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Coronary Flow Reserve Improves After Aortic Valve Replacement for Aortic Stenosis: An Adenosine Transthoracic Echocardiography Study

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OBJECTIVES The goal of this study was to assess coronary flow reserve (CFR) before and after aortic valve replacement (AVR).

BACKGROUND Coronary flow reserve is impaired under conditions of left ventricular (LV) hypertrophy. It is not known whether CFR improves with regression of LV hypertrophy in humans.

METHODS We investigated 35 patients with pure aortic stenosis, LV hypertrophy and normal coronary arteriograms. Patients underwent adenosine transthoracic echocardiography on two occasions—immediately before AVR and six months postoperatively. Left ventricular mass, distal left anterior descending coronary artery (LAD) diameter, flow and CFR were assessed on each occasion.

RESULTS Distal LAD diameter was successfully imaged in 30 patients (86%), and blood flow was successfully imaged in 27 (77%). Paired data were subsequently available in 24 patients, of whom 14 were men, mean age 68.1 ± 12.5 years, body mass index 24.5 ± 2.0 kg/m^2, aortic valve gradient 93 ± 32 mm Hg. Pre- to post-AVR a significant decrease was seen in LV mass (271 ± 38 vs. 236 ± 32g, $p < 0.01$) and LV mass index (154 ± 21 vs. 134 ± 21g/m^2, $p < 0.01$). Distal LAD diameter fell from 2.27 ± 0.37 to 2.23 ± 0.35 mm, $p = 0.08$). Pre- to post-AVR there was no significant change in resting parameters of peak diastolic velocity (0.43 ± 0.16 vs. 0.41 ± 0.11 m/s), distal LAD flow 23.3 ± 10.1 vs. 20.9 ± 5.2 ml/min or distal LAD flow scaled for LV mass (8.7 ± 3.8 vs. 9.0 ± 2.5 ml/min/100 g LV mass), but there was significant increase in hyperemic peak diastolic velocity (0.71 ± 0.26 vs. 1.08 ± 0.24 m/s; $p < 0.01$), distal LAD flow (37.8 ± 11.3 vs. 53.5 ± 16.1 ml/min; $p < 0.01$) and distal LAD flow scaled for LV mass (14.3 ± 5.0 vs. 23.3 ± 8.5 ml/min/100 g LV mass; $p < 0.01$). Coronary flow reserve, therefore, increased from 1.76 ± 0.5 to 2.61 ± 0.7.

CONCLUSIONS Coronary flow reserve increases after AVR for aortic stenosis. This increase occurs in tandem with regression of LV hypertrophy. (J Am Coll Cardiol 2000;36:1889–96) © 2000 by the American College of Cardiology

Coronary flow reserve (CFR) is impaired in the presence of left ventricular (LV) hypertrophy (1–3). Regression of LV hypertrophy may, therefore, be accompanied by improvement in CFR, and, indeed, there are animal studies that suggest that this is the case (4–6). However, in humans, the invasive nature of the assessment of CFR (usually undertaken with intracoronary Doppler guidewires) has hitherto prevented investigation of this hypothesis.

Transthoracic echocardiography has recently been shown to be capable of measuring CFR (7–10), and we, therefore, sought to utilize this simple noninvasive technique to assess whether CFR improves after aortic valve replacement (AVR).

METHODS

Study population. From October 1997 to June 1998, patients awaiting AVR at this specialist cardiothoracic center were identified from the surgical waiting list. On admission patients were assessed for study eligibility. Inclusion criteria were aortic stenosis with an aortic valve gradient (on echocardiography or at catheterization) ≥50 mm Hg; echocardiographic evidence of LV hypertrophy (11) and angiographically-normal coronary arteries. Exclusion criteria were: a history of systemic hypertension (systolic blood pressure >160 mm Hg or diastolic >100 mm Hg on two or more occasions) and aortic regurgitation >grade 1. Patients whose preoperative assessments met these entry criteria were approached with a view to recruitment. The study was approved by the local ethics committee, and those participants who agreed to participate gave written informed consent.

