Muscle pump-dependent self-perfusion mechanism in legs in normal subjects and patients with heart failure

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Shiotani, Issei, Hideyuki Sato, Hiroshi Sato, Hiroshi Yokoyama, Yozo Ohnishi, Eiji Hishida, Kunihiro Kinjo, Daisaku Nakatani, Tsunehiko Kuzuya, and Masatsugu Hori. Muscle pump-dependent self-perfusion mechanism in legs in normal subjects and patients with heart failure. J Appl Physiol 92: 1647–1654, 2002; 10.1152/japplphysiol.01096.2000.—Leg venous pressure markedly falls during upright exercise via a muscle pump effect, creating de novo perfusion pressure. We examined physiological roles of this mechanism in increasing femoral artery blood flow (FABF) and its alterations in chronic heart failure (CHF). In 10 normal subjects and 10 patients with CHF, standard hemodynamic variables, mean ankle vein pressure (MAVP), and FABF with Doppler techniques were obtained during graded upright bicycle exercise. To evaluate a nonspecific blood flow response, normal subjects also performed supine exercise. In normal subjects, MAVP rapidly declined by 45 mmHg and FABF correspondingly increased 5.3-fold without a systemic pressor response during 10 s of light upright exercise at 5 W. Approximately 67% of the blood flow response was attributed to the venous pressure drop-dependent mechanism. In CHF patients, MAVP declined by only 36 mmHg and FABF increased only 1.7-fold during the same upright exercise. The muscle venous pump has an ability to increase FABF at least threefold via the venous pressure drop-dependent mechanism. This mechanism is impaired in CHF patients.

Doppler techniques; ankle vein pressure; femoral artery blood flow

AT REST IN THE UPRIGHT POSITION, the venous pressure in the leg is elevated, reflecting the hydrostatic pressure difference between the heart and legs. During rhythmic leg exercise, however, the venous pressure at the ankle level markedly declines because of transfer of blood into central circulation by muscle contraction, with backflow prevented by venous valves (16, 25, 32). Although the extent is less, the venous pressure drop is also observed at the popliteal level (31). This implies that de novo perfusion pressure is created in the leg during upright exercise via the venous pressure drop. Moreover, a drop in venous pressure may elicit local vasodilatation through the vеноarteriolar reflex (18–20). Thus exercising legs appear to have a potent self-perfusion mechanism, independent of cardiac function. It is possible that a light exercise such as walking is achieved with only the muscle-pump dependent mechanism. However, it is still unclear what amount of leg blood flow and what level of exercise can be achieved via this mechanism.

The extent of drop in venous pressure depends primarily on the frequency of skeletal muscle contraction (18, 19) and the duration of exercise (13). However, the central venous pressure and skeletal muscle mass may also contribute to pump function of skeletal muscles because they determine the afterload of venous return and power of the muscle pump, respectively. Hence, the muscle pump-dependent blood flow in the leg may be limited in patients with chronic heart failure, whose central venous pressure is often elevated and whose skeletal muscles are often atrophied (17, 33).

In the present study, we determined physiological roles of muscle pump-induced venous pressure drop in increasing leg blood flow and exercise performance during upright exercise in normal subjects, by measuring the ankle vein pressure as an index of venous pressure changes in exercising legs. To evaluate a nonspecific blood flow response independent of the venous pressure drop, we also performed the measurements during supine exercise by normal subjects because the drop in venous pressure due to skeletal muscle contraction is minimal in the supine posture. We further investigated alterations of the muscle pump-dependent blood flow response in patients with chronic heart failure.

METHODS

Subjects. To assess the muscle pump-dependent leg blood flow and exercise performance in normal subjects, we evaluated 10 sedentary healthy male volunteers, ranging in age from 42 to 71 yr (mean 53 yr; Table 1). None had a history, symptoms, or signs of cardiovascular diseases. All had normal 12-lead electrocardiograms at rest and during exercise.
and normal echocardiograms at rest. None was receiving medication during the study.

