Effects of acute leg ischemia during cycling on oxygen and carbon dioxide stores

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Abstract—This study estimated changes in whole body oxygen stores (O2s) and carbon dioxide stores (CO2s) during steady state exercise with leg ischemia induced by leg cuff inflation. Six physically fit subjects performed 75 W steady state exercise for 15 min on a cycle ergometer. After 5 min of exercise, cuffs on the upper and lower legs were inflated to 140 mmHg. Cuffs were deflated after 5 min and exercise continued for another 5 min. O2 uptake (VO2) and CO2 output (VCO2) significantly increased during the first 30 s after inflation, significantly decreased between 60 and 90 s, and then rose linearly until deflation. VO2 and VCO2 significantly increased further after cuff deflation, peaking between 30 and 60 s and then returned to near baseline exercise levels. Model-estimated changes in total O2s and CO2s were compared with time-integrated store changes from VO2 and VCO2. During 5 min after cuff deflation, VO2 and VCO2 exceeded the model-estimated change in stores by 273 and 697 mL, respectively. These results reflect the O2 cost repayment of the anaerobic component and lactate buffering to neutralize circulating metabolites caused by the preceding ischemia.

Key words: anaerobic exercise, bicarbonate buffering, carbon dioxide stores, ergoreflex, ischemia, lactate, oxygen deficit, oxygen stores, rehabilitation, ventilation/perfusion ratio, ventilation response.

INTRODUCTION

Progressive physical deconditioning is common in patients with chronic diseases, such as congestive heart failure and chronic obstructive pulmonary disease. One limitation these patients face is an inability to exercise with sufficient intensity to provide adequate training stimuli. However, regional training of muscles without taxing the central circulation can improve whole-body exercise capacity in these patients [1]. An unusual potential tool to facilitate regional muscle rehabilitation is exercise training during reduced limb blood flow [2–3]. Such “ischemic

Abbreviations: ADS = anatomical dead space (mL), BE = base excess (measure of whole blood buffer base [mmol/L]), CO2 = carbon dioxide, CO2s = CO2 stores (mL), f = breathing frequency (breaths/min), FIO2 = fraction of inspired oxygen, H+ = hydrogen ion concentration (nmol/L), Hb = hemoglobin concentration (g%), HCO3− = bicarbonate concentration (mmol/L), O2 = oxygen, O2s = O2 stores (mL), PACO2 = partial pressure of alveolar CO2 (mmHg), PAO2 = partial pressure of blood oxygen (mmHg), PBl = barometric pressure, PCO2 = partial pressure of CO2 (mmHg), pHA = arterial pH, PO2 = partial pressure of O2 (mmHg), Q = cardiac output (L/min), RER = respiratory exchange ratio (CO2 output/O2 uptake), VA = alveolar ventilation ([L/min] body temperature, ambient pressure, saturated), VCO2 = CO2 output ([mL/min] standard temperature and pressure, dry), VE = pulmonary ventilation ([L/min] body temperature, ambient pressure, saturated), VO2 = O2 uptake ([mL/min] standard temperature and pressure, dry), VO2max = maximal VO2.

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limb training” with limb pressure cuffs has improved limb strength and exercise endurance in physically fit subjects [4–5], diminished postoperative disuse atrophy of knee extensors [6], and induced favorable biochemical and structural changes in muscles [7–8]. Ischemic limb training with low-intensity exercise in patients with congestive heart failure has also reduced exertional dyspnea [9]. We recently demonstrated that leg-extension exercise endurance was enhanced with a 6-week training program of very light leg-extension exercise with ischemia induced by thigh cuff inflation [10].

Superimposing ischemia on exercising limbs provokes the muscle metaboreflex, whereby pulmonary ventilation ($V_{E}$) and systemic blood pressure are elevated by a chemoreflex stimulated by buildup of metabolic by-products in the ischemic limbs; the most likely candidate is hydrogen ion concentration ($H^+$) [11]. The oxygen ($O_2$) stores ($O_{2s}$) and carbon dioxide ($CO_2$) stores ($CO_{2s}$) in the region where blood flow is occluded, as well as in the whole body, will be affected during this ischemia and after circulation is restored as a result of ventilatory, blood flow, and biochemical perturbations. The magnitude and time course of these gas store changes will affect regional and whole-body acid-base status, will cause secondary ventilatory and gas exchange fluctuations during and after exercise, and may induce transient hypoxemia and hypercapnia, such as noted following passive changes in posture [12].

