Mechanisms of Coronary Microcirculatory Dysfunction in Patients With Aortic Stenosis and Angiographically Normal Coronary Arteries

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Background—Development of left ventricular hypertrophy in aortic stenosis (AS) is accompanied by coronary microcirculatory dysfunction, demonstrated by an impaired coronary vasodilator reserve (CVR). However, evidence for regional abnormalities in myocardial blood flow (MBF) and the potential mechanisms is limited. The aims of this study were to quantitatively demonstrate differences in subendocardial and subepicardial microcirculation and to investigate the relative contribution of myocyte hypertrophy, hemodynamic load, severity of AS, and coronary perfusion to impairment in microcirculatory function.

Methods and Results—Twenty patients with isolated moderate to severe AS were studied using echocardiography to assess severity of AS, cardiovascular magnetic resonance to measure left ventricular mass (LVM), and PET to quantify resting and hyperemic (dipyridamole 0.56 mg/kg) MBF and CVR in both the subendocardium and subepicardium. In the patients with most severe AS (n=15), the subendocardial to subepicardial MBF ratio decreased from 1.14±0.17 at rest to 0.92±0.17 during hyperemia (P<0.005), and subendocardial CVR (1.43±0.33) was lower than subepicardial CVR (1.78±0.35; P=0.01). Resting total LV blood flow was linearly related to LVM, whereas CVR was not. Increase of total LV blood flow during hyperemia (mean value, 89.6±59.6%; range, 17% to 233%) was linearly related to aortic valve area. The decrease in CVR was related to severity of AS, increase in hemodynamic load, and reduction in diastolic perfusion time, particularly in the subendocardium.

Conclusions—CVR was more severely impaired in the subendocardium in patients with LVH attributable to severe AS. Severity of impairment was related to aortic valve area, hemodynamic load imposed, and diastolic perfusion rather than to LVM. (Circulation. 2002;105:470-476.)

Key Words: valves ■ microcirculation ■ blood flow ■ myocardium ■ imaging

Development of left ventricular hypertrophy (LVH) in patients with aortic valve stenosis (AS) is an adaptive response that attempts to reduce wall stress in the left ventricle.1 Development of LVH also affects the coronary circulation, and patients with AS have a reduced coronary vasodilator reserve (CVR) despite angiographically normal coronary arteries.2 This impairment of CVR is mainly attributable to a curtailment in maximal myocardial blood flow (MBF),3 which, in the absence of epicardial stenosis, reflects dysfunction of the coronary microcirculation.4 Hyperemia is hindered by a series of unfavorable hemodynamic changes, including high LV cavity pressure, low coronary perfusion pressure, and increased extravascular compressive forces that lead to an increased minimal coronary resistance.5 In addition, characteristic pathological changes that contribute to impair microvascular function have been described in the hypertrophied ventricle of patients with AS. These consist of perimyocytic fibrosis6 and reduction in the number of resistance vessels per unit of weight.2 However, the interplay among microvascular dysfunction, severity of AS, hemodynamic overload, and coronary perfusion remains poorly understood.7

Although PET allows the noninvasive quantification of MBF, limitations in the spatial resolution of PET cameras have thus far allowed the demonstration of subendocardial hypoperfusion only in massively hypertrophied septa (>25 mm) of hypertrophic cardiomyopathy patients.8 Recent advances in PET scanner technology9 have now made it possible to study the transmural distribution of MBF in patients with lesser degrees of LVH, as in AS. Therefore, the

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aims of the present study were to measure subendocardial and subepicardial MBF and CVR using high-resolution PET with oxygen 15–labeled water (H$_{2}^{15}$O) and to determine the relative effect of LV mass (LVM), severity of AS, hemodynamic load, and coronary perfusion on subendocardial and subepicardial MBF and CVR in patients with AS and angiographically normal epicardial arteries using echocardiography and cardiovascular magnetic resonance (CMR).

Methods

Patient Selection

Patients with isolated moderate to severe AS were enrolled. Selection criteria included a peak transvalvular gradient of >50 mm Hg, no more than minimal aortic regurgitation (grade≤1 of 4), angiographically normal coronary arteries, systemic systolic blood pressure <160 mm Hg, and diastolic blood pressure <90 mm Hg. Patients were excluded if they had asthma, because this precluded the use of dipyridamole as a stressor agent, or if they were taking β-blockers, ACE inhibitors, calcium channel blockers, or diuretic therapy. In all, 20 patients (16 male) completed all the scans. The research and ethics committees of all the participating hospitals approved the study, and the subjects gave informed written consent before any investigations. All procedures were carried out in accordance with institutional guidelines, and radiation exposure was approved by the UK Administration of Radioactive Substances Advisory Committee.