To investigate the muscle pump-dependent blood flow response in chronic heart failure, we evaluated 10 male patients with chronic heart failure, ranging in age from 45 to 72 yr (mean 60 yr). Although they were somewhat older than the normal subjects, the difference was not statistically significant. Eight patients were classified in New York Heart Association functional class II, and two were in class III. Seven patients had dilated cardiomyopathy, and three had an old myocardial infarction without angina pectoris. The peak oxygen uptake during a preliminary ramp maximal bicycle exercise test ranged from 11.2 to 19.5 ml·min⁻¹·kg⁻¹ (mean 16.6 ml·min⁻¹·kg⁻¹). Left ventricular fractional shortening assessed by M-mode echocardiography with the guidance of two-dimensional images ranged from 5 to 24% (mean 16%), and the end-diastolic dimension ranged from 57 to 88 mm (mean 63 mm). All patients were in sinus rhythm, and none had overt peripheral edema. All patients had been treated with cardiovascular drugs for >5 mo before the study; diuretic agents in 10 patients, digitalis in 6 patients, and converting-enzyme inhibitors in 9 patients. These drugs were continued throughout the study.

Written informed consent was obtained from each subject before the study. The protocol for this study was approved by the Ethics Committee of the hospital.

Exercise protocol. The upright bicycle exercise test was performed during a postabsorptive state in the afternoon. In the present study as well as in several previous studies (15, 24, 32), the pressure in the ankle vein was measured to estimate the venous pressure changes in exercising legs. Before the exercise test, a 22-gauge Teflon needle was inserted into the superficial ankle vein. The ankle vein pressure was measured with a strain-gauge transducer with zero reference at the height of the pedal axis of the bicycle. The actual ankle vein pressure could not be assessed during exercise because of the noise due to leg movement. Hence, mean ankle vein pressure was obtained by electronic filtration in this study. Heart rate was derived from a continuously recorded electrocardiogram, and forearm blood pressure was measured with a sphygmomanometer. In the present study, femoral artery blood flow was measured with pulsed Doppler techniques, according to the method of Rådegran (26). The flow velocity profile was recorded with an ultrasonic system (model SSH-160A, Toshiba, Tokyo, Japan) with a transducer array of 7.5 MHz and a pulsed repetition rate of 4 kHz. The recording was made while the subject’s leg was relaxed and extended. The transducer was hand held with a beam angle of 45° with respect to the bloodstream direction by using an angle stabilizer attached to the transducer. The width of the sample volume was set at 1 cm to cover the entire internal diameter of the vessel. Resting hemodynamic variables were measured after a 5-min rest on the upright ergometer.

After the resting measurements were obtained, the subjects first performed upright bicycle exercise for 10 s at a workload of 5 W with a pedaling rate of 60 cycles/min. Mean ankle vein pressure, electrocardiogram, and blood flow velocity profiles of the femoral artery were simultaneously recorded at a paper speed of 25 mm/s during and after exercise (Fig. 1). To measure forearm blood pressure during brief exercise, the cuff of the sphygmomanometer was inflated immediately before exercise and deflated at the end of exercise.

To investigate the relationships of hemodynamic changes to the duration and intensity of exercise, exercise was performed six times with the same measurements but for different durations: 10, 20, 30, 60, 120, and 180 s. Exercise episodes were at 10-min intervals. The exercise workload was set at 5 W with a pedaling rate of 60 cycles/min during the brief exercise within 60 s. During the longer exercise for 120 and 180 s, the workload was set at 5 W for the first minute, followed thereafter by ramp loading of 4 W every 6 s in the normal subjects and 2 W every 6 s in the patients with chronic heart failure. Oxygen uptake was measured with a breath-by-breath respiratory gas-analysis system (model RM-300, Minato, Tokyo, Japan), which was calibrated immediately before each study by a 2-liter calibration syringe and a gas mixture of 15% O₂-5% CO₂-80% N₂.

Ten minutes after completion of the final 180-s exercise, the same intermittent six-grade exercise test was repeated to assess the changes in the cross-sectional area of the femoral artery during exercise. Two-dimensional images of the femoral artery were video digitized at rest and immediately after each exercise episode.

A week after the upright exercise test, the normal subjects performed supine exercise with the same exercise protocol, time intervals, and hemodynamic measurements. The pedal axis of the bicycle was set at the level of 25 cm above the bed during supine exercise. The exercise conditions and hemodynamic measurements, except for the posture, were reproduced as exactly as possible. In patients with chronic heart failure, the supine exercise was not performed because of the difficulty in obtaining informed consent for repetitive exercise in the presence of an indwelling needle in the superficial ankle vein.

Reproducibility of Doppler measurements. The reproducibility of Doppler measurements was tested by repeated exercise tests in 3 of the 10 normal subjects. A week after the supine exercise test, we conducted the intermittent six-grade upright exercise test twice at an interval of 10 min. The blood flow velocity profiles and cross-sectional area of the femoral artery at rest and at each exercise level were obtained.