Although rapid transient changes in $O_{2s}$ and $CO_{2s}$ during exercise workload transitions have been studied and quantified [13], gas store changes induced by limb ischemia have received little attention. Specifically, the quantitative relationship is not well defined between $O_2$ repayment and $CO_2$ elimination after exercise requiring energy partially derived from anaerobic sources [14] and these measurements with the anaerobic component artificially superimposed have not been reported. Therefore, this study was an initial attempt to estimate the time course and magnitude of changes in $O_{2s}$ and $CO_{2s}$ during and after acute, temporary ischemia of the legs applied by cuff inflation during steady state exercise on a cycle ergometer.

**METHODS**

**Subjects**

Five men and one woman volunteered as subjects. Informed consent was obtained from each person, as approved by the University of New Mexico Human Research Review Committee. All were physically fit and regularly taking part in physical recreation and fitness activities, including jogging and cycling. Their ages ranged from 24 to 62 yr, with a mean body weight and body mass index of 82.5 kg and 25.0 kg/m², respectively. Their maximal $O_2$ uptake ($V_{O2max}$) averaged 48 mL·min⁻¹·kg⁻¹ (range: 42–56). The $O_2$ uptake ($\dot{V}O_2$) during exercise before ischemia (baseline) averaged 35.7 percent (range: 30%–42%, standard error of the mean = 1.7%) of the subjects’ $V_{O2max}$. This percentage was not related to age ($r = -0.22$).

**Ergometer Exercise and Inflation Cuffs**

We placed cuffs on each upper thigh (SC-17, Hokanson Co; Bellevue, Washington) and each lower leg (SC-22) using adhesive tape to keep them in position during exercise. Lower leg cuffs were used to minimize trapping of blood and to enhance ischemia of the calf muscles. Cuffs were inflated to 140 mmHg during exercise. This cuff pressure, slightly exceeding systolic pressure, was chosen after preliminary trials indicated that discomfort at this pressure could be tolerated and gas exchange transients stabilized in about 5 min at the chosen workload. Although the blood pressure response of each subject to the inflation pressure varied, we maintained the pressure at the same level for all to reduce variations in blood “pooling” and thereby reduce variability in the measured responses. Resting measurements were made for 5 min while subjects sat on the ergometer before and after exercise. Subjects cycled for 15 min at 75 W on an electrically load-controlled Bosch ergometer (model ERG 551; Munich, Germany) at 50 to 60 rpm. After 5 min, the four cuffs were simultaneously inflated over a $\approx 10$ s period from a gas cylinder pressure source. Cuff pressure was maintained for 5 min and then deflated rapidly in 3 s, with exercise continuing for another 5 min.

**Measurements and Calculations**

We measured gas exchange at the mouth while subjects sat on the ergometer at rest, during exercise, and at rest after exercise, using a TrueMax 2400 breath-by-breath automated system (Parvomedics, Inc; Sandy, Utah) with incorporated software and model 2700 Rudolph breathing valve and mouthpiece (Hans Rudolph, Inc; Shawnee, Kansas). The measurements included $\dot{V}O_2$, $CO_2$ output ($\dot{V}CO_2$), $V_E$, calculated respiratory exchange ratio (RER), and $V_E/\dot{V}CO_2$ as an index of ventilatory drive. Alveolar ventilation ($V_A$) was calculated from anatomical
dead space (ADS) taken as apparatus dead space + milli-
liter = body weight in pounds [15] and breathing frequency
(f) as $\dot{V}_{A} = \dot{V}_{E} - f \times ADS$. Experiments were conducted at
an average barometric pressure ($P_B$) of 631 mmHg (range:
630–635 mmHg) and ambient fraction of inspired O$_2$
($FIO_2$) of 0.2094. Partial pressure of CO$_2$ ($PCO_2$) in alve-
oli ($PACO_2$) and partial pressure of O$_2$ ($PO_2$) in alveoli
($PAO_2$) were calculated from alveolar gas equations [16]:

$$PACO_2 = \frac{\dot{V}CO_2 \times 0.863}{\dot{V}A} \quad (1)$$

and

$$\dot{V}O_2 = (P_B < 47.1)FIO_2 \times PACO_2 \times [FIO_2 + (1 \times FIO_2)/RER]. \quad (2)$$

We averaged breath-by-breath measurements continu-
ously over 30 s intervals for each subject throughout exer-
cise and the pre- and postexercise rest periods. We then
averaged these values for the six subjects to obtain repre-
sentative temporal patterns for analysis.

