Myocardial Blood Flow
in Congestive and Hypertrophic Cardiomyopathy

Relationship to Peak Wall Stress
and Mean Velocity of Circumferential Fiber Shortening

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SUMMARY Myocardial blood flow/unit mass (MBF) and the determinants of myocardial oxygen consumption were measured in seven control subjects (group I) and 15 patients (pts) with cardiomyopathy (CM), group II (group IIa-congestive CM: 10 pts; group IIb-hypertrophic CM: 5 pts). In group I left ventricular (LV) MBF was 64±8 (SD) ml/100g·min; it was significantly lower in IIa (45±15 ml/100g·min, P < 0.01) and IIb (39±7 ml/100g·min, P < 0.01). However, calculated total LV flow (LV mass × MBF) was increased in the two CM groups. In nine CM pts, LV MBF increased in response to atrial pacing from 41±7 to 63±13 ml/100g·min.

PATIENTS WITH CARDIOMYOPATHY frequently complain of chest pain suggestive of ischemic heart disease despite the presence of widely patent coronary arteries. In addition, these patients often manifest varying degrees of myocardial hypertrophy and impaired ventricular performance. The relationship between these abnormalities and myocardial perfusion is largely unknown. There have been only a few studies, each involving small numbers of patients, of the myocardial circulation in cardiomyopathies and these studies have yielded conflicting results.

The first purpose of this study was to measure average left ventricular as well as regional myocardial perfusion at rest in patients with cardiomyopathy and to compare the values obtained with those in a control group of patients with normal coronary arteriograms and normal ventricular performance. For the study, patients with cardiomyopathy were divided into two functional categories, congestive cardiomyopathy and hypertrophic cardiomyopathy, by criteria developed by Goodwin. In nine of the cardiomyopathy patients, myocardial blood flow was also measured during right atrial pacing in order to evaluate the circulatory response to an increase in myocardial oxygen consumption.

The second purpose of this study was to investigate in man the relationship between myocardial blood flow and three of the major determinants of myocardial oxygen consumption: heart rate, myocardial contractility, and wall stress. For this purpose, heart rate, mean velocity of circumferential fiber shortening (MVcf), and peak left ventricular (LV) systolic wall stress were measured in the control subjects and in the patients with congestive and hypertrophic cardiomyopathy. The aim of this part of the study was to determine if the measured myocardial blood flow at rest could be related to these factors in patients with widely varying levels of ventricular performance.

METHODS

Patient Selection

All patients who were scheduled for cardiac catheterization and coronary arteriography at Columbia Presbyterian Medical Center for clinical indications were considered as potential candidates for this study. Informed consent was obtained from each patient for measurements of regional myocardial blood flow according to protocols approved by the Human Investigation Committee and the Joint Radioisotope Committees of this institution. The clinical indications for catheterization included chest pain suggestive of coronary artery disease, cardiomegaly of unknown etiology, or symptoms of congestive heart failure. Patients were excluded from the study if they had a history of hypertension, findings indicative of valvular heart disease, pulmonary disease, pericardial disease, diabetes mellitus, or the presence of a stenosis of greater than 50% by arteriography. Eight patients were excluded from the study because the ventriculograms were technically inadequate for accurate quantitative analysis.

Group I (control subjects) consisted of seven patients. At the time of study all seven were considered normal on physical examination and had normal chest X-rays and electrocardiograms. All had normal intracardiac pressures, coronary arteriograms, and left ventriculograms.

Group II consisted of 15 patients with the clinical diagnosis of cardiomyopathy. All of this group had hemodynamic and/or ventriculographic evidence of abnormal left ventricular function, i.e., the left ventricular end-diastolic pressure was increased above normal at rest or in response...
to exercise or there was angiographic evidence of an increased left ventricular end-diastolic volume or left ventricular mass. The patients were subsequently divided into congestive and hypertrophic cardiomyopathy subgroups according to criteria developed by Goodwin, which depend upon the ventricular functional characteristics apparent on the left ventriculograms. Clinical, hemodynamic, and angiographic data of all groups are summarized in table 1 and figure 1.

Group IIa (congestive cardiomyopathy) consisted of ten patients. All of the patients presented with symptoms and signs of left ventricular failure. In this group left ventricular hypertrophy was associated with left ventricular dilatation. The patients fit the classification of congestive cardiomyopathy because left ventricular systolic and diastolic volumes were increased, left ventricular mass was increased, the ejection fraction was reduced below the normal (i.e., < 55%) and the ratio of left ventricular end-diastolic volume to wall thickness was increased above normal (LVEDV/h). The etiology of the cardiomyopathy varied: ethanol, 3; peripartum, 2; viral, 1; idiopathic, 4.

Group IIb (hypertrophic cardiomyopathy, obstructive and nonobstructive) was composed of five patients. All five patients had unexplained cardiomegaly and four of the five complained of chest pain. The patients fit the classification of hypertrophic cardiomyopathy because their ventriculograms revealed marked hypertrophy of the left ventricular free wall, septal and papillary regions, with a left ventricular mass that increased above normal but end-diastolic and systolic volumes and ejection fractions that were within the range of normal found in this and other laboratories. The LVEDV/h ratio in this group was lower than normal. In group IIb, three of the five patients had resting gradients across the aortic outflow tract and one patient developed a significant gradient (160 mm Hg) after two minutes of isoproterenol infusion (4 μg/min).