Data analysis. After all measurements were obtained, the blood flow velocity profiles of the femoral artery were coded and analyzed by an investigator blinded to subject and the sequence of recordings. The blood flow velocity increased immediately after the onset of exercise; however, the exact flow velocity could not be determined during exercise because of the noise due to leg movement (Fig. 1). Because the flow velocity remained increased for several beats after exercise despite the cessation of muscle contraction, three consecutive beats immediately after exercise were employed to estimate
the femoral artery blood flow during exercise; the mean value was used for analysis. Heart rate was determined from R-R interval of the same beats. The drop of mean ankle vein pressure also remained unchanged during this postexercise period. The flow velocity profile was analyzed with a digitizing pad (model KD 4300, Graphic, Tokyo, Japan) interfaced with a computer system (model PC-9801, NEC, Tokyo, Japan). The flow velocity-time integral for an entire cardiac cycle was computed in the selected beats. The flow velocity-time integral was corrected for the beam angle of 45°. Femoral artery blood flow was defined as the product of the corrected flow velocity-time integral, the cross-sectional area of the femoral artery, and the heart rate. The variability of measurements of femoral artery blood flow was tested by repeated analysis of 15 pulsed Doppler recordings of the femoral artery. The SD for intraobserver measurements was 0.006 l/min (n = 15, r = 0.99, y = 0.98x – 0.0001, P < 0.0001), and the SD for interobserver measurements was 0.004 l/min (n = 15, r = 0.99, y = 0.99x – 0.007, P < 0.0001). The overall coefficient of variation for Doppler measurements was 2.5%. Mean forearm blood pressure was calculated from the following standard equation: [diastolic pressure – (systolic pressure – diastolic pressure)/3] (9). Mean leg blood pressure at the level of ankle was obtained by adding the hydrostatic pressure difference between the heart and the pedal axis of the bicycle to the mean forearm blood pressure (27). Lower perfusion pressure was defined as the pressure gradient between the mean leg blood pressure and the mean ankle vein pressure (27). Leg vascular conductance was calculated by dividing the femoral artery blood flow by leg perfusion pressure (4, 14, 22).

Statistical analysis. Data are expressed as means ± SE. Intragroup comparisons were performed by ANOVA with repeated measurements. Intergroup comparisons were performed by using ANOVA and the Scheffé’s test or nonpaired t-test, as appropriate. Correlation between two variables was tested by the linear regression analysis. A P value <0.05 was regarded as statistically significant.

RESULTS

Normal responses to upright exercise. The femoral artery blood flow rapidly increased 5.3-fold (by an average of 1.25 l/min) during 10 s of upright exercise at 5 W (Table 2). This increase was attributed mainly to an increase in the flow velocity-time integral because the cross-sectional area of the femoral artery and heart rate did not significantly increase during this period. Although systemic blood pressure remained unchanged, mean ankle vein pressure rapidly declined from 69 ± 1 to 24 ± 2 mmHg during this period. Hence, the calculated perfusion pressure in the leg increased by 48% despite the absence of a systemic pressor response. Vascular conductance in the leg also rapidly increased 3.6-fold (by an average of 7.6 ml·min⁻¹·mmHg⁻¹) during 10 s of upright exercise. These characteristic hemodynamic changes were observed at each time interval during upright exercise at 5 W (Fig. 2). This level of exercise was comparable to metabolic equivalents (3 METs) because oxygen uptake increased 2.9-fold, from 3.4 ± 0.3 to 9.8 ± 1.2 ml·min⁻¹·kg⁻¹, during this period.

During subsequent ramp exercise, systemic oxygen uptake and femoral artery blood flow progressively
Table 2. Changes in hemodynamic parameters and oxygen uptake during exercise in normal subjects

