Performance in endurance exercise is closely linked to the capacity of contracting muscle cells to utilize aerobic metabolism, expressed in the laboratory as the maximal oxygen uptake ($\dot{V}O_2\max$). Most data\textsuperscript{1} suggest that $\dot{V}O_2\max$, in turn, is limited by oxygen delivery, which in healthy individuals is defined by the pumping capacity of the heart, or maximal cardiac output.

In this traditional schema, the heart is considered to act as a forward or force pump, serving to satisfy the augmented circulatory needs of exercise. According to this concept, then, factors that influence the systolic pumping function of the heart should be expected to act as key determinants of not only $\dot{V}O_2\max$ but also of endurance performance.

It has long been recognized, however, that the circulation of blood during exercise must involve a two-pump system, a central cardiac pump and a second peripheral pump, presumably multifactorial, which is responsible for returning blood to the heart. In considering this dual system, it is obvious that the two pumps are interdependent and must, axiomatically, generate equivalent outputs. Given these observations, it is not unreasonable to suggest that determinants of peripheral pump function are as likely to serve as limiting factors to oxygen delivery as is the systolic function of the heart.\textsuperscript{2} Indeed, the concept that the peripheral pump may play a key role in defining cardiac output and oxygen uptake is supported by the observation in some studies\textsuperscript{3,4} that the diastolic filling time of the heart at maximal exercise is approximately two thirds that of systolic ejection time. That is, the circulatory system may face a greater challenge in maintaining diastolic cardiac filling than in providing for systolic ejection.

Despite their potential importance, the components and characteristics of the peripheral pump are poorly understood, reflecting the technical difficulty in assessing variables that influence cardiac diastolic filling during exercise. Several factors have been
suggested to contribute, including the pumping action of peripheral exercising muscle, a bellows function of increased ventilation, systemic venoconstriction, a “suction” effect of the left ventricle, and abdominal muscle contraction. But the role that each might play as critical determinants of peripheral pump function and circulatory sufficiency with exercise is unclear.

Opening of the mitral valve and filling of the left ventricle in diastole is contingent on a pressure differential, or gradient, between the left atrium and left ventricle. Studies in resting individuals indicate that such filling occurs in two diastolic phases. The early or rapid-filling phase occurs when left ventricular (LV) pressure falls below that of the left atrial (LA) pressure at the onset of diastole, causing the mitral valve to open and blood to flow into the ventricle. During the middle portion of diastole, LV pressure rises, the gradient is eliminated, the valve floats shut, and flow ceases (diastasis). Toward the end of diastole, atrial contraction (atrial systole) again creates an LA-LV gradient with flow across the mitral valve. The two phases of LV filling can be observed using Doppler echocardiography as an initial tall E wave (flow from the gradient created by decreasing LV pressure) and a smaller A wave (the effect of an increased gradient by pressure created by LA contraction).

During exercise, the E wave and A wave are observed to merge at light work intensities. The time-velocity profile of this combined diastolic mitral filling wave measured by Doppler echocardiography can provide information regarding beat-to-beat LA-LV peak and mean pressure gradients during exercise, since these gradients can be calculated from the mitral flow velocity by the Bernoulli equation \[ \text{gradient} = 4 \left( \frac{\text{velocity}}{\text{radius}} \right)^2 \]. Furthermore, systolic and diastolic time intervals, mitral flow volume (considered equivalent to stroke volume), and calculated systolic and diastolic flow rates can be estimated by this technique.

To our knowledge, mitral flow and LA-LV gradients during high-intensity upright exercise have not previously been described in human subjects. Cheng et al described LV inflow dynamics in instrumented dogs during treadmill running. Between an average resting heart rate of 116 beats per minute (bpm) and an exercise rate of 185 bpm, the peak LA-LV gradient rose from 5.5 to 11.8 mm Hg. This increase was due entirely to an exaggerated fall in LV diastolic pressure, as LA pressure did not change. Nonogi et al reported that minimum LV diastolic pressure fell from 9 to 3 mm Hg and mitral flow rose by a factor of 2.5 when older adults performed supine cycle exercise to a heart rate of 118 bpm.

