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Original Article

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Safety of Stress Cardiac Magnetic Resonance in Patients With Moderate to Severe Aortic Valve Stenosis

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ABSTRACT

BACKGROUND: Dobutamine and adenosine stress cardiac magnetic resonance (CMR) imaging is relatively contraindicated in patients with moderate to severe aortic valve stenosis (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 for exclusion of obstructive coronary artery disease were enrolled. We recorded clinical data, CMR and echocardiography findings, and complications as well as minor symptoms. Patients with AS were compared to matched individuals without AS.
RESULTS: A total of 187 patients with AS were identified and compared to age-, gender- and body mass index-matched 187 patients without AS. No severe complications were reported in the study nor the control group. The reported frequency of non-severe complications and minor symptoms were similar between the study and the control groups. Nineteen patients with AS experienced non-severe complications or minor symptoms 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 minor symptoms (p = 0.562). Four examinations were aborted because of chest pain, paroxysmal atrial fibrillation and third-degree atrioventricular block. Inducible ischaemia, prior coronary artery bypass grafting, prior stroke and age were associated with a higher incidence of complications and minor symptoms.
CONCLUSIONS: Moderate to severe AS was not associated with complications during CMR stress test. The incidence of non-severe complications and minor symptoms was greater with dobutamine.

Keywords: Aortic valve stenosis; Magnetic resonance imaging; Safety; Adenosine; Dobutamine

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INTRODUCTION

Dobutamine and adenosine stress cardiac magnetic resonance (CMR) imaging 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 (WMAs) 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 is the most common form of valvular heart disease in elderly patients.[10)11)] The evaluation of the functional significance of CAD in patients with severe AS before transcatheter aortic valve replacement (TAVR) or surgical aortic valve replacement (SAVR) is clinically relevant for planning a potential percutaneous coronary intervention or even coronary artery bypass grafting (CABG). 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 patients with moderate to severe AS is however still lacking. Likewise, the drop of arterial blood pressure (ABP) 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 left ventricular (LV), cause an increase of transvalvular resistance, leading to a further, possibly critical reduction of blood pressure (BP).[14)]

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.

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 or evaluation of the functional significance of known CAD. The study was approved by the local institutional ethics committee following 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) ≤ 1.5 cm^2. Reasons for dobutamine stress CMR were the following: contraindications for adenosine stress CMR, such as bronchoconstrictive or bronchospastic lung disease (e.g. asthma) and adenosine hypersensitivity, history of CABG, history of myocardial infarction with ST-segment elevation with reduced left ventricular ejection fraction (LV-EF), chronic total or subtotal coronary occlusion.[15)] Patients with prior TAVR and prior SAVR 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 CABG, prior stroke, chronic kidney disease and chronic obstructive pulmonary disease) were assessed using medical reports. CAD was defined as anatomic coronary narrowing > 50% as previously described.[16)]

High-sensitive troponin T and N-terminal pro B-type natriuretic peptide (NT-proBNP) were retrospectively collected if available. Creatinine was available in all patients. Glomerular filtration rate (mL/min/1.74m^2) was presented in all patients.

Adverse events were subdivided into severe and non-severe complications. Severe complications were defined as the following: death, myocardial infarction, severe arrhythmias, unstable angina, and stroke. Non-severe complications were defined as following: paroxysmal atrial fibrillation,

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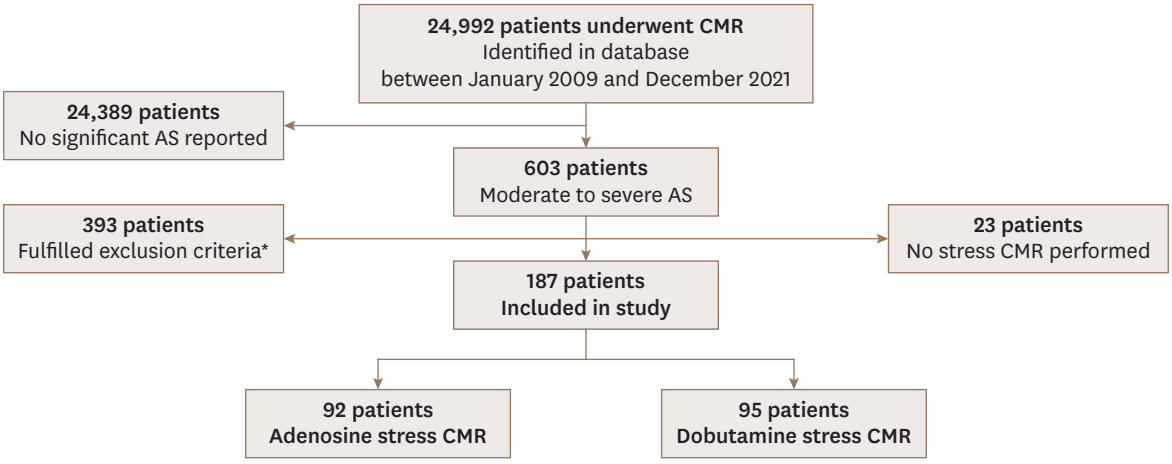

