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Vasoplegia after heart failure surgery

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CHAPTER 6

Diminished vasoresponsiveness in heart failure patients: an observational study

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Submitted

Abstract

Objectives: Heart failure patients undergoing cardiac surgery have a higher risk of postoperative vasoplegia. We hypothesize that they are more susceptible to vasoplegia due to a diminished vasoresponsiveness. The aim of this study is to objectify this altered vasoresponsiveness perioperatively.

Design: Prospective, observational study.

Setting: Leiden University Medical Center, Leiden, The Netherlands.

Patients: Patients with and without heart failure undergoing cardiac surgery on cardiopulmonary bypass (CPB) were enrolled.

Interventions: None.

Measurements and Results: The vascular reactivity in response to a vasoconstrictor (phenylephrine) and a vasodilator (nitroglycerin) was assessed perioperatively by measuring changes in systemic vascular resistance (SVR). 36 patients were included. 17% of the heart failure patients developed vasoplegia, compared to 6% of controls (P=0.603). At baseline, heart failure patients had an increase of 26% (16-35%) in SVR in response to phenylephrine, compared to 51% (38-64%) in control patients (P=0.002). Delta SVR remained significantly lower in heart failure patients perioperatively The same pattern was found when excluding patients that received norepinephrine. There was no difference in the dosage of nitroglycerin needed to achieve a drop of at least 10% in mean arterial pressure. Delta SVR after CPB is significantly associated with the amount of norepinephrine received during the first postoperative day (P=0.001).

Conclusions: We found that heart failure patients have a diminished response to a vasoconstrictor at baseline compared to control patients. This reduced vasoresponsiveness persists throughout the perioperative period, independent of used norepinephrine. Furthermore, we showed that vasoresponsiveness intra-operatively is associated with the amount of norepinephrine received postoperatively.

Registration: The Netherlands Trial Register, NTR5647. Registered 26 January 2016.
http://www.trialregister.nl/trialreg/admin/rctview.asp?TC=5647

Introduction

When optimal medical therapy and cardiac interventions fail to improve a heart failure (HF) patient's condition, HF surgery may be a valid option.[1-3] Unfortunately, surgical intervention in this vulnerable patient population is associated with increased risk of vasoplegia with a reported incidence of 11-31%.[4-9] Vasoplegia is characterized by hypotension and the excessive need of vasopressors, despite a normal or even high cardiac output (CO) and is shown to be associated with increased morbidity and mortality.[7]

The mechanism responsible for vasoplegia remains to be unraveled. It is thought to be multifactorial in origin, including both activation of vasodilator pathways and inactivation of vasoconstrictor pathways, resulting in resistance to vasopressors. We postulate that the pathophysiological characteristics of HF patients make them more prone to develop postoperative vasoplegia.[10] In particular, the fragile balance of vasoconstrictor and vasodilatory abilities of their vascular system could easily be disturbed by the systemic inflammatory response reaction caused by cardiopulmonary bypass (CPB) and surgical trauma.[11] This results in an impaired responsiveness to exogenous vasopressors and leads to a downward spiral of end-organ hypoperfusion resulting in multiple-organ failure.

Understanding the mechanisms leading to vasoplegia in HF patients could contribute to the development of preventive measures and treatment strategies, thereby reducing morbidity and mortality in this vulnerable patient group. The aim of the current study is to objectify the altered vasoresponsiveness in HF patients undergoing cardiac surgery.

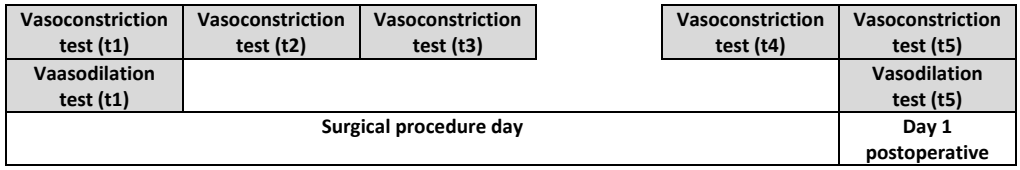
Materials and methods

A more extensive description of the study methods was recently published online.[10]

Study design

VASOR is a prospective, observational study, conducted at Leiden University Medical Center. Patients with and without HF undergoing cardiac surgery on CPB were compared. The study protocol was executed intraoperatively and on the first postoperative day (Figure 1). The study is registered at The Netherlands Trial Register (NTR5647). The Medical Ethical Committee of Leiden The Hague Delft approved the protocol (P14.298) which was performed in line with the Declaration of Helsinki.

Figure 1. Flowchart study.



Study population

Patients scheduled for elective or urgent cardiac surgery with CPB were screened for eligibility. In order to yield comparable study groups, patients were selected according to the expected CPB duration and level of surgical trauma. Patients were assigned to either the HF or the non-HF group. HF was defined according to the European Society of Cardiology guidelines.[12] Inclusion criteria for the HF group were: 1) diagnosed with HF and 2) left ventricular ejection fraction (LVEF) ≤ 35%. Patients that were included in the non-HF group were 1) not diagnosed with HF and 2) had a LVEF > 50%. Exclusion criteria were: 1) age <18 years; 2) incapacitated adults; 3) emergency operation; 5) patients in preoperative need of moderate or high dosages of intravenous inotropic support (>4 gamma dobutamine or dopamine), vasopression and/or mechanical support; 6) patients with aortic valve insufficiency > grade 1; 7) patients using a daily dosage of nitrates and 8) α-adrenergic blockers or 9) phosphodiesterase type 5 inhibitors; 10) patients with endocarditis; and 11) patients with acute heart failure. Factors named in exclusion criteria 5-11 would influence the primary outcome. All patients gave written informed consent for study participation.

