Exertional dyspnea in mitochondrial myopathy: clinical features and physiological mechanisms

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Submitted 3 January 2011; accepted in final form 29 July 2011

Exertional dyspnea was first described as a symptom that limited exercise in mitochondrial myopathy (MM) in patients with a familial disorder studied by Linderholm and coworkers in the 1960s (36, 38), a disease now recognized to be attributable to a mutation in the iron-sulfur cluster scaffold (ISCU) gene (40, 42) and associated with deficiency of multiple iron-sulfur proteins, including succinate dehydrogenase and aconitase (20, 21). Exertional dyspnea has since been described as a dominant feature of exercise intolerance in other mitochondrial myopathies that severely restrict muscle oxidative phosphorylation (3a, 22). Moreover, mitochondrial disease has been suggested to be an unrecognized cause of unexplained exertional dyspnea (16, 25), although, these reports lacked genetic confirmation and, in most cases, did not include biochemical assessment to indicate the presence and severity of the putative mitochondrial defect (16). To better define the physiological manifestations of exertional dyspnea in mitochondrial myopathy, we have evaluated two patients with ISCU myopathy, the disease originally described by Linderholm et al. (38), and three patients with exertional dyspnea with mitochondrial myopathy attributable to heteroplasmic mitochondrial DNA mutations.

Our previous studies have suggested that the severity of impaired muscle oxidative metabolism is a key variable in MM patients who experience dyspnea as a symptom that limits physical exertion (51). A consequence of severely impaired muscle oxidative phosphorylation is activation of glycolysis, resulting in marked increases in blood lactate in relation to exercise intensity (51, 53). Lactic acidosis is considered an important mediator of the compensatory hyperventilation that normally occurs at high-intensity exercise by stimulation of carotid chemoreceptors (55), and thus would be presumed to be an important contributor to the ventilatory response to exercise in MM patients. Exercise ventilation is also regulated by feedforward mechanisms via central command (15) and by feedback reflexes mediated by activation of metaboreceptors or mechanoreceptors (ergoreflexes) in working muscle (2, 13, 23, 31). Peak increases in blood lactate and maximal decreases in pH occur during the first minutes of recovery from exercise when the influence of central command ceases and ergoreflexes are rapidly withdrawn. To differentiate the contribution of acidosis from other regulators of exercise ventilation, we assessed ventilation in these patients both during incremental cycle
exercise and during recovery from exercise to better define the role of lactic acidosis in this syndrome.

MATERIALS AND METHODS

Subjects. We studied five genetically, biochemically, and physiologically defined MM patients and four age- and sex-matched, healthy control subjects (C). The diagnosis of mitochondrial myopathy was established by biochemical and genetic analysis, and patients were evaluated by prior exercise testing (Table 1). Three patients (1-MM, 2-MM, and 3-MM) had heteroplasmic mitochondrial DNA mutations in which the mutation was in high abundance (>90%) in skeletal muscle and resulted in deficiency of respiratory chain complexes containing mitochondrially encoded subunits affected by the mutation. In patient 1-MM with a 3243A>G mutation, enzymatic deficiency was most pronounced in complex I (27). In patient 2-MM with a cytochrome b mutation, the enzymatic block exclusively affected complex III (52). In patient 3-MM, a novel tRNAtrp mutation was associated with deficiency of multiple respiratory chain complexes, especially complex IV (52). Two patients had a mitochondrial myopathy with deficiency of multiple iron-sulfur cluster containing enzymes, particularly the tricarboxylic acid (TCA) cycle enzymes succinate dehydrogenase and aconitate, due to a mutation in the ISCU gene (20, 21, 40). The main clinical feature in all patients was severe exercise intolerance with prominent exertional dyspnea provoked by low-intensity exercise that had been present since childhood. Patients did not have muscle weakness and had no clinical evidence of impaired cardiac or pulmonary function. All patients showed a low peak rate of muscle oxidative phosphorylation with a severely restricted capacity to increase oxygen extraction during exercise, as indicated by a low peak systemic arteriovenous oxygen difference (a-vO2 diff., ranging from 3.4 to 5.7 ml O2/dl, Table 1, compared with normal subjects, who have peak a-vO2 difference of ~15 ml O2/dl). Correspondingly, oxygen transport during exercise increased in great excess relative to the increase in oxygen uptake, as indicated by exaggerated increases in cardiac output relative to the increase in oxygen uptake (ΔQ/ΔVO2 ranging from 16 to 42, Table 1) compared with a normal ΔQ/ΔVO2 of ~5 in healthy control subjects (21, 22, 51).