Figure 1. Flowchart of patient selection. Flowchart of patient selection who underwent stress cardiac magnetic resonance imaging and had an aortic valve stenosis.
AS: aortic stenosis, CMR: cardiac magnetic resonance.
*Exclusion criteria: prior transcatheter aortic valve replacement, prior surgical aortic valve replacement.

supraventricular tachycardia, premature ventricular complexes, AV-Blocks, decrease of BP (systolic BP [SBP] < 60 mmHg), and increase in BP (SBP > 180 mmHg).

We also recorded minor symptoms that disappeared during the test or shortly after the administration of beta-blockers or sublingual nitroglycerin. Minor symptoms were the following: chest pain (defined as mild to moderate thoracic discomfort described as pressure or squeezing in the chest, with or without radiation in shoulders, arms, as well as the back, neck, and jaw), nausea, emesis, dyspnea, pain besides chest pain.

Selection of controls

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

Echocardiography

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). Aortic valve gradients were calculated using continuous-wave Doppler signals 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. Details of echocardiography are available in the **Supplementary Data 1**.

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 were obtained using a breath-hold, segmented-k-space balanced steady-state free precession sequence (bSSFP) employing retrospective electrocardiogram or pulse oximetric gating. Data were analyzed using commercially available workstations (Viewforum™ and IntelliSpace™ Portal, ISP™; Philips Healthcare) and a certified software (cmr[42] Version 5.6.6, Circle Cardiovascular Imaging Inc., Calgary, Canada) as semi-automatic software for volumetric analysis. LV volumes and ejection fraction was acquired in short axis stacks. Details of acquisition and post-processing are available in the **Supplementary Data 1**.

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 140 μg/kg body weight/min (optional 210 μg/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) 0.2 mmol/kg body weight (before February 2016) or Gadobutol (Gadovist™, Bayer HealthCare, Leverkusen, Germany) 0.14 mmol/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

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of 5 mL/sec 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). The adenosine perfusion stress CMR protocol was the same for all three vendors. Adenosine Stress CMR is displayed in **Supplementary Figure 1**.

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 μg/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 0.25 mg increments (up to a maximal dose of 2.0 mg) if the target heart rate was not achieved. Cine loops were viewed online as they were acquired. Perfusion imaging was performed at maximum heart rate. A single-shot, turbo field GRE-EPI sequence was used as described above in 3-short-axis planes (apical, mid-ventricular, and basal). Images were acquired during the first pass of a 0.2 mmol/kg of body weight Magnevist™ (Schering, Berlin, Germany) or Gadovist™ (Bayer HealthCare) 0.14 mmol/kg body weight (1.5T) or 0.1 mmol/kg body weight (3T) (after February 2016).

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 SBP of > 40 mmHg, hypertension of > 220/120 mmHg, severe arrhythmias, new or worsening WMAs in at least 1 segment. Failure to attain 85% of age-predicted maximal heart rate was considered nondiagnostic. During the stress studies, the electrocardiographic rhythm, symptoms, peripheral BP, and oxygen saturation were continuously monitored. The dobutamine stress CMR protocol was the same for all three vendors. Dobutamine Stress CMR is displayed in **Supplementary Figure 1**.

Statistical analysis

Statistical analysis was performed using MedCalc™, version 15.7 (Ostend, Belgium), with $p < 0.05$ to indicate statistical significance for all statistical tests. Continuous and normally distributed variables (Kolmogorov-Smirnov test, $p \geq 0.05$) 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 the median and interquartile range, and group differences were tested using the nonparametric Mann-Whitney U test. Categorical variables were compared using the χ^2 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. We included 4 and 5 of the most significant variables for multivariable modeling. Results are reported as odds ratio (OR) 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, particularly hypertension and hypercholesterolemia, and suffered from CAD. Patients with AS had more severe heart failure, as defined by a higher NYHA (New York Heart Association) 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. The prevalence of inducible ischaemia in stress CMR was similar in both study groups (**Table 1**).

Patients undergoing adenosine stress CMR had a significantly higher stroke prevalence than controls ($p < 0.01$). 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, peak pressure gradient (PPG), and mean pressure gradient were similar in both study groups. The number of patients with severe AS was similar in the adenosine and the dobutamine group (**Table 1**).