Surgical procedures

All patients undergoing cardiac surgery with comparable durations of CPB and similar level of surgical trauma were eligible. The indication and timing for surgery was assessed by the multidisciplinary Heart Team. In the HF group patients underwent mitral valve plasty (mainly treatment of functional mitral regurgitation with the use of restrictive mitral annuloplasty),[9] surgical left ventricular restoration (Dor technique),[3] left ventricular assist device (HeartWare Inc, Framingham, MA) implantation[1] and aorta surgery. Tricuspid valve annuloplasty, aortic valve replacement and coronary revascularization were performed concomitant if indicated. In the control group, mainly patients undergoing mitral valve plasty were included. Tricuspid valve annuloplasty and coronary revascularization were performed concomitant if indicated. All surgeries were performed via conventional midline sternotomy using CPB and (when cardioplegic arrest was indicated) with intermittent antegrade warm blood cardioplegia. Patients did not receive angiotensin-

converting-enzyme inhibitors, angiotensin receptor blockers and diuretics on the day of surgery.

Anesthetics and hemodynamics

All patients received anesthesia according to a standardized protocol, using target-controlled infusion of propofol and remifentanil or sufentanil. Cannulation of the radial artery was performed in all patients before induction for invasive hemodynamic blood pressure monitoring. A central venous catheter was inserted in the internal jugular vein and a flow-directed balloon-tipped pulmonary artery catheter was introduced after induction. PulseCO™ software (LiDCO, London, UK) was used for measurement of cardiac output and systemic vascular resistance. The cardiac output derived from the Vigilance-II monitor (Edwards LifeSciences, Irvine, CA, USA), connected to the pulmonary artery catheter, was used to calibrate the cardiac output as measured by PulseCO. Software of the LiDCOplus (LiDCOviewSE, LiDCO Ltd, London, UK) was used for off-line analysis of the vasoreactivity tests.

Intra- and 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 > 65 mmHg and adequate end-organ perfusion. When a norepinephrine dosage >0,5 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. In this situation, terlipressin was reduced first.

Patients did not receive angiotensin-converting-enzyme (ACE) inhibitors, angiotensin receptor blockers and diuretics on the day of surgery.

Study outcomes

The objective of VASOR study was to determine the peri-operative vasoresponsiveness to an exogenous vasoconstrictor in patients with and without HF. We hypothesized that HF patients would demonstrate a reduced response. The primary end-point was the change in systemic vascular resistance (SVR) after phenylephrine administration at baseline. Secondary end points included: 1) change in SVR after phenylephrine administration intra- and postoperatively; 2) dosage nitroglycerin needed for a 10% decrease in mean arterial pressure (MAP) pre- and postoperatively; 3) correlation between change in SVR after phenylephrine administration pre- and intraoperatively and the amount of norepinephrine used postoperatively; 4) the occurrence of vasoplegia (defined as the continuous need of

vasopressors (norepinephrine ≥ 0.2 μg/kg/min for at least 12 consecutive hours or terlipressin) in combination with a cardiac index ≥2,2 l/min/m2 for at least 12 consecutive hours, starting within the first 3 days postoperatively).

Vascular reactivity test

The vasoreactivity in response to a vasoconstrictor (phenylephrine, an α_1-adrenoreceptor agonist) and vasodilator (nitroglycerin) was assessed in all patients. During the vasoconstriction test, a bolus of 2 μg/kg phenylephrine was administered intravenously and the effect on SVR was registered. The vasoconstrictor test was performed 5 times: t1) at baseline (before induction); t2) before induction, after start of cardiotropic drugs and/or vasopressors (e.g. dobutamine, milrinone, norepinephrine) when necessary; t3) after induction; t4) 15 minutes after cessation of CPB; and t5) on the first postoperative day.

For the vasodilation test a bolus of 10 μg nitroglycerin was administered using peripheral intravenous access. The effect on MAP was registered. Dosages were increased to 20, 40 and 60 μg until a drop of 10% in MAP was reached. The vasodilation test was performed twice: t1) at baseline (before induction) and t5) 1 day postoperatively.

Both the vasoconstriction and the vasodilation test were only performed when the patient's clinical condition allowed an increase or decrease in MAP.

Statistical analysis

The study was designed to achieve 90% power to detect a difference in means of 400 dyn·s/cm^5 in SVR assuming that the common standard deviation (SD) was 350 dyn·s/cm^5 using a student t-test with a 0.05 two-sided significance level.[13]

Baseline patient characteristics were described using summary statistics. Continuous variables were reported as mean ± SD or as median with interquartile range. Differences between groups (HF versus non-HF) were compared using an unpaired Student's t-test, or Mann-Whitney U-test. Categorical data were reported as numbers and percentages. Fisher's exact test was used to compare differences between groups. Pairwise deletion was used to handle missing data.

