The Rate-Pressure Product as an Index of Myocardial Oxygen Consumption during Exercise in Patients with Angina Pectoris

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SUMMARY In order to evaluate hemodynamic predictors of myocardial oxygen consumption (MVO₂), 27 normotensive men with angina pectoris were studied at rest and during a steady state at symptom-tolerated maximal exercise (STME). Myocardial blood flow (MBF) was measured by the nitrous oxide method using gas chromatography. MBF increased by 71% from a resting value of 57.4 ± 10.2 to 98.3 ± 15.6 ml/100 g LV/min (P < 0.001) during STME while MVO₂ increased by 81% from a resting value of 6.7 ± 1.3 to 12.1 ± 2.8 ml O₂/100 g LV/min (P < 0.001). MVO₂ correlated well with heart rate (HR) (r = 0.79), with HR × blood pressure (BP) (r = 0.83), and, adding end-diastolic pressure and peak LV dp/dt as independent variables, slightly improved this correlation (r = 0.86). Including the ejection period (tension-time index) did not improve the correlation (r = 0.80). Thus, HR and HR × BP, both equally measured hemodynamic variables, are good predictors of MVO₂ during exercise in normotensive patients with ischemic heart disease. Including variables reflecting the contractile state of the heart and ventricular volume may further improve the predictability.

EASILY MEASURED PREDICTORS of myocardial blood flow (MBF) are necessary to evaluate objectively functional improvement in patients with ischemic heart disease. Symptomatic improvement may occur as a result of a change in lifestyle with little or no ability to increase MBF or to perform more external work. In turn, a medical regimen might result in an increase in the ability to perform external work with little or no ability to increase MBF. Direct measurement of exercising MBF requires use of an indicator and catheterization of the coronary sinus (CS) and is therefore not applicable to a large patient population. Previous work has demonstrated that changes in heart rate (HR) and the product of HR and blood pressure (BP) effect parallel changes in MBF and myocardial oxygen consumption (MVO₂) in normal young men during upright exercise in a variety of circumstances. Because myocardial oxygen extraction (MA-VO₂) may change from rest to exercise, hemodynamic predictors (HR × BP) appear to correlate better with MVO₂ than MBF. Although HR alone correlates well with MVO₂ it is necessary to include BP in situations where BP does not rise pari passu with HR, e.g., isoametric exercise or pacing-induced tachycardia. Including the systolic ejection period (SEP) (e.g., the tension-time index or the triple product) does not improve this correlation in normal young men. Extrapolation from normal young men to patients with ischemic heart disease must be made with caution because changes in ventricular volume, geometry, compliance and contractility, not included in currently used indices of MVO₂, may not change to the same extent during exercise in patients with ischemic heart disease. However, there is some information to suggest that HR × BP is also a good index of MVO₂ in patients with ischemic heart disease. Furthermore, the duration of upright exercise and the HR × BP product at the onset of angina pectoris are reproducible in a given patient with ischemic heart disease when there is adherence to a suitable protocol. Patients may exercise to a slightly higher HR × BP product after nitrates and a slightly lower HR × BP after beta adrenergic blockade with propranolol indicating that other factors are involved in determining MVO₂. These factors may include changes in ventricular volume and contractility.

The present study extends the evaluation of hemodynamic predictors of MVO₂ from normal subjects to patients with ischemic heart disease. Changes in the contractile state of the heart and ventricular volume have been estimated in this study.

Measurement of MVO₂ by the nitrous oxide (N₂O) method using Van Slyke manometry is laborious and time consuming and requires a considerable volume of blood. We have alleviated these problems by using gas chromatography for the measurement of N₂O.

Methodology

Patient Material

The study population consists of 27 men symptomatic from ischemic heart disease. One patient did not have coronary arteriography but had electrocardiographic (ECG) evidence of an inferior myocardial infarction. The other 26 patients had coronary arteriography: patients 2–4 had coronary arterial obstruction of greater than 70% of one coronary artery, patients 5–9 had greater than 70% obstruction of two coronary arteries, and patients 10–27 had greater than 70% obstruction of three coronary arteries (table 1). All patients complained of chest pain; ten patients also complained of dyspnea. The mean age was 50 ± 7 years (range 39–67 years). Patients were similar in size with the mean body surface area being 1.94 ± 0.15 m². Patients with a resting diastolic BP greater than 100 mm Hg, ECG evidence of left ventricular hypertrophy, valvular heart disease or other serious systemic disease were excluded from the study. Also excluded were patients who were unable to exercise.
against at least a 25 watt external workload and remain free of chest pain. All patients were in sinus rhythm and had ECG evidence of either infarction (19 patients) or ischemic ST-segment depression at rest or during exercise. Digitalis was given to five patients and was the sole medication administered prior to the study. All patients underwent diagnostic cardiac catheterization for the evaluation of ischemic heart disease, and informed consent for the additional studies was obtained in each case.

