A Comparison of Regional Blood Flow and Oxygen Utilization During Dynamic Forearm Exercise in Normal Subjects and Patients with Congestive Heart Failure

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SUMMARY

Patients with severe congestive heart failure (CHF) have been found to have a diminished response to the metabolic arteriolar dilator stimulus of ischemia. In order to evaluate a more physiologic stimulus and the possible metabolic consequences of this vascular abnormality, 22 normal subjects (N) and seven patients with severe CHF performed rhythmic forearm exercise by squeezing a rubber bulb to 25, 50, or 100 mm Hg for 5 sec, four times/min, for 5 min. During the last half of the 10 sec relaxation phases, forearm blood flow (FBF) was measured plethysmographically. Not only was FBF reduced at rest in CHF (CHF: 2.00 ± 0.31; N: 3.10 ± 0.27 ml/min · 100 ml, P < 0.02) but it was reduced at each level of exercise as well (CHF: 4.05 ± 0.71, 5.57 ± 0.71, 6.68 ± 3.09; N: 7.10 ± 0.76, 11.15 ± 1.24, 20.32 ± 1.93 ml/min · 100 ml, P < 0.01). Forearm oxygen extraction, calculated from brachial venous and systemic arterial blood, was consistently increased in CHF and was sufficient to maintain a normal forearm oxygen consumption at rest (CHF: 0.14 ± 0.04; N: 0.12 ± 0.01 ml O₂/min · 100 ml, P < 0.5). During exercise the calculated index of oxygen consumption was reduced at all levels of exercise (CHF: 0.30 ± 0.04, 0.48 ± 0.09, 0.54 ± 0.14; N: 0.51 ± 0.05, 0.89 ± 0.08, 1.63 ± 0.13 ml O₂/min · 100 ml, P < 0.01). These differences persisted despite alpha-adrenergic blockade with phentolamine and suppression of skin flow in N by epinephrine iontophoresis. Therefore, at comparable levels of dynamic forearm exercise patients with CHF have an inadequate arteriolar dilation and their augmented oxygen extraction is not sufficient to prevent them from shifting more completely to anaerobic metabolism.

Additional Indexing Words:
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During dynamic exercise patients with congestive heart failure (CHF) appear to have an exaggerated sympathoadrenal response which results in a decreased perfusion of regional circulations that have low metabolic requirements and adequate alpha-adrenergic receptor sites. A similar increase in alpha-adrenergic tone also occurs in exercising skeletal muscle. However, these constrictor impulses are offset by the local accumulation of metabolites and a vasodilation occurs. Therefore, in exercising muscle, vascular resistance falls and oxygen delivery increases. It is important to note that patients with CHF demonstrate a reduced metabolic arteriolar dilator response following restoration of flow to an ischemic limb (reactive hyperemia) which is considerably reduced when compared with that of normal subjects. This relative arteriolar stiffness has been postulated to be a possible protective mechanism for

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the heart failure patient which might serve to maintain an adequate systemic blood pressure in the face of a limited cardiac output response to dynamic exercise. Although this abnormality might be partially advantageous, it is not known whether any adverse metabolic consequences result from this reduced dilator capacity. The purpose of these studies was to evaluate total forearm blood flow (FFB), oxygen extraction, and oxygen consumption during steady-state graded dynamic forearm exercise.

Material and Methods

Studies were performed in seven patients with CHF (ages 41 to 67 yrs) and 22 normal volunteers (ages 23 to 59 yrs). All patients had rheumatic etiologies for their heart failure, were in functional class III-IV (New York Heart Association classification), and had evidence of right-sided decompensation and fluid retention. The normal subjects were inmate volunteers from the California Medical Facility and patients admitted to the Sacramento Medical Center for cardiac evaluation who were found to have no heart disease. The protocol of these studies was evaluated and approved by the Chancellor’s Advisory Committee for Research Involving Physiological or Clinical Studies of Human Subjects. The research proposal was also evaluated and approved by a comparable committee of the Solano Institute for Medical and Psychiatric Research, a noninstitutional group supervising all research on inmate volunteers. Informed consent was obtained in all cases.

