Differences in skeletal muscle between men and women with chronic heart failure

BRIAN D DUSCHA,1 BRIAN H ANNEX,1 STEVEN J KETEYIAN,3 HOWARD J. GREEN,4 MARTIN J. SULLIVAN,1 GREGORY P. SAMSA,1 CLINTON A. BRAWNER,3 FRED H. SCHACHAT,2 AND WILLIAM E. KRAUS1,4

1Division of Cardiology, Department of Medicine, and 2Department of Cell Biology, Duke University Medical Center, Durham, North Carolina 27710; 3Henry Ford Heart and Vascular Institute, Detroit, Michigan 48202-3006; and 4Department of Kinesiology, University of Waterloo, Waterloo, Ontario, Canada N2L 3G1

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Duscha, Brian. D, Brian H. Annex, Steven J. Ketye-ian, Howard J. Green, Martin J. Sullivan, Gregory P. Samsa, Clinton A. Brawner, Fred H. Schachat, and William E. Kraus. Differences in skeletal muscle between men and women with chronic heart failure. J Appl Physiol 90: 280–286, 2001.—Men with chronic heart failure (CHF) have alterations in their skeletal muscle that are partially responsible for a decreased exercise tolerance. The purpose of this study was to investigate whether skeletal muscle alterations in women with CHF are similar to those observed in men and if these alterations are related to exercise intolerance. Twenty-five men and thirteen women with CHF performed a maximal exercise test for evaluation of peak oxygen consumption (V˙O2) and resting left ventricular ejection fraction, after which a biopsy of the vastus lateralis was performed. Twenty-one normal subjects (11 women, 10 men) were also studied. The relationship between muscle markers and peak V˙O2 was consistent for CHF men and women. When controlling for gender, analysis showed that oxidative enzymes and capillary density are the best predictors of peak V˙O2. These results indicate that aerobically matched CHF men and women have no differences in skeletal muscle biochemistry and histology. However, when CHF groups were separated by peak exercise capacity of 4.5 metabolic equivalents (METs), CHF men with peak V˙O2 >4.5 METs had increased citrate synthase and 3-hydroxyacyl-CoA dehydrogenase compared with CHF men with peak V˙O2 ≤4.5 METs. CHF men with a lower peak V˙O2 had increased capillary density compared with men with higher peak V˙O2. These observations were not reproduced in CHF women. This suggests that differences may exist in how skeletal muscle adapts to decreasing peak V˙O2 in patients with CHF.

oxygen consumption; exercise; capillary density

SEVERAL LARGE TRIALS HAVE shown the prevalence of chronic heart failure (CHF) is higher in women than men (13, 23). In addition, a number of epidemiological studies have identified discordant survival rates between male and female patients with CHF. Both the Framingham Study (11) and National Health and Nu-

trition Examination Survey (18) revealed lower mortality for women compared with men after the initial diagnosis of CHF. The Framingham study revealed increased survival at 1, 2, 5, and 10 yr in women compared with men. The improved survival in women is more striking when viewed in the context that women were older at diagnosis. The improved survival in women remained after controlling for age and etiology. The recently completed Flolan International Randomized Survival Trial also demonstrated that women with advanced CHF experience better survival than men (1).

Interestingly, women present with more advanced symptoms of CHF (dyspnea, leg fatigue) compared with men, despite better systolic function (9). Although it is unknown whether the increased symptoms observed in women with CHF are a result of age and comorbid illnesses (diabetes, hypertension) or have a physiological underlying etiology unique to gender, it is reasonable to hypothesize that gender differences in functional capacity may play a role. Several studies have shown peak oxygen consumption (V˙O2) to be a strong predictor of mortality in patients with CHF, in addition to its use for ascertaining suitability for transplantation (12, 15, 16). Numerous studies in the past 15 yr have attempted to explain exercise intolerance in CHF by examining both peripheral alterations and central hemodynamics. These studies have found skeletal muscle alterations in CHF patients to be partially responsible for the exercise intolerance observed in this population (4, 7, 21, 22). Although cardiac output is related to aerobic capacity, resting ejection fraction has consistently been observed to be unrelated to exercise capacity or symptom status in CHF (6, 10, 24). Furthermore, our laboratory has observed an inverse relationship between capillary density and peak V˙O2 in men with CHF (5). Most of these studies have used predominantly male CHF patients.

