Impaired pulmonary oxygen uptake kinetics and reduced peak aerobic power during small muscle mass exercise in heart transplant recipients


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Heart transplantation is a life-saving surgical intervention for select individuals with end-stage refractory heart failure. Despite an improvement in left ventricular systolic function after surgery (27), heart transplant recipients’ (HTR) pulmonary oxygen uptake (\(V_{O2p}\)) during peak aerobic exercise remains 50% lower than healthy individuals (13, 17, 29). Further, the kinetics of \(V_{O2p}\) following a step transition to moderate-intensity exercise (below the gas exchange ventilatory threshold) is markedly slower in HTR compared with healthy individuals (12, 22). The reason for the abnormal \(V_{O2p}\) on-kinetics is markedly slower in HTR compared with healthy individuals (12, 22). The reason for the abnormal \(V_{O2p}\) on-kinetics is markedly slower in HTR compared with healthy individuals (12, 22).

The phase II \(V_{O2p}\) time delay was greater (HTR: 38 ± 1 s) than CON (28 ± 4 s), and HHb (HTR: 27 ± 8 s vs. CON: 13 ± 3 s) were significantly slower in HTR. The HR half-time was slower in HTR (113 ± 21 s) vs. CON (21 ± 2 s). However, no significant difference was found between groups for SV kinetics (HTR: 59 ± 8 s vs. CON: 31 ± 6 s). The lower peak \(V_{O2p}\) and prolonged \(V_{O2p}\) kinetics in HTR were secondary to impairments in both cardiovascular and skeletal muscle function that result in reduced oxygen delivery and utilization by the active muscles.

METHODS

Participants

The participants for this study included five clinically stable male HTR (mean ± SE, age: 53 ± 3 years; body mass index: 27 ± 2 kg·m\(^{-2}\); time post transplant: 6 ± 4 years) and five age-, gender-, and activity-matched healthy CON (age: 53 ± 3 years; body mass index: 28 ± 1 kg·m\(^{-2}\)). The HTR participants were clinically stable and had no biopsy or clinical evidence of rejection. This investigation received approval from the University of Alberta Health Research Ethics Board (Biomedical Panel) and informed consent was obtained prior to study participation.

Experimental Protocol

Participants reported to our exercise laboratory on two separate occasions. On the first day, an incremental ULKE test was performed to determine the gas exchange ventilation threshold (2), peak and reserve \(V_{O2p}\), HR, SV, Q, \(a-Vo2\), and skeletal muscle HHb. The test was performed on a custom built knee-extensor ergometer as previ-
ously described (1), with the dominant limb used for exercise. Initial practice sessions were performed to allow for protocol familiarity, and to ensure that the exercising limb remained passive during the knee flexion phase by allowing the momentum of the flywheel to pull the participant’s limb back to the resting position. The incremental test began with 0-watt kicking for 1 min and increased by 3–5 watts/min to volitional exhaustion, or until a cadence of 50 contractions/min was no longer attainable.

On a second day, four repetitions of a square-wave protocol were conducted with a minimum rest of 20 min or greater between each exercise bout, to ensure HR, blood pressure, and VO₂p reached pre-exercise baseline values. The square-wave protocol began with a 3-min, 0-watt kicking baseline, followed by an unannounced step increase in work rate corresponding to 50% peak VO₂p (~90% of the ventilatory threshold) for 5 min. The cadence during this test was strictly maintained at 50 contractions/min.

Measurements

Pulmonary oxygen uptake and cardiovascular function. Expired gas analysis was obtained at rest and during exercise by means of a commercially available metabolic measurement system (Parvomedics, Salt Lake City, UT). A 12-lead electrocardiogram was monitored, and systolic (SBP) and diastolic (DBP) blood pressure (cuff sphygmomanometer) were recorded. The rate of change in thoracic bioimpedance (dZ/dt), first and second heart sounds, ejection time, and HR via an integrated electrocardiogram were sampled at 600 Hz (Minnesota Impedance Cardiograph, model 304B; Surcom, Minneapolis, MN). The individual dZ/dt waveforms were then measured offline independently by two investigators, and SV was calculated by means of Bernstein’s formula (4). Cardiac output (SV × HR), mean arterial pressure [MAP = 1/3 (SBP – DBP) + DBP], systemic a-vO₂diff (VO₂p/Q), and systemic vascular resistance (SVR = MAP/Q) were also calculated. The highest VO₂p over a 30-s period defined the peak score, while peak HR, SV, and Q were averaged over 5 cardiac cycles within the same period.

