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Hemodynamic changes during aortic valve surgery among patients with aortic stenosis

Rasmus Carter-Storch^{a,b} , Søren Mose Hansen^c, Jordi S. Dahl^a, Kasper Enevold^c, Nils Sofus Borg Mogensen^a, Henrik Berg^c, Marie-Annick Clavel^d  and Jacob E. Møller^{a,b}

^aDepartment of Cardiology, Odense University Hospital, Odense, Denmark; ^bInstitut Universitaire de Cardiologie et de Pneumologie de Quebec/Quebec Heart and Lung University Institute, Université Laval, Quebec City, Canada; ^cOPEN Odense Patient Data Explorative Network, Odense, Denmark; ^dDepartment of Anesthesiology and Intensive Care, Odense University Hospital, Odense, Denmark

ABSTRACT

Introduction. Patients with severe aortic stenosis (AS) undergoing surgery are at increased risk of hypotension and hypoperfusion. Although treatable with inotropic agents or fluid, little is known about how these therapies affect central hemodynamics in AS patients under general anesthesia. We measured changes in central hemodynamics after dobutamine infusion and fluid bolus among patients with severe AS and associated these changes with preoperative echocardiography. **Methods.** We included 33 patients with severe AS undergoing surgical AVR. After induction of general anesthesia, hemodynamic measurements were obtained with a pulmonary artery catheter, including Cardiac index (CI), stroke volume index (SVi) and pulmonary capillary wedge pressure (PCWP). Measurements were repeated during dobutamine infusion, after fluid bolus and lastly after sternotomy. **Results.** General anesthesia resulted in a decrease in CI and SVi compared to preoperative values. During dobutamine infusion CI increased but mean SVi did not (38 ± 12 vs 37 ± 13 ml/m², $p = .90$). Higher EF and SVi before surgery and a larger decrease in SVi after induction of general anesthesia were associated with an increase in SVi during dobutamine infusion. After fluid bolus both CI, SVi (48 ± 12 vs 37 ± 13 ml/min/m², $p < .0001$) and PCWP increased. PCWP increased mostly among patients with a larger LA volume index. **Conclusion.** In patients with AS, CI can be increased with both dobutamine and fluid during surgery. Dobutamine's effect on SVi was highly variable and associated with baseline LVEF, and an increase in CI was mostly driven by an increase in heart rate. Fluid increased SVi at the cost of an increase in PCWP.

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Introduction


Aortic valve stenosis (AS) is the most common valvular disease in the Western World [1]. It is caused by progressive calcification of the aortic valve, leading to reduced aortic valve area (AVA). Increased valvular resistance leads to the buildup of a transvalvular gradient, causing left ventricular (LV) pressure overload. To counterbalance this and attempt to maintain a normal LV wall stress, LV wall thickness increases. However, this occurs at the expense of reduced LV compliance and increased myocardial oxygen demand [2]. When AS becomes severe and symptoms occur, aortic valve surgery (AVR) is indicated, unless comorbidities preclude this, and potential high-risk non-cardiac surgery is usually postponed until after AVR is performed [3]. However, non-cardiac surgery is sometimes performed on severe AS, when it is imperative not to delay this till after AVR.

General anesthesia may cause hypotension and myocardial depression which can be detrimental in patients with

severe AS, who are at increased risk for death, heart failure and myocardial infarction compared to patients without AS [4,5], with the highest risk among symptomatic patients [6]. This risk is in part attributed to the increased risk of intraoperative hypotension caused by sudden decreases in preload during induction of general anesthesia and blood loss. This may lead to poor subendocardial perfusion and decreased cardiac output (CO) which may further exacerbate hypotension leading to a vicious circle [7–10]. Additionally AS patients are susceptible to fluid overload due to increased valvular resistance and diastolic dysfunction [10].

It is recommended to perform non-cardiac surgery under strict hemodynamic surveillance in symptomatic AS patients [3], because it is imperative to maintain adequate CO and pulmonary capillary wedge pressure (PCWP). This may be obtained by infusion of catecholamines, inotropes or fluid, however, the individual AS patient may react differently to these agents during surgery. Studies regarding individual variation in hemodynamic response to catecholamines and fluid under general anesthesia are scarce.

CONTACT Rasmus Carter-Storch  rcarterstorch@gmail.com  Department of Cardiology, Odense University Hospital, Sdr.Boulevard, 5000 Odense C, Denmark

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The purpose of this study was therefore to: 1) Describe hemodynamic changes during general anesthesia, during low-dose infusion of dobutamine and after fluid challenge among patients with severe symptomatic AS undergoing AVR; 2) To associate these changes with preoperative clinical and echocardiographic values.