The study was approved by the Institutional Review Board of the University of Texas Southwestern Medical Center and Texas Health Presbyterian Hospital, Dallas. All experiments were performed in accordance with the Declaration of Helsinki. Written informed consent was given by all subjects.

Pulmonary function testing. All subjects underwent standard measurements of spirometry, lung volume, and diffusing capacity, as determined by whole body plethysmography (model V62W; Viastys Healthcare, Yorba Linda CA), according to American Thoracic Society guidelines (3). Maximum inspiratory pressure was also measured. Predicted values were based on established norms (7, 9, 10, 18, 33–35).

Hypoxic ventilatory response and hypercapnic ventilatory response. To evaluate respiratory chemosensitivity, hypoxic ventilatory response (HVR) and hypercapnic ventilatory response (HCVR) were measured using a modification of the established progressive isocapnic hypoxia and hypercapnic technique (58, 59), as described previously (17).

Incremental exercise testing. All subjects performed the exercise test twice on an electromagnetically braked cycle ergometer (MedGraphics, 2000), with the first test to familiarize subjects with the testing protocol. A radial artery catheter was placed for arterial blood sampling during the second test. Subjects were seated on the ergometer for resting data collection for 3 min, followed by 3 to 4 min of constant submaximal steady-state workload cycling after which the workload was increased every 60 s until the subject could no longer maintain pedal rate of 50 rpm. Workload increments were determined for each subject based on prior testing (MM, 5–10 W; C, 20–30 W). Subjects were encouraged to continue to exhaustion and remained seated on the ergometer for 5 min of resting (no cycling) recovery data collection. Throughout the testing, heart rate (HR) was monitored continuously by 12-lead ECG, blood pressure by an automated monitor (SunTech Tango, Morrisville, NC). Subjects’ ratings of exercise effort were obtained at the end of each minute using Borg 6–20 scale for rating of overall perceived exertion (RPE) and 0–10 scale for rating of perceived breathlessness (RPB) (8). Arterial blood was collected at rest, every minute during submaximal exercise, at peak workload, and repeatedly during 5 min of recovery for measurement of lactate, pH, PiaO2, PacO2, and standard bicarbonate (HCO3−). Whole blood samples were placed on ice, and analyzed immediately after the exercise test using a Yellow Springs Instruments analyzer (2300 STAT +) for lactate and an Instrumentation Laboratories analyzer (GEM 3000) for pH, blood gases, and HCO3−. In control subject 2-C, only venous blood samples were collected.

Cardiac output (Q) and VO2 were measured during a separate incremental maximal cycle exercise test in all patients and three control subjects using acetylene rebreathing and standard gas exchange, in which systemic arteriovenous oxygen difference (a-vO2 diff.) was calculated from the Fick equation: VO2 = Q × a-vO2 diff., as previously described (51).

Ventilatory and gas exchange measurements. O2 uptake (VO2), carbon dioxide production (VCO2), respiratory exchange ratio (RER, VCO2/VO2), expired minute ventilation (VE, BTPS), and respiratory frequency were recorded on a custom-built computerized breath-by-breath system and averaged over 20-s intervals, which we used for trend analyses. Additionally, expired gas was collected for 3 min at rest, for 60 s at submaximal workloads, and during peak exercise in 200-liter PVC bags (Harvard Apparatus, Holliston, MA). The fractional

Table 1. Genetic and physiological characteristics of mitochondrial myopathy patients

