Regional Myocardial Perfusion during Atrial Pacing in Patients with Coronary Artery Disease

Donald H. Schmidt, M.D., Melvin B. Weiss, M.D., William J. Casarella, M.D., Deborah L. Fowler, B.S., Robert R. Sciaccia, M.S., and Paul J. Cannon, M.D.

SUMMARY Regional myocardial perfusion (RMP) was measured with \(^{133}\)Xe and a multiple-crystal scintillation camera at rest and during atrial pacing in 24 patients with normal coronary arteriograms or \(<50\%\) lesions, Group I, and in 24 with significant (\(>50\%\) lesions) left coronary artery disease (CAD), Group II. Pacing-induced increases in the double product (DP) of heart rate and systolic blood pressure, an index of myocardial oxygen consumption, were not different for Groups I and II. In Group I average mean LV perfusion rate was subnormal at rest but rose from 49 to 73 ml/100 g-min during pacing to 150/min without angina. A response index (RI), (\(\Delta MP \times 10^7/\Delta DP\)), averaged 2.93. Twenty patients in Group II developed angina during pacing. The average mean LV perfusion rose less than in Group I, from 48 to 64 ml/100 g-min (\(P < 0.05\)) and the average RI, 1.76, was lower (\(P < 0.01\)). In 19 of these patients, average RMP distal to the major coronary lesion increased from 46 to 58 ml/100 g-min; this increase during pacing was significantly less than in the remainder of the LV of 48 to 66 ml/100 g-min (\(P < 0.05\)).

Average regional RIs were 1.39 and 2.18, respectively. In three patients the presence of collaterals termed adequate by radiological criteria was not associated with preferential decreases in the distal regional RI. The data support the hypothesis that in some patients with CAD, angina pectoris results when an obstructive coronary lesion restricts the total or regional myocardial blood flow response to an increased rate of myocardial oxygen consumption.

AN ASSOCIATION between the clinical syndrome of angina pectoris and the presence of obstructing lesions of two or more coronary arteries was clearly established in the 1940s and 1950s by the pathological studies of Zoll et al.1 The etiology of the syndrome is unclear. A current hypothesis holds that in many patients with coronary artery disease, angina pectoris results when there is a disparity between the amount of oxygen delivered to the myocardium by the coronary blood supply and the requirements of the cardiac muscle for oxygen.2 Studies in which radioactive ions were administered during exercise7 and measurements of coronary sinus blood flow8 and of myocardial lactate extraction and performance during pacing6,10 have provided indirect evidence for this hypothesis. More direct measurements of regional myocardial perfusion in relation to the oxygen requirements of the heart have not been performed. However, other studies have indicated that spasm of normal or diseased coronary arteries may be observed angiographically in association with Prinzmetal's variant angina,11,12 and that angina pectoris may also occur in patients with normal coronary arteriograms.13

In order to study the adequacy of coronary blood flow in patients with angina, investigators in this laboratory have been developing a method to estimate quantitatively myocardial capillary blood flow in different regions of the heart in patients using \(^{133}\)Xe and a multiple-crystal scintillation camera.14,15 The initial studies of patients with coronary artery disease were performed at rest.15,17 Although the average mean left ventricular myocardial blood flow/unit mass of tissue was subnormal in patients with radiographically significant lesions of two or more coronary vessels, it was not significantly different from normal in patients with significant isolated obstructions of the left anterior descending (LAD) artery.17 In addition, selective reductions of regional myocardial perfusion distal to significant LAD lesions were found at rest only with total occlusions of the artery.17

Coronary blood flow normally increases in direct proportion to increases in myocardial oxygen consumption induced by increases in heart rate, myocardial contractility or ventricular wall stress.18,21 Because abnormalities of mean LV and regional myocardial perfusion were not found at rest in many patients with angina pectoris who had significant coronary lesions, it was decided to measure regional myocardial blood flow also during an intervention which increases myocardial oxygen consumption. Accordingly, measurements of regional myocardial perfusion were performed at rest and during right atrial pacing in a group of 24 patients with left coronary arteriograms that were normal or revealed only insignificant lesions and in another group of 24 patients with radiographically significant obstructions of one or more left coronary branches. The aim of the studies was to make statistical comparisons between the two groups of: 1) the incidence of angina during pacing, 2) the changes in heart rate and the double product of heart rate \(\times\) systolic blood pressure, and 3) the mean LV and regional myocardial blood flow responses to the increased heart rate.

Methods

Cardiac catheterization and coronary arteriography were performed only on patients for whom the studies were indicated clinically. Usual indications were a history of angina pectoris, atypical cardiac pain, congestive heart failure of uncertain etiology and evaluation for cardiac valve surgery. Coronary arteriography was performed by a modified Judkin's technique22 in the postabsorptive state after administration of seconal, phenergan and atropine. Images of contrast material injected into each coronary artery were recorded on cine and/or serial cut films at a framing rate of 50 frames per second using a six inch image intensifier and 35 millimeter film.