![Diagram](http://circ.ahajournals.org/content/84/6/485/F1.large.jpg)

**Figure 1.** Summary of angiographic determinations in the three study groups. Group I: control, group IIa: congestive cardiomyopathy, group IIb: hypertrophic cardiomyopathy. Left ventricular end-diastolic volume (LVEDV) normalized to body surface area was elevated in group IIa. Ejection fraction (EF) was depressed in group IIa. Left ventricular wall thickness was increased in both group IIa and group IIb and LVEDV/wall thickness was increased in group IIa and depressed in group IIb.
Cardiac Catheterization Technique

Left ventricular catheterization and coronary arteriography were performed with the patients in the postabsorptive state premedicated with secobarbital 100 mg, promethazine hydrochloride 25 mg, and atropine sulfate 0.5 mg. No patient had received propranolol within 48 hours of study. Intracardiac pressures were recorded on a switched beam oscillographic recorder* using Statham P23db pressure transducers.

Initially the coronary arteriography was performed. Then the patient was positioned for myocardial blood flow studies. A small amount of Renograin (1–2 cc) was used to locate the coronary arteries. A period of approximately 10 min was allowed to elapse before the measurement of myocardial blood flow was performed. The left ventriculograms were then performed after another lapse of approximately 20 min.

Coronary arteriography was performed using the Judkins technique. All coronary arteriograms were filmed in multiple views on both 35 mm cine film exposed at 50 frames per second and on serial cut films after a hand injection of from 3–9 ml of contrast material. All films were reviewed by at least three independent observers.

The left ventriculograms were performed at least 20 min following the last injection of contrast material into the coronary arteries. In mid-inspiration, approximately 40 ml of sodium and meglumine diatrizoates (Hypaque-76) was power injected over 2–3 sec into the cavity of the left ventricle. The ventriculograms were recorded in a shallow right anterior oblique position, using 6 or 9 inch image intensifiers on 35 mm cine film at a filming rate of 50 frames per second. The earliest well-visualized beat in each study was analyzed. Cardiac cycles following an extrasystole were not used. Analysis was limited to the first five beats after the injection of contrast material and only to those ventriculograms in which all chamber margins were well visualized. All patients were in normal sinus rhythm except E.L. (group IIa) who was in atrial fibrillation; a beat representing an average cycle length was analyzed in this instance.

Myocardial Blood Flow Determination

Myocardial perfusion was measured at rest using radioactive 133xenon and a multiple-crystal scintillation camera as is described and illustrated in detail elsewhere. In brief, a left anterior oblique coronary angiogram was obtained with radioactive-radiopaque markers on the chest wall in order to localize the heart borders. Without changing the patient’s position the cine camera was removed and replaced by the multiple-crystal scintillation camera. The multiple-crystal scintillation camera used for these studies contains a rectangular grid of 294 separate, collimated, thallium activated NaI crystals arranged in 21 columns of 14 crystals. After the locations of the radioactive markers were recorded by the camera, approximately 20–25 mCi of 133xenon was injected as a bolus into the left coronary artery. The washout of radioactivity from the heart was recorded by the scintillation camera and rate constants of tracer clearance were computed by a monoexponential analysis of the initial portions of the washout curves. Myocardial blood flow (MBF) rates were calculated using the Schmidt-Kety formula:

\[ F = \kappa \times \lambda / \rho \]

where \( F \) is myocardial capillary blood flow in ml/100g · min, \( \kappa \) is the experimentally determined rate constant, \( \lambda \) is the blood:myocardium partition coefficient (0.72) for xenon obtained by Conn in the normal dog heart and \( \rho \) is the specific gravity of myocardium (1.05). Using the radioactive-radiopaque markers, the crystals overlying the left ventricle were then averaged and are presented as mean left ventricular myocardial blood flow (ml/100g · min) along with the standard deviation. Total left ventricular flow (ml/min) was estimated by multiplying the mean left ventricular flow expressed in ml/100g · min by left ventricular mass calculated from the left ventriculogram.

Pacing Studies

In nine of the cardiomyopathy patients right atrial pacing was instituted using a temporary demand pacing box.§ Heart rate was increased in graded increments until a maximum heart rate of 150 beats/min was attained. The tachycardia was then sustained for five minutes under electrocardiographic monitoring before another myocardial blood flow determination was performed. No patient developed chest pain or ECG changes in response to atrial pacing.

In five of the nine patients with cardiomyopathy who underwent pacing, simultaneous myocardial metabolic studies were successfully performed. A Goodale-Lubin catheter was placed at least two centimeters into the coronary sinus and its position was verified by an injection of a small amount of contrast material. The catheter was then secured in place and was used to obtain blood samples for pH, Pco2, oxygen, and lactate analysis. Blood samples were obtained simultaneously at the time of the myocardial blood flow determination from both the coronary sinus and the proximal ascending aorta at the resting heart rate and after five minutes of atrial pacing. Blood pH, Pco2 and Po2 were measured using a pH meter and a blood gas analyzer.¶ Arterial and coronary sinus lactate concentrations were measured in duplicate by an enzymatic technique.** Hemoglobin concentration was measured from a venous blood sample.†† Oxygen saturation was determined from a nomogram relating blood pH and Po2 to oxygen saturation.†† Oxygen content was subsequently calculated from the formula:

\[ O_2 \text{ content} = \text{hemoglobin concentration} \times \text{oxygen saturation} \times 1.34. \]

The oxygen and lactate extraction ratios were calculated as the difference between the arterial and coronary sinus blood concentrations divided by the arterial concentration.