<table>
<thead>
<tr>
<th>Patient</th>
<th>Nature of Mutation</th>
<th>Genome</th>
<th>Muscle Mutation Load, %</th>
<th>Reference of DNA Mutation</th>
<th>Peak a-vO2 diff., ml O2/dl</th>
<th>ΔQ/ΔVO2</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-MM</td>
<td>tRNA A3243G</td>
<td>mtDNA</td>
<td>92</td>
<td></td>
<td>4.3</td>
<td>21.0</td>
</tr>
<tr>
<td>2-MM</td>
<td>G14846A Cytochrome b</td>
<td>mtDNA</td>
<td>98</td>
<td>(3a)</td>
<td>3.4</td>
<td>42.1</td>
</tr>
<tr>
<td>3-MM</td>
<td>tRNAtrp T5543C</td>
<td>mtDNA</td>
<td>95</td>
<td>(3b)</td>
<td>5.7</td>
<td>16.5</td>
</tr>
<tr>
<td>4-MM</td>
<td>ISCU</td>
<td>nDNA</td>
<td>N/A</td>
<td>(40)</td>
<td>3.9</td>
<td>36.0</td>
</tr>
<tr>
<td>5-MM</td>
<td>ISCU</td>
<td>nDNA</td>
<td>N/A</td>
<td>(40)</td>
<td>5.6</td>
<td>20.0</td>
</tr>
</tbody>
</table>

Values for control subjects are expressed as means ± SD. MM, mitochondrial myopathy patients; ISCU, iron-sulfur scaffold protein; mtDNA, mitochondrial DNA; nDNA, nuclear DNA; a-vO2 diff., systemic arteriovenous oxygen difference; ΔQ/ΔVO2, level of increase in cardiac output relative to increase in oxygen utilization. *Significantly different from MM patients, P ≤ 0.05, †P ≤ 0.001.

AJP-Regul Integr Comp Physiol • VOL 301 • OCTOBER 2011 • www.ajpregu.org
Table 2. Physical characteristics

<table>
<thead>
<tr>
<th>Subject</th>
<th>Sex</th>
<th>Age, yr</th>
<th>Height, cm</th>
<th>Weight, kg</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-MM</td>
<td>female</td>
<td>19</td>
<td>154</td>
<td>48</td>
</tr>
<tr>
<td>2-MM</td>
<td>female</td>
<td>57</td>
<td>170</td>
<td>58</td>
</tr>
<tr>
<td>3-MM</td>
<td>male</td>
<td>60</td>
<td>170</td>
<td>76</td>
</tr>
<tr>
<td>4-MM</td>
<td>male</td>
<td>37</td>
<td>183</td>
<td>80</td>
</tr>
<tr>
<td>5-MM</td>
<td>male</td>
<td>38</td>
<td>180</td>
<td>79</td>
</tr>
<tr>
<td>Mean (SD)</td>
<td></td>
<td>42 ± 17</td>
<td>171 ± 11</td>
<td>68 ± 14</td>
</tr>
<tr>
<td>1-C</td>
<td>female</td>
<td>24</td>
<td>174</td>
<td>79</td>
</tr>
<tr>
<td>2-C</td>
<td>female</td>
<td>20</td>
<td>178</td>
<td>65</td>
</tr>
<tr>
<td>3-C</td>
<td>male</td>
<td>35</td>
<td>180</td>
<td>104</td>
</tr>
<tr>
<td>4-C</td>
<td>male</td>
<td>56</td>
<td>178</td>
<td>86</td>
</tr>
<tr>
<td>Mean (SD)</td>
<td></td>
<td>34 ± 16</td>
<td>178 ± 3</td>
<td>83 ± 16</td>
</tr>
</tbody>
</table>

Values are expressed individually as group means ± SD. MM, mitochondrial myopathy patients; C, control subjects.

Results

Pulmonary function and chemosensitivity. A summary of physical characteristics of the MM patients and control group is presented in Table 2. Pulmonary function values are shown in Table 3. There were no statistically significant differences in subject characteristics or pulmonary function values between the patients and the control group.

The HVR (slope of $\Delta$Ve $\cdot$ min$^{-1}$/\DeltaSaO2%) was higher in MM patients than in our controls (MM $=$ 0.85 ± 0.13, C $=$ 0.28 ± 0.02, mean ± SD, $P$ $<$ 0.05) but within the range of normal for data collected previously by our laboratory (17). The HCVR (slope of $\Delta$Ve $\cdot$ min$^{-1}$/\DeltaPetCO2, $\cdot$ min$^{-1}$/Torr$^{-1}$; PetCO2, end-tidal Pco2) for patients was not significantly different from control subjects (MM $=$ 2.18 ± 1.34, range 0.72–4.0; C $=$ 0.95 ± 0.30) and within the range of normal for data collected previously by our laboratory (17) or reported elsewhere (24).