The patients were divided into two groups according to
the radiographic abnormalities apparent on their left coronary arteriograms. Group I patients had normal or insignificant lesions of the left coronary artery; many of this group had hemodynamic or ventriculographic evidence of heart disease and five had abnormal right coronary arteriograms (table 1). Group II patients had one or more radiographically significant lesions apparent on the left coronary arteriograms (table 2). The coronary vascular lesions apparent on cine and cut film coronary arteriograms were interpreted independently by at least one cardiologist and one radiologist and were coded by a modification of the scheme of Abrams.23 The right, left main (LM), left anterior descending (LAD), and left circumflex (Circ) arteries were assessed individually (one, two, three, four vessel disease). Insignificant or mild coronary disease was defined arbitrarily as the presence of no obstruction or obstructions of less than 50% of the lumen diameter. The grading 1A indicated minor irregularity, whereas 1B indicated obstructions of up to 50% which were not associated with a prolonged transit of contrast material. Significant coronary disease was defined as obstruction greater than 50% of any vessel or obstructions of 50% which were accompanied by delayed passage of contrast material. Significant disease was subdivided into grades: 2A = 50–60% obstruction, or 50% with slow transit of contrast material, 2B = 60–80% obstruction, 2C = 80–99% obstruction, 2D = total obstruction. Total obstructions of major branches with a diameter of 50% of the parent vessel, such as the obtuse marginal, were classified as 2D.

The obstructive lesions in the four coronary arteries were also numerically scored in the following manner. In the right, left anterior descending and the circumflex branches of each patient, the lesions that had been graded were assigned the following numerical scores: 1A = 5, 1B = 10, 2A = 20, 2B = 30, 2C = 40, 2D = 50. Lesions of the left main artery were given a score two times the other vessels, e.g., 1A = 10, 1B = 20, etc. The total score in each patient was calculated by summing the scores in the four coronary arteries.

Radiographic criteria for the presence of collateral vessels were: 1) visualization of accessory blood vessels which either filled the distal segment of an occluded or stenotic blood vessel or supplied an area of myocardium distal to such a lesion, and 2) visualization of a coronary artery after injection of contrast material into the contralateral artery. Collaterals were termed inadequate if the coronary artery supplied by the collateral vessels did not fill to a diameter of 1 mm or if contrast material remained in the collateral vessels or the arterial segment supplied by these vessels after it had been cleared from the rest of the arterial tree. Adequate collateral vessels were those that were clearly visualized, had a normal transit time of contrast material and which filled the arterial segment beyond the coronary stenosis to a diameter of at least 1 mm.

Informed consent for the radioisotopic measurements of myocardial blood flow was obtained from each patient. The investigative protocols were approved by the Human Investigation and Joint Radioisotope Committees of the Columbia Presbyterian Medical Center. There were no complications related to the blood flow studies. At the conclusion of diagnostic coronary arteriography, a left anterior oblique (LAO) cineangiogram was obtained with a series of radiopaque-radioactive markers positioned on the chest wall. Five to ten minutes were then allowed to elapse. Without any change in the patient’s position, the cine camera was removed and replaced by the multiple-crystal scintillation detector which was positioned in the same plane and location over the patient’s precordium. The multiple-crystal detector used for these studies (Autofluoroscope, Model 5600) consists of a grid of 294 individual NaI(Tl) scintillation crystals arranged in 21 columns of 14 crystals. Each crystal is coupled by light pipes to two photomultiplier tubes arranged in an X and Y coordinate system. Scintillations occurring in each crystal are registered in a digital core memory and are recorded onto magnetic tape in locations which correspond to the positions of the separate crystals in the radiation detector. The positions of the precordial markers were recorded by the instrument and the markers were removed. The radioisotopic measurements of regional myocardial perfusion were made by a method reported previously21,24 and outlined below.

Twenty to twenty-five mCi of 133Xenon dissolved in 1–2 ml of sterile pyrogen-free saline were injected rapidly into the main right or left coronary artery. 133Xenon passes by diffusion instantaneously into the myocardial tissue supplied by the coronary artery and is washed out from the tissue as a direct function of (nonradioactive) myocardial capillary blood flow.25 The 81 keV gamma radiation emitted by the radioisotope during its arrival and washout from the myocardium was collimated by a 1.5 inch multichannel collimator and recorded externally by the multiple-crystal detector. Previous studies25 indicated that the radius of tissue viewed by each crystal using this collimator was 6 mm at 3 cm distance (corresponding to the anterior myocardial wall) and 13 mm at 9–10 cm distance (corresponding to the posterior cardiac wall). Overlap of the field of view of adjacent crystals, an important consideration when measuring multiple regional 133Xenon washout curves, was negligible up to 5 cm distance but about 16% at 9–10 cm.18 Scintillations produced by incident photons were converted to an electrical signal, conditioned by anticoincidence circuitry and pulse height analysis (window settings 70-250 keV), stored in the digital memory and recorded onto the tape as counts per second for 2–4 minutes.