To explore the effects of HF on vasoreactivity, generalized estimating equations (GEE) was performed, utilizing an independent working correlation structure. The analysis was

repeated including only patients that did not receive norepinephrine to exclude its effect on vasoreactivity.

Univariable linear regression analysis was used to assess whether vasoreactivity could predict the amount of norepinephrine used in the first 24 hours postoperatively. Subsequently, this analysis was repeated in a multivariable linear regression whilst adjusting for HF and norepinephrine use.

The significance level was set at $P < 0.05$. Statistical analysis was performed using SPSS (version 25.0).

Results

Study population

Among 1864 adult patients who underwent cardiac surgery in our center during the study period (2016-2018), 347 patients were eligible for inclusion. Of these patients 36 patients were enrolled (Figure 2). Overall, median age was 67 (IQR 61-71) years and 78% were male. At baseline, HF and control patients were comparable with respect to age, sex and co-morbidities. HF patients had a significantly higher Body Mass Index (27±4 vs 24±3, P=0.024) and, as expected, a higher EuroSCORE II (9.76 (IQR 6.59-15.49) vs 1.45 (IQR 1.07-2.71), P<0.001). Furthermore, the use of betablockers (89% vs 33%, P=0.002) and diuretics (89% vs 28%, <0.001) was more prevalent in the HF group (Table 1).

In both groups CPB times, aortic cross clamp times and procedural durations (Table 2) were comparable. HF patients were more likely to receive inotropic support intra- and postoperatively, compared to control patients. During the first 24 hours postoperatively, the MAP was significantly lower in HF patients (72±8 vs 77±5, P=0.037), despite more inotropic and vasopressor support (Table 3). Postoperative vasoplegia occurred in 17% of the HF patients as compared to 6% in the control group (P=0.603).

Figure 2. Patient selection flow diagram.

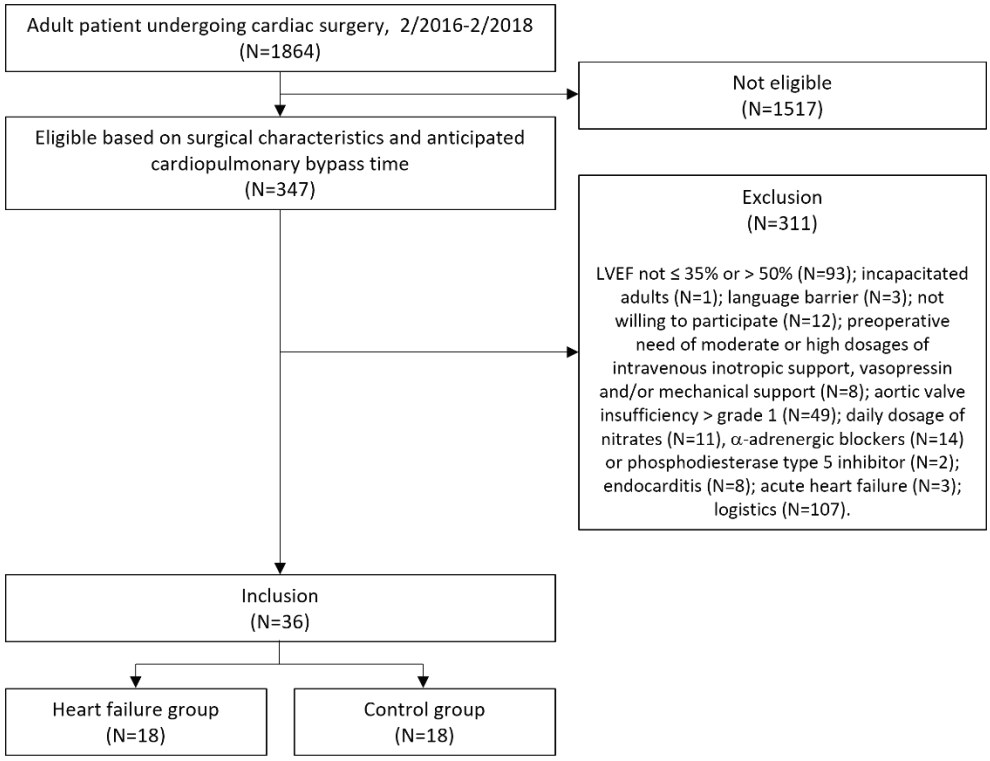


Table 1. Baseline characteristics.

