

## Myocardial Ischemia in Severe Aortic Regurgitation Despite Angiographically Normal Coronary Arteries

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Patients with severe aortic regurgitation frequently present with angina pectoris. The exact pathophysiology for angina in aortic regurgitation is not clear. Left ventricular hypertrophy and myocardial blood supply-demand mismatch have been the suggested mechanisms to explain ischemia. However, no conclusive clinical study exists to define the incidence of ischemia in patients with severe aortic regurgitation and normal coronary arteries. We, therefore, investigated the frequency of myocardial ischemia in relation to left ventricular hypertrophy or dilatation in patients with severe aortic regurgitation and normal coronary arteries. We reviewed the medical records of all patients ( $n = 311$ ) with aortic valve replacement due to aortic regurgitation between 2007 and 2010. We selected subjects with normal coronary arteries ( $n = 182$ ) for the study purpose, and we identified 35 patients who underwent myocardial perfusion scintigraphy prior to the coronary angiography (19 female and 16 male subjects; age  $45.0 \pm 8.9$  years). Left ventricular hypertrophy and dilatation were detected in 9 (26%) and 5 (14%) patients, respectively. Myocardial perfusion scintigraphy showed evidence of ischemia in 10 (29%) patients with normal coronary arteries. The presence of ischemia did not relate to the presence of left ventricular hypertrophy and/or dilatation. As a potential mechanism, aortic regurgitation causes backflow of blood from the aorta into the left ventricle, hence disturbs coronary flow dynamics. In conclusion, myocardial ischemia is common (nearly one-third) among patients with severe aortic regurgitation even in the absence of coronary obstruction, left ventricular hypertrophy and/or dilatation.

**Keywords:** aortic valve regurgitation; coronary angiography; myocardial ischemia; myocardial perfusion scintigraphy; normal coronary arteries

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Aortic regurgitation (AR) is a significant valvular pathology and defined as the backflow of blood from the aorta into the left ventricle due to insufficiency of the aortic semilunar valve. Aortic regurgitation may be caused by a number of different etiologies, including congenital malformation (i.e., bicuspid aortic valve), calcific degeneration, rheumatic disease, infective endocarditis, dissection of the ascending aorta, systemic hypertension, and Marfan syndrome (Dujardin et al. 1999; Bonow et al. 2006). Aortic regurgitation can be categorized by chronicity (acute vs. chronic) and severity (mild, moderate, severe). In contrast to acute aortic regurgitation (develops suddenly), chronic aortic regurgitation may often remain asymptomatic for many years until late in the course of the disease (Tabayashi et al. 1990). In chronic aortic regurgitation, volume overload in the left ventricle (LV) is gradually compensated for

by left ventricular dilatation and hypertrophy (Ross 1974; Tezuka 1982).

Angina pectoris is a common symptom of severe aortic regurgitation. Myocardial ischemia can occur even in the absence of coronary obstruction in patients with severe aortic regurgitation (Segal et al. 1956). Without surgery, mortality remains high for patients with severe aortic regurgitation after the onset of angina (Dujardin et al. 1999). Therefore, it is crucial to monitor ischemia in subjects with aortic regurgitation. The etiology of myocardial ischemia in the absence of coronary obstruction has been the subject of clinical observational studies. Supply/demand mismatch in the presence of increased ventricular afterload and wall stress has been put forward as a potential mechanism to cause ischemia with severe aortic regurgitation. However, the exact mechanism(s) for angina pectoris in patients with

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severe aortic regurgitation remains unclear. Segal et al. (1956) reported that out of 100 patients with severe aortic regurgitation, 38% had angina pectoris. Yet the autopsy results of those who died after surgery revealed no signs of coronary artery disease. Myocardial perfusion scintigraphy (MPS) can provide an accurate estimation of the presence and location of myocardial ischemia in subjects with severe aortic regurgitation. We aim to study the frequency of myocardial ischemia, in relation to left ventricular hypertrophy or dilatation, in the presence of angiographically normal coronary arteries and severe aortic regurgitation.

## Materials and Methods

### *Study population*

The study is cross-sectional. We reviewed the medical records of all patients ( $n = 311$ ) with aortic valve replacement due to aortic regurgitation between January 2007 and January 2010. All patients had coronary angiograms prior to surgery. We reviewed coronary angiography findings of all patients ( $n = 311$ ). We selected subjects with normal coronary arteries ( $n = 182$ ) for the study purpose, and we identified 35 patients who underwent MPS prior to the coronary angiography (19 female and 16 male subjects; age  $45.0 \pm 8.9$  years). We investigated the presence and location of ischemia by MPS findings in 35 patients with normal coronary arteries and severe aortic regurgitation.

