New Redistribution Index of Nutritive Blood Flow to Skeletal Muscle During Dynamic Exercise

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Background. Cardiac output is effectively redistributed to working muscle by regional changes in vascular resistance. However, there has been no suitable method to quantify blood flow distribution to large working and nonworking muscles involved in ergometer or treadmill exercise.

Methods and Results. To quantify the redistribution of blood flow, we compared thallium activity in a bicycle pedaling leg with that in the contralateral resting leg in 10 normal subjects. The regional thallium activity was expressed as a percentage of the whole-body radioisotope activity. Comparison of thallium activity between legs was performed at rest and at the work rates of anaerobic threshold and peak exercise during one-leg exercise. Thallium distribution of both legs was essentially the same at rest. At the anaerobic threshold, thallium activity increased about threefold in the exercising thigh and about twofold in the exercising calf. The thallium distribution in these muscles at peak exercise was the same as at the anaerobic threshold. In the nonexercising calf, thallium distribution during exercise decreased significantly, and it was unchanged in the nonexercising thigh. Consequently, the ratio of thallium activity between the exercising and nonexercising thighs increased from 1.1±0.1 to 4.0±0.9 at the anaerobic threshold and to 3.3±0.6 at peak exercise. Similarly, the ratio between the exercising and nonexercising calves increased from 1.0±0.0 to 3.8±1.3 at the anaerobic threshold and to 3.5±1.0 at peak exercise. The ratios at peak exercise, however, did not differ significantly from those at the anaerobic threshold.

Conclusions. These findings suggest that the redistribution of blood flow occurs predominantly during mild to moderate exercise; therefore, blood flow in the leg during strenuous exercise would depend primarily upon an increased cardiac output. Thus, the thallium activity ratio of exercising and nonexercising legs reflects the difference in vascular tone of each leg and could provide a noninvasive and quantitative index of blood flow redistribution. (Circulation 1992;85:1457–1463)

KEY WORDS • exercise thallium-201 • scintigraphy • skeletal muscle blood flow

Nutritive blood flow to skeletal muscle is determined by a combination of cardiac function and regional vascular resistance and is closely proportional to the relative consumption of oxygen.1 As exercise becomes more strenuous, the metabolic vasodilator stimulus to working muscle and the sympathetic vasoconstrictor forces to nonworking areas are augmented progressively.2,3 Therefore, the relative magnitude of vascular resistance of exercising muscle and nonexercising tissues is important to the distribution of regional blood flow. In patients with chronic heart failure, an impaired dilatory capacity of resistance vessels within the working muscle may contribute to the decrease in muscle flow.4,5 Thus, the redistribution of blood flow during muscular exercise would vary depending on the intensity of the exercise and the presence or absence of heart disease. Although previous studies6–8 have documented changes in regional vascular resistance during exercise, no quantitative index exists for describing the extent of redistribution of regional blood flow.

Accordingly, to quantify the redistribution of flow during exercise, we evaluated the results of one-leg bicycle exercise in normal subjects, comparing the muscle blood flow in the working leg with that of the contralateral resting leg. Because muscle mass and arterial blood pressure are equal in the right and left legs, the ratio of nutritive blood flow to these muscles reciprocally represents the ratio of vascular tone of each leg muscle.

Methods

Subjects

We studied 10 normal men aged 32 to 49 years (mean 36 years). None performed regular athletic activities off the job. No subject showed abnormalities on physical examination, the ECG, or the echocardiogram. Informed consent was obtained from all subjects. The research protocol was approved by the research committee of our institution.
Exercise Protocol and Gas Exchange