Calculations

From the cineangiogram, silhouettes of the left ventricular cavity were drawn at end-diastole and end-systole. The drawings were always made to the outside margins of the papillary muscles. The long axis of the left ventricle was

†Autofluoroscope Model 5600, Baird Atomic, Bedford, Mass.
‡Comparison of blood pressure and heart rate prior to the measurement of myocardial blood flow and after the injection of 133xenon showed no significant changes in blood pressure (115.8/74.7 to 113.5/74.8 mm Hg) and a small, but significant change in heart rate (85.6 to 88.7, \( P < 0.01 \)).
§Medtronic, Inc., Model 5880 A, Minneapolis, Minn.
¶Radiometer, Copenhagen, Denmark.
**Biochemica Test Combination, Boehringer, Mannheim GBH.
††Instrumentation Laboratory, Inc., Co-Oximeter Model 182, Lexington, Mass.
taken as the longest measured line from the apex to the margin of the aortic valve. Ventricular volumes were calculated using the single plane area-length method:21

$$V = \frac{4}{3} \pi \left(\frac{L_f}{2}\right) \left(\frac{D_f}{2}\right)^2$$  (1)

where $V =$ volume, $L_f =$ length of the major axis in the frontal projection and $D_f =$ diameter of the minor axis in the frontal projection (calculated by the area-length method). However, the irregular shape of the ventricular chamber at end-systole in hypertrophic cardiomyopathy may limit somewhat the accuracy of this technique. Correction factors for magnification were obtained from a grid filmed in the plane occupied by the left ventricle. Regression equation corrections were not used for reasons previously reported.20 A representative left ventricular wall thickness was measured from the RAO projection of the ventriculogram in end-diastole for the four centimeter segment just below the equator and left ventricular mass was then calculated.21 Ejection fraction was calculated from the formula:

$$EF = \frac{EDV - ESV}{EDV} \times 100$$  (2)

where $EF =$ ejection fraction; $EDV =$ left ventricular end-diastolic volume; and $ESV =$ left ventricular end-systolic volume.

Mean velocity of circumferential fiber shortening (MVcf) was calculated from the formula:22

$$MVcf = \frac{EDD - ESD}{EDD \times LVET}$$  (3)

where $EDD =$ left ventricular minor diameter at end-diastole; $ESD =$ left ventricular minor diameter at end-systole (both derived by the area-length method in order to eliminate the effect of irregularities in the LV wall20); and $LVET =$ left ventricular ejection time (sec), measured from the central aortic pressure tracing immediately prior to the ventriculogram. There were no appreciable changes in heart rate during the filming of the angiograms. Qualitative evaluation of all the ventriculograms did not detect any apparent wall motion abnormality.

Left ventricular tension and stress were calculated for the minor equatorial circumference assuming a thin-walled ellipsoid as a model of the left ventricle,23 where:

$$\text{Tension} = \text{Stress} \times h$$  (5)

$$\text{Stress} = \frac{Pb}{h} \left[1 - \frac{b^4}{a^2(2b + h)}\right]$$  (4)

$P =$ pressure in dynes/cm², $b =$ minor semiaxis, $a =$ major semiaxis, and $h =$ wall thickness in centimeters. Values obtained by this formula overestimate values obtained assuming a thick walled ellipsoid, but only slightly and to an extent which is similar when groups of patients are compared.24, 26 LV tension was calculated by the following:

$$\text{Peak tension and stress were calculated by substituting into equation (4) the dimensions of the left ventricle at end-diastole and peak systolic pressure. Pressure was measured from the left ventricular pressure curves immediately before the ventriculogram.}$$

The double product was calculated as the product of the aortic peak systolic pressure and the heart rate recorded immediately after the intracoronary injection of $^{133}$Xenon for the determination of myocardial blood flow. Stroke work was calculated by multiplying the average developed left ventricular pressure by the stroke volume determined angiographically.

**Results**

The mean left ventricular myocardial blood flow per unit mass of tissue averaged $64 \pm 8$ ml/100g · min at rest in group I (table 2, fig. 2). In both cardiomyopathy groups the mean left ventricular myocardial blood flow was significantly reduced (group IIa : $45 \pm 15$ ml/100g · min, $P < 0.01$, and group IIb: $39 \pm 7$ ml/100g · min, $P < 0.01$). Figure 3 demonstrates the regional perfusion pattern over the left ventricle in patient M.J. (male) with hypertrophic cardiomyopathy. Local myocardial perfusion rates were diffusely depressed throughout the left ventricle in this patient as in all of the other subjects with either type of cardiomyopathy. Although blood flow/unit mass was depressed in the cardiomyopathy patients, estimated total LV myocardial blood flow (the product of flow per unit mass and calculated LV mass) was significantly increased in the patients with either form of cardiomyopathy (group I: $86 \pm 14$ ml/min; group IIa: $128 \pm 42$ ml/min, $P < 0.05$; group IIb: $134 \pm 48$ ml/min, $P < 0.05$) (fig. 2).
Regional myocardial blood flow was also measured during right atrial pacing in nine patients (seven in group IIA; two in group IIb) (figs. 3, 4). During atrial pacing, the double product rose and mean LV myocardial blood flow increased significantly in all of the patients (41.7 ml/100 g.min to 63.1 ml/100 g.min). Table 3 shows results of metabolic studies in five of these patients. Myocardial oxygen and lactate extraction ratios were normal at rest. During atrial pacing, none of the patients demonstrated a significant increase in myocardial oxygen extraction and myocardial lactate extraction did not change significantly. Only one patient (S. A.) manifested a slight amount of lactate production during pacing which was unassociated with chest pain or altered ECG.