After the myocardial blood flow was measured at rest, the heart rate was artificially increased by right atrial pacing.26 A bipolar pacing catheter was positioned under fluoroscopic control in the high lateral right atrial wall near the junction with the superior vena cava. Right atrial pacing was then instituted using a Medtronic temporary demand pacing box. Heart rate was increased in graded 10–20 beat increments lasting one to two minutes until a maximum heart rate of 150 beats/min was attained or chest pain occurred. The tachycardia was then sustained for five minutes under electrocardiographic monitoring while the myocardial blood flow determination was repeated. If chest pain was significant, the heart rate was lowered to a new steady state prior to making the measurements or the procedure was terminated. The double product of heart rate times systolic blood pressure was used as an index of myocardial oxygen
### Table 1. Group I: Clinical and Hemodynamic Data

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<tr>
<th>Patient</th>
<th>Diagnosis</th>
<th>Angina</th>
<th>MI</th>
<th>BP</th>
<th>Ventriculogram</th>
<th>Coronary arteriogram</th>
<th>Type study</th>
<th>Double product</th>
<th>MBF (ml/100 g/min)</th>
<th>RI (Δ Flow / Δ DP)</th>
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**Abbreviations:** UHD = unknown heart disease; AI = aortic insufficiency; HCVD = hypertensive cardiovascular disease; ASCVD = atherosclerotic cardiovascular disease; CM = cardiomyopathy; ATYP = atypical chest pain; MI = myocardial infarction; BP = blood pressure; NL = normal; LVE = left ventricular hypertrophy; DAM = diffuse abnormal motion; L = left main; LAD = left anterior descending; LC = left circumflex; R = right; Collat = collaterals; - = absent; I = inadequate; A = adequate; C = control; P = paced; LV = left ventricle; DP = double product; RI = response index; MBF = myocardial blood flow.
<table>
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<th>MI</th>
<th>↑BP</th>
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*Patient experienced chest pain or had ECG changes.  
**Distal perfusion could not be measured due to overlap of normal vessels with the myocardial region distal to the coronary occlusion.
REGIONAL MYOCARDIAL PERFUSION DURING PACING/ Schmid et al.

811

consumption. Only studies in which the double product was increased by at least 5000 units during atrial pacing are included in this report. Upon completion of the pacing studies, left ventricular volume and contractility were measured in most patients after contrast material was injected into the left ventricle.

The tracer data from each study on magnetic tape was processed by a digital computer (IBM 360/91) located at the Columbia University Computer Center. Crystals which had recorded the washout of 133Xenon from myocardial tissue were distinguished from those which recorded the excretion of 133Xenon from the lungs by a computer printout of the peak counts per second (cps) recorded by each crystal and the number of seconds after the coronary injection of tracer that the peak cps occurred. Crystals overlying the myocardium supplied by the coronary artery recorded higher peak cps early; crystals monitoring the arrival and excretion of 133Xenon by the lungs recorded lower peak cps later. Using the method of least squares, the computer fit a monoeponential equation to the first 40 data points after the peak count recorded by each crystal and calculated the slope (k) of the initial portion of the myocardial 133Xenon washout curve, i.e., the clearance constant of 133Xenon washout from the myocardium viewed by the crystal. Using the Kety formula, the nutrient myocardial blood flow rates in the different areas viewed by the multiple crystals were calculated, along with the standard deviation of each blood flow measurement. F = k \times \lambda / \rho where F is the myocardial capillary blood flow in ml/100 g-min, \lambda is the blood:myocardium partition coefficient for 133Xenon obtained by Conn in the normal dog heart (0.72) and \rho is the specific gravity of the tissue (1.05).

A computer printout of the local myocardial blood flow rates was then superimposed upon a tracing of the patient's LAD left coronary arteriogram so that regions of myocardial perfusion could be distinguished by anatomical features of the coronary vasculature. Alignment and appropriate magnification of the two were facilitated by the presence of the radioactive-radiopaque markers present on both the arteriogram and the myocardial perfusion pattern. A mean left ventricular myocardial perfusion rate in each patient was calculated by averaging the local blood flows recorded by all of the crystals overlying the left ventricle. The local perfusion rates of left ventricular subregions supplied by the anterior descending or the circumflex arteries were determined by averaging the perfusion rates of crystals in the appropriate areas of the perfusion pattern as determined from the tracing of the coronary arteriogram. In many studies, average perfusion rates in areas of myocardium distal to discrete coronary artery stenoses and in the remainder of the left ventricle were also estimated in a similar fashion.

Statistical analysis of the data obtained in the two groups of patients was performed by standard techniques. Comparisons between the patient groups at rest and during atrial pacing were performed by an analysis of variance. Differences were deemed significant if P < 0.05.

Table 1 lists the clinical, hemodynamic and angiographic data in the individual patients of Group I along with the mean LV and regional myocardial perfusion values at rest and during right atrial pacing. The average hemodynamic and myocardial blood flow responses to pacing in Group I are compared to those of Group II in table 3.

Figure 1 illustrates the regional myocardial blood flow patterns of Group I patient J.S. at rest and during atrial pacing to a heart rate of 150/min. At the faster heart rate, the index of myocardial oxygen consumption (MVO2), the double product, increased by 9720 units. The patient did not experience chest pain and the ECG was unchanged. In response to pacing there were increases in the regional myocardial blood flow rates diffusely throughout the left ventricle with the mean LV myocardial blood flow rate increasing from 59 to 98 ml/100 g-min; regional perfusion in the left anterior descending area increased from 61 to 105 ml/100 g-min and in the circumflex area from 55 to 87 ml/100 g-min. A myocardial response index relating the increment in myocardial perfusion to the increment in metabolic demand produced by the faster heart rate was calculated as 104 times the increase in myocardial blood flow divided by the simultaneous increase in the double product; the LV response index to atrial pacing was 4.01.

