Myocardial Blood Flow Response to Isometric (Handgrip) and Treadmill Exercise in Coronary Artery Disease

By Daniel K. Lowe, M.D., Donald A. Rothbaum, M.D., Paul L. McHenry, M.D., Betty C. Cohya, M.D., and Suzanne B. Knoebel, M.D.

SUMMARY
Thirty patients undergoing coronary cineangiography for diagnosis or evaluation of coronary artery disease had myocardial blood flow studies pre and post handgrip (isometric) exercise just prior to cineangiography. The handgrip was maintained at one-third maximum effort for three minutes. The patients also had treadmill exercise testing a day or two prior to the study. Treadmill testing was carried out until angina or positive ST-segment changes occurred or the patient attained 90% of predicted maximal heart rate.

Of the 30 patients, seven had no coronary artery disease and 23 had significant disease, i.e., greater than 75% occlusion of at least one major coronary artery. Six of the 23 patients (26%) with disease had angina with handgrip and demonstrated a decreased myocardial blood flow, a significantly different response from the patients without angina (P < 0.001). For the group without angina, the blood flow response was not significantly different from the normal group. Treadmill tests were positive in 19 of the 23 patients with coronary disease (83%). The arterial systolic and diastolic pressure rise was almost identical with the two stresses. The heart rate response, however, was significantly different (P < 0.001), the rate increase being greater with treadmill exercise.

The myocardial blood flow data demonstrate the relative insensitivity of handgrip exercise for the diagnosis of coronary artery disease. In terms of the supply demand ratio (diastolic pressure time/systolic pressure time) concept for subendocardial perfusion, it is possible that the difference between handgrip and treadmill stress may be due to the different heart rate response, more rapid heart rates having a relatively greater effect on diastolic than on systolic time indices, all other factors being equal.

Additional Indexing Words: Rb<sup>84</sup> Tension time index Coincidence counting Diastolic pressure time index

Isometric Exercise, usually in the form of sustained handgrip, because of the resultant increase in heart rate and blood pressure and, thus, myocardial oxygen requirements, has been used as a stress test to evaluate patients with coronary artery disease. Previous studies of isometric stress testing have dealt primarily with the effects on left ventricular performance or have assessed electrocardiographic evidence for ischemia. Depending on the measurement used to reflect ischemia, i.e., regional or total contractility abnormalities or the electrocardiogram, the stress has been determined to be of variable usefulness. Analyses of left ventricular response to the stress imposed by sustained handgrip have indicated that the test is valuable to determine left ventricular reserve in patients with diverse types of heart disease. However, as a stress test for patients with coronary artery disease when ST-segment depression or angina is used as the ischemic indicator, isometric handgrip exercise has been felt to have no value. Explanations for the superiority of dynamic exercise stress testing over isometric exercise have revolved primarily around heart rate-blood pressure product responses to the two types of stress.

The myocardial blood flow response to isometric exercise has not been extensively studied. Coronary
sinus blood flow response to handgrip in six patients with coronary disease has been reported. The purposes of this paper are 1) to report the effects of isometric handgrip exercise on myocardial blood flow in patients with coronary disease, and 2) to compare handgrip and treadmill exercise responses in the same patients.

Methods

Thirty patients undergoing coronary cineangiographic studies for the diagnosis or evaluation of coronary occlusive disease had myocardial blood flow studies pre and post handgrip stress just prior to cineangiography. The patients were unsedated and in the fasting state. All studies were performed in the supine position.

A catheter was passed through the basilic vein and positioned in the high right atrium. A short polyethylene catheter (approximately 18 gauge) was introduced percutaneously into the right femoral artery and connected to a Statham P23D strain gauge transducer. The phasic arterial pressure was 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 per minute expressed in mm Hg seconds per minute was calculated as the product of mean systolic 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. Diastolic pressure time index was calculated as the product of heart rate, diastolic period and mean diastolic pressure determined by planimetry. Heart rate was measured from a simultaneously recorded electrocardiogram. Calculations of systemic vascular resistance were made from the standard formula. The cardiac output was determined using $^{85}$RbCl as the indicator. Myocardial blood flow in ml/min per total heart was calculated using the formula:

$$MBF = \frac{q(t)}{\int zA_o(t) dt}$$

where $q(t)$ is the myocardial uptake of $^{85}$RbCl as measured by a coincidence counting system and $\int zA_o(t) dt$ represents the concentration of the isotope in arterial blood during the first circulation, determined by extrapolation after recirculation begins. The experimental, theoretical and clinical applications of this technique have been previously discussed in detail.

