Safety of stress cardiovascular magnetic resonance in patients with moderate to severe aortic valve stenosis

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Abstract

Aims: Dobutamine and adenosine stress cardiac magnetic resonance imaging (CMR) are relatively contraindicated in patients with moderate to severe AS. We aimed to determine the safety of dobutamine and adenosine stress CMR in patients with moderate to severe AS.

Methods: In this retrospective study patients with AS who underwent either dobutamine or adenosine stress CMR between January 2009 and December 2021 for exclusion of obstructive CAD were enrolled. We recorded clinical data, CMR and echocardiography findings and side effects (major complications, minor complications and complaints). Patients with AS were compared to matched individuals without AS.

Results: 187 patients with AS were identified and compared to age-, gender- and BMI-matched 187 patients without AS. No major complications were reported in the study nor the control group. The reported frequency of complaints and minor complications were similar between the study and the control groups.

Nineteen patients with AS experienced side effects during dobutamine stress CMR compared to eighteen patients without AS (p=0.855). One patient with AS and two patients without AS undergoing adenosine stress CMR experienced side effects (p=0.562). Four examinations were aborted because of severe chest pain, paroxysmal atrial fibrillation and third-degree atrioventricular block. Age, prior coronary artery bypass grafting, prior stroke and inducible ischaemia were associated with a higher incidence of complications.

Conclusion: Moderate to severe AS was not associated with side effects of complications during CMR stress test. The data suggest CMR stress testing to be safe in patients with AS.

Introduction

Dobutamine and adenosine stress cardiac magnetic resonance imaging (CMR) are widely used and well-established modalities to diagnose significant coronary artery disease (CAD) [1-4]. Dobutamine-atropine stress cardiac magnetic resonance (Dobutamine stress CMR) is used to detect inducible wall motion abnormalities in patients with CAD and is largely considered to be safe [1, 2]. Arrhythmia including sustained and non-sustained ventricular tachycardia have been reported even though they occurred incidentally [5]. However, severe adverse effects such as myocardial infarction, ventricular tachycardia and even death have been reported in dobutamine-atropine stress echocardiography [6]. Adenosine perfusion stress cardiac magnetic resonance (adenosine stress CMR) is used to identify myocardial perfusion deficits indicating ischaemia and has recently been demonstrated to be non-inferior to invasive measurement of fractional flow reserve (FFR) [4]. Adenosine stress CMR is generally considered to be safe due to the short half-time of the vasodilating agent [7]. While minor adverse effects such as flushing, chest pain and dyspnea occur frequently, transient atrioventricular block, sinus bradycardia and significant hypotension are incidental complications (0.2-0.5% of cases) [8, 9].

Aortic valve stenosis (AS) is often associated with CAD and the most common form of valvular heart disease in elderly patients [10, 11]. However, dobutamine and adenosine stress CMR are contraindicated in patients with severe AS [5, 12]. Dobutamine stress echocardiography has been associated with somewhat serious cardiac arrhythmias in patients with moderate to severe AS, such as non-sustained ventricular tachycardia, paroxysmal supraventricular tachycardias and severe symptomatic hypotension [13]. Similar rates of adverse effects might be expected during stress CMR. Knowledge about complications during dobutamine stress CMR in patient with moderate to severe AS is however still lacking. Likewise, the drop of arterial blood pressure that can be triggered by adenosine may lead to a transient increase of the transvalvular pressure gradient and, especially in patients with insufficient preload of the LV,

cause an increase of transvalvular resistance, leading to a further, possibly critical reduction of blood pressure [14]. Regadenoson stress positron emission tomography (PET) has been demonstrated to be safe in patients with severe AS [15]. However, regadenoson is associated with a faster and greater peak increase in heart rate and less adverse effects, in particular in patients with bronchoconstrictive disease, compared to adenosine [16]. Hence, both agents are only comparable to a limited extent.

Therefore, the purpose of this study was to determine the incidence of adverse effects in patients with moderate to severe AS undergoing dobutamine or adenosine stress CMR.

Materials And Methods

Study population and design

Potential patients with AS underwent CMR at the Department of Cardiology, Angiology and Pneumology of the Heidelberg University Hospital between January 2009 and December 2021 and were retrospectively identified from our local clinical database. Patients underwent CMR for exclusion of significant CAD. The study was approved by the local institutional ethics committee in accordance with the Declaration of Helsinki (S-154/2015). All patients had undergone stress CMR with either adenosine or dobutamine and two-dimensional echocardiography Doppler study within 12 months of each other and had evidence of AS by echocardiography with aortic valve area (AVA) $\leq$1.5 cm^2. Patients with prior transcatheter aortic valve replacement (TAVR), prior surgical aortic valve replacement were excluded (Figure 1).

Cardiovascular risk factors (arterial hypertension, hypercholesterolemia, diabetes mellitus, obesity, history of smoking and family history of cardiovascular disease) and comorbidities (history of CAD, prior myocardial infarction, prior percutaneous coronary intervention, prior coronary artery bypass grafting (CABG), prior stroke or transitory ischaemic attack, chronic kidney disease and chronic obstructive pulmonary disease (COPD) were assessed using medical reports.

We recorded major complications such as death, myocardial infarction, severe arrhythmias, unstable angina, stroke and new hospital admission as well as minor complications such as induction of supraventricular tachycardia, drop of blood pressure (<60mmHg) and other non-severe complications that did not require a new hospital admission. We also documented complaints, such as chest pain, nausea and emesis or dyspnea that disappeared during CMR or shortly after administration of beta-blockers or sublingual nitroglycerin.

Selection of controls

Age-, sex-, body-mass-index (BMI) matched individuals without AS (controls), who underwent stress CMR with either adenosine or dobutamine, were selected from our CMR database. The same number of controls undergoing adenosine or dobutamine stress CMR were randomly selected from our CMR database.