This study sought to examine LV filling dynamics by Doppler echocardiography in boys aged 10 to 14 years during maximal upright cycle exercise. Measurement of time-velocity contours was utilized to estimate changes in peak and mean LA-LV pressure gradients with increasing work rate. The purpose was to examine the magnitude of changes in these gradients during progressive exercise and assess the relationships to mitral per-beat volume flow.

**Materials and Methods**

Twelve boys aged 10 to 14 years (mean \( \pm \) SD age, 12.0 \( \pm \) 1.3 years) were recruited from the families of hospital staff to participate in exercise testing. All were in good health, nonobese, and receiving no medications that would influence cardiovascular fitness. By questionnaire, five boys reported shaving, voice change, and/or appearance of pubic hair, indicative of early puberty.

The subjects were a physically active group, but none were involved in program of structured aerobic training. Parents were asked to rate their child’s level of habitual activity on a 5-point scale, with 1 = inactive (watches television, reads, or does homework after school; no extracurricular sports) and 5 = very active (participates regularly in sports; great deal of energy; dislikes sedentary activities). The mean score for the group was 3.7 \( \pm \) 0.7. Of the 12 boys, 10 had participated on a community-organized sports team in the previous 6 months (mainly basketball and soccer).

The subjects performed an upright progressive cycle test to exhaustion in an air-conditioned laboratory (temperature of 20°C to 22°C) with moderate humidity. Prior to testing weight was determined without shoes using a calibrated balance beam scale, and height was measured with a stadiometer. Scapular and triceps skinfold thicknesses were determined in triplicate on the right side of the body using standard procedures. Average values were summed to create a skinfold score.

The cycle seat height was adjusted to create a small knee angle at full extension. Initial and incremental workloads were 25 W, with 3-min work stages. Pedaling cadence was maintained at 50 revolutions per minute. The test was terminated when the subject could not sustain the pedaling rate. A peak heart rate \( > 185 \) bpm was considered consistent with an exhaustive effort. Peak work capacity was defined as the highest workload achieved, prorated for partial stages completed.

To assess the reproducibility of the Doppler echocardiographic measures of mitral flow velocities, subjects returned 1 week later for an identical test performed at the same time of day. Subjects were asked to duplicate the endurance time achieved on the first test. At the follow-up session, staff members were not aware of the results of the first test.

Heart rate was measured using ECG in the final 30 s of each work stage and at peak exercise, using the average of 10 successive beats. Cardiac output was assessed as the product of heart rate and stroke volume, estimated by standard Doppler echocardiographic techniques. Velocity of ascending aorta blood flow was determined with a 1.9-MHz continuous-wave transducer positioned in the suprasternal notch. Off-line measurement of the integral of blood velocity over time (velocity-time integral [VTI]) for each beat was performed by tracing the velocity curve contour. The termination of each contour was marked by aortic valve closure. Five to eight curves with the highest values and most distinct spectral envelopes were averaged for rest, each workload, and peak exercise.

Stroke volume was estimated by the product of the mean VTI...
and the cross-sectional area of the ascending aorta. The latter was calculated at rest with subjects in the sitting position from the maximal diameter of the aorta measured by two-dimensional echocardiography (long-axis view) at the sinotubular junction (inner edge to inner edge), assuming the aorta to be circular. Cardiac output and stroke volume values were expressed relative to body surface area (cardiac index, stroke index). Documentation of reliability and concurrent validity of this technique has been previously reported from this laboratory.¹²,¹³

Average systolic ejection time per beat at peak exercise was calculated as VTI divided by the mean ejection velocity. An average systolic ejection rate (milliliters per second) was then estimated as peak cardiac output divided by (ejection time × maximal heart rate × 1,000).

