
To the Editor:

The existence of muscle metabolic alterations in patients with chronic heart failure (CHF) (1) led us to test the hypothesis that even a light exercise mimicking a daily life activity (2) in CHF may induce an excess of muscle amino acid release. We focused in particular on phenylalanine (Phe) release because this amino acid is neither synthesized nor degraded within muscle (3).

Twenty untrained, clinically stable, normonourished fasting male patients (Table 1) with moderate to severe CHF at morning underwent hemodynamic procedures to measure femoral blood flow, arterial and venous amino acid concentrations (branched chain amino acids [BCAAs: valine, leucine, isoleucine], histidine, alanine, glutamic acid, glutamine, and taurine), as well as pH and lactate and free fatty acid (FFA) levels both at baseline and at 20 W bicycle exercise oxygen consumption (VO2, ml·kg·1·min−1) steady state.

The net uptake and/or release of muscle amino acids was calculated as: Net balance = ([A]−[P]) × F where A − P is the femoral arteriovenous difference in amino acid concentrations and F is leg blood flow. Thus, a net muscle uptake means amino acid utilization, whereas a net muscle release indicates increased protein breakdown and/or amino acid alteration.

At rest, controls and CHF had similar arterial amino acid concentrations (unpaired t test). Net muscle uptake and/or release of amino acids by controls and CHF, at rest and during exercise, are illustrated in Figure 1. At rest, CHF took up all amino acids except taurine, which was released, whereas controls released amino acids with the exception of glutamic acid and taurine, which were taken up. During exercise, CHF, but not controls, released significant amounts of Phe (from 38.2 ± 2.4 to −42.3 ± 3.2 μmol·l−1·min−1; p < 0.01), the three BCAAs; histidine, alanine (p < 0.05 in all cases), and glutamine (p < 0.01). The uptake of glutamic acid declined (p < 0.01) and taurine was taken up (p < 0.01), resulting in levels higher than in controls (p < 0.05) (paired t test).

At rest, arterial FFA concentration as well as FFA release was higher in CHF than in controls (p < 0.05 and <0.001, respectively). During exercise the difference in FFA release between CHF and controls declined but remained significant (p < 0.01). At rest, blood femoral vein was acidic in CHF (pH = 7.34 ± 0.02 vs. 7.41 ± 0.01 in controls; p < 0.05); during the effort, the pH of CHF further decreased (7.31 ± 0.01; p < 0.01).

This investigation shows that patients with CHF exercising at a light workload have a net muscle release of both Phe and other amino acids. The mechanisms responsible for the net release of Phe during exercise in CHF patients may include alterations in intermediary and energy metabolism within muscle cells, intracellular acidosis, and cytokine production. Indeed, the low intramuscular glycogen concentration in resting CHF patients (4) may make muscle energy metabolism more dependent on alternative substrates such as amino acids derived from cellular-free pool

Table 1. Clinical, Functional, Hemodynamic, and Hormonal Characteristics of Controls and CHF Patients

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Controls (n = 10)</th>
<th>Patients (n = 20)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yrs)</td>
<td>60.2 ± 2.1</td>
<td>59.5 ± 2.5</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>70.5 ± 3.5</td>
<td>72.3 ± 9.1</td>
</tr>
<tr>
<td>Duration of disease</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;18 months</td>
<td>—</td>
<td>8/20</td>
</tr>
<tr>
<td>≥18 months</td>
<td>—</td>
<td>12/20</td>
</tr>
<tr>
<td>NYHA functional class II/III</td>
<td>—</td>
<td>12/8</td>
</tr>
<tr>
<td>Medications</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ACE inhibitors</td>
<td>—</td>
<td>17/20 (85%)</td>
</tr>
<tr>
<td>Digoxin</td>
<td>—</td>
<td>7/20 (35%)</td>
</tr>
<tr>
<td>Diuretics</td>
<td>—</td>
<td>20/20 (100%)</td>
</tr>
<tr>
<td>Oral nitrates</td>
<td>—</td>
<td>8/20 (40%)</td>
</tr>
<tr>
<td>Left ventricular ejection fraction (%)</td>
<td>56.5 ± 1.5</td>
<td>22 ± 0.9*</td>
</tr>
<tr>
<td>Peak VO2 (ml·kg·1·min−1)</td>
<td>33.3 ± 1.4</td>
<td>13.5 ± 0.4*</td>
</tr>
<tr>
<td>Cardiac index (l·min−1·m−2)</td>
<td>—</td>
<td>2.16 ± 0.15</td>
</tr>
<tr>
<td>Pulmonary wedge pressure (mm Hg)</td>
<td>—</td>
<td>17.6 ± 2.5</td>
</tr>
<tr>
<td>Right atrial pressure (mm Hg)</td>
<td>—</td>
<td>6.7 ± 0.9</td>
</tr>
<tr>
<td>Hemoglobin (g·dl−1)</td>
<td>14.1 ± 0.8</td>
<td>13.3 ± 0.11</td>
</tr>
<tr>
<td>Noradrenaline (pg·ml−1)</td>
<td>278 ± 72</td>
<td>412 ± 22*</td>
</tr>
<tr>
<td>Serum sodium level (mEq·l−1)</td>
<td>140 ± 5</td>
<td>136 ± 3</td>
</tr>
<tr>
<td>Arterial lactate concentration (mg·dl−1)</td>
<td>3.9 ± 1.1</td>
<td>4.3 ± 1.2</td>
</tr>
<tr>
<td>Midarm muscle area (cm2)</td>
<td>46 ± 2.1</td>
<td>46.0 ± 1.6</td>
</tr>
</tbody>
</table>

Values are expressed as mean ± SEM. Statistical analysis: unpaired t test controls vs. patients; *p < 0.01.