Echocardiography

Study patients underwent conventional transthoracic echocardiographic studies, digitally stored on PACS (Picture Archiving and Communication System) and offline available on workstations (Centricity, GE Healthcare Vingmed, Trondheim, Norway). Echocardiography examinations were performed on commercially available ultrasound systems (Vivid 7, GE Healthcare Vingmed, Trondheim, Norway; ie33, Philips, Eindhoven, The Netherlands and SSD-5500 PureHD, Hitachi Aloka Medical, Tokyo, Japan) according to the guidelines of the American Society of Echocardiography [17] including standard 2D echocardiography for anatomic imaging and continuous wave and

color flow Doppler for the analysis of the Aortic valve gradients. Aortic valve gradients were calculated using continuous wave Doppler signals that afforded the highest peak velocity across the aortic valve using the continuity equation as previously described in the guidelines from the European Association of Cardiovascular Imaging and the American Society of Echocardiography form 2017 [17]. The examinations were analyzed by experienced readers.

Cardiac Magnetic Resonance Imaging

Standard CMR was performed supine in a 1.5T Achieva™, 1.5T Ingenia™ (1.5T) or 3T Ingenia™ (3T) whole body scanner (Philips Healthcare, Best, The Netherlands), with a commercial cardiac phased array receiver coil as previously described [18, 19]. Cine long axis 2-, 3- and 4-chamber views as well as short axis cine images covering the whole left ventricle (LV) from the annulus of the atrioventricular valves to the apex (8 mm slice thickness) were obtained using a breath-hold, segmented-k-space balanced steady-state free precession sequence (bSSFP) employing retrospective electrocardiogram or pulse oximetric gating with 40 (1.5T Achieva™) or 35 (1.5T and 3T) phases per cardiac cycles. Scan parameters were: repetition time (TR) 2.8ms; echo time (TE) 1.4ms; flip angle (FA) 60° (1.5T Achieva™ and 1.5T), TR 2.9ms, TE 1.4ms, FA 45° (3T); with a breath-hold time of 7–10 s per image and prospective gating. Data were analyzed using commercially available workstations (Viewforum™ and IntelliSpace™ Portal, ISP™, Philips Healthcare, Best, The Netherlands) and a certified software (cmr^{42} Version 5.6.6, Circle Cardiovascular Imaging Inc., Calgary, Canada) as semi-automatic software for volumetric analysis. Ventricular volumes, ejection fraction of LV and right ventricle (RV) and LV myocardial mass were acquired in short axis stacks by manually tracing epi- and endocardial borders, excluding papillary muscles from the myocardium.

Adenosine Perfusion Stress CMR

A three-slice turbo field gradient echo-echo-planar imaging (GRE-EPI) sequence was used as described previously [20]. Stress perfusion imaging was performed using a continuous intravenous infusion of 140µg/kg body weight/min (optional 210µg/kg body weight/min, in case of an inadequate heart rate response or recent caffeine intake) for three minutes over an antecubital vein. Three heartbeats after initiation of the sequence a bolus of gadolinium diethylenetriamine pentaacetic acid /DTPA (Magnevist™, Schering, Berlin, Germany) 0.2mmol/kg body weight (before February 2016) or Gadobutol (Gadovist™, Bayer HealthCare, Leverkusen, Germany) 0.14mmol/kg body weight (1.5T) or 0.1mmol/kg body weight (3T) (after February 2016) was injected over a separate peripheral venous catheter at a rate of 5 ml/s flushed with 20 ml 0.9% saline solution. Semi-quantification of myocardial perfusion was conducted in three LV short-axis slices using IntelliSpace™ Portal, ISP™ (Philips Medical Systems, Best, The Netherlands). The adenosine perfusion stress CMR protocol was the same for all three vendors.

Dobutamine stress CMR

Dobutamine stress CMR was performed as previously described [21, 22]. A 4, 2, and 3-chamber and three short-axis views (apical, mid-ventricular, and basal) were used. Dobutamine was infused during 3-min stages at incremental doses of 10, 20, 30, and 40 g/kg of body weight/min until at least 85% of the age-predicted heart rate was reached (220-age in years). Atropine was administered in 0.25mg increments (up to maximal dose of 2.0mg) if the target heart rate was not achieved. Cine loops were viewed online as they were acquired. Stress testing was stopped when the target heart rate was achieved or when one of the following occurred: severe chest pain or dyspnea, decrease in systolic blood pressure of >40mmHg, hypertension of >220/120mmHg, severe arrhythmias, new or worsening wall motion abnormalities (WMA) in at least 1 segment. Failure to attain 85% of age-predicted maximal heart rate was considered as a nondiagnostic result. Electrocardiographic rhythm, symptoms, peripheral blood pressure and oxygen saturation were continuously monitored during the stress studies. Inclusion criteria for using dobutamine stress CMR were the following; patients with 3-vessel CAD or after CABG, which is specific for the study center or if

contraindications for the use of adenosine were known (known or suspected bronchoconstrictive or bronchospastic disease) [23]. The dobutamine stress CMR protocol was the same for all three vendors.

Statistical analysis

Statistical analysis was performed using MedCalc™, version 15.7 (Ostend, Belgium), with $p<0.05$ taken to indicate statistical significance for all statistical tests. Continuous and normally distributed variables (Kolmogorov-Smirnov test, $p\geq0.05$) were expressed as mean ± standard deviation. Group differences for continuous variables were tested using the independent t-test. Continuous variables without normal distribution were stated as median and interquartile range (IQR), group differences were tested using the nonparametric Mann-Whitney U test. Categorical variables were compared using chi-squared test. Correlation analysis for the occurrence of complications was performed using Spearman's rank correlation. Univariable logistic regression models were used to assess the association between each variable and the occurrence of complications. For multivariable modeling, we included 4 and 5 of the most significant variables. Results are reported as odds ratio with 95% confidence intervals (CI).