Methods

This is a sub-study from a previously described single-centre prospective study on myocardial fibrosis in AS [11]. Thirty-three of these patients with severe AS ($AVA < 1 \text{ cm}^2$), who after heart team evaluation were scheduled for elective surgical AVR from 2015 to 2016, were enrolled. Consenting patients scheduled for concomitant coronary artery bypass graft surgery, as well as patients with at least moderate mitral regurgitation, estimated glomerular filtration rate $< 40 \text{ ml/min/1.73 m}^2$, permanent atrial fibrillation or permanent pacemaker were excluded.

The study was approved by the Danish Data Protection Agency and the Regional Scientific Ethical Committees for Southern Denmark (S-20130064). All patients gave written informed consent. Study data were collected and managed using REDCap electronic data capture tools hosted at Odense Patient data Explorative Network. The study was registered at <https://clinicaltrials.gov/> (NCT02316587).

Before surgery, all patients underwent comprehensive echocardiography and a blood test was taken after at least 20 min of bed rest. A majority of patients also had a preoperative coronary CT. All patients underwent surgical AVR, and during surgery hemodynamic measurements and TEE were performed. During AVR, an endomyocardial biopsy was taken and analyzed for interstitial volume fraction as previously described [12].

Preoperative transthoracic echocardiography

Transthoracic preoperative echocardiography was performed by an experienced operator on a GE medical Vivid 9 ultrasound machine (GE Medical System, Horten Norway). Images were analyzed offline on EchoPAC PC 08 (GE Medical system, Horten, Norway) in a blinded fashion. Measurements were indexed to body surface area as appropriate.

AVA index and mean flow velocities across the valve were measured as recommended by the European Society of Cardiology (ESC) guidelines [13]. LV ejection fraction was estimated using Simpson's biplane method. Stroke volume index (SVi) was calculated using Doppler as described before [11]. Transaortic flow rate was calculated as stroke volume divided by LV ejection time from Doppler curves [14]. E/e' was used as a marker of LV filling pressure and $E/e' > 14$ was considered elevated. Two-dimensional deformation was assessed with speckle tracking measuring global longitudinal strain from the three apical views.

Systemic vascular resistance was calculated as $80 \times (\text{mean arterial blood pressure} - \text{central venous pressure (CVP)})/(\text{CO})$. Pulmonary vascular resistance was calculated

as $80 \times (\text{mean pulmonary artery pressure} - \text{PCWP})/(\text{CO})$. Preoperative CVP was estimated from the size of the inferior caval vein size at rest and during sniff tests according to guidelines [15].

Preoperative CT

CT was performed prior to surgery on a Siemens Somatom Definition Flash 128 slice scanner (Siemens Healthcare Solutions, Forchheim, Germany) and the aortic valve calcification score was estimated as previously described [11]. Severity of AS was graded with the use of the "aortic valve calcification index," calculated by dividing the measured aortic valve calcium score by the sex-specific thresholds identifying severe AS [16].

Intraoperative protocol

An arterial line was placed in the radial artery. General anesthesia was induced with Propofol and maintained with sevoflurane; Sufentanil was used as an analgesic and Rocuronium as a muscle relaxant. After induction and intubation, an introducer sheath was placed in the internal jugular vein. Through this, a 7Fr CCO-SvO₂ pulmonary arterial catheter was advanced into the pulmonary artery and wedged as appropriate for the measurement of PCWP. A TEE probe was placed in the esophagus.

Perioperative TEE

TEE was performed by experienced operators with a Philips iE33 (Philips Healthcare, Best, The Netherlands) cardiac ultrasound machine with a multi-plane phased array transducer. Images were stored digitally for offline analysis using Philips Xcelera software (Philips Healthcare). Strain parameters were analyzed with Qlab (Philips Healthcare).

In the mid-esophageal view, images of the LV were obtained at 4-chamber, 2-chamber, and long-axis views. Aortic and LV outflow tract flow velocities were measured at the trans-gastric view aligning the Doppler cursor as parallel as possible with LVOT flow. Right ventricular area change was measured as $(\text{right ventricular diastolic area} - \text{right ventricular systolic area})/\text{right ventricular diastolic area}$. All other parameters were calculated as described for transthoracic echocardiography.

Hemodynamic measurements

Hemodynamic and TEE measurements were performed at four different stages (Figure S1): At baseline (Stage 1: Baseline); after infusion of dobutamine at 5 microg/kg/min for 3 min followed by 3 min infusion of 10 microg/kg/min until all measurements were obtained (stage 2: Dobutamine infusion); following termination of dobutamine infusion a fluid bolus of saline 10 ml/kg body weight was infused at a rate of 150 ml/min. Immediately after completion of infusion measurements were repeated (stage 3: Fluid challenge);

after the opening of the sternum, measurements were repeated for the last time (stage 4: Sternotomy).

With balloon inflation, the pulmonary artery catheter was advanced to wedged position and PCWP was measured and averaged over 20 s during end inspiration. Ventilator settings were kept constant during the hemodynamic manipulations. Automated CO was measured every 2 min using thermodilution and the average of the last three measurements was recorded at each point in the protocol. Cardiac index (CI) was calculated as CO/body surface area, while SVi was measured by dividing CI with heart rate. Normal resting PCWP and SVI were defined as ≤ 15 mmHg and ≥ 35 ml/m², respectively.

