Physiological Significance of Maximal Oxygen Intake in “Pure” Mitral Stenosis

By John R. Blackmon, M.D., Loring B. Rowell, Ph.D., J. Ward Kennedy, M.D., Richard D. Twiss, M.D., and Robert D. Conn, M.D.

SUMMARY
Acute circulatory and respiratory adjustments to mild through maximal upright exercise were studied in seven patients with “pure” mitral stenosis. Maximal oxygen uptake was determined objectively by demonstrating a plateau of oxygen uptake with increasing workloads. Time to reach a plateau of oxygen uptake was normal (2 to 3 minutes) at all workloads. At any given oxygen uptake, cardiac output and hepatic clearance of indocyanine green (ICG) were abnormally low while total arteriovenous (A-V) oxygen difference, heart rate, blood lactate, and ventilation were abnormally high. However, with respect to relative oxygen uptake (per cent of maximal oxygen uptake), the reduction in cardiac output was exaggerated, but A-V oxygen difference, heart rate, blood lactate, and hepatic clearance of ICG were essentially normal. RQ and $V_E/V_O_2$ were quantitatively abnormal even with respect to relative oxygen uptake, but the pattern of changes from mild to maximal exercise was normal. Low maximal oxygen uptake defined the reduction in stroke volume while other circulatory responses were normal with respect to relative oxygen uptake.

Additional Indexing Words:
Mitral stenosis
Exercise, upright

Maximal oxygen uptake
Hepatic clearance of indocyanine green

In normal man the maximal oxygen uptake is a measure of the functional capacity of the cardiovascular system to transport oxygen. The measurement represents the product of maximal heart rate, stroke volume, and A-V oxygen difference. Accordingly, a significant reduction in any one of these parameters as a result of disease or other stress will be sensitively indicated by an objective and highly reproducible technique for determining maximal oxygen uptake. In this respect, the measurement provides a far more sensitive and quantitative index of impaired function than responses to impairment at rest or during submaximal exercise. During the latter, heart rate, for example (and probably stroke volume), is subject to large and unpredictable variations. However, the validity of the maximal oxygen uptake in mitral stenosis has been questioned. There is suspicion that time to reach a steady state of oxygen uptake in these patients may be prolonged beyond their endurance time. In this study, time required to achieve a plateau of oxygen intake was determined

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Dr. Conn is a Teaching and Research Scholar of the American College of Physicians.
during exercise in upright posture. The subjects were cardiac patients with essentially normal cardiac output and only moderately elevated pulmonary arterial pressures at rest, but with total blood flow limited during exercise primarily by a reduced mitral valve orifice. Total A-V oxygen difference and cardiac output were determined during upright exercise requiring from 32 to 100% of maximal oxygen uptake of these patients.

Our purpose was to indicate whether cardiovascular adjustments involved in approaching and attaining maximal oxygen uptake in these patients are similar to those of normal subjects. Clearly, there are great differences in total A-V oxygen difference and systemic partitioning of left ventricular output at a given absolute oxygen uptake in normal and disease-limited subjects during supine exercise.5 Although there is information regarding the extent of redistribution of cardiac output in normal subjects with upright exercise,6 similar information is not available for patients. Perhaps differences between responses of normal subjects and these patients to a given level of submaximal exercise merely reflect differences in the fractions of their respective maximal oxygen uptakes. We have assessed the extent of repartitionment of cardiac output away from nonexercising tissues during upright exercise by measuring the magnitude of total body oxygen extraction (total A-V oxygen difference) and percentage decrements in rates of hepatic clearance of indocyanine green. The latter reflects percentage decrements in hepatic-splanchnic blood flow (HBF) when hepatic function is normal.7 These data were related to absolute and relative (per cent of maximal oxygen uptake) oxygen consumptions.