Results

Population Characteristics

We included 187 patients, who were predominantly male (156 males, 83%) with a median age of 76 ± 8 years (range 48-92) (Table 1). A large proportion of patients had cardiovascular risk factors, in particular hypertension and hypercholesterolemia and suffered from CAD. Patients with AS had more severe heart failure, as defined by a higher NYHA classification ($p<0.01$) and an elevated high-sensitive Troponin T (dobutamine: $p<0.01$) and NT-proBNP (adenosine: $p<0.05$; dobutamine: $p<0.001$) compared to controls. Prevalence of inducible ischaemia in stress CMR were similar in both study groups (Table 1).

Patients undergoing adenosine stress CMR had a significantly higher prevalence of stroke or transitory ischaemic attacks compared to controls ($p<0.01$). LV ejection fraction (LV-EF) was similar between the study groups and the control groups, however LV end-diastolic volume (EDV) was increased in patients with AS (adenosine: $p<0.05$; dobutamine: $p<0.001$) Patients with AS in the dobutamine group had a significantly larger LV-EDV compared to controls ($p<0.01$) (Table 1).

Patients with AS undergoing dobutamine stress CMR had a higher prevalence of prior myocardial infarction ($p<0.05$) and CABG ($p<0.001$), a reduced LV-EF ($p<0.01$), and a larger LV-EDV ($p<0.05$) compared to patients with AS and adenosine stress CMR. AVA and peak pressure gradient (PPG) were similar in both study groups. There were no significant differences in the number of patients with severe AS between the between the adenosine and the dobutamine group (Table 1).

Frequency and character of side effects during stress CMR

Considering both stress agents, a total of twenty patients with AS (11%) experienced side effects during stress CMR compared to nineteen patients without AS (10%), which was not significantly different (Table 2). The majority of these side effects occurred during dobutamine stress CMR. Only one patient with AS experienced side effects during adenosine stress CMR. There were no major complications reported in stress CMR (Table 2).

One patient (1.1%) with AS undergoing adenosine stress CMR experienced third degree atrioventricular block (AV-Block III°). Two patients (2.2%) without AS undergoing adenosine stress CMR complained about chest pain and nausea. All of these adenosine stress CMR examinations had to be terminated prematurely (Table 2).

Nineteen patients (20%) with AS and dobutamine stress CMR experienced side effects, which was not significantly different compared to patients without AS (n=18; 19%, p=0.855). Twelve patients (13%) with AS complained about chest pain, one about nausea and emesis (1.1%) and one about dyspnea (1.1%) during dobutamine stress CMR. The rate of complaints was similar compared to patients without AS (with AS: n=15 (16%); without AS: n=18 (19%), p=0.567).

Five patients (5.3%) with AS suffered from minor complications during dobutamine stress CMR compared to three patients (3.2%) without AS (p=0.471). Paroxysmal atrial fibrillation was induced in two patients (2.1%), supraventricular tachycardia, a decrease of systolic blood pressure (<60mmHg) and an increase of systolic blood pressure (>180mmHg) occurred in one patient each (1.1%) with AS during dobutamine stress CMR. Two patients without AS had a drop of systolic blood pressure (2.1%) and one patient suffered from premature ventricular complexes (1.1%). Three dobutamine stress CMR examinations had to be terminated in the patient group with AS and four in the one without AS (p=0.701) (Table 2 and 6).

Risk factors for stress induced side effects

Patients with AS and side effects during dobutamine stress CMR were significantly older than patients without side effects (patients with side effects: 80 ± 5 years; patients without side effects: 74 ± 9 years; p<0.05). The reported frequency of complaints and minor complications were similar between the study and the control groups. Additionally, they had more often undergone prior CABG (patients with side effects: 47%; patients without side effects: 24%; p<0.05) and suffered from stroke or transitory ischaemic attacks in the past (patients with side effects: 26%; patients without side effects: 7%; p<0.05). High-sensitive troponin T was significantly elevated in patients with side effects during dobutamine stress CMR (Troponin T: patients with side effects: 52 (28-216) vs. patients without side effects: 27 (14-69); p<0.05). Also, significantly more patients with side effects had a positive stress CMR results compared to patients without side effects (63% vs. 26%; p<0.01) (Table 3).

Increasing age, hypercholesterolemia, prior stroke, prior CABG and inducible ischemia moderately correlated moderately with the occurrence of side effects in dobutamine stress CMR (p<0.05). There was no significant correlation between high sensitive Troponin T, NT-proBNP, LV-EF or AVA and the occurrence of side effects (Table 4).

Univariable logistic regression analyses revealed that age, hypercholesterolemia, prior CABG, prior stroke or transitory ischaemic attack and inducible ischaemia were associated with side effects in dobutamine stress CMR (Table 5). In a multivariable model older age, prior CABG and prior stroke or transitory ischaemic attack and inducible ischaemia were independently associated with the incidence of side effects (OR 1.10, 95% CI 1.00-1.20, p<0.05; OR 6.77, 95% CI 1.70-26.92, p<0.01; OR 6.69, 95% CI 1.30-34.35, p<0.05; OR 4.00, 95% CI 1.13-14.07, p<0.05; respectively). In a second multivariable model excluding inducible ischaemia, increased age and prior CABG and prior stroke or transitory ischaemic attack remained significantly associated (OR 1.01, 95% CI 1.01-1.20, p<0.05; OR 1.49, 95% CI 1.49-19.45, p<0.01; OR 9.00, 95% CI 1.92-42.30, p<0.01; respectively) (Table 5).

Discussion

This single-center study of 187 consecutive patients with moderate to severe aortic stenosis reports the safety of dobutamine and adenosine stress CMR.