Average changes in O$_2$s and CO$_2$s were calculated
from differences between measured and predicted gas exchange
time courses integrated over time. We based pre-
dicted values on baseline gas exchange measurements dur-
ing the 5th min, assuming these represented steady state
values required by the workload, and an increase during ischemia based on assumptions given in the subsequent
section for predicted gas exchange. An increase in O$_2$s was
indicated when measured $\dot{V}O_2$ is greater than predicted
$\dot{V}O_2$ over time, and a decrease in CO$_2$s was indicated
when measured $\dot{V}CO_2$ is greater than predicted $\dot{V}CO_2$
and vice versa. Differences in these gas store changes dur-
ing and after blood flow restriction were attributed to the
ischemia. In addition, we obtained total body gas stores
present during baseline, 5th min during cuff inflation, and
5th min after cuff deflation from a model using gas exchange,
blood flow, and blood volume values. We also used differences between these modeled total store values and the time-integrated measured values of changes in O$_2$s and CO$_2$s to extract effects of leg ischemia.

**Predicted Gas Exchange**

During cuff inflation, we assumed the predicted time
course for $\dot{V}O_2$ would increase linearly during the 6th
through 10th min from the steady state exercise value at
5 min because of—

1. A gradual loss of mechanical efficiency by increasing
   recruitment of ancillary muscles of the hip, torso, and
   arms to maintain leg work as fatigue increased.
2. Increased $O_2$ cost of ventilation stimulated by the
   metaboreflex, which may account for as much as one-
   third of the observed $\dot{V}O_2$ rise [17–18].
3. The partial restoration of curtailed leg circulation by
   the reflex rise in blood pressure that would enhance $O_2$
   delivery to the legs despite restricted blood flow dur-
   ing cuff inflation.
4. The subjects’ subjective reports that the last minute of
   exercise seemed less stressful than the previous min-
   utes, indicating that the anaerobic component of the
   energy supply had stabilized.

During the 5 min following cuff deflation, $\dot{V}O_2$ was
assumed to decline exponentially to the baseline exercise
value by 15 min because the factors just listed were
removed by cuff deflation and the elevated $\dot{V}O_2$ was
expected to return similarly to that following the removal
of an additional acute exercise workload. The predicted
$\dot{V}CO_2$ was similarly assumed to increase linearly from
baseline to 10 min, but to a value calculated as measured
$\dot{V}O_2 \times$ measured baseline RER before cuff inflation (for
correcting the elevated $\dot{V}CO_2$ from the increase in $\dot{V}E$
resulting from the metaboreflex), and then decline expo-
nentially to the baseline value by 15 min.

**Total Gas Stores Model with Blood Flow and Volume
Redistribution**

Computations and assumptions are shown in the fol-
lowing list for compartmental and total whole body O$_2$s
and CO$_2$s during exercise at three exercise conditions A,
B, and C: A = baseline, 5th min before cuff inflation; B =
5th min of cuff inflation; and C = 5th min after cuff defla-
tion. Arterial and mixed venous blood $O_2$ and CO$_2$
contents and mixed venous PO$_2$ and PCO$_2$ were calculated
from a computer model integrating gas exchange and
blood flow values [19–20].

- Blood volume.
  - Total = 71.5 mL/kg body weight = 5,900 mL.
  - Venous compartment for exercise conditions A and
    C = total $\times$ 0.8 = 4,720 mL.
  - Arterial compartment for exercise conditions A and
    C = total $\times$ 0.2 = 1,180 mL.
  - During condition B, a 300 mL blood volume shift
    from the venous to arterial compartment was pre-
    dicted based on transient increases in measured $\dot{V}O_2$
    and a $\dot{V}CO_2$ from 30 to 60 s after cuff deflation.
- Lung: $O_2$ and CO$_2$ were calculated from PAO$_2$ and
  PACO$_2$ and an assumed functional residual capacity
  of 4.0 L.
• Arterial O₂: Content based on Hb (hemoglobin concentration) = 15 g%, arterial PO₂ = PAO₂, saturation = standard dissociation curve [21] at pHₐ (arterial pH, the negative log of H⁺ in arterial blood) calculated to maintain whole blood base excess (BE) equal to baseline [22], where a pHₐ value of 7.420 was assumed.

• Venous O₂: Content from Fick equation with arterial content and measured VO₂ at exercise conditions A, B, and C and cardiac output (Q) = 15 L/min at conditions A and C, with 1 L/min reduction during condition B, based on observations during cuff-induced ischemia by Asmussen and Nielsen [23].

• Tissue O₂
  – PO₂ from venous content and saturation from standard curve.
  – PO₂ × body weight (82.5 kg) × 0.64 × 0.024 [24].

• Arterial CO₂
  – Content based on arterial PCO₂ = PACO₂.
  – Content from CO₂ dissociation curve at Hb and pHₐ [25].

• Venous CO₂: Content from Fick equation with arterial CO₂ content and measured VCO₂ and predicted Q at exercise conditions A, B, and C.

• Tissue CO₂
  – PCO₂ for venous content from CO₂ dissociation curve.
  – PCO₂ × body weight × 1.02.

