Myocardial Blood Flow in Coronary Artery Disease

Effect of Right Atrial Pacing and Nitroglycerin

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Summary
Sixteen patients, 10 with significant three-vessel coronary artery disease (>50% occlusion of each vessel) and six without coronary disease, had nutrient myocardial blood flow, cardiac output, pressure time/min and arterial pressure determinations at rest, with atrial pacing and with right atrial pacing plus nitroglycerin. In the patients with coronary disease, nutrient myocardial blood decreased an average of 16% (P < 0.001) with pacing alone but increased by 22% (P < 0.001) from the pacing flows with the addition of 0.4 mg sublingual nitroglycerin at the same pacing rate. The directional changes in myocardial blood flow were unrelated to perfusion pressure or pressure work. In the patients without coronary disease, opposite effects were observed. With right atrial pacing, nutrient myocardial blood flow increased by 23% (P < 0.02). With the addition of nitroglycerin, myocardial blood flow decreased by 15% (P < 0.02). These changes were directionally related to changes in pressure-work of the heart.

It is suggested that the findings in this study are consistent with observations made in the experimental animal which indicate that the effect of nitroglycerin may be partly due to a redistribution of myocardial blood flow.

Additional Indexing Words:
Autoregulation Coincidence technic
"Rubidium

Nutrient blood flow Perfusion pressure

In the past few years a number of studies have been reported utilizing acceleration of the heart rate by right atrial pacing as a stress intervention to study the hemodynamic, metabolic, and coronary flow characteristics in patients with coronary artery disease.1-14 The intervention has been of considerable interest because it is relatively safe, repeatable, and defines a threshold in terms of the tension-time index, pressure time/min, or triple product, having fewer independent variables than exercise or other forms of stress testing.4, 5, 9, 13 The studies have demonstrated manifestations of ischemia such as impaired left ventricular function, electrocardiographic alterations, and lactate production. More recently, demonstrations of coronary flow inadequacy with atrial pacing in coronary artery disease have also been reported.15, 16

In addition, nitroglycerin has been shown to increase the threshold to right atrial pacing in that indirect reflections of myocardial blood flow deficiency have been reversed at identical pacing rates through the concomitant use of nitroglycerin.4, 17, 18 Whether the effect of nitroglycerin in this situation is manifested by reducing myocardial oxygen requirement or by altering the distribution of myocardial blood flow is unresolved.19 Many of the problems concerning the effect of nitroglycerin are compounded by the varying methods used to determine myocardial blood flow. Some methods measure total coronary flow, not necessarily nutrient flow, some methods may be relatively insensitive to poorly perfused areas, some technics measure regional perfusion, and so forth.20-23 This study was designed to evaluate alteration in nutrient myocardial blood flow produced by sublingual nitroglycerin administered during right atrial pacing in patients with three-vessel coronary artery disease, as compared with patients without coronary artery disease. Nutrient myocardial blood
flow was measured utilizing a coincidence counting system and single bolus of \(^{82}\)Rb.\(^{24,28}\)

**Material and Methods**

Sixteen patients undergoing selective coronary cinearteriographic studies for diagnosis or evaluation of the severity of coronary arteriosclerotic occlusive disease had myocardial blood flow determinations at rest, with right atrial pacing, and with right atrial pacing concomitant with the administration of sublingual nitroglycerin. The studies were performed just prior to the arteriographic evaluation.

All studies were performed in the morning with the patients in a fasting state and without sedation. Measurements were made with patients in the supine position.

A bipolar pacing catheter was passed through the basilic vein, positioned in the right atrium so that its tip was in contact with the high lateral wall, and connected to a battery-powered pacemaker (Medtronic). A short polyethylene catheter (approximately 18 gauge) was introduced percutaneously into the right femoral artery.

