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

Jack A. Loeppky, PhD;[1*] Burke Gurney, PhD;[2] Milton V. Icenogle, MD[3]
[1]Research Service, Department of Veterans Affairs Medical Center (VAMC), Albuquerque, NM; [2]Department of Orthopaedics and Division of Physical Therapy, University of New Mexico Health Sciences Center, Albuquerque, NM; [3]Cardiology Section, VAMC, Albuquerque, NM

Abstract—This study estimated changes in whole body oxygen stores (O_2s) and carbon dioxide stores (CO_2s) 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. O_2 uptake $(\dot{V}O_2)$ and CO_2 output $(\dot{V}CO_2)$ significantly increased during the first 30 s after inflation, significantly decreased between 60 and 90 s, and then rose linearly until deflation. $\dot{V}O_2$ and $\dot{V}CO_2$ 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 O_2s and CO_2s were compared with time-integrated store changes from $\dot{V}O_2$ and $\dot{V}CO_2$. During 5 min after cuff deflation, $\dot{V}O_2$ and $\dot{V}CO_2$ exceeded the model-estimated change in stores by 273 and 697 mL, respectively. These results reflect the O_2 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

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Abbreviations: ADS = anatomical dead space (mL), BE = base excess (measure of whole blood buffer base [mmol/L]), CO_2 = carbon dioxide, CO_2s = CO_2 stores (mL), f = breathing frequency (breaths/min), FIO_2 = fraction of inspired oxygen, H^+ = hydrogen ion concentration (nmol/L), Hb = hemoglobin concentration (g%), HCO_3^- = bicarbonate concentration (mmol/L), O_2 = oxygen, O_2s = O_2 stores (mL), $PACO_2$ = partial pressure of alveolar CO_2 (mmHg), PAO_2 = partial pressure of alveolar O_2 (mmHg), P_B = barometric pressure, PCO_2 = partial pressure of CO_2 (mmHg), pHa = arterial pH, PO_2 = partial pressure of O_2 (mmHg), $\dot{Q}$ = cardiac output (L/min), RER = respiratory exchange ratio (CO_2 output/O_2 uptake), $\dot{V}_A$ = alveolar ventilation ([L/min] body temperature, ambient pressure, saturated), $\dot{V}CO_2$ = CO_2 output ([mL/min] standard temperature and pressure, dry), $\dot{V}_E$ = pulmonary ventilation ([L/min] body temperature, ambient pressure, saturated), $\dot{V}O_2$ = O_2 uptake ([mL/min] standard temperature and pressure, dry), $\dot{V}O_{2max}$ = maximal $\dot{V}O_2$.

*Address all correspondence to Jack A. Loeppky, PhD; Research Service, VAMC, 1501 San Pedro Dr SE, Albuquerque, NM 87108; 250-489-4597; fax: 250-489-8256. Email: loeppkyj@telus.net or loeppky@unm.edu**
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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 ($\dot{V}_E$) and systemic blood pressure are elevated by a chemoreflex stimulated by buildup of metabolic byproducts 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/m^2, respectively. Their maximal O_2 uptake ($\dot{V}O_{2max}$) 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' $\dot{V}O_{2max}$. 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 ≈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 ($\dot{V}CO_2$), $\dot{V}_E$, calculated respiratory exchange ratio (RER), and $\dot{V}_E/\dot{V}CO_2$ as an index of ventilatory drive. Alveolar ventilation ($\dot{V}_A$) was calculated from anatomical dead space (ADS) taken as apparatus dead space + milliliter = 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 alveoli ($PACO_2$) and partial pressure of O_2 (PO_2) in alveoli (PAO_2) were calculated from alveolar gas equations [16]:

$$PACO_2 = (\dot{V}CO_2 \times 0.863)/\dot{V}_A \qquad (1)$$

and

$$PAO_2 = (P_B - 47.1)FIO_2 - PACO_2[FIO_2 + (1 - FIO_2)/RER]. \qquad (2)$$

We averaged breath-by-breath measurements continuously over 30 s intervals for each subject throughout exercise and the pre- and postexercise rest periods. We then averaged these values for the six subjects to obtain representative temporal patterns for analysis.