<table>
<thead>
<tr>
<th></th>
<th>Rest</th>
<th>10 s</th>
<th>20 s</th>
<th>30 s</th>
<th>60 s</th>
<th>120 s</th>
<th>180 s</th>
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<tr>
<td>Upright</td>
<td>76 ± 3</td>
<td>82 ± 4</td>
<td>82 ± 3</td>
<td>86 ± 4</td>
<td>86 ± 4</td>
<td>96 ± 5*</td>
<td>108 ± 6*</td>
</tr>
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<td>70 ± 4†</td>
<td>77 ± 3†</td>
<td>73 ± 5†</td>
<td>76 ± 4†</td>
<td>81 ± 5</td>
<td>92 ± 5*</td>
<td>106 ± 6*</td>
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<tr>
<td>Upright</td>
<td>91 ± 1</td>
<td>90 ± 2</td>
<td>93 ± 3</td>
<td>92 ± 2</td>
<td>93 ± 2</td>
<td>101 ± 2*</td>
<td>103 ± 3*</td>
</tr>
<tr>
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<td>97 ± 2</td>
<td>95 ± 2</td>
<td>96 ± 2</td>
<td>96 ± 4</td>
<td>97 ± 3</td>
<td>103 ± 3</td>
<td>107 ± 3*</td>
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<td>159 ± 3</td>
<td>162 ± 4</td>
<td>161 ± 3</td>
<td>162 ± 3</td>
<td>170 ± 3*</td>
<td>172 ± 4*</td>
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<td>91 ± 4†</td>
<td>92 ± 4†</td>
<td>92 ± 6†</td>
<td>93 ± 5†</td>
<td>99 ± 5†</td>
<td>103 ± 5†</td>
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<td>MAVP, mmHg</td>
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<tr>
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<td>69 ± 1</td>
<td>24 ± 2*</td>
<td>25 ± 3*</td>
<td>25 ± 3*</td>
<td>24 ± 3*</td>
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<td>−3 ± 2†</td>
<td>−4 ± 2†</td>
<td>−4 ± 2†</td>
<td>−4 ± 2†</td>
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<tr>
<td>Upright</td>
<td>92 ± 1</td>
<td>136 ± 2*</td>
<td>138 ± 3*</td>
<td>138 ± 3*</td>
<td>139 ± 3*</td>
<td>148 ± 2*</td>
<td>150 ± 2*</td>
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<tr>
<td>Supine</td>
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<td>98 ± 2†</td>
<td>100 ± 2†</td>
<td>100 ± 4†</td>
<td>101 ± 3†</td>
<td>107 ± 3</td>
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<td>FABF, l/min</td>
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<tr>
<td>Upright</td>
<td>0.29 ± 0.02</td>
<td>1.54 ± 0.11*</td>
<td>1.50 ± 0.12*</td>
<td>1.59 ± 0.12*</td>
<td>1.69 ± 0.12*</td>
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<td>2.85 ± 0.13*</td>
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<td>0.95 ± 0.08* †</td>
<td>0.89 ± 0.05* †</td>
<td>1.09 ± 0.05* †</td>
<td>1.36 ± 0.08* †</td>
<td>2.06 ± 0.18*</td>
<td>2.95 ± 0.32*</td>
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<td>LVC, ml·min⁻¹·mmHg⁻¹</td>
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<tr>
<td>Upright</td>
<td>2.9 ± 0.4</td>
<td>10.5 ± 1.5*</td>
<td>9.9 ± 1.7*</td>
<td>10.4 ± 1.7*</td>
<td>11.2 ± 1.8*</td>
<td>13.5 ± 1.6*</td>
<td>18.5 ± 2.1*</td>
</tr>
<tr>
<td>Supine</td>
<td>5.3 ± 0.3†</td>
<td>9.7 ± 0.6*</td>
<td>8.9 ± 3.0*</td>
<td>10.9 ± 5.3*</td>
<td>13.6 ± 3.4*</td>
<td>19.6 ± 7.3*</td>
<td>27.0 ± 16.8*</td>
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<tr>
<td>VO₂, ml·min⁻¹·kg⁻¹</td>
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</tr>
<tr>
<td>Upright</td>
<td>3.4 ± 0.3</td>
<td>7.8 ± 1.2*</td>
<td>8.7 ± 1.1*</td>
<td>9.7 ± 1.1*</td>
<td>9.8 ± 1.2*</td>
<td>12.7 ± 0.5*</td>
<td>18.3 ± 1.0*</td>
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<tr>
<td>Supine</td>
<td>3.6 ± 0.2</td>
<td>7.1 ± 1.0*</td>
<td>7.9 ± 2.1*</td>
<td>8.9 ± 2.1*</td>
<td>9.0 ± 2.2*</td>
<td>12.5 ± 0.3*</td>
<td>17.5 ± 0.7*</td>
</tr>
<tr>
<td>CSA, mm²</td>
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</tr>
<tr>
<td>Upright</td>
<td>17.2 ± 1.6</td>
<td>17.4 ± 1.4</td>
<td>16.3 ± 1.5</td>
<td>16.3 ± 1.5</td>
<td>16.7 ± 1.5</td>
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<td>16.0 ± 1.6</td>
</tr>
<tr>
<td>Supine</td>
<td>17.2 ± 1.4</td>
<td>16.8 ± 1.2</td>
<td>16.2 ± 1.4</td>
<td>16.0 ± 1.3</td>
<td>16.6 ± 1.3</td>
<td>16.3 ± 1.4</td>
<td>15.7 ± 1.4</td>
</tr>
</tbody>
</table>