Forearm blood flow was measured by the venous occlusion technique with a single strand mercury-in-rubber strain gauge plethysmograph placed at mid forearm in the non-dominant extremity using a Parks bridge. A collection pressure of 30 mm Hg was used. The forearm was elevated above heart level and the hand was occluded from the circulation by inflation of a wrist cuff to suprasystolic pressures at least one minute prior to any determination of FBF. Arterial pressure was measured directly with a Statham P23db pressure transducer by means of a needle placed in the contralateral brachial or radial artery which was also used for the sampling of arterial blood. A 19 gauge Deseret Intracath was inserted in the antecubital vein of the extremity to be exercised and the catheter passed percutaneously to the midbrachial vein for the sampling of mixed forearm venous blood. Oxygen saturation and hemoglobin were determined with a model 182 IL CoOximeter and oxygen content was calculated. Recordings were made with a Hewlett Packard model 4560 optical recorder with a rapid developer.

All subjects were studied in the basal postabsorptive state and were allowed to rest for 15 to 30 min following instrumentation. Following the determination of six to ten control measurements of FBF, the subjects performed rhythmic grip exercise by squeezing a pneumatic bag which was inflated to a basal pressure of 50 mm Hg prior to exercise. The subjects varied the intensity of their grip to increase the pressure in the manometer by 25, 50, or 100 mm Hg. The grips were held for 5 sec and were repeated four times/min for 5 min. Blood flow was measured during the last 5 sec of the 10 sec rest period between grips. Venous and arterial blood samples were drawn in duplicate prior to the beginning of exercise and during each minute of the exercise period. Oxygen extraction was calculated as the arterial-venous difference (vols %) × 100 divided by the averaged arterial oxygen content. In all instances, venous oxygen content varied little over the last 3 min of exercise, and an average value was therefore taken for calculations. Forearm oxygen consumption (ml O₂/min · 100 ml) during the basal state was calculated as the arterial-venous oxygen difference (vols %) × FBF (ml/min · 100 ml) divided by 100. During exercise an index of oxygen consumption was similarly calculated during each minute of exercise and averaged after a steady-state was achieved between 2 and 5 min of exercise. It is acknowledged that FBF measured in this manner during exercise is not true mean FBF. Muscle blood flow has a regular phasic pattern during exercise and is reduced during the period of time when the muscle develops tension. Previously, it was determined that blood flow calculated in this manner was proportionally related to mean integrated blood flow averaged throughout the exercise period as measured by a flowmeter placed on the brachial artery at the time of cardiac catheterization. A steady-state flow pattern develops after 2 min of exercise whether measured with flowmeter or plethysmograph and was highly reproducible. Importantly, the relationship between mean integrated flowmeter blood flow and average plethysmographic blood flow was linear and the function did not vary with the severity of exercise; plethysmographic flow was always 1.7 times higher. Thus, the systematic error that was introduced in the calculation of forearm oxygen consumption was the same for both high and low exercise flows.

In 12 normal subjects and six subjects with CHF, exercise was repeated at the 50 mm Hg level following alpha-adrenergic blockade of the forearm induced by the intra-arterial injection of 2 mg of phentolamine. This dose markedly attenuates the forearm vascular response to ice applied to the forehead. In four normal subjects exercise was repeated at the 100 mm Hg level following epinephrine iontophoresis of the forearm as described previously. This procedure effectively reduces skin blood flow to indeterminable levels for a period of one to two hours. In six normal subjects cardiac output was determined by the dye dilution technique and systemic oxygen consumption measured during an exercise period in which the subjects gripped the hand dynamometer and increased the pressure by 150 mm Hg.