Skeletal muscle oxygenation. Skeletal muscle oxygenation was measured with a NICO 300 (Hamamatsu Photonics, Japan) spatially resolved near-infrared oxygenation spectroscopy monitor that employed four laser diodes to pulse near-infrared light at 775, 810, 850, and 905 nm and a photomultiplier tube for near-infrared light detection (15). Emission and detection probes were placed midway between the greater trochanter and lateral epicondyle of the femur on the biceps of the exercising vastus lateralis muscle. Probes were fixed in a cradle initially by two investigators, and SVR was calculated by means of an impedance cardiograph (model 304B; Surcom, Minneapolis, MN) in the supine position. The kinetics of near-infrared spectroscopy-derived HHb data were sampled and recorded continuously at 2 Hz. A differential pathlength factor of 3.83 was used as previously described (11). Measurement of near-infrared spectroscopy-derived HHb signals was sampled continuously at 2 Hz. An exponential curve (phase I-phase II interface) to 180 s into exercise (5).

Cardiopulmonary and skeletal muscle deoxygenation kinetic analysis. Breath-by-breath VO₂p, beat-by-beat HR, SV, Q, and instantaneous near-infrared spectroscopy-derived HHb data were sampled and recorded continuously throughout exercise. Data points were removed if greater than ±3 standard deviations from the local mean (16) and interpolated to 1-s intervals. Data from the four square-wave protocols were then time aligned and averaged to yield a single response profile for respective variables. These data were averaged into 5-s time bins to further clarify the response profiles.

The onset of phase II VO₂p kinetics was carefully determined from the phase-I-phase-II interface as previously described (30). Data for phase II VO₂p were then fit from the phase-I-phase-II interface to 180 s into exercise with a monoexponential equation of the form:

\[ Y(t) = Y_{0} + A \left[ 1 - e^{(-t/TD)} \right] \]

where \( Y \) is the VO₂p at any time \( t \), \( b \) is the baseline value of \( Y \) over 60 s prior to the step increase in work rate, \( A \) is the amplitude change in \( Y \) above the baseline, \( \tau \) is the time to reach a 63% change in \( Y \), and \( TD \) is the time delay prior to the exponential increase in \( Y \). Additionally, we calculated and reported the amplitude of the phase II VO₂p response as the amplitude in VO₂p starting from the onset of the exponential curve (phase I-phase II interface) to 180 s into exercise (5).

The same monoexponential model above was used for determining kinetic parameter estimates for SV and Q. However, curve-fitting parameter estimates were initiated at time 0 with a time delay to model the evolution of the responses from exercise onset (i.e., the time of the step increase in work rate). Given that HR increased in a linear fashion in the HTR group, the halftime of this response was used to evaluate the time course of HR. The kinetics of near-infrared spectroscopy-derived HHb data were also determined by means of the equation above. The exponential increase in HHb was modeled following a time delay, which was defined as the first data point greater than 1 standard deviation above the mean baseline value (11).

A Levenberg-Marquardt iterative procedure was used for curve fitting, where the best fit was defined by minimization of the residual sum of squares (Origin 7.5, OriginLab, Northampton, MA). Two investigators independently determined the goodness of fit of the derived nonlinear regressions to the measured data by 1) visual inspection of the curve for appropriateness of fit, 2) visual inspection of the residuals for clustering and systematic deviations from the x-axis, 3) a sudden increase in the \( \tau \) value, and 4) by demonstration of a local threshold in the reduced chi-squared value.

Statistical Analysis

Statistical analysis was performed with independent t-tests for between-group comparisons at rest, peak exercise, reserve function, and derived curve-fitting parameters. Data are expressed as mean ± SE, and \( P < 0.05 \) was considered significant.

RESULTS

Resting Cardiovascular Function and Skeletal Muscle Deoxygenation

Resting SV was significantly lower in HTR (60 ± 2 ml/beat) compared with CON (76 ± 4 ml/beat, Table 1). No significant difference was found between groups for any other resting measure (Table 1).