The mitral flow gradient (pressure difference between left atrium and left ventricle) was derived from measurements of flow velocity across the valve by continuous-wave Doppler echocardiography with two-dimensional echo guidance (Sonos 1000; Hewlett Packard; Andover, MA). Using a 3.0-MHz transducer positioned at the cardiac apex, VTIs of mitral flow were obtained with a four-chamber view and the cursor was positioned in line with LV inflow. Videotape recording of VTIs over a 45-s to 60-s time segment permitted identification of at least five consistent maximal values with sharp contours for off-line measurement of average values of peak velocity, mean velocity, and VTI at all work levels. At rest and during the first work stage, only the E wave of the mitral flow pattern was included in this measurement. At subsequently higher work rates, the E waves and A waves merged and the single spectral envelope was measured.

Hemodynamic variables were measured at rest, during each workload, and at peak exercise. At each submaximal stage, mitral Doppler echocardiography was performed between minute 1 and minute 2, and aortic velocities were recorded between minute 2 and minute 3. Similarly, mitral and aortic velocities were measured during the penultimate and final minute of exercise, respectively.

Indicators of LV diastolic filling dynamics were examined as follows: (1) peak and mean mitral flow velocity; (2) the LA-LV peak and mean pressure gradient, derived from the Bernoulli equation [gradient = 4(velocity)²]; (3) the magnitude of change in these gradients (maximal/rest values); (4) acceleration time of LV inflow (in centimeters per second squared), or the ascending slope of the VTI contour, and the time to peak velocity during diastolic LV filling; (5) diastolic filling time, estimated by subtracting the systolic ejection time from the total cycle time (60/heart rate), ignoring the systolic pre-ejection and diastolic isovolumic relaxation periods; (6) diastolic filling rate, calculated as cardiac output divided by (diastolic filling time × heart rate × 1,000); and (7) mitral flow volume per beat, considered equivalent to the stroke volume estimated by suprasternal notch aortic Doppler echocardiography.

Test-retest reliability of mean and peak LV inflow velocities at rest and during submaximal exercise were assessed by repeated-measures analysis of variance (workload × trial). At the second test, two of the subjects were unable to duplicate testing endurance time achieved on the first test. Reproducibility of peak and mean gradients at peak exercise was examined by dependent Student’s t test and coefficient of variation (SDs of the individual differences in the two tests divided by the mean). Statistical significance was defined as p < 0.05.

Informed consent and assent were obtained from the parents and children, respectively. This study was reviewed and approved by the Institutional Review Board of the Baystate Medical Center.

Results

The mean weight of the subjects was 45.1 ± 7.7 kg, height was 149 ± 13 cm, and body surface area was 1.38 ± 0.17 m². Average skinfold sum was 17.6 ± 5.7 mm. These values indicate that body size and composition of the subject cohort reflected that of the age-specific general pediatric population.¹⁴

Average peak work capacity was 2.70 ± 0.33/kg, with a mean peak heart rate of 191 ± 10 bpm (range, 173 to 208 bpm). Three subjects had peak heart rates < 185 bpm. Because of the time required to acquire both aortic and mitral Doppler echocardiographic recordings, it was necessary for the staff to identify a point in time 1 to 2 min before the subject’s exhaustion. The inability to accurately predict this point in all subjects resulted in failure of several subjects to reach a truly exhaustive state. Nevertheless, all the boys were considered to have achieved a high-intensity, near-maximal effort as evidenced by heart rate level and subjective staff observations.

Average peak cardiac index was 9.94 ± 1.07 L/min/m² and stroke index was 52 mL/m². The values compare to those previously obtained in this laboratory of 11.98 ± 2.33 L/min/m² and 61 mL/m², respectively, in a group of 36 similar-aged boys who were considered to have reached a true exhaustive cycling effort.¹⁵

Values for diastolic filling variables at rest and during exercise are outlined in Table 1. Peak and mean mitral valve flow velocities rose progressively.