None of the patients in Group I experienced chest pain or manifested ECG changes of myocardial ischemia during atrial pacing. The average increments in heart rate and in the double product did not differ significantly from the comparable changes in Group II (table 3). In Group I, the average mean LV myocardial blood flow at rest, 49 ml/100 g-min, was not significantly different from that of Group II; however, it was significantly lower than the resting value of 61 ± 6 ml/100 g-min found previously in patients with normal left and right coronary arteriograms who had normal intracardiac pressures and ventriculograms. During right atrial pacing, average mean LV myocardial perfusion in Group I increased 49% from 49 to 73 ml/100 g-min and average coronary vascular resistance/100 g declined from 2.07 to 1.53. The average LV myocardial response index was 2.93 ± 1.43. Both in the resting state and during atrial pacing, there were no significant differences between the average regional myocardial blood flow rates in the LAD and the Circ myocardial subregions in the Group I patients (table 3). The average LAD and Circ myocardial response indices were likewise not significantly different, 3.17 and 3.03, respectively.

Figure 2 illustrates the regional myocardial blood flow responses of a Group II patient to atrial pacing. A.S. had an 80% proximal obstruction of the LAD artery and no visible collateral blood vessels to the myocardial area distal to the lesion. In the myocardial perfusion study performed at rest, the mean LV myocardial blood flow rate was 56 ml/100 g-min. The average perfusion rate observed in the myocardial region distal to the LAD lesion on the myocardial perfusion pattern, 55 ml/100 g-min, was not significantly different from the average of the local myocardial blood flow rates elsewhere in the ventricle, 58 ml/100 g-min. During atrial pacing the patient experienced mild angina at a heart...
rate of 130/min; at this heart rate the double product was increased by 6780 units. The mean LV myocardial blood flow rate rose 18% from 56 to 67 ml/100 g-min in response to atrial pacing. The increase in regional perfusion in the myocardium distal to the left anterior descending lesion (55 to 62 ml/100 g-min) was significantly less than the increase observed in the remainder of the ventricle (58 to 71 ml/100 g-min). The myocardial response index calculated for the LV in this study was 1.65. The regional response index calculated for the area of myocardium distal to the lesion was 1.05 whereas it was 1.95 for the remainder of the ventricle.

The clinical, hemodynamic, angiographic and myocardial perfusion data for the patients of Group II with radiographically significant left coronary lesions are listed in table 2. Twenty of the 24 patients experienced precordial pain or had ECG changes of ischemia during atrial pacing despite the fact that the induced changes in heart rate and double product were not statistically different from Group I (table 3). The average of the mean LV perfusion rates in Group II patients rose 33% during pacing from 48 to 64 ml/100 g-min, and coronary vascular resistance/100 g declined from 2.13 to 1.77. The increment in average mean LV perfusion in Group II during pacing (+ 16 ml/100 g-min) was significantly lower than the increment in mean LV perfusion observed in Group I (+ 24 ml/100 g-min) \( (P<0.01) \). The average LV myocardial response index in Group II, 1.76±1.28, was significantly lower than that in Group I \( (P<0.01) \) (table 3).

In the 19 Group II studies in which a comparison was possible, the regional myocardial blood flow rate distal to the most significant left coronary lesion was not significantly different at rest from the average of the local perfusion rates elsewhere in the ventricle (46 vs 48 ml/100 g-min) (table 3). During atrial pacing to 150/min or to angina, the regional myocardial perfusion rates in Group II patients increased significantly in both myocardial subregions. However, the increase in average regional myocardial blood flow distal to the lesions (46 to 58 ml/100 g-min) was significantly smaller than the increase in regional perfusion which was induced in the remainder of the left ventricle (48 to 66 ml/100 g-min) \( (P < 0.01) \). The myocardial response index in the distal region, 1.39, was also significantly lower than the regional response index for the remainder of the ventricle, 2.18 \( (P < 0.01) \). Both of these regional response indices in Group II patients were significantly lower than the response indices in the LAD and Circ regions of the patients in Group I. There were no significant correlations, however, in the 19 patients between the degree of coronary obstruction apparent on the arteriogram and either the change in flow distal to the lesion \( (r = 0.07) \) or the distal regional myocardial response index \( (r = 0.06) \).

In four of the patients of Group II (J.M., N.L., A.W., J.K.), the blood flow response to atrial pacing in the myocardial region distal to the most significant coronary lesion was directionally different from the response of the remainder of the left ventricle (table 2). Figure 3 illustrates the effect of atrial pacing in patient J.M. (table 2). At a heart rate of 130 the patient experienced moderately severe chest pain. The average myocardial perfusion in the region distal to the
LAD lesion declined from 34 to 28 ml/100 g-min while in the remainder of the LV average perfusion increased from 46 to 52 ml/100 g-min.

In a few Group II patients, the presence of collateral blood vessels which were adequate by radiographic criteria appeared to influence the regional myocardial blood flow responses to pacing (L.R., J.J., B.M., table 2). Figure 4 is the right coronary arteriogram of patient L.R. which shows a rich collateral vasculature extending from the right coronary artery to the area of left ventricle supplied by a diseased left anterior descending artery. The myocardial perfusion pattern obtained after $^{133}$Xe was injected into the right coronary artery (fig. 5) revealed that at rest the myocardial capillary blood flow rates were higher in the left ventricle than the right ventricle and that in the LAD regions they approached the range of normal values. Figure 6 shows the myocardial perfusion patterns obtained after left coronary injection of $^{133}$Xe in the same patient. At rest the myocardial perfusion rate measured in the distal LAD region, 51 ml/100 g-min, was lower than that in the remainder of the ventricle, 61 ml/100 g-min. During atrial pacing the patient experienced mild chest pain at a heart rate of 145/min. The average myocardial perfusion rates in the two subregions increased in response to pacing to 69 and 72 ml/100 g-min, respectively. The response index for the distal LAD region was 1.80; that for the circumflex and proximal LAD region was 1.10.