Rest. Resting Ve was not significantly different between the two groups except for a higher RER and lower PaCO2 in control subjects (mean data, Table 5), indicating that control subjects were hyperventilating at rest. MM patients showed a tendency for elevated arterial lactate levels and significantly lower pH values compared with controls.

Exercise. Peak oxidative capacity was markedly lower in MM patients than in control subjects expressed as % of predicted values (28), (Table 4). There were no significant differences in HRpeak, HR% of predicted values (26), peak VT, or peak respiratory frequency.

During incremental exercise (Table 5, Fig. 1 and 2), Ve increased disproportionately in relation to workload and metabolic rate in MM patients (Fig. 1, A and B). At the VCP, workload, VO2, VCO2, and Ve were low in MM patients (Table 5), whereas the ventilatory equivalents for O2 and CO2, and RER were increased compared with controls. MM patients had higher arterial lactate levels and PaO2, and lower PaCO2, and HCO3$^-$ at the VCP.

At peak exercise work capacity, VO2, VCO2, and Ve were lower in MM patients (Table 5). The ventilatory equivalents for O2 and CO2, and RER were markedly elevated, and perceived breathing effort (RPB) was significantly higher in MM patients at peak exercise. There were no differences in patients and controls for perceived overall exertion at peak exercise (RPE, MM $=$ 19 ± 1, C $=$ 18 ± 2). MM patients showed increased arterial lactate concentrations and decreased PaO2, and HCO3$^-$, with no significant difference in pH compared with controls. PaO2 values were increased at peak exercise.

The exercise ventilatory response as indicated by the slope of $\Delta$Ve/$\Delta$VCO2 (Fig. 3) was increased in MM patients from rest to exercise at the VCP (MM $=$ 30.7 ± 3.8, C $=$ 22.6 ± 1.5, $P$ $<$ 0.01), as well as for the complete slope from rest to peak exercise (MM $=$ 50.0 ± 6.9, C $=$ 32.2 ± 6.6, $P$ $<$ 0.01) compared with controls. In control subjects, values for both Ve/VCO2 slopes were in the normal range (41, 49).

During peak exercise, the Ve/maximum volume ventilation ratio was lower in MM patients (55%) compared with control subjects (82%). Maximal and tidal flow-volume loops measured at rest and during exercise for MM patients and controls were typical for their age and sex (Figs. 4 and 5), with no observable differences in subject characteristics or pulmonary function values between the patients and the control group.
DISCUSSION

This is the first physiological study of the regulation of ventilation during exercise and recovery in patients with genetically and biochemically defined skeletal muscle mitochondrial defects in whom exercise is limited by symptoms of exertional dyspnea.

The main findings of our study are 1) exertional dyspnea is a feature of skeletal muscle mitochondrial defects that severely impair muscle oxidative phosphorylation and result in a hyperkinetic circulatory response to exercise, irrespective of the specific site of the metabolic block within the respiratory chain or TCA cycle; 2) exertional dyspnea in these patients is marked by exaggerated ventilation relative to metabolic rate, as indicated by high Ve/VCO₂; Ve/VCO₂; and RER and by an increased slope of ΔVe/ΔVCO₂ with no apparent signs of pulmonary insufficiency; 3) high arterial lactate concentrations in association with low PaCO₂, low HCO₃⁻, and markedly elevated VCO₂/VO₂ imply that ventilatory compensation to metabolic acidosis contributes to this exaggerated ventilation during exercise; and 4) normalization of ventilation during recovery from exercise despite further increases in arterial lactate and decreases in pH indicates that severely impaired oxidative phosphorylation in working muscle stimulates ventilation by mechanisms that are specific to exercise and independent of metabolic acidosis.