Statistics

Normally distributed data are presented as mean \pm standard deviation; non-normally distributed data as median (25th percentile to 75th percentile); categorical data as the number and (percentages). Normality was assessed visually by q-q plots and histograms. Changes between the different stages were compared with 1-way ANOVA for repeated measurements. Post-hoc analysis to assess changes from baseline to each individual stage was done with paired t-test (for normally distributed data) or Wilcoxon's signed-rank test (for non-parametric data). Uni- and multivariable linear regression analyses were performed to determine predictors of change in SVi and PCWP after dobutamine and fluid infusion. All variables with $p < .20$ in univariable analysis were entered into the multivariable model; age and sex were forced into the model. Variables were then sequentially excluded from the model, until only age, sex, and variables with a p -value $< .20$ were left.

Given the exploratory nature of the study, no formal power analysis was performed. In a post hoc power analysis based on observed mean SVi of 37 ml/m² and SD 13 ml/m² the current sample size had a power of 0.8 to detect a difference in SVi of 7 ml/m² (19% increase) with alpha 0.05. A p -value $< .05$ was considered significant. STATA/IC 14.1 (StataCorp LP, Texas, USA) software was used.

Results

Baseline demographics are shown in Table 1 for the 33 patients (age 69 ± 7 years, 58% men), all with severe AS (AVA index 0.38 ± 0.09 cm²/m², mean gradient 55 ± 18 mmHg). Only three patients (9%) had LV ejection fraction $< 50\%$, however, the global longitudinal strain was frequently abnormal with a mean of $-16.0 \pm 3.1\%$, and E/e' was elevated in 15 patients (45%). All but 2 patients were operated on due to a combination of dyspnea, chest pain or syncope; one patient was operated on due to an abnormal stress test and one patient prior to knee surgery.

Perioperative hemodynamics

After induction of general anesthesia (Table 2, baseline), PCWP was 15 ± 4 mmHg, with 32% having abnormal

Table 1. Baseline demographics.

Number of patients	33
Demographics	
Age (years)	69 ± 7
Sex (male)	19 (58)
NYHA class (1/2/3/4)	5/19/8/1
CCS class (1/2/3/4)	19/12/2/0
Hypertension	16 (48)
Diabetes	5 (15)
Systolic blood pressure (mmHg)	145 ± 16
Diastolic blood pressure (mmHg)	77 ± 8
Heart rate (min ⁻¹)	63 ± 10
No. of antihypertensive drugs (0/1/2/ ≥ 3)	16/5/8/4
Beta blocker	9 (27)
Preoperative echocardiography	
LV mass index (g/m ²)	128 ± 33
LV end-diastolic volume index (ml/m ²)	51 ± 12
LV ejection fraction (%)	61 ± 9
LV stroke volume index (ml/m ²)	42 ± 8
LV ejection time (ms)	333 ± 31
Mean aortic flow rate (ml/s)	241 ± 41
Cardiac index (L/min/m ²)	2.6 ± 0.6
TAPSE (mm)	25 ± 5
Left atrial volume index (ml/m ²)	39 ± 7
Tricuspid jet (m/s)	2.4 ± 0.4
E/e'	14.2 ± 4.5
Global longitudinal strain (%)	-16.0 ± 3.1
Aortic mean gradient (mmHg)	55 ± 18
Aortic peak jet (m/s)	4.5 ± 0.7
Aortic valve area index (cm ² /m ²)	0.38 ± 0.09
Systemic vascular resistance (dynes s cm ⁻⁵)	1938 ± 446
Cardiac Computed Tomography	
Aortic valve calcium score (AU)	2613 [1905–4654]
Aortic valve calcification index	1.88 ± 0.9

Abbreviations: NYHA is New York Heart Association, CCS Canadian Cardiovascular Society, LV left ventricle, TAPSE tricuspid annular plane systolic excursions.

PCWP. Baseline CI was 2.0 L/min/m² and SVi was 37 ± 13 ml/m², with 46% having abnormal SVi. Both SVi and CI were lower compared to preoperative values, while LV ejection fraction and GLS were higher (all $p < .0001$) (Tables 1 and 2). SVi decreased more in women than in men (-12.3 ± 17.2 vs 0.5 ± 12.7 ml/m², $p = .03$). Systemic vascular resistance decreased significantly from preoperative values ($1,938 \pm 446$ vs $1,299 \pm 408$ dynes s cm⁻⁵, $p < .0001$).