### Table 1—Diastolic Variables With Progressive Exercise (Test 1)*

<table>
<thead>
<tr>
<th>Variables</th>
<th>Rest</th>
<th>25 W</th>
<th>50 W</th>
<th>75 W</th>
<th>100 W</th>
<th>Peak</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peak gradient, mm Hg</td>
<td>2.62 ± 0.47</td>
<td>4.76 ± 1.23</td>
<td>5.64 ± 1.07</td>
<td>7.26 ± 1.47</td>
<td>8.71 ± 1.70</td>
<td>10.06 ± 1.78</td>
</tr>
<tr>
<td>Mean gradient, mm Hg</td>
<td>1.25 ± 0.19</td>
<td>2.28 ± 0.47</td>
<td>2.74 ± 0.56</td>
<td>3.33 ± 0.80</td>
<td>4.26 ± 0.66</td>
<td>4.91 ± 0.82</td>
</tr>
<tr>
<td>Time to peak, s</td>
<td>0.094 ± 0.012</td>
<td>0.091 ± 0.014</td>
<td>0.087 ± 0.014</td>
<td>0.087 ± 0.013</td>
<td>0.082 ± 0.012</td>
<td>0.082 ± 0.011</td>
</tr>
<tr>
<td>Acceleration, cm/s²</td>
<td>873 ± 114</td>
<td>1,229 ± 293</td>
<td>1,444 ± 319</td>
<td>1,602 ± 226</td>
<td>1,785 ± 362</td>
<td>1,983 ± 388</td>
</tr>
<tr>
<td>Mitral flow, mL/beat</td>
<td>52 ± 9</td>
<td>65 ± 12</td>
<td>70 ± 13</td>
<td>73 ± 12</td>
<td>71 ± 12</td>
<td>72 ± 13</td>
</tr>
<tr>
<td>Systolic ejection time, s</td>
<td>0.241 ± 0.019</td>
<td>0.239 ± 0.018</td>
<td>0.228 ± 0.016</td>
<td>0.209 ± 0.014</td>
<td>0.192 ± 0.016</td>
<td>0.176 ± 0.011</td>
</tr>
<tr>
<td>Estimated diastolic filling time, s</td>
<td>0.479 ± 0.043</td>
<td>0.314 ± 0.036</td>
<td>0.235 ± 0.035</td>
<td>0.204 ± 0.034</td>
<td>0.163 ± 0.026</td>
<td>0.138 ± 0.015</td>
</tr>
</tbody>
</table>

*Data are presented as mean ± SD.
with exercise with a significant main effect for workload, but there was no main group effect between the two trials (p > 0.05; Fig 1). The calculated average peak flow gradient rose from 2.62 ± 0.47 mm Hg at rest to 10.06 ± 1.78 mm Hg at peak exercise (maximal:rest ratio, 3.92 ± 0.87). Respective values for the average mean gradient were 1.26 ± 0.19 mm Hg and 4.91 ± 0.82 mm Hg (maximal:rest ratio, 3.90 ± 0.73). Considering only those 10 subjects who duplicated endurance time on the two tests, average peak gradients at end exercise were 10.10 ± 1.86 mm Hg and 10.43 ± 1.28 mm Hg for the two trials, respectively (p > 0.05). For mean gradients, the values were 4.95 ± 0.79 mm Hg and 5.17 ± 0.69 mm Hg (p > 0.05). Coefficients of variation for peak and mean mitral gradients for the two tests were 12.7% and 13.0%, respectively.

A progressive shortening of time-to-peak velocity was observed with increasing work intensity, with an average value of 0.094 ± 0.012 s at rest and 0.082 ± 0.011 s at peak exercise. At the same time, the average acceleration of diastolic inflow rose by a factor of 2.25, from 873 ± 114 cm/s² at rest to 1,983 ± 388 cm/s² at peak exercise.

At rest, mean systolic and diastolic time occupied 33% and 67% of the total cycle period, respectively. With increasing work, the rise in heart rate shortened both portions of the cardiac cycle, but the decrease was greater with diastole. At peak exercise, systolic ejection period was 56% of the cycle, while the estimated diastolic time was 44%. Consequently, at peak exercise the calculated systolic and diastolic flow rates were 407 ± 71 mL/s² and 501 ± 98 mL/s², respectively.