Study design in brief. Patients were recruited to undergo adenosine transthoracic echocardiography on two occasions—the day before AVR and six months postoperatively. Left ventricular mass, distal left anterior descending coronary artery (LAD) diameter, flow and CFR were to be calculated on each occasion.

Echocardiographic equipment. Echocardiographic studies were performed by a single operator using a Vingmed CFM 750 ultrasound unit. This utilizes annular phased array technology and incorporates a 512-line scan converter.

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Abbreviations and Acronyms

AVR = aortic valve replacement
BMI = body mass index
BSA = body surface area
CFR = coronary flow reserve
cosθ = cosine incident angle of Doppler beam
GTN = glyceryl trinitrate
IVST = interventricular septal thickness
LAD = left anterior descending coronary artery
LV = left ventricle or ventricular
LVID = left ventricular internal diameter
LVMI = left ventricular mass index
PWT = posterior wall thickness
VTI = velocity-time integral

M-mode analysis of ventricular wall and cavity dimensions was undertaken with a 3.5 MHz transducer. Two-dimensional visualization of the LAD was undertaken with a broad bandwidth 5 MHz transducer (focal length 40 mm, lateral resolution 0.6 mm, axial resolution 0.3 mm). This was operated at 6.3 MHz for maximum near-field resolution. Doppler analysis of blood flow was at 4 MHz.

Echocardiographic technique. Patients were asked to refrain from caffeine intake on the preoperative day and similarly at the six-month review (12). In the echocardiography laboratory a venous cannula was sited. Sublingual glyceryl trinitrate (GTN) 400 μg was given to dilate and fix epicardial coronary diameter in order to prevent further flow-induced vasodilatation (13,14). Patients were placed in the left lateral decubitus position. Simultaneous M-mode analysis of interventricular septal thickness (IVST), LV internal diameter (LVID) and posterior ventricular wall thickness (PWT) was made at or just below the tips of the mitral valve leaflets. A measurement of wall thickness was made in diastole at the peak of the R wave according to the Penn convention. Left ventricular mass was calculated using the formula of Devereux et al. (15).

A low left parasternal window was employed to image the LAD in cross-section as previously described (16–18). The LV was imaged in short axis, and the distal LAD was identified as a circular radiolucency lying in epicardial fat in the anterior interventricular sulcus (Fig. 1). The ultrasound probe was rotated counterclockwise 90° and was angled laterally to allow Doppler analysis of the anterior interventricular sulcus at the smallest possible incident angle. Simultaneous magnified color flow mapping identified the LAD as a thin red diastolic jet (Fig. 2). Frame rate and low velocity cut-off were minimized to optimize color-flow imaging of resting coronary flow. The Doppler sampler was adjusted to incorporate LAD data alone; wall motion signals were rejected, and flow was analyzed (Fig. 3A). Throughout, images were recorded on videotape for off-line analysis.

Once adequate images of resting LAD diameter and flow had been obtained, a 6-min intravenous infusion of adenosine was initiated (140 μg/kg/min) during which time hyperemic LAD flow was recorded as above (Fig. 3B).

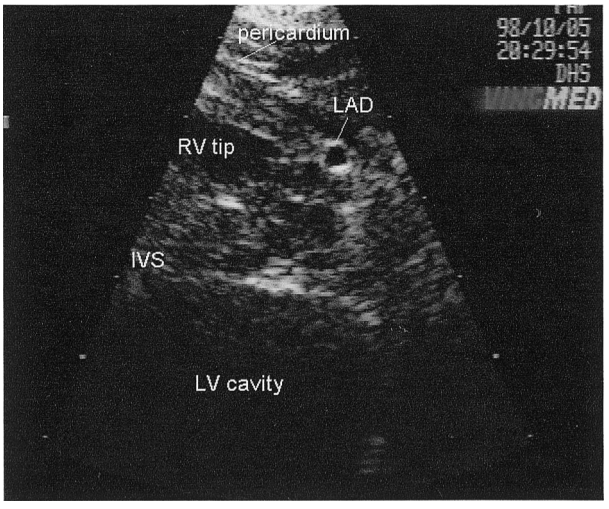

Figure 1. A low left parasternal short axis section through the left ventricle. The distal LAD is identified as a circular radiolucency with increased circumferential opacification lying in the anterior interventricular sulcus. IVS = interventricular septum; LAD = left anterior descending coronary artery; LV = left ventricle; RV = right ventricle.