Each of our patients had a severe limitation in muscle oxidative phosphorylation in which peak oxygen uptake during exercise was low and oxygen extraction from blood was severely restricted, as indicated by a systemic arteriovenous O₂ difference that remained at or below resting levels during maximal effort exercise (Table 1). Associated was a hyperkinetic circulation during exercise in which the increase in oxygen transport (A cardiac output) relative to the increase in oxygen utilization (ΔVO₂) was 3–8 times normal.

In our patients, ventilation at rest was normal. In particular, there was no evidence of significant weakness of the muscles of respiration by the criteria of maximal inspiratory pressure and maximal voluntary ventilation. HVR and HCVR trended higher in MM patients but were generally consistent with values reported for healthy controls in our laboratory (mean, range; HVR, 0.71, 0.26–1.35; HCVR, 1.41, 0.88–2.13), (17). There is a considerable variation in normal ventilatory responses to hypoxia (57) and hypercapnia (mean, range; 2.69, −0.32–5.70), (24). Responses of all of our patients fell within these normal ranges to support the conclusion that there were no consistent alterations in respiratory chemosensitivity in our MM patients.

During exercise, patients developed dyspnea that was marked by greatly increased ventilation relative to workload and metabolic rate, as indicated by elevated peak Ve/VCO₂ and Ve/VCO₂, and an abnormally steep slope of increase in ΔVe/ΔVCO₂. Exaggerated ventilation also was indicated by steep increases in VCO₂/VO₂, with values during peak exercise that ranged from 1.6 to 2.3. Although ventilation as a percentage of maximal voluntary ventilation (Ve/MVV) at peak exercise was lower in patients than controls, values for both groups were in the normal range for maximal exercise in healthy subjects (5), and ventilatory flow volume loops during peak exercise were estimated.
Table 5. Ventilatory and blood variables during incremental exercise and recovery

<table>
<thead>
<tr>
<th>Recovery - min 5</th>
<th>Recovery - min 2</th>
<th>Recovery - min 1</th>
<th>Recovery - min 0</th>
<th>Recovery - min 0</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Workload, W</strong></td>
<td>25</td>
<td>25</td>
<td>25</td>
<td>25</td>
</tr>
<tr>
<td><strong>V˙O2, l/min</strong></td>
<td>0.36 ± 0.10</td>
<td>0.32 ± 0.05</td>
<td>0.31 ± 0.05</td>
<td>0.31 ± 0.05</td>
</tr>
<tr>
<td><strong>V˙CO2, l/min</strong></td>
<td>0.29 ± 0.08</td>
<td>0.29 ± 0.08</td>
<td>0.28 ± 0.08</td>
<td>0.27 ± 0.08</td>
</tr>
<tr>
<td><strong>V˙E, l/min</strong></td>
<td>10.17 ± 3.31</td>
<td>7.65 ± 2.01</td>
<td>6.70 ± 1.85</td>
<td>5.70 ± 1.65</td>
</tr>
<tr>
<td><strong>V˙E/MVV, %</strong></td>
<td>9.13 ± 11.17</td>
<td>7.60 ± 10.01</td>
<td>6.30 ± 9.25</td>
<td>5.10 ± 8.05</td>
</tr>
<tr>
<td><strong>pH</strong></td>
<td>7.42 ± 0.03</td>
<td>7.40 ± 0.05</td>
<td>7.40 ± 0.05</td>
<td>7.40 ± 0.05</td>
</tr>
<tr>
<td><strong>PaCO2, mmHg</strong></td>
<td>37.13 ± 4.32</td>
<td>43.65 ± 5.24</td>
<td>48.75 ± 6.34</td>
<td>53.85 ± 7.45</td>
</tr>
</tbody>
</table>