Peak Exercise and Reserve Cardiovascular Function and Skeletal Muscle Deoxygenation

Peak and reserve VO₂p, Q, and a-vO₂diff were 23–52% lower (\( P < 0.05 \)) in HTR than in CON (Table 1 and Fig. 1). The reduced Q reserve was due to a lower HR reserve, as SV reserve was not different between groups (Fig. 1). Peak exercise and reserve SVR and HHb, as well as peak TOI, were not significantly different between groups (Table 1 and Fig. 1). Peak and reserve MAP were significantly different between groups (Table 1 and Fig. 1). Finally, the trend line for the HHb/VO₂p relationship appeared greater in HTR than in CON at any given submaximal power output (Fig. 2).
Pulmonary Oxygen Uptake, Cardiac Output and Skeletal Muscle Deoxygenation Kinetics

During baseline (0 watt) exercise, HR was higher (HTR: 98 ± 2 beats/min vs. CON: 81 ± 7 beats/min, \( P < 0.05 \)) and SV was lower in HTR (HTR: 61 ± 3 ml/beat vs. CON: 77 ± 5 ml/beat, \( P < 0.05 \)). No significant difference was found for \( \dot{V}O_2p \) (HTR: 518 ± 54 ml/min vs. CON: 493 ± 35 ml/min), \( Q \) (HTR: 6.0 ± 0.3 l/min vs. CON: 6.2 ± 0.3 l/min), or HHb (HTR: 2.7 ± 0.6 \( \mu \)M vs. CON: 0.8 ± 1.1 \( \mu \)M) during the 0-watt kicking baseline.

The power output during constant load exercise was significantly lower in HTR (18 ± 2 watts) compared with CON (31 ± 3 watts). Figure 3 illustrates \( \dot{V}O_2p \) responses and monoequation curve fits for a representative HTR and CON. Cardiac output, \( \dot{V}O_2p \), and HHb kinetics were significantly slower in HTR compared with CON (Table 2). Using the formula from Lamarra et al. (16), we calculated the 95% confidence interval for the \( \dot{V}O_2p \) time constant to be ±2 s for HTR and ±1 s for CON. The HR halftime was significantly longer in HTR (13 ± 2 s) than in CON (21 ± 2 s); however, no significant difference was found between groups for SV kinetics (HTR: 39 ± 8 s vs. CON: 31 ± 6 s). Finally, the phase II \( \dot{V}O_2p \) amplitude was lower \( (P < 0.05) \), while the phase II \( \dot{V}O_2p \) time delay and the \( \dot{V}O_2p \) and \( Q \) mean response times were greater \( (P < 0.05) \) in HTR (Table 2).

**DISCUSSION**

Two novel findings emerged from the present investigation. First, the reduced peak \( \dot{V}O_2p \) found in HTR during ULKE exercise was the result of a lower peak \( Q \), systemic a-v\( \dot{O}_2 \)diff, and skeletal muscle \( O_2 \) extraction (as measured by near-infrared spectroscopy-derived HHb). Second, the prolonged \( \dot{V}O_2p \) kinetics during moderate-intensity ULKE exercise was associated with slower HR, \( Q \), and HHb kinetics. Accordingly, the abnormal \( \dot{V}O_2p \) kinetics and peak \( \dot{V}O_2p \) during small muscle exercise found in heart transplant recipients are due to both an \( O_2 \) delivery limitation and skeletal muscle \( O_2 \) utilization limitation.

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**Table 1. Cardiovascular function and skeletal muscle oxygenation at rest and during peak unilateral knee extension exercise**

<table>
<thead>
<tr>
<th></th>
<th>Rest</th>
<th>Peak Exercise</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HTR</td>
<td>CON</td>
</tr>
<tr>
<td>PO, watts</td>
<td>—</td>
<td>36 ± 3*</td>
</tr>
<tr>
<td>( \dot{V}O_2p ), ml/min</td>
<td>309 ± 24</td>
<td>310 ± 26</td>
</tr>
<tr>
<td>HR, beats/min</td>
<td>92 ± 4</td>
<td>78 ± 7</td>
</tr>
<tr>
<td>SV, ml/beat</td>
<td>60 ± 2*</td>
<td>76 ± 4</td>
</tr>
<tr>
<td>Q, 1/min</td>
<td>5.5 ± 0.4</td>
<td>5.9 ± 0.4</td>
</tr>
<tr>
<td>MAP, mmHg</td>
<td>98 ± 5</td>
<td>107 ± 4</td>
</tr>
<tr>
<td>a-v( \dot{O}_2 )diff, ml/100 g s(^{-1}) min(^{-1})</td>
<td>5.7 ± 0.7</td>
<td>5.3 ± 0.3</td>
</tr>
<tr>
<td>SVR, dynes s(^{-1}) cm(^{-5})</td>
<td>1.441 ± 0.96</td>
<td>1.490 ± 1.40</td>
</tr>
<tr>
<td>HHb, ( \mu )M</td>
<td>-0.4 ± 0.4</td>
<td>0.9 ± 0.6</td>
</tr>
<tr>
<td>TOI, %</td>
<td>65.2 ± 1.8</td>
<td>68.2 ± 1.1</td>
</tr>
</tbody>
</table>