Mitral flow volume per beat rose 40% from rest to the second workload (average heart rate, 125 bpm) and then plateaued with little change as work intensity increased. Thus, the per-beat flow across the valve was constant during the higher work intensities while peak and mean mitral pressure gradient rose and diastolic filling time declined (Fig 2).

**Discussion**

The average estimated diastolic filling rate of the left ventricle at peak exercise in this study was 501 ± 98 mL/s. This value is comparable (relative to body size) to maximal values reported in adult subjects of 1,010 mL/s (Gledhill et al³) and 1,050 mL/s. At rest, the duration of diastole was twice that of systole (0.479 ± 0.043 s vs 0.241 ± 0.019 s). With the rise in heart rate accompanying increased work intensity, diastolic time fell more precipitously than that of systole. The two were approximately equal at an average heart rate of 150 bpm, and at peak exercise estimated diastolic filling period was 78% of the systolic ejection period (0.138 ± 0.015 s vs 0.176 ± 0.011 s, respectively). This duplicates findings observed in previous studies in this laboratoy and mimics patterns previously observed in adults. Gledhill et al³ described systolic ejection and diastolic filling times of 0.155 ± 0.004 s and 0.177 ± 0.009 s, respectively, at maximal exercise in young men. Higginbotham et al⁴ reported an average LV ejection time of 0.190 s and diastolic filling time of 0.169 s in adult subjects at a heart rate of 167 bpm. However, others have found similar systolic and diastolic times at high work intensities.

In this study, average peak LA-LV gradient rose fourfold from a mean at rest of 2.62 ± 0.47 mm Hg to 10.06 ± 1.78 mm Hg at peak exercise. Values for

![Figure 1](http://journal.publications.chestnet.org/pdftoc21964/)

**Figure 1.** Test-retest values for peak and mean mitral flow velocity during rest and submaximal exercise (p > 0.05 for all trial comparisons).

![Figure 2](http://journal.publications.chestnet.org/pdftoc21964/)

**Figure 2.** Comparison of patterns of change in mean mitral flow gradient (G), per-beat mitral flow volume (MF), and estimated diastolic filling time (DFT) with progressive exercise. Max = maximal.
average mean gradient were 1.26 ± 0.19 mm Hg and 4.91 ± 0.82 mm Hg, respectively. This rise in transmirtal gradient during exercise can serve to increase the speed of LV filling and/or the diastolic volume entering the ventricle (velocity over time). Findings in this study suggest that increasing filling velocity rather than flow volume is the principal function of the rise in LA-LV gradient with exercise. The mitral flow volume per beat rose 39% from rest to moderate exercise intensity and then remained stable to peak exercise. Meanwhile, average estimated diastolic filling time shortened progressively by 71%. In the early stages of progressive exercise, then, the increased LA-LV gradient provided for both greater ventricular filling velocity and volume. Beyond moderate work intensity, however, the rise in gradient served solely to deliver the same volume to the left ventricle in a shorter time period.

A rise in transmirtal gradient can occur by either an increase in LA pressure or fall in early LV diastolic pressure. Information from the present study does not permit an identification of which of these factors was responsible for the fourfold rise in gradient at peak exercise. However, certain inferences can be made from previous studies demonstrating that LA mean pressure in adults increases two to three times above resting values at maximal upright exercise. Thadani and Parker22 showed an increase in average pulmonary capillary wedge pressure (reflecting LA mean pressure) from 4 to 8 mm Hg as adults subjects performed upright cycling to a heart rate of 184 bpm. Higginbotham et al4 described an increase in mean wedge pressure from 3 to 10 mm Hg at a heart rate of 167 bpm with upright cycling, and a similar threefold rise was described by Reeves et al23 in young adult men. The observation in the present study that the mean transmirtal pressure gradient rose by a greater, fourfold magnitude suggests that both increased per-beat LA pressure and decreased LV diastolic pressure contributed to the augmented gradient at peak exercise.