The clinical indications for coronary angiography included symptoms of angina pectoris, chest discomfort, shortness of breath, diminished exercise tolerance, and/or ischemia work-up before the planned aortic valve surgery. The coronary angiography and MPS findings of 35 subjects were reviewed by independent operators.

Patients with a prior history of coronary artery disease, aortic stenosis, and/or significant comorbidities including risk factors for cardiovascular disease (diabetes mellitus, end-stage renal disease, smoking, arterial hypertension, hypercholesterolemia, obesity, previous history of atherosclerosis) were excluded from the study.

The severity of aortic regurgitation was assessed by echocardiography (Vivid 7, General Electric-Vingmed, Milwaukee, Wisconsin). Both visual estimation of the regurgitant jet area and regurgitant volume were required to confirm the severity of aortic regurgitation.

In all subjects, the regurgitation volume was calculated by echocardiography. Severe aortic regurgitation was defined as a regurgitant volume of  $\geq 60$  ml/beat and a regurgitant jet pressure half time (PHT) of  $< 200$  msec. Moderate to severe aortic regurgitation is defined as a regurgitant volume between 45-59 ml/beat and a regurgitant PHT between 200-500 msec (Zoghbi et al. 2003).

The Devereux formula was used to assess left ventricular hypertrophy by echocardiography. LV mass over  $108 \text{ g/m}^2$  for female patients and over  $131 \text{ g/m}^2$  for male patients was considered as hypertrophy. LV diastolic diameter over 5.7 cm for female patients and over 6.3 cm for male patients was accepted as LV dilatation (Lang et al. 2005).

### *Coronary angiography and myocardial perfusion scintigraphy (MPS)*

Patients with angiographic evidence of coronary artery disease were excluded from the study. All patients had angiographically normal coronary arteries by report. Angiographic findings were reviewed by three independent operators. Normal coronary angiogram was

defined as absence of any visible angiographic signs of atherosclerosis, thrombosis, or spontaneous spasm.

MPS (Siemens e.cam dual-head gamma camera, Erlangen, Germany) was performed by exercise-technetium-99m (Tc-99m) sestamibi single-photon emission computed tomography (SPECT) imaging procedure in all patients. Three independent experts reviewed the study.

The patients were divided into two groups, based on the presence or absence of ischemia. Statistical analysis was performed using the Statistical Program for Social Sciences (version 15.0; SPSS Inc., Chicago, IL, USA). Descriptive statistics were expressed as the mean  $\pm$  standard deviation (s.d.) for numerical variables and percentage (%) for categorical variables. Mean  $\pm$  s.d. values were provided for continuous variables with normal distribution. Absolute and relative percentages (%) were provided for categorical variables. Univariate comparisons of continuous variables were performed by Student's *t*-tests. Chi-square tests or Fisher's exact tests were used to compare the categorical variables. Statistical significance was set at a  $p < 0.05$ .

The study was approved by the institutional ethics committee of Dr. Siyami Ersek, Thoracic and Cardiovascular Surgery Training and Research Hospital, with human subjects, and informed consent was obtained from all subjects.

## Results

### *Study population*

Thirty-five patients were identified from the medical records. These patients had undergone aortic valve replacement for severe aortic regurgitation (19 female and 16 male; age  $45.0 \pm 8.9$ ). Surface echocardiographic examination, exercise-Tc-99m MPS, and selective coronary angiography were performed on all patients. Presenting symptoms included angina pectoris, chest discomfort, shortness of breath, and diminished exercise tolerance. Patient characteristics, as well as echocardiographic and catheterization data are summarized in Table 1.

### *Myocardial perfusion scintigraphy (MPS) and coronary angiographic findings*

Exercise-Tc-99m MPS showed evidence of ischemia in 10 (29%) patients. Ischemia was located at the antero-septal ( $n = 5$ ), anterior ( $n = 1$ ), inferior ( $n = 3$ ), or apical ( $n = 1$ ) segments. MPS did not demonstrate ischemia in the remaining 25 patients.

Previous studies reported a false positive rate for MPS with Tc-99m of approximately 10% (Abdelmoneim et al. 2010). Internal sensitivity and specificity of MPS with Tc-99m in our hospital was similar to that in the literature (11%). Therefore, we observed nearly a threefold increase in the incidence of myocardial ischemia among patients with severe aortic regurgitation even in the absence of coronary obstruction. There was no significant relationship between the presence of ischemia and left ventricular hypertrophy ( $p = 0.393$ ) or dilatation ( $p = 1.000$ ).