In the three patients of Group II with radiographically adequate collaterals, there was no significant difference in the regional response index between the the myocardial area distal to the lesion and the rest of the LV (1.57 and 1.81, respectively). However, in ten patients without adequate collaterals, the regional response index for the distal region (0.54) was significantly lower than for the remainder of the LV (1.87). In both groups the regional response indices were less than those observed in Group I patients (table 3).
CONTROL

MEAN LV FLOW (40ml/100g min)

DISTAL TO LAD LESION
REST OF LV

40% STENOSIS

24 22 26 32 46 19 41 57 64

20 27 41

PACING

MEAN LV FLOW (38ml/100g min)

DISTAL TO LAD LESION
REST OF LV

40% STENOSIS

28 22 34 37 54 59 62

33 44 55 50 58 60

FIGURE 3. The regional myocardial blood flow response to atrial pacing in patient W.M. of Group II.

Discussion

Study Plan

Two physiological characteristics of the myocardial circulation provided the impetus to make measurements of regional myocardial blood flow during atrial pacing in patients with coronary artery disease. First: It has been demonstrated in animal preparations that coronary blood flow is proportional to myocardial oxygen consumption, which is in turn determined by factors such as heart rate, wall stress and inotropic state. Increases in myocardial oxygen consumption are accompanied by vasodilatation of precapillary arterioles affecting proportional increases in myocardial blood flow. Second: The coronary circulation is normally autoregulated so that blood flow remains constant during induced changes in coronary perfusion pressure from 70–150 mm Hg. As the lumen of a large epicardial coronary artery is narrowed experimentally (or by an atherosclerotic plaque), vasodilatation of small coronary vessels distal to the lesion maintains constancy of blood flow. Experimental studies have indicated, however, that with increasing obstruction of a large artery, the compensation provided by coronary arteriolar dilatation diminishes, and blood flow through the coronary bed becomes more critically dependent upon the blood pressure drop across the obstructing lesion. Therefore, it seemed reasonable to attempt to assess the hemodynamic significance of coronary arteriographic lesions by measuring regional myocardial perfusion distal to the lesions during an intervention which increases myocardial oxygen consumption. For this purpose two groups of patients were selected who had <50% or >50% obstructions apparent on the left coronary arteriograms. The incidence of angina and the mean left ventricular and regional myocardial blood flow responses during a procedure which increases heart rate were compared in the two groups.

Atrial pacing was selected as the means to increase myocardial oxygen consumption. The technique used was to gradually increase heart rate by 20 beat/min increments and to perform measurements of regional flow only when a steady state had been attained at the new heart rate. Pacing induces smaller alterations in systemic hemodynamics and

FIGURE 4. The right coronary arteriogram of patient L.R. showing adequate collateral vessels to a diseased LAD artery.

FIGURE 5. The myocardial perfusion pattern after 133xenon was injected into the right coronary artery of L.R.
smaller rises in myocardial oxygen consumption than exercise or isoproterenol infusion. This probably accounts for the fact that four of the patients with significant coronary artery disease (and a history of angina) failed to develop chest pain or ECG evidence of ischemia when their heart rates were increased by pacing to 150/min (table 2). Nevertheless, this disadvantage is counterbalanced by enhanced patient safety and the resulting lack of complications. Abnormalities of cardiac function during induced angina also return more rapidly to normal with cessation of atrial pacing than with cessation of exercise.

133Xe and a multiple-crystal scintillation camera were used to make the measurements of regional myocardial perfusion in the patients. It must be re-emphasized that the primary data obtained in each study were the rate constants of 133Xe clearance from the areas of myocardium viewed by each of the multiple precordial detectors. These clearance constants were calculated by monoexponential analysis of the initial portions of each tracer washout curve. The expressions of the primary data in terms of nutrient blood flow must be interpreted with caution to the extent that they involve the use of an assumed partition coefficient and of the assumptions involved in the monoexponential analysis.

Comparative measurements of regional myocardial perfusion with 133Xe and the multiple-crystal scintillation camera and with radioactive microspheres have not yet been performed in experimental animals. As discussed previously, initial slope monoexponential analysis of the local 133Xe washout curves was chosen: 1) because good correlations between mean LV myocardial blood flow measured by a coronary flow meter and by radioxenon have been reported in normal dog hearts over a blood flow range of 30 to 80 ml/100 g min, and 2) because it is likely that this form of analysis minimizes possible errors due to elimination of 133Xe in the retrocardiac lungs or due to 133Xe diffusion into pericardial fat.