Low-dose dobutamine infusion (Table 2, dobutamine) resulted in an overall increase in systolic arterial and pulmonary pressure (Table 2, dobutamine) compared to baseline, with a decrease in systemic and pulmonary vascular resistance. LV outflow tract peak jet and mean transaortic flow rate increased significantly during dobutamine infusion, but there was a correspondingly opposite shortening in LV ejection time, leading to an overall unchanged SVi (38 ± 12 vs 37 ± 13 ml/m², $p = .90$) (Figure 1B). CI, however, increased (2.6 ± 0.8 vs 2.0 ± 0.7 L/min/m², $p = .0001$) through an increase in heart rate (71 ± 14 vs 56 ± 10 min⁻¹, $p < .0001$). Hemodynamic changes during the different stages are shown in Figure 2.

After a washout period and subsequent rapid administration of a fluid bolus (Table 2, fluid), systolic arterial pressure returned to baseline, while pulmonary systolic pressure remained elevated compared to baseline (42 ± 9 vs 31 ± 6 mmHg, $p < .0001$). CI after fluid administration was significantly higher than at baseline and during dobutamine

Table 2. Hemodynamic changes during DSE, bolus fluid and sternotomy among patients in the operative room for aortic valve replacement for severe aortic stenosis.

	Baseline	Dobutamine	Fluid	Sternotomy	p-value*
Preload					
PCWP (mmHg)	15 ± 4	16 ± 5§	21 ± 5#	17 ± 4#	<.0001
LV end-diastolic volume index (ml/m ²)	45 ± 15	46 ± 15	54 ± 16#	47 ± 14	<.0001
LA 4-chamber area index (cm ² /m ²)	24 ± 3	24 ± 3	26 ± 3#	25 ± 3§	.0002
Central venous pressure (mmHg)	12 ± 3	12 ± 3	14 ± 4#	13 ± 4	<.0001
Afterload					
Peak aortic jet (m/s)	4.1 ± 0.8	4.8 ± 1.3§	4.3 ± 1.0	4.0 ± 1.0	.0004
Systolic arterial pressure (mmHg)	98 ± 13	122 ± 33#	104 ± 20	98 ± 21	<.0001
Systolic pulmonary pressure (mmHg)	31 ± 6	41 ± 11#	42 ± 9#	34 ± 7§	<.0001
AVA index (cm ² /m ²)	0.38 ± 0.10	0.45 ± 0.13#	0.39 ± 0.10	0.37 ± 0.08	<.0001
Systemic vascular resistance (dynes/s/cm ⁻⁵)	1299 ± 408	998 ± 390#	895 ± 399#	1028 ± 413§	<.0001
Pulmonary vascular resistance (dynes/s/m ⁻⁵)	145 ± 93	107 ± 50§	97 ± 64§	126 ± 51	.02
LV systolic function					
LV global longitudinal strain (%)	-18.5 ± 4.3	-20.0 ± 3.0§	-21.0 ± 3.4#	-20.4 ± 3.5§	.002
LV ejection fraction (%)	66 ± 8	72 ± 9#	71 ± 9§	68 ± 8	.0006
RV fractional area change (%)	49 ± 11	54 ± 12#	54 ± 10§	48 ± 11	.0008
LV Diastolic function					
e' average (cm/s)	6.4 ± 1.5	7.7 ± 1.6#	7.5 ± 1.3#	6.6 ± 1.4	<.0001
E (cm/s)	72 ± 17	84 ± 15#	94 ± 17#	78 ± 18§	<.0001
E/e'	12 ± 4	11 ± 3	13 ± 4§	11 ± 3	.0005
Output					
Heart rate (min ⁻¹)	56 ± 10	71 ± 14#	67 ± 12#	63 ± 10#	<.0001
Cardiac index (L/min/m ²)	2.0 ± 0.7	2.6 ± 0.8#	3.2 ± 0.7#	2.8 ± 0.7#	<.0001
Stroke volume index (ml/m ²)	37 ± 13	38 ± 12	48 ± 12#	46 ± 13§	<.0001
LV ejection time (ms)	350 ± 37	292 ± 45#	365 ± 38§	378 ± 45#	<.0001
Mean aortic flow rate (ml/s)	215 ± 82	260 ± 88§	264 ± 67§	244 ± 79	.01

Abbreviations: DSE is dobutamine stress echo, PCWP pulmonary capillary wedge pressure, LV left ventricle, LA left atrium, AVA aortic valve area, RV Right ventricle, CI Cardiac index, SVI stroke volume index.