Control measurements were made at rest. Following the control measurements, maximum voluntary contraction was determined from two attempts with a spring-loaded, calibrated handgrip dynamometer. Each patient then maintained a grip of 33% of the maximum. At three minutes of sustained handgrip, the second injection of isotope was given and repeat myocardial blood flow and hemodynamic measurements made, with the exception of left ventricular end-diastolic pressure, which was done at rest only.

After completion of the myocardial blood flow and hemodynamic determinations coronary cineangiography was performed. Multiple oblique views were obtained and recording was performed with 35 mm Double-X film developed in Ethol-90. A Phillips 6 inch image intensifier was utilized with a 100 mm lens at 64 frames/sec.

Classification of the coronary arterial lesions was done as follows: Each of the three major coronary vessels (right, left anterior descending and circumflex) was given a rating of 100. A value of 200 was assigned to the left mainstem coronary artery. The number of vessels involved was then determined from one to three and the percentage of 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 technique of Rowe et al. 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).

All patients had been tested on the treadmill a day or two before the blood flow and arteriographic studies. The treadmill electrocardiograms were quantitated both visually and by a previously described computer technique. Arterial pressures were determined by sphygmomanometer. Treadmill testing was terminated when the patients had angina or positive ST-segment changes, or had reached 90% of the predicted maximal heart rate for their age. Hypotension developing during exercise was the indication for discontinuing the test in two patients.

Results

Of the 30 patients, seven had no coronary occlusive disease (group 1) and 23 had significant disease (greater than 75% occlusion of at least one major coronary vessel). Of the 23 patients with coronary artery disease, six had angina with handgrip (group 2) and 17 did not (group 3).

A summary of hemodynamic and myocardial blood flow changes with handgrip exercise for all three groups is shown in table 1. The mean data for each group are given in table 2. There were significant changes in heart rate, systolic blood pressure, diastolic blood pressure, mean arterial blood pressure, and pressure time per minute for all groups. Changes in systemic vascular resistance were not significant in any group. The change in cardiac output with handgrip stress was significant for group 3 patients only ($P < 0.001$). The percent increase in myocardial blood flow was 35% ($P < 0.005$), -17% (NS) and 23% ($P < 0.01$) for groups 1, 2 and 3, respectively.

There were no significant differences between the groups except for 1) severity of disease (group 2 being significantly different, $P < 0.001$, from both groups 1 and 3), 2) change in diastolic pressure in response to handgrip (significant difference between group 2 and groups 1 and 3, $P < 0.02$ and $P < 0.005$, respectively), and 3) myocardial blood flow, group 2 patients being significantly different from both group 1 and group 3 ($P < 0.001$).

Treadmill tests were positive in 19 of the 23 patients with coronary artery disease, 14 by ST-segment
criteria and five by the production of their typical angina. The average heart rate was 134 beats/min at the time of termination of the test, systolic blood pressure was 169 mm Hg, and diastolic blood pressure was 95 mm Hg. By comparison only six of this group of 23 had a positive response on handgrip. Following three minutes of handgrip exercise the average heart rate was 98 beats/min, systolic blood pressure, 167 mm Hg, and diastolic pressure, 94 mm Hg. Differences between the two stresses were significant only with respect to the heart rate response ($P < 0.001$).

**Discussion**

The hemodynamic responses to handgrip exercise observed in this study are not significantly different from those previously reported. An increase in systolic, mean and diastolic blood pressures and heart rate is characteristic for normal volunteers$^{6, 20, 21}$ as well as patients with diverse types of heart disease.$^{5, 7, 10}$ Cardiac output and systemic vascular resistance responses have been variable,$^{4, 7, 8}$ the latter increasing to a greater extent in those patients with less cardiac output rise.