ACE = angiotensin-converting enzyme; CHF = congestive heart failure; NYHA = New York Heart Association.
and/or accelerate protein degradation. Carbohydrate depletion, in fact, favors muscle protein breakdown, whereas carbohydrate loading significantly restricts protein degradation (5). Furthermore, the documented glycolytic and oxidative pathway alterations in CHF (4) could contribute to increasing muscle protein utilization and amino acid oxidation.

The muscle metabolic acidosis can worsen the net negative balance of Phe in CHF; this is because low pH acts as a catabolic stimulus in normal adults (6). Notably, the acidosis in our CHF patients may be enhanced by the net loss of muscle histidine, the main intracellular buffer in the muscle. A possible cytokine overproduction in exercising CHF may also contribute to release of Phe from muscles (7). The release of BCAAs confirms the existence of abnormal amino acid metabolism in exercising CHF because exercise normally causes muscle to extract BCAAs from the plasma and not to release them into the bloodstream (8).

The finding of a positive net balance of muscle amino acids (with the exception of glutamic acid), particularly of alanine, in resting overnight fasting CHF patients, together with increased serum catecholamine levels, may have counteracted muscle release of amino acids in the fasting state (9,10). During exercise, CHF patients release alanine, as do normal subjects at rest.

The persistence of muscle glutamic acid uptake, the increased glutamine release, and the increased taurine uptake may all indicate an increased muscle utilization of these amino acids by CHF during exercise (11,12). The release of FFA may suggest that, in CHF, an increased muscle lipolysis also occurred (13).

In brief, the study shows that, during light exercise, untrained patients with CHF release a number of muscle amino acids, suggesting a possible abnormal muscle amino acid metabolism. Based on these data and on Phe release (3) we hypothesize an occurrence of muscle protein overdegradation in deconditioned exercising CHF. If so, it is conceivable that repeated daily-life physical activities by untrained CHF patients may contribute to a negative nitrogen balance (14) and to muscular wasting.

Finally, in this context appropriate physical training can counteract muscle amino acid release and protein degradation in untrained CHF (15).

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Letters to the Editor

Cautious Interpretation of Data Regarding Myopericarditis Associated With Smallpox Vaccination

We congratulate Cassimatis et al. (1) for their excellent review of myopericarditis associated with smallpox vaccination. We suggest a different interpretation of the data regarding some important issues.

First, the true incidence of myopericarditis secondary to smallpox vaccination with Dryvax (NYBOH strain) vaccine remains unknown and it is likely higher than the quoted rates of one case per 9,360 (1), 10,000 (2), or 12,819 (3) vaccinations, which represent the recognition of overt, symptomatic myopericarditis in a highly selected, very fit military population. We suspect myopericarditis is underdiagnosed in this population because of the wide spectrum of presenting clinical symptoms and signs that confound accurate diagnosis, the potential for minimal or no-symptom cases that could lead to missed cases, and the characteristics of young, volunteer, military personnel who could conceivably overlook or minimize symptoms that do not limit their service duties. A higher rate of myopericarditis is supported by the 2% to 3% incidence of electrocardiographic changes after smallpox vaccination in Swedish military personnel in the 1960s (4,5). Importantly, a higher incidence of myopericarditis would likely be recognized if mass smallpox vaccination were applied to the general population with higher prevalence rates of cardiovascular and immunologic disease, in an attempt to protect citizens against smallpox bioterrorism.

Second, the long-term sequelae of myopericarditis due to smallpox vaccination remain unknown. Subclinical or overt abnormalities due to vaccinia viremia or its immunologic responses, such as direct viral toxicity or immune-mediated myocyte necrosis, persistent myocardial inflammatory infiltrates, or development of myocardial fibrosis, may manifest years later, with ventricular dysfunction, conduction system abnormalities, or sudden death. Although almost all recently vaccinated patients with myopericarditis recovered clinically, the possibility of residual low-grade myocardial inflammation and fibrosis cannot be excluded or prevented.

Third, endomyocardial biopsy probably is of greater than “limited utility” after smallpox vaccination. We advocate endomyocardial biopsy for all patients with suspected new-onset ventricular dysfunction (ejection fraction ≤45%) and symptoms of heart failure after smallpox vaccination. The rationale for this approach is the documentation of possible steroid responsive cosinophilic myocarditis, which occurred in one recent patient after smallpox vaccination, and the need to exclude uncontrolled vaccinia virus replication within the myocardial that may be responsive to immune globulin. Endomyocardial biopsy under echocardiographic guidance is a relatively safe procedure in experienced hands and may provide a definitive actionable diagnosis in high-risk patients (6).

It is a profound tragedy that vaccination against an eradicated disease whose elimination marked the single greatest human success against a communicable disease is now required for U.S. soldiers because of the threat of biowarfare. Current smallpox vaccine appears to carry significant risks of serious adverse events. The true incidence and long-term sequelae of current smallpox vaccine remain unknown.

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REPLY

We appreciate the comments on our review (1) of myopericarditis associated with smallpox vaccination. The recently published rates of myopericarditis may indeed be underestimates, for they are based on reporting of clinical encounters with symptomatic patients from an occupational cohort, as we noted previously (2). To better assess the true incidence rate, we will soon enroll volunteers in a prospective trial of smallpox vaccinees with baseline and follow-up electrocardiography, laboratory markers, and questionnaires.

We described the need to follow patients diagnosed with postvaccinal myopericarditis to establish whether long-term sequelae exist (1), and we recently have published the results of such follow-up (3). On the basis of these data, long-term sequelae are