Values are group mean ± SEM. **V˙O2** oxygen uptake, **V˙CO2** carbon dioxide production, **V˙E** expired minute ventilation, **V˙E/MVV** ratio of minute ventilation and maximal voluntary ventilation, **V˙E/V˙O2** ventilatory equivalent for O2, **V˙E/V˙CO2** ventilatory equivalent for CO2, **RER** respiratory exchange ratio, **W** workload, **PaO2** arterial PO2, **PaCO2** arterial PCO2, **HCO3** standard bicarbonate. *Significantly different from control group, P < 0.05; † significantly different from control group, P < 0.01; ‡ decreases in PaCO2 and HCO3 levels in MM patients.*
also been argued that such buffering of H\(^+\) does not increase CO\(_2\) production in the muscle over that which is produced by aerobic metabolism (44). Direct measurement of Pco\(_2\) in effluent venous blood from working muscle of patients with mitochondrial myopathies reveals low Pco\(_2\), despite high levels of lactate production, implying that this is not a major metabolic source of CO\(_2\) (50). This observation in combination with a steep decline in PaCO\(_2\) (Fig. 2G) indicates that high Vco\(_2\) relative to VO\(_2\) during exercise in MM patients is a consequence rather than a cause of hyperventilation.

While increased lactic acidosis is an essential feature of exercise in patients with severe mitochondrial myopathy (22, 51), and acidosis is an established mechanism of stimulating ventilation (55), the question may be asked whether lactic acidosis is sufficient to account for the increased ventilatory drive during exercise in MM patients or whether other regulatory mechanisms may be operative. Central command by which ventilation is activated by a feedforward mechanism in parallel with the activation of cortical and spinal motor neurons is presumed to be an

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**Fig. 1.** Ventilatory and perceptual response during incremental exercise as function of workload in mitochondrial myopathy patients (MM; A, C, E, G, I) and control subjects (C, B, D, F, H, J). V\(_{ti}\), expired minute ventilation; V\(_{t}/V\_O2\), ventilatory equivalent for O\(_2\); V\(_{t}/V\_CO2\), ventilatory equivalent for CO\(_2\); RER, respiratory exchange ratio, V\(_{CO2}/V\_O2\); RPB, rating for perceived breathing effort. Starting values are resting values for both groups in some MM patients followed by unloaded cycling.
important regulator of exercise ventilation (14, 32). Both MM patients and control subjects performed maximal effort cycle exercise, and there were no differences in ratings of overall perceived exertion or maximal heart rate. Thus, we consider exaggerated central command in patients to be an unlikely mechanism for increased ventilatory drive. However, since thin-fiber muscle afferents may provide a somatosensory feedback signal that modulates central command (2), the level of contribution from central command to exaggerated exercise ventilation in patients is uncertain (30, 60). Medullary respiratory centers may be activated by peripheral neuronal reflexes originating in skeletal muscle through activation of mechanoreceptors and metaboreceptors in active muscle. The role of reflex activation of the circulation, the exercise pressor reflex, mediated by stimulation of predominantly mechanically sensitive group III neural fi-
bers, and predominantly metabolically sensitive group IV fibers, is well established (47). A central feature of normal circulatory regulation in exercise is a close matching of oxygen delivery to skeletal muscle oxygen utilization. Our previous studies indicate that mitochondrial defects in skeletal muscle dramatically disrupt this relationship (21, 22, 51, 53). During exercise in mitochondrial myopathies, oxygen utilization is blocked as indicated by low peak systemic a-v\(\text{O}_2\) difference and high oxygen levels in active muscle (19). At the same time, oxygen transport is exaggerated (indicated by high cardiac output relative to workload and \(\text{VO}_2\)) with the most severe mismatches in \(\text{O}_2\) delivery relative to utilization found in the most severe mitochondrial defects (51). High exercise cardiac output in MM patients is associated with exaggerated increases in norepinephrine and epinephrine compared with healthy subjects exercising at the same absolute or relative workload (53), indicating an exaggerated sympathetic neural response to exercise in these patients consistent with the view that an exaggerated ergoreflex, originating in working muscle is an important mechanism of the hyperkinetic circulatory response to exercise in mitochondrial myopathy. The patients in our study have a classical hyperkinetic circulatory response to exercise, so it seems plausible that a similar mechanism may contribute to exaggerated exercise ventilation in these patients.