Data obtained at rest for LV peak wall stress and mean velocity of circumferential fiber shortening appear in table 2 and figure 5. In group I, calculated peak stress averaged 4.51 ± 1.10 dynes/cm² × 10⁹ and the mean velocity of the circumferential fiber shortening averaged 1.26 ± 0.12 circum/sec. In patients of group IIA, the average calculated peak stress (4.39 ± 0.77 dynes/cm² × 10⁹) was not statistically different from the control patients. The average MVcf in the patients of group IIA was significantly below control values (0.53 ± 0.18 circum/sec, P < 0.01). In the patients of group IIb, calculated peak stress was significantly reduced below the control patients (2.80 ± 0.75 dynes/cm² × 10⁹, P < 0.05). However, MVcf was not significantly different (1.39 ± 0.35 circum/sec). Thus, in group IIA, congestive cardiomyopathy, MVcf was depressed...
TABLE 2. Myocardial Perfusion and Determinants of Myocardial Oxygen Consumption

<table>
<thead>
<tr>
<th>Pt/Sex</th>
<th>LV MBF (ml/100 g · min)</th>
<th>LV MBF/beat (ml/100 g · beat)</th>
<th>MBF† (ml/min)</th>
<th>MVCF (circum/sec)</th>
<th>Peak stress (dynes/cm² · 10⁶)</th>
<th>Peak tension (dynes/cm² · 10⁶)</th>
<th>Stroke work (g · m)</th>
<th>Double product (HR · BP)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group I</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MF / F</td>
<td>61 ± 11</td>
<td>0.76</td>
<td>59 ± 10</td>
<td>0.68</td>
<td>63 ± 9</td>
<td>1.21</td>
<td>3.12</td>
<td>61 ± 10</td>
</tr>
<tr>
<td>PH / F</td>
<td>61 ± 9</td>
<td>0.71</td>
<td>60 ± 10</td>
<td>0.68</td>
<td>63 ± 9</td>
<td>1.43</td>
<td>3.75</td>
<td>63 ± 10</td>
</tr>
<tr>
<td>MO / F</td>
<td>59 ± 10</td>
<td>0.68</td>
<td>60 ± 10</td>
<td>0.68</td>
<td>63 ± 9</td>
<td>1.40</td>
<td>3.20</td>
<td>63 ± 10</td>
</tr>
<tr>
<td>CS / M</td>
<td>77 ± 20</td>
<td>1.08</td>
<td>77 ± 20</td>
<td>1.08</td>
<td>77 ± 20</td>
<td>1.20</td>
<td>4.45</td>
<td>77 ± 20</td>
</tr>
<tr>
<td>MS / F</td>
<td>74 ± 8</td>
<td>0.94</td>
<td>56 ± 10</td>
<td>0.63</td>
<td>63 ± 9</td>
<td>1.11</td>
<td>4.04</td>
<td>56 ± 10</td>
</tr>
<tr>
<td>SK / F</td>
<td>64 ± 7</td>
<td>0.79</td>
<td>64 ± 7</td>
<td>0.79</td>
<td>64 ± 7</td>
<td>1.26</td>
<td>4.51</td>
<td>64 ± 7</td>
</tr>
<tr>
<td>Mean</td>
<td>64 ± 7</td>
<td>0.79</td>
<td>64 ± 7</td>
<td>0.79</td>
<td>64 ± 7</td>
<td>1.26</td>
<td>4.51</td>
<td>64 ± 7</td>
</tr>
</tbody>
</table>

SD ± 8 ± 0.16 ± 14 ± 0.12 ± 1.10 ± 0.52 ± 15 ± 1064

Group IIa

NC / F 45 ± 8 0.45 140 0.65 4.49 4.53 73 10500
GO / M 40 ± 11 0.60 123 0.30 4.01 3.67 67 13300
MJ / F 43 ± 9 0.43 123 0.45 3.72 3.67 67 13300
EL / M 45 ± 13 0.50 185 0.58 4.45 5.22 133 11500
EC / M 83 ± 14 0.65 145 0.78 6.25 4.84 95 18800
AM / M 50 ± 10 0.49 165 0.56 4.48 4.48 80 11900
MD / M 36 ± 7 0.36 72 0.25 3.93 3.20 26 10700
LG / M 43 ± 7 0.50 175 0.40 4.24 4.45 87 8000
FL / F 24 ± 5 0.26 74 0.61 3.51 3.49 81 8800
SA / F 44 ± 13 0.53 77 0.75 4.86 4.01 79 9800
Mean 45 0.48 128 0.53 4.39 4.16 76 10670
SD ± 15 ± 0.11 ± 42 ± 0.18 ± 0.77 ± 0.65 ± 29 ± 2954
*
P < 0.01 P < 0.01 P < 0.05 P < 0.01 NS P < 0.01 NS NS