Values are mean ± SE. PO, power output; \( \dot{V}O_2p \), pulmonary oxygen uptake; HR, heart rate; SV, stroke volume; Q, cardiac output; MAP, mean arterial pressure; a-v\( \dot{O}_2 \)diff, systemic arterial-venous oxygen difference; SVR, systemic vascular resistance; HHb, skeletal muscle deoxygenation; TOI, tissue oxygenation index; HTR, heart transplant recipient; CON, control. *\( P < 0.05 \) vs. CON.

**Impaired Pulmonary Oxygen Uptake During Peak ULKE Exercise Post-Heart Transplantation**

A characteristic feature post-heart transplantation is the persistent impairment in exercise tolerance despite normal left ventricular systolic function (13, 14, 27). Kao and colleagues (13, 14) and Mettauer et al. (20), using right heart catheterization and expired gas analysis during two-legged bicycle exercise, demonstrated that the reduced peak \( \dot{V}O_2p \) was primarily due to a lower \( Q \), and to a lesser extent, a lower a-v\( \dot{O}_2 \)diff. In turn, the blunted peak \( Q \) was the result of a slower chronotropic response and lower end-diastolic volume, as peak ejection fraction was similar between HTR and CON (13, 14). Our data confirm and extend prior study findings by demonstrating that peak exercise and reserve \( \dot{V}O_2p \) are 40–50% lower in HTR during aerobic exercise involving a small muscle mass. Our
finding that Q reserve is secondary to a blunted HR reserve (Fig. 1) is also consistent with previous study findings (13, 14). However, in contrast to others and our own hypothesis, the lower peak \( \dot{V}O_2p \) during ULKE exercise was the result of reductions in both peak Q (−23%) and a\( \dot{V}O_2diff \) (−23%).

The disparity between our findings and those of others may be due to different muscle mass involvement during aerobic exercise. Specifically, Andersen and Saltin (1) demonstrated that the capacity of the skeletal muscle to accommodate blood flow exceeds the upper limit of Q during large muscle mass aerobic exercise. Given that peak Q is 40% lower in HTR than in healthy sedentary individuals (13, 14), only 5 kg of muscle mass would need to be engaged in exercise for skeletal muscle perfusion capacity to exceed the upper limit of the cardiac allograft’s ability to supply blood to the systemic circulation. Consistent with this hypothesis, our peak \( \dot{V}O_2p \) (11.5 ml·kg\(^{-1}\)·min\(^{-1}\)), HR (119 beats/min), SV (78 ml/beat), and Q (9.4 l/min) during ULKE exercise (estimated quadriceps muscle mass = 1.2 kg) are similar to those reported by Kao et al. (13) for HTR during peak two-legged bicycle exercise (peak \( \dot{V}O_2p \): 11.1 ml·kg\(^{-1}\)·min\(^{-1}\); HR: 113 beats/min; SV: 82 ml/beat; Q: 9.0 l/min). Thus, the central (cardiac) limit to exercise performance that occurs with large muscle mass aerobic exercise is less prominent during small muscle mass exercise, and as a result, a peripheral limitation to peak exercise performance appears to play an equally important limiting role.