	Heart failure (N=18)	Control (N=18)	P-value
Age (years)	68 (62-71)	64 (59-69)	0.279
Male sex (%)	67	89	0.228
Body mass index (kg/m2)	27±4	24±3	**0.024**
Diabetes (%)	28	6	0.177
Prior hypertension (%)	39	17	0.264
Pulmonary hypertension (%)	28	11	0.402
Previous cardiac surgery (%)	22	6	0.338
Hemoglobin (mmol/l)	8.5±1.0	9.1±1.0	0.093
Creatinine clearance (ml/min/1,73m2)	67±20	78±16	0.090
EuroSCORE II (%)	9.76 (6.59-15.49)	1.45 (1.07-2.71)	**<0.001**
Left ventricular ejection fraction (%)			
Normal, >60%	0	94	**<0.001**
Mildly abnormal, 45-60%	0	6	
Moderately abnormal, 30-45%	11	0	
Poor, <30%	89	0	
Medication use			
Betablocker (%)	89	33	**0.002**
ACE-inhibitor/ARB (%)	61	50	0.738
Antiarrhythmics (%)	28	11	0.402
MRA (%)	44	11	0.060
Diuretics (%)	89	28	**<0.001**
Inotropes (%)	11	0	0.486

Numbers are mean±SD, median (IQR) or %. ACE: Angiotensin-converting-enzyme; ARB: angiotensin receptor blockers; MRA: Mineralocorticoid receptor antagonists

Table 2 Intraoperative characteristics

	Heart failure (N=18)	Control (N=18)	P-value
Procedure type			
Mitral valve plasty (%)	56	94	**0.018**
Tricuspid valve plasty (%)	33	50	0.500
Surgical left ventricular restoration (%)	39	0	**0.008**
Left ventricular assist device implantation (%)	22	0	0.104
Coronary artery bypass grafting (%)	39	6	**0.041**
Aortic valve replacement (%)	17	0	0.229
Aorta surgery (%)	11	6	1.000
Medication use			
Epinephrine (%)	28	0	**0.045**
Norepinephrine (%)	94	44	**0.003**
Dobutamine (%)	83	33	**0.006**
Milrinone (%)	94	17	**<0.001**
Procedure characteristics			
Hypothermia during CPB (°C)	32 (32-37)	32 (30-33)	0.265
CPB time (min)	174 (120-214)	143 (103-225)	0.696
Cross clamp time (min)	135±37	132±52	0.854
Procedure time (min)	300 (254-388)	243 (188-326)	0.064

Numbers are mean±SD, median (IQR) or %. CPB: cardiopulmonary bypass.

Table 3 Postoperative characteristics

	Heart failure (N=18)	Control (N=18)	P-value
SVR 0-24 hours	1132 (929-1283)	1189 (952-1472)	0.377
MAP 0-24 hours	72±8	77±5	0.037
CI 0-24 hours	2.3±0.4	2.5±0.6	0.217
Medication use			
Epinephrine (%)	28	0	**0.045**
Norepinephrine (%)	94	56	**0.018**
Dobutamine (%)	94	28	**<0.001**
Milrinone (%)	94	17	**<0.001**
Terlipressin (%)	17	0	0.229
Max dose Nor on ICU (ug/kg/min)	0.18 (0.08-0.6)	0.03 (0-0.13)	**0.002**
Total duration Nor on ICU (min)	1281 (215-1615)	177 (0-882)	**0.009**
Total Nor on ICU (ug/kg)	186.51 (14.77-345.03)	3.61 (0-41.60)	**0.003**
Nor on ICU 0-24 hours (ug/kg)	169.80 (14.77-318.97)	3.61 (0-41.60)	**0.003**
Vasoplegia (%)	17	6	0.603
ICU time (days)	2 (1-3)	1 (1-2)	0.133

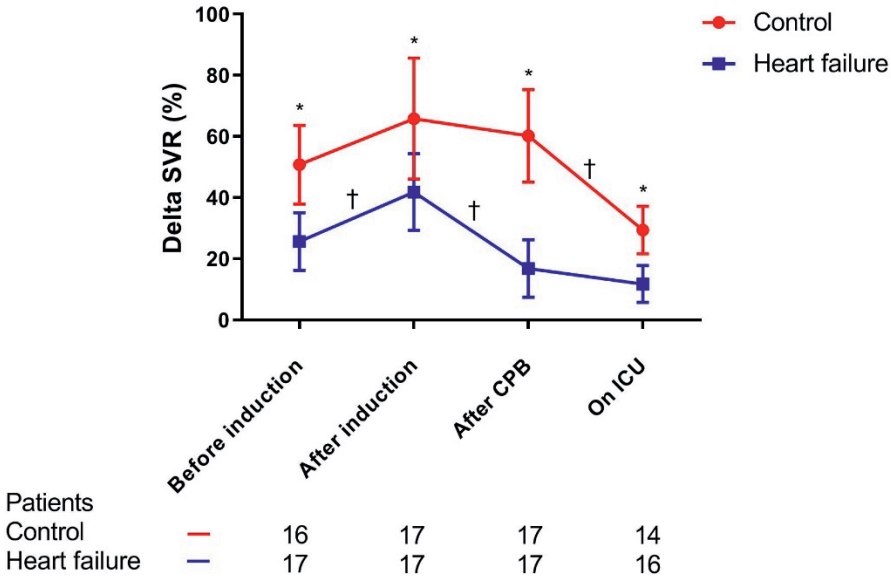
Numbers are mean±SD, median (IQR) or %. CI: cardiac index; ICU: Intensive Care Unit; MAP: mean arterial pressure; Nor: norepinephrine; SVR: systemic vascular resistance.