During the final minute of infusion, LAD diameter was again recorded in short axis to exclude further flow-induced vasodilatation (19).

Data collection. The Vingmed CFM 750 incorporates an internal analysis package for use with the video playback facility. Distal LAD diameter was measured at end-diastole with internal calipers applied to endothelial borders; therefore, intraluminal diameter was gauged as previously validated (18). Peak velocities were read with spectrum calipers. Velocity-time integral was computed from envelope tracings of the Doppler signal over complete cardiac cycles, incorporating both systolic and diastolic envelopes. A mean of 3 measures was calculated for LAD diameter, flow velocity

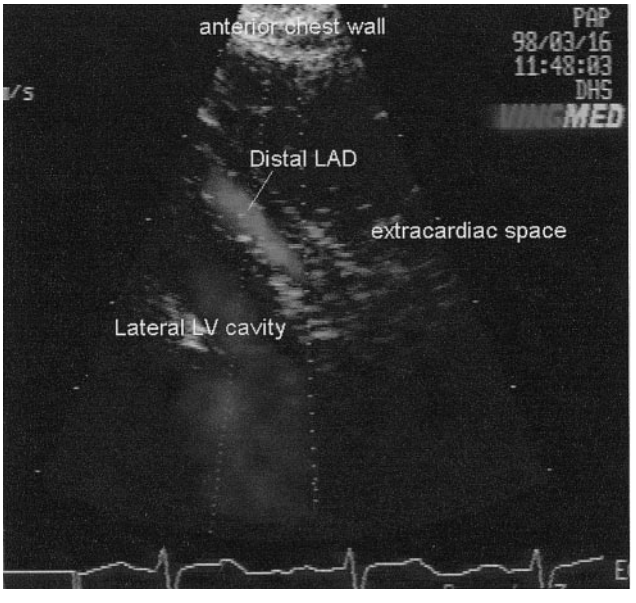

Figure 2. Low left parasternal long axis view of the anterior interventricular sulcus. Distal LAD flow is visualized as a thin red diastolic flame. LAD = left anterior descending coronary artery; LV = left ventricle.