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Address for reprint requests and other correspondence: B. D. Duscha, Duke Univ. Medical Center, Box 3022, Duke Center for Living, Durham, NC 27710 (E-mail: dusch001@mc.duke.edu).

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Although outcome-driven research is discovering many gender-specific differences in morbidity and mortality in CHF between genders, very few studies have examined pathophysiological differences between men and women with CHF and no study has compared the skeletal muscle of men and women with CHF with that of normal men and women. More importantly, no study has investigated whether potential skeletal muscle differences might explain differences in functional capacity between genders in CHF. Therefore, the purposes of this study were 1) to examine whether biochemical or histological differences in skeletal muscle exist between men and women with CHF when matching for peak \( \text{VO}_2 \), age, and pharmacological therapy; 2) to determine whether skeletal muscle capillary density alterations relative to peak \( \text{VO}_2 \) previously observed (5) in CHF men are reproduced in CHF women; and 3) to determine whether any skeletal muscle markers are predictors of functional capacity (as measured by peak \( \text{VO}_2 \)) after controlling for any effects of gender in CHF patients.

**METHODS**

**Patient population.** Twenty-five male patients with CHF (16 from Duke Medical Center and 9 from Henry Ford Hospital) with New York Heart Association functional class II–IV CHF due to left ventricular systolic dysfunction and 13 female patients with CHF (from Duke Medical Center) participated in this study. Additional breakdown by aerobic capacities of patients with CHF was as follows: men >4.5 metabolic equivalents (METs); \( n = 10 \), men <4.5 METs; \( n = 15 \), women >4.5 METs; \( n = 3 \), women <4.5; \( n = 10 \). Groups were selected so that the overall distribution of peak \( \text{VO}_2 \), age, and pharmacological therapy were similar for men and women. All patients with CHF were on a stable medical regimen for a minimal of 3 mo before study. All patients with CHF were symptom limited by dyspnea and/or leg fatigue. All subjects were free of claudication, rales, and peripheral bruits. Exclusion criteria included insulin-dependent diabetes, clinically significant chronic obstructive pulmonary disease, and peripheral vascular disease. All patients with CHF were sedentary and not involved in any form of regular physical activity. An additional 21 normal subjects (10 men and 11 women) from Duke Medical Center volunteered to participate in this study. There was no indication of cardiovascular disease in the normal subjects by either history or physical examination, and none exhibited symptoms of ischemic heart disease. Normal subjects were on no medications. All normal subjects were sedentary and not involved in any type of regular aerobic exercise.

**Study protocol.** All studies were performed under research protocols approved by the Institutional Review Boards of the Duke University, the Durham Veterans Affairs Medical Centers, and Henry Ford Hospital. Each subject was informed of testing protocols and the potential risks and benefits of participation. All subjects provided written consent before participation.

**Exercise testing.** All subjects underwent graded upright bicycle exercise to a symptom-limited maximum on a cycle ergometer [Fitron, Lumex (Ronkonkoma, NY) or Monark (Varberg, Sweden)] with a 12-lead electrocardiogram as previously described in our laboratory (21). The workload began at 150 kpm/min (25 W) and advanced in 3-min stages of 150 kpm/min. Equilibrium radionuclide angiograms were obtained for Duke University subjects at rest using a low-energy, mobile gamma camera. Expired gases were analyzed continuously using a SensorMedics 4400 unit or SensorMedics Horizon II (Yorba Linda, CA). Henry Ford patients with CHF were included if left ventricular ejection fraction was <35% via equilibrium radionuclide angiograms or catheterization within 6 mo of study or echocardiogram showing left ventricular ejection fraction <30%.

**Muscle biopsies.** Biopsy samples were obtained from the vastus lateralis using a modified Bergstrom needle technique (2). Biopsy sites were anesthetized with a 2% lidocaine solution, and 0.5-cm incisions were made through the skin and fascia lata. The needle was consistently inserted to a depth of 40–60 mm. All samples were snap frozen at −80°C. Histology samples were mounted, in cross section, in optimal cutting temperature compound (Miles Pharmaceutical, West Haven, CT) beds, and snap frozen at −80°C.