It is apparent that, as a diagnostic test with angina as the end point, handgrip stress at the level of exertion utilized in this study does not have high sensitivity, since only six of 23 patients experienced their usual type of chest discomfort. Myocardial blood flow measurement does not increase the sensitivity appreciably. If two patients from group 3 with significantly decreased myocardial blood flow are included with the six group 2 patients with anginal response to handgrip stress, and there is reason to believe this might be legitimate as neither had angina on the treadmill, the percent diagnostic response would be only 35%. Furthermore, the lack of sensitivity is supported when a select group of patients with significant two or three vessel disease are considered. Sixteen patients of the 23 had coronary artery indices of less than 150 and only eight had either angina or significant decreases in myocardial blood flow, a 50% positive response. It has been recommended that 50 or 100% of maximum voluntary contraction be used in handgrip stress testing rather than lesser degrees for longer time periods, as the cardiovascular responses have been measured to be greater with the former.$^8$ Thus, the incidence of positive response might be expected to increase. However, in comparison, our patients reached approximately the same level of pressure work as those previously reported at 50% maximum contraction for one minute.$^9$

**Table 1**

**Hemodynamic and Myocardial Blood Flow Response to Isometric (Handgrip) Exercise by Group**

<table>
<thead>
<tr>
<th></th>
<th>Group 1 (N = 7)</th>
<th>Group 2 (N = 6)</th>
<th>Group 3 (N = 17)</th>
<th>Significance of change between groups</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>% change from rest</td>
<td>$P$ of change</td>
<td>% change from rest</td>
<td>$P$ of change</td>
</tr>
<tr>
<td>Heart rate</td>
<td>20 &lt;0.02</td>
<td></td>
<td>30 &lt;0.005</td>
<td></td>
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<tr>
<td>Systolic blood pressure (mm Hg)</td>
<td>34 &lt;0.001</td>
<td></td>
<td>25 &lt;0.01</td>
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<td>Diastolic blood pressure (mm Hg)</td>
<td>37 &lt;0.001</td>
<td></td>
<td>20 &lt;0.01</td>
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<td>Mean arterial pressure (mm Hg)</td>
<td>36 &lt;0.001</td>
<td>24 &lt;0.03</td>
<td>36 &lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Cardiac output (liters/min)</td>
<td>14 NS</td>
<td>14 NS</td>
<td>26 &lt;0.001</td>
<td></td>
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<tr>
<td>Pressure time per minute (mm Hg secs/min)</td>
<td>62 &lt;0.002</td>
<td>54 &lt;0.002</td>
<td>74 &lt;0.001</td>
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<tr>
<td>Diastolic pressure time per minute (mm Hg secs/min)</td>
<td>23 NS</td>
<td>12 &lt;0.02</td>
<td>19 &lt;0.001</td>
<td></td>
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<tr>
<td>Systemic vascular resistance (dyne secs/cm²)</td>
<td>22 NS</td>
<td>10 NS</td>
<td>NS</td>
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<tr>
<td>Myocardial blood flow (ml/min)</td>
<td>35 &lt;0.005</td>
<td>-17 NS</td>
<td>23 &lt;0.01</td>
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</table>

Group 1 = No coronary artery disease.
Group 2 = Coronary artery disease and angina with handgrip stress.
Group 3 = Coronary artery disease and no angina with handgrip stress.