Previously, dobutamine stress CMR revealed a highly diagnostic accuracy for the detection of angiographically defined CAD with a sensitivity of 0.83 (95% CI: 0.79-0.88) and a specificity of 0.86 (95% CI: 0.81-0.91) [24]. Inducible wall motion abnormalities in patients with suspected or known CAD are independently associated with all-cause

mortality, cardiac death, cardiac transplantation and myocardial infarction [25]. Likewise, adenosine stress CMR demonstrated a high sensitivity of 0.89 (95% CI: 0.88-0.91) and specificity of 0.80 (95% CI: 0.78-0.83) for the detection of significant CAD [3]. Inducible perfusion defects were independently associated with major adverse cardiac events (MACE) [25]. Furthermore, adenosine stress CMR is noninferior to invasive angiography with FFR-measurement with respect to the incidence of MACE at one year [4]. Dobutamine and adenosine stress CMR are largely considered as safe also in high-risk patients e.g. with complex congenital heart disease or prior kidney transplantation [5, 9, 26-28].

In this study we included patients with a high pre-test probability of inducible ischaemia and moderate to severe AS. Dobutamine and adenosine stress CMR were tolerated without major complications in this high-risk patient group. Additionally, patients with AS did not have significantly more complications compared to patients without AS. Previously, Wahl et al. reported the incidence of side effects in 1075 consecutive dobutamine stress CMR examinations. Their population was comparable to ours in terms of the severity of CAD with a relatively large number of patients with prior percutaneous coronary intervention (40%) and CABG (18%) [5]. The incidence of paroxysmal atrial fibrillation, drop in systolic blood pressure, severe increase in blood pressure (>240/120 mmHg) and transient AV-blocks can be confirmed by our results. The authors also reported sustained (0.1%) and non-sustained ventricular tachycardia (0.4%), which did not occur in our study [5]. However, these adverse effects were rare, incidental observations in a large cohort. In another large multicenter study safety study, dobutamine stress CMR was performed in 554 patients [28]. Only two patients (0.36%) had severe complications; sustained ventricular tachycardia and persistent atrial fibrillation. In the same study dipyridamole stress CMR was performed in 11,430 patients, which is comparable to adenosine. Ten patients (0.08%) had severe complications including unstable angina, acute pulmonary, persistent atrial fibrillation, asystole, transient ischaemic attack and anaphylactic shock after admission of gadolinium contrast medium [28]. Their study cohort was healthier compared to ours, with a lower prevalence of CAD, percutaneous coronary intervention and CABG. To our knowledge, death during stress CMR has not been reported in previous studies. However, major adverse events including death have been reported during dobutamine stress echocardiography. The incidences were due to acute cardiac rupture with pericardial tamponade in patients with recent myocardial infarction [29-31].

There was only one patient with AS suffering from third-degree AV-Block who underwent adenosine stress CMR in our study. We did not observe complications related to a drop in arterial blood pressure as induced by the vasodilatory effect of adenosine in combination with high pressure gradients. Interestingly, observed adverse effects of adenosine stress CMR using a standard dose are generally minor. Flushing, headache and dizziness are reported in about one third of patients undergoing adenosine stress CMR. Also, chest pain and shortness of breath are reported frequently. Transient AV-blocks are minor complications and occur in about 1% of patients [9].

Patients with side effects in our study were older and with more severe atherosclerotic disease burden. Additionally, patients were more likely to suffer from a more severe form of CAD with myocardial ischaemia, indicated by a higher prevalence of CABG, inducible ischaemia and elevated baseline Troponin T compared to patients without side effects. Chest pain, as the most often reported side effect, might therefore be more related to inducible ischaemia than to the severity of AS.

We attempted to develop a risk stratification model to predict the incidence of side effects in patients with AS during dobutamine stress CMR. Our results indicate that older age, a higher prevalence of hypercholesterolemia, prior CABG, prior stroke and myocardial ischaemia are independent predictors for a higher incidence of side effects in patients undergoing dobutamine stress CMR. Interestingly, inducible ischaemia has been found to be an independent factor associated with a higher incidence of severe complications during stress CMR using dobutamine or dipyridamole in

previous studies [28]. Overall, an older population with a severe form of vascular disease and inducible myocardial ischaemia seems to be at higher risk for complications during dobutamine stress CMR.

With respect to CMR safety, it is important to consider that the observation of the patient may be limited due to physical separation of patient and health care staff. In case of a cardiac arrest, staff members would need to initiate and continue any required basic or advanced life support while the patient is being removed from the room with an active magnetic field, specifically in the case of required defibrillation. The magnet can be switched off causing a quick evacuation of liquid helium contained in the cooling circuit (quenching). Quenching however is not advised in a medical emergency, because the process itself takes more than a minute and can itself be hazardous. It is therefore recommended to initiate such measures immediately while removing the patient to a location where the use of life support devices is safe [32].

All stress CMR examinations were performed by at least one experienced MR technologist and one physician at our center. In our center, a manual table release and a trolley permanently placed under the table of the patient allow for performing a rescue maneuver in about 30 seconds. An adequate reaction to complications and in particular the quick removal of a patient from the magnet in a life threating situation, needs to be trained with experienced MR-staff members frequently at the MR center. Patients need to be always closely monitored and resuscitation equipment including automated external defibrillator must be available.

Limitations

This retrospective study performed at a single center has a relatively small sample size, limiting the support for the conclusions regarding infrequent complications. Also, clinical variables and the presence of complications could only be retrospectively reviewed. However, no serious adverse effects in these elderly patients with multimorbidity occurred. Major complications seem to be unlikely in stress CMR in this high-risk cohort. A larger prospective and registered multicenter clinical trail of patients with severe AS is needed to confirm our results. Additionally, patients were always informed explicitly that flushing, mild chest pain, dizziness, headache and shortness of breath might occur for a few seconds during adenosine stress CMR. Therefore, a lack of reporting of these minor adverse effects might have occurred. However, patients were monitored throughout the entire examinations allowing an immediate response to more moderate or even severe adverse effects.

Our studies showed significantly more complications in examinations with dobutamine compared to adenosine, however randomized studies are needed to confirm these findings.