Average changes in O_2s and CO_2s were calculated from differences between measured and predicted gas exchange time courses integrated over time. We based predicted values on baseline gas exchange measurements during 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_2s was indicated when measured $\dot{V}O_2$ is greater than predicted $\dot{V}O_2$ over time, and a decrease in CO_2s 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 during 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_2s and CO_2s 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 during cuff inflation.
4. The subjects' subjective reports that the last minute of exercise seemed less stressful than the previous minutes, 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 $\dot{V}O_2$ × 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 exponentially to the baseline value by 15 min.

Total Gas Stores Model with Blood Flow and Volume Redistribution

Computations and assumptions are shown in the following list for compartmental and total whole body O_2s and CO_2s 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 deflation. 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 × 0.8 = 4,720 mL.
  - Arterial compartment for exercise conditions A and C = total × 0.2 = 1,180 mL.
  - During condition B, a 300 mL blood volume shift from the venous to arterial compartment was predicted 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 O_2: Content based on Hb (hemoglobin concentration) = 15 g%, arterial PO_2 = PAO_2, 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 O_2: Content from Fick equation with arterial content and measured $\dot{V}O_2$ at exercise conditions A, B, and C and cardiac output ($\dot{Q}$) = 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 O_2.
  - PO_2 from venous content and saturation from standard curve.
  - PO_2 × body weight (82.5 kg) × 0.64 × 0.024 [24].
- Arterial CO_2.
  - Content based on arterial PCO_2 = $PACO_2$.
  - Content from CO_2 dissociation curve at Hb and pHa [25].
- Venous CO_2: Content from Fick equation with arterial CO_2 content and measured $\dot{V}CO_2$ and predicted $\dot{Q}$ at exercise conditions A, B, and C.
- Tissue CO_2.
  - PCO_2 for venous content from CO_2 dissociation curve.
  - PCO_2 × 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 $\dot{V}O_2$ and $\dot{V}CO_2$ 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 $\dot{V}O_2$ of 1,410 mL/min (minus the resting $\dot{V}O_2$ 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 $\dot{V}O_2$ and $\dot{V}CO_2$ were both significantly larger than the 5 min $\dot{V}O_2$ deficits following exercise onset. The averages of the corresponding changes in gas stores calculated from time-integrated values for measured and predicted $\dot{V}O_2$ and $\dot{V}CO_2$ are detailed in **Figure 2**.

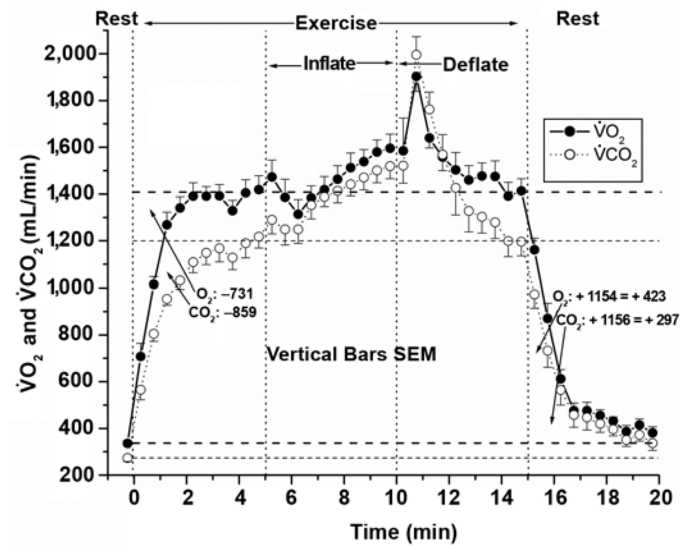

Figure 1.
$\dot{V}O_2$ and $\dot{V}CO_2$ during rest, 15 min of cycle ergometer exercise at 75 W, and 5 min postexercise rest. Each point is an average of 30 s values for six subjects. Values (milliliters) are shown for total 5 min exercise onset deficit and 5 min postexercise rest and sum for $\dot{V}O_2$ and $\dot{V}CO_2$. Postexercise excess is significantly greater than preexercise deficit for O_2 (p = 0.003) and CO_2 (p = 0.031). CO_2 = carbon dioxide, O_2 = oxygen, SEM = standard error of the mean, $\dot{V}CO_2$ = CO_2 output, $\dot{V}O_2$ = O_2 uptake.

Oxygen

Measured $\dot{V}O_2$ 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). $\dot{V}O_2$ then rose steadily until cuffs were deflated. The O_2s cumulative loss over 5 min of cuff inflation was 227 mL (**Figure 2**). $\dot{V}O_2$ peaked 45 s after cuff deflation, being 150 mL above adjacent measurements (p = 0.001). The 5 min postdeflation exercise $\dot{V}O_2$ excess indicated that O_2s increased by 518 mL.