*1-way ANOVA for repeated measurements. Post hoc analysis of change from baseline is performed with paired t-test or Wilcoxon Signed Rank test as appropriate. § = p-value < .05. # = p-value < .001.

infusion (fluid vs. dobutamine: 3.2 ± 0.7 vs 2.6 ± 0.8 L/min/m², $p < .0001$), through a significant increase in SVi (fluid vs. dobutamine: 48 ± 12 vs 38 ± 12 ml/min/m², $p < .0001$) albeit a small decrease in heart rate (67 ± 12 vs 71 ± 14 , $p = .04$). The mean transaortic flow rate was similar during dobutamine and fluid infusion, but LV ejection time was significantly longer during fluid infusion (Figure 1C). Compared to dobutamine infusion, PCWP (21 ± 5 vs 16 ± 5 , $p < .0001$) and CVP (14 ± 4 vs 12 ± 3 , $p < .0001$) both increased significantly. Twenty-six (87%) patients had elevated PCWP after fluid bolus (range: 14–32 mmHg). After sternotomy (Table 2, sternotomy), CI was higher than at baseline (2.8 ± 0.7 vs 2.0 ± 0.7 , $p = .001$) owing to an increase in both SVi and heart rate. PCWP was slightly higher than at baseline (17 ± 4 vs 15 ± 4 , $p = .0005$).

Correlations with SVi during dobutamine infusion

Compared to baseline characteristics and preoperative echocardiography, preoperative SVi, EF and GLS were all univariably and positively associated with an increase in SVi during dobutamine infusion. Conversely, a reduction in SVi from preoperative values to general anesthesia was associated with an increase in SVi during dobutamine infusion, although with a wide scatter ($r^2 = 0.29$, $p = .004$) (Table S1 and Figure S2A–B). In a multivariable linear regression analysis adjusting for age, male sex, EF and change in SVi from preoperative values remained significantly associated with the change in SVi during dobutamine infusion.

Correlations with SVi after fluid bolus

Compared to baseline characteristics and preoperative echocardiography, EF was positively associated with an increase in SVi after fluid bolus. In contrast, baseline heart rate was borderline negatively associated ($p = .07$) with an increase in SVi, and as with dobutamine infusion, a reduction in SVi after general anesthesia was associated with an increase during fluid bolus, again with a wide scatter ($r^2 = 0.22$, $p = .02$) (Table S2, Figure S2C–D). In a multivariable model adjusting for age and male sex, EF was no longer significant, while the change in SVi from preoperative values and baseline heart rate were significantly associated with the change in SVi after fluid bolus.

Correlations with PCWP after fluid bolus

Compared to preoperative values, treatment with a beta-blocker and LV mass index were both positively associated with an increase in PCWP after fluid bolus, while E/e' and LA volume index were borderline significant and AVA index was negatively associated with changes in PCWP (Table S3, Figure S3). In a multivariable linear regression model, LA volume index and beta-blocker treatment were the only significant predictors of change in PCWP after fluid bolus.

Discussion

In this prospective study on patients with severe AS undergoing AVR we found, as expected, that CI can be increased