Results

Forearm blood flow during the basal state was 3.10 ± 0.27 ml/min · 100 cc in the normal subjects (N) and 2.00 ± 0.31 ml/min · 100 cc in the patients with CHF (P < 0.02). During each of the three levels of exercise, the normal subjects increased their mean FBF during the steady-state to 7.10 ± 0.76, 11.15 ± 1.24 and 20.32 ± 1.93 ml/min · 100 ml respectively (P < 0.01) (fig. 1). Although patients with CHF also increased their FBF during each of the three levels of exercise, it was considerably less than that achieved by the normal subjects at each level (4.05 ± 0.43, P < 0.01; 5.57 ± 0.71, P < 0.01; 6.68 ± 3.09 ml/min · 100 ml, P < 0.01). Forearm oxygen extraction likewise was considerably greater in the heart failure subjects than in the normal subjects at
rest (N: 34.86 ± 2.45. CHF: 50.20 ± 5.99%, P < 0.05) and during each level of exercise (N: 43.08 ± 2.64; 47.21 ± 1.93; 48.31 ± 2.08. CHF: 53.21 ± 4.92, P < 0.05; 59.27 ± 4.52, P < 0.05; 55.24 ± 0.85%, P < 0.01) (fig. 2). Forearm oxygen consumption at rest was similar in the two groups (N: 0.12 ± 0.01. CHF: 0.14 ± 0.04 ml O2/min · 100 ml, P < 0.5). During exercise, however, the calculated forearm oxygen consumption was considerably reduced at each level of exertion (N: 0.51 ± 0.05; 0.89 ± 0.08; 1.63 ± 0.13. CHF: 0.30 ± 0.04, P < 0.01; 0.48 ± 0.09, P < 0.01; 0.54 ± 0.14 ml O2/min · 100 ml, P < 0.01) (fig. 3).

Following intra-arterial phentolamine basal FBF significantly increased (N: 9.47 ± 1.08. CHF: 5.76 ± 0.77 ml/min · 100 ml, P < 0.02) as did oxygen consumption (N: 0.42 ± 0.07. CHF: 0.18 ± 0.02 ml O2/min · 100 ml, P < 0.01). During the middle level of exercise, however, the differences persisted between the two groups (FBF — N: 13.59 ± 1.47. CHF: 7.88 ± 1.05 ml/min · 100 ml, P < 0.01. Forearm oxygen consumption —N: 0.99 ± 0.10. CHF: 0.49 ± 0.08 ml O2/ml · 100 ml, P < 0.01) (fig. 4). Epinephrine iontophoresis in the normal subjects partially attenuated the blood flow response at the highest exercise level (16.88 ± 0.90 ml/min · 100 ml) and also reduced the calculated oxygen consumption (1.22 ± 0.21 ml O2/min · 100 ml); however, these values were still significantly greater than those of the heart failure subjects (P < 0.02) (fig. 5). When a separate group of normal subjects performed exercise at a level higher than that used for the above comparisons between groups (150 mm Hg level), they minimally increased their cardiac output from 6170 ± 3.81 to 6848 ± 4.19 cc/min (P > 0.05) and their systemic oxygen consumption from 343 ± 58 to 376 ± 52 cc O2/min (P > 0.1), values which were not significantly different from control.
Discussion

In the present study it was demonstrated that with rhythmic grip exercise of three different intensities, the patients with heart failure did not increase their FBF to the same extent as normal subjects (fig. 1). These findings are similar to previous results from this laboratory which employed the reactive hyperemia response to evaluate metabolically induced changes in skeletal muscle blood flow. This study is also in agreement with those of Epstein et al. and Vatner et al. who demonstrated that systemic vascular resistance and limb vascular resistance did not decrease normally in patients or animals with CHF during exercise. In part, their results could be explained by the augmented sympathoadrenal response that is seen with exercise in heart failure subjects resulting in a marked increase in resistance in the cutaneous, renal, and splanchnic vascular beds. It should be noted that not all investigators have demonstrated a reduced arteriolar dilator capacity in heart failure. Utilizing an isolated gracilis muscle preparation, Mayer et al. found a normal dilator response to papaverine in an animal model of CHF. The reason for this discrepancy is unclear; however, we have found that the abnormal vascular dilator response can only be seen in patients with chronic severe symptomatic CHF and is not demonstrable with minimal or moderate cardiac disease. Despite the significant pump failure which was present in these patients, the factors which determined FBF during the rhythmic grip exercise employed in this study were not cardiac in origin but rather regional. When normal subjects performed exercise at one grade above the most strenuous level used for intergroup comparisons, there was a small and insignificant mean increase in cardiac output of 668 ml/min and systemic oxygen consumption of 33 ml O₂/min. It is likely that these small increases in cardiac output during forearm exercise could have been attained even by patients with considerable impairment in ventricular function.