**Cardiopulmonary and Skeletal Muscle Deoxygenation Kinetics During Moderate-Intensity ULKE Exercise**

Several prior investigators have reported that \( \dot{V}O_2p \) kinetics during the onset to moderate-intensity exercise is delayed in HTR compared with age-matched healthy individuals (9, 10, 12, 17, 18, 21, 22). This finding has been attributed to a reduction in O\(_2\) supply to the active muscles (22) and to impaired skeletal muscle oxidative metabolism (12). Paterson et al. (22) examined the role that warm-up exercise had on \( \dot{V}O_2p \) on-kinetics during moderate-intensity bicycle exercise. The delayed \( \dot{V}O_2p \) kinetics found in HTR during the initial exercise on-transient was mitigated (i.e., a faster response) during the second exercise bout. Given that HR was 8% higher prior to initiating the second exercise test, the sluggish \( \dot{V}O_2p \) kinetics were attributed in part to a reduction in O\(_2\) delivery. In a similar study, Grassi et al. (12) examined the role of warm-up exercise on \( \dot{V}O_2p \) and Q (impedance cardiography) on-kinetics. Contrary to the findings by Paterson’s group, the faster Q kinetics during the second on-transient was not associated with a change in \( \dot{V}O_2p \) on-kinetics (12), leading the investigators to conclude that abnormalities in skeletal muscle oxidative metabolism results in delayed \( \dot{V}O_2p \) on-kinetics in HTR (12). Our data extend prior investigations by showing that the delayed \( \dot{V}O_2p \) kinetics in HTR vs. CON during moderate-intensity ULKE exercise was associated with a prolonged (cardiodynamic) phase II \( \dot{V}O_2p \) time delay and slower phase II \( \dot{V}O_2p \) kinetics, which contributed to an overall slower \( \dot{V}O_2p \) mean response time (Table 2). However, this finding contrasts those of Borrelli et al. (5) and Matteauer et al. (21), who reported that the cardiodynamic component of \( \dot{V}O_2p \), and not the phase II \( \dot{V}O_2p \) response, in HTR during cycling exercise accounted for slower overall \( \dot{V}O_2p \) kinetics. In the present investigation dur-

### Table 2. Cardiopulmonary and skeletal muscle deoxygenation kinetic responses during the transition to moderate-intensity unilateral knee extension exercise

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Amplitude (( \mu M ))</th>
<th>Time Delay (( \mu M ))</th>
<th>Time Constant (( \mu M ))</th>
<th>Mean Response (( \mu M ))</th>
<th>Steady State (( \mu M ))</th>
</tr>
</thead>
<tbody>
<tr>
<td>( SV ), ml/beat</td>
<td>HTR 1.3 ± 0.2</td>
<td>21 ± 0.3</td>
<td>28 ± 4</td>
<td>67 ± 8*</td>
<td>7.3 ± 0.4</td>
</tr>
<tr>
<td></td>
<td>CON 1.4 ± 0.3</td>
<td>21 ± 0.3</td>
<td>28 ± 4</td>
<td>67 ± 8*</td>
<td>7.6 ± 0.3</td>
</tr>
<tr>
<td>( Q ), l/min</td>
<td>HTR 5.3 ± 2</td>
<td>21 ± 0.3</td>
<td>27 ± 4</td>
<td>48 ± 7</td>
<td>7.9 ± 1.3</td>
</tr>
<tr>
<td></td>
<td>CON 5.4 ± 1.4</td>
<td>22 ± 3</td>
<td>13 ± 3</td>
<td>35 ± 4</td>
<td>6.2 ± 1.2</td>
</tr>
<tr>
<td>( \dot{V}O_2p ), ml/min</td>
<td>HTR 152 ± 11*</td>
<td>38 ± 2*</td>
<td>54 ± 8*</td>
<td>92 ± 9*</td>
<td>722 ± 64</td>
</tr>
<tr>
<td></td>
<td>CON 227 ± 20</td>
<td>25 ± 1</td>
<td>31 ± 3</td>
<td>56 ± 2</td>
<td>861 ± 54</td>
</tr>
</tbody>
</table>

Values are mean ± SE. *P < 0.05 vs. CON. The amplitude for \( \dot{V}O_2p \) reflects that of the phase II component.
ing small muscle mass exercise, the delayed phase II $V_{O2p}$ time delay was likely due to the slower HR kinetics at exercise onset, while the prolonged phase II $V_{O2p}$ kinetics were associated with both slower $Q$ and $Hb$ on-kinetics (Table 2).