Materials and Methods

Subjects

The subjects were one male and six female inpatients undergoing evaluation for mitral com-

Table 1

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<th>Subject</th>
<th>Sex</th>
<th>Age (yr)</th>
<th>Ht (cm)</th>
<th>Wt (kg)</th>
<th>Body surface (m²)</th>
<th>Maximal O₂ uptake (ml/kg X min)</th>
<th>Maximal heart rate (beats/min)</th>
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<th>Functional class*</th>
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*Criteria of New York Heart Association.

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missurotomy (table 1). All were characterized by very low tolerance to work during a multi-stage exercise test to exhaustion on a treadmill.8 The criteria for selection of subjects for these studies were absence of clinical pulmonary and systemic venous congestion and normal liver function as judged by lack of hepatomegaly clinically, normal clearance of indocyanine green (ICG), and normal right atrial pressures (table 2). Results of diagnostic catheterization (supine rest) revealed an increased total A-V oxygen difference and subnormal cardiac output in only one subject (BR) (table 2). All had low stroke volumes and elevated pulmonary arterial and right ventricular pressures.

**Procedures**

Each subject was studied (without catheterization) twice daily Monday through Wednesday in an air-conditioned room maintained at 70 F. The final experiments (with catheterization) were completed on Thursdays. After familiarizing the subjects with the treadmill and respiratory apparatus, they exercised repeatedly each morning and afternoon (several hours of rest were interspersed) at various speeds and grades on the treadmill. The objectives were to establish the time required to achieve a steady state of oxygen consumption during work; (2) to determine maximal oxygen uptake by the criteria of Taylor and associates1 but with speed reduced to 3.5 mph,* and (3) to select moderate levels of exercise at known fractions of maximal oxygen uptake that could be maintained for 15 minutes.

To assess the rate of rise of oxygen uptake, expired air collections were made at 30-second intervals from the start to 5 minutes of exercise, at both maximal and submaximal levels during the 3 days of standardization of the subjects. These intervals of expired gas collection were staggered at different intervals on each day so that midpoints of collection covered 15-second intervals. Expired air was collected through specially constructed low-resistance “triple J” valves (100 ml dead space) and tubing into a 350 L balanced spirometer and a series of 120 L neoprene bags arranged on a low-resistance manifold. Gas samples were analyzed for carbon dioxide and oxygen within ±0.03 vol% by the Scholander microtechnique.

On the fourth day subjects reported to the laboratory at 8:00 a.m. in the fasting state. Under local anesthesia a no. 7 Cournand catheter was inserted into a vein at the antecubital fossa and directed into the pulmonary artery under fluoroscopic control. A Cournand needle was inserted into the radial artery of the same arm. During supine rest cardiac output, oxygen consumption, and systemic, pulmonary (arterial and wedge), and right atrial pressures were measured. Pressures were measured with a Statham P-23Db transducer, and oxygen consumption was measured by the open-circuit technique. Resting clearance of ICG was determined from six 3-ml arterial blood samples taken at 2-minute intervals. Sampling began 5 minutes after injection of 12.5 mg of ICG into the pulmonary artery. Absorbancy of ICG in separated plasma was determined at 805 m,u in a Beckman DU spectrophotometer. Details of these techniques were described previously.8,7 During rest and exercise, cardiac output was determined by the

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**Table 1**

<table>
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<tr>
<th>Radial artery</th>
<th>Pulmonary artery</th>
<th>Right atrium</th>
<th>Right ventricle</th>
<th>Pulmonary vascular resistance (dyne-cm sec^-1</th>
<th>Mitral valve orifice (cm^2)</th>
<th>ICG t_{90} (min)</th>
<th>Arterial lactate (mg/100 ml)</th>
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*Since oxygen uptake increases in a predictable manner with increments in treadmill grade, at constant speed, this approach was taken to determine maximal oxygen uptake. When grade is held constant and speed increased, problems related to changes in mechanical efficiency of fast walking or running make maximal oxygen uptake difficult to determine even in normal men.8*
Table 3