We obtained half-times for rest-to-exercise (“on”) responses and (“off”) transitions from exponential fits to the 10 measured breath-by-breath intervals. We used paired t-tests to determine significance (p < 0.05) of selected individual transient changes over time and used least squares linear regressions to estimate the significance of relationships between selected variables.

RESULTS

The average VO₂ and VCO₂ measurements during rest, exercise, and postexercise rest are shown in Figure 1. A plateau for both measurements was reached after ≈3 min of exercise, because the 5th min values were not significantly above the 3 min values (p > 0.13). Transient changes induced by ischemia and cuff deflation appeared to have stabilized by the end of exercise. The baseline mechanical efficiency at 75 W for a VO₂ of 1,410 mL/min (minus the resting VO₂ of 335 mL/min) was 20.0 percent, decreasing to 17.1 percent at 1,595 mL/min by the end of inflation. During the 5 min postexercise rest period, the total excess VO₂ and VCO₂ were both significantly larger than the 5 min VO₂ deficits following exercise onset. The averages of the corresponding changes in gas stores calculated from time-integrated values for measured and predicted VO₂ and VCO₂ are detailed in Figure 2.

Oxygen

Measured VO₂ increased significantly during the first 30 s after cuffs were inflated (p = 0.042) and then declined transiently, but significantly, at 6.5 min by 72 mL/min (p = 0.049). VO₂ then rose steadily until cuffs were deflated. The O₂s cumulative loss over 5 min of cuff inflation was 227 mL (Figure 2). VO₂ peaked 45 s after cuff deflation, being 150 mL above adjacent measurements (p = 0.001). The 5 min postdeflation exercise VO₂ excess indicated that O₂s increased by 518 mL.

Carbon Dioxide

Measured VCO₂ during ischemia is related to similar circulatory and biochemical events affecting VO₂ but is partially overridden by the large increase in VE (Figure 3),
because of the metaboreflex stimulation by leg ischemia. CO₂S decreased by 497 mL by the end of the 5 min inflation, and 5 min after cuff deflation at 10 min. Values averaged for 30 s. Predicted time course for VO₂ and VCO₂ is described in main text. Values for changes in stores (milliliters) are indicated for time-integrated totals over 5 min of inflation and 5 min after cuff deflation. req = required.

Ventilation

After exercise termination, the off-responses for VCO₂ and V̇E (Figure 3) were similar to each other and their on-responses (36–39 s) but slower than the on-response for VO₂. VO₂ and VCO₂ were slightly above baseline at the end of the 5 min postexercise rest period (Figure 1). The RER was significantly higher during the 5th min postexercise rest compared with the preexercise rest because VCO₂ was significantly higher (30%) than VO₂ (18%), indicating a residual enhanced ventilatory drive.

Whole Body CO₂S

By superimposing controlled hyperventilation, one can obtain estimates of whole-body CO₂S during exercise. From measurements in these “hyperventilation” experiments during ischemic exercise, the whole-body CO₂ capacitance (dissociation curve) was 1.2 L·mmHg⁻¹·kg⁻¹, as calculated
from the excess of measured vs predicted $\dot{V}CO_2$ (497 mL) (Figure 2) per change in PACO$_2$ (5 mmHg) (Figure 3) per body weight (82.5 kg).

**Model of Total and Changing Gas Stores**

Table 1 shows the compartmental and total gas stores calculated for the three exercise conditions from the flow and volume redistribution model. Because lactate, bicarbonate concentration (HCO$_3^-$), and BE changes are linearly related [22], we incorporated a decrease in whole blood BE of 4 mmol/L estimated from other studies (see “Discussion”) during the 5th min after cuff deflation to account for circulating lactate. The values from the total stores model from Table 1 are indicated in Figure 4 in relation to the 5 min-integrated stores changes obtained from measured gas exchange (Figure 2). According to the model, during cuff inflation, total O$_2$s did not change and CO$_2$s decreased 164 mL, whereas the 5 min totals (Figure 2) decreased 227 and 497 mL, respectively. The difference indicates that the redistribution of blood volume and flow, the anaerobic work component, and hyperventilation resulted in losses of 227 mL and 333 mL in O$_2$s and CO$_2$s, respectively. During the 5th min after cuff deflation, O$_2$s increased by 18 mL and CO$_2$s decreased another 465 mL, whereas the 5 min totals showed that O$_2$s increased by 518 mL and CO$_2$s decreased by 1,162 mL. For O$_2$s, reducing the 518 mL gain after cuff deflation by the 18 mL increase in total stores, as well as the 227 mL deficit during prior inflation (which is being repaid), leaves a net gain of 273 mL used to repay the anaerobic cost during ischemia. The 1,162 mL 5 min loss in CO$_2$s after cuff deflation exceeds the 465 mL loss in absolute stores by 697 mL (Figure 4). Over the total 10 min, 5 min before and 5 min after inflation, the ratio of the total loss in CO$_2$s versus gain in O$_2$s is 3.7 (1,030/273), which includes the hyperventilation “artifact” during ischemia.