Procedure

The experimental protocol was as follows:

Day 1 — supine exercise to determine symptom-tolerated maximal exercise (STME);

Day 2 — hemodynamic studies.

On day 1 patients were brought to the cardiac catheterization laboratory in a fasting state. Supine bicycle exercise was performed against an external workload for a 10-minute interval followed by a 20-minute recovery period by which time the HR \( \times \text{BP} \) had returned to baseline. Following each recovery period the workload was increased by 25 watt increments until the patient developed grade II chest pain prior to completion of ten minutes of work. Patients were instructed to grade chest pain from 0 to IV. Grade I chest pain was considered to be mild pain, approximately 25% of the most severe pain experienced by the patient. On occasion this was atypical of the patient’s usual anginal pain and was felt to be due to musculoskeletal discomfort and not myocardial ischemia. Grade II pain, about 50% of the most severe pain, was considered to be of a quality such that the patient would usually take a nitroglycerin tablet. Grade III pain would be equivalent to 75% of the patient’s most severe pain, while grade IV would be equivalent to the most severe pain that the patient experienced, comparable in many instances to that of acute myocardial infarction. This grading system has been used successfully by others. The test was stopped at grade II chest pain regardless of the degree of ST-segment depression. Thus, the greatest external workload that could be performed for ten minutes without chest pain was determined and used as the external workload on day 2.

On day 2 patients were brought to the catheterization laboratory in a fasting state. The resting study preceded the exercise study in all cases. Woven Dacron catheters were positioned with the tips in the pulmonary artery wedge (PAW) and the CS 3 cm from the left heart border. A 75 cm Teflon arterial catheter was introduced percutaneously into the right brachial artery and the tip positioned in the apex of the left ventricle (LV). The mid-crest level at the angle of Louis was used as the zero reference. Left ventricular end-diastolic pressure (LVEDP) was measured at the onset of isovolumic contraction where the downstroke of the A wave met the upstroke of the LV pressure wave. Cardiac output (CO) was determined from indocyanine-green dye (Cardio-Green) curves.

Immediately following the indicator dilution curves, inhalation of 15% \( \text{N}_2\text{O} \) commenced simultaneously with sampling from the CS and central Ao. Four samples were obtained during the initial two minutes and seven samples during the subsequent seven minutes.

For the exercise study the feet were positioned on a Lanoo supine bicycle ergometer with the resistance set at the predetermined workload. Pressures were continuously monitored from the LV, PAW and CS and were recorded after three minutes of exercise. Inhalation of 15% \( \text{N}_2\text{O} \) commenced simultaneously with sampling from the CS and Ao. Five samples were obtained during the initial two minutes and twenty seconds and four samples during the next four minutes. CO was then measured as at rest. Pressures were recorded and the exercise procedure was terminated. The left atrium or LV and each coronary artery were then selectively injected with contrast material.

An Electronics for Medicine oscillographic photographic recorder and Statham P23 Db strain gauge transducers were used for recording pressure. The catheter-manometer recording systems for the arterial measurements exactly as used in our study, had a frequency response which was flat to 50 ± 27 Hz.

The tension time index (TTI)/beat was measured from Ao pressure tracings recorded at paper speeds of 200 mm/sec by integrating the systolic portion of the Ao tracing with a polar planimeter. Complexes were measured over several respiratory cycles prior to and after the inhalation of \( \text{N}_2\text{O} \). Systolic ejection period (SEP) was estimated to the nearest 0.002 sec. The TTI/min was calculated as the product of the TTI/beat and the HR. The HR \( \times \) BP refers to the product of the peak systolic Ao pressure and HR. The triple product (HR \( \times \) BP \( \times \) SEP) was calculated from the HR, peak systolic Ao pressure and SEP. Left ventricular minute work (LVMW) in kg-m/min was calculated as the product of the CO (L/min), mean systolic Ao pressure and 0.0144.