Vasoresponsiveness at baseline

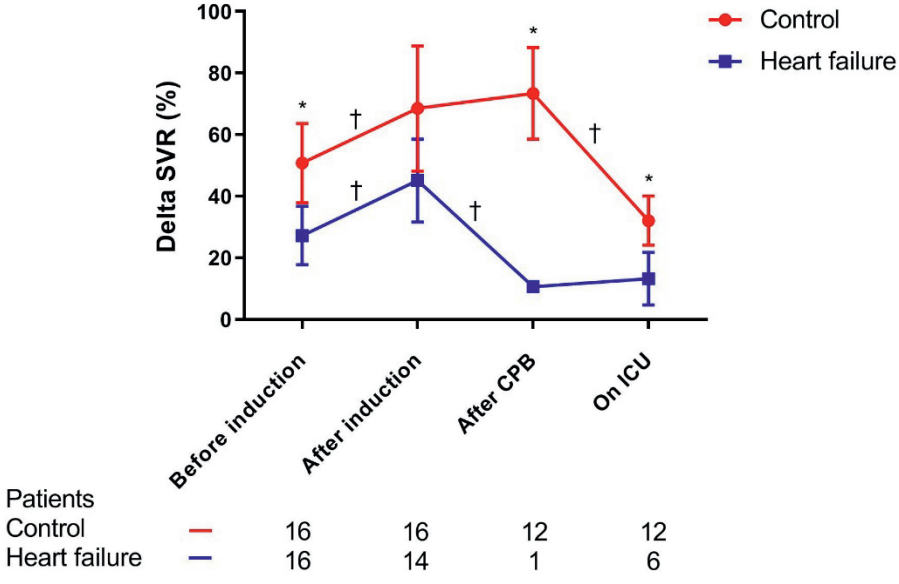
The increase in SVR in response to phenylephrine at baseline was significantly diminished in HF patients as compared to controls (Figure 3A). On average, the increase in SVR in HF patients was 26% (95%CI 16-35) compared to 51% (95%CI 38-64) in controls (P=0.002). The change in cardiac index and MAP after administration of a standardized dosage of phenylephrine at baseline are depicted in Figure 4. Of note, in none of the patients was it necessary to start cardiotropic drugs and/or vasopressors before induction, therefore vasoconstriction test 2 (t2) was not performed.

Figure 3. Vasoconstriction test

A. Total population.



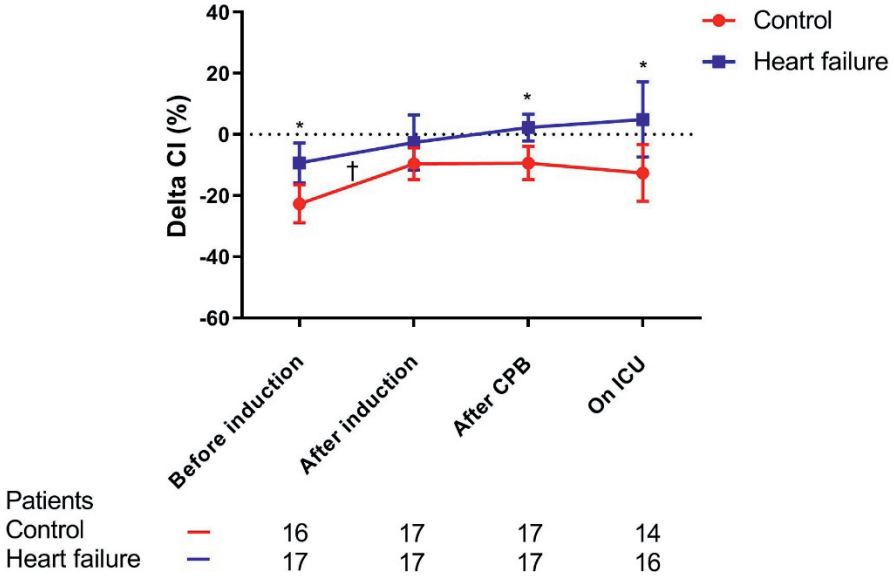
B. Patients not receiving norepinephrine.



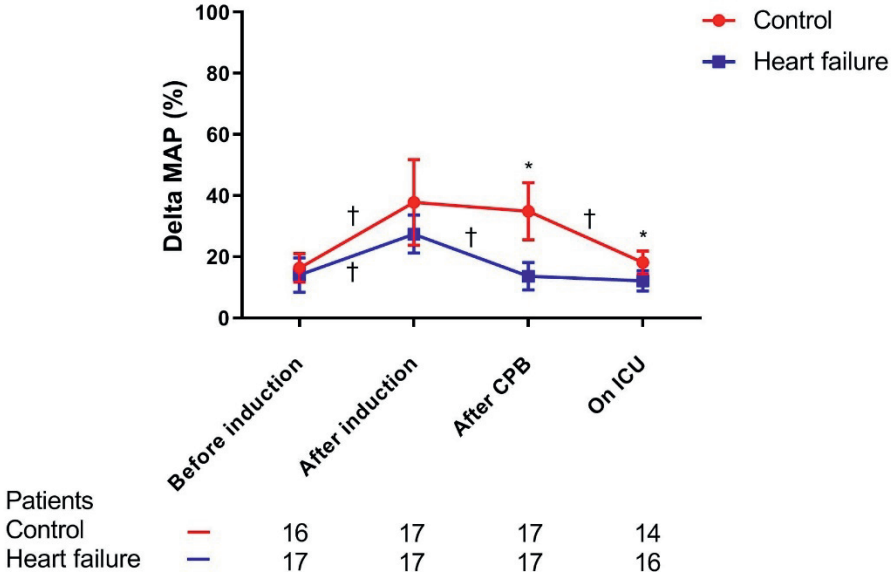
*Delta systemic vascular resistance (SVR, %) with 95%CI. * Significant difference (P<0.05) between groups; † significant difference between timepoints.*