<table>
<thead>
<tr>
<th>Condition</th>
<th>Location</th>
<th>PO$_2$</th>
<th>O$_2$ Stores</th>
<th>PCO$_2$</th>
<th>CO$_2$ Stores</th>
</tr>
</thead>
<tbody>
<tr>
<td>A. 5th Min Baseline</td>
<td>Arterial</td>
<td>84.1</td>
<td>232</td>
<td>33.8</td>
<td>479</td>
</tr>
<tr>
<td>(BE = –1.8 mmol/L, pHa = 7.420, $Q = 15$ L/min)</td>
<td>Venous</td>
<td>28.9</td>
<td>486</td>
<td>45.4</td>
<td>2,293</td>
</tr>
<tr>
<td></td>
<td>Tissue</td>
<td>28.9</td>
<td>37</td>
<td>45.4</td>
<td>3,824</td>
</tr>
<tr>
<td></td>
<td>Lung</td>
<td>84.1</td>
<td>576</td>
<td>33.8</td>
<td>231</td>
</tr>
<tr>
<td>Total</td>
<td>—</td>
<td>—</td>
<td>1,331</td>
<td>—</td>
<td>6,827</td>
</tr>
<tr>
<td>B. 5th Min Cuff Inflation</td>
<td>Arterial</td>
<td>92.1</td>
<td>293</td>
<td>28.9</td>
<td>559</td>
</tr>
<tr>
<td>(BE = –1.8 mmol/L, pHa = 7.462, $Q = 14$ L/min)</td>
<td>Venous</td>
<td>25.3</td>
<td>375</td>
<td>44.7</td>
<td>2,146</td>
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<tr>
<td></td>
<td>Tissue</td>
<td>25.3</td>
<td>32</td>
<td>44.7</td>
<td>3,760</td>
</tr>
<tr>
<td></td>
<td>Lung</td>
<td>92.1</td>
<td>631</td>
<td>28.9</td>
<td>198</td>
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<tr>
<td>Total</td>
<td>—</td>
<td>—</td>
<td>1,331</td>
<td>—</td>
<td>6,663</td>
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<tr>
<td>B – A</td>
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<td>—</td>
<td>0</td>
<td>—</td>
<td>–164</td>
</tr>
<tr>
<td>C. 5th Min Cuff Deflation$^*$</td>
<td>Arterial</td>
<td>86.6</td>
<td>232</td>
<td>31.4</td>
<td>402</td>
</tr>
<tr>
<td>(BE = –5.8 mmol/L, pHa = 7.370, $Q = 15$ L/min)</td>
<td>Venous</td>
<td>30.3</td>
<td>486</td>
<td>42.7</td>
<td>1,986</td>
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<tr>
<td></td>
<td>Tissue</td>
<td>30.3</td>
<td>38</td>
<td>42.7</td>
<td>3,595</td>
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<tr>
<td></td>
<td>Lung</td>
<td>86.6</td>
<td>593</td>
<td>31.4</td>
<td>215</td>
</tr>
<tr>
<td>Total</td>
<td>—</td>
<td>—</td>
<td>1,349</td>
<td>—</td>
<td>6,198</td>
</tr>
<tr>
<td>C – B</td>
<td>—</td>
<td>—</td>
<td>18</td>
<td>—</td>
<td>–465</td>
</tr>
<tr>
<td>C – A</td>
<td>—</td>
<td>—</td>
<td>18</td>
<td>—</td>
<td>–629</td>
</tr>
</tbody>
</table>

Note: O$_2$s and CO$_2$s are based on model given in “Methods” of main text with assumptions:
- Total blood volume = 5,900 mL.
- Venous volume = total × 0.8 = 4,720 mL; arterial = total × 0.2 = 1,180 mL in conditions A and C.
- 300 mL was shifted from venous to arterial compartment in condition B; i.e., venous = 4,420 mL and arterial = 1,480 mL.

$^*$Adjusted for ABE = –4.0 mmol/L.