Echocardiography

Transthoracic echocardiography was performed using an ATL HDI 3000 (ATL Ltd, Bothwell) cardiac ultrasound scanner according to American Society of Echocardiography guidelines. LV dimensions were measured at end diastole by two-dimensional guided M-mode echocardiography, and continuous wave (CW) Doppler was used to derive the peak transvalvular pressure gradient across the aortic valve (peak transvalvular pressure gradient). Aortic valve area (AVA) was calculated according to the American College of Cardiology and American Heart Association guidelines to determine severity of aortic stenosis. Left ventricular ejection time (LVET, seconds) was measured on the CW Doppler trace from the opening to the closure of the aortic valve. To assess diastolic LV function, pulsed-wave Doppler transmural inflow was obtained from the apical 4-chamber view, and the following measurements were obtained in accordance with published standards: rapid LV filling-phase peak velocity of E wave (E), atrial contraction-phase peak velocity of A wave (A), and the E to A ratio. Isovolumic relaxation time was measured from the apical 5-chamber view from the end of aortic flow to the beginning of mitral inflow with the sample volume placed between the mitral valve and the LV outflow. The mean of 3 separate readings was used for each parameter.

Cardiovascular Magnetic Resonance

LV function and mass were assessed using a Picker Edge 1.5-T scanner (Picker) with ECG triggering and a standard body coil. The cardiac short axis was determined from 3 scout images. The initial transaxial scout was used to define the vertical long-axis scout from the LV apex to the center of the mitral valve. The horizontal long-axis scout was aligned through the apex and mitral valve on the vertical long-axis scout image. A diastolic image at end expiration on the horizontal long-axis image provided the reference image on which short-axis slices were positioned. Contiguous 10-mm short-axis slices were acquired during a single breathhold using a segmented gradient-echo TurboFLASH sequence, and end-diastolic volume, end-systolic volume, ejection fraction, and mass were calculated. Presence of LVH was determined using criteria described by Lorenz et al. (LVM index ≥113 or 95 g/m² in men and women, respectively). Image analysis was performed on a personal computer using dedicated software developed in house (CMRtools, Imperial College). In our center, the interstudy percentage variability is 2.5% for end-diastolic volume, 3.1% for end-systolic volume, 4.8% for ejection fraction, and 3% for LVM.

PET

The studies were performed on an ECAT EXACT three-dimensional positron tomograph (CTI) with an axial field of view of 23.4 cm. All subjects abstained from caffeine-containing drinks for 24 hours before the PET scan and were positioned on the scanning bed so that the left ventricle lay as close as possible to the center of the axial field of view. Before performing the emission study, a single photon point source filled with 150 MBq $^{15}$Cs was used for transmission scan data acquisition. After the transmission scan, MBF was measured at baseline using 1.4±0.4 MBq/kg $^{15}$O injected intravenously over 20 seconds. Scanning commenced at the start of buildup of $^{15}$O activity (2 minutes before injection) and continued for 13 minutes. After allowing an additional 3 minutes for decay, a second MBF measurement was carried out after intravenous dipyridamole (0.56 mg/kg over 4 minutes) to achieve near-maximal coronary vasodilatation. The delivery of the second injection of $^{15}$O was timed to coincide with peak dipyridamole effect. Blood pressure (Dynamap, Critikon Inc) and 12-lead ECGs were recorded (Marquette Electronics Inc, Diagnostic Division) every 3 minutes during the baseline scan and every 1 minute from the start of dipyridamole infusion for 15 minutes.

PET Data Analysis

The sinograms were corrected for attenuation and reconstructed by dedicated array processors and a reproject reconstruction algorithm using a Hann filter (Nyquist cutoff). This allows a transaxial spatial resolution of 6.7±0.1 mm full-width-half-maximum to be achieved. The $^{15}$O list mode acquisitions were sorted into 27 frames each. Data were normalized by correcting for geometrical effects and scatter. After rebinning into two-dimensional sinograms using a Fourier rebinning algorithm, all images and two-dimensional sinograms were transferred to a SUN Ultra 10 workstation (Sun Microsystems) and analyzed with dedicated software. The creation of factor sinograms requires estimates of vascular (right and left heart) and myocardial tissue time activity curves (TACs). Cluster analysis was used to segment the dynamic data into 3 identifiable regions with similar TACs. The resulting 3 cluster TACs were entered into the factor analysis to provide 2 factor sinograms. Factor images describing tissue and blood distributions were generated by iterative reconstruction as previously described.