Figure 4. Vasoconstriction test

A. Change in cardiac index



B. Change in mean arterial pressure



*Delta systemic cardiac index (CI, %) and mean arterial pressure (MAP, %) with 95%CI. * Significant difference (P<0.05) between groups; † significant difference between timepoints.*

Vasoresponsiveness after induction and during cardiac surgery

As shown in Figure 3A, delta SVR increased in both groups after induction, indicating an increased vasoresponsiveness. However, delta SVR remained significantly lower in HF patients on all timepoints. Interestingly, vasoresponsiveness was almost abolished after cessation of CPB in HF patients (decline from 42% (95%CI 29-54) to 17% (95%CI 7-26) after cessation, P=0.002). In contrast, the response to phenylephrine did not significantly change in control patients after cessation of CPB (66% (95%CI 46-86) to 60% (95%CI 45-75), P=0.623).

Both intra-operatively and post-operatively, significantly more HF patients received norepinephrine when compared to controls (Table 2 and 3). Conceptually, the higher use of norepinephrine in HF patients in the intra- and post-operative phase could have interfered with the response to phenylephrine. Accordingly, the analyses were repeated in the subgroup of patients who did not receive norepinephrine. As shown in Figure 3B, roughly the same pattern was found. This indicates that HF patients have a decreased vasoconstrictor response compared to control patients which is independent from the effect of norepinephrine.

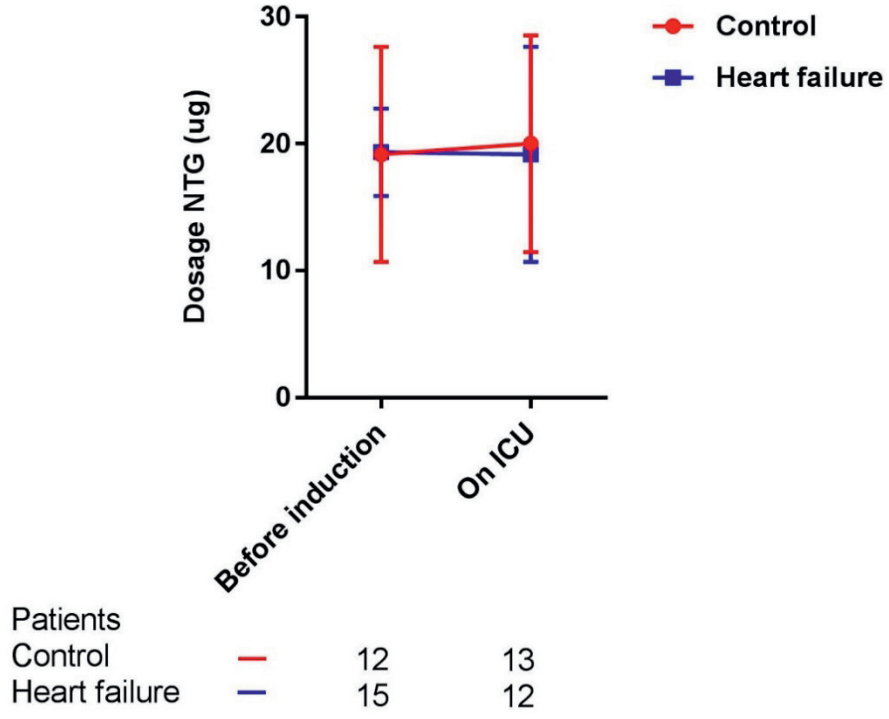
Vasoresponsiveness in the early postoperative period

The almost abolished vasoresponsiveness to phenylephrine continued to persist in HF patients on day 1 postoperatively. In particular, delta SVR was 12% (95%CI 6-18) in the HF group as compared to 29% (95%CI 22-37) in the control group (P<0.001). Remarkably, there was a significant decrease in SVR in control patients at the ICU compared to intraoperatively (60% (45-75%) to 29 (22-37%), P<0.001).

Vasoresponsiveness to a vasodilator

Both at baseline and at the first postoperative day there was no difference in the dosage of nitroglycerin needed to achieve a decrease of at least 10% in MAP between both groups (Figure. 5).

Figure 5. Vasodilation test: Dosage nitroglycerin (with 95% CI) needed for 10% decrease in MAP.