Conclusion

In patients with moderate and severe aortic valve stenosis, stress CMR for ruling out inducible myocardial ischemia appears safe. The safety profile and rate of side effects are similar to those reported for other indications for stress CMR and to those of other methodologies using pharmacological stress agents. Age, prior CABG, prior stroke and inducible myocardial ischaemia are independent variables associated with side effects. Adenosine perfusion CMR was associated with significantly less complications and side effects than dobutamine stress CMR.

Abbreviations

AS = aortic valve stenosis

AVA = aortic valve area

BMI = body-mass-index

BSA = body-surface area

CABG = coronary artery bypass grafting

CAD = coronary artery disease

CMR = cardiac magnetic resonance

FFR = fractional flow reserve

IQR = interquartile range

LV = left ventricular

MACE = major adverse cardiac events

PPG = peak pressure gradient

Statements And Declarations

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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Competing Interests

The authors have no relevant financial or non-financial interests to disclose.

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Tables

Table 1 Baseline characteristics of patients with aortic stenosis and controls

	Adenosine			Dobutamine			Adenosine vs. Dobutamine
	Patient Population (n=92)	Controls (n=92)	p	Patient Population (n=95)	Controls (n=95)	p	p
Demographics							
Age (years)	76 ± 8	76 ± 8	0.895	75 ± 8	76 ± 8	0.891	0.473
Male sex (n)	75 (82%)	75 (82%)	1.000	81 (85%)	81 (85%)	1.000	0.493
BMI (kg/m²)	27 (25-31)	27 (25-29)	0.676	27 (24-30)	27 (25-29)	0.799	0.584
NYHA class	2 (1-3)	2 (1-2)	0.004**	2 (1-3)	2 (1-2)	0.009**	0.859
Cardiovascular risk factors							
Hypertension (n)	82 (89%)	80 (87%)	0.650	88 (93%)	81 (85%)	0.106	0.406
Hypercholesterolemia (n)	64 (70%)	62 (67%)	0.752	66 (69%)	70 (74%)	0.521	0.989
Diabetes mellitus (n)	34 (37%)	22 (24%)	0.055	39 (41%)	28 (29%)	0.096	0.567
History of Smoking (n)	36 (39%)	27 (29%)	0.163	33 (35%)	43 (45%)	0.119	0.535
Family history of coronary artery disease (n)	23 (25%)	25 (27%)	0.738	25 (26%)	31 (33%)	0.366	0.972
Comorbidities							
Coronary artery disease (n)	83 (90%)	78 (85%)	0.525	90 (95%)	89 (94%)	0.223	0.242
Prior myocardial infarction (n)	24 (26%)	20 (22%)	0.302	38 (40%)	29 (31%)	0.173	0.044*
Prior percutaneous coronary intervention (n)	43 (47%)	46 (50%)	0.306	56 (59%)	55 (58%)	0.883	0.095
Prior coronary artery bypass grafting (n)	4 (4.3%)	6 (6.5%)	0.288	27 (28%)	27 (28%)	1.000	0.0001***
Prior stroke / transitory ischaemic attack (n)	14 (15%)	3 (3%)	0.008*	10 (11%)	7 (7%)	0.447	0.339
COPD (n)	8 (9%)	3 (3%)	0.115	13 (14%)	8 (8%)	0.249	0.281
Laboratory data							
high sensitive Troponin T (pg/ml)	25 (17-42)	21 (13-47)	0.158	33 (16-92)	20 (11-36)	0.004**	0.174

NT-proBNP (ng/l)	897 (483-2038)	806 (126-1844)	0.031*	1576 (539-4311)	427 (182-1019)	0.0001***	0.074
GFR (ml/min/1.73m²)	74 (56-84)	76 (59-85)	0.391	68 (45-85)	67 (52-81)	0.700	0.042*
Cardiac morphology							
LV-EF (%)	59 (52-66)	60 (51-65)	0.934	52 (40-61)	56 (49-62)	0.120	0.004*
LV-EDV (ml)	157 (127-189)	139 (118-168)	0.021*	181 (141-215)	153 (121-191)	0.003**	0.010*
Heart rate (bpm)	65 (59-75)	63 (59-78)	0.843	66 (58-73)	67 (60-75)	0.275	0.828
BP systolic (mmHg)	135 (120-146)	129 (114-139)	0.010**	130 (119-144)	132 (115-144)	0.904	0.135
BP diastolic (mmHg)	66 (60-75)	67 (59-74)	0.940	64 (57-75)	66 (60-73)	0.549	0.360
AVA (cm²)	1.1 (0.9-1.4)	-	-	1.2 (1.0-1.3)	-	-	0.860
PPG (mmHg)	36 (26-48)	-	-	34 (24-45)	-	-	0.240
moderate AS (AVA 1.0 – 1.5cm^2) (n)	64 (70%)	-		77 (81%)	-		0.069
severe AS (AVA <1.0 cm^2) (n)	28 (30%)	-		18 (19%)	-		0.069
Inducible Ischemia (positive Stress CMR n (%))	25 (27%)	27 (29%)	0.744	32 (34%)	21 (22%)	0.076	0.335

Baseline characteristics of patients with aortic stenosis and controls. BMI - body-mass-index; NYHA – New York Heart Association functional classification; COPD – chronic obstructive pulmonary disease; NT-proBNP – N-terminal pro B-type Natriuretic Peptide; GFR – glomerular filtration rate. LV – left ventricle; EF – ejection fraction; EDV – end-diastolic volume; BP – blood pressure; AVA – aortic valve area; PPG – peak pressure gradient; AS – aortic stenosis; CMR – cardiac magnetic resonance. Values are mean ± SD, median (interquartile range) or n (%). Differences between patients with aortic stenosis controls without aortic stenosis were calculated using t-test, Mann-Whitney U test or chi-squared test. *p < 0.05; **p < 0.01; ***p < 0.001.