Factor images were resliced into short-axis images in an orientation perpendicular to the long axis of the left ventricle. Regions of interest (ROIs) were defined on these images corresponding to septal, anterior, lateral, and posterior walls of the left ventricle in the apical, mid, and basal planes. A separate set of ROIs was defined for the right ventricular cavity and left atrium. Tissue TACs were then generated from the dynamic image and fitted to a single tissue compartment tracer kinetic model to give values of MBF (mL/g per min). Previous studies in our institution have shown that the values for MBF and CVR are highly reproducible (mean difference of 10% and 2%, respectively). Subendocardial and subepicardial layers were identified by dividing myocardial ROIs with a central line, and a model for MBF, which accounts for spillover from subendocardium to subepicardium, was used. CVR was calculated as the ratio of hyperemic MBF (after dipyridamole) to resting MBF. Rate pressure product (RPP)-corrected CVR was calculated using resting MBF corrected for RPP. To calculate total ventricular blood flow (mL/min), the transmural MBF (mL/min per g) measured was multiplied by LVM (g) assessed by CMR.

In the normal human heart, oxygen consumption is linearly related to the RPP, an index of external cardiac work, and both are related to coronary blood flow. In patients with AS, where the resting cardiac work depends on LV pressure, a better measure may be LVRPP, given by the following equation: LV pressure (peak AVG+systolic blood pressure) × heart rate.
Demographic, Echocardiographic, and CMR Data

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* Indicates female; M, male; CCS, Canadian Chest pain Score; NYHA, New York Heart Association class of breathlessness; SWT, septal wall thickness at end diastole; LVID, left ventricular internal dimension at end diastole; PWT, posterior wall thickness at end diastole; Peak AVG, peak transvalvular Doppler gradient across aortic valve; AVA, aortic valve area; LVMI, left ventricular mass index; Echo, echocardiography.

Diastolic Perfusion Time Calculation

The R-R interval was measured at rest and during hyperemia on the ECGs obtained during the PET scans. Diastolic perfusion time (DPT) (s/min) = [(R-R interval − LVET) × heart rate]14 was calculated both at rest and at maximal heart rate during dipyridamole infusion.

Statistical Analysis

All values are reported as mean±SD (range). Data were analyzed using a commercially available computer analysis package (Graphpad PRISM, Graphpad software Inc.). Data were tested for equality of variance with F-test. Normal distribution was assessed by the Kolmogorov-Smirnov test. A paired or unpaired Student’s t test was used where appropriate to assess differences between continuous variables, and linear or nonlinear regression was used to test the relationship between variables. P < 0.05 was considered significant.

Results

Population Characteristics

Age ranged from 41 to 81 years (66.3±10.3 years). All subjects had echocardiographic septal and posterior wall thickness ≥12 mm (15±2 [12 to 18] mm). All subjects had at least moderate AS (peak AVG, 89.2±18.7 [52 to 112] mm Hg; AVA, 0.72±0.24 [0.41 to 1.29] cm²), and 17 of 20 fulfilled criteria for severe aortic stenosis.20 Eight patients were taking lipid-lowering drugs, 4 presently smoked up to 10 cigarettes per day, and 1 had type II diabetes mellitus. Half of the subjects described symptoms of either chest pain or breathlessness but no more than Canadian Chest Pain score 2 or NYHA class II, respectively (Table). Fifteen of 20 subjects fulfilled CMR criteria for LVH (135±30 [83 to 204] g/m²).

All subjects had normal systolic LV function, with an ejection fraction >50% (70±8% [53 to 80]),. Peak E was 81±15 cm/s, peak A was 92±30 cm/s, E to A ratio was 1.0±0.6, and isovolumic relaxation time was 78±17 ms for the patient group.