When inert gas washout curves are measured from a tissue with topographical variation in regional blood flow such as results from coronary artery constrictions or occlusions, the curves obtained by a single external detector over the LV or by coronary sinus sampling deviate from a single exponential. In this situation prolonged times for saturation and desaturation of the tissue are required so that low flow areas can contribute proportionally to the initial washout measurement. The problem created by increased spatial heterogeneity of myocardial blood flow in coronary artery disease is obviated to a great extent, however, by the use of multiple detectors, each of which records tracer washout from a different discrete area of tissue. Nevertheless, heterogeneity of blood flow across the heart wall cannot be distinguished by the form of analysis used in these studies. Despite this we believe that the measurements yield a weighted average of all of the flow compartments within the field of view of each of the multiple crystals.

Myocardial Perfusion at Rest

The average mean LV myocardial blood flow at rest in the control patients (Group I) was significantly lower (table 3) than that observed previously in patients with normal coronary arteries who had normal ventricular function. The separation of the patients into Groups I and II was done solely according to the severity of arterial disease apparent on the left coronary arteriogram. Thus among the patients of Group I with no or insignificant abnormalities of the left coronary arteriogram there were many with impaired myocardial performance due to cardiomyopathy, right coronary disease, hypertension or heart disease of unknown etiology. In patients with congestive or hypertrophic cardiomyopathy reduced levels of mean LV myocardial perfusion/unit mass of tissue were found to relate in a predictable fashion to depressions of two of the major determinants of myocardial oxygen consumption, myocardial contractility (measured as the mean velocity of circumferential fiber shortening) and peak ventricular wall stress (unpublished observations).

Group II patients, with one or more significant lesions visible on the left coronary arteriograms, had an average mean LV myocardial perfusion rate at rest that was also below that found in patients with normal coronary arteriograms and cardiac function (table 3). Klocke et al., who used the He washout technique with coronary sinus

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**Figure 6.** The regional myocardial blood flow response to atrial pacing in L.R.
sampling, also found reductions of mean LV perfusion per unit mass of tissue in patients with radiographically significant coronary artery disease.

The average regional blood flow rate at rest in myocardium distal to the most significant coronary lesion in 19 Group II patients was not significantly lower than in the remainder of the same ventricles (table 3). In a study of isolated LAD lesions in this laboratory it was also observed that selective reductions of regional blood flow distal to the lesions were found only in groups of patients with total LAD occlusions. Similarly, in a study of dogs with experimental coronary artery constriction, resting coronary artery blood flow did not fall until the arterial diameter was reduced >85–90%.

Responses to Atrial Pacing: Hemodynamic and Mean LV Myocardial Blood Flow

Heart rate and the double product (heart rate × systolic blood pressure) increased significantly in the Group I patients during atrial pacing (table 3). In these studies the double product was used as an index of myocardial oxygen consumption since it has correlated closely with myocardial oxygen consumption in animal preparations in which coronary flow and myocardial oxygen extraction were measured directly. The average mean LV myocardial blood flow rate increased 49% in Group I in response to the increased myocardial oxygen consumption produced by the faster heart rate (table 3). This is consistent with previous observations that coronary blood flow increases directly with increases in heart rate in normal dogs and that average LV myocardial perfusion increases directly with increases in the double product in patients with normal coronary arteriograms during graded exercise or pacing.

The increments in heart rate and in the double product induced by pacing in Group II were not significantly different from those in Group I (table 3). The similar rise in the double product implies that myocardial oxygen consumption was increased to the same extent in both groups. Nevertheless, the average mean LV myocardial blood flow increased significantly less (33%) in Group II than in Group I during atrial pacing (table 3); the coronary vascular resistance declined 24% in the control subjects and only 17% in those with significant left coronary arteriographic lesions. The calculated LV myocardial response index was significantly lower in Group II than in Group I.

These results showing a lower increment in mean LV perfusion per increment of an index of metabolic demand (the double product) in patients with radiographically significant coronary artery disease differ from those reported previously by several groups. Mean LV myocardial blood flow increases in patients with significant coronary artery disease equal to or greater than those of control patients have been reported by investigators who used 133Xe or 82Kr as tracers and a single precordial scintillation detector or coronary sinus sampling to measure myocardial washout curves. It is possible that regions of myocardium where flow responses were inadequate were obscured by larger areas with rapid flow in those studies in which only single myocardial washout curves were measured. Klocke et al. have provided evidence that single myocardial washout curves using N2O, 133Xe or 82Kr overestimate average left coronary flow in the presence of heterogeneous myocardial perfusion associated with experimental narrowing or occlusion of a coronary artery. In contrast, the technique to measure regional myocardial perfusion in the present studies employed a multichannel collimator and a mosaic of individual scintillation crystals to subdivide the myocardium spatially. In this way, areas of reduced perfusion were identified, related to the arteriographic lesions and given proportionate representation in the mean LV flow calculated for a given ventricle.

The present observations are consistent with data reported by Ganz and coworkers who found no significant difference in coronary sinus flow at rest between subjects with normal coronary arteriograms and those with radiographically significant coronary disease. During pacing, however, coronary sinus blood flow increased proportionately to the rise in heart rate in both groups only until angina developed; then the increment in coronary sinus flow/beat was significantly lower in the coronary disease group. Knoebel et al. have used the potassium analogue, 82Rb, and a coincidence counting system to study the myocardial responses to pacing, isoproterenol infusion and treadmill and handgrip exercise. Although there was no difference in myocardial 82Rb clearance at rest between patients with normal coronary arteriograms and patients with significant coronary disease, the increment in myocardial 82Rb clearance observed during induced angina in the latter group was significantly lower than in the former.