Group IIb

MJ / M 44 ± 7 0.51 155 0.82 2.49 3.59 67 12000
BJ / F 48 ± 10 0.72 167 1.63 3.57 5.59 131 15600
HJ / M 33 ± 7 0.55 181 1.29 1.68 3.55 59 7000
BJ / M 32 ± 6 0.52 85 1.68 3.32 3.92 113 9100
KW / F 40 ± 6 0.50 80 1.54 2.94 2.94 77 10000
Mean 39 0.55 134 1.39 2.80 3.92 89 10920
SD ± 7 ± 0.10 ± 45 ± 0.35 ± 0.75 ± 1.00 ± 31 ± 3014
*
P < 0.01 P < 0.05 P < 0.05 NS P < 0.05 NS NS NS

*Statistical comparisons are against group I.
†MBF is total myocardial blood flow calculated using ventriculographic assessment of LV mass.

Abbreviations: Group I = control; Group IIa = congestive cardiomyopathy; Group IIb = hypertrophic cardiomyopathy; LVMBF = left ventricular myocardial blood flow; MVCF = mean velocity of circumferential fiber shortening; HR = heart rate; BP = systolic blood pressure; SD = standard deviation; NS = not significantly different.

and calculated peak wall stress was not different from control; whereas in group IIb, hypertrophic cardiomyopathy, peak wall stress was depressed and MVCF was not different from control. There were no significant differences among the three groups of patients in the double product or stroke work.

Multiple regression analysis was performed in order to explore whether the observed variation in measured LV myocardial blood flow rates (range: 24 to 83 ml/100g · min) was related to the major determinants of myocardial oxygen consumption. The heart rate, MVCF, peak wall stress and myocardial perfusion rates in the 22 patients were fit* to yield the following relationship:

$$MBF = 16.9 \text{MVCF} + 9.30 \text{Stress} + 0.26 \text{HR} - 26.4$$

where MBF = myocardial blood flow (ml/100g · min), Stress = calculated peak systolic stress (dynes/cm² × 10⁶), MVCF = mean velocity of circumferential fiber shortening (circum/sec) and HR = heart rate (beats/min). The analysis indicated that 63% of the total variation in LV myocardial blood flow was explained by these three variables. In addition, further testing by stepwise addition of each variable to the multiple regression equation showed that each variable,

PEAK STRESS

\[ \text{(dynes/cm}^2 \cdot 10^6) \]

MVCF

\[ \text{(circum./sec)} \]

*Biomedical Computer Programs, Health Sciences Computing Facility, University of California, Los Angeles.
individually, was significantly related to myocardial blood flow. The standard deviation of the estimated myocardial blood flow after these three variables are included was 9.9 ml/100 g·min as compared to the average observed standard deviation of the LV flow measurements, 9.6 ml/100 g·min (table 2). This analysis indicated that MVcf, peak wall stress, and heart rate were significantly related to myocardial blood flow in these patients.

**Discussion**

**Left Ventricular Myocardial Perfusion in Cardiomyopathy: Reduced Flow/Mass; Increased Total Flow**

The present study of myocardial blood flow and ventricular performance in patients with cardiomyopathy was prompted by two considerations. First, there are few studies of cardiomyopathy in which myocardial blood flow has been systematically measured. Second there is a paucity of information concerning the relationship between ventricular performance and myocardial blood flow in man.

Regional left ventricular myocardial blood flow and the three major determinants of myocardial oxygen consumption [heart rate, ventricular performance (MVcf) and peak wall stress] were measured at rest in three groups of patients with normal coronary arteriograms. The control subjects had normal physical examinations, ECGs, and chest films, and their hemodynamic and ventriculographic measurements were within normal limits. The study population consisted of 15 patients with the clinical diagnosis of cardiomyopathy. These patients were divided into two functional subgroups, congestive cardiomyopathy and hypertrophic cardiomyopathy, based upon the ventriculographic findings according to criteria of Goodwin.

The results indicated that mean left ventricular myocardial blood flow rates were reduced in the patients with cardiomyopathy. Significant reductions in blood flow/unit mass of tissue from control values were found in both the congestive cardiomyopathy and hypertrophic cardiomyopathy subgroups (fig. 2). As illustrated in figure 3, the flow reductions occurred diffusely throughout the ventricle; the coefficient of variation of the regional LV flow rates in the cardiomyopathy patients was not significantly greater than in the controls. However, estimated total LV myocardial blood flow (mean LVMBF × LV Mass) in the patients with cardiomyopathy was not reduced but was in fact significantly higher than in the control group (fig. 2). This finding is consistent with large coronary arteries and rapid transit of contrast material observed frequently on the coronary arteriograms of cardiomyopathy patients.