Table 2 Side effects during stress cardiac magnetic resonance imaging in patients with aortic stenosis

	Adenosine			Dobutamine			Adenosine vs. Dobutamine
	Patient Population (n=92)	Controls (n=92)	p	Patient Population (n=95)	Controls (n=95)	p	p
Total side effects (no. of patients)	1 (1.1%)	2 (2.2%)	0.562	19 (20%)	18 (19%)	0.855	0.0001***
Complaints (no. of patients)	1 (0%)	2 (2.2%)	0.562	15 (16%)	18 (19%)	0.567	0.0003***
Chest Pain	1 (0%)	1 (1.1%)	1.000	12 (13%)	14 (15%)	0.674	0.002**
Nausea (and emesis)	0 (0%)	1 (1.1%)	0.317	1 (1.1%)	1 (1.1%)	1.000	0.325
Dyspnea	0 (0%)	0 (0%)	-	1 (1.1%)	1 (1.1%)	1.000	0.325
Severe headache	0 (0%)	0 (0%)	-	0 (0%)	1 (1.1%)	0.317	-
Severe backpain	0 (0%)	0 (0%)	-	0 (0%)	1 (1.1%)	0.317	-
Minor Complications (no. of patients)	1 (1.1%)	0 (0%)	0.317	5 (5.3%)	3 (3.2%)	0.471	0.106
Paroxysmal atrial fibrillation	0 (0%)	0 (0%)	-	2 (2.1%)	0 (0%)	0.156	0.163
Supraventricular tachycardia	0 (0%)	0 (0%)	-	1 (1.1%)	0 (0%)	0.317	0.325
Premature ventricular complexes	0 (0%)	0 (0%)	-	0 (0%)	1 (1.1%)	0.317	-
AV-Block III°	1 (1.1%)	0 (0%)	0.317	0 (0%)	0 (0%)	0.317	0.310
Decrease of BP systolic (<60mmHg)	0 (0%)	0 (0%)	-	1 (1.1%)	2 (2.1%)	0.562	0.325
Increase of BP systolic (>180mmHg)	0 (0%)	0 (0%)	-	1 (1.1%)	0 (0%)	0.562	0.325
Major Complications (no. of patients)	0 (0%)	0 (0%)	-	0 (0%)	0 (0%)	-	-
Termination of Stress CMR	1 (1.1%)	2 (2.2%)	0.562	3 (3.2%)	4 (4.2%)	0.701	0.329

Side effects were divided in three categories; complaints, minor complications and major complications. BP – blood pressure; CMR – cardiac magnetic resonance. Values are n (%). Differences between patients with aortic stenosis and controls without aortic stenosis were calculated using chi-squared test. **p < 0.01; ***p < 0.001.

Table 3 Comparison of patients with aortic stenosis with and without side effects during dobutamine stress cardiac magnetic resonance imaging

	Patients with side effects (n=19)	Patients without side effects (n=76)	p
Demographics			
Age (years)	80 ± 5	74 ± 9	0.015*
Male sex (n)	16 (84%)	65 (84%)	0.886
BMI (kg/m²)	28 (25-29)	27 (24-30)	0.787
NYHA class	2 (1-3)	2 (1-3)	0.836
Cardiovascular risk factors			
Hypertension (n)	18 (95%)	71 (93%)	0.834
Hypercholesterolemia (n)	18 (95%)	49 (64%)	0.010*
Diabetes mellitus (n)	6 (32%)	34 (45%)	0.301
History of Smoking (n)	4 (21%)	29 (38%)	0.164
Family history of coronary artery disease (n)	6 (32%)	13 (17%)	0.161
Comorbidities			
Coronary artery disease (n)	18 (95%)	73 (96%)	0.659
Prior myocardial infarction (n)	9 (47%)	29 (38%)	0.466
Prior percutaneous coronary intervention (n)	13 (68%)	43 (57%)	0.351
Prior coronary artery bypass grafting (n)	9 (47%)	18 (24%)	0.042*
Prior stroke / transitory ischaemic attack (n)	5 (26%)	5 (7%)	0.013*
COPD (n)	4 (21%)	9 (12%)	0.299
Laboratory data			
high sensitive Troponin T (pg/ml)	52 (28-216)	27 (14-69)	0.018*
NT-proBNP (ng/l)	1780 (847-3202)	1266 (464-4404)	0.724
GFR (ml/min/1.73m²)	65 (49-79)	69 (44-85)	0.281
Cardiac morphology			
LV-EF (%)	57 (42-63)	52 (40-61)	0.443
LV-EDV (ml)	182 (125-206)	180 (152-215)	0.545
Heart rate (bpm)	67 ± 11	67 ± 14	0.741
BP systolic (mmHg)	133 ± 24	130 ± 19	0.542
BP diastolic (mmHg)	63 ± 13	67 ± 11	0.052
AVA (cm²)	1.2 (1.1-1.3)	1.2 (1.0-1.3)	0.910

PPG (mmHg)	35 (24-45)	34 (23-45)	0.810
Inducible Ischemia (positive Stress CMR n (%))	12 (63%)	20 (26%)	0.0025**

Comparison of patients with aortic stenosis with and without complications during dobutamine stress cardiac magnetic resonance imaging. BMI - body-mass-index; NYHA – New York Heart Association functional classification; COPD – chronic obstructive pulmonary disease; NT-proBNP – N-terminal pro B-type Natriuretic Peptide; GFR – glomerular filtration rate; LV – left ventricle; EF – ejection fraction; EDV – end-diastolic volume; bpm – beats per minute; BP – blood pressure; AVA – aortic valve area; PPG – peak pressure gradient; CMR – cardiac magnetic resonance. Values are mean ± SD, median (interquartile range) or n (%). Differences were calculated using t-test, Mann-Whitney U test or chi-squared test. *p < 0.05; **p < 0.01.