Blood pressure was measured via the indwelling catheter in the femoral artery, connected to a Statham P23D strain-gauge transducer and recorded on a Sanborn recorder (model 150). The mean arterial pressure was obtained by electrical integration and the mean systolic arterial pressure by planimetric integration. Pressure time/min, expressed in mm Hg-sec/min, was obtained as the product of systolic mean arterial pressure, heart rate, and systolic ejection period. Systolic ejection period, in seconds, was measured from the pressure records as the time interval between the onset of the femoral artery pulse and the dicrotic notch, and was expressed as the average figure of at least six beats taken at the extremes of respiratory fluctuation. Heart rate was measured from a simultaneously recorded electrocardiogram. The cardiac output was determined using \(^{82}\)RbCl as the indicator.\(^{26}\)

Myocardial blood flow, in ml/min per total heart, was calculated using the formula: \(\text{MBF} = q(t) \int_{0}^{t} A_{0}(t) \, dt\) where \(q(t)\) is the myocardial uptake of \(^{82}\)RbCl as measured by the coincidence counting system and \(\int_{0}^{t} A_{0}(t) \, dt\) represents the concentration of the isotope in arterial blood during the first circulation, determined by extrapolation after recirculation begins. The theoretic basis of this formulation, experimental verification, and critique have been reported in detail.\(^{25,27}\)

Control measurements were made during sinus rhythm, after which pacing was begun. The heart rate was gradually elevated to the point where 1:1 A-V conduction could just be maintained or angina intervened. The maximal heart rate achieved was maintained for 3 min before and during the taking of repeat measurements unless angina intervened. If angina intervened, the pacing was continued for the time period necessary to make the myocardial blood flow measurement (45 sec). Following a recovery period of 10 min, pacing was instituted at the same rate as on the previous determination and concomitantly 0.4 mg nitroglycerin was given sublingually. Repeat measurements were made at the precise time as the first stress measurement.

After completion of the myocardial blood flow and hemodynamic determinations coronary cineangiography was performed. Multiple oblique views were obtained using renographic contrast media. Injections were made before and after administration of sublingual nitrates. Recording was performed with 35-mm Double-X film developed in Ethol-90. A Phillips 6-in image intensifier was utilized with a 100-mm lens at 64 frames/sec.

Only patients whose cineangiograms were of good quality in multiple projections of all three major coronary vessels were included in this study. Coronary arterial lesions were classified as follows: Each of the three major coronary vessels (right, left anterior descending, and circumflex) was assigned a value of 100. A value of 200 was assigned to the left mainstem coronary artery. The number of vessels involved was then determined and the percentage of each vessel which remained open was estimated in increments of 25%. In the case of branch stenosis, the degree of occlusion was estimated according to the technic of Rowe et al.\(^{20}\) For example, if the anterior descending artery bifurcated, giving off a branch about 50% of the size of the parent vessel and if this vessel were 50% occluded, the estimated occlusion of the anterior descending vessel would be equivalent to 25% occlusion of the anterior descending coronary artery. A final coronary artery index was then based on the estimated percentage of lumen of all three vessels remaining open (300 equaling no occlusive disease). The cineangiograms were interpreted independently by three investigators without availability of the physiologic data. Ten consecutive patients with coronary artery indices of 50 or less and six patients without coronary artery disease were included in this study. All data analyzed as the significances of the difference between the means of paired data.

**Results**

**Coronary Artery Disease Patients**

None of the 10 patients with coronary artery disease and coronary artery indices of 50 or less was able to increase myocardial blood flow significantly with pacing to an average rate of 131 beats/min (range 120–158) (table 1). Seven of the 10 experienced angina with pacing. All of these patients experienced pain after at least 2 min of pacing so that the disparity between pacing times for patients with and without angina was minimal. The average myocardial blood flow for the group changed from 207 ± 53 ml/min, representing 4% of the cardiac output at rest, to 178 ± 50 ml/min, 3.4% of the cardiac output, with atrial pacing (\(P < 0.001\)). Pressure time/min rose 34% with pacing (\(P < 0.001\)). Mean arterial blood pressure increased from an average of 95 ± 14 to 107 ± 22 mm Hg (\(P < 0.05\)), and the diastolic pressure from 75 ± 10 to 90 ± 17 mm Hg (\(P < 0.01\)). There was a
Table 1
The Effects of Right Atrial Pacing and Pacing plus Nitroglycerin in Patients with Three-Vessel Coronary Artery Disease