\( \text{N}_2\text{O} \) was measured using a Beckman gas chromatograph equipped with a thermal conductivity detector. The apparatus for liberating \( \text{N}_2\text{O} \) from blood consisted of a specially constructed chamber with a ground glass joint under a stainless steel head with a septum for injecting blood samples. Blood samples (250 \( \mu l \)) were injected into the chamber and mixed with reagents for three minutes at 100°C; helium then carried the gas from the reaction chamber to the column where \( \text{N}_2\text{O} \) was separated from \( \text{O}_2, \text{CO}_2 \) and \( \text{N}_2 \) and detected by thermal conductivity. The quantity of \( \text{N}_2\text{O} \) was directly proportional to the integrated area which was calibrated using blood with known \( \text{N}_2\text{O} \) concentrations. \( \text{N}_2\text{O} \) concentration measured by gas chromatography was compared with \( \text{N}_2\text{O} \) concentration measured by the manometric technique.

MBF was calculated from exponential curves fitted to the data points by a Control Data 3300 computer program, using the Hartley modification of the Gauss-Newton iterative procedure. A smooth aortic curve was best fitted to a two exponential equation and a smooth CS curve to a three exponential equation. The area between the curves was calculated using the trapezoid method. MFB was then calculated from the venous \( \text{N}_2\text{O} \) content at equilibrium and the mean arteriovenous \( \text{N}_2\text{O} \) difference. A \( \text{N}_2\text{O} \) partition coefficient of 1.0 was used to make our data more comparable to previous data even though 0.934 has recently been shown to be more correct. MFB was calculated after inhalation of \( \text{N}_2\text{O} \) for seven minutes at rest and for four minutes during exercise. MA-VO\(_2\) difference was measured directly using a Beckman spectrophotometer and arterial blood as a blank. \( \text{MVO}_2 \) was then calculated as the product of MBF and the MA-VO\(_2\) difference and expressed as ml O\(_2\).
consumption/100 g LV/min. Coronary vascular resistance was calculated as the quotient of the difference of the Ao and CS pressure and MBF and expressed as mm Hg/ml/100 g LV/min.

LV function was evaluated by measuring the rate of rise of pressure (dp/dt) in the Ao and LV with a resistance capacitance differentiator. Single plane cineangiography at 60 frames per second in the 45° right anterior oblique position was used to determine ventricular dimensions in all patients at rest. Seventy-six percent methylglucamine diatrizoate (Renografin) was injected either as an 80 ml bolus into the left atrium (23 patients) or as a 50 ml bolus into the LV (four patients). Angiography was performed 30 minutes after termination of the exercise study. X-ray magnification was calculated from a wire grid. Ventricular volumes were then calculated according to the method of Greene et al. with the short axis calculated from the area of the ventricle. Volumes were calculated from the first three consecutive beats after opacification to avoid making measurements where the contrast material may influence ventricular function. In two patients premature ventricular contractions precluded measurements of ventricular volume.

The contractile state of the heart was estimated at rest and during exercise from the rate of rise of aortic and left ventricular pressure. In five patients (nos. 2, 7, 8, 10, 14) a break in the rise of the LV pressure curve indicated mechanical interference with the recording and derivatives of these pressure curves were excluded. LV dp/dt at a developed pressure (DP) of 40 mm Hg and dp/dt at a total pressure (TP) of 50 mm Hg were measured at rest and during exercise in an attempt to exclude changes due to the Frank-Starling mechanism as previously reported. Regression analysis was carried out by two variable analysis and multiple variable analysis where products (e.g., HR × BP) were considered as a single variable (table 3).

**Results**

In 46 consecutive studies N2O measurements made by the gas chromatographic method were nearly the same as measurements made by the manometric method. Linear regression analysis demonstrated a strong positive correlation (r = 0.99, N = 553) between volume % N2O by the two methods. Although nearly the same, the mean difference between the two methods was 0.39 ± 0.30 volume % with the gas chromatographic method giving the higher reading (P < 0.001). Linear regression analysis of MBF determined by the two methods also demonstrated a positive correlation (r = 0.90, N = 46). The mean difference between the two methods was 2.9 ± 10.0 ml blood/100 g LV/min and was not significant.