It is recognized that the plethysmograph may not actually be measuring true averaged blood flow during exercise. However, it has previously been shown in this laboratory that there is a predictably systematic error produced when FBF is measured during exercise by this technique. It should be noted that this error is similar during both high intensity exercise and lower level exertion. In these studies it was demonstrated that a steady-state pattern of blood flow develops after the second minute of exercise, and it could be reliably and reproducibly quantitated with both plethysmograph and flowmeter. If static exercise were evaluated rather than dynamic exercise, it might have been easier to measure flow by the plethysmographic technique; however, dynamic exercise was chosen because it more nearly simulates the physiologic stress encountered clinically by the cardiac patient.

A second finding in this study was an increased oxygen extraction at rest and during each level of exercise in the heart failure patients (fig. 2). This is consistent with the widened arterial-venous oxygen difference and the marked depression in pulmonary oxygen...
saturation seen when heart failure patients perform maximal upright exercise. Part of the increased oxygen extraction in the heart failure subjects could be explained if there were a longer than normal transit time of blood through the metabolically active muscles. However, it is possible that transit time may not be prolonged if the reduced flow were caused by a smaller cross-sectional area of the vascular tree or if parallel circuits were totally constricted. We have postulated that the observed inadequate increase in flow is secondary to an increased arteriolar stiffness seen in heart failure and may be secondary to increased vascular sodium content. This could also possibly be related to the increased tissue pressure seen in edematous states which would have a major effect to compress capillaries at their distal end. If the inadequate increase in flow led to forearm tissue hypoxia the resultant acidosis might be expected to shift the hemoglobin oxygen dissociation curve more to the right and enhance oxygen transfer to metabolically active tissues. Similarly, the higher red blood cell 2,3-diphosphoglyceric acid (DPG) levels seen in heart failure would also be expected to increase red cell P50 and facilitate oxygen transfer from hemoglobin to the exercising muscle.

Since oxygen extraction was higher in heart failure while FBF was abnormally low, it is possible that forearm oxygen consumption might be normal. This is true when the forearm was in a nonexercising resting state (fig. 3). This indicates that the increased extraction of oxygen was sufficient to provide for the basal metabolic needs despite a lower FBF. In contrast to the resting state, the calculated oxygen consumption during each level of exercise was significantly reduced when the heart failure patients were compared with the normal subjects (fig. 3). This was the most important finding in this study and one that deserves careful consideration of possible causes and consequences.

One possible explanation for the abnormally low forearm oxygen consumption during exercise is that the heart failure subjects may have had an exaggerated sympathoadrenal response to regional exercise. A functional sympatholysis normally occurs during strenuous exercise in the metabolically active vascular bed. Although this would be expected to significantly negate the effects of increased alpha-adrenergic tone with maximum exercise with the submaximal levels utilized here, the metabolic factors might compete less effectively with the neurogenic determinants of regional muscle blood flow. In order to evaluate this further, representatives of both groups of subjects repeated the middle level of exercise following alpha-adrenergic blockade of the forearm with phentolamine. The amount of drug that was used provides for complete blockade of the constrictor effect of circulating catecholamines and markedly attenuates the cold pressor response. Despite adequate alpha-adrenergic blockade which tended to enhance blood flow in both groups during exercise, forearm oxygen consumption was still significantly lower in the patients with heart failure (fig. 4).