Representative cases of patients with severe AS undergoing adenosine and dobutamine stress CMR are shown in **Figures 2** and **3** respectively.

Frequency and characteristics of complications and minor symptoms during stress CMR

There were no severe complications in either dobutamine or adenosine stress CMR in patients with AS. Considering both stress agents, a total of twenty patients with AS (11%)

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Table 1. Baseline characteristics of patients with aortic stenosis and controls

Variables	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	75 (82)	75 (82)	1.000	81 (85)	81 (85)	1.000	0.493
BMI (kg/m^2)	27 (25–31)	27 (25–29)	0.676	27 (24–30)	27 (25–29)	0.799	0.584
NYHA stage			0.024*			0.012*	0.149
1	25 (27)	41 (45)	-	27 (28)	43 (45)	-	
2	39 (42)	37 (40)	-	37 (39)	38 (40)	-	
3	26 (28)	14 (13)	-	29 (31)	14 (15)	-	
4	2 (2)	0 (0)	-	-	-	-	
n.a.	-	1 (1)	-	2	-	-	
Cardiovascular risk factors							
Hypertension	82 (89)	80 (87)	0.650	88 (93)	81 (85)	0.106	0.406
Hypercholesterolemia	64 (70)	62 (67)	0.752	66 (69)	70 (74)	0.521	0.989
Diabetes mellitus	34 (37)	22 (24)	0.055	39 (41)	28 (29)	0.096	0.567
History of Smoking	36 (39)	27 (29)	0.163	33 (35)	43 (45)	0.119	0.535
Family history of coronary artery disease	23 (25)	25 (27)	0.738	25 (26)	31 (33)	0.366	0.972
Comorbidities							
Coronary artery disease	83 (90)	78 (85)	0.525	90 (95)	89 (94)	0.223	0.242
Prior myocardial infarction	24 (26)	20 (22)	0.302	38 (40)	29 (31)	0.173	0.044*
Prior percutaneous coronary intervention	43 (47)	46 (50)	0.306	56 (59)	55 (58)	0.883	0.095
Prior coronary artery bypass grafting	4 (4.3)	6 (6.5)	0.288	27 (28)	27 (28)	1.000	0.0001‡
Prior stroke	14 (15)	3 (3)	0.008†	10 (11)	7 (7)	0.447	0.339
COPD	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 (483–2,038)	806 (126–1,844)	0.031*	1,576 (539–4,311)	427 (182–1,019)	0.0001‡	0.074
GFR (mL/min/1.73m^2)	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 (cm^2)	1.1 (0.9–1.4)	-	-	1.2 (1.0–1.3)	-	-	0.860
PPG (mmHg)	36 (26–48)	-	-	34 (24–45)	-	-	0.240
MPG (mmHg)	21 (15–28)	-	-	20 (14–26)	-	-	0.379
Moderate AS (AVA 1.0–1.5cm^2)	64 (70)	-		77 (81)	-		0.069
Severe AS (AVA < 1.0 cm^2)	28 (30)	-		18 (19)	-		0.069
Inducible ischemia (positive stress CMR)	25 (27)	27 (29)	0.744	32 (34)	21 (22)	0.076	0.335

Baseline characteristics of patients with aortic stenosis and controls. Values are mean ± SD, median (interquartile range) or number (%). Differences between patients with aortic stenosis controls without aortic stenosis were calculated using t-test, Mann-Whitney U test or χ^2 test.
AS: aortic stenosis, AVA: aortic valve area, BMI: body mass index, BP: blood pressure, CMR: cardiac magnetic resonance, COPD: chronic obstructive pulmonary disease, EDV: end-diastolic volume, EF: ejection fraction, GFR: glomerular filtration rate, LV: left ventricle, MPG: mean pressure gradient, NT-proBNP: N-terminal pro B-type natriuretic peptide, NYHA: New York Heart Association functional classification, PPG: peak pressure gradient.
*p < 0.05; †p < 0.01; ‡p < 0.001.

experienced non-severe complications or minor symptoms during stress CMR compared to nineteen patients without AS (10%), which was not significantly different (**Table 2**). The majority occurred during dobutamine stress CMR. Only one patient with AS experienced non-severe complications during adenosine 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 adenosine stress CMR examinations had to be aborted prematurely (**Table 2**).