**Histological and biochemical analysis.** Vascular density, expressed as endothelial cells per muscle fiber, was determined by examining the total number of endothelial cells relative to the total number of muscle fibers. Endothelial cells were identified in histological sections using immunohistochemical techniques with an established endothelial cell-specific monoclonal antibody in methods previously described (5). Myosin heavy chain (MHC) analysis is reported as relative percentages of each isoform as described previously (5). Enzyme assays were performed fluorometrically using an end-point assay as previously described (8, 17).

**Statistical analysis.** All data were screened for normality and outlying data points. No data were excluded based on this analysis. Statistical analysis was consistent of three components: 1) Student’s t-test, 2) analysis of covariance (ANCOVA), and 3) stepwise linear regression. The rationale for each analysis is cited below.

The first set of analyses compared men and women according to various skeletal muscle characteristics. The continuous variables of enzyme activity, capillary density, and MHC isoforms were compared using t-tests.

To examine the relationship between the indicators of enzyme activity, capillary density, and MHC isoforms with peak \( \text{VO}_2 \) while controlling for gender, we fit two ANCOVA models. The first ANCOVA model included gender, the indicator in question, and a gender-by-indicator interaction (i.e., allowing for heterogeneous slopes). We used a partial \( F \)-test to assess the statistical significance of this interaction term (i.e., assessing whether the relationship between the indicator and peak \( \text{VO}_2 \) was mediated by gender). If the interaction term failed to attain statistical significance, we fit a second ANCOVA model containing only main effects for gender and the indicator. Assessing the statistical significance of the indicator in question (i.e., again using a partial \( F \)-test) allowed us to determine whether the indicator was associated with peak \( \text{VO}_2 \), after accounting for the effect of gender. Each of the above analyses was repeated for each of the eight potential indicators.

To determine which indicators were the strongest predictors of peak \( \text{VO}_2 \), as well as how many indicators are independent predictors of peak \( \text{VO}_2 \), we implemented a forward stepwise variable-selection procedure. All models included gender. Variables were added in indicator-specific groups (i.e., 1 group including capillary density and a gender-by-capillary density interaction), and the contribution of each group was assessed using a multiple partial \( F \)-test. The forward stepwise selection algorithm concluded when the contribution of the most significant group of candidate variables failed to attain statistical significance (\( P > 0.05 \)). It should be noted that our sample size is small to moderate, implying that some of the above tests will have low power.
and that negative results should not be interpreted as definitive. This is particularly true for tests for interaction, as well as the steps in the forward stepwise selection algorithm. Any results should be subsequently validated using additional subjects. A $P$ value $< 0.05$ was considered significant in all analysis.

**RESULTS**

Table 1 contains clinical characteristics for the normal subjects and patients with CHF. There were no significant differences in peak $V_{\text{O}_2}$, age, pharmacological therapy, or body mass index between men and women with CHF, thus indicating that the groups were well matched for these clinical characteristics.

Table 2 provides a summary of relative content of MHC type I, IIa, and IIx between all subjects. Although women demonstrated a trend toward an increased oxidative phenotype (type I myosin content), no statistical differences were found between genders for either patients with CHF or normals. Relative percentage for MHC IIx was increased in men with CHF compared with normal men ($29.2 \pm 3.0\%$ vs. $19.5 \pm 3.0\%$; $P < 0.05$).

Table 3 contains enzyme activities that represent three separate energy pathways: glycolysis [phosphofructokinase (PFK), lactate dehydrogenase (LDH)], citric acid cycle [citrate synthase (CS)], and $\beta$-oxidation of fatty acids [3-hydroxyacyl-CoA dehydrogenase (3-HAD)]. The glycolytic enzyme LDH ($P < 0.05$) was increased in men with CHF compared with women with CHF. LDH in men with CHF was also increased compared with normal men ($P < 0.05$). The aerobic enzyme 3-HAD was increased in both normal men and women compared with their male and female CHF counterparts ($P < 0.002$).

An example of vascular density staining is shown in Fig. 1. Overall, the number of endothelial cells per muscle fiber was $1.42 \pm 0.05$ for CHF men and vs. $1.39 \pm 0.08$ (not significant) in CHF women. Normal men demonstrated increased capillary density vs. normal women ($1.77 \pm 0.12$ vs. $1.14 \pm 0.02$; $P = 0.001$). Normal men had increased capillary density vs. men with CHF ($P < 0.03$). In surprising contrast, women with CHF had increased values vs. normal women ($P < 0.02$). There was no difference in fiber area or diameter between any of the groups.