### *Left ventricle ischemia and echocardiographic parameters*

Bicuspid aortic valve (having 2 cusps instead of 3) is a common congenital heart anomaly and common cause of

Table 1. Clinical, Echocardiographic and Catheterization data, among subjects with and without ischemia.

	Patients with ischemia (n = 10)	Patients without ischemia (n = 25)	P value
Female, n (%)	5 (50)	14 (56)	1.0
Age, years (Mean $\pm$ s.d.)	47.0 $\pm$ 7.2	44.2 $\pm$ 9.6	0.4
Rheumatic disease, n (%)	8 (80)	20 (80)	1.0
Bicuspid aorta, n (%)	2 (20)	5 (20)	1.0
Severe AR, n (%)	10 (100)	22 (88)	0.2
Left ventricular hypertrophy, n (%)	5 (20)	4 (40)	0.3
Left ventricular dilatation, n (%)	4 (16)	1 (10)	1.0
EF %	64.0 $\pm$ 4.5	62.6 $\pm$ 5.0	0.4
LV MASS (g/m <sup>2</sup> )	243.3 $\pm$ 105.5	216.7 $\pm$ 74.0	0.4
LVEDD (cm)	5.5 $\pm$ 0.7	5.3 $\pm$ 0.7	0.6
LVESD (cm)	3.5 $\pm$ 0.5	3.4 $\pm$ 0.8	0.9
IVST (cm)	1.0 $\pm$ 0.2	1.0 $\pm$ 0.1	0.6
PWT (cm)	1.0 $\pm$ 0.2	1.0 $\pm$ 0.1	0.5
AR- PHT (msec)	173.0 $\pm$ 15.6	188.0 $\pm$ 15.7	<b>0.02</b>
RV (ml / beat)	72.2 $\pm$ 2.44	69.7 $\pm$ 2.27	<b>0.01</b>
LV Systolic Pressure (mmHg)	163.1 $\pm$ 18.0	169.3 $\pm$ 11.8	0.2
LV Diastolic Pressure (mmHg)	20.3 $\pm$ 4.0	21.0 $\pm$ 4.1	0.6
Aortic Systolic Pressure (mmHg)	144.9 $\pm$ 14.9	149.9 $\pm$ 11.9	0.2
Aortic Diastolic Pressure (mmHg)	54.0 $\pm$ 10.5	57.8 $\pm$ 9.2	0.2
Mean Aortic Pressure (mmHg)	84.3 $\pm$ 10.2	88.5 $\pm$ 8.3	0.2
Mean aortic gradient (mmHg)	18.2 $\pm$ 5.67	19.4 $\pm$ 5.95	0.6

AR, Aortic Regurgitation; LVEDD, Left Ventricular End-Diastolic Diameter; LVESD, Left Ventricular End-Systolic Diameter; IVST, Interventricular Septum Thickness; PWT, Posterior Wall Thickness; EF, Ejection Fraction; AR PHT, Aortic Regurgitation Pressure Half Time; RV, Regurgitan Volume.

aortic regurgitation and aortic stenosis. Bicuspid aortic valve was present in seven (20%) patients. Aortic stenosis can cause ischemia (Julius et al. 1997). None of the patients included with bicuspid aortic valve had evidence of significant aortic stenosis. Stenosis of the aortic valve leads to a pressure gradient between the left ventricle and aorta. Mean aortic gradient were similar among patients with and without ischemia ( $18.2 \pm 5.6$  versus  $19.4 \pm 5.9$  mmHg,  $p = 0.6$ ).

Aortic regurgitation was due to rheumatic heart disease in the remaining 28 patients (80%). Mild mitral regurgitation or stenosis was detected in four patients (11%). Subjects with ischemia displayed significantly higher regurgitant volume (RV) and significantly lower PHT compared to subjects without ischemia (Table 1). Left ventricular hypertrophy or dilatation was present in 14 patients (40%). The average left ventricular ejection fraction was calculated to be  $64.6 \pm 9.4\%$ .

### Discussion

The exact mechanism(s) for angina pectoris and ischemia in patients with severe aortic regurgitation remain unclear. Prior small clinical studies failed to elucidate the prevalence, location and mechanisms of myocardial ischemia in the setting of aortic regurgitation. In this cross-sectional

study, we investigated the frequency of myocardial ischemia and its relation to left ventricular hypertrophy or dilatation in the setting of normal coronary arteries and severe aortic regurgitation. We observed a nearly threefold increase in the incidence of myocardial ischemia among patients with severe aortic regurgitation even in the absence of coronary obstruction. Furthermore, the presence of ischemia did not relate to the presence of left ventricular hypertrophy and/or dilatation.