Anaerobic Threshold

One-leg exercise testing was performed with the subject sitting upright on an electronically braked bicycling ergometer (Lode Corival-400, The Netherlands). During one-leg exercise, the nonexercising leg rested in a sling suspended adjacent to the ergometer, and the foot of the active leg was secured to the pedal. Breath-by-breath measurements of oxygen usage, carbon dioxide output, ventilation volume, and end-tidal oxygen and carbon dioxide concentrations were taken with a Minato RM-280 (Japan) metabolic measurement cart equipped with an oxygen and carbon dioxide analyzer. The anaerobic threshold was estimated in each subject before study. Initially, each subject performed 3 minutes of unloaded cycling using one leg to pedal. The work rate was uniformly increased by a ramp incremental protocol (4–12 W every minute). When a higher work load could not be achieved because of severe leg fatigue, the subject was considered to have achieved his peak oxygen uptake. The increase in work rate was that required to reach volitional fatigue in each subject within 8–12 minutes. The anaerobic threshold was identified when minute ventilation and carbon dioxide production began to increase non-linearly despite a linear increase in oxygen uptake (Figure 1) and the end-tidal oxygen concentration began to rise without a concomitant decline in end-tidal carbon dioxide concentration. We also determined the anaerobic threshold by the V-slope method described by Beaver et al. Throughout the test, the subject’s heart rate and arrhythmia were monitored, and blood pressure was measured by the cuff method at 1-minute intervals. All subjects were exercised at least twice to ensure their familiarity with one-leg exercise and to establish reproducibility of the exercise test.

Scintigraphic Data Acquisition

Whole-body $^{201}$TI scintigraphy was performed in each subject on three separate days under three separate conditions: at rest, at the work rate of the anaerobic threshold, and at peak exercise. $^{201}$TlCl (1.5–2.0 mCi) was injected into the antecubital vein, and 10 ml saline was added to flush the system. Five minutes after the injection, the subject was placed supine on the imaging table. Scintigraphic data collection was started from the anterior projection and then continued to the posterior projection, using a single field of view of the gamma camera. A high-sensitivity, low-energy collimator was used most often so as to maximize the counts, although a high-resolution, low-energy collimator was used occasionally for convenience with equally good results. A 70–90-keV window was used for acquisition. The scan speed was 40 cm/min, and all scans were completed in 5 minutes.

Analysis

Images were acquired on computer in a 512×512-pixel matrix. The anterior view of the thigh and the posterior view of the calf were used for quantitative analysis. Rectangular regions of interest of equal size were drawn around the whole body, the thighs, and the calves (Figure 2). Correction was made for background activity. Total counts in each region were determined by computer and expressed as a percentage of whole-body...
activity. An interextremity comparison of thallium activity was performed by dividing the average pixel value of any given region by the average pixel value of the contralateral region at the same level. These ratios were determined for thighs and calves.

Methodological Consideration

To validate the use of the thallium distribution as an estimate of muscle blood flow, we compared the ratio of calf blood flow measured by venous occlusion technique using a single-strand strain-gauge plethysmograph and the simultaneously measured thallium activity ratio of the calves. An additional 11 subjects were allowed to rest in supine position for 15 minutes. After baseline measurements, the subjects performed rhythmic ankle extension of either foot. The intensity of the exercise was varied in each patient to encompass a wide range of the blood flow ratio. $^{201}$TI CI was injected at 3 minutes of extensor exercise of one foot, and the measurement of calf blood flow by plethysmograph was performed immediately after cessation of the exercise (Table 1). Within a calf flow ratio ranging from 1 to 6, the correlation between the thallium activity ratio of calves and calf blood flow ratio by plethysmography was highly linear ($r=0.98$) (Figure 3).

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<thead>
<tr>
<th>Case</th>
<th>Leg blood flow (ml/min/100 ml)</th>
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Ex, exercising calf; R, resting calf.

Statistical Analysis

Values are expressed as mean±SD. The statistical significance of differences was tested by ANOVA, and multiple comparisons were made by the Bonferroni method. Values of $p<0.05$ were considered statistically significant.

Results

Results are summarized in Tables 2 and 3 and Figure 4. All subjects terminated exercise primarily because of leg fatigue. There were no complications associated with the procedure. Data at the anaerobic threshold were obtained in eight of the 10 patients.