Hemodynamics and Myocardial Blood Flow

To compare transmural (ie, full-thickness) CVR in these patients with healthy volunteers, 20 sex- and age-matched volunteers (patients 66.3±10.3 years versus volunteers 66.3±11.3 years) previously studied within our institution were used.21 In patients, heart rate increased from 64±8 beats/min at rest to 80±9 beats/min (P < 0.01) after dipyridamole infusion and was comparable to the change observed in healthy volunteers (Δ = 17±8 beats/min and Δ = 22±13 beats/min, respectively). Diastolic pressure remained constant in both groups (−2±7 mm Hg from 74±10 mm Hg in patients and −2±6 mm Hg from 71±6 mm Hg in healthy volunteers). Systolic arterial pressure decreased in patients by 9±11 mm Hg from 132±25 mm Hg (P = 0.001), whereas it increased in healthy volunteers by 4±14 mm Hg from 123±15 mm Hg (P = 0.09) (P < 0.01 between the 2 groups).

Resting transmural MBF in patients was not different from healthy subjects both before (1.05±0.26 versus 0.98±0.29

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Relationship between LVM and total ventricular blood flow at rest (A) and during dipyridamole-induced hyperemia (B).

**Figure 1.** Relationship between LVM and total ventricular blood flow at rest (A) and during dipyridamole-induced hyperemia (B).

mL/min per g; \( P = 0.43 \) and after (1.28±0.30 versus 1.34±0.42 mL/min/g; \( P = 0.61 \)) correction for RPP. As expected, hyperemic transmural MBF (1.99±0.78 versus 2.70±1.08 mL/min per g; \( P = 0.02 \)) and CVR were reduced in patients compared with healthy volunteers (1.90±0.60 versus 2.79±1.12; \( P = 0.003 \)). In patients, subendocardial MBF was significantly higher than subepicardial MBF under resting conditions (1.07±0.24 versus 0.98±0.26 mL/min per g; \( P = 0.003 \)), although this difference was no longer detectable after dipyridamole (1.94±0.93 versus 1.98±0.73 mL/min per g; \( P = 0.74 \)).

Under resting conditions, total LV blood flow was directly proportional to LVM (Figure 1A), but the relationship lost its significance during hyperemia (Figure 1B). CVR was also not related to the degree of hypertrophy in the subepicardium or subendocardium or transmurally.

**Interrelation Among Measured Parameters**

In patients under resting conditions, subendocardial and subepicardial MBF were not related to changes in the hemodynamic load of the left ventricle (LVRPP). By contrast, a significant logarithmic relationship was found between LVRPP at rest and transmural CVR (Figure 2A), indicating a progressive decrease of CVR with increasing ventricular load. The same relationship with LVRPP was observed for subendocardial and subepicardial CVR (Figure 2B), with the 2 regression lines crossing at 12.1×10^7 mm Hg/ beats per min, suggesting a greater impact of hemodynamic load on subendocardial CVR at higher LVRPP. Similarly, a significant logarithmic relationship between AVG and CVR was found (Figure 2C), with subendocardial and subepicardial regression lines crossing at 66 mm Hg (Figure 2D).

The increase of total LV blood flow during dipyridamole-induced hyperemia (mean value, 89.6±59.6%; range, 17% to 233%) was linearly related to the degree of AVA (Figure 3). At rest, neither transmural nor subendocardial or subepicardial MBF was related to the severity of AS. On the contrary, hyperemic MBF in all layers (transmural, \( r = 0.76 \); subepicardium, \( r = 0.73 \); subendocardium, \( r = 0.77 \)) and CVR (Figure 4) was significantly related to AVA. As shown in Figure 4, the lines fitting subendocardial and subepicardial CVR cross at an AVA value of 0.92 cm², with a more severe exhaustion of CVR in the subendocardium. In the subset of patients with AVA <0.92 cm² (n=15), CVR in the subendocardium was significantly lower than in the subepicardium (1.43±0.33 and 1.78±0.35, respectively, \( P = 0.01 \)). In addition, the subendocardial to subepicardial blood flow ratio decreased significantly from 1.14±0.17 under resting conditions to 0.92±0.17 during hyperemia (\( P < 0.005 \)).

There was no relationship between any parameter of diastolic LV function and AVA, peak AVG, MBF, or CVR. A significant inverse relationship was found between LVET (298±55 [170 to 380] ms) and AVG (1.415 to 161x; \( r = 0.72 \); \( P = 0.0003 \)) and a linear relationship between resting DPT (41.0±4.4 [34.3 to 49.6] s/min) and AVA (\( y = 14.8x + 30.3; r = 0.82; P < 0.0001 \)). DPT was not correlated to resting MBF. Nevertheless, there was a significant relationship between hyperemic DPT (36.1±5.0 [31.2 to 47.3] s/min) and hyperemic MBF (\( r = 0.54; P = 0.01 \)) and CVR in the subendocardium (Figure 5, top). A similar but less-consistent relationship existed between hyperemic DPT and CVR in the subepicardium (Figure 5, bottom).