Impaired Pulmonary Oxygen Uptake On-Kinetics and Peak Pulmonary Oxygen Uptake: Role of Abnormal Cardiovascular Function

The lower peak $V_{O2p}$ and delayed $V_{O2p}$ kinetics that we found in HTR during ULKE exercise were due, in part, to impaired cardiovascular function. Specifically, the lower peak $Q$ and slower $Q$ on-kinetics are secondary to the blunted HR and chronotropic reserve associated with cardiac denervation (13, 14). Posttransplant diastolic dysfunction manifested as prolonged acceleration of left ventricular relaxation (23), and increased diastolic passive chamber and myocardial stiffness (13, 14) may also reduce preload and $Q$ reserve. Indeed, Mettau et al. (21) found that the delayed $V_{O2p}$ phase I duration was positively related to isovolumic relaxation time in HTR. Although we did not assess diastolic function, if the absolute change in ejection fraction from rest to peak exercise was 8% (14), then the increase in estimated end-diastolic volume (+15%) would be greater than the decline in estimated end-systolic volume (−8%) during ULKE exercise. Thus, the preserved SV reserve and SV kinetics during ULKE exercise (Fig. 1 and Table 2) may be due to greater utilization of the Starling mechanism. A final reason for the blunted peak and reserve exercise $Q$ is that it may be due to an increased afterload associated with pre- and posttransplant vascular dysfunction. For example, peak SVR is 45–70% higher while SVR reserve is 15–35% lower in HTR than in normal individuals during bicycle exercise (13, 14, 20). Consistent with these findings, peak SVR was higher and SVR reserve was lower in HTR than in CON during ULKE exercise. A consequence of abnormal vascular function is an associated reduction in exercise capacity, as Bussieres et al. (7) found that HTR with the lowest peak $V_{O2p}$ also had the highest peak exercise SVR. Taken together, the lower peak $V_{O2p}$ and $V_{O2p}$ on-kinetics may be secondary to an impaired $Q$ and SVR that result in a reduction in $O2$ delivery to the exercising muscles.

Impaired Pulmonary Oxygen Uptake On-Kinetics and Peak Pulmonary Oxygen Uptake: Role of Abnormal Skeletal Muscle Oxygenation

We extend these prior research findings by revealing that the time course of near-infrared spectroscopy-derived $Hb$ is significantly delayed in HTR vs. CON during the transition to moderate-intensity small muscle mass exercise. Taken together, our findings suggest that the reduced peak $V_{O2p}$ and delayed $V_{O2p}$ on-kinetics during ULKE are also mediated, in part, by abnormal skeletal muscle function and metabolism resulting in reduced $O2$ utilization by the exercising muscles.

Limitations

A limitation of this investigation is that resting and exercise SV and $Q$ were indirectly determined via impedance cardiography. Moreover, the $a-vO2_{diff}$ was indirectly measured as $V_{O2p}$ divided by $Q$. Belardinelli et al. (3) have shown, in individuals with normal and impaired left ventricular systolic function, that impedance cardiography determined $Q$ was well correlated ($r = 0.9$) with values obtained from thermodilution and direct Fick methods. Despite this previous report, a limitation of impedance cardiography during exercise is movement-related artifact (28); however, we were able to eliminate this potential problem by having the participants isolate any movement to the exercising limb only. Further, the peak $Q$ in our CON group was similar to that reported by Magnusson et al. (19) for healthy males during peak ULKE exercise. Also, our peak $a-vO2_{diff}$ values are similar to those previously reported for HTR (20). Another limitation was that resting or exercise limb blood flow was not measured. However, given that HTR had a greater impairment in peak exercise and reserve $Q$ and SVR, we would expect HTR to have lower limb blood flow compared with the CON group. Indeed, a consequence of the reduced limb blood flow was that skeletal muscle $O2$ extraction at any given submaximal $V_{O2p}$ was higher in HTR than CON (Fig. 2).

Summary

Heart transplant recipients have a severe and marked reduction in peak $V_{O2p}$ and prolonged $V_{O2p}$ on-kinetics during ULKE exercise. Unlike large muscle mass aerobic exercise, the lower peak $V_{O2p}$, that we found during small muscle mass exercise was secondary to equal reductions in both peak exercise $Q$ and $a-vO2_{diff}$. Further, the abnormal peak and reserve $Q$ is due to a blunted HR reserve, while the lower peak $a-vO2_{diff}$ is due to reduced $Hb$. Finally, the delayed $V_{O2p}$ on-kinetics is associated with prolonged HR, $Q$, and near-infrared spectroscopy-derived $Hb$ kinetics.

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