Past studies of myocardial blood flow in patients with cardiomyopathies are quite contradictory. Wendt et al., using the nitrous oxide washout technique, found diminished myocardial blood flow per unit mass of tissue in five patients with idiopathic cardiomyopathy. Henry et al., using the more sensitive helium washout technique, obtained similar results. However, Gorlin et al. reported that both myocardial blood flow and myocardial oxygen consumption were normal in a group of patients with hypertrophic cardiomyopathy. Horwitz et al., using 133Xenon and a single crystal detector, also reported normal average left ventricular myocardial blood flow per unit mass of tissue in a small group of patients with primary myocardial disease. Some of the discrepancies may be related to the differences in techniques employed to measure myocardial blood flow. An alternative explanation for the wide range of reported LV perfusion values is that ventricular performance characteristics varied between the different patient groups chosen for study (see below).

**Technical Considerations**

Regional left ventricular myocardial blood flow rates in the present studies were measured with 133Xenon and a multiple-crystal scintillation camera. The mean LV myocardial perfusion rate in each patient was calculated by averaging the flow rates from all of the detectors located over the left ventricle. It must be recalled, however, that the primary data obtained in these studies were the rate constants of 133Xenon clearance from the myocardium calculated by monoexponential analysis of the initial portions of the multiple precordial washout curves. The expression of the primary data in terms of myocardial capillary blood flow (ml/100 g·min) must be interpreted with caution to the extent that it involves use of an assumed partition coefficient.
and assumptions inherent in monoexponential analysis of the data. As discussed elsewhere, the principle reasons for selecting this form of analysis were 1) the close correlations between myocardial flow/g measured in this manner with radiogenous and flow/g measured with a coronary artery flowmeter in normal dogs and 2) data which indicated that possible errors due to 125I xenon in retrocardiac lung or in cardiac fat would most probably be minimized by this form of analysis.

Possible Explanations for Reduced Flow/Mass in Cardiomyopathy

First, it is possible that the low average LV myocardial blood flow/unit mass of tissue found in the patients with cardiomyopathy was not real but apparent because a large amount of myocardium had been replaced by fibrous tissue. This seems unlikely for three reasons: 1) The blood flow rate in fibrous tissue or myocardial scar is very low (<20 ml/100g·min). A monoexponential analysis of the initial slope of the local 125I xenon myocardial washout curves was made in the present study. If a significant amount of low flow tissue were present, it would constitute a second flow compartment in parallel with the normal myocardial tissue. The amount of tracer initially distributed to each flow compartment following a bolus injection is proportional to the relative total flow to each compartment, i.e., flow rate per unit mass times the mass of each compartment. However, the flow rate per unit mass of fibrous tissue is less than 25% of normal healthy myocardium. Thus, relatively little tracer would enter or leave fibrotic tissue relative to normal myocardium during the first 40 seconds of the washout curve and therefore analysis of the initial slope of the radioxenon washout curve would be less affected by the content of fibrosis and/or fat. 2) The increment in LV myocardial blood flow induced by atrial pacing in the patients with cardiomyopathy was similar to that produced by atrial pacing in a control group of patients with normal coronary arteriograms studied by Conti et al. If the 30% reduction in resting LV perfusion in the cardiomyopathy group were due exclusively to replacement fibrosis, the increment in flow produced by pacing would be expected to be proportionately less, not equal to that of a group of normal subjects. 3) Histological studies of hearts of autopsied patients with congestive or hypertrophic cardiomyopathy have revealed variable but not large amounts of intramyocardial fibrous tissue.

A second possible explanation for reduced resting LV perfusion in cardiomyopathy patients is the presence of "small vessel" coronary disease involving vessels below the resolution of current diagnostic coronary arteriography (200µ). Some pathological studies have shown scattered small vessel occlusive disease in patients with congestive and hypertrophic types of cardiomyopathy. However, no physiological evidence to support the hypothesis of coronary small vessel disease was obtained in the present study. Left ventricular myocardial blood flow rates increased during atrial pacing (fig. 4) and there was no associated chest pain, ECG abnormalities or increase in myocardial oxygen extraction or evidence for myocardial lactate production (table 3).

The fact that mean LV myocardial blood flow increased significantly in the cardiomyopathy patients during atrial pacing does not prove that patients with cardiomyopathy do not experience myocardial ischemia. The method for measuring regional myocardial perfusion in the present studies cannot distinguish subendocardial from subepicardial blood flow. In the presence of a heterogeneous transmural distribution of blood flow, we believe that the regional measurements using the present form of mathematical analysis provide a weighted average of all flow compartments present in the cross-section of myocardial tissue viewed by each of the scintillation crystals. Buckberg et al., using radioactive microspheres, have shown that subendocardial myocardial ischemia can be induced in dogs with normal coronary arteries by procedures which lower coronary driving pressure and shorten diastolic coronary filling time. It is conceivable that during exercise or other stresses which increase myocardial oxygen consumption to a greater degree than atrial pacing, regions of subendocardial ischemia might develop, particularly in the markedly hypertrophied myocardial walls of group IIb patients with LV outflow gradients. Alternatively, the intercapillary distance for diffusion of oxygen within the myocardium may increase as cardiac muscle cells hypertrophy. A reduction of tissue oxygen tension might occur during an abrupt increase in metabolic demand in this situation even if the myocardial capillary blood flow increased by an amount appropriate for nonhypertrophied muscle.