Cardiovascular-Respiratory Data During Moderate to Maximal Exercise

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<tr>
<th>Subject</th>
<th>Oxygen uptake (ml/min)</th>
<th>% of maximal</th>
<th>Ventilation (L/min STPD)</th>
<th>Arterial O₂, ml/100 ml</th>
<th>% Satn.</th>
<th>A-V O₂ difference ml/100 ml</th>
<th>% Extract.</th>
<th>Cardiac output (L/min)</th>
<th>Heart rate (beats/min)</th>
<th>Stroke volume (ml)</th>
<th>Arterial lactate (mg/100 ml)</th>
<th>t₀ (min)</th>
<th>ICG clearance (% of resting)</th>
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<td>96.6</td>
<td>12.9</td>
<td>71</td>
<td>5.2</td>
<td>112</td>
<td>46</td>
<td>9.7</td>
<td>4.7</td>
<td>72</td>
</tr>
</tbody>
</table>
direct Fick method from duplicate pulmonary and radial arterial blood samples.

After completion of measurements at rest, subjects got up and walked on the treadmill for 15 minutes at each previously established speed and grade. During exercise, the catheterized arm rested on an arm board adjusted to minimize possible support. Fifteen- to 20-minute recovery periods (seated) were interspersed between workloads. During these experiments, 3-minute expired air collections were made only during the steady state for oxygen uptake, coincident with cardiac output measurements at submaximal levels. One-minute collections were obtained between 2 and 3 minutes at maximal exercise. Pulmonary and radial arterial blood samples were drawn during the seventh and thirteenth minutes of submaximal exercise, and during 2.5 to 3 minutes of exercise at the level of maximal oxygen uptake. Oxygen content of these blood samples was determined by the manometric technique of Van Slyke and Neill.

Rates of clearance of ICG during each level of submaximal exercise were determined as described previously.6,7 Immediately after withdrawal of 3 ml of arterial blood (for spectrophotometric blank) at the third to fourth minutes of exercise, 12.5 mg of ICG was injected (pulmonary artery). Clearance rate was determined from five successive 3-ml samples drawn at 2-minute intervals starting 3 to 4 minutes after injection. ICG clearance could not be determined at the final workload, which lasted only 3 minutes. This “maximal” load was the lowest workload that was previously shown to elicit a maximal oxygen uptake.

One-milliliter arterial blood samples for lactate determination were drawn at the twelfth minute of submaximal exercise and 1 to 2 minutes after completion of exercise at the level of maximal oxygen uptake. Concentration of lactate was determined according to Ström’s modification of the Barker-Summon technique.9 In one patient (BR), systemic arterial blood PO2, pCO2, pH, and bicarbonate concentration were determined at rest and during submaximal and maximal exercise. PO2 and pCO2 were determined by means of Clarke and Severinghaus electrodes, respectively, calibrated with gases standardized by Scholander microtechnique. Bicarbonate was calculated from pH (measured by Astrup [Radiometer] pH electrode type G-297) and pCO2 with the Henderson Hasselback nomogram.

Results

Data obtained during exercise are presented in table 3. In the figures that follow, these
Times required for submaximal (o) and maximal (△) levels of oxygen uptake to reach the highest value attained (100%) are shown. Each observation is expressed as a per cent of the highest value noted for a given workload. Included between 95 and 100% is the variation of the method and the subjects' responses once a steady state was achieved.

Oxygen Consumption

Oxygen consumption during rest was well within normal limits (table 2). Percentage data have been contrasted with appropriate regression lines computed from results from normal men and women, recently published by I. Astrand and P. O. Astrand and associates, and from data collected in this laboratory during the past 3 years. Since it is body weight—not surface area—that determines oxygen uptake and cardiac output during exercise and since measurement of body weight is more accurate, all values are normalized for body weight.*

*Excellent reasons for discontinuing the use of surface area in these conditions have been cited previously.12-15
OXYGEN INTAKE IN MITRAL STENOSIS

Figure 3
(A) Ratio of pulmonary ventilation ($V_o$ STPD) to oxygen uptake ($V_o$) and (B) respiratory exchange ratio (RQ), both in relation to relative metabolic rate. Solid circles show all observations made on each of the seven patients. The solid lines in A and B show the average responses of 30 normal young men and the range of their values (shaded area).