Gas Exchange Responses

The mean anaerobic threshold for the eight subjects obtained by the respiratory gas exchange method was 1,024±181 ml/min at work rates of 58±12 W. Peak oxygen uptake averaged 1,494±432 ml/min at the work rate of 86±28 W (Table 2). Mean blood pressure was 94±7 mm Hg at rest, rising to 131±11 mm Hg at the anaerobic threshold and to 152±5 mm Hg at peak exercise. Mean heart rate was 72±5 beats per minute at rest, increasing to 116±15 beats per minute at the anaerobic threshold and to 152±22 beats per minute at peak exercise.

Comparison of Blood Flow in Exercising Versus Nonexercising Leg

Anterior and posterior whole-body images in a representative case appear in Figure 4. The total counts ranged from 100,000 to 340,000. Thallium activity in both legs was nearly identical at rest, the thallium activity ratio of the legs being almost 1.0 (Table 3). At the anaerobic threshold, thallium activity increased from 5.2±1.2% to 17.8±2.2% in the exercising thigh and from 2.1±0.3% to 4.6±1.2% in the exercising calf. At peak exercise, the activity increased to 17.6±2.2% in the thigh and to 4.7±0.9% in the calf. There were no significant differences in the thallium distribution between anaerobic threshold and peak exercise. In the

Figure 3. Graph shows comparison between thallium activity ratio of calves and calf blood flow ratio by plethysmography. Although the thallium activity ratio somewhat underestimates the flow ratio as exercise becomes strenuous, there is a highly linear correlation between these ratios.
nonexercising calf, the thallium distribution decreased significantly from 2.1 ± 0.3% to 1.3 ± 0.3% at the anaerobic threshold and to 1.4 ± 0.3% at peak exercise, whereas in the nonexercising thigh it remained unchanged from the resting values. Consequently, the ratio of thallium activity between the exercising and nonexercising thighs and between the exercising and nonexercising calves increased to 4.0 ± 0.9 and 3.8 ± 1.3, respectively, at the anaerobic threshold and to 3.3 ± 0.6 and 3.5 ± 1.0, respectively, at peak exercise. The ratios obtained at peak exercise did not differ significantly from those at the anaerobic threshold.

**Discussion**

We measured the relative changes in the vascular tone of exercising and nonexercising muscles of healthy men using one-leg exercise and whole-body $^{201}$TI scintigraphy. This new method offers several advantages for assessing the redistribution of blood flow during exercise.

In a normal subject, during graded exercise involving 40% or more of the total muscle mass, such as pedaling a bicycle with both legs, the maximal functional capacity is limited by the ability of the heart to increase its output. In contrast, when graded exercise involves a smaller percentage of the total muscle mass, such as pedaling with one leg, the maximal exercise capacity is attained before the maximal cardiac output is reached, suggesting that cardiac output is no longer the limiting factor.

Previous studies have demonstrated that blood flow and vascular conductance in the working limb at maximal effort are greater during one-leg than during two-leg bicycle exercise. Thus, bicycling with one leg is viewed as a physiological approach to evaluate the ability of the vasculature of the skeletal muscle to dilate or to extract oxygen (peripheral response) rather than to evaluate the cardiac response (central response) to exercise.

Until recently, methodological limitations to comparing blood flow to working versus nonworking muscles have prevented the quantitative evaluation of flow distribution in the clinical settings. Strain-gauge plethysmograph has been widely used to measure limb blood flow but is limited in its ability to measure blood flow to large working muscles involved in ergometer or treadmill exercise. The measurement of femoral vein flow by thermodilution techniques is unsuited to the direct comparison of relative changes in the vascular resistance of working and nonworking muscles. Whole-body $^{201}$TI scintigraphy has recently been established as a noninvasive method for measuring blood flow to the lower extremities. Like $^{4}$K, $^{201}$TI is useful in tracing blood flow because it is rapidly taken up in the tissues after an intravenous injection. Although the uptake of thallium depends on the presence of an active Na,K-ATPase transport system as well as blood flow to the organ and tissue permeability to this agent, the initial distribution of thallium in an organ adequately reflects the blood flow to that organ.