A third possible explanation for the reduced left ventricular myocardial blood flow in the cardiomyopathy patients is that myocardial metabolic demand is reduced as a consequence of altered functional characteristics of the hypertrophied ventricles. Therefore, lower myocardial perfusion rates would be appropriate for reduced levels of myocardial performance. The data of this study suggest that this may be the most likely explanation. In group IIa, congestive cardiomyopathy, the reduction in ventricular performance as estimated by Mvcf was associated with a decrease in LV myocardial perfusion; whereas in group IIb, hypertrophic cardiomyopathy, lowered peak wall stress was associated with diminished myocardial perfusion.

Mvcf and Peak Wall Stress in Cardiomyopathy

There is no general consensus concerning the optimal clinical index which reflects the inotropic state of the heart in patients with heart disease. Mean velocity of circumferential fiber shortening (Mvcf) was selected as the parameter of cardiac performance to be measured in this regard in the present study because it has been more sensitive in identifying differences in cardiac performance among groups of cardiac patients than indices based upon pressure measurements during the isovolumic phase of ventricular contraction. Mvcf was significantly and markedly depressed in the patients with congestive cardiomyopathy, group IIa, confirming previous observations in this disorder and was normal in most of the patients with hypertrophic cardiomyopathy. Mvcf has not been measured in any large group of patients with hypertrophic cardiomyopathy and the concept that ventricular performance in hypertrophic cardiomyopathy may be normal is controversial. However, Hugenholtz et al., using Vmax as an index of ventricular performance found that nine of 11 young patients with left ventricular hypertrophy due to aortic stenosis and one of two patients with hypertrophic car-
diomyopathy had a normal $V_{\text{max}}$. Cardiac performance in hypertrophied cardiac muscle may depend on the length of time that hypertrophy has been present, as well as other neural and hormonal influences.46

In the present study, wall stress was calculated assuming a thin wall ellipsoid model for the left ventricle. Values obtained by this formula are higher than values obtained assuming a thick wall ellipsoid.28 However, the degree of overestimation is slight and does not differ greatly between patient groups.24 Heterogeneity across the wall, bending movement, and shear stresses are not accounted for in such analysis.47 The calculated wall stress is therefore considered only a rough index of mean wall stress.

Peak stress was calculated using the peak systolic pressure and the dimensions of the left ventricle at end-diastole. This approximation overestimates peak stress as evidenced by the higher values for peak stress found in the controls (group I) when compared with values obtained in control patients by other investigators.24-48 Nevertheless, in normal ventricles peak stress occurs shortly after aortic valve opening, i.e., before any substantial decrease in ventricular dimensions48,49 and before the production of peak systolic pressure. Therefore peak stress measured in the manner utilized in these studies is probably not very different from the true peak stress. In addition, the calculation of peak stress was performed in the same manner in all three study groups. In congestive cardiomyopathy (group IIa) peak stress has been shown to occur slightly later and to be maintained longer than in normal ventricles.48 The ventricles of these patients, however, are dilated and have low ejection fractions48,50,51 so that relatively little change in ventricular dimensions occurs before developed peak pressure is maximal. Thus, equatorial wall stress calculated from end-diastolic dimensions and peak pressure cannot differ substantially from the peak stress calculated on the basis of simultaneously measured pressures and dimensions throughout ventricular systole.

In the hypertrophic cardiomyopathy subjects (group IIb), calculated peak left ventricular stress was significantly reduced.48 In this group ventricular emptying has been shown to be rapid in early systole.52 Peak stress is more likely to occur very early in systole52 while chamber dimensions are still relatively unchanged from those at end-diastole. The quick rise in systolic pressure enhances this probability. Therefore, the use of end-diastolic dimensions seems reasonable. If anything, calculated peak stress done by this method would overestimate true peak stress. Despite this negative bias, the hypertrophic cardiomyopathy group still had significantly lower peak stress, thus adding further significance to this finding.

**Determinants of Myocardial Perfusion in Cardiomyopathy**

Numerous studies in animals and a few in humans have established that there is a direct relationship between the rate of myocardial blood flow per unit mass and the rate of myocardial oxygen consumption.30,53-56 Another body of experimental evidence has indicated that the major determinants of myocardial oxygen consumption are heart rate, myocardial contractility and peak ventricular wall stress.5,12 Variations of these three factors in animal preparations were associated with directionally similar and proportional changes in the oxygen consumption of the heart. Although the implication of these experiments is that at rest the rate of myocardial blood flow per unit mass is determined by the performance characteristics of the ventricle, there has been only one attempt to document this relationship in man. Henry et al.4 found that mean LV myocardial blood flow per unit mass of tissue was related directly to ventricular function as estimated by MVcf in a small series of patients with ventricular failure of diverse etiologies. No relationship of blood flow to wall stress was found in that study in which stress did not differ significantly between the control group and the group with impaired cardiac performance.

