



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 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 $\mu\text{g/kg/min}$ 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) $\leq 35\%$, 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 $\leq 35\%$ 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 perioperative 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.