Values are means ± SE. HR, heart rate; MBP, mean forearm blood pressure; MLBP, mean leg blood pressure; MAVP, mean ankle vein pressure; LPP, leg perfusion pressure; FABF, femoral artery blood flow; LVC, leg vascular conductance; CSA, cross-sectional area of the femoral artery. *P < 0.05 vs. rest. †P < 0.05 vs. upright.

Increased with increases in systemic blood pressure, heart rate, and vascular conductance in the leg (Fig. 2). In contrast, mean ankle vein pressure showed no further drop.

Normal responses to supine exercise. Resting hemodynamics in the supine posture were characterized by a low (nearly zero) mean ankle vein pressure, increased leg vascular conductance, and increased femoral artery

Fig. 2. Hemodynamic responses during exercise in the upright (○) and supine (■) postures in normal subjects. A: femoral artery blood flow. B: mean ankle vein pressure. C: leg perfusion pressure. D: leg vascular conductance. The exercise mode is shown by the schematic diagram at bottom. Values are means ± SE. †P < 0.05 vs. rest. †P < 0.05 vs. upright exercise.
blood flow compared with those in the upright posture. Because the mean ankle vein pressure was nearly zero even at rest, no further drop was observed during supine exercise (Fig. 2). Therefore, hemodynamic changes during supine exercise were independent of the venous pressure drop in the leg. Because of the absence of the venous pressure drop and systemic pressor response, leg perfusion pressure remained unchanged during supine exercise at 5 W. Femoral artery blood flow increased by an average of only 0.41 l/min during 10 s of exercise at 5 W in the supine posture. The value was equivalent to 33% of that observed in the upright posture. The blood flow response during 10 s of supine exercise could be primarily attributed to vasodilatation in the leg because leg vascular conductance significantly increased by an average of 4.4 ml·min⁻¹·mmHg⁻¹. However, this increase in leg vascular conductance tended to be less than the corresponding 7.6 ml·min⁻¹·mmHg⁻¹ increase during upright exercise (P < 0.1). There was no significant difference in this parameter between the two postures during subsequent exercise at 5 W (Fig. 2). During subsequent ramp exercise, femoral artery blood flow and leg vascular conductance more rapidly increased in the supine posture than in the upright posture; however, the differences were not statistically significant.

Responses to upright exercise in chronic heart failure. There was no significant difference in any hemodynamic measurement at upright rest between the group with heart failure vs. the normal group, although the vascular conductance in the leg tended to decrease in the group with heart failure (P < 0.1; Table 3). However, we observed several characteristic hemodynamic responses to upright exercise at 5 W in the group with heart failure compared with those in the normal group (Fig. 3). First, the increase in femoral artery blood flow was markedly blunted; the blood flow increased only 1.7-fold (by an average of 0.17 l/min) during 10-s exercise at 5 W, in contrast to the 5.3-fold (1.25 l/min) increase seen in the normal group. Second, the drop in mean ankle vein pressure and, therefore, the increase in leg perfusion pressure during exercise were significantly blunted. Third, the increase in vascular conduc-

### Table 3. Changes in hemodynamic parameters and oxygen uptake during upright exercise in patients with chronic heart failure