BE = base excess (measure of whole blood buffer base), pHa = arterial pH (negative log of H$^+$ in arterial blood), PCO$_2$ = partial pressure of carbon dioxide, PO$_2$ = partial pressure of oxygen, $Q =$ cardiac output.
DISCUSSION

The initial increase in VO₂ during the 1st min of ischemia can be accounted for by the bolus of venous blood from the legs moving into the central circulation during cuff inflation and its oxygenation to arterial blood as it traverses the pulmonary capillaries. This ≈30 mL of O₂ (Figure 2) would reoxygenate 300 mL of venous blood having an O₂ content of 10 vol%. This rise in VO₂ and the ≈30 mL significant simultaneous loss of CO₂ (p = 0.004) indicated a 300 mL shift of blood from the venous to arterial compartment. A redistribution of blood flow accounted for the transient reduction in VO₂ during the 2nd min of ischemia, whereby cuffs restricted O₂ delivery to the legs by arterial blood, reducing VO₂ temporarily and increasing O₂ content of mixed venous blood. Similar cardiovascular readjustments with breath holds during exercise have been noted to reduce VO₂ [26]. The linear rise during the last 3 min with ischemia reflects the decreasing mechanical efficiency and the progressive partial restoration of leg circulation. The peak 45 s after cuff deflation signifies lung reoxygenation of venous blood returning from the legs, extracting more O₂ to repay the aerobic and anaerobic deficit incurred during the prior ischemia. Most of the anaerobic deficit was repaid over the last 3 min of uncuffed exercise as VO₂ returned to near baseline exercise levels. However, some residual debt repayment probably occurred during the postexercise rest because the repayment exceeded the deficit at the start of exercise by 423 mL (Figure 1) and the half-time of the off-response (37 s) was significantly (p = 0.001) slower than the on-response (27 s); the latter value agreed with previous reports [27–28].

The estimated CO₂ capacitance value of 1.2 L·mmHg⁻¹·kg⁻¹ is lower than that (1.6) interpolated for the same exercise workload from a report [29] during 15 min of hyperventilation, although values twice as high have also been reported [30]. Capacitance values are directly related to the length of experiments, because more CO₂ is then washed out of slower compartments [31]. Because leg perfusion was impaired during our experiments, one would have expected a relatively low capacitance value because CO₂ in blood and tissue of the legs are then washed out at a slower rate, being somewhat isolated from the lung. Another consideration is that CO₂S change significantly slower than O₂S, having a half-time of 4.0 min versus 0.5 min for O₂S, based on studies on dogs by Farhi and Rahn [24]. This finding suggests that part of the loss in CO₂S following cuff deflation may be attributed to the hyperventilation during the prior ischemia.

After cuff deflation, the larger CO₂ loss relative to O₂ gain resulted from the HCO₃⁻ buffering of lactate entering the circulation. Correlation of lactate levels with excess VCO₂ in relation to VO₂ during and after heavy exercise resulted in the “anaerobic threshold” concept [32–33]. Excess VCO₂ during exercise has also been used to estimate lactate accumulation in physically fit subjects [34] and cardiac patients [35]. The elevated VCO₂ and CO₂S depletion is caused by carbonic acid, arising from the combination of H⁺ with HCO₃⁻; dissolved CO₂ from the muscle tissue being transported to the lungs once circulation is restored; and elevated V̇E. As shown by V̇E/VCO₂ in Figure 3, the metaboreflex ventilatory drive was quickly diminished after cuff deflation, but the drive was then taken over by the chemoreflex stimulated by elevated H⁺ and PCO₂ in blood arriving at central chemoreceptors and continuing during subsequent rest.

In studies somewhat similar to this one, a rise of arterial blood lactate of ≈4 mmol/L was reported 4 to 5 min after cuff deflation [36] and also a 4 mmol/L loss of plasma HCO₃⁻ [37]. This amount of lactate release was incorporated into the model shown in Table 1 and Figure 4. If 4 mmol/L of lactate release from the legs to central
circulation was entirely buffered by $\text{HCO}_3^-$ during the 5 min postinflation period, it would amount to a $\text{CO}_2$S loss of 4 mmol/L × 5.9 L × 22.3 mL/mmol = 526 mL [33]. This amount accounts for 75 percent of the 697 mL estimate. However, the ratio of $\text{CO}_2$ loss to $\text{O}_2$ gain of 2.6 (697/273) suggests that a part of the lactate may have been converted by oxidation, in addition to being buffered [38]. These and other biochemical processes must have continued beyond the postexercise resting measurement period to fully restore $\text{O}_2$S and $\text{CO}_2$S to baseline levels of 1,331 and 6,827 mL, respectively. However, most of the excess $\text{CO}_2$ was eliminated by the time exercise stopped because $\text{VCO}_2$ had returned to baseline (Figure 1). Without prolonged lactate turnover measurements, we can only generalize that the majority of the lactate was buffered in preference to other chemical pathways to account for the $\text{CO}_2$S loss exceeding the $\text{O}_2$S gain. Qualitatively, $\text{V}_E$ increases during exercise with cuffs inflated, depleting $\text{CO}_2$S, while the partially anaerobic exercise continues. When cuffs are deflated and after exercise stops, metabolic by-products from the legs returning to the central circulation keep ventilation elevated to repay $\text{O}_2$S, while $\text{CO}_2$S remains below baseline for a longer time.