Figure 4
Arterial blood gases and acid-base at rest and during three intensities of work. Results from a single subject (BR) reflecting the hyperventilation in mitral stenosis with low pCO₂ and HCO₃⁻, and high pH during rest and exercise.

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response times for oxygen uptake at the start of exercise are shown in figure 1. The highest oxygen uptake measured at any time during a given intensity of exercise was set as 100%. All other values during that test were expressed as a per cent of this value. Variation of repeated measurements is illustrated by inclusion of measurements made during a steady state at later times during submaximal exercise. The variation between 95 and 100% is the sum of methodological errors including expired gas concentration and volume measurement, and reproducibility in setting treadmill speed and grade plus variations in the subjects’ own responses. The 95 to 100% response time for oxygen uptake was almost always 2 to 3 minutes. Accordingly, measurements of A-V oxygen difference, ICG clearance rate, and so forth during submaximal exercise
were obtained during a steady state of oxygen uptake.

Oxygen uptake and ventilation were abnormally high at lower workloads. Slopes relating oxygen uptake to work intensity were flatter than normal and fell to (or below) normal values as maximal oxygen uptake was approached (fig. 2). Even when ventilatory equivalent ($V_E/V_O2$) was related to the fraction of the maximal oxygen uptake (relative oxygen uptake)—excessive ventilation was evident in most (fig. 3A). Respiratory exchange ratio (RQ) was quite variable, tending toward lower than normal values at lower workloads, with no trend away from normal values at greater exertion, when related to maximal oxygen uptake (fig. 3B). Acid-base data indicating the extent of hyperventilation at rest and during exercise are shown in subject BR (fig. 4).

The low maximal oxygen uptake of 21.6 to 25.0 (average 23.3) ml per kg per minute resulted from reduced circulatory transport of oxygen rather than from a delayed response time for oxygen uptake.

**Arteriovenous Oxygen Differences**

At any absolute level of oxygen uptake, A-V oxygen difference was very much higher than equivalent values for normal young men and women (fig. 5A). However, at any given relative oxygen uptake the response was midway between the values of normal young men and women (fig. 5B). As maximal oxygen uptake was approached, maximal A-V oxygen difference (average 16.3 ml/100 ml at 90 to 100% of maximum oxygen uptake) rose close to maximal values in normal young men (average 17.0 ml/100 ml) but was slightly higher than maximal values for normal women.

**Cardiac Output**

With one exception (BR) resting cardiac output was within the 95% confidence limits.

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**Figure 5**

Total body A-V oxygen difference at rest and during exercise. Regression lines for the seven patients (solid lines) with individual data (solid circles) are contrasted with regression lines (dashed lines) for 11 normal young women ($\bigcirc$) and 12 normal young men ($\bigtriangleup$) (calculated from data of Astrand and co-workers). Regression equations are shown for normal subjects and for the patients (MS, upper left). These data are plotted with respect to absolute oxygen uptake ($ml/kg \times min$) (A) and relative oxygen uptake (B). Regression lines were terminated at observed average maximal A-V oxygen differences. In B, open circles (o) are from data of Rowell and colleagues from six normal young men (at 25.6 C).
OXYGEN INTAKE IN MITRAL STENOSIS

Figure 6
Cardiac output in relation to absolute (A) and relative oxygen uptake (B) at rest and during exercise. Regression lines for the seven patients (solid lines) with individual data (solid circles) are contrasted with regression lines (dashed lines) for normal young men (♂) and women (♀) (calculated from data of Astrand and co-workers). Regression lines were terminated at observed average maximal oxygen uptakes. Each line is accompanied by appropriate regression equations.

of normal values. During exercise, cardiac output was always subnormal (fig. 6A). This was accentuated when cardiac output was related to relative oxygen uptake (fig. 6B). Average cardiac output at 88 to 100% of maximal oxygen uptake was only 8.31 ± 1.21 L per minute, or 150 ml per kg per minute in contrast to values of 350 and 300 ml per kg per minute for normal young men and women, respectively. Since heart rates were close to normal for appropriate age groups in women (fig. 7), low cardiac output resulted from very low stroke volumes (table 2).