**Discussion**

Previous experimental studies have demonstrated a more pronounced reduction of CVR in the subendocardium in animals with severe LHV because of pressure overload. Changes in the septal subendocardial-subepicardial blood flow ratio during stress have been demonstrated noninvasively in patients with hypertrophic cardiomyopathy and septal thickness ≥25 mm. In the present investigation, we demonstrate for the first time that CVR is more severely impaired in the subendocardial layers of the LV in patients with angiographically normal coronaries and LHV attributable to severe AS. In addition, our study demonstrates that CVR impairment is related to the severity of AS, hemodynamic load on the LV, and reduced diastolic perfusion time rather than to the increase in LVM.

**Myocardial Blood Flow and Left Ventricular Mass**

In our patients, resting total LV blood flow increased proportionally with LVM. Morphological studies in patients with AS have demonstrated a reduced arteriolar density in these hypertrophied hearts, and, therefore, it is likely that the increase in total LV blood flow found in the present study is mainly sustained through metabolic vasodilation in response to increased demand. This is responsible for a partial
exhaustion of the autoregulatory capacity of the coronary microcirculation under resting conditions, which contributes to limitation of CVR.\textsuperscript{25} The relationship between flow and LVM, however, is lost during hyperemia, a finding previously demonstrated in patients with hypertrophic cardiomyopathy,\textsuperscript{26} which implies that coronary microcirculatory dysfunction is independent of the degree of myocyte hypertrophy.

Mechanisms of Impaired CVR in Patients With LVH Without Significant Epicardial Coronary Artery Disease

In patients with coronary artery disease, there is a progressive reduction of CVR that parallels the severity of coronary stenoses.\textsuperscript{27} However, a reduced CVR can also be found in patients with angiographically normal coronary arteries.\textsuperscript{3} In the absence of significant coronary artery disease, a reduction

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**Figure 2.** Relationship between LVRPP or peak AVG and CVR transmurally (A and C) and in the subendocardial and subepicardial layers (B and D).

**Figure 3.** Relationship between percentage increase in total ventricular blood flow during hyperemia and AVA.

**Figure 4.** Relationship between CVR and AVA in the subepicardium and subendocardium. The lines intersect at 0.92 cm$^2$. 
deformation of these vessels by the mechanical motion of the beating heart (extravascular resistance). Total coronary resistance is determined by two phenomena, the caliber of the resistance vessels (vascular resistance) and the deformation of these vessels by the mechanical motion of the beating heart (extravascular resistance).

A reduced CVR has been demonstrated in patients with hypertrophic cardiomyopathy and those with LVH secondary to systemic hypertension. In these 2 patient groups, the reduction of CVR is primarily sustained by an increase in minimal coronary resistance. Total CVR reduction was related to indices of extravascular compression, the latter was in turn related to the impairment in coronary microcirculatory function, lending weight to the hypothesis that, in combination with extravascular compression, the underlying mechanism responsible for myocardial ischemia in aortic stenosis is a critical reduction in DPT. 

In our study, DPT was reduced in proportion to the severity of aortic stenosis. The latter was in turn related to the impairment in coronary microcirculatory function, lending weight to the hypothesis that, in combination with extravascular compression, the underlying mechanism responsible for myocardial ischemia in aortic stenosis is a critical reduction in DPT.

Study Limitations
A limitation of the present study is that we did not obtain a direct measurement of LV pressure or the transvalvular gradient at cardiac catheterization and thus calculate AVA. Previous studies, however, have demonstrated a close relationship between echocardiographic assessment of the peak transvalvular gradient and invasively assessed LV pressure. Furthermore, Doppler-derived AVA calculated by the continuity equation has been shown to correlate well with catheterization-derived AVA calculated by the Gorlin equation. In the present study, we cannot provide any evidence of myocardial ischemia after dipyridamole administration, such as the occurrence of LV contractile dysfunction. It would have been impractical to perform an echocardiogram during PET scanning, because this might have led to patient movement and degradation of the PET data quality. In addition, it is unlikely that the vasodilator stressor used on its own would have been enough to generate myocardial ischemia. Nevertheless, we believe that the reduced CVR demonstrated in our patients can play a role in the pathogenesis of subendocardial ischemia that has been surmised on the basis of the electrocardiographic changes during stress.

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