Clearly, the assumptions in the total gas stores model demonstrated in Table 1 and Figure 4 will affect the absolute values and changes in gas store values. Some quantities, such as tissue water and arterial and venous blood volumes, are not easily measured and were taken from estimates in the literature. To quantify the effect of variations in these assumed values, in Table 2, we show changes in total $\text{O}_2$S and $\text{CO}_2$S resulting from variations in values from those used in Table 1 during the three exercise conditions. We varied indicated values for relevant physiological components individually, assuming the other variables remained constant. Table 2 indicates that calculations of total $\text{O}_2$S and $\text{CO}_2$S and phase differences in stores are most sensitive to values for Hb and reductions in $\text{Q}$ during the ischemic phase. Any alveolar-arterial differences in $\text{PO}_2$ and $\text{PCO}_2$ greatly influence total stores, especially $\text{CO}_2$S, but the effect on store differences is smaller, somewhat similar to changing values for the other components. Therefore, performing invasive measurements, including arterial and mixed venous blood gases and lactate, in more definitive future studies is important.

Most studies using cuffs to induce acute exercise ischemia have focused on the $\text{V}_E$ response following cuff deflation to study $\text{CO}_2$ chemoreceptor response mechanisms. Data from some of these reports [23,36–37,39–40] allowed a gas store pattern estimation to compare with this study and are shown in Table 3. Generalizations from these limited data include (1) an inverse relationship between cuff pressure and $\text{O}_2$S reduction during inflation, (2) a direct relationship between workload and the increase in $\text{O}_2$S and reduction in $\text{CO}_2$S after cuff deflation, and (3) the $\text{CO}_2$S loss after cuff deflation exceeds the change during inflation and also exceeds the $\text{O}_2$S gain in recovery. From the time trends in the present study and those prior studies where time resolution was presented [37,39], apparently during inflation, the decrease in $\text{O}_2$S is attenuated as exercise duration increases. This finding is probably associated with the increasing $\text{VO}_2$ required by the

### Table 2.
Effect on total gas stores of variations in assumed values for gas stores model during three conditions A, B, and C of 15 min exercise: 5th min baseline, 5th min of cuff inflation, and 5th min after cuff deflation, respectively.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Value</th>
<th>Exercise Condition</th>
<th>Value Change</th>
<th>$\text{O}_2$S Difference</th>
<th>$\text{CO}_2$S Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Functional Residual Capacity (L)</td>
<td>4.0</td>
<td>A, B, C</td>
<td>+10%</td>
<td>60 (4.5)</td>
<td>21 (0.3)</td>
</tr>
<tr>
<td>Blood Volume (L)</td>
<td>5.9</td>
<td>A, B, C</td>
<td>+10%</td>
<td>69 (5.2)</td>
<td>263 (4.0)</td>
</tr>
<tr>
<td>Hb (g%)</td>
<td>15.0</td>
<td>A, B, C</td>
<td>+10%</td>
<td>118 (8.8)</td>
<td>110 (1.7)</td>
</tr>
<tr>
<td>Alv-Art Diff (mmHg)</td>
<td>PCO$_2$ &amp; PO$_2$ = 0</td>
<td>A, B, C</td>
<td>3, 13</td>
<td>112 (8.4)</td>
<td>536 (8.2)</td>
</tr>
<tr>
<td>H$^+$ (mmol/L)</td>
<td>pH$_a$ = 7.42 at base</td>
<td>A, B, C</td>
<td>+10%</td>
<td>4 (0.3)</td>
<td>193 (2.9)</td>
</tr>
<tr>
<td>Q Decrease (L/min)</td>
<td>1.0</td>
<td>B</td>
<td>0 &amp; 2</td>
<td>37 (2.8)</td>
<td>141 (2.1)</td>
</tr>
<tr>
<td>BE Decrease (mmol/L)</td>
<td>4.0</td>
<td>C</td>
<td>-3 &amp; -5</td>
<td>2 (0.1)</td>
<td>73 (1.2)</td>
</tr>
</tbody>
</table>

Note: $\text{CO}_2$S decreases 73 mL per 1.0 mmol/L decrease in BE.

*Mean absolute differences in total gas stores (milliliters) from values in Table 1 (see main text).
†These mean differences as % of values in Table 1.
‡Mean of differences in gas store changes between conditions from those in Table 1.