**Table 2. Gas Exchange Responses to One-Leg Exercise in Normal Subjects**

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**HR, heart rate; bpm, beats per minute; MBP, mean blood pressure; $\dot{V}O_2$, oxygen uptake; AT, anaerobic threshold; W, watts; *p<0.01 vs. rest; †p<0.01 vs. AT.**
the present study, we have chosen venous occlusive plethysmography and adopted the method by which Zelis et al.20 had measured blood flow during dynamic forearm exercise. Although the thallium activity ratio of calves somewhat underestimated the distribution of calf blood flow as exercise became strenuous, there was a highly linear correlation between the thallium activity ratio and the flow ratio determined by plethysmography within the flow ratio range of 1 to 6. Because the blood flow measured by plethysmography includes both muscle and skin blood flow unless epinephrine iontophoresis is not performed,21 the higher flow ratio obtained by plethysmography during exercise might reflect the changes in skin blood flow. The workload of flexing and
extending the ankle is considerably less than that of bicycle exercise. Therefore, these results from the small muscles might not be applied to large muscles involved during one-leg ergometer test. Although these limitations could result in modest error, quantitative factors probably would little affect the directional changes in the flow ratio during exercise.

In the resting state, the thallium activity ratio of both legs was nearly 1; therefore, the vascular resistance of both legs is considered the same. During one-leg exercise, the ratio rose substantially, being about four times greater at the anaerobic threshold than at rest. The thallium activity ratio at the maximal work rate, however, remained the same as at anaerobic threshold. One possible explanation for this inability to increase the blood flow ratio during strenuous exercise involves the thermoregulatory mechanisms that eliminate the increased heat load. As body temperature rises during strenuous exercise, a large percentage of the cardiac output must be shifted to the skin for cooling purposes and thus is no longer available to the working musculature.1,22 Another possibility is a reduction of the vascular dilatory capacity during strenuous exercise. Wilson et al19 recently showed that vascular resistance of the leg fell substantially during mild to moderate levels of exercise and then declined gradually during strenuous exercise. Systemic vasoconstrictor influences may interfere with vasodilation in the working muscle in that strenuous exercise is associated with enhanced sympathetic activity and an elevated concentration of circulating norepinephrine and angiotensin II. Those investigators, however, also demonstrated that α-adrenergic blockade or converting enzyme inhibitors have only a little effect on leg vascular resistance during strenuous exercise and suggested that the vasoconstriction mediated by these neurohumoral mechanisms is attenuated by local vasodilatory factors in the working leg muscles.23,24 Therefore, the resistance vessels in working muscle are dilated to nearly the maximum before the maximal work rate is attained.

Although the resting limb may be a target of blood flow redistribution, the reserve of blood flow from the resting leg is quite limited, and the major part of redistribution is the splanchnic region. In the present study, we did not aim to examine the amount of blood redistributed but rather to quantify the difference in vascular tone of exercising and nonexercising tissues as exercise becomes strenuous. We demonstrated that during one-leg exercise, thallium distribution decreased significantly in the nonexercising calf. Bevegard and Shepherd6 demonstrated that when the arm was sympathectomized, blood flow substantially increased during leg exercise after the rise in blood pressure, whereas blood flow in the normal arm remained close to control levels. Thus, during exercise, the vascular resistance in the muscle of a resting limb is reflexively increased via the sympathetic nerves. Our data, however, showed that in normal subjects, vasoconstrictor mechanisms at peak exercise did not influence the arterioles so as to increase the flow ratio of exercising and nonexercising legs more than at anaerobic threshold. These findings indicate that the redistribution of blood flow occurs predominantly during mild to moderate exercise; therefore, leg blood flow during strenuous exercise would depend primarily upon an increase in cardiac output.

In conclusion, the thallium activity ratio of exercising and nonexercising legs would provide a noninvasive and quantitative index of blood flow redistribution because the ratio reciprocally reflects the relative magnitude in vascular tone of these leg muscles. Differences between blood flow redistribution of patients with and without heart failure have already been demonstrated.21 Thus, the difference in the response of the flow ratio to one-leg exercise may provide useful diagnostic information on the reduced exercise capacity of patients with heart failure. The present results would justify further studies to determine the influence of various diseased states on the response of the flow ratio to exercise.
References

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