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<th>Case</th>
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<th>Sex</th>
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<th>CO (l/min)</th>
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<th>HR (beats/min)</th>
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P for change from preceding column <0.001 <0.001 ns ns <0.001 0.05 0.02 <0.01 <0.02

Abbreviations: MBF = myocardial blood flow; CO = cardiac output; PTM = pressure-time/min; HR = heart rate; BPM = mean systemic blood pressure; BPD = systemic diastolic pressure; C = control; P = right atrial pacing; PN = pacing and nitroglycerin.

A graphic presentation of the changes in myocardial blood flow with pacing plus nitroglycerin in both groups is shown in figure 1.

Table 2
Patients without Coronary Disease

- In the six patients without coronary disease, myocardial blood flow increased significantly with atrial pacing and significantly with pacing plus nitroglycerin (P < 0.02).
- The mean arterial blood pressure increased by 25 mm Hg (P < 0.01).

Patients with Coronary Disease

- In the six patients with coronary disease, myocardial blood flow increased significantly with atrial pacing and significantly with pacing plus nitroglycerin (P < 0.02).
- The mean arterial blood pressure increased by 25 mm Hg (P < 0.01).

The change was not significant in patients with three-vessel coronary disease (P > 0.05).

Five patients with three-vessel coronary disease had previously been studied with pacing alone. The change was not significant in patients who were not paced but with pacing plus nitroglycerin (P > 0.05).
The hemodynamic data from this study are similar to those reported in a number of other studies. Right atrial pacing has been demonstrated to increase pressure time/min and not to affect cardiac output significantly. Nitroglycerin decreases pressure time/min with pacing, reduces systemic blood pressure, and probably results in decreased ventricular dimensions. In addition, nitroglycerin seems to decrease myocardial blood flow in normal subjects if the pressure time-work of the heart also decreases. This has been taken to suggest that nitroglycerin does not affect autoregulatory mechanisms in the normal heart. Further comparison with previous studies is probably not warranted as there is great variation in experimental design, amount, and route of nitroglycerin administration, times at which measurements were made, sedation used and, in particular, methods of determination of coronary and myocardial blood flow.

The validity of the myocardial blood flow changes demonstrated in this study needs to be assessed. The possible problems inherent in the coincidence technic itself have been previously discussed at length. Basically, the ability to quantitate flows has been questioned, changing extraction ratios have been an issue, and clearance dependency on flow rate is a consideration. For these reasons we have not attempted to place significance on absolute flows in ml/min, but have relied on directional changes; and directional changes in coronary patients have been interpreted only as compared to patients without large-vessel coronary artery disease.

While the exact mechanisms for the reduction in nutrient myocardial blood flow with right atrial pacing and the increase with sublingual nitroglycerin are not resolved by the study, the following considerations may be applicable. The same considerations also may be a partial explanation for the discrepancy between these data and data from previous studies measuring coronary blood flow with other technics. Further resolution of the mechanisms operative in patients with coronary artery disease, in particular, will come through the use of technics measuring regional flow more directly than does the coincidence system. A characteristic of the coincidence system for measuring myocardial blood flow is that detection of a decrease in regional perfusion, if of sufficient size, is possible as total myocardial uptake of isotope.
decreases. Thus, the coincidence system may reflect alterations in regional perfusion. Other technics measuring single-vessel flow or dominated by single-vessel flow might register no increase (fixed flow) with an intervention which acts primarily by redistribution of flow or an actual increase in flow through nonoccluded vessels. With these considerations in mind, we propose that our data support the concept that, in the patient with coronary artery disease, when ischemia is caused by an increase in myocardial oxygen requirement with atrial pacing, a redistribution of blood flow occurs, the nutritional flow to the endocardium being limited by flow in the large conducting vessels. The decreased nutritional flow to the endocardium, by adding a zero count to the myocardial uptake of rubidium, results in the coincidence system measuring a decreased flow. Nitroglycerin, in addition to reducing cardiac work so that a better ratio exists between nutritional circulation to the endocardium and requirement, also results in a redistribution of nutritional blood supply, reflected by an increased flow measured by the coincidence system.