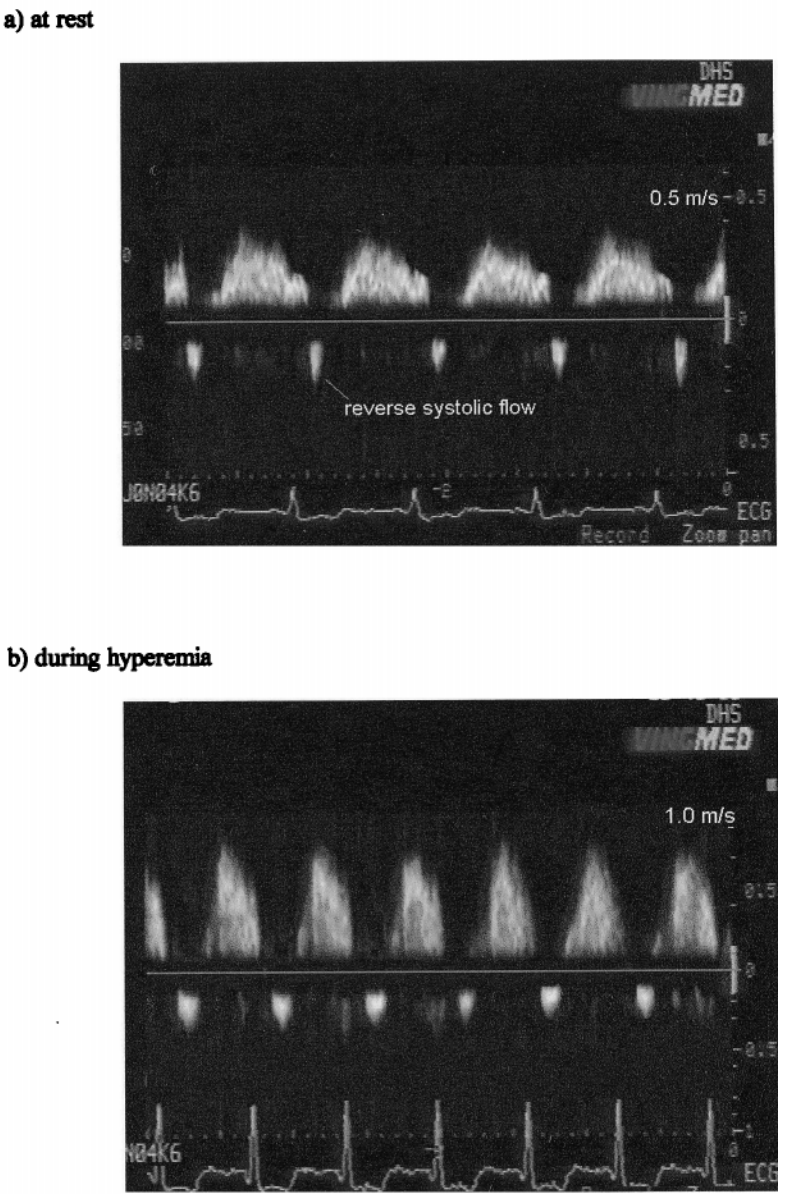

Figure 3. Doppler analysis of flow in the distal left anterior descending coronary artery before aortic valve replacement: **(A)** at rest and **(B)** during hyperemia. Note reverse systolic flow.

and velocity-time integral (VTI). Heart rate was calculated from R-R intervals of simultaneously recorded electrocardiograms.

Definitions, measurements and calculations

- Body surface area (BSA) was calculated from height and body mass measurements according to the formula of Du Bois and Du Bois (20): height $(cm)^{0.725} \times$ mass $(kg)^{0.425} \times 0.007184$.
- Body mass index (BMI) was calculated as mass (kg)/height $(m)^2$.
- Left ventricular mass (LVM) was calculated according to the Penn convention (15): LV mass = $1.04\ [(LVID + PWT + IVST)^3 - LVID^3] - 13.6$ g.
- Left ventricular mass index (LVMI) was calculated as LVM/BSA.
- Left ventricular hypertrophy was defined according to Devereux's criteria (11): LVMI $>$ 134 g/m^2 (men); $>$ 110 g/m^2 (women).
- Coronary flow calculations were made according to the method of Doucette et al. (21) ($F = \pi(d/2)^2 \times$ heart rate $\times$ VTI (cm) $\times 1/\cos\theta \times 0.5$. (F = flow [ml/min]; d = distal LAD; diameter [cm]; HR = heart rate [beat/min]; VTI = velocity-time integral [cm]; $\cos\theta$ = cosine incident angle of Doppler beam.)
- Coronary flow reserve was calculated as: $CFR = F^h/F^b$ where F^h is hyperemic coronary flow; F^b is baseline coronary flow.