The extent that the left ventricle acts as a suction pump during exercise has been unclear.24 Filling of the ventricle by suction occurs when LV pressure drops below LA pressure in early diastole, increasing the LA-LV gradient. The rate and degree of decay of LV pressure that dictates the effect of this suction is a function of myocardial relaxation as well as ventricular elastic recoil.25 It is clear that the inotropic function of the left ventricle in systole is directly related to the extent of LV diastolic pressure decline and resultant LA-LV pressure gradient. Udelson et al26 reported that an isoproterenol infusion (mimicking adrenergic stimulation of the myocardium with exercise) lowered minimum LV pressure in diastole and increased transmirtal flow in adult humans. The degree of fall in early LV diastolic pressure (ranging from −0.5 to −2.4 mm Hg) was directly related to end-systolic volume. Thus, LV systolic function with exercise may serve as a direct determinant of the LA-LV diastolic gradient and ventricular filling.

On the upstream side of the LA-LV gradient, several factors influence LA pressure, including atrial size and compliance as well as strength of LA contraction. During exercise, however, the LA pressure would appear to mainly reflect the balance between peripheral factors that influence increases in vena caval blood flow (via the right ventricle and pulmonary circulation) and heart rate. That is, if heart rate does not match the volume of blood returning to the heart, atrial hypertension and systemic/pulmonary venous congestion would ensue. However, a fall in atrial pressure, decline in stroke volume, and ultimate collapse of venous vessels would occur with an exaggerated heart rate response.

An attempt to synthesize this information with the following scenario appears reasonable: during progressive exercise, the skeletal muscle pump and other peripheral factors generate an increasing volume of venous return to the heart. In the left atrium, this increased volume is matched by a rise in heart rate to prevent an unacceptably high LA pressure. The peripheral pump, then, acts to maintain a pressure head to sustain, or modestly increase, the per-beat LA-LV gradient as exercise intensity increases. The LA-LV gradient is further increased by an exaggerated decay in early LV diastolic pressure, reflecting augmented elastic recoil as end-systolic volume decreases. This increased suction effect serves to “unload” the left atrium at a greater velocity.

These observations suggest potential mechanisms whereby diastolic filling—and resulting maximal cardiac output and \( \dot{V}_{O_2\text{max}} \)—might serve as determinants of higher levels of aerobic fitness, including greater myocardial contractility, more effective skeletal muscle pump, and increased bellows function of ventilation. Van Overschelde et al27 examined the relationship between LV diastolic filling features at rest and aerobic fitness in healthy adults. Significant correlations were observed between \( \dot{V}_{O_2\text{max}} \) and both the ratio of early to late transmirtal filling velocity, and LV end-systolic volume. Conversely, similar elements might be responsible for the limited circulatory functional capacity in those patients with heart disease.16

In examining the results of this study, certain caveats are in order. The generalizability of the findings in a group of circumpubertal boys is uncertain. Given the lack of standardization of transducer position and motion of the heart with exercise, the Doppler echocardiographic method might not be
expected to be a highly precise indicator of changes in transmitral flow velocities. Nevertheless, identification of velocity-time curves was not difficult given the videotaping method employed, and the consistent individual rises with exercise and the adequate reproducibility suggest that reasonable accuracy was achieved.

The continuous-wave Doppler echocardiographic technique was used in this study, which provides information regarding the highest velocities not just across the mitral valve but along the entire course of the cursor through the LV inflow tract. Thus, recorded velocities may have also included intraventricular gradients,8 inertial flow after mitral valve closure,25 and pulmonary venous inflow. However, these inputs should not be expected to contaminate peak velocity measurements or peak:resting ratio values.

Other factors may also affect the Doppler echocardiographic technique. For instance, the extent to which respirations, mitral valve area, plasma volume, and nonhomogeneity of flow might influence the findings in this study are uncertain.

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