Data from experimental animal studies utilizing microsphere injection technics and intramyocardial oxygen tension measurements are in accord with the concepts outlined above. It has been demonstrated that, in addition to a reduction in total blood flow following acute experimental coronary artery occlusion, there is also a disproportionate reduction in subendocardial flow within the ischemic area. The possible mechanisms for this altered flow pattern have been discussed by Becker and Pitt, including a change in resistance gradient between endo- and epicardium, a possible perfusion pressure drop in perforating vessels, and an increase in extravascular compressive forces, all essentially mechanical effects following ischemia. Another model proposed by McGregor and Fam also warrants consideration and is, perhaps, more appropriate for the chronic state. In their model, a decrease in resistance at the arteriolar level of nonoccluded vessels when oxygen requirement is increased, might result in a decrease in blood flow to a portion of the myocardium previously supplied by that artery through collaterals, a "coronary steal" syndrome. Whichever mechanism, i.e., mechanical
effects as proposed by Becker and Pitt or "coronary steal" as proposed by McGregor and Fam, is operative in patients with coronary disease, nitroglycerin could result in a redistribution of flow into an ischemic area as has been shown in the experimental animal.\textsuperscript{4-3} By decreasing myocardial oxygen demands through reduction in arterial pressures, wall tension, and ventricular volume, the increased extravascular compressive forces caused by ischemia could be reversed and flow reestablished. Or, by allowing vasoconstriction to again maintain in nonoccluded vessels, the "steal" might be eliminated by reestablishing resting pressure relationships.

Another possibility is that nitroglycerin may dilate collateral vessels in coronary patients and, thus, partially decrease the resistance quantum of the proximal occlusive lesions, effectively allowing a greater coronary reserve.\textsuperscript{19, 38} Nitroglycerin has been shown to dilate collateral vessels and increase flow to areas supplied by such vessels.\textsuperscript{38} However, it would seem that if the arteriolar bed were fully dilated because of increased oxygen demand by right atrial pacing, or if extravascular resistance were increased in an ischemic area, an increased volume of flow through collaterals would simply continue to traverse the path of least resistance and would not necessarily become nutrient flow. It is possible, however, that nitroglycerin by decreasing wall tension could permit collateral flow, which had been prevented by the ischemic changes, to resume\textsuperscript{35} and, perhaps, be augmented.\textsuperscript{50}

The questions raised may prove to have some clinical relevance. Regardless of the mechanisms involved, the diseased coronary circulation does not appear to be entirely a passive one. It is not a perfusion pressure-dependent system, in the sense of epicardial vessel perfusion pressure, within normal ranges of blood pressure. The nutrient myocardial blood flow can be manipulated through the use of drugs which either decrease the pressure time/min, redistribute myocardial blood flow, or, perhaps, increase collateral flow. If, for example, it were necessary to artificially increase heart rate in patients with coronary artery disease for the control of ventricular tachycardia or other tachyarrhythmia, it might be possible to "protect" the blood supply to the myocardium through the concomitant use of an agent such as nitroglycerin. Other combinations of interventions could be similarly considered. Elevation of arterial blood pressure designed to increase coronary perfusion pressure might rather increase pressure work and myocardial consumption to the point where coronary reserve would be exceeded. These considerations are of particular importance in dealing with patients with myocardial infarction or impending infarction where a prime concern is in preserving as much myocardial blood flow as possible in order to reduce to a minimum the area of myocardial ischemia. Each patient, however, should be assessed individually. Not all of our patients had angina induced by pacing nor did nitroglycerin consistently relieve induced angina. Other investigators have observed similar variability.\textsuperscript{12} The relationship between myocardial oxygen demand induced by any particular stress, the mechanisms by which various agents exert influence on collateral vessels, and work of the heart may vary considerably from patient to patient. It is the algebraic sum of all effects that is probably important and may account for differing clinical responses.

References

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