Variability and validation. Reproducibility of echocardiographic assessment of CFR, interobserver and intraobserver variability, have been previously assessed at this institution

Table 1. Patient Characteristics (n = 27)

Variable	
Age (yrs)	68.1 (12.5)
BSA (m^2)	1.77 (0.17)
BMI (kg/m^2)	24.5 (2.0)
Gender (M:F ratio)	14:10
NYHA class 1,2,3,4	2,16,6,0
CCS angina scale 0,1,2,3,4	5,12,6,1,0
Mean blood pressure (mm Hg)	134 (20)/89 (10)
Cardiac rhythm (SR:AF)	21:3
Aortic valve gradient (mm Hg)	93 (32)
Aortic regurgitation grade	
0	11
1	13

Figures in parentheses represent standard deviations.
AF = atrial fibrillation; BMI = body mass index; BSA = body surface area; CCS = Canadian Cardiovascular Society; NYHA = New York Heart Association; SR = sinus rhythm.

and have been found to be well within the limits of clinical acceptability (22). For LAD diameter, interobserver variability was 3.7%; intraobserver variability was 3.2%, and reproducibility was 4.1%. For CFR, interobserver variability was 5.8%; intraobserver variability was 3.8%, and reproducibility was 9.1%. The technique has also been validated in comparison with intracoronary Doppler guidewires, with good correlation (7,23).

Statistics. Normality of data was assessed using P-P plots and the one-sample Kolmogorov-Smirnov test. Paired data were assessed with the Student *t* test or the Wilcoxon signed ranks test, as appropriate. Data relating to LAD diameter before and after AVR, with and without GTN, was analyzed using a two-way repeated measures analysis of variance test, incorporating the interaction term. Measurements are given as mean (standard deviation) unless otherwise indicated. Significance was accepted at the level $p < 0.05$.

RESULTS

Thirty-five patients were recruited to the study. Distal LAD diameter was successfully imaged in 30 (86%), and blood flow was imaged in 27 (77%). Patient characteristics are shown in Table 1. All patients had LV hypertrophy by echocardiographic criteria. Patients in whom LAD diameter or flow were not imaged (n = 8) tended to be older, with greater BMI.

Of the 27 patients who, therefore, formed the study group, one tolerated the adenosine infusion poorly and was not asked to return; one moved out of the region and was unable to return, and one patient died of multiorgan failure postoperatively. Paired data were, therefore, available for 24 patients.

Mean time to follow-up echocardiogram was 171 (33) days. Analysis of LV wall thickness, LV mass and distal LAD diameter before and after AVR is shown in Table 2 and demonstrates reduction in LV indexes after AVR. There was no statistically-significant reduction in distal LAD diameter after AVR. Endothelium-independent vasodilatation (after sublingual GTN) tended to be greater after AVR, but, again, this did not reach statistical significance.

Distal LAD flow velocities, flow volumes and flow reserve are shown in Table 3. Reverse systolic flow was observed in 15 patients before AVR (Fig. 3). Systolic flow was often observed to be biphasic, with both retrograde and antegrade components. Net systolic contribution to coronary flow was, therefore, minimal. Resting and hyperemic peak systolic velocities were both significantly greater after AVR, as flow became antegrade. Resting peak diastolic velocity decreased after AVR, while hyperemic peak diastolic velocity increased (Fig. 4). Resting LAD flow was, therefore, similar before and after AVR, but hyperemic flow was significantly greater after AVR, particularly once corrected for LV mass. Coronary flow reserve was, therefore, significantly greater after AVR.

DISCUSSION

We have demonstrated that CFR in aortic stenosis improves after AVR. This improvement occurs in tandem with regression of LV hypertrophy following relief of outflow tract obstruction. We suggest that regression of LV hypertrophy is likely to be the main mechanism whereby CFR improves after AVR.

The effect of LV pressure overload on CFR has been widely studied both in animals (1,2,4–6,24–30) and hu-

Table 2. Ventricular Parameters and Distal LAD Diameter Before and After AVR

Parameter	Pre-AVR	Post-AVR	p Value
IVST (mm)	13.9 (1.2)	12.6 (1.1)	< 0.01
LVID (mm)	45.4 (4.0)	44.1 (3.1)	NS
PWT (mm)	13.5 (1.3)	12.3 (1.1)	< 0.01
LVM (g)	271 (38)	226 (32)	< 0.01
LVMI (g/m^2)	156 (21)	129 (21)	< 0.01
Angle correction	37 (9)	36 (8)	NS
Distal LAD diameter (mm)	2.27 (0.37)	2.23 (0.35)	0.07
Distal LAD diameter post-GTN (mm)	2.37 (0.38)	2.35 (0.35)	NS
% diameter increase post-GTN	4.4 (3.3)	5.6 (4.6)	NS

Figures in parentheses represent standard deviations.
AVR = aortic valve replacement; GTN = glyceryl trinitrate; IVST = interventricular septal thickness; LAD = left anterior descending coronary artery; LVID = left ventricular internal diameter; LVM = left ventricular mass; LVMI = left ventricular mass index; PWT = posterior wall thickness.