Blood Lactate Concentration
Blood lactate concentrations were high with respect to absolute oxygen uptake. However, the relationship of blood lactate concentration to relative oxygen uptake during exercise was in the low-normal range. As in normal subjects, the rise in lactate occurred between 50 and 70% of maximal oxygen uptake (fig. 8). Lactate concentrations at 88 to 100% of maximal oxygen uptake range from 49.5 to

Figure 7
Heart rates during mild to maximal exercise in the six female patients during the final experiment are contrasted with normal values from women in appropriate age groups (data of Astrand).

Figure 8
Arterial blood lactate concentration in relation to relative metabolic rate. This relationship in the seven patients was very similar to that observed in normal young men. The solid line represents an average response for normal subjects.
Figure 9

Correlation between fractional clearance rate of ICG as per cent of the resting value (100%) and absolute (A) and relative (B) metabolic rates. Regression lines with appropriate regression equations and correlation coefficients (r) are shown for the seven patients (solid lines [MS]) and for normal young men (δ) from data of Rowell, Blackmon, and Bruce. In part B the shaded area represents the 95% confidence interval for normal subjects.

107 mg per 100 ml. The average lactate concentration at 94% of maximal oxygen uptake was 68.6 mg per 100 ml. The value previously noted at maximal oxygen uptake in normal older women (40 to 49 years) was 86 mg per 100 ml. The equivalent value for normal younger women (20 to 29 years) was 121 mg per 100 ml.

Hepatic Clearance of ICG

Resting clearance of ICG at rest was normal at a half-time ($t_{1/2}$) of $3.1 \pm 0.5$ minutes. With increments in oxygen uptake, ICG clearance rate fell much more steeply than normal (fig. 9A). However, when the reduction in ICG clearance was related to the per cent of maximal oxygen uptake required (fig. 9B), the response was similar to that of normal young men.

Discussion

Circulatory responses to supine exercise in patients with mitral stenosis have been studied extensively, and were recently reviewed by Wade and Bishop. However, these authors had difficulty in relating cardiac responses of different patients with different degrees of functional limitation and exercise tolerance. Further complication has resulted from the predominant use of supine exercise. In this posture, heart rate and A-V oxygen difference are decreased, and cardiac output and stroke volume are increased above values for upright work at a given oxygen uptake; thus, a given quantity of oxygen is supplied by a smaller total blood flow and greater oxygen extraction by the tissues in upright exercise. Chapman and co-workers, on the other hand, saw the advantage of determining maximal oxygen uptake during upright exercise in these patients as an objective but approximate guide to the degree of functional disability.

Allegedly a major problem in establishing the functional limits of the cardiovascular system in cardiac patients has been the slow response time of oxygen uptake at the onset of exercise. Evidence supporting this contention has come from other studies on patients with myocardial failure and other
complicating factors (valvular incompetence, and others). Furthermore, results from non-standardized forms of exertion lacking well-regulated intensity are impossible to interpret. Despite these problems, Meakins and Long found no outstanding abnormality in the rapidity of the response of oxygen uptake in patients with cardiac failure. Indeed, Donald, and associates observed a steady state within 2 to 3 minutes in 10 of 16 patients during supine cycling at regulated, constant loads. Only the severely disabled patients showed a delayed response. Accordingly, our patients, who manifested no clinical evidence of myocardial failure or venous congestion, responded to increased demands for oxygen with an essentially normal time lag of about 2 minutes for upright exercise. This was also true at maximal exertion. Occasionally a slight rise in submaximal oxygen uptake with time was observed in a given subject but not repeatedly (this has been noted occasionally in normal subjects, also).