In order to fully accept the conclusion that forearm oxygen consumption during dynamic exercise fails to rise normally in heart failure, it must be demonstrated that possible technical problems involved in venous blood sample collection and metabolic blood flow estimation were adequately controlled. Since normal subjects tend to dilate their cutaneous vessels late during an exercise period to dissipate heat, it is possible that oxygen-rich cutaneous blood may have been shunted to deep venous sampling sites. Although the valves of the communicating veins might favor such a redistribution of effluent blood, Wahren has shown virtual complete separation of forearm cutaneous and muscle circulations during strenuous forearm exercise. Based on known values for systemic and forearm muscle mass, if one assumed that an individual were to use all body muscle groups equally at the 100 mm Hg level of exercise and that the forearm VO2 during exercise actually reflected the true oxygen consumption of the forearm muscle, normal individuals would be expected to utilize about 30 cc O2/kg/min and heart failure subjects 11 cc O2/kg/min. Thus, the higher level of forearm exercise was in fact strenuous and separation of the circulations should have occurred. To further evaluate this problem selective catheterization of the median cubital vein, which drains only forearm muscle, might have been done. Unfortunately, in our heart failure patients this was technically impossible to do. Although oxygen-rich cutaneous blood reaching deep venous channels might have led to an underestimation of forearm oxygen consumption during exercise, an isolated cutaneous vasodilation per se could have led to a significant overestimation of forearm oxygen consumption in normal subjects.

To completely resolve this question and determine whether or not the variable nature of the cutaneous circulation in normal subjects during exercise had a significant effect on the above observations, the technique of epinephrine iontophoresis was employed. Normal subjects were allowed to exercise at the higher level of exertion (100 mm Hg) before and following epinephrine iontophoresis, which effectively suppresses skin blood flow. The differences in forearm oxygen consumption persisted despite suppression of cutaneous blood flow in the normal subjects, thereby validating the conclusion that the lower forearm oxygen consumption seen in heart failure during exercise is not a function of superficial and
deep venous admixture, or a function of a cutaneous hyperemia, but is in fact a true difference (fig. 5).

One of the reasons for reduced oxygen consumption in CHF might be simply that oxygen availability is reduced. In order to compensate, the patient with heart failure might switch more completely to anaerobic metabolism than the normal subject. Another possibility is that with chronic hypoxia there may have been changes induced in the cytoplasmic glycolytic enzymes which facilitated the utilization of the Emden-Meyerhof pathway for production of high energy phosphates. Both of these mechanisms might be operative to explain or be the consequence of reduced regional oxygen consumption. Either would result in a systemic lactic acidemia. This is a common finding in cases of CHF and accounts in part for the increased oxygen debt seen when such patients exercise. Of interest is that the marked cutaneous vasoconstriction seen during exercise in the heart failure patients might result in impaired thermal regulation, induce a temperature elevation, and might explain why the alactic portion of the oxygen debt is increased as well. Another possibility is that with chronic hypoxia there may have been changes induced in the cytoplasmic glycolytic enzymes which facilitated the utilization of the Emden-Meyerhof pathway for production of high energy phosphates. Both of these mechanisms might be operative to explain or be the consequence of reduced regional oxygen consumption. Either would result in a systemic lactic acidemia. This is a common finding in cases of CHF and accounts in part for the increased oxygen debt seen when such patients exercise. Of interest is that the marked cutaneous vasoconstriction seen during exercise in the heart failure patients might result in impaired thermal regulation, induce a temperature elevation, and might explain why the alactic portion of the oxygen debt is increased as well.

In summary, it would appear that patients with CHF do not adequately dilate their forearm arterioles when they exercise. This suggests that they would sacrifice adequate tissue perfusion to maintain blood pressure during systemic dynamic exercise. The metabolic cost of this abnormality appears to be significant. There may be a prolongation of repayment of an increased oxygen debt and an increased level of circulating lactate. Normally, a considerable postexercise active hyperemia is seen in normal subjects. This may not be necessary to completely repay the oxygen debt in the active muscle; however, it probably plays a role in reduction of recovery time. In previous studies it was shown that patients with heart failure have a reduced postexercise hyperemia. Thus, they would be expected to be fatigued longer than normal patients following simple exercise. Such symptoms are the hallmark of the low cardiac output syndrome.

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