We were interested to see whether the inverse relationship between aerobic capacity and capillary density, previously observed for CHF men (5), would hold also in CHF women. Consistent with previous work, Fig. 2 illustrates that CHF men with peak $V_{\text{O}_2} < 4.5$ METs had increased capillary density vs. CHF men with peak $V_{\text{O}_2} > 4.5$ METs ($P < 0.05$). In contrast,

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### Table 1. Clinical characteristics of patients with CHF

<table>
<thead>
<tr>
<th></th>
<th>CHF</th>
<th>Normal</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>Men</td>
<td>Women</td>
</tr>
<tr>
<td>n</td>
<td>25</td>
<td>13</td>
</tr>
<tr>
<td>Age, yr</td>
<td>57.4 ± 2.5</td>
<td>52.5 ± 3.2</td>
</tr>
<tr>
<td>LVEF, %</td>
<td>21 ± 2†</td>
<td>28 ± 2†</td>
</tr>
<tr>
<td>Peak $V_{\text{O}_2}$, ml·kg$^{-1}$·min$^{-1}$</td>
<td>14.8 ± 0.5†</td>
<td>13.7 ± 0.7†</td>
</tr>
<tr>
<td>BMI</td>
<td>28.3 ± 0.8</td>
<td>29.4 ± 2.5†</td>
</tr>
</tbody>
</table>

Values are means ± SE; n, no. of subjects. CHF, chronic heart failure; LVEF, left ventricular ejection fraction; $V_{\text{O}_2}$, oxygen consumption; BMI, body mass index; CAD, coronary artery disease; NYHA, New York Heart Association; ACE, angiotensin-converting enzyme. *$P < 0.05$ between genders of same group (CHF vs. CHF or normal vs. normal). †$P < 0.05$ between genders of different groups (CHF vs. normal).

### Table 2. Relative content of myosin heavy chain in patients with CHF and in normal men and women

<table>
<thead>
<tr>
<th></th>
<th>MHC I</th>
<th>MHC IIa</th>
<th>MHC IIx</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHF men</td>
<td>35.2 ± 2.9</td>
<td>35.8 ± 1.9</td>
<td>29.2 ± 2.6*</td>
</tr>
<tr>
<td>CHF women</td>
<td>42.5 ± 3.5</td>
<td>32.4 ± 2.2</td>
<td>25.1 ± 4.0</td>
</tr>
<tr>
<td>Normal men</td>
<td>41.2 ± 2.8</td>
<td>39.3 ± 3.0</td>
<td>19.5 ± 3.0</td>
</tr>
<tr>
<td>Normal women</td>
<td>48.0 ± 5.0</td>
<td>33.2 ± 3.4</td>
<td>18.8 ± 3.9</td>
</tr>
</tbody>
</table>

Values are means ± SE. MHC, myosin heavy chain. *$P < 0.05$ between genders of different groups (CHF men vs. normal men).

### Table 3. Skeletal muscle enzyme activity in patients with CHF and in normal men and women

<table>
<thead>
<tr>
<th>Enzyme</th>
<th>CHF</th>
<th>Normal</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Men</td>
<td>Women</td>
</tr>
<tr>
<td>3-Hydroxyacyl-CoA</td>
<td>2.9 ± 0.3†</td>
<td>2.8 ± 0.2†</td>
</tr>
<tr>
<td>dehydrogenase</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Citrate synthase</td>
<td>3.8 ± 0.2</td>
<td>4.0 ± 0.2</td>
</tr>
<tr>
<td>Lactate dehydrogenase</td>
<td>46.4 ± 2.9†</td>
<td>35.8 ± 4.0</td>
</tr>
<tr>
<td>Phosphofructokinase</td>
<td>11.8 ± 0.6</td>
<td>10.1 ± 0.9</td>
</tr>
</tbody>
</table>

Values are means ± SE in mol·kg protein$^{-1}$·h$^{-1}$. *$P < 0.05$ between genders of same group (CHF men vs. CHF women). †$P < 0.002$ between genders of different groups (CHF men vs. normal men; and CHF women vs. normal women).
women with CHF show no differences in capillary density relative to aerobic capacity (4.5 METs).