Table 3. Distal Left Anterior Descending Coronary Artery Flow Velocities and Flow Reserve Before and After AVR

Variable	Resting			Hyperemia		
	Pre-AVR	Post-AVR	p Value	Pre-AVR	Post-AVR	p Value
PSV (m/s)	0.05 (0.11)	0.16 (0.08)	< 0.01	0.02 (0.26)	0.25 (0.21)	< 0.01
PDV (m/s)	0.43 (0.16)	0.41 (0.11)	NS	0.71 (0.26)	1.08 (0.24)	< 0.01
VTI (mm)	15.4 (6.7)	13.4 (3.4)	NS	22.5 (5.2)	30.2 (5.2)	< 0.01
Heart rate (beats/min)	70 (11)	73 (9)	NS	78 (11)	81 (7)	NS
Flow (ml/min)	23.3 (10.1)	20.9 (5.2)	NS	37.8 (11.3)	53.5 (16.1)	< 0.01
Flow (ml/min/100 g LV mass)	8.7 (3.8)	9.0 (2.5)	NS	14.3 (5.0)	23.3 (8.5)	< 0.01
Coronary Flow Reserve				**1.76 (0.5)**	**2.61 (0.7)**	**< 0.01**

Figures in parentheses represent standard deviations.
AVR = aortic valve replacement; PDV = peak diastolic velocity; PSV = peak systolic velocity; VTI = velocity time integral.

mans (3,31–37). Without exception, these studies have revealed impairment of CFR in the presence of LV hypertrophy. The effect on CFR of changes in ventricular hypertrophy, however, have been less extensively studied.

CFR and regression of LV hypertrophy. Five animal studies have been undertaken examining the effect of regression of LV hypertrophy on CFR (4–6,30,38). In all of these studies CFR improved after regression of experimental LV hypertrophy, although Ito et al. (30) found improvement only after short-term, as opposed to long-term, hypertrophy.

There are two human studies concerning the effect of relief of pressure overload on CFR. Doty et al. (39) examined CFR intraoperatively during surgery for supravalvular aortic stenosis and found that CFR did not immediately improve despite reduction of the outflow gradient. They concluded that regression of LV hypertrophy was required for improvement in CFR. Eberli et al. (35) investigated patients with aortic valve disease. This study was, however, compromised by the fact that study groups before and after AVR consisted of entirely different patients. Coronary flow reserve was found to be greater among postoperative patients. In our study we have compared the same patients pre- and postoperatively and have considered a homogeneous group with aortic stenosis alone. Paired data are therefore available, providing statistically-robust evidence that CFR improves after AVR for aortic stenosis.

Transthoracic imaging of the distal LAD. Transthoracic echocardiographic imaging of distal LAD diameter and flow has a reported success rate of 30% to 90%, depending on patient selection (8,17,18,23,40–42). Success rates are higher for patients with LV hypertrophy, who have greater coronary diameter (41,42) and in younger, leaner subjects (22). They are lower for patients who are older, of greater BMI or who have coronary artery disease (40). Our success rate of 77% in this study is in keeping with previous results. Recent work using intravenous contrast agents, however, suggests that improved success rates might be achieved with this technique in the future (10,23).

LV wall thickness and mass. Patients with aortic stenosis have increased IVST, PWT and LV mass (37,43–45). Mean measurements in this study of IVST (13.9 mm) LV mass (271 g) and LVMI (154 g) are representative (37,45).