Regional Myocardial Blood Flow Responses to Pacing

The present studies also demonstrate inadequate flow responses in specific regions of the LV during pacing-induced angina (figs. 2 and 3, table 3). In contrast to the uniform increases in regional LAD and Circ perfusion observed in Group I during pacing, the increase in perfusion in the region distal to the coronary lesions in Group II was significantly lower than that observed elsewhere in the myocardium (table 3). Abnormal regional myocardial blood flow responses in coronary disease such as these were anticipated by Friedberg from consideration of the patchy location of coronary atherosclerotic lesions and by workers who had observed increases in coronary sinus blood lactate concentrations during pacing-induced angina in patients in whom overall myocardial blood flow (*82Kr myocardial washout) had risen normally. Regions of diminished myocardial uptake of *82K or *82Rb have also been observed during angina by investigators who performed precordial scintiscans with rectilinear scanners or scintillation cameras in association with exercise stress testing of patients with coronary disease.

McGregor and Fam in 1966 postulated that if coronary arterioles were maximally dilated in an ischemic region distal to a critical coronary occlusion, an increase in myocardial oxygen consumption induced by pacing or exercise might produce vasodilatation selectively in nonischemic tissue. Thus, the pressure differential driving blood to the ischemic region might decline and blood flow to the ischemic area would fall during pacing or exercise. Contrary to this speculation, the average regional myocardial blood flow distal to significant coronary lesions in Group II did not fall but increased, albeit to a lesser extent than elsewhere in the LV (table 3). In four individuals, however, distal myocardial
perfusion did not change or fell in association with increases in myocardial blood flow in the rest of the LV (table 2). Possible mechanisms for the discrepant findings in these four patients include that proposed by McGregor and Fam,33 depressed regional or global myocardial performance during angina.10, 50 coronary spasm or compression of vessels by an altered ventricular wall in the ischemic region.50

The data, therefore, differ from a report41 concerning the effect of atrial pacing upon regional myocardial 133Xe clearance in patients with isolated left anterior descending stenoses of >85%. In those studies the heart rate was abruptly increased to 150/min after 133Xe had been injected into the coronary artery. The assumptions of steady state required for perfusion measurements with inert gases were violated by such a protocol. In addition, it is likely that the sudden onset of such rapid tachycardia induced abnormalities of ventricular wall function in the ischemic zone which mechanically impeded tracer removal. Dwyer et al. have demonstrated that pacing-induced angina may be associated with reversible abnormalities of regional wall motion and also with alterations of ventricular compliance.50

There has been controversy over the functional significance of the collateral blood vessels which are visualized arteriographically in patients with coronary disease.52-54 Measurements of regional myocardial blood flow in several of the Group II patients indicate that collateral blood vessels are capable of maintaining the resting level of myocardial perfusion distal to coronary obstructions at or near normal values (e.g., fig. 3). Normal levels of resting blood flow in the area distal to an occlusion have also been observed via collaterals in dogs three to four weeks following ligation of a coronary artery.58

In the three patients with collateral blood vessels which were judged to be adequate by radiographic criteria, the average response index of the region distal to the most significant coronary arterial obstruction was not significantly different from the remainder of the ventricle. In contrast, the regional response index for the involved area was significantly less than for the remainder of the ventricle in ten patients who lacked adequate or had inadequate collaterals to the myocardial region beyond the coronary lesion. In all 13 of these patients, the response indices in both regions of the ventricle were significantly lower than those of Group I patients who had normal or insignificant left coronary abnormalities and no visible collaterals (table 3). These observations plus other studies55, 56 suggest that collateral vessels may contribute significantly to myocardial blood flow reserve in patients with coronary occlusive disease. However, the variability of the responses observed (table 2) and the subjectivity involved in the radiographic evaluation of collateral adequacy suggest that blood flow measurements will have to be performed in order to assess the significance of collateral vessels visualized in an individual patient.

Relationship of Myocardial Blood Flow Responses to Angina during Pacing

Twenty of the 24 patients in Group II who exhibited reduced average increments in regional and mean LV perfusion developed angina pectoris during right atrial pacing. In contrast, none of the patients in Group I developed chest pain or ECG evidence of ischemia despite equivalent increases of double product in the two groups. The data, therefore, provide direct evidence in man in support of the hypothesis2 that in many patients with coronary atherosclerosis, angina pectoris results when coronary artery disease restricts the total or regional myocardial blood flow response to an increased level of myocardial oxygen consumption.

Angina occurred in four Group II patients during pacing, however, even though regional or mean myocardial perfusion increases as large as those in Group I were found. This failure to detect blood flow abnormalities during angina is unexplained. Angina may have resulted from ischemia in a small region of the myocardium below the spatial resolution of the multidetector system used, or it may have resulted from a region of subendocardial ischemia that was not identified. Several investigators have demonstrated that subendocardial blood flow falls preferentially during partial occlusion of a coronary artery or when aortic pressure is increased coincident with a sharp decline in diastolic coronary filling time.57-59 In the present studies, each scintillation crystal monitored 133Xe washout from all of the myocardial tissue within its field of view. Using the monoexponential analysis of the initial portion of each myocardial washout curve, the technique is currently not able to distinguish subendocardial from subepicardial blood flow rates nor is it able to measure redistributions of blood flow across the heart wall. As explained in detail elsewhere,64 this form of mathematical analysis approximates the time zero derivative of the myocardial tracer curve which is equivalent to an average of the separate rate constants from any different flow compartments in the tissue viewed by a crystal weighted by the total flow to each compartment. Therefore, it is our belief that the values for regional perfusion obtained at rest and during pacing represent weighted average flow rates within the myocardial areas viewed by the different crystals.15 Experiments to test this hypothesis in dogs using both 133Xe and radioactive microspheres are currently being initiated in this laboratory.