Nineteen patients (20%) with AS and dobutamine stress CMR experienced non-severe and minor symptoms, which was not significantly different from 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

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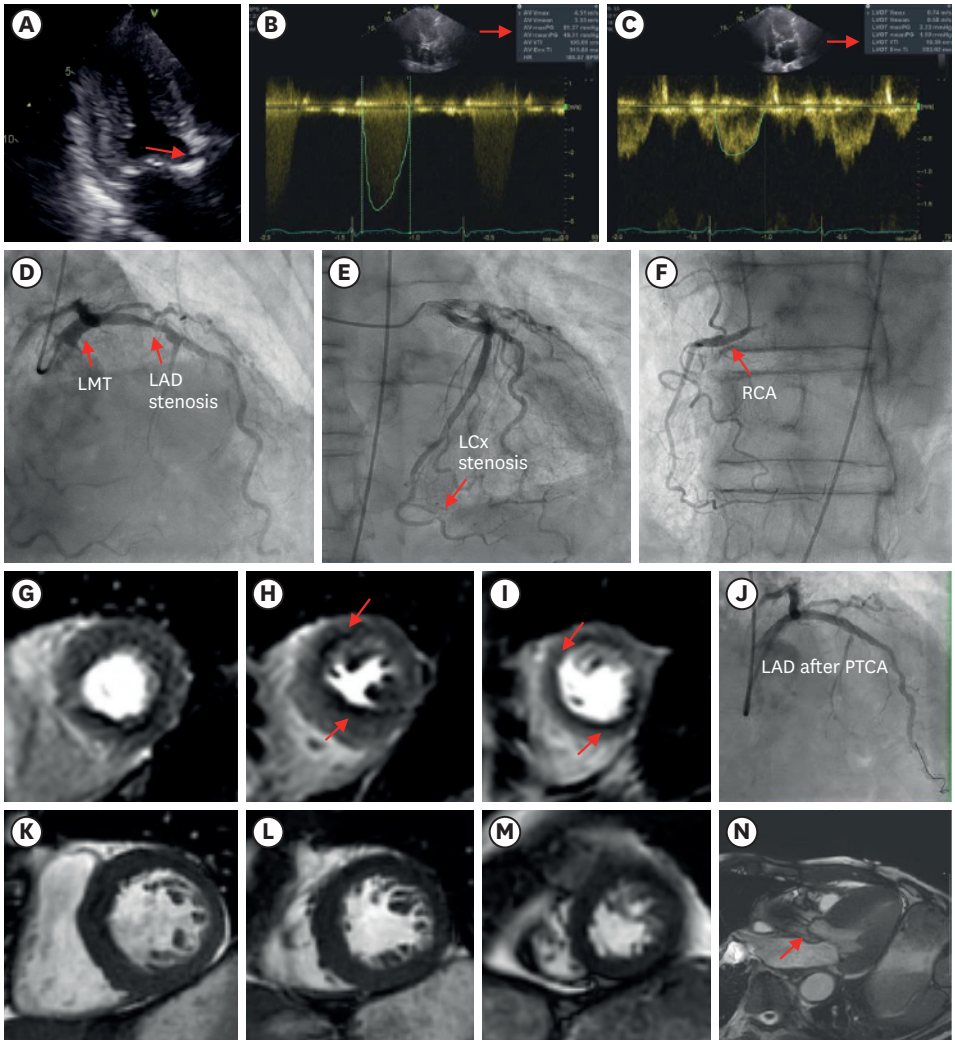

Figure 2. Representative case of adenosine stress cardiac magnetic resonance imaging in a patient with severe aortic valve stenosis. Representative case of adenosine stress CMR in a patient with severe AS: male patient (85 years old) with severe AS was referred for evaluation of transcatheter aortic valve replacement. In-house echocardiography confirmed the severe AS with an AVA of 0.5 cm^2. (A) 3-chamber view shows the severe calcification of the aortic valve with reduced AVA (red arrow). (B) Using continuous-wave doppler AS jet velocity (4.5 m/s), mean pressure gradient (49 mmHg), peak pressure gradient (81 mmHg) and VTI were calculated. (C) Using pulsed-wave Doppler was used to calculate VTI of left ventricular outflow tract to further calculate AVA. ICA was used to evaluate the degree of CAD. (D) ICA revealed a 75% stenosis of the proximal LAD (red arrow) (LMT). (E) 75% stenosis of the LCx (red arrow). (F) no significant stenosis of the right coronary artery. Adenosine Perfusion stress CMR was used to evaluate the functional significance of CAD–Perfusion image in basal (G), mid (H) and apical (I) short-axis plane. (G-I) Adenosine-perfusion revealed a new perfusion deficit in the LAD and LCx territory (red arrow). (J) In a second ICA, successful PTCA and stenting of the proximal LAD was performed with good results (red arrow). (K-N) CMR cine (K – basal, L – mid, M – apical) images also confirmed a hypertrophic LV with a normal LV ejection fraction (68%) and an AS (N) (red arrow).
AS: aortic valve stenosis, AVA: aortic valve area, CAD: coronary artery disease, CMR: cardiac magnetic resonance, ICA: invasive coronary angiography, LAD: left anterior descending artery, LCx: left circumflex artery, LMT: left main trunk, LV: left ventricle, PTCA: percutaneous transluminal coronary angioplasty, RCA: right coronary artery, VTI: velocity-time integral.