Carbon Dioxide

Measured $\dot{V}CO_2$ during ischemia is related to similar circulatory and biochemical events affecting $\dot{V}O_2$ but is partially overridden by the large increase in $\dot{V}_E$ (**Figure 3**),

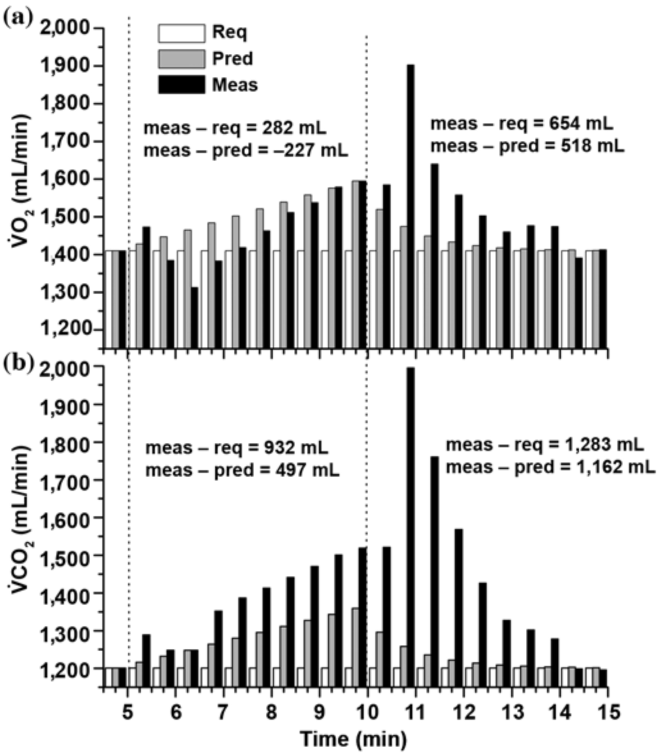

Figure 2.
Changes in gas stores represented by differences between measured (meas) (**Figure 1**) and predicted (pred) time course for **(a)** oxygen uptake ($\dot{V}O_2$) and **(b)** carbon dioxide output ($\dot{V}CO_2$) during 5 min of cuff inflation and 5 min after cuff deflation at 10 min. Values averaged for 30 s. Predicted time course for $\dot{V}O_2$ and $\dot{V}CO_2$ 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.