Hemodynamic data are indicated in table 1. For the entire group the CO increased by 58% and the stroke volume by 14% (74 ± 13 to 84 ± 18 ml/beat) during exercise (both P < 0.001). Seven patients had a resting cardiac index below 2.5 L/min/m² (nos. 4, 8, 18, 19, 22, 25, 27). In patient 27 grade II chest pain developed after measurement of MBF and precluded measurement of an exercise CO. During exercise the mean HR increased by 36%, the mean LVEDP doubled and the PAW increased by 88% (all P < 0.001). Since the measurement of LVEDP was made after the A wave, the mean PAW was usually lower than the LVEDP. Elevation of the legs immediately prior to exercise resulted in a mean 1 mm Hg rise in PAW pressure. Eight patients had an increase in the exercising PAW greater than 8 mm Hg and two patients (nos. 10, 27) had an increase in PAW pressure greater than 20 mm Hg from rest to exercise. The latter two patients had severe three vessel coronary artery disease but neither developed chest pain at the time the PAW pressure was measured or during measurement of MVO2. In no patient were measurements made at grade II pain and in most patients measurements were made in the complete absence of pain.

The LV was outlined without premature ventricular contractions in 25 patients. Thirteen of the 27 patients had no discernible contraction abnormality. Two patients (nos. 21, 26) had dyskinetic aneurysms and 12 patients had akinesis or hypokinesis of either the anterior or inferior ventricular wall. The mean ventricular end-diastolic (181 ± 76 ml) and end-systolic volumes (70 ± 44 ml) were normal (table 1).

There was no correlation between resting EDV and LVEDP (r = 0.08) or resting PAW (r = −0.15) or the increase in PAW during exercise (r = 0.31). The ejection fraction was greater than 70% in seven patients and less than 50% in only four patients, with a mean value of 62 ± 14%.

During exercise the HR × BP increased by 54%, the HR × BP × SEP by 45%, the TTI by 42% and the LVMW by 79% (all P < 0.001). The ratio of LVMW and MVO2 did not change (table 2).

Mean peak LV dp/dt increased by 64% during exercise (P < 0.001) (table 2). Since the mean diastolic BP also increased by 8% from a resting value of 79 ± 10 to an exercise value of 85 ± 11 mm Hg and the LVEDP increased by 100%, the resulting increase in LV dp/dt may have been influenced by these changes in ventricular loading. The increase in exercising LVEDP made measurement of the derivative at a total pressure of 50 mm Hg difficult and it did not change during exercise. The LV derivative, measured at a DP of 40 mm Hg, was significantly increased by 374 mm Hg/sec during exercise (28%, P < 0.01). Aortic dp/dt also increased significantly during exercise.

MBF increased by 72% during exercise (P < 0.001) and the MA-VO2 difference widened slightly by 5% (P < 0.02). MVO2 correlated well with HR alone (0.79) and with HR × BP (r = 0.83) (fig. 1, table 3). The TTI and HR × BP × SEP were slightly poorer correlates than HR × BP. When LVEDP and LV dp/dt measured both at rest and during exercise were added to HR × BP the correlation was slightly better (r = 0.86) (table 3).

**Discussion**

Results from this study indicate that HR × BP, easily measured hemodynamic variables, are valid predictors of MVO2 during exercise in a population of men with ischemic heart disease when appropriately selected. The many forms of therapy available for the treatment of angina pectoris coupled with the complex nature of the response to treatment make such objective methods of evaluating improvement mandatory. In addition to the placebo effect from both medical and surgical treatment, factors such as a change in life style or physical size may result in symptomatic but not functional improvement. Physical conditioning and medical
## Table 1. Hemodynamic Data

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<th>External workload (Watts)</th>
<th>Heart rate (bpm/min)</th>
<th>Cardiac output (L/min)</th>
<th>Pulmonary artery wedge (mm Hg)</th>
<th>Left ventricular end-diastolic pressure (mm Hg)</th>
<th>Aortic systolic pressure (mm Hg)</th>
<th>End diastolic volume (mL)</th>
<th>Myocardial blood flow (ml/100 g LV/min)</th>
<th>Myocardial A-V O₂ difference (vol %)</th>
<th>Myocardial oxygen consumption (ml O₂/100 g LV/min)</th>
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Table 2. Average Changes in Response to Exercise

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therapy may result in an increased exercise tolerance and an increased exercise capacity. The ability to document MBF or MVO2 during exercise or at rest may be of considerable help in evaluating patients. Currently available methods for measuring MBF or MVO2 are too complex to be applied to a large patient population. Thus, an exercise-induced change in MBF or MVO2 is the best available method for identifying patients with myocardial ischemia.

In this study, the HR alone was related to changes in MBF and MVO2 as well as MBF and MVO2 at rest and during exercise. However, HR changes were too small to be of diagnostic value. The HR changes observed after exercise could be considered to be of diagnostic value, as well as the MBF and MVO2 at rest and during exercise.
bubbles and by including only those pressures where the upstroke was smooth and the pressure contour was optimum. In spite of these precautions additional subtle changes in the contractile state may have been overlooked.