dyspnea (1.1%) during dobutamine stress CMR. The frequency of minor symptoms 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 non-severe 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 in SBP (< 60 mmHg) and an increase of SBP (> 180 mmHg) occurred in one patient each (1.1%) with AS. Two patients without AS had a drop of SBP (2.1%) and one patient suffered from premature ventricular complexes (1.1%). Three dobutamine stress CMR examinations had to be aborted in the patient group with AS and four in the one without AS (p = 0.701) (**Table 2**). Details of all patients with AS and complications during stress CMR examinations are presented in **Supplementary Table 1**.

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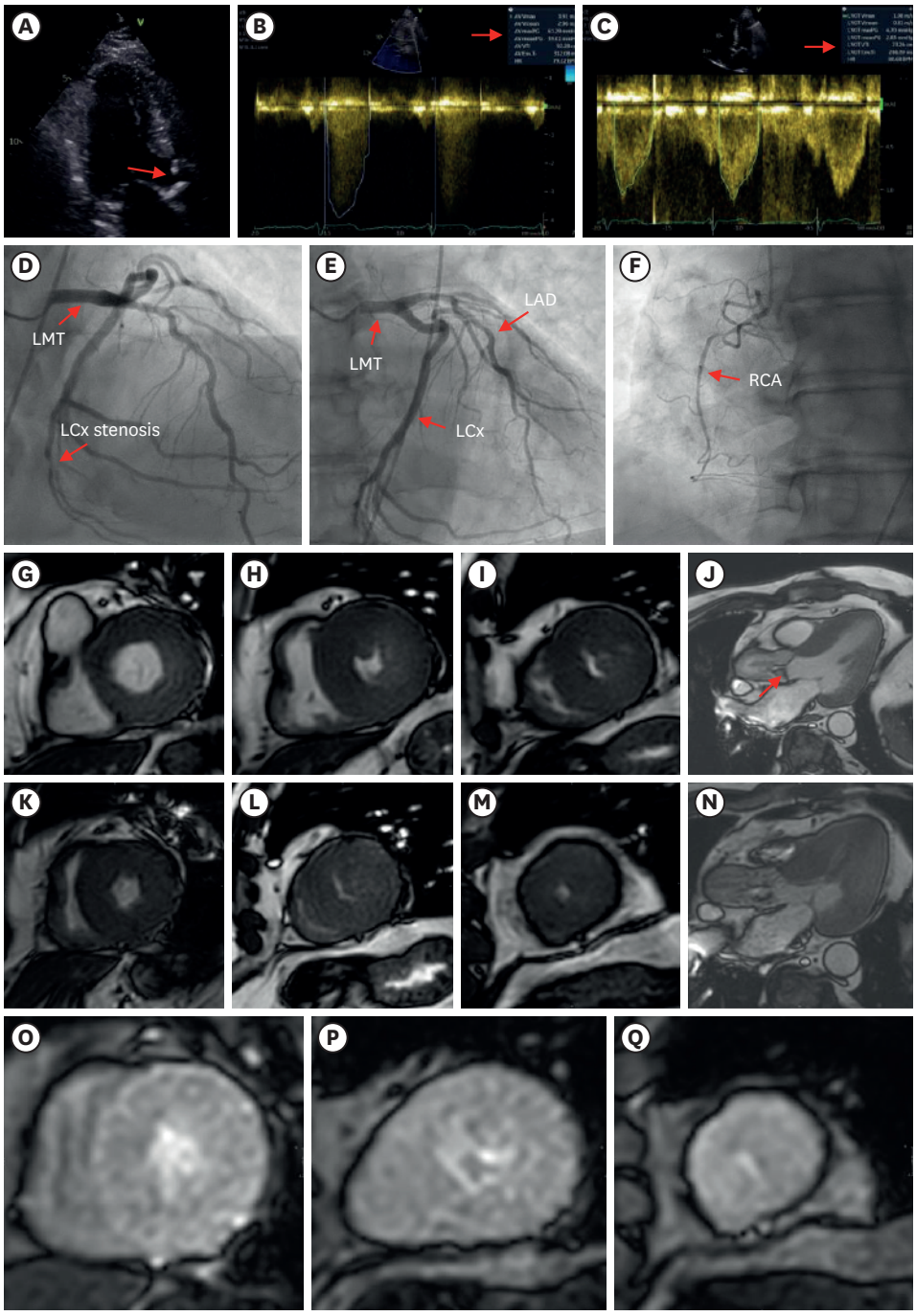