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Rest</th>
<th>10 s</th>
<th>20 s</th>
<th>30 s</th>
<th>60 s</th>
<th>120 s</th>
<th>180 s</th>
</tr>
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<tbody>
<tr>
<td>HR, beats/min</td>
<td>82 ± 4</td>
<td>85 ± 4</td>
<td>87 ± 4</td>
<td>85 ± 3</td>
<td>89 ± 3*</td>
<td>93 ± 3*</td>
<td>98 ± 4*</td>
</tr>
<tr>
<td>MBP, mmHg</td>
<td>83 ± 4</td>
<td>88 ± 3</td>
<td>84 ± 4</td>
<td>85 ± 3</td>
<td>87 ± 4*</td>
<td>93 ± 4*</td>
<td>96 ± 4*</td>
</tr>
<tr>
<td>MLBP, mmHg</td>
<td>150 ± 5</td>
<td>150 ± 4</td>
<td>152 ± 4</td>
<td>154 ± 5*</td>
<td>160 ± 5*</td>
<td>163 ± 5*</td>
<td></td>
</tr>
<tr>
<td>MAVP, mmHg</td>
<td>67 ± 1</td>
<td>33 ± 2</td>
<td>30 ± 1</td>
<td>31 ± 1</td>
<td>31 ± 1</td>
<td>34 ± 2</td>
<td>38 ± 2</td>
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<td>127 ± 5*</td>
<td>130 ± 5*</td>
<td>130 ± 6*</td>
</tr>
<tr>
<td>FABF, l/min</td>
<td>0.25 ± 0.03</td>
<td>0.42 ± 0.07*</td>
<td>0.55 ± 0.08*</td>
<td>0.60 ± 0.11*</td>
<td>0.61 ± 0.08*</td>
<td>0.86 ± 0.15*</td>
<td>1.00 ± 0.16*</td>
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<tr>
<td>LVC, ml·min⁻¹·mmHg⁻¹</td>
<td>2.5 ± 0.3</td>
<td>2.9 ± 0.4*</td>
<td>3.7 ± 0.7*</td>
<td>3.7 ± 0.8*</td>
<td>4.1 ± 0.6*</td>
<td>5.0 ± 1.1*</td>
<td>6.5 ± 1.0*</td>
</tr>
<tr>
<td>VO₂, ml·min⁻¹·kg⁻¹</td>
<td>3.1 ± 0.2</td>
<td>5.1 ± 0.5*</td>
<td>6.5 ± 0.5*</td>
<td>7.0 ± 0.5*</td>
<td>7.3 ± 0.5*</td>
<td>10.4 ± 0.6*</td>
<td>12.7 ± 0.9*</td>
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<td>CSA, mm²</td>
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<td>16.5 ± 1.2</td>
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<td>15.3 ± 1.3</td>
<td>15.6 ± 1.3</td>
<td>15.1 ± 1.4</td>
<td>14.8 ± 1.4</td>
</tr>
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</table>

Values are means ± SE. *P < 0.05 vs. rest.

Fig. 3. Hemodynamic responses during upright exercise in normal subjects (○) and patients with chronic heart failure (▲). A: femoral artery blood flow. B: mean ankle vein pressure. C: leg perfusion pressure. D: leg vascular conductance. The exercise mode is shown by the schematic diagram at bottom. Values are means ± SE. *P < 0.05 vs. rest. †P < 0.05 vs. upright exercise.
tance in the leg was also markedly attenuated during exercise at 5 W.

Oxygen uptake during upright exercise at 5 W was substantially greater in the normal group than in the heart failure group ($P < 0.1$; Tables 2 and 3). Other hemodynamic variables were not significantly different between groups during this period. In both groups, oxygen uptake rapidly increased during subsequent ramp exercise; however, hemodynamic responses during this period were not compared between the two groups because of the difference in incremental loading.

Reproducibility of Doppler measurements. The Doppler measurements of the femoral artery blood flow during upright exercise were highly reproducible in the two exercise tests performed 2 wk apart (Fig. 4).

**DISCUSSION**

Postural effect on resting hemodynamics. Femoral artery blood flow at rest in the supine posture was significantly greater than that in the upright posture. Because the perfusion pressure (arteriovenous pressure gradient) in the leg was not significantly different between the two postures, the increased blood flow in the supine posture was attributed to increased vascular conductance in the leg (Table 2). In addition to sympathetic deactivation via arterial baroreflex, vasodilation triggered by a low venous pressure (venoarteriolar reflex) may be important in increasing vascular conductance in the leg at rest in the supine posture (18–20).

