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# Vasoplegia after heart failure surgery

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

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

# CHAPTER 4

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

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Ann Thorac Surg. 2018;106(5):1371-1378

## 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 |

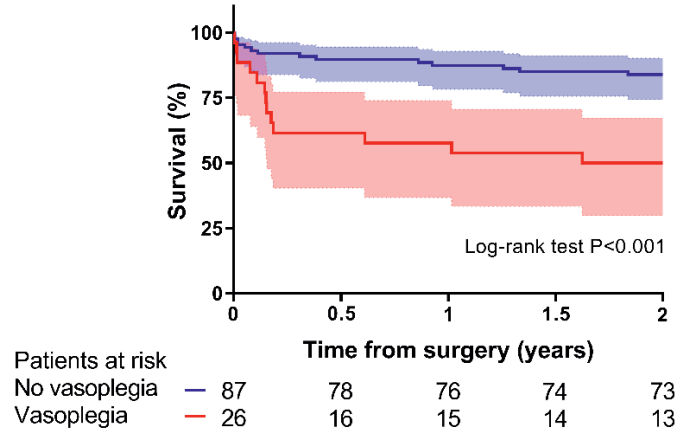
**112, **76, ***77 patients. Continuous data are presented as mean ± SD or median (IQR). Categorical data are presented as %. CVA: cerebrovascular accident; ECMO: extracorporeal membrane oxygenation; IABP: intra-aortic balloon pump; ICU: intensive care unit; IQR: interquartile range; TAPSE: tricuspid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

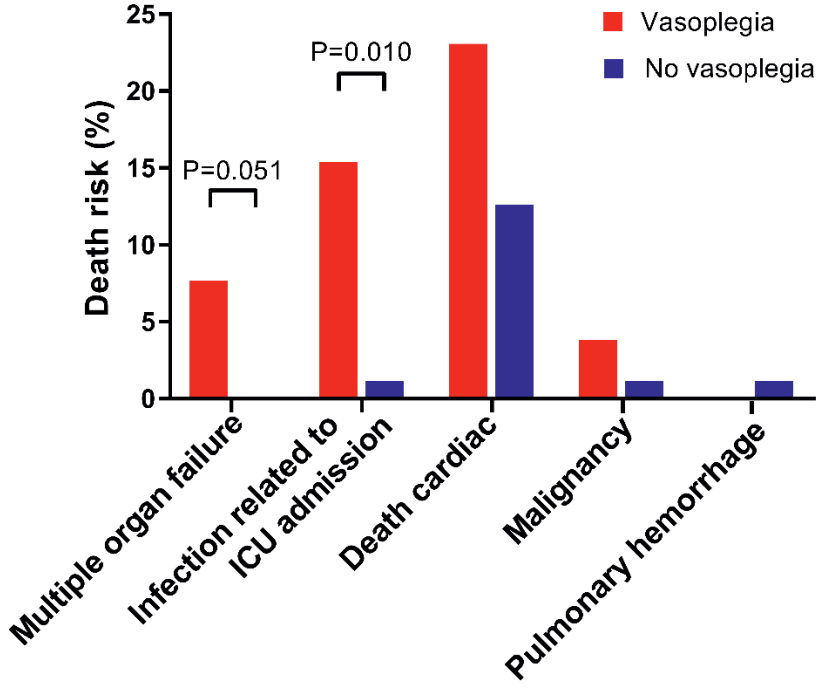


**Table 3.** Crude risk of death preoperatively.

| | 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**

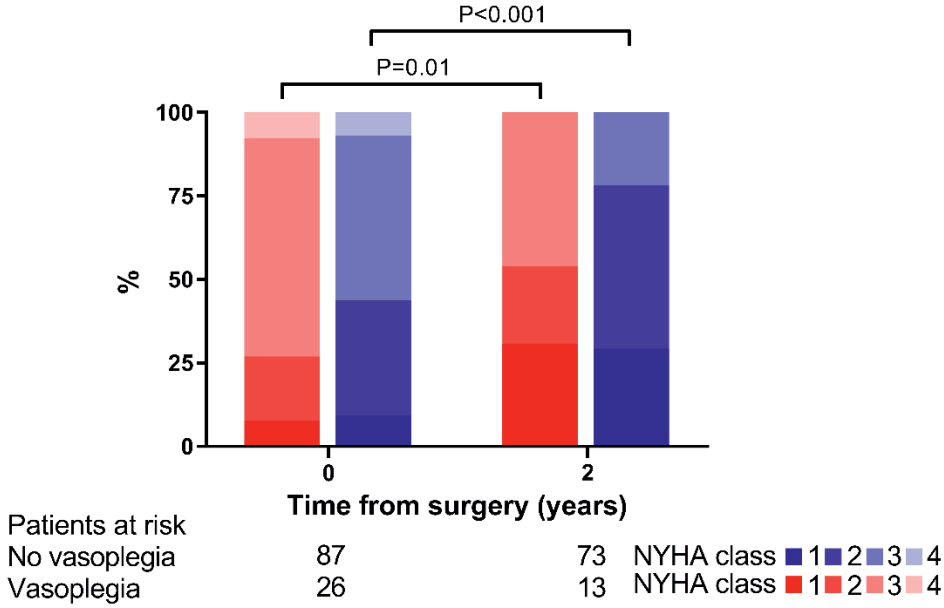
Clinical and echocardiographic findings at baseline and 2-year follow-up are depicted in Figure 3. At 2-year follow-up, there was an improvement in NYHA class and LVEF, in both vasoplegic and non-vasoplegic patients. Of importance, at 2-year follow-up, NYHA class (*P*=0.319) and LVEF (*P*=0.444) were 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.**