Figure 3. Representative case of dobutamine stress cardiac magnetic resonance imaging in a patient with severe aortic valve stenosis. Representative case of dobutamine stress CMR in a patient with severe AS: male patient (71 years old) with severe AS was referred for evaluation of transcatheter aortic valve replacement. In-house echocardiography confirmed the severe AS with an AVA of 0.8 cm^2. (A) 3-chamber view shows the severe calcification of the aortic valve with reduced AVA (arrow). (B) Using continuous-wave doppler AS jet velocity (3.9 m/s), mean pressure gradient (39 mmHg), peak pressure gradient (61 mmHg) and VTI were calculated. (C) Using pulsed-wave Doppler was used to calculate VTI of left ventricular outflow tract to further calculate AVA. ICA was used to evaluate the degree of CAD. (D-F) ICA revealed a 3-vessel disease with severe stenosis of the distal LCx (arrow) (LMT). No significant stenosis of the RCA. Dobutamine stress CMR was used to evaluate the functional significance of CAD. (G-I) CMR cine images at rest showed a hypertrophic LV with a normal LV ejection fraction (63%) (cine image in basal (G), mid (H) and apical (I) short-axis plane in end-systole). (J) 3-chamber view at end-systole shows the reduced opening of the aortic valve (arrow). (K-M) Dobutamine stress CMR at the highest stage (40 μg/kg of body weight/min) revealed a good contraction of all segments without inducible wall motion abnormalities, presumably due to good coronary collateral circulation (cine image in basal (K), mid (L) and apical (M) short-axis plane in end-systole). (N) 3-chamber view at end-systole shows the increased flow through the aortic valve with significant stenosis. (O-Q) Perfusion imaging at maximum heart rate revealed no significant perfusion deficit.
AS: aortic valve stenosis, AVA: aortic valve area, CAD: coronary artery disease, CMR: cardiac magnetic resonance, ICA: Invasive coronary angiography, LAD: left anterior descending artery, LCx: left circumflex artery, LMT: left main trunk, LV: left ventricle, RCA: right coronary artery, VTI: velocity-time integral.

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Table 2. Complications and minor symptoms during stress cardiac magnetic resonance imaging in patients with aortic stenosis

Variables	Adenosine			Dobutamine			Adenosine vs. dobutamine
	Patient population (n = 92)	Controls (n = 92)	p	Patient population (n = 95)	Controls (n = 95)	p	p
Total number of patients with complications/minor symptoms	1 (1.1)	2 (2.2)	0.562	19 (20)	18 (19)	0.855	0.0001†
Minor symptoms	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
Headache	0 (0)	0 (0)	-	0 (0)	1 (1.1)	0.317	-
Backpain	0 (0)	0 (0)	-	0 (0)	1 (1.1)	0.317	-
Non-severe complications	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 (> 180 mmHg)	0 (0)	0 (0)	-	1 (1.1)	0 (0)	0.562	0.325
Severe complications	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

Adverse events were divided in three categories; minor symptoms, non-severe complications and severe complications. Values are number (%). Differences between patients with aortic stenosis and controls without aortic stenosis were calculated using χ^2 test.
BP: blood pressure, CMR: cardiac magnetic resonance.
*p < 0.01; †p < 0.001.

Risk factors for stress-induced complications

Patients with AS and complications during dobutamine stress CMR were significantly older than patients without one (80 ± 5 years vs. 74 ± 9 years; p < 0.05). Additionally, patients with AS and complications had more often undergone prior CABG (patients with adverse events: 47%; patients without adverse events: 24%; p < 0.05) and suffered from a stroke in the past (patients with adverse events: 26%; patients without adverse events: 7%; p < 0.05). High-sensitive troponin T was significantly elevated in patients with complications during dobutamine stress CMR (Troponin T: patients with adverse events: 52 (28–216) vs. patients without adverse events: 27 (14–69); p < 0.05). Also, significantly more patients with complications had positive stress CMR results compared to patients without adverse events (63% vs. 26%; p < 0.01) (**Table 3**).

Increasing age, hypercholesterolemia, prior stroke, prior CABG, and inducible ischaemia mainly due to functional significant CAD moderately correlated moderately with the occurrence of complications in dobutamine stress CMR (p < 0.05). There was no significant correlation between high sensitive Troponin T, NT-proBNP, LV-EF, AVA, or PPG and the occurrence of complications (**Table 4**).