**Physiological roles of muscle pump-dependent mechanisms.** The increase in leg blood flow seen during light upright exercise at 5 W in normal subjects appeared to be independent of sympathetic-mediated positive inotropic and chronotropic responses of the heart, because it occurred in the absence of increases in systemic blood pressure and heart rate. Several possible mechanisms are responsible: 1) an increase in the leg perfusion pressure due to the muscle pump-dependent leg venous pressure drop; 2) local reflex vasodilatation triggered by the venous pressure drop (venoarteriolar reflex); 3) a nonspecific blood flow response independent of the venous pressure drop in the leg, which is mediated by metabolic vasodilatation (6), endothelial flow-dependent vasodilatation (10), and/or cholinergic sympathetic fibers from the motor cortex (28); and 4) a venous suction effect of muscle contraction (12, 30). However, the suction effect was excluded because we measured femoral artery blood flow immediately after cessation of exercise. Moreover, the nonspecific blood flow response independent of the venous pressure drop could be evaluated from the blood flow response to supine exercise. Femoral artery blood flow increased by an average of 0.41 l/min during 10 s of exercise at 5 W in the supine posture via a vasodilating response even in the absence of the venous pressure drop in the leg (Fig. 2). This increase was equivalent to 33% of the 1.25 l/min increase observed during upright exercise. Thus 67% of the 5.3-fold increase in femoral artery blood flow observed during upright exercise at 5 W could be attributed to the venous pressure drop-dependent mechanisms. Thus our results strongly suggest that the muscle pump-dependent venous pressure drop has a potential to increase leg blood flow at least threefold during upright exercise via the increase in leg perfusion pressure and/or reflex vasodilation in the leg.

The relative roles of two components of the venous pressure drop-dependent mechanism may be addressed from our results. The absolute value of leg blood flow at 10 s during upright exercise was greater by an average of 0.59 l/min than that during supine exercise (Table 2, Fig. 2). This difference was attributed to the increased leg perfusion pressure during upright exercise because vascular conductance was similar between the two postures at this time point. Thus 0.59 l/min (47%) of the 1.25 l/min increase in femoral artery blood flow seen during upright exercise could be explained by the increase in leg perfusion pressure due to venous pressure drop. The residual component (i.e., ~20%) of the blood flow response during 10 s of upright exercise may be explained by the venoarteriolar reflex triggered by venous pressure drop, because the initial response of leg vascular conductance during upright exercise tended to be greater than the nonspecific vasodilating response during supine exercise (7.6 vs. 4.4 ml·min$^{-1}$·mmHg$^{-1}$; $P < 0.1$). Thus it appears that both the increase in perfusion pressure and venoarteriolar reflex contribute to the venous pressure drop-dependent blood flow response during upright exercise.

**Alterations of muscle pump-dependent mechanism in chronic heart failure.** In patients with chronic heart failure, the rapid blood flow response in the leg immediately after the onset of upright exercise was not observed (Fig. 3). Their femoral artery blood flow increased only 1.7-fold (by an average of 0.17 l/min) during 10 s of upright exercise at 5 W through the 40% increase in leg perfusion pressure due to the venous
pressure drop and 1.2-fold increase in vascular conductance in the leg. These values were significantly less than the corresponding values in normal subjects, which were 5.3-fold (1.25 l/min), 48%, and 3.6-fold, respectively. Thus the blunted blood flow response in patients with chronic heart failure was the combined result of a modest reduction in the muscle pump-dependent venous pressure drop and marked attenuation of the vasodilating response in the leg.

In normal subjects, 33% (0.41 l/min) of the 5.3-fold (1.25 l/min) increase in femoral artery blood flow during 10 s of upright exercise was explained by the nonspecific blood flow response (Fig. 2). Because our patients with chronic heart failure did not perform supine exercise, the nonspecific blood flow response could not be quantitatively assessed in these patients. However, their overall increase in femoral artery blood flow during 10 s of upright exercise was equivalent to only 14% of that observed in normal subjects (0.17 vs. 1.25 l/min). This indicates that both the muscle pump-dependent and nonspecific blood flow responses are markedly blunted in patients with chronic heart failure.

The blunted flow response might be a reflection of decreased metabolic demand because oxygen uptake during this level of exercise was substantially less in the heart failure group than in the normal group (Tables 2 and 3), probably because of changes in the skeletal muscle metabolism (1–3, 11, 23, 29). This mechanism is, however, unlikely because in patients with chronic heart failure, the leg vascular conductance gradually increased during exercise (Fig. 3), as is characteristic of metabolic vasodilation (6).