Figure 3 illustrates the oxidative enzyme activities of CS and 3-HAD of men and women with CHF separated by peak V̇O₂ greater or less than 4.5 METs. Although no difference existed between women patients with CHF, men had increased activity of CS (P < 0.05) and 3-HAD (P < 0.02) when peak V̇O₂ > 4.5 METs.

Examining all matched CHF patients together, the relationship between each of the skeletal muscle markers and peak V̇O₂ was consistent for men and women (no interactions were present). Table 4 illustrates the ability to predict peak V̇O₂ from the main effects of all skeletal muscle markers measured while accounting for gender effects: 3-HAD (P = 0.01) and CS (P = 0.02) were significantly related to peak V̇O₂ and capillary density (P = 0.06) approached significance. Stepwise regression analysis revealed that only 3-HAD was a significant predictor of peak V̇O₂ in the presence of all other enzyme markers (P < 0.02).

DISCUSSION

Our findings suggest that few skeletal muscle differences exist between men and women with CHF matched for peak V̇O₂, age, and pharmacological ther-
apy. In studying patients with CHF matched for these parameters, the interpretation of the data is as follows:

1) gender does not appear to have a heterogeneous effect on skeletal muscle, although women show a consistent trend toward increased oxidative potential; 2) the relationship between each of the skeletal muscle markers and peak V\textsubscript{\text{\text{\text{\text{O}}}}\text{\text{2}}}} is similar between men and women with CHF; 3) after gender is controlled, 3-HAD and CS, and to a lesser extent capillary density, are predictors of peak V\textsubscript{\text{\text{\text{\text{O}}}}\text{\text{2}}}}; 4) 3-HAD is the strongest univariate predictors of peak V\textsubscript{\text{\text{\text{\text{O}}}}\text{\text{2}}}}.

However, our data indicate that, as peak aerobic capacity decreases, the skeletal muscle of men and women may adapt to CHF in different ways. Despite the lack of gender differences when analyzed as a whole, we found heterogeneous skeletal muscle adaptive patterns when men and women patients with CHF were separated by a peak V\textsubscript{\text{\text{\text{O}}}}\text{\text{2}}} of 4.5 METs. A value of 4.5 METs was chosen because this is the midpoint value of a previous study from our laboratory (5) that showed an inverse relationship between capillary density and peak V\textsubscript{\text{\text{\text{O}}}}\text{\text{2}}} in men with CHF. Figure 2 illustrates that, although men with peak V\textsubscript{\text{\text{\text{O}}}}\text{\text{2}}} >4.5 METs have increased CS and 3-HAD compared with men with peak V\textsubscript{\text{\text{\text{O}}}}\text{\text{2}}} <4.5 METs, women had no difference in aerobic enzymes when separated by 4.5 METs. Also, confirming our laboratory's previous findings (5), in this study (Fig. 3) CHF men with a lower peak V\textsubscript{\text{\text{\text{O}}}}\text{\text{2}}} had increased capillary density compared with men with higher peak V\textsubscript{\text{\text{\text{O}}}}\text{\text{2}}}.

Although CHF women show no differences in capillary density with aerobic capacity, they demonstrated a trend in the opposite direction to that of the men. Another intriguing finding was that women with CHF, in contradistinction to the finding in men, demonstrated an increased capillary density compared with normal women. We hypothesize that mildly compromised aerobic capacities (peak V\textsubscript{\text{\text{\text{O}}}}\text{\text{2}}} >4.5 METs) in women stimulate peripheral skeletal muscle angiogenesis and increase capillary density to values similar or above that of normal women, whereas men with CHF do not mount an adaptive response until peak aerobic capacity drops below 4.5 METs. This adaptive response may also partially account for the decreased symptoms observed in women with CHF at the time of presentation. Although it is cautioned that this is only suggestive and has a small number of CHF women with peak V\textsubscript{\text{\text{\text{O}}}}\text{\text{2}}} >4.5 METs, these observations imply that subsequent studies should control for gender when modeling the effects of skeletal muscle characteristics on aerobic capacity in patients with CHF. Future studies should be powered to address the possibility that the adaptive responses in skeletal muscle to CHF have different thresholds in women compared with men.