The effect of AVR on ventricular parameters has been widely studied (46–51). Most authors have reported an approximately 10% reduction in wall thickness and an approximately 25% reduction in LVMI in the first year after AVR. Over the long term, LV hypertrophy continues to regress (48,50). We demonstrated a 9% reduction in IVST and a 17% reduction in LVMI six months after AVR.

LAD diameter. Coronary artery diameter increases in the presence of LV hypertrophy (45,52–56). However, the increase is not proportional to the increase in muscle mass (45,56), and this results in relative "inadequacy" of the coronary circulation, rendering the myocardium susceptible to ischemia in the absence of coronary stenoses (3,31).

Distal LAD diameter in normal individuals is 1.9 ± 0.4 mm, increasing to 2.1 ± 0.5 mm in men with LV hypertrophy (55). Our measurements of 2.3 ± 0.4 mm for patients with marked LV hypertrophy are in keeping with these.

The effect of regression of LV hypertrophy on coronary diameter has also been studied (57,58). Under these circumstances, coronary cross-section decreases proportionately less than does ventricular hypertrophy, with the result that the ratio of coronary cross-section to LV mass normalizes. We demonstrated a decrease in distal LAD diameter after AVR, though this did not reach statistical significance.

The effect of nitrocompounds on coronary diameter has been widely studied (13,42,56,59–61). In individuals without coronary artery disease, distal LAD diameter may be expected to increase by approximately 20% with 400 μg sublingual GTN (42,59). For patients with LV hypertrophy, however, the degree of vasodilatation is significantly reduced as a result of structural remodeling of the vascular wall (42,56,60). We noted an increase of 4.4% in distal LAD diameter in response to 400 μg sublingual GTN, consistent with previous data, and a nonsignificant trend towards greater coronary vasodilatation in response to sublingual GTN after partial regression of LV hypertrophy.

LAD flow. Distal LAD flow comprises a small systolic and a larger diastolic component. Under conditions of LV hypertrophy, the characteristic pattern of coronary flow is altered, with decreased diastolic deceleration (62). Interpretation of flow volumes depends on how data are presented. Baseline coronary flow is augmented, but baseline coronary