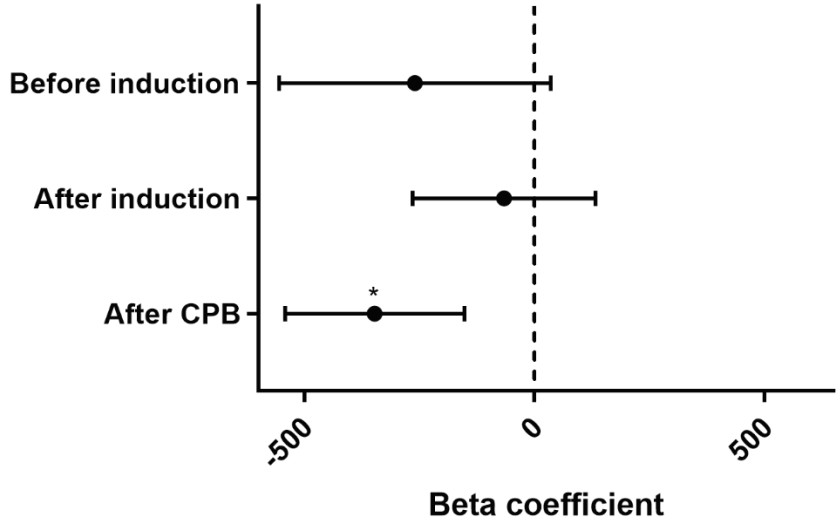


Predicting vasoplegia

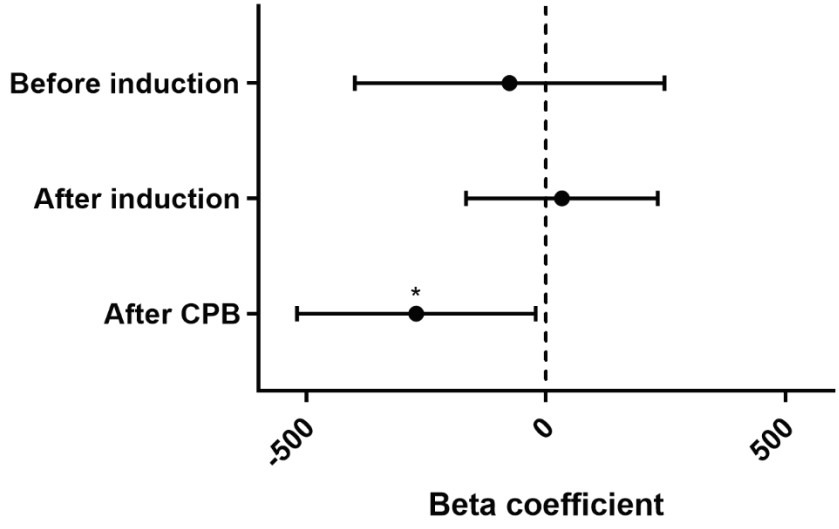
As shown in Figure 6, the change in SVR upon phenylephrine administration after CPB significantly associates with the total amount of norepinephrine received during the first 24 hours on the intensive care unit (P=0.001). This association persists after adjusting for HF and the norepinephrine dosage at this time point (P=0.034).

Figure 6. Predicting the total amount of norepinephrine given during the first 24 hours on the ICU, using the % SVR at baseline, after induction and after cessation of the cardiopulmonary bypass.

A. Univariate.



B. Multivariate, adjusted for heart failure and norepinephrine dosage at that time point.



*Beta coefficient with 95%CI. * Significant association (P<0.05)*

Discussion

We found that HF patients have a diminished response to a vasoconstrictor compared to control patients during the pre-, intra- and postoperative phase, independent of norepinephrine use. Furthermore, we showed that vasoresponsiveness intraoperatively is associated with the amount of norepinephrine received postoperatively.

Diminished vasoresponsiveness in HF patients at baseline

Chronic endogenous adrenergic (over)stimulation is known to lead to downregulation and desensitization of myocardial β1-adrenergic receptors and desensitization β2-adrenergic receptors in HF.[14] Our study shows that the response to phenylephrine, an α_1-adrenoreceptor agonist, is diminished in HF patients at baseline. This support our hypothesis that continuous adrenergic stimulation also results in downregulation and/or desensitization of vascular α_1-adrenoreceptors, leading to an altered responsiveness of the vascular system of HF patients.

Recently, Kaykı-Mutlu et al. performed a systematic meta-analysis examining the role of both cardiac and vascular α_1-adrenoreceptors.[15] They concluded that there is no consistent evidence for down-regulation or desensitization of vascular α_1-adrenoreceptors in HF. The heterogenous results might be due to interspecies differences, variations in expression levels of the three subtypes of α_1-adrenoreceptors in specific cell and tissue types, the effects of the pathophysiological mechanism underlying HF (e.g. ischemic versus non-ischemic) or due to poorly reproducible results.

Two of the presented studies measured the effect of α_1-adrenoreceptor agonists on SVR in HF patients. Goldsmith et al. concluded that HF patients have a diminished vasoresponsiveness to norepinephrine, since exogenous norepinephrine infusion did not had an significant effect on SVR.[16] In contrast to our study, Schwinn et al. failed to demonstrate a significant difference in a_1-adrenergic responsiveness between patients with LVEF ≤40% undergoing CABG on CPB versus controls when measured pre-induction.[13] However, patients with impaired ventricular function had reduced vasoresponsiveness after induction before CPB started. They explained their inability to demonstrate reduced vasoresponsiveness pre-induction by patient selection: all patients were in good condition and none of the patients had end-stage HF. This is an important contrast to our study. Other differences in patient population included: 1) patients with impaired ventricular function used less often betablockers compared to control patients; 2) patients using nitrates were included in the study; 3) the control group also included one patient with congestive HF and 4) use of norepinephrine was not documented.