Ventilation in exercising healthy subjects has been shown to be influenced by ergoreflexes using the method employed by Alam and Smirk to demonstrate the role of muscle metaboreflexes in the exercise pressor response (1). Postexercise restriction of limb venous return by applying suprasystolic pressure, which traps metabolites produced during exercise, results in sustained increased ventilation (11, 45). This approach isolates central command and mechanoreflexes from the metaboreflex. The metabolic effectors of this reflex are incompletely understood and may be multiple (32). Research in cats suggests that H\(^+\) accumulation in skeletal muscle arising from lactic acid is a potent metabolic stimulus for both ventilatory and cardiovascular reflexes (46). Also it has been demonstrated that acid-sensing ion channels, the receptors for lactic acid, contribute to the metaboreceptor component of the exercise pressor reflex (39). Other studies have implicated a combination of metabolites in the activation of muscle afferents, including lactate, protons, and ATP (30, 37). However, Amann et al. (2) showed that group III and IV muscle afferents augment exercise ventilation at low levels of dynamic exercise that do not increase muscle lactate or proton concentrations (2).

Our study was designed to illuminate the relative contribution of these regulatory mechanisms by assessing ventilation during exercise, when central command, ergoreflexes, and circulating metabolites may modulate ventilation and during recovery from exercise, when central command is withdrawn and ergoreflexes rapidly decline but acidosis is increasing. During early recovery, ventilation decreases precipitously in all subjects, despite continued elevation of blood lactate, and decreasing pH levels. Muscle continues to release lactate following exercise and interstitial pH falls for 1–2 min postexercise (29). Acidosis-mediated hyperventilation following exercise in control subjects is suggested by an increase in RER (Fig. 5H) and \(\text{Ve}/\text{V}\text{O}_2\) (Fig. 5D) and by the fact that \(\text{PaCO}_2\) falls (Fig. 6H, Table 5). In contrast, in MM patients, RER (Fig.
and V˙E/V˙O2 (Fig. 5) rapidly falls and PaCO2 rises (Fig. 6, Table 5). This suggests that increased ventilation that would be expected to accompany increased lactic acidosis during recovery from exercise in patients is masked by the withdrawal of exaggerated ventilatory drive that is specific to exercise.

Our results highlight the critical role of normal skeletal muscle oxidative phosphorylation in the regulation of ventilation during exercise and reveal the extent to which ventilation is exaggerated to account for dyspnea as a factor limiting exercise, when muscle mitochondrial oxidative phosphorylation is severely impaired. Muscle mitochondrial dysfunction likely promotes exaggerated ventilation in exercise, in part by lactic acidosis, mediated by increased anaerobic glycolysis; however, we conclude that enhanced lactic acidosis alone cannot fully account for hyperventilation. Our results strongly suggest that direct activation of ventilation via reflexes originating in active muscle is a key mechanism of exaggerated exercise ventilation to account for symptoms of exertional dyspnea in patients with severe mitochondrial myopathy.

Fig. 5. Ventilatory and perceptional response during recovery as function of recovery time in MM patients and C subjects. VE, expired minute ventilation (A, B); V˙E/V˙O2, ventilatory equivalent for O2 (C and D); V˙E/V˙CO2, ventilatory equivalent for CO2 (E and F); RER, respiratory exchange ratio, V˙CO2/V˙O2 (G and H); and RPB (I and J). Starting values are peak exercise values for both groups.
Perspectives and Significance

This study demonstrates that exertional dyspnea in patients with severe mitochondrial myopathies is associated with greatly exaggerated ventilation relative to muscle metabolic rate that is not fully explained by increased lactic acidosis. Our results suggest that activation of ventilatory reflexes via metaboreceptors in working muscle contributes to increased ventilatory drive in MM and thus implicates metabolites that reflect limited muscle oxidative phosphorylation in mediating this response.

ACKNOWLEDGMENTS

We sincerely thank the subjects who participated in the study, and M. Newby, P. Fowler, M. Klocko, T. Semon, K. Ranasinghe who assisted with data collection and analysis. We thank Karlman Wasserman for fruitful discussions.
GRANTS
This work has been supported by grants from the National Institutes of Health (NIAMS Grant RO1 AR050597), a Department of Veterans Affairs Merit Review, King Charitable Foundation, Cain Foundation, and Texas Health Presbyterian Hospital Dallas. TT is a Chercheur Boursier Investigator of the Fonds de Recherche en Santé du Québec.

DISCLOSURES
No conflicts of interest, financial or otherwise, are declared by the authors.

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