To the best of our knowledge, our observations constitute the largest study to document the prevalence and location of myocardial ischemia in patients with severe aortic regurgitation and normal coronary arteries. The etiology of myocardial ischemia in the absence of coronary stenosis may be related to supply/demand mismatch in the presence of increased ventricular afterload. Our observations suggest that potential mechanisms for ischemia in the setting of severe aortic regurgitation may involve disturbed coronary flow dynamics by the reversal of blood flow from the aorta into the left ventricle. Severe aortic regurgitation may create coronary steal and myocardial ischemia in patients, particularly in the presence of increased left ventricular afterload. Our observations may elucidate the pathophysiology of aortic regurgitation. Furthermore, we did not observe any association between the ischemia and left ventricular

hypertrophy or dilatation, suggesting that the disturbed coronary flow dynamics may result in ischemia in the setting of severe aortic regurgitation.

Yasuda et al. (2005) reported that myocardial perfusion defects were present in all patients in a series of 11 cases with aortic regurgitation. The authors suggested that abnormal perfusion was indicative of both structural changes in the myocardium (i.e., cellular hypertrophy and interstitial fibrosis) and ischemia. A number of transesophageal Doppler echocardiography studies in patients with chronic aortic regurgitation displayed a decreased coronary flow reserve during systole and diastole (Nitenberg et al. 1988; Tamborini et al. 1995; Kisanuki et al. 1996, 1997). In these studies, decreased coronary flow reserve was attributed to increased left ventricular mass and decreased vascular resistance of the coronary arteries. However, myocardial perfusion was not assessed in these studies. Therefore, the question arises whether decreased coronary blood flow as a result of aortic regurgitation is associated with abnormal myocardial perfusion. Small pilot clinical studies have demonstrated myocardial perfusion abnormalities in patients with aortic regurgitation by thallium 201 MPS (Abe et al. 1992; Yamazaki et al. 1996; Yasuda et al. 2005). However, larger studies are needed to understand the prevalence and pathophysiology of myocardial ischemia with severe aortic regurgitation.

We observed that 7 of 10 patients had anterior, antero-septal, or apical ischemia. The localization of perfusion defects in our study (mainly involving the anterior segment) supports the prior observations in an animal model. Retrograde coronary flow was demonstrated in a dog model by Nakao et al. (1987). Shortly after the onset of aortic regurgitation, left anterior descending artery (LAD) flow decreased significantly (Nakao et al. 1987). The anatomical location of the left coronary cusp (anatomically higher than right coronary cusp) might make the left coronary system more prone to flow reversal in the setting of disturbed flow dynamics.

We observed a significant difference in regurgitant volume and aortic regurgitant jet pressure half time among subjects with ischemia compared to subjects without ischemia, suggesting that severity of valvular regurgitation is crucial in determining myocardial perfusion. Carroll and Falsetti (1976) studied coronary flow in 8 patients with pure aortic regurgitation. Retrograde coronary flow was detected during end diastole in 6 (75%) of the subjects. The authors concluded that intramyocardial stress in the left ventricle played an important role in the reversal of coronary flow in the setting of aortic regurgitation.

Our study is cross-sectional and comes with several limitations. Even though we reviewed the medical records of all patients with aortic valve replacement due to severe aortic regurgitation between January 2007 and January 2010, we included only a subset of patients with MPS prior to the coronary angiography. Therefore we cannot rule out a selection bias. However, angina is very common for sub-

jects with aortic regurgitation and it is likely that several mechanisms play a role in production ischemia in the setting of severe aortic regurgitation. Our study was observational and small in size. We obviously need future experimental models to confirm mechanisms of ischemia in the setting of severe aortic regurgitation. Fractional flow reserve (FFR) was not performed in any of the cases. FFR could have documented disturbed coronary flow dynamics in severe aortic regurgitation.

In conclusion, severe aortic regurgitation may be associated with myocardial ischemia even in the absence of coronary obstruction. In support of our hypothesis, we determined that nearly one-third of our patients had myocardial ischemia and there was no relation between ischemia and left ventricular hypertrophy or dilatation. Future prospective studies with FFR are needed to clarify coronary physiology in patients with severe aortic regurgitation.

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### Conflict of Interest

The authors have no conflict of interest to disclose regarding this paper.

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