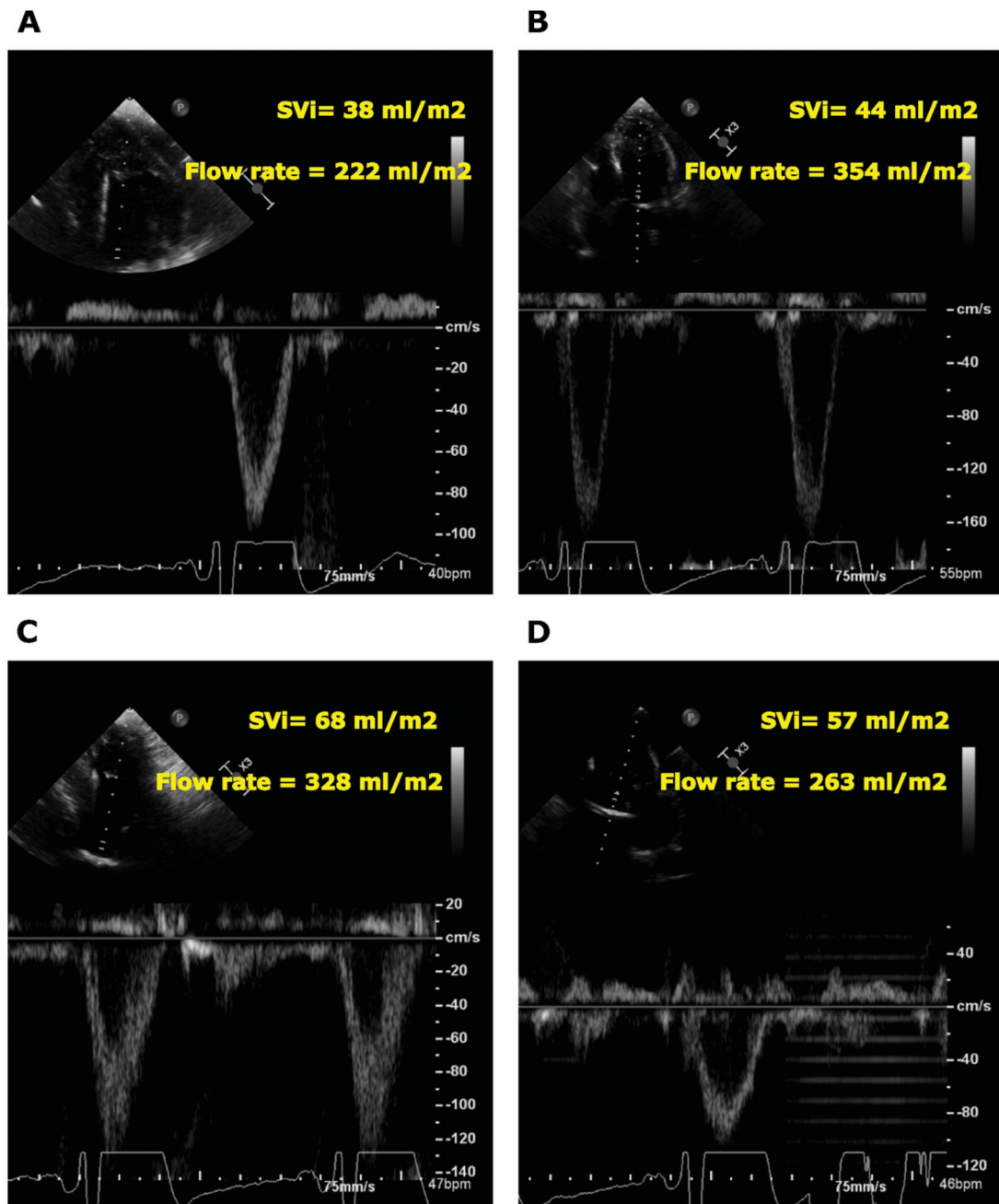


Figure 1. TEE Doppler profiles in the LV outflow tract in a representative patient with severe AS (AVA 0.8 cm^2 , mean gradient 47 mmHg). Note that the y-axis changes between the images. (A) At baseline SVi is 38 ml/m^2 , LV ejection time is 317 ms and aortic flow rate is 222 ml/s . (B) During dobutamine infusion, SVi increases to 44 ml/m^2 , aortic flow rate increases to 354 ml/s and LV ejection time decreases to 232 ms . (C) After fluid infusion, SVi increases to 68 ml/m^2 , aortic flow rate decreases to 328 ml/s and LV ejection time increases to 383 ms . (D) After sternotomy, SVi decreases to 57 ml/m^2 , aortic flow rate decreases to 263 ml/s and LV ejection time increases to 402 ms .

through either dobutamine infusion or fluid load during general anesthesia. However, with dobutamine infusion, the increase in CI was primarily caused by an increase in heart rate, while with fluid bolus the increase was caused more by an increase in SVi but at the expense of increased filling pressure. Lower EF and SVi before surgery were associated with a reduction in SVi during dobutamine infusion. Furthermore, the patients with a larger decrease in SVi after general anesthesia had a larger increase in SVi after both dobutamine and fluid treatment. LA volume index was associated with a larger increase in PCWP after fluid bolus.

Impact of general anesthesia

General anesthesia affects the vascular smooth muscles and thereby reduces systemic vascular resistance [17]. In accordance with this, we observed a reduction in systemic vascular resistance and systolic arterial blood pressure after induction of anesthesia compared to preoperative values. Several other studies have shown that patients with severe AS undergoing non-cardiac surgery are at increased risk of developing perioperative hypotension [7–10] because they are believed to be more vulnerable to vasodilatation induced by anesthesia as a fixed valvular obstruction may impede the increase of