Univariable logistic regression analyses revealed that age, hypercholesterolemia, prior CABG, prior stroke, and inducible ischaemia were associated with complications in dobutamine stress CMR (**Table 5**). In a multivariable model older age, prior CABG and prior stroke and inducible ischaemia were independently associated with the incidence of complications (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 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 high 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).[23] Inducible WMAs in patients with suspected or known CAD are independently associated with all-cause mortality, cardiac death, cardiac transplantation, and myocardial infarction.[24] 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

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Table 3. Comparison of patients with aortic stenosis with and without complications or minor symptoms during dobutamine stress cardiac magnetic resonance imaging

Variables	Patients with complications/minor symptoms (n = 19)	Patients without complications/minor symptoms (n = 76)	p
Demographics			
Age (years)	80 ± 5	74 ± 9	0.015*
Male sex	16 (84)	65 (84)	0.886
BMI (kg/m²)	28 (25–29)	27 (24–30)	0.787
NYHA stage			0.588
1	5 (26)	22 (29)	
2	7 (37)	30 (40)	
3	6 (32)	23 (30)	
4	0 (0)	0 (0)	
n.a.	1 (5)	1 (1)	
Cardiovascular risk factors			
Hypertension	18 (95)	71 (93)	0.834
Hypercholesterolemia	18 (95)	49 (64)	0.010*
Diabetes mellitus	6 (32)	34 (45)	0.301
History of Smoking	4 (21)	29 (38)	0.164
Family history of coronary artery disease	6 (32)	13 (17)	0.161
Comorbidities			
Coronary artery disease	18 (95)	73 (96)	0.659
Prior myocardial infarction	9 (47)	29 (38)	0.466
Prior percutaneous coronary intervention	13 (68)	43 (57)	0.351
Prior coronary artery bypass grafting	9 (47)	18 (24)	0.042*
Prior stroke	5 (26)	5 (7)	0.013*
COPD	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)	1,780 (847–3,202)	1,266 (464–4,404)	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
MPG (mmHg)	20 (14–27)	19 (14–26)	0.696
Inducible ischemia (positive stress CMR)	12 (63)	20 (26)	0.003†

Comparison of patients with aortic stenosis with and without complications during dobutamine stress cardiac magnetic resonance imaging. Values are mean ± SD, median (interquartile range) or number (%). Differences were calculated using t-test, Mann-Whitney U test or χ^2 test.
AVA: aortic valve area, BMI: body mass index, BP: blood pressure, bpm: beats per minute, CMR: cardiac magnetic resonance, COPD: chronic obstructive pulmonary disease, EDV: end-diastolic volume, EF: ejection fraction, GFR: glomerular filtration rate, LV: left ventricle, NT-proBNP: N-terminal pro B-type natriuretic peptide, NYHA: New York Heart Association functional classification, PPG: peak pressure gradient.
*$p < 0.05$; †$p < 0.01$.

independently associated with major adverse cardiac events (MACE).[24] Furthermore, adenosine stress CMR is non-inferior to invasive angiography with FFR-measurement concerning the incidence of MACE at one year.[4] Dobutamine and adenosine stress CMR are also considered safe in high-risk patients, e.g. with complex congenital heart disease or prior kidney transplantation.[5][9][25-27]

We included patients with a high pre-test probability of inducible ischaemia and moderate to severe AS in this study. This high-risk patient group tolerated dobutamine and adenosine stress CMR without severe complications. Additionally, patients with AS did not have significantly more complications or minor symptoms compared to patients without AS. Previously, Wahl et al.[5] reported complications 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%). The incidence of paroxysmal atrial fibrillation, drop in SBP, severe increase in BP (> 240/120 mmHg), and transient AV-blocks can be confirmed by our results. The

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Table 4. Correlation analysis for the occurrence of complications and minor symptoms during dobutamine stress cardiac magnetic resonance imaging in patients with aortic stenosis

Occurrence of complications/minor symptoms	Spearman's rank correlation coefficient (r_s)	p
Age	0.199	0.032*
Hypercholesterolemia	0.266	0.009*
Prior stroke	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 in patients with aortic stenosis. Correlation analysis was calculated using Spearman's rank correlation.
AVA: aortic valve area, EF: ejection fraction, LV: left ventricle, NT-proBNP: N-terminal pro B-type natriuretic peptide, rs: Spearman's rank correlation coefficient.
*$p < 0.05$.