Practical Considerations and Conclusion

The method used in these studies to measure perfusion in different regions of the myocardium of patients at coronary arteriography is still under development.15, 24 At this time, the optimal way to assess the physiological significance of a specific coronary lesion visualized on the arteriogram of an individual patient has not been devised.

In the present study there was no significant correlation within the group of patients with radiographically significant coronary disease between the regional myocardial flow response distal to the lesion and the extent of obstruction as assessed from the arteriogram. This lack of correlation probably relates to multiple factors which include: inherent imprecisions in the visual quantitation of coronary obstructions from arteriograms, limitations in the method used to estimate regional myocardial perfusion,24 physiological effects of atrial pacing upon regional wall motion and other determinants of myocardial flow (such as left ventricular end-diastolic pressure), and influences of collateral blood vessels. The focus of the present study has been to develop statistical comparisons between two groups of patients.
selected by their left coronary arteriographic findings. As the methodology improves, it is our belief that a promising approach to the study of the individual patient will be to make multiple measurements of regional myocardial perfusion with radioisotopes in different projections at rest and also during an intervention which increases myocardial oxygen consumption, and to correlate the flow measurements with indices of metabolic demand and of total and regional ventricular performance. Despite the current limitations and uncertainties, the present study of two groups of patients provides a body of data which supports the hypothesis that in many patients with radiographically significant coronary disease, angina pectoris results when the diseased coronary vascular bed is unable to deliver the required amount of blood to the left ventricular myocardium or to a region of the LV during an intervention such as atrial pacing which increases myocardial oxygen consumption.

Acknowledgment

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References

18. Gregg DE, Shipley RE: Augmentation of left coronary inflow with elevation of left ventricular pressure and observations on the mechanism for increased coronary inflow with increased cardiac load. Am J Physiol 142: 44, 1944
Prophylactic Digitalization for Coronary Artery Bypass Surgery

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SUMMARY One hundred and twenty patients undergoing aortocoronary bypass procedures were randomly placed into control and digitalized groups. All were initially in normal sinus rhythm and without evidence of congestive heart failure. Supraventricular arrhythmias occurred in 17 of 66 controls and in only three of 54 digitalized patients (P < 0.01). There was no evidence of digitals toxicity. Based on this evidence we recommend prophylactic digitalization for patients having aortocoronary bypass operations.

PREOPERATIVE PROPHYLACTIC DIGITALIZATION before thoracotomy and open heart surgery remains controversial.1-17 Coronary artery bypass surgery is a relatively new procedure which is now widely accepted in the treatment of coronary artery disease. The purpose of this study was to determine if patients undergoing coronary artery bypass surgery, without the usual medical indications for digitalis, are benefited by such prophylactic digitalization.

Methods

One hundred and twenty consecutive patients undergoing coronary artery bypass surgery comprise this study. Only patients already on digitalis or having concomitant aneurysmectomy or valve replacement were excluded. All patients in the study group were in normal sinus rhythm and had no history of congestive heart failure.

After obtaining informed consent the assignment of patients to therapeutic groups was randomized by using a table of random numbers. Randomization resulted in the distribution of 66 patients to the control group and 54 to the treated group. Those in the control group received no digitalis before surgery. Patients in the digitalis group received 1 to 1.5 mg of digoxin orally over a 12-24 hour period 2-3 days prior to surgery. The exact digitalizing dose was determined by the physician in charge of the patient's care and was adjusted to achieve a therapeutic level. The patients in the digitalis group were then given 0.25 mg of digoxin daily. Digoxin was withheld on the day of surgery and the maintenance dose was restarted on the first postoperative day.

Multiple preoperative, intraoperative and postoperative factors were analyzed and monitored (table 1). The major coronary risk factors of cigarette smoking, hypertension, and hyperlipidemia were tabulated. Cigarette smoking was defined as greater than one pack per day, hypertension as a cuff blood pressure > 140/90 mm Hg and hyperlipidemia as a fasting serum cholesterol greater than 300 mg% or triglyceride greater than 150 mg%. Angiographic data analyzed included presence or absence of left ventricular asynergy and number of coronary arteries involved. The preoperative electrocardiogram was analyzed specifically for evidence of a previous myocardial infarction and the presence of arrhythmias. The anesthetic agents for both groups were nitrous oxide and oxygen supplemented with either halothane or morphine. Intraoperatively and postoperatively serum electrolytes were monitored and abnormalities were corrected. Serum digoxin levels were deter-
Regional myocardial perfusion during atrial pacing in patients with coronary artery disease.
D H Schmidt, M B Weiss, W J Casarella, D L Fowler, R R Sciacca and P J Cannon

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