The relationship between HR × BP and MVO₂ in this study [MVO₂ = 0.08 (HR × BP × 10⁻²) − 0.15] was slightly different from that reported in young men during upright exercise [MVO₂ = 0.17 (HR × BP × 10⁻²) − 5.31]²

**Figure 1.** The correlations between myocardial oxygen consumption (MVO₂) (left panel) and myocardial blood flow (MBF) (right panel) and hemodynamic variables are illustrated. The regression line for the 27 patients is indicated by the solid line, while dashed lines indicate 95% confidence zones for the individual points. The shaded area indicates 95% confidence limits for the slope of the regression line.

**Table 3. Correlations of MBF and MVO₂ with Several Variables**

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<th>Independent variables</th>
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<th>MBF</th>
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<tr>
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</table>

Abbreviations: HR = heart rate; BP = blood pressure; MVO₂ = myocardial oxygen consumption; MBF = myocardial blood flow; SEP = systolic ejection period; TTI = tension-time index; Ao = aorta; LV = left ventricle; DP = developed pressure; LVEDP = left ventricular end-diastolic pressure; PAW = pulmonary artery wedge.
FIGURE 2. Regression line for patients from this study (line 4) compared with the regression line from data reported for patients with ischemic heart disease during supine exercise (line 1).4 The regression lines for normal subjects are indicated by line 1 (upright exercise) and line 2 (supine exercise).6

but it agrees closely with the relationship reported by Holmberg during supine exercise in men with ischemic heart disease using different methodology [MVO2 = 0.08 (HR × BP × 10^-2) + 2.45, r = 0.86] (fig. 2).4 At the lower HR × BP products measured in patients in this study MVO2 was just slightly less than reported for normal subjects, and at higher HR × BP products this difference increased. This difference may be partly explained by differences in posture36, 30 and blood catecholamine levels which are significantly higher in the upright than in the supine posture.40, 41 Alternatively, a reduction in oxygen supply may decrease contractility in patients with ischemic heart disease which would, in turn, further reduce oxygen supply.4 The use of central aortic catheters in our studies obviates the effects of differences in peripheral augmentation of systolic BP due to age. This difference in the relationship between HR × BP and MVO2 was not due to overestimating coronary blood flow nor to increases in ventricular volume in these patients since these factors would have resulted in changes in the opposite direction.

The question arises as to whether these results obtained using the BP measured through an aortic catheter can be extrapolated to the situation using a pneumatic BP cuff and Korotkoff sounds, since the systolic BP may be significantly higher peripherally than centrally and the degree of augmentation may vary with age.42-44 Although it may be occasionally difficult to accurately measure the cuff BP during exercise, good agreement between direct and indirect measurement of brachial artery systolic pressure has been reported.47 Available data indicate that although peripheral augmentation of the systolic BP may change the slope of the relationship between MVO2 and HR × BP, the same degree of correlation remains.46, 48

Certain methodological precautions must be considered in the measurement of MBF by inert gas methods. There must be a sufficient period of myocardial saturation and the analytical technique must be sufficiently sensitive to allow for resolution of small A-V differences.49 Our analytical technique is sufficiently sensitive to quantify small changes in tracer concentration (0.77 ± 0.052 volume % or 1.75% of final aortic N2O concentration). It is possible that we have overestimated the contribution from portions of the heart with normal blood flow and underestimated the contribution from areas with reduced blood flow. The fact that our mean resting coronary blood flow (57.4 ± 10.1 ml/100 g LV/min) is nearly identical to that reported using helium as an indicator (54 ± 11 ml/100 g LV/min)49 in a similar group of patients lends support to our data. Attempts to assess the importance of these methodological considerations are limited by the lack of a primary standard of measurement against which the N2O technique can be compared in exercising man.

The HR × BP product (or the shorter term “rate-pressure product”)9, 10, 25, 28 which we also prefer) is the index which best correlates with MVO2 and is therefore the critical one in defining the response of the coronary circulation to myocardial metabolic demands. The relationship between the rate-pressure product (RPP) and MVO2 may change slightly with interventions that alter ventricular volume and contractility, which is the most likely explanation for the fact that patients develop chest pain at a slightly higher RPP after nitrates and a slightly lower RPP after beta adrenergic blockade with propranolol.10, 26

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