Table 4 Correlation analysis for the occurrence of side effects during dobutamine stress cardiac magnetic resonance imaging in patients with aortic stenosis

Occurrence of Side effects	Spearman's Rank Correlation Coefficient (r_s)	p
Age	0.199	0.032*
Hypercholesterolemia	0.266	0.009*
Prior stroke / transitory ischaemic attack	0.257	0.012*
Prior coronary artery bypass grafting	0.210	0.041*
Inducible Ischemia	0.312	0.002*
high sensitive Troponin T	0.195	0.060
NT-proBNP	0.052	0.640
LV-EF	0.013	0.888
AVA	0.069	0.462

Correlation analysis for the occurrence of complications during dobutamine stress cardiac magnetic resonance imaging (CMR) in patients with aortic stenosis. LV – left ventricle; EF – ejection fraction; AVA – aortic valve area; r_s - Spearman's rank correlation coefficient. Correlation analysis was calculated using Spearman's rank correlation. *p < 0.05.

Table 5 Univariable Analysis and Multivariable Analysis Models for the prediction of complications during dobutamine stress cardiac magnetic resonance imaging in patients with aortic stenosis

	Univariable Analysis			Multivariable Analysis Model 1			Multivariable Analysis Model 2		
Characteristics	**OR**	**95% CI**	**p**	**OR**	**95% CI**	**p**	**OR**	**95% CI**	**p**
Age	1.09	1.01 - 1.18	0.037*	1.10	1.00 - 1.20	0.042*	1.10	1.01 - 1.20	0.034*
Male sex	1.45	0.37 - 5.76	0.60						
BMI	1.00	0.89 - 1.11	0.95						
NYHA class	1.05	0.54 - 2.05	0.89						
Cardiovascular risk factors									
Hypertension	1.91	0.23 – 15.92	0.55						
Hypercholesterolemia	8.50	1.08 - 66.67	0.042*	5.12	0.55 – 47.94	0.15	4.99	0.54 - 46.06	0.16
Diabetes mellitus	0.71	0.25 - 2.03	0.52						
History of Smoking	0.40	0.11 - 1.48	0.17						
Family history of coronary artery disease	1.52	0.48 – 4.76	0.47						
Comorbidities									
Coronary artery disease	0.61	0.05 – 5.53	0.61						
Prior myocardial infarction	2.09	0.76 – 5.78	0.15						
Prior percutaneous coronary intervention	1.67	0.60 – 4.80	0.34						
Prior coronary artery bypass grafting	4.50	1.57 – 12.93	0.0052**	6.77	1.70 – 26.92	0.007**	5.39	1.49 – 19.45	0.005**
Prior stroke / transitory ischaemic attack	5.05	1.40 – 18.29	0.014*	6.69	1.30 – 34.35	0.023*	9.00	1.92 – 42.30	0.003**
COPD	2.29	0.64 – 8.19	0.20						
Laboratory data									
high sensitive Troponin T	1.00	1.00 - 1.01	0.10						
NT-proBNP	1.00	1.00 - 1.00	0.64						

GFR	0.99	0.97 - 1.01	0.26			
Cardiac morphology						
LV-EF	1.00	0.96 - 1.04	0.89			
LV EDV	1.00	0.99 - 1.01	0.80			
Heart rate	1.00	0.96 - 1.04	0.90			
BP systolic	1.01	0.98 - 1.04	0.66			
BP diastolic	0.97	0.92 - 1.02	0.18			
AVA	2.25	0.26 - 19.32	0.46			
PPG	0.99	0.96 - 1.02	0.52			
Inducible Ischemia	3.79	1.34 - 10.75	0.012*	4.00	1.13 – 14.07	0.031*

Univariable and Multivariable logistic analysis models for the prediction of the occurrence of complications during dobutamine stress cardiac magnetic resonance imaging in patients with aortic stenosis. BMI - body-mass-index; NYHA – New York Heart Association functional classification; COPD – chronic obstructive pulmonary disease; NT-proBNP – N-terminal pro B-type Natriuretic Peptide; GFR – glomerular filtration rate; LV – left ventricle; EF – ejection fraction; EDV – end-diastolic volume; BP – blood pressure; AVA – aortic valve area; PPG – peak pressure gradient; CMR – cardiac magnetic resonance. *p < 0.05; **p < 0.01.

Table 6 Details of patients with aortic stenosis and complications during stress during stress cardiac magnetic resonance imaging

Patient ID	Age	Gender (f=female; m=male)	AVA (cm²)	LV-EF (%)	Stress test result	Relevant comorbidities	Complication
1	86	f	1.4	69	positive (apical Tardokinesia)	HCM, bronchial Asthma	Chest pain (angina pectoris), quick recovery after stress test
2	83	m	1.0	46	positive	Severe 3 vessel disease, prior CABG 1991	Light chest pain (angina pectoris)
3	84	f	1.5	67	negative	3 vessel disease, prior CABG (LAD) 2015	Chest pain (atypical), quick improvement
4	81	m	1.3	39	negative	Severe 3 vessel disease, occluded LCx, COPD	Dobutamine induced paroxysmal atrial fibrillation
5	78	m	1.2	58	positive (in all vessels)	Severe 3 vessel disease, prior MI	Chest pain (angina pectoris), recovery 5 min after stress test
6	85	m	1.3	78	negative	Severe 3 vessel disease, prior CABG 1993	Chest pain (angina pectoris), recovery after administration of sublingual nitroglycerin
7	74	m	1.1	51	positive	3 vessel disease, prior CABG 1986, prior MI (RCA) 1984	Light chest pain (angina pectoris), quick recovery
8	82	m	1.0	38	negative	Severe 3 vessel disease, prior MI 2018, prior CABG 1994	Strong chest pain (angina pectoris), stress test was terminated at maximum dobutamine dose, recovery after administration of sublingual nitroglycerin
9	77	m	1.1	62	positive	3 vessel disease, chronic occluded RCA, prior MI 1979	Dobutamine induced paroxysmal atrial fibrillation, nausea and emesis, stress test was terminated at maximum dobutamine dose
10	79	m	0.6	36	negative	3 vessel disease, prior CABG 2006, COPD IV	Moderate chest pain (angina pectoris)
11	79	m	1.1	47	positive	Severe 3 vessel disease, prior CABG 2014	Chest pain (angina pectoris), recovery after administration of sublingual nitroglycerin
12	77	m	1.1	58	negative	3 vessel disease, chronic occluded RCA, prior CABG 2013	Strong chest pain (angina pectoris), quick recovery after stress test
13	73	m	1.1	57	negative	3 vessel disease, prior	Chest pain (angina pectoris)