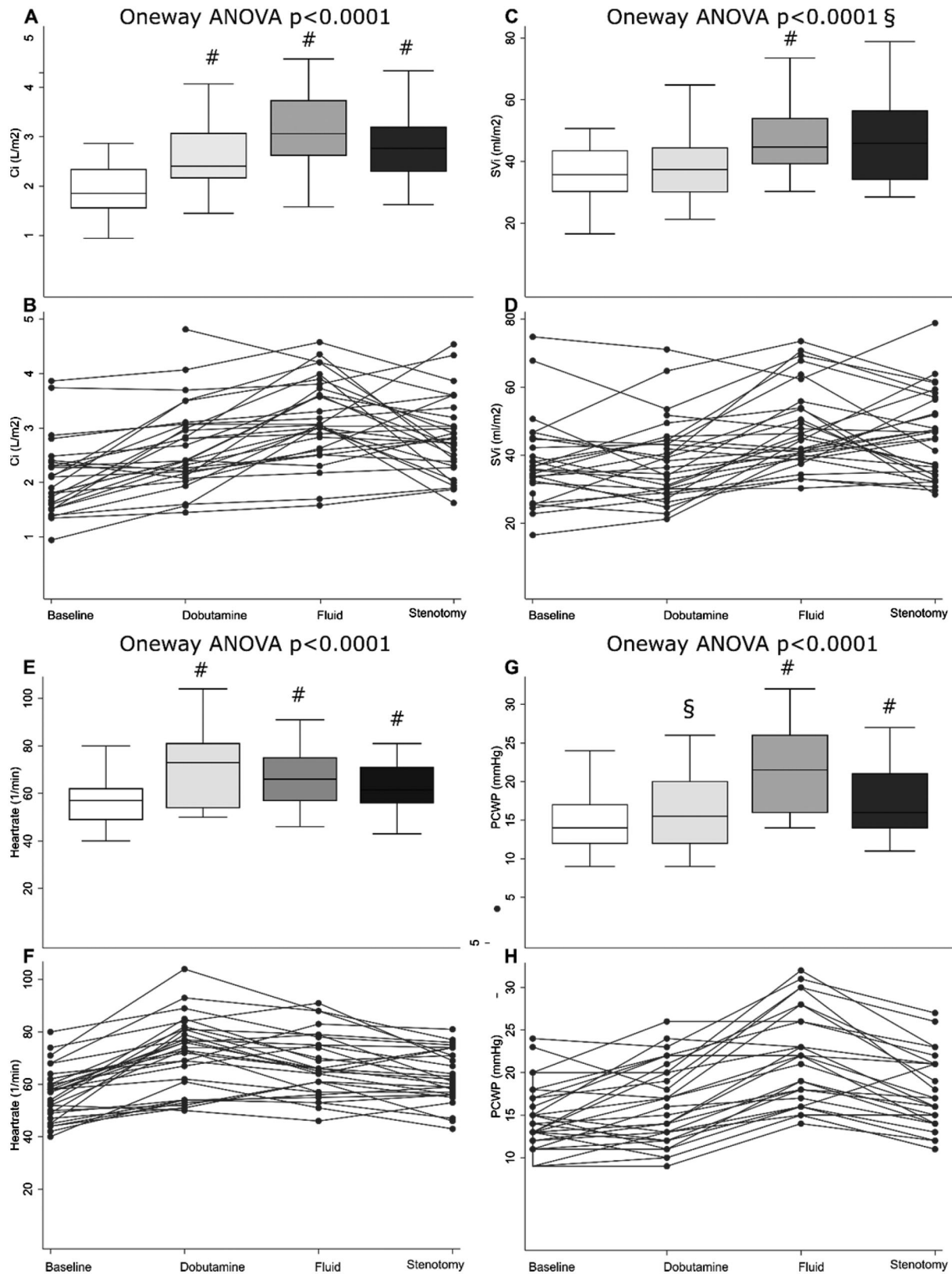


Figure 2. Hemodynamic changes in CI (A + B), SVi (C + D), heartrate (E + F) and PCWP (G + H) at baseline, after dobutamine infusion, after fluid bolus and after sternotomy. One-way ANOVA for repeated measurements with post-hoc paired t-test against baseline measurements. §: P -value $< .05$. #: p -value $< .001$. CI indicates cardiac index, Svi stroke volume index, PCWP pulmonary capillary wedge pressure

stroke volume, leading to hypotension and reduction in systemic vascular resistance [18]. General anesthesia may also directly impair cardiac contractility through several mechanisms [19], and may reduce levels of circulating

catecholamines and thereby reducing stroke volume. Although both EF and GLS increased compared to preoperative values, we observed a decrease in SVi compared to preoperative values, although this should be interpreted

with caution as we here comparing preoperative echocardiographic estimation of SVi with perioperative invasive measurement of SVi. This decrease could be caused by a decrease in preload causing decreased filling of the ventricles and thereby decreased SVi, and accordingly, we also observed lower E/e' and LVEDVi compared to preoperative values. The observed decrease in SVi and arterial blood pressure illustrates the risk AS patients are subject to when undergoing surgery. In AS patients reduced coronary flow may occur even in the absence of coronary artery disease as increasing LV pressures reduce the coronary artery-LV pressure gradient and coronary flow [20,21] If not reverted, this may cause a progressive negative spiral of reduced coronary pressure, inducing ischemia, reduced left ventricular systolic function and further exacerbation of hypotension.

Dobutamine and stroke volume

During infusion of dobutamine, we surprisingly found no change in mean SVi, and an increase in CI was achieved through an overall increase in heart rate. This is unexpected, as dobutamine would be expected to increase myocardial contractility through beta-receptor stimulation. This effect is commonly used as a diagnostic method to increase SVi in low-flow, low-gradient severe AS to distinguish it from pseudo-severe AS [22]. We studied patients where the majority had normal SVi at baseline. We observed that patients with higher EF and SVi preoperatively, paradoxically had a larger increase in SVi during dobutamine infusion. This could be due to a lower contractile reserve among the patients with reduced EF, but more likely the patients with higher EF and SVi at baseline had a larger decrease in SVi during general anesthesia due to reduced catecholamines levels, and the increase in SVi during dobutamine infusion was merely a recovery of preoperative values. In other words, we speculate that dobutamine worked best when there was a catecholamine deficit. We thus found a negative association between how much SVi increased from before to after induction of general anesthesia and how much SVi increased after dobutamine infusion (Figure S2D). Pellikka and colleagues have studied the normal SVi response to dobutamine in patients without the valvular disease [23], and found that at higher dobutamine doses, SVi tended to decrease and that the SVi of older patients peaked at lower dobutamine doses. This could be due to a combination of a less compliant LV, shortened diastolic filling time and thereby decreased LV volume. Accordingly, we observed relative tachycardia even at low dobutamine dosages leading to decreased diastolic filling and a shortened systolic LV ejection time, both contributing to a lack of increase in SVi despite an increase in mean aortic flow rate.