Although the response time for oxygen uptake was normal, values for oxygen uptake and ventilation were abnormally high at lower workloads. Since there is marked hyperventilation and reduced pulmonary compliance in mitral stenosis, higher costs of breathing may have been contributory. Otherwise the elevation in oxygen uptake was unexplained. At high workloads the gradual approach of oxygen uptake toward normal values (the slope decreased) merely represents the normal asymptotic approach to maximal oxygen uptake. This merely occurred at a much lower work intensity than that seen in normal subjects. The respiratory exchange ratios are difficult to interpret. The low values during mild exercise suggest chronic hyperventilation. Data from BR (fig. 4) substantiate marked hyperventilation both at rest and during exercise.

Since publication of the work of Chapman and his colleagues, Astrand has provided values for maximal oxygen uptake in normal men and women with respect to age. These studies have provided a broader frame of reference for assessing the magnitude of reduction of the measurement due to disease. For female age groups 20 to 29 years and 40 to 49 years, maximal oxygen uptake in Astrand's study averaged 39.9 ± 1.66 and 32.5 ± 0.96 ml per kg per minute, respectively. In contrast, values for women in our study of 21.6 and 24.4 per kg per minute (age, 24 and 25 years) and 22.0 and 25.0 (average, 23.0) ml per kg per minute (age, 41 to 48 years) indicate a large reduction. Also, the maximal oxygen uptake of the only male in the study (RB) was reduced approximately 50% below a normal average.

In a qualitative sense, normal subjects and patients with pure mitral stenosis approached maximum oxygen uptake in the same manner; that is, at a given relative oxygen uptake or percentage of maximal oxygen uptake relative increments in heart rate, A-V oxygen difference, blood lactate concentration, and decrements in hepatic clearance of ICG were normal. Although increments in ventilatory equivalent (VE/VO2) and RQ were exaggerated, even with respect to relative oxygen uptake, these data still tended to follow normal curves.

Unfortunately, four patients were not able to reach maximal oxygen uptake during the final experiment (three were at 88 to 90% and one at 94% of maximal oxygen uptake). This probably resulted from our failure to prevent the patients from leaning slightly upon the arm rest supporting the catheterized arm. However, Astrand and colleagues noted that maximal oxygen uptake was slightly lower with catheters even without the problem of arm support. Accordingly, the average maximal A-V oxygen difference of 16.35 ml per 100 ml in our patients was actually a slightly submaximal value in four cases. The magnitude of A-V oxygen difference at or near maximal oxygen uptake indicates that total extraction of oxygen approached limits that are normal for young adults. However, these limits vary with age, sex, and physical conditioning, and are highest in well-conditioned young men. Average maximal A-V oxygen difference was 18.5 ml per 100 ml in five well-trained endurance athletes.
were 17.0 and 14.3 ml per 100 ml in physically active young men and women, respectively. Physical conditioning increased maximal A-V oxygen difference from 15.4 to 16.4 ml per 100 ml in six sedentary young men. The A-V oxygen difference during exercise appears to decrease with age in both men and women. "Maximal" A-V oxygen differences were well within the normal range for our three younger subjects. However, values of 14.2 to 16.3 (average 15.3) ml per 100 ml at 88 to 100% (average 94%) of maximal oxygen uptake in the four older subjects could be abnormally high. Unfortunately, maximal A-V oxygen differences have not been determined in normal women in this age range (that is, 40 to 48 years). Maximal values for well-trained older men (45 to 55 years) averaged 13.3 (range 12.1 to 15.8) ml per 100 ml. Indeed, in mitral stenosis extreme widening of A-V oxygen difference is an exaggeration of a normal mechanism for oxygen transport at any given level of oxygen uptake. However, when this response is related to percentages of the maximal oxygen uptake required, this conclusion is still unfounded. Furthermore, the average femoral venous oxygen content of 3.0 ml per 100 ml at maximal oxygen uptake in two of Chapman and colleagues' subjects is higher than equivalent values of 2.7 (1.8 to 3.4) ml per 100 ml in six normal young men, again suggesting normal oxygen extraction.