Alv-Art = alveolar-arterial, BE = base excess (measure of whole blood buffer base), $\text{CO}_2$S = carbon dioxide stores, diff = differences, H$^+$ = hydrogen ion concentration, Hb = hemoglobin concentration, $\text{O}_2$S = oxygen stores, PCO$_2$ = partial pressure of carbon dioxide, pH$_a$ = arterial pH, PO$_2$ = partial pressure of oxygen, Q = cardiac output.
Table 3.
Cumulative time-integrated oxygen uptake ($\dot{V}O_2$), carbon dioxide output ($\dot{V}CO_2$), and pulmonary ventilation ($\dot{V}_E$) differences from baseline during leg cuff inflation and after cuff deflation.

<table>
<thead>
<tr>
<th>Studies</th>
<th>n</th>
<th>Work (W)</th>
<th>Cuff Pressure (mmHg)</th>
<th>Work Time Before Inflation (min)</th>
<th>Inflation Time (min)</th>
<th>$\dot{V}O_2$ (mL)</th>
<th>$\dot{V}CO_2$ (mL)</th>
<th>$\dot{V}_E$ (L)</th>
<th>Recovery Time (min)</th>
<th>$\dot{V}O_2$ (mL)</th>
<th>$\dot{V}CO_2$ (mL)</th>
<th>$\dot{V}_E$ (L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stegemann, 1963 [1]</td>
<td>None given</td>
<td>0</td>
<td>250–300</td>
<td>0</td>
<td>10</td>
<td>-495</td>
<td>-387</td>
<td>-13</td>
<td>20</td>
<td>448</td>
<td>599</td>
<td>14</td>
</tr>
<tr>
<td>Asmussen &amp; Nielsen, 1964 (CO2 added to maintain PACO2) [2]</td>
<td>1</td>
<td>31</td>
<td>300–350</td>
<td>10–15</td>
<td>3</td>
<td>-358</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Sargeant et al., 1981 [3]</td>
<td>5</td>
<td>100</td>
<td>250</td>
<td>0</td>
<td>2</td>
<td>-130</td>
<td>350</td>
<td>32</td>
<td>4</td>
<td>770</td>
<td>1,591</td>
<td>45</td>
</tr>
<tr>
<td>Stanley et al., 1985 [4]</td>
<td>8</td>
<td>49</td>
<td>200</td>
<td>6</td>
<td>2</td>
<td>-274</td>
<td>129</td>
<td>8</td>
<td>4</td>
<td>547</td>
<td>799</td>
<td>16</td>
</tr>
<tr>
<td>Roth et al., 1988 [5]</td>
<td>9</td>
<td>98</td>
<td>200</td>
<td>6</td>
<td>2</td>
<td>-428</td>
<td>106</td>
<td>10</td>
<td>4</td>
<td>643</td>
<td>1,151</td>
<td>23</td>
</tr>
<tr>
<td>This Study</td>
<td>6</td>
<td>75</td>
<td>140</td>
<td>5</td>
<td>5</td>
<td>282</td>
<td>932</td>
<td>55</td>
<td>5</td>
<td>654</td>
<td>1,283</td>
<td>57</td>
</tr>
</tbody>
</table>

Note: See legend to Figure 2 for “predicted” values for $\dot{V}O_2$, $\dot{V}CO_2$, and $\dot{V}_E$ for this study; here all “predicted” values were assumed equal to baseline.


CO2 = carbon dioxide, PACO2 = partial pressure of alveolar CO2 (mmHg).

Elevated $\dot{V}_E$ and extra muscular effort and partial restoration of leg blood flow that diminish the O2S deficit and increase the CO2S deficit. Apparently, leg cuff pressures must be >90 mmHg during exercise to affect measured $\dot{V}CO_2$ and $\dot{V}O_2$ during exercise [41–42].

SUMMARY AND CONCLUSIONS

The events in these experiments can be described as a respiratory alkalosis during ischemia, followed by a metabolic acidosis after cuff deflation when metabolites from the anaerobic portion of leg work return to the central circulation. Changes in O2S depend mainly on perfusion through lung and tissue, while CO2S changes are primarily determined by $\dot{V}_E$, venous blood redistribution, and HCO3⁻ buffering of lactate. This study estimated that the ischemia required a repayment of 273 mL of O2 and produced 697 mL of CO2. These values depend on workload, work duration with ischemia, the cuff pressure determining the perfusion impairment, and the intensity of the metaboreflex. The amount of anaerobic debt incurred and tolerated and the recovery from a given ischemic exercise scenario will depend on the aerobic fitness of the subject and related blood pressure reflex response. These factors must be considered if this form of exercise is further evaluated and implemented for rehabilitation.

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