Fluid and stroke volume

Conversely, after fluid challenge, we observed a marked increase in both SVi and CO, likely caused by increased preload and the Frank-Starling mechanism. This is in contrast to a study by Sonny *et al.*, studying the CO response to

passive leg raise in sedated patients with severe AS [24]. They found that passive leg raise did not improve CO, and concluded that patients with severe AS were already in the upper end of the Starling curve and consequently did not benefit from increased preload. In our study, the majority of patients had normal ejection fraction and only mildly elevated LV filling pressure, and it is likely that the increase in SVi would be lower in patients with heart failure and ischemic heart disease. Although patients almost uniformly increased SVi after fluid bolus, this increase was negatively associated with baseline heart rate. The combination of decreased LV compliance associated with AS and shortened LV filling time caused by relative tachycardia may have caused a reduced SVi response. Further, similarly to the findings regarding dobutamine infusion, the patients with a larger decrease in SVi after general anesthesia also had the largest increase in SVi after fluid bolus, which would support that the decrease in SVi after general anesthesia is in part caused by a reduction in preload [25], which can be restored when preload is increased.

Fluid bolus carries the risk of heart failure and pulmonary congestion in patients with severe AS [10], and we also observed a significant increase in PCWP and pulmonary artery pressure after fluid bolus. This increase was associated with LA size and illustrates that LA volume index is a good marker of elevated PCWP in patients with AS [12,26]. The balance between fluid deficiency and fluid overload can be delicate among patients with symptomatic severe AS patients undergoing surgery, for which reason it is recommended to perform non-cardiac surgery under strict hemodynamic surveillance in symptomatic AS patients [3]. We also observed that patients on beta-blocker treatment had a larger increase in PCWP after fluid bolus, but this is likely not a causal effect, but rather a spurious finding or it could be related to the indication for beta-blocker treatment. We did not find an association between the extent of myocardial fibrosis and PCWP which has previously been reported [12], but this is likely due to the limited sample size.

Clinical implications

Although the data set is small and the study should be considered hypothesis-generating, our data suggest that in the AS patient undergoing general anesthesia, a decrease in cardiac output may be expected. Some reluctance towards using fluid bolus may exist, due to fear of flooding the patients and causing pulmonary congestion. However, we did not find this to be a clinical problem, contrary fluid was effective in increasing SVi without evidence of pulmonary congestion. Dobutamine is also possible to use because it increases heart rate, but it had a much more modest effect on SVi. In AS patients without decompensated heart failure, the fluid bolus may therefore be a safe and effective first-line treatment of peri-surgical hypoperfusion.

Limitations

The estimation of CI using thermodilution may be limited in patients with valvular regurgitations and in low CI states.

Although significant valvular comorbidities were excluded in this study, small regurgitations may still have affected results to a smaller degree. As we averaged three invasive measurements of CI over a period of 6 min, the resulting time delay may have resulted in insufficient recordings of more acute changes in CI. We may therefore have underestimated the true change in CI after dobutamine and fluid infusion. Our findings on dobutamine stress echocardiography and fluid bolus were influenced by the hemodynamic effects of anesthesia and can therefore not be transferred to non-anesthetized patients.

We compared preoperative echocardiographic values with perioperative invasive and TEE-values of EF, GLS, SVi and systemic vascular resistance. Although these values should correlate, TEE and transthoracic echocardiographic estimations of e.g. AVA and aortic mean gradient may vary because of differences in angulation and different measurements of LV outflow tract. The study size was small, increasing the risk of type 2 errors.

Conclusion

In patients with severe symptomatic AS undergoing AVR, general anesthesia overall results in a reduction in SVi and CI. Although dobutamine causes an increase in heart rate, it is not effective in increasing stroke volume except if general anesthesia has resulted in a fall in SVi; if SVi was already low before surgery it is less efficient. The fluid bolus may be a reasonable alternative to restore stroke volume in well-compensated patients, however in patients with larger LAVi care has to be taken to avoid pulmonary congestion.

Disclosure statement

All authors take responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation. All authors state that they have no conflicts of interest.

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ORCID

Rasmus Carter-Storch  <http://orcid.org/0000-0002-0359-8728>
Marie-Annick Clavel  <http://orcid.org/0000-0002-8924-740X>

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