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It is not clear that the problem with handgrip is simply failure to achieve\textsuperscript{10} or maintain\textsuperscript{11} a pressure-rate product commensurate with other stresses such as dynamic exercise. While this would be suggested by comparing the greater systolic pressure-rate product achieved at the time of the positive treadmill test with that following three minutes of handgrip, it is apparent that the significant difference between the treadmill and handgrip stresses is the heart rate response. This partial dependence on heart rate, rather than the pressure-rate product, for an ischemic response has been observed previously with treadmill exercise,\textsuperscript{21} which showed a better correlation between heart rate and a positive response than between pressure-rate product and a positive response. Similarly, in a comparative study on handgrip versus dynamic exercise by bicycle ergometry,\textsuperscript{11} while the pressure-rate product was greater with handgrip, the evidence of positive ST-segment changes was considerably less, suggesting that other factors might be influential. Analysis of this study showed that the heart rate response was less following handgrip than at the end of maximal dynamic exercise, the greater index resulting from greater pressure elevations. Thus, it may be that the heart rate rather than tension index is the important variable when comparing handgrip with dynamic stresses. Perhaps some of the conflicting data on handgrip as well as other stresses could be resolved by consideration of both the supply and the demand factors regulating the coronary circulation. Experimental subendocardial ischemia has been shown to occur despite increasing mean blood flows commensurate with increasing oxygen demands when the diastolic pressure time index (the supply factor to the subendocardium) is reduced out of proportion to the time-tension index (the demand factor).\textsuperscript{23, 24} An ischemic response to sudden strenuous exercise in healthy subjects has also been shown to result from a transient alteration in the oxygen supply-demand relationship, and not simply because the time-tension index rose more in the ischemic responders.\textsuperscript{25} While direct pressure tracings were not obtained in our treadmill studies, and thus no definite conclusions can be reached, the data are compatible with the concept that treadmill testing may not be more useful for the diagnosis of coronary heart disease because of an increased oxygen demand alone, but because through the greater increase in heart rate it effectively reduces the supply demand ratio to a greater degree. Heart rate was the only significant difference between the two stresses and proportionally, a decreased diastolic time has more influence on a calculated supply demand ratio than the increment in systolic ejection time resulting from increased rate.\textsuperscript{25} Pursuing similar considerations as outlined above, explanations can be offered for why some patients had angina and a decreased myocardial blood flow while others with similar severity of coronary artery disease (coronary artery indices of 100 or less) did not. Since subendocardial flow is primarily diastolic, and thus dependent on diastolic time and diastolic pressure, a lesser rise in diastolic pressure would also contribute to decreasing the supply demand ratio.\textsuperscript{26} In comparing the patients who did not have angina with those who did, there was a significant difference in diastolic pressure rise between the two groups, those with angina having the lesser rise in diastolic pressure. In addition, while not statistically significant, the group with angina tended to have a higher left ventricular end-diastolic pressure at rest. Presuming a similar increase in left ventricular diastolic pressure with handgrip to that previously demonstrated,\textsuperscript{8} subendocardial perfusion would be further impeded. Changing epicardial to endocardial flow relationships have been demonstrated in the experimental animal with increased preload in the presence of coronary artery occlusion.\textsuperscript{27} These relationships between myocardial oxygen demand, supply and blood flow need further study in larger groups of patients with diverse stresses.

It is to be noted that the term myocardial blood flow, as opposed to nutrient, total or effective flow, has been used throughout this paper. Admittedly, myocardial blood flow is a nondescriptive term although it does imply flow through exchanging channels\textsuperscript{17} in the case of a diffusible indicator such as rubidium. The term, however, avoids the difficult problem of extraction ratio considerations upon which the terms total and nutrient flow are so mathematically dependent.\textsuperscript{18} Recently, evidence has been presented that the rubidium bolus technique more nearly approximates total flow than nutrient flow.\textsuperscript{19} Regardless of which flow is being measured (or if “flow” is being measured at all, see below), we have felt that a decreased flow as measured by the coincidence technique reflects unperfused areas as such areas affect the myocardial blood flow measurement by adding a zero value to the myocardial count (q in the formula presented), provided a constant amount of myocardium is seen by the external counters. The patients presented here were monitored with echocardiographic determination of left ventricular internal dimension. While this dimension increased with handgrip by a small amount (1 mm average), there were as many normal patients as those in the diseased group showing such an increase. Furthermore, several of the patients with the largest decreases in flow showed no change in left ventricular internal dimension. The relative insensitivity of the coincidence
technique to small differences in heart size has been previously commented upon.17

Basically, as it is not possible to determine regional extraction ratios in the human by the coincidence technique, a requirement for flow quantitation in coronary artery disease because coronary sinus sampling may or may not reflect the inhomogeneous extraction conditions demonstrated to exist in this disease,28 it cannot be absolutely stated that the coincidence technique is measuring flow. While statistically the coincidence flows in numerous studies have correlated with other indices of myocardial ischemia, in particular the treadmill ST-segment response, until further techniques for measuring regional extraction ratios are proven, it is possibly preferable to call the measurement determined by the coincidence technique "coronary flow equivalent" or "ischemic equivalent." This equivalence has been demonstrated in this study, i.e., a decreased myocardial blood flow which statistically correlates with angina pectoris.

References

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### MYOCARDIAL BLOOD FLOW WITH EXERCISE

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<th>MBF (ml/min)</th>
<th>Pressure time per minute (mm Hg secs/min)</th>
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<th>Systemic vascular resistance (dyne sec/cm²)</th>
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