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

Characteristics	Univariable analysis			Multivariable analysis model 1			Multivariable analysis model 2		
	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	0.607						
BMI	1.00	0.89–1.11	0.949						
NYHA stage	1.05	0.54–2.05	0.888						
Cardiovascular risk factors									
Hypertension	1.91	0.23–15.92	0.550						
Hypercholesterolemia	8.50	1.08–66.67	0.042*	5.12	0.55–47.94	0.150	4.99	0.54–46.06	0.160
Diabetes mellitus	0.71	0.25–2.03	0.521						
History of Smoking	0.40	0.11–1.48	0.170						
Family history of coronary artery disease	1.52	0.48–4.76	0.473						
Comorbidities									
Coronary artery disease	0.61	0.05–5.53	0.606						
Prior myocardial infarction	2.09	0.76–5.78	0.154						
Prior percutaneous coronary intervention	1.67	0.60–4.80	0.344						
Prior coronary artery bypass grafting	4.50	1.57–12.93	0.005†	6.77	1.70–26.92	0.007†	5.39	1.49–19.45	0.005†
Prior stroke	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	0.204						
Laboratory data									
High sensitive Troponin T	1.00	1.00–1.01	0.097						
NT-proBNP	1.00	1.00–1.00	0.638						
GFR	0.99	0.97–1.01	0.265						
Cardiac morphology									
LV-EF	1.00	0.96–1.04	0.887						
LV EDV	1.00	0.99–1.01	0.800						
Heart rate	1.00	0.96–1.04	0.899						
BP systolic	1.01	0.98–1.04	0.657						
BP diastolic	0.97	0.92–1.02	0.184						
AVA	2.25	0.26–19.32	0.459						
PPG	0.99	0.96–1.02	0.519						
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.
AVA: aortic valve area, BMI: body-mass-index, BP: blood pressure, CI: confidence interval, CMR: cardiac magnetic resonance, COPD: chronic obstructive pulmonary disease, EDV: end-diastolic volume, EF: ejection fraction, GFR: glomerular filtration rate, LV: left ventricle, NT-proBNP: N-terminal pro B-type natriuretic peptide, NYHA: New York Heart Association functional classification, OR: odds ratio, PPG: peak pressure gradient.
*$p < 0.05$; †$p < 0.01$.

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 sizeable multicenter safety study, dobutamine stress CMR was performed in 554 patients.[27] 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, 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 the admission of gadolinium contrast medium.[27] Their study cohort was healthier than 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, severe complications 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.[28][29]

In our study, one patient with AS who underwent adenosine stress CMR suffered from third-degree AV-Block. We did not observe complications related to a drop in ABP induced by adenosine's vasodilatory effect 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] Adenosine stress CMR should be preferred in terms of safety in patients with severe AS.

In our study, patients with complications and minor symptoms were older and with a 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 than patients without complications. Chest pain, as the most often reported adverse event, 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 adverse events 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 adverse events in patients undergoing dobutamine stress CMR. Interestingly, inducible ischaemia is an independent factor associated with a higher incidence of severe complications during stress CMR using dobutamine or dipyridamole in previous studies.[27] Overall, an older population with severe vascular disease and inducible myocardial ischaemia seems to be at higher risk for complications during dobutamine stress CMR.

Concerning CMR safety, it is essential to consider that the observation of the patient may be limited due to the physical separation of the patient and health care staff. 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 patient's table allow for performing a rescue maneuver in about 30 seconds. An adequate reaction to complications, particularly the quick removal of a patient from the magnet in a life-threatening situation, needs to be trained with experienced MR-staff members frequently at the MR center. Patients need to be closely monitored, and resuscitation equipment, including an automated external defibrillator, must be available.

This retrospective study performed at a single center has a relatively small sample size, limiting the support for the conclusions regarding infrequent complications. The number of patients with severe AS (n = 30) was limited in our study. 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 trial of patients with severe AS is needed to confirm our results.

Additionally, patients were explicitly informed 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 happened. However, patients were monitored throughout the entire examination allowing immediate response to more moderate or 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.

Inducible myocardial ischaemia, assessed using adenosine stress CMR, is most likely due to significant CAD. However, patients with severe AS without obstructive CAD might suffer from microvascular dysfunction due to LV hypertrophy, as previously demonstrated.[30] To investigate microvascular dysfunction caused by severe AS, first-pass perfusion measurements at stress and rest states are required to calculate the myocardial perfusion reverse index.[30] Unfortunately, the first-pass perfusion measurement

at rest was not included in our standard protocol for adenosine stress CMR and additional studies would be necessary to evaluate possible microvascular dysfunction.

Stress CMR for ruling out inducible myocardial ischaemia appears safe in patients with moderate and severe aortic valve stenosis. The safety profile and rate of adverse events 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 adverse events. Adenosine perfusion CMR was associated with significantly fewer complications and minor symptoms than dobutamine stress CMR.

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SUPPLEMENTARY MATERIALS

Supplementary Data 1

Supplementary Methods

Click here to view

Supplementary Table 1

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

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Supplementary Figure 1

Dobutamine and adenosine stress CMR protocols. Protocols for dobutamine and adenosine stress CMR including time duration.

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Conflict of Interest

The authors have no financial conflicts of interest.

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