Since 25 to 30% of the cardiac output is normally partitioned to the hepatic splanchic circulation at rest, extreme widening of total A-V oxygen difference could only be achieved in patients with low cardiac output in exercise by marked diversion of blood flow from this region to working muscle. Therefore, Donald and associates used percentage changes in hepatic A-V oxygen difference to assess percentage changes in hepatic blood flow. Splanchnic oxygen uptake was assumed to remain constant during exercise (this was approximately true during the brief periods of exercise used). Since hepatic venous catheterization was not possible in the present study, our experimental design necessitated reliance upon changes in hepatic clearance of ICG to assess changes in hepatic-splanchnic blood flow. Accordingly, our assumption was that hepatic extraction efficiency for ICG does not decrease during exercise. Actually the efficiency of extraction of ICG increases slightly from rest to exercise. The tendency is for percentage changes in clearance rates of ICG to underestimate changes in estimated hepatic blood flow by about 9%. Recent studies from this laboratory have corroborated this finding. It can be assumed that patients in this study responded similarly as all had normal hepatic function.

As with total A-V oxygen difference, percentage decrements in ICG clearance were exaggerated at a given absolute oxygen uptake but not at relative oxygen uptake. All but three measurements of ICG clearance fell within the 95% confidence limits for normal young male subjects when related to relative oxygen uptake. However, the slopes of the regression lines were slightly different. This relationship has never been established for normal women—young or old. The flatter slope for these patients, if real, could reflect a normally smaller reduction in hepatic blood flow in women with exercise. This might contribute to their normally narrower A-V differences during exercise. Although these quantitative differences indeed may exist, qualitatively left ventricular output appears to be partitioned normally to visceral organs, and working skeletal muscle as well, during exercise in pure mitral stenosis. Appearance of increments in blood lactate concentration in normal subjects and in our patients at 50 to 70% of maximal oxygen uptake suggests that oxygen supply to working muscle becomes limited at the same fraction of maximal oxygen uptake in both groups. Furthermore, the rates at which this limitation proceeds as maximal oxygen uptake is approached are similar.

Mitchell and associates concluded that the maximal oxygen uptake is a measure of cardiac capacity and the ability to increase A-V oxygen difference rather than the ability
of the peripheral vasculature to receive cardiac output. Our data suggest that the physiological significance of maximal oxygen uptake as defined by these authors is applicable to our patients. Arterial oxygen saturation is well maintained (even though it may have been somewhat reduced to start with) even at maximal oxygen uptake.\textsuperscript{4} Our results confirm this finding. Alveolar-arterial oxygen transport was not a limiting factor for total oxygen transport in these patients.

When mechanisms of increasing oxygen uptake are examined in the rearrangement of the Fick equation where oxygen uptake = heart rate $\times$ stroke volume $\times$ A-V oxygen difference, stroke volume stands out as the only factor limiting maximal oxygen uptake, since the remaining factors increase over a normal range to essentially normal limits. Thus, when oxygen uptake is set at maximum and stroke volume is only one half that of a normal subject, maximal cardiac output is similarly subnormal. As this study has shown in pure mitral stenosis, this defect is quantitatively reflected in an equivalent reduction in maximal oxygen uptake. The physiological significance of the reduction in maximal oxygen uptake in these patients was the reduction in stroke volume resulting from mechanical obstruction imposed by a diseased mitral valve.

We conclude that the measurement of maximal oxygen uptake provides the most information for the least amount of clinical procedure in assessing the restriction imposed upon cardiovascular functional capacity by pure mitral stenosis. Since other circulatory adaptations to increased demands for oxygen transport appear to be normal, the test defines the extent to which stroke volume has been restricted.

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Physiological Significance of Maximal Oxygen Intake in "Pure" Mitral Stenosis
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