Vasoplegia after heart failure surgery

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CHAPTER 2

Incidence and predictors of vasoplegia after heart failure surgery

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Abstract

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

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

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

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

Introduction

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

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

Materials and methods

Study design

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

Endpoints and data collection

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

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

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

Surgical procedures

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

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

Statistical analysis

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

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

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

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

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

Results

Study population

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

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

Table 1. Characteristics of the study population.

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

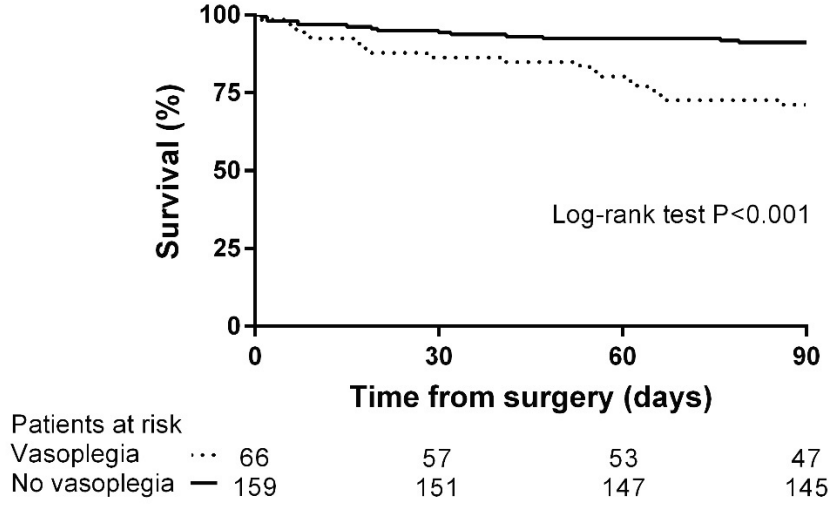
** Data based on 159 patients. ** Data based on 156 patients. Continuous data are presented as mean ± SD or median (IQR). Categorical data are presented as numbers (%). ACE: Angiotensin-converting enzyme; ARB: angiotensin receptor blocker; CVA: cerebrovascular accident; IQR: interquartile range; LVAD: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

Vasoplegia

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

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

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



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

Preoperative factors associated with vasoplegia

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

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

Table 2. Univariable regression analysis.

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

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

Table 3. Multivariable regression analyses.

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

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

Derivation of risk model

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

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

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

Figure 2. Vasoplegia risk score calculator.

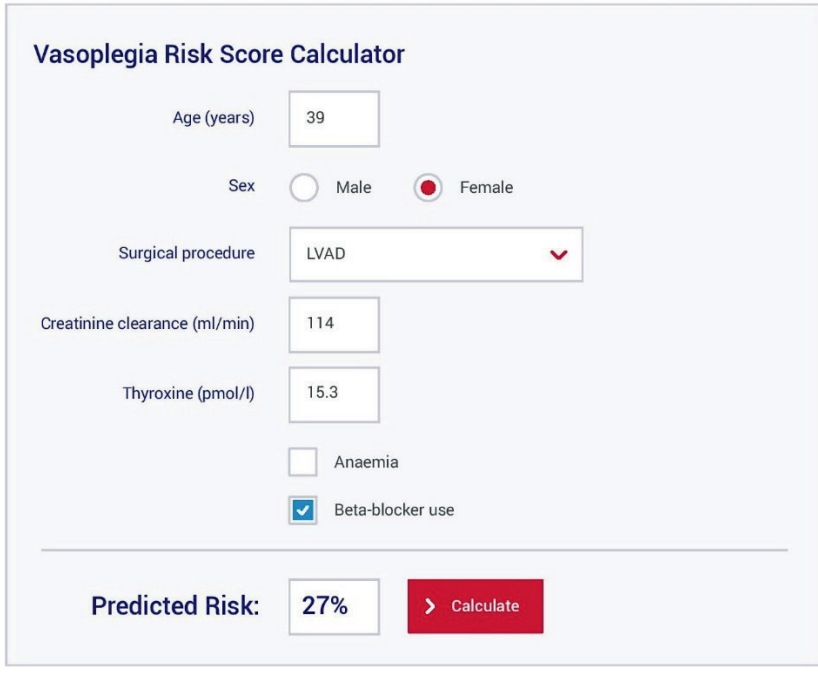
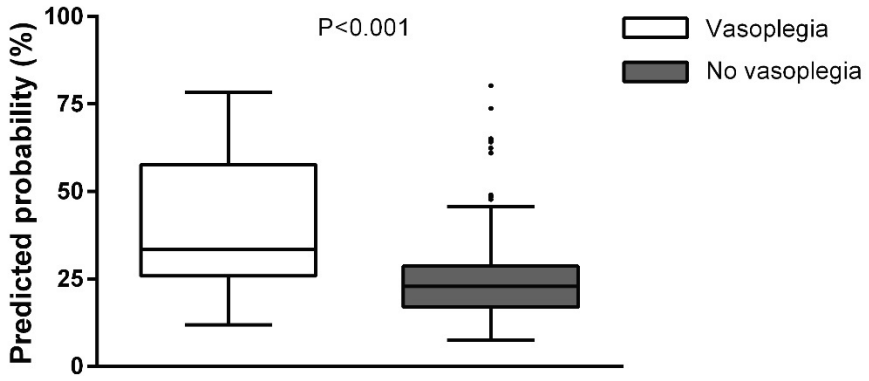


Figure 3. Predicted probability for patients with vasoplegia and without vasoplegia.



Discussion

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

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

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

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

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

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

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

Limitations

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

Clinical implications

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

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

Conclusion

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

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