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 3

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

M.E van Vessem*, A.H.J. Petrus*, M. Palmen, J. Braun, M.J. Schalij, R.J.M. Klautz, S.L.M.A. Beeres

* Both authors contributed equally to this publication

J Cardiothorac Vasc Anesth. 2019;33(12):3273-3280

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.

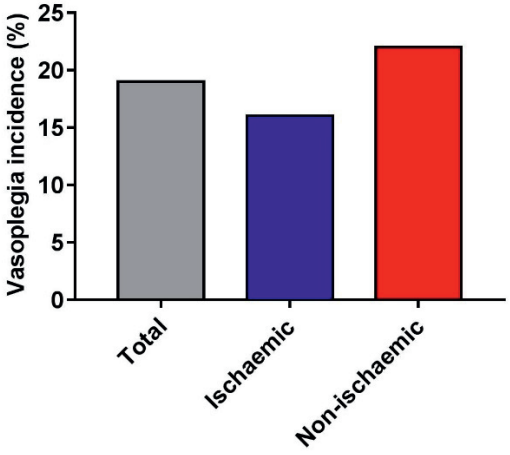
	Overall (N=122)	RMA non-ischemic (N=64, 52%)	RMA ischemic (N=58, 48%)	P-value
Age (years)	65±9	62±9	69±9	**<0.001**
Male sex	66%	61%	72%	0.249
Body mass index (kg/m^2)	26±4	26±3	27±4	0.093
Diabetes	28%	27%	29%	0.840
Prior CVA or TIA	10%	11%	9%	0.766
Prior hypertension	38%	30%	47%	0.063
LVEF (%)	27±6	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

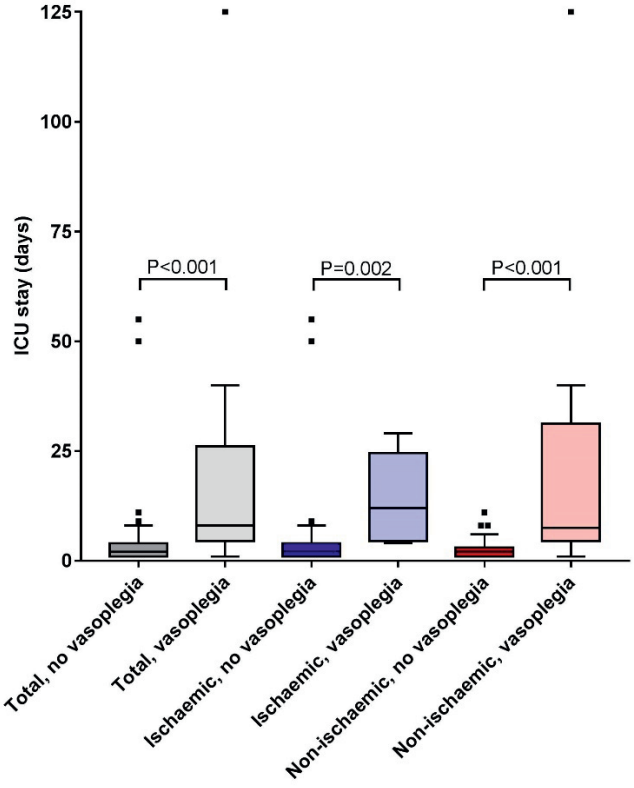
The incidence of vasoplegia in heart failure patients with functional MR was 19% (Figure 1). The incidence of vasoplegia was not significantly different between ischemic and non-ischemic MR patients (16% versus 22%, P=0.488).

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.



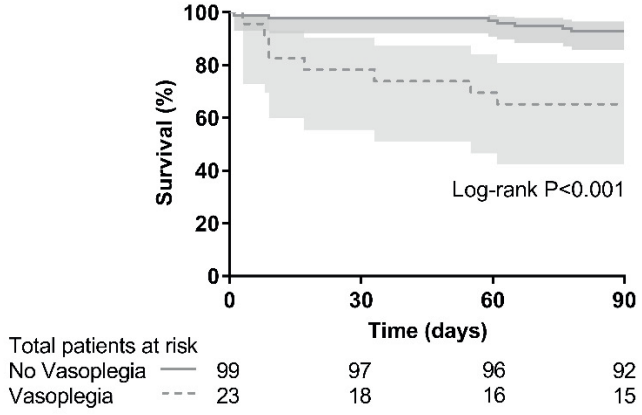
Predictors of vasoplegia

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).

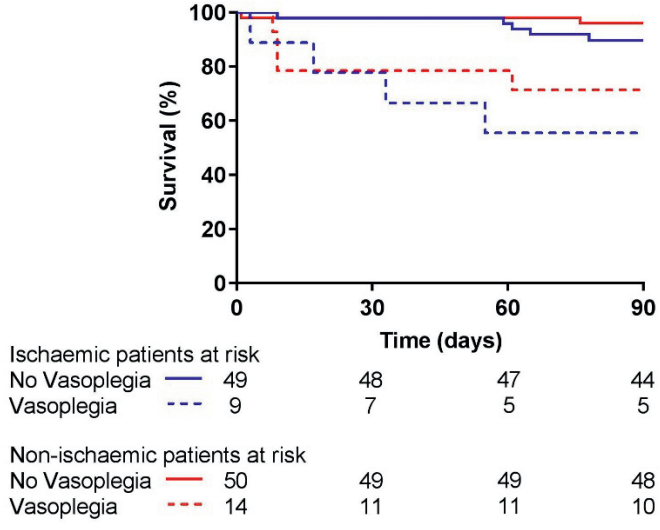


Table 2. Univariable analysis for vasoplegia.

	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.