It is important to note that women in this study had an increased resting ejection fraction compared with men (21 \pm 2 vs. 28 \pm 2; \( P < 0.05 \)). In general, women with CHF present with preserved left ventricular function compared with men and, as previously noted, fewer symptoms compared with men (9). It is unlikely that the increased resting ejection fraction in the women contributed to differences in peak V\textsubscript{\text{\text{\text{O}}}}\text{\text{2}}}.

Data from our laboratory demonstrated that ejection fraction was not related to peak V\textsubscript{\text{\text{\text{O}}}}\text{\text{2}}} in a larger group of women with CHF (not shown). In addition, when controlling for gender, we did not observe ejection fraction to be a predictor of peak V\textsubscript{\text{\text{\text{O}}}}\text{\text{2}}}.

Although not measured in this study, women with CHF may rely more heavily on...
central hemodynamic factors such a stroke volume or end-diastolic volume than on skeletal muscle factors for exercise endurance. Correspondingly, men with CHF may be more limited by alterations in skeletal muscle and not by central factors during exercise. To accurately test this hypothesis, an adequately powered study assessing central (stroke volume, end-diastolic volume) and peripheral (arteriovenous $O_2$ extraction, leg blood flow and skeletal muscle characteristics) determinants of cardiovascular performance (cardiac output and exercise tolerance) should be undertaken.

Although not statistically significant, our findings in normal men and women were consistent with other studies examining skeletal muscle in normal sedentary subjects, implying that we have a characteristic population of normal subjects. Simonneau et al. (19, 20) showed decreased type I fibers, and increases in the enzymes PFK and LDH in men vs. women. Other studies in normal subjects also support increased glycolytic enzymes in men compared with women (14). Interestingly, we found an increase in capillary density in normal men compared with normal women ($P = 0.001$). This finding was surprising and, to our knowledge, has only been reported in one previous study (3). This could not be explained by differences in exercise fraction or age observed between the normal men and women.

It is possible that gender differences may also be explained, in part, by other gender-specific differences not addressed in this study (sex hormones, pharmacokinetics, and metabolism). The results of this study suggest that a different adaptive pattern to decreased aerobic capacity may exist in skeletal muscle between men and women with CHF. However, because of the small sample size in the present study, findings must be interpreted with caution. If confirmed, such a finding may provide clues to the pathophysiological underpinnings of differences in the presentation of CHF in men and women. For example, if women tend to have a preserved skeletal muscle physiology in advanced stages of heart failure, this may account for why they present later in the course of their disease and survive longer, despite having more symptoms, as has been observed in several studies. Ultimately, the demonstration of gender differences in the pathophysiological adaptations to CHF might influence the need for differences in treatment options in men and women, such as the role and timing of interventions to treat or modify the disease process. To properly address these issues, a large trial is needed that investigates both clinical outcomes and surrogate pathophysiological markers, including skeletal muscle, between men and women with CHF. Such a study should be powered to examine the relationships in men and women separately.

In conclusion, we have observed that when matched for peak $V_{O_2}$, age, and pharmacological therapy men and women patients with CHF display few baseline differences in skeletal. However, there are indications that, as the disease progresses, the skeletal muscle of women demonstrate less severe pathophysiological adaptations to the disease than do their male counterparts. If confirmed with further study, this observation may have significant implications for understanding differences in disease progression and disease management requirements in men and women with CHF.

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### REFERENCES


### Table 4. Main effects on peak oxygen consumption of skeletal muscle markers in patients with CHF after accounting for Gender via ANCOVA

<table>
<thead>
<tr>
<th>Skeletal Muscle Marker</th>
<th>$P$ Value (peak $V_{O_2}$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>3-Hydroxy-CoA dehydrogenase</td>
<td>0.01</td>
</tr>
<tr>
<td>Citrate synthetase</td>
<td>0.02</td>
</tr>
<tr>
<td>Phosphofructokinase</td>
<td>0.75</td>
</tr>
<tr>
<td>Lactate dehydrogenase</td>
<td>0.35</td>
</tr>
<tr>
<td>Capillary density</td>
<td>0.06</td>
</tr>
<tr>
<td>Myosin heavy chain I</td>
<td>0.57</td>
</tr>
<tr>
<td>Myosin heavy chain IIA</td>
<td>0.13</td>
</tr>
<tr>
<td>Myosin heavy chain IIX</td>
<td>0.11</td>
</tr>
</tbody>
</table>

ANCOVA, analysis of covariance.


