higher: vasopressor use; intubation time; ICU and hospital stay. No difference: 30-day survival.	After 1 year: Higher: CVVH; hemodialysis. No difference: non-fatal major adverse cardiac events; cardiac allograft vasculopathy; infection; survival; rejection. No difference: rejection; renal replacement therapy; liver cirrhosis; infection; survival at 1 year. No difference: 1 year mortality.
Chan 2018 <sup>30</sup>	Orthotopic heart transplantation (N=244)	34.8% (N=85) Mild: 74.1% (N=63) Moderate/severe: 25.9% (N=22)	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.	
Tecson 2018 <sup>32</sup>	Left ventricular assist device implantation (N=252)	49.2% (N=124) Mild: 26.6% (N=67) Moderate/severe: 22.6% (N=57)	Preoperative univariate: dopamine use; VIS; bilirubin; creatinine.	Higher: VIS; re sternotomy; 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.
De Waal 2018 <sup>33</sup>	Short-term (N=19) and long-term (N=99) continuous flow left ventricular assist device implantation (total N=118)	33.1% (N=39) Short-term: 52.6% (N=10) Long-term: 29.3% (N=29)			

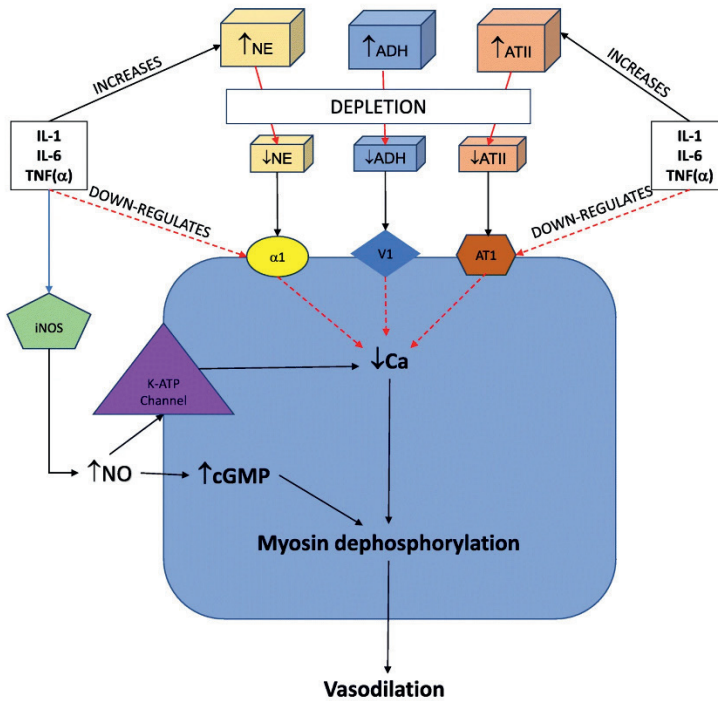
Asleh 2019 <sup>34</sup>	Heart transplantation after bridging with LVAD (N=94)	46.8% (N=44)	<p>Preoperative</p> <p>Univariate: age; duration of LVAD support; Charlson comorbidity index; creatinine.</p> <p>Multivariate: age; duration of LVAD support; creatinine.</p> <p>Intraoperative</p> <p>Univariate: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

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.<sup>19</sup> 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).<sup>19</sup> 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.<sup>35</sup> 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.<sup>19,36</sup> Furthermore, the chronic endogenous adrenergic stimulation in heart failure patients seems to result in downregulation and/or desensitization of vascular  $\alpha$ 1-adrenoreceptors which alternates the responsiveness of the vascular system to vasoconstrictors.<sup>37</sup> 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 (TNF $\alpha$ ) can lead to: 1) downregulation of alpha-1 adrenergic receptor ( $\alpha$ 1) 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), antidiuretic 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.<sup>19</sup>



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

Drugs		Mechanism	Hemodynamic effects
Beta-blockers		Receptor antagonists that block $\beta_1$ (selective) $\beta_1$ and $\beta_2$ (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 blood 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 output and 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).<sup>19</sup> Norepinephrine is considered the first-line agent for treatment of vasoplegia.<sup>38</sup> Second-line agents include other catecholamines or vasopressin.<sup>19</sup> 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<sup>29-31, 34</sup> and received more frequently extracorporeal membrane oxygenation,<sup>20, 29</sup> reoperation for bleeding<sup>20, 29, 31</sup> and resternotomy<sup>33</sup>. Furthermore, respiratory failure<sup>32</sup> and major bleeding<sup>32</sup> were more often seen in vasoplegic patients. Vasoplegia seemed not to effect the rate of left ventricular assist device<sup>20</sup> and right ventricular assist device<sup>20, 33</sup> implantation, pneumonia,<sup>20, 33</sup> gastrointestinal bleed,<sup>32, 33</sup> pump thrombosis<sup>32, 33</sup> and stroke<sup>20, 32, 33</sup> in the early post-operative period. Results on the occurrence of mediastinitis,<sup>29, 33</sup> right ventricular failure,<sup>32-34</sup> IABP use,<sup>20, 29</sup> dialysis,<sup>20, 33</sup> and open chest treatment<sup>20, 29, 33</sup> were inconclusive. Vasoplegic patients were admitted longer to the intensive care unit<sup>20, 29-31, 33, 34</sup> and the total hospital stay was prolonged as well.<sup>29-34</sup> Most studies showed a higher 30-day mortality rate in vasoplegic patients<sup>25, 29, 32, 33</sup> and a higher hospital mortality<sup>20</sup>. However, two studies did not find a difference in 30-day mortality.<sup>30, 34</sup>

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,<sup>30-32</sup> whereas two research groups found a higher 1-year mortality rate in vasoplegic patients<sup>33, 34</sup>. After a mean follow-up of 4 years, a higher all-cause mortality was found in vasoplegic patients.<sup>34</sup> Asleh et al. showed that vasoplegic patients had a lower eGFR after 1 year, but the results on renal replacement therapy were inconclusive.<sup>30, 31</sup> Vasoplegia had no effect on the risk of rejection,<sup>30, 31, 34</sup> treated infection,<sup>30, 31, 34</sup> non-fatal major adverse cardiac events,<sup>31</sup> cardiac allograft vasculopathy,<sup>31</sup> liver cirrhosis<sup>30</sup> and allograft left ventricular ejection fraction<sup>34</sup>. 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, Gelijs 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, Palmén M, van Vessel 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 cardi thoracic 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.