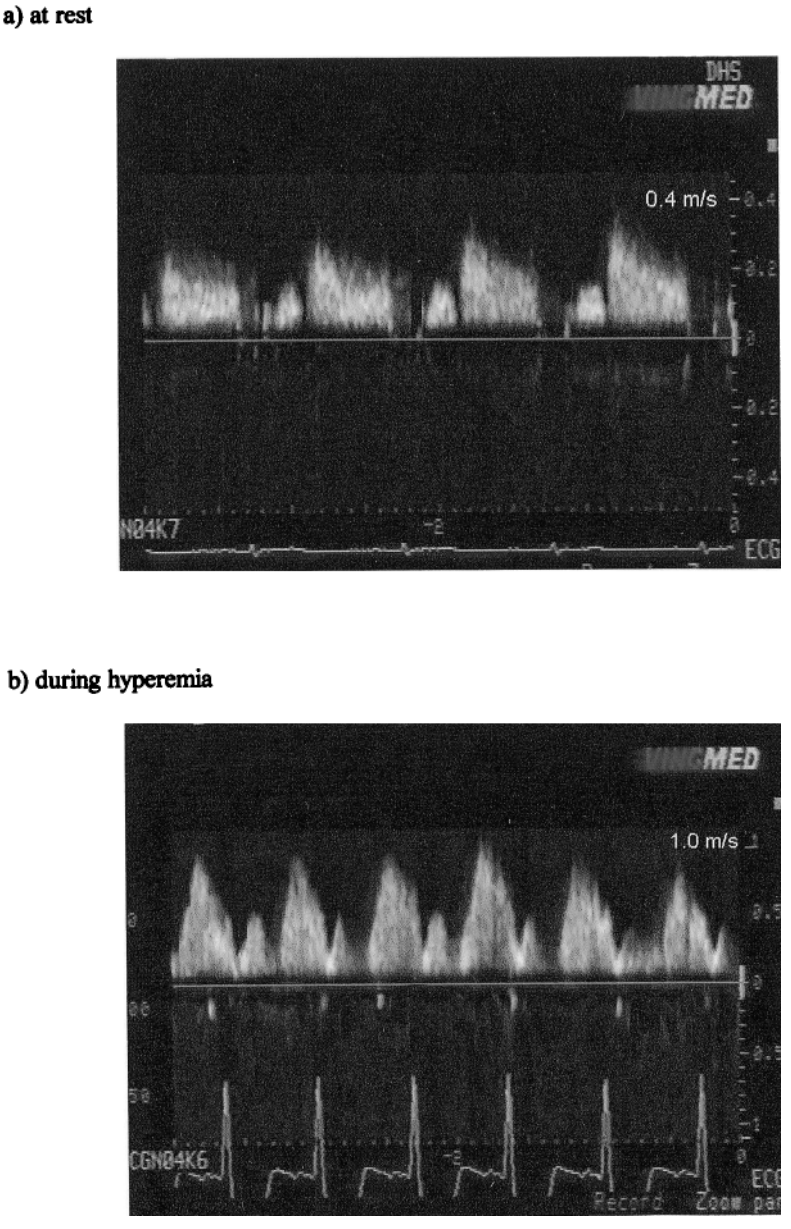

Figure 4. Doppler analysis of flow in the distal left anterior descending coronary artery after aortic valve replacement: **(A)** at rest and **(B)** during hyperemia. Note the forward systolic flow, the reduced resting peak diastolic velocity and the increased hyperemic peak diastolic velocity.

flow per 100 g LV mass is normal. Hyperemic blood flow is normal, but hyperemic blood flow per 100 g LV mass is impaired (1,2,28,31,63,64).

In aortic stenosis interpretation of coronary flow is further complicated by reverse systolic flow. Intramyocardial pressure, myocardial bulk and the Bernouilli effect created by the jet of high-velocity supraaortic flow combine to generate reverse systolic flow in a significant proportion of patients (41,65,66). After surgical correction of outflow obstruction, systolic flow normalizes in the majority of patients (41). We found reverse systolic flow in 15 patients before AVR (Fig. 3) and in two after AVR. Mean systolic contribution to forward flow was, therefore, minimal both at rest and during hyperemia before AVR.

Resting peak diastolic velocity and flow were both greater than comparative values assessed by the same technique in normal controls (22). Post-AVR hyperemic coronary flow scaled for ventricular mass was also similar to that recorded in normal individuals as predicted by Nitenberg and Antony (64).

Study limitations. The main limitation of adenosine transthoracic echocardiography is that imaging is not possible in all subjects. This factor has limited widespread application of the technique. Additionally, only the distal LAD can be adequately visualized. Nonetheless, as a truly noninvasive means of assessing CFR, adenosine transthoracic echocardiography shows promise, and imaging success may be optimized by the use of intravenous contrast agents (10,23).

Continuous monitoring of blood pressure was not undertaken. However, for a given coronary perfusion pressure

(within limits of autoregulation) alterations in aortic pressure produce parallel increases in basal and maximal coronary flow, such that CFR remains the same (67,68).

In recording blood flow, angles of incidence above 30° are undesirable as cosθ begins to assume greater overall importance (cos 30 = 0.87). However, the prime purpose of the study was comparison of CFR, which, as a ratio, was unaffected by the angle of incidence in a given study.

Accurate measurement of CFR depends on obtaining true resting coronary flow. Echocardiography is relatively unstressful and certainly less so than coronary angiography, but, even in this study, true resting flow may not have been achieved in all participants, thus artificially reducing CFR.

Conclusions. Coronary flow reserve improves after AVR for aortic stenosis. This improvement occurs in association with regression of LV hypertrophy. Transthoracic adenosine echocardiography continues to be a promising technique for the evaluation of CFR.

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