It is unclear from our results why vasodilation in response to exercise is blunted in patients with chronic heart failure. However, it is likely that this abnormality is associated with changes in neural, metabolic, and/or endothelial regulation of vasomotor tone in patients with chronic heart failure (7, 8, 10, 15). It is also unclear in this study why the muscle pump-dependent venous pressure drop in the leg is limited in patients with chronic heart failure. However, there are several possible mechanisms: 1) an elevated central venous pressure, which may impede the pump effect; 2) venous valve insufficiency, which may increase the venous backflow; and 3) skeletal muscle atrophy, which may reduce the power of the muscle pump. Further studies are needed to clarify the mechanisms of the blunted blood flow response in the leg during upright exercise in patients with chronic heart failure.

Study limitations. We evaluated the blood flow response of the femoral artery by using the Doppler techniques. The accuracy of the techniques has been validated (25). However, we evaluated the postural effect on the blood flow response on different days. It was, therefore, possible that the postural effects we observed were due partly to day-by-day variabilities of Doppler measurements. This is, however, unlikely because Doppler measurements were highly reproducible in the two exercise tests performed 2 wk apart (Fig. 4). Bias related to analysis of the flow velocity profiles was also excluded because the investigator was blinded to subjects and the sequence of recordings.

In this study, the blood flow response was evaluated immediately after exercise when the legs were relaxed. Because the blood flow in exercising legs is phasically decreased at the contraction phase (34), values we obtained may overestimate the actual blood flow response. Our data may be interpreted that the venous pressure drop-dependent mechanism has a potential to increase blood flow in the legs more than threefold at the noncontraction phase during cycling.

In this study, the mean ankle vein pressure declined by an average of 45 mmHg during upright exercise. However, because most of the skeletal muscles employed in cycling are located far above the ankle, the drop of hydrostatic pressure assessed in the ankle vein may overestimate the actual venous pressure drop in exercising muscles. Indeed, a previous study reported, using a retrograde catheter technique in a man, that the venous pressure at the popliteal level declined by only 20 mmHg during running (31). Thus the actual venous pressure drop in exercising muscles may be far less than that in the ankle vein. However, we clearly demonstrated in this study that the blood flow response in the leg during upright exercise largely depended on the venous pressure drop. The effect of venous pressure drop on leg blood flow may be more potent than that estimated from the pressure drop in the ankle vein.

The cross-sectional area of the femoral artery did not show a definite change throughout exercise in this study. Hambrecht et al. (10) also reported, using angiographic techniques, that the femoral artery diameter increased by only 0.64 ± 0.11 mm when the femoral artery blood flow was increased approximately threefold with administration of acetylcholine. The flow-dependent vasodilation of the femoral artery during exercise may be too small to be detected with the ultrasonic techniques. However, it is unlikely that this minor measurement error influenced our results.

In the present study, cardiac output was not measured. An increase in regional blood flow should be followed by an instantaneous increase in cardiac output to prevent circulatory collapse. However, we observed no significant increase in heart rate and blood pressure during light exercise at 5 W in the normal subjects, despite a marked increase in leg blood flow. It was most plausible that the Frank-Starling mechanism operated in response to an increase in venous return (21, 35).

Clinical implications. Because we only assessed the low-intensity bicycle exercise of short duration, the functional role of the muscle pump-dependent blood flow response in exercise performance could not be directly addressed in this study. However, when the level of exercise was assessed with systemic oxygen uptake, the upright bicycle exercise at 5 W was comparable to 3 METs. Moreover, walking at ordinary speeds is reportedly equivalent to 3 METs. Thus the muscle pump-dependent self-perfusion mechanism of exercising legs may be designed to allow for walking without recruitment of sympathetic-mediated cardio-
vascular reserves, although further studies are needed to test this hypothesis.

In the present study, we demonstrated that the leg blood flow response during upright exercise is markedly blunted in patients with chronic heart failure. We further suggested that this abnormality is the combined result of a modest reduction in the muscle pump-dependent venous pressure drop and marked attenuation of the vaso-
dilating responses in the leg. The blunted blood flow response may explain why patients with chronic heart failure walk slowly (5). Moreover, the blunted blood flow response may cause compensatory activation of sympa-
thetic nerves even during light exercise such as walking, imposing an additional load on the failing heart. Indeed, it has been reported that the increase in plasma norepi-
nephrine concentration while walking is much greater in patients with chronic heart failure than in normal sub-
jects (24). Thus, as well as improvements of nonspecific vasodilating responses, an improvement in the muscle pump-dependent blood flow response may be a novel therapeutic strategy for chronic heart failure, which al-
ows for an improvement of the quality of life with a cardioprotective effect.

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