In order to test whether the reduced mean LV myocardial blood flow rates in the patients with cardiomyopathy might be related to altered ventricular performance, a multiple regression analysis was performed. In the three groups of patients with normal coronary arteries but differing patterns of ventricular function, heart rate, MVcf and peak wall stress were tested as factors relating to myocardial perfusion. The analysis indicated that 63% of the total variation in the mean LV myocardial blood flow rates measured at rest in the 22 patients was explained by these three variables. Further testing by stepwise addition of each variable to the multiple regression equation indicated that each variable individually (including peak wall stress) was related to the rate of myocardial blood flow. It must be noted, however, that the regression equation is merely descriptive of the relationship in these patients. It is presented only to show the order of magnitude of the regression coefficients and is not intended to be used in a predictive fashion. The standard deviation of the estimated LV myocardial blood flow was 9.9 ml/100g·min. This represents the variation that was not accounted for by the three variables and closely approaches the measurement variance as assessed by the average intercrystal variation observed in each study. Thus, the analysis indicated that heart rate, MVcf, and peak wall stress were major determinants of the differing rates of myocardial blood flow in the three groups of patients with normal coronary arteries. The assumptions inherent in the techniques utilized in this study limit our ability to quantify the interrelationships between the determinants of myocardial oxygen consumption and myocardial blood flow. More definitive studies await the advent of more accurate quantitative imaging techniques.

The results of this study imply, therefore, that the reductions in myocardial blood flow per unit mass of tissue found in the cardiomyopathy patients resulted from reductions in myocardial performance: depressed ventricular performance in congestive cardiomyopathy, depressed peak wall stress in the hypertrophic cardiomyopathy. However, the relationship between heart rate, MVcf, and peak wall stress and myocardial blood flow found in the control and cardiomyopathy groups needs to be confirmed and extended by study of patients with other forms of heart disease. In any case, the demonstration that mechanical characteristics of ventricular performance at rest significantly influence the basal rates of LV myocardial blood flow in patients with normal coronary arteriograms has implications for the study of myocardial perfusion in patients with coronary artery disease. It implies that the physiological effects of a coronary lesion which affects regional myocardial blood flow must be interpreted against the relationship between myocardial per-
fusion and ventricular performance which exists in that individual patient.

Appendix

The computer program employed for the stepwise regression was BMD02R. Health Sciences Computing Facility, UCLA. The computation proceeded in the following manner:

Step 1

The program selected the independent variable with the highest correlation with blood flow, peak stress, which had a correlation coefficient of 0.66. This variable was entered into the regression to yield the following equation:

\[ \text{Flow} = 9.18 \times \text{Stress} + 12.7 \]

The F value at this stage was 15.75 (P < 0.01) and the standard error was 11.6.

Step 2

The program then selected the remaining independent variable with the highest partial correlation with blood flow. This variable was MvC which had a partial correlation of 0.51. The regression equation at this stage was:

\[ \text{Flow} = 10.32 \times \text{Stress} + 13.07 \times \text{MvC} - 4.6 \]

The F value at this step was 13.41 (P < 0.01) and the standard error was 10.3.

Step 3

The remaining variable, heart rate, with a partial correlation of 0.33, was then included in the regression equation. This yielded:

\[ \text{Flow} = 9.30 \times \text{Stress} + 16.9 \times \text{MvC} + 0.26 \times \text{H.R.} - 26.4 \]

The final F value was 10.22 (P < 0.01) with a standard error of 9.9.

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References

24. Wong AYK, Rautaharuji PM: Stress distribution within the left ventricular wall approximated as a thick ellipsoidal shell. Am Heart J 75: 649, 1968
Retrograde Coronary Artery Flow in Aortic Valve Disease

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SUMMARY Retrograde coronary artery flow was observed angiographically in 43 patients with aortic stenosis and/or regurgitation.

In the 24 patients with pure or predominant aortic stenosis, retrograde flow was seen in all 24 during end-systole. In the eight patients with pure aortic regurgitation, retrograde flow was seen mainly during end-diastole (6/8). Among the 11 patients with stenosis and regurgitation, retrograde flow was both end-systolic and end-diastolic. Dominant left coronary arteries were seen in 13 patients; 13 showed retrograde flow in the dominant arteries. Dominant right coronary arteries were seen in 25 patients: all 25 showed retrograde flow equally in the right and left coronary. Five of the 43 patients could not be evaluated for dominance because of coronary artery occlusions. The severity of retrograde flow did not correlate with usual clinical, hemodynamic or tension-stress parameters: angina, electrocardiographic abnormality, end-diastolic pressure or volume, end-systolic pressure or volume, ejection fraction, severity of aortic regurgitation, peak or mean valve gradient, aortic valve area, myocardial tension and stress calculations, or DPTI:SPTI.

In summary, retrograde coronary artery flow was seen in all 43 patients with severe aortic valve disease. The time in the cardiac cycle when retrograde flow occurred was related to the type of valve disease. Retrograde flow was seen mainly in the coronary arteries supplying the left ventricle and may result from increased regional myocardial stresses.

THE MECHANISM OF ANGINA PECTORIS is a subject of great interest, especially in patients with aortic valve disease and normal coronary arteries. It is suspected that these patients have inadequate coronary flow in spite of normal coronary arteries. Several experimental studies of phasic coronary flow have shown reverse systolic flow in dogs with congenital subaortic stenosis1 and reverse diastolic flow in dogs with mechanically induced aortic regurgitation.2 Although phasic coronary flow has not been investigated in patients with aortic valve disease, it has been shown that patients with aortic stenosis have impaired coronary vascular reserve3 and subendocardial underperfusion.4 Abnormalities of phasic coronary flow can be seen on the coronary arteriograms of patients with aortic stenosis and/or aortic regurgitation, but have not yet been described in detail. The purpose of this study is to describe angiographic retrograde coronary flow in a series of patients with aortic valve disease and to correlate it with clinical information and hemodynamic parameters.

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