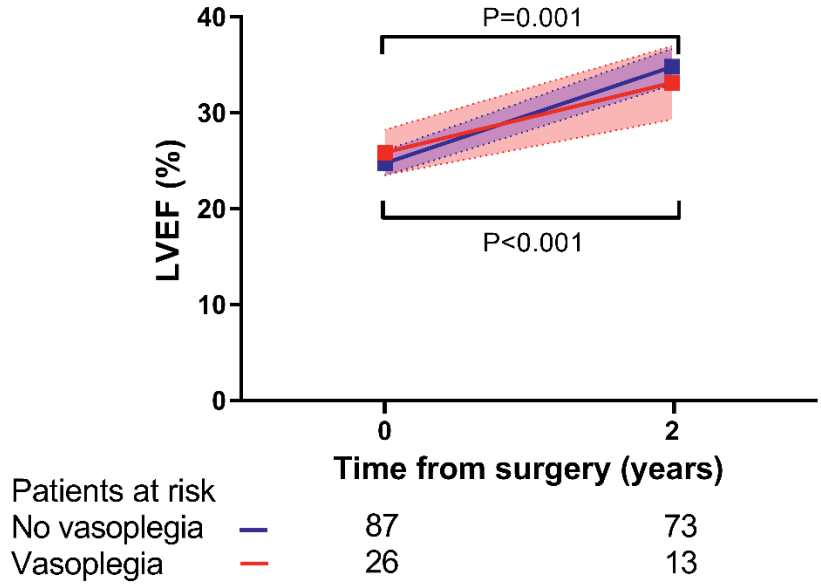
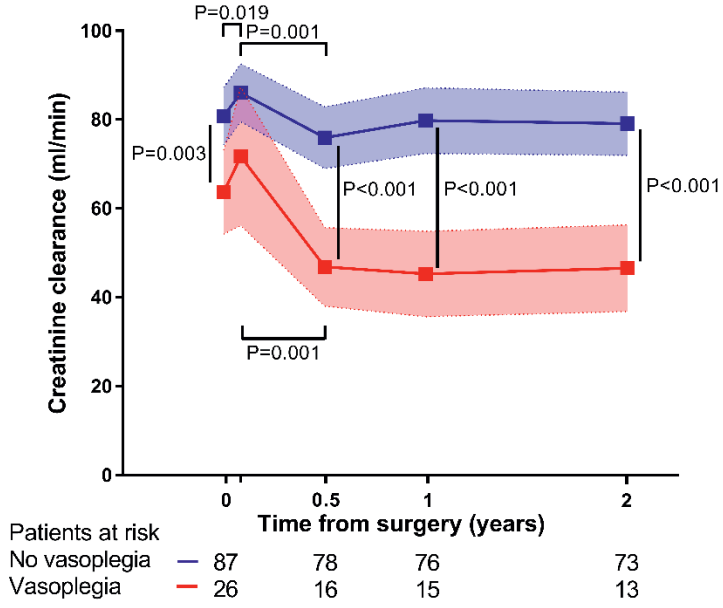
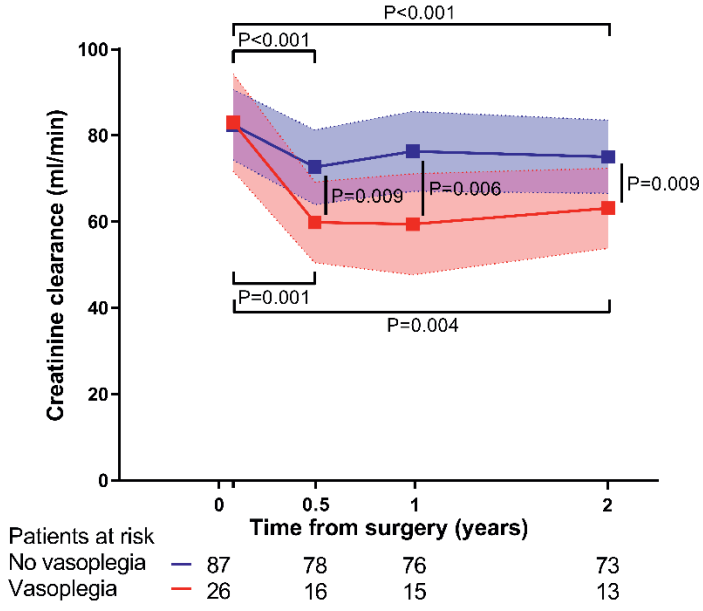


**Figure 4.** Follow up of creatinine clearance (A) and creatinine clearance, corrected for baseline creatinine clearance (B) for vasoplegic (red) and non-vasoplegic patients (blue) with 95% confidence intervals.

**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.

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