						CABG 2005, CKD III	
14	88	f	1.5	41	positive	3 vessel disease, prior MI 2018, Pericarditis Epistenocardica, prior hemorrhagic shock 4 days before stress CMR	Decrease of systolic blood pressure (60mmHg), recovery after administration of 500ml saline solution
15	83	m	1.2	44	positive (1 segment apical)	3 vessel disease, prior stroke	Induced atrial tachycardia, recovery after administration of 10mg metoprolol
16	85	m	1.2	68	positive (1 segment anterior)	3 vessel disease, chronic RCA obstruction	Dyspnea
17	70	m	1.3	33	positive	Severe 3 vessel disease, prior MI 1991 and 1998	Chest pain (atypical) and dyspnea, stress test was terminated a maximum dobutamine dose
18	71	m	0.8	63	negative	3 vessel disease	Symptomatic hypertensive crisis, recovery after administration of 2.5mg metoprolol
19	81	m	0.9	62	positive (1 segment inferior-lateral)	Severe 3 vessel disease, severe stenosis of LCx	Chest pain (angina pectoris), recovery after administration of 7.5mg metoprolol and sublingual nitroglycerin
20	83	m	1.0	73	positive (6 segments anterior and lateral)	Severe 3 vessel disease, chronic occluded LCx, severe stenosis of left main stem	AV-Block III° after administration of Adenosine, stress test was terminated and Dobutamine stress test was performed instead. Hereby patient experienced chest pain (angina pectoris), with recovery after administration of 2.5mg metoprolol and sublingual nitroglycerin.

Details of patients with aortic stenosis and complications during stress during stress cardiac magnetic resonance imaging AVA – aortic valve area; HCM – hypertrophic cardiomyopathy; CABG – coronary artery bypass grafting; LAD – left anterior descending artery; LCx – left circumflex artery; COPD – chronic obstructive pulmonary disease; RCA – right coronary artery; MI – myocardial infarction; CKD - Chronic kidney disease.

Figures

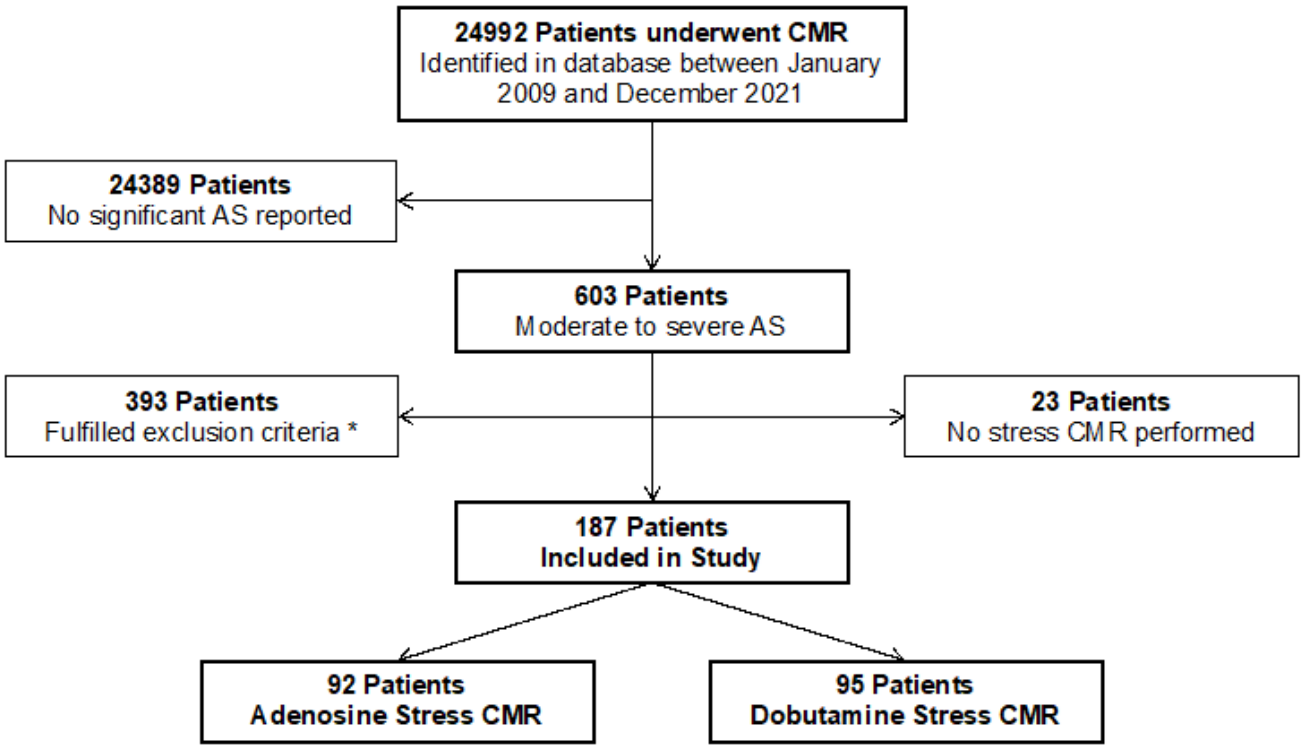

Figure 1

Flowchart of patient selection

Flowchart of patient selection who underwent stress cardiac magnetic resonance imaging and had an aortic valve stenosis.

*Exclusion criteria: prior transcatheter aortic valve replacement (TAVR), prior surgical aortic valve replacement. CMR - cardiac magnetic resonance, AS – aortic stenosis.