A reduced response to an α_1-adrenoreceptor agonist in HF might derive from lower expression levels of the receptor or from alterations in signal transduction and could be influenced by disease progression.[15] More research is required to understand the changes in α_1 adrenergic function in HF and to identify the specific mechanisms that are involved.

Reduced vasoresponsiveness in HF patients intra- and postoperatively

We showed that the diminished response to phenylephrine in HF patients continues to exist throughout the study period, independent of the received norepinephrine dosage. Interestingly, vasoresponsiveness was almost abolished after cessation of CPB in HF patients, which persisted on day 1 postoperatively. The use of CPB is a known risk factor for vasoplegia.[17] The combination of surgical trauma and the use of CPB induces a systemic inflammatory response.[11] Our results support the hypothesis that the fragile balance of the vascular system of HF patients is easily disturbed by this response. This leads to the severely impaired vasoresponsiveness after cessation of CPB and contributes to the high risk for postoperative vasoplegia in HF patients.[6]

The response to nitroglycerin is not affected by HF

It is suggested that activation of inducible nitric oxide synthase (iNOS) plays a role in the pathogenesis of vasoplegia.[18-20] Activation of iNOS results in nitric oxide (NO) production which stimulates the production of cyclic guanosine monophosphate (cGMP), leading to smooth muscle relaxation and thereby vasodilation. Inhibition of cGMP by methylene blue is used to prevent and treat postoperative vasoplegia, however there is a limited level of evidence at this time.[21]

We found no difference in the response to nitroglycerin between our study groups. We postulate that this is a result of the endothelium-independent mechanism of nitroglycerin, which is accomplished by its conversion into NO.[22] This suggests that the vascular responsiveness to NO is comparable between HF patients and controls and that this does not influence the risk of vasoplegia. Considering that endothelial dysfunction is usually present in HF, endothelium-dependent mechanisms should be further investigated in relation to vasoplegia.[23]

Predicting vasoplegia

We showed that the change in SVR after CPB is significantly associated with the amount of norepinephrine received during the 24 hours on the intensive care unit. Unfortunately, due to the small sample size we were not able to find a direct association with vasoplegia. However, this finding indicates a link between reduced vasoresponsiveness intra-

operatively and vasoplegia. When confirmed in a larger cohort, this could provide a screening tool that could be used for a strategy to prevent vasoplegia or to start early treatment.

Fluid resuscitation and sympathomimetic agents (norepinephrine, epinephrine, and phenylephrine) are first-line treatment for vasoplegia. When catecholamines fail to restore hemodynamics, arginine vasopressin or angiotensin II could be used.[19, 20] Other treatment options are non-vasopressors, including methylene blue, ascorbic acid, hydroxocobalamin and corticosteroids. Thus far, few studies have focused on the prevention of vasoplegia. Future studies should focus on pre- and intraoperative strategies like early intervention with vasopressin.[24, 25]

Study strengths and limitations

Due to broad inclusion criteria, our study population properly represents the real-world population undergoing HF surgery. Of importance, factors that were previously reported to influence the risk of vasoplegia (prior hypertension, creatinine clearance, hemoglobin level, previous cardiac surgery, CPB time, aortic cross clamp time and procedural duration),[7, 9, 26] were comparable in both groups. Only the use of betablockers, which has earlier been suggested to be a protective factor for vasoplegia,[7, 9] was more prevalent in HF patients as advised by the HF guidelines.[12, 27]

There are limitations that should be taken into account while interpreting these results. As expected in this study population, there were some missing data (9% of the phenylephrine and 14% of the nitroglycerin measurements) since the patients' clinical condition did not always allow the tests to be performed. Importantly, however, the baseline data were complete. Moreover, this study was not powered to detect differences in vasodilation. Another limitation is that the central venous catheter and the pulmonary artery catheter were introduced post-induction for measurement of CO and SVR. These data were used to calibrate CO as measured by PulseCO. Due to the absence of catheters before induction, calibration was not possible at that timepoint. Therefore, SVR at baseline was not directly comparable with the other timepoints, so we had to use relative numbers for the change in SVR.

Conclusions

We found that HF patients have a diminished response to phenylephrine compared to control patients perioperatively. The reduced vasoresponsiveness is already present at baseline and persists throughout the entire perioperative period, independent of norepinephrine use. After cessation of CPB, vasoresponsiveness is almost abolished in HF patients. Furthermore, we showed that intraoperative vasoresponsiveness is associated with the amount of norepinephrine received postoperatively, suggesting a link between reduced vasoresponsiveness and the occurrence of vasoplegia. The diminished vasoresponsiveness in HF patients might explain the increased risk of developing postoperative vasoplegia. The current results provide insight in the mechanisms underlying vasoplegia. This could yield therapeutic options or preventive strategies for vasoplegia, leading to safer surgical interventions and improvement in outcome.

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