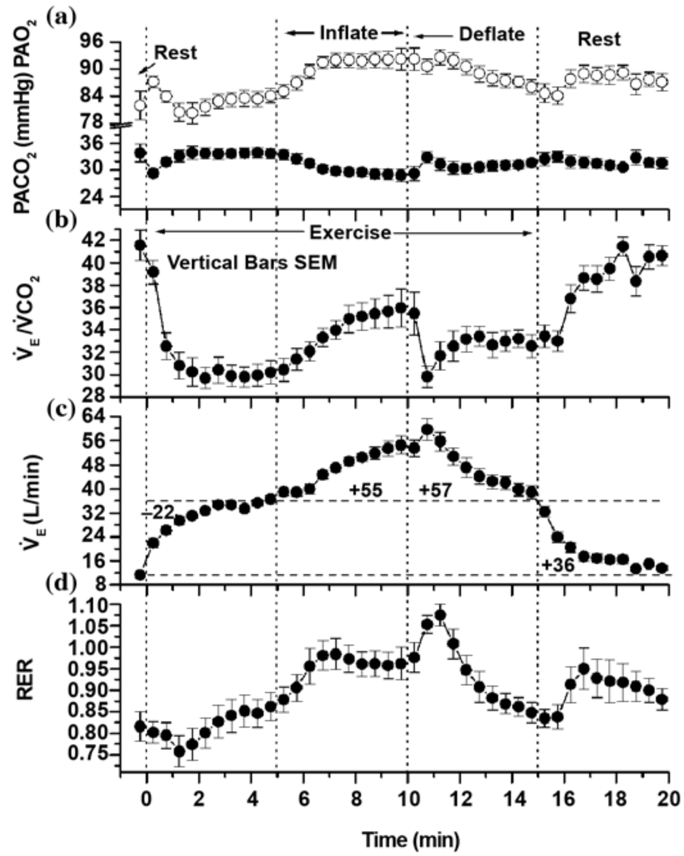

Figure 3.
Average values for six subjects for **(a)** alveolar gases; **(b)** $\dot{V}_E/\dot{V}CO_2$; **(c)** $\dot{V}_E$; and **(d)** RER during rest, 15 min of exercise at 75 W, and 5 min postexercise rest. Values (liters) are shown for cumulative time-integrated $\dot{V}_E$ deficit following exercise onset, cumulative excess during 5 min of cuff inflation, 5 min after cuff deflation, and 5 min of postexercise rest. Latter value is significantly greater than deficit at beginning of exercise. $PACO_2$ = partial pressure of alveolar carbon dioxide, PAO_2 = partial pressure of alveolar oxygen, RER = respiratory exchange ratio, SEM = standard error of the mean, $\dot{V}CO_2$ = carbon dioxide output, $\dot{V}_E$ = pulmonary ventilation.

because of the metaboreflex stimulation by leg ischemia. CO_2s decreased by 497 mL by the end of the 5 min inflation, as indicated in **Figure 2**. Similar to $\dot{V}O_2$, the $\dot{V}CO_2$ peaked 45 s after cuff deflation, indicating an additional 180 mL loss in CO_2s above the adjacent measurements ($p = 0.002$), corresponding to the 150 mL of O_2 taken up. The loss in CO_2s over 5 min after cuff deflation was 1,162 mL, about double that of the O_2s gain (518 mL). Over the 10 min of exercise during cuff inflation and deflation, the total O_2s gain was –227 + 518 = 291 mL and the total CO_2s loss was 497 + 1,162 = 1,659 mL.

Ventilation

After exercise termination, the off-responses for $\dot{V}CO_2$ and $\dot{V}_E$ (**Figure 3**) were similar to each other and their on-responses (36–39 s) but slower than the on-response for $\dot{V}O_2$. $\dot{V}O_2$ and $\dot{V}CO_2$ 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 $\dot{V}CO_2$ was significantly higher (30%) than $\dot{V}O_2$ (18%), indicating a residual enhanced ventilatory drive.

Whole Body CO_2s

By superimposing controlled hyperventilation, one can obtain estimates of whole-body CO_2s during exercise. From measurements in these "hyperventilation" experiments during ischemic exercise, the whole-body CO_2 capacitance (dissociation curve) was 1.2 $L \cdot mmHg^{-1} \cdot kg^{-1}$, 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_2s did not change and CO_2s 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_2s and CO_2s, respectively. During the 5th min after cuff deflation, O_2s increased by 18 mL and CO_2s decreased another 465 mL, whereas the 5 min totals showed that O_2s increased by 518 mL and CO_2s decreased by 1,162 mL. For O_2s, 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_2s 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_2s versus gain in O_2s is 3.7 (1,030/273), which includes the hyperventilation "artifact" during ischemia.

Table 1.
Estimated oxygen stores (O_2s) and carbon dioxide stores (CO_2s) (milliliters) during three conditions (A, B, and, C) of 15 min exercise: 5th min baseline, 5th min of inflation, and 5th min after cuff deflation, respectively.

Condition	Location	PO_2	O_2 Stores	PCO_2	CO_2 Stores
A. 5th Min Baseline	Arterial	84.1	232	33.8	479
(BE = –1.8 mmol/L,	Venous	28.9	486	45.4	2,293
pHa = 7.420, $\dot{Q}$ = 15 L/min)	Tissue	28.9	37	45.4	3,824
	Lung	84.1	576	33.8	231
Total	—	—	**1,331**	—	**6,827**
B. 5th Min Cuff Inflation	Arterial	92.1	293	28.9	559
(BE = –1.8 mmol/L,	Venous	25.3	375	44.7	2,146
pHa = 7.462, $\dot{Q}$ = 14 L/min)	Tissue	25.3	32	44.7	3,760
	Lung	92.1	631	28.9	198
Total	—	—	**1,331**	—	**6,663**
B – A	—	—	**0**	—	**–164**
C. 5th Min Cuff Deflation*	Arterial	86.6	232	31.4	402
(BE = –5.8 mmol/L,	Venous	30.3	486	42.7	1,986
pHa = 7.370, $\dot{Q}$ = 15 L/min)	Tissue	30.3	38	42.7	3,595
	Lung	86.6	593	31.4	215
Total	—	—	**1,349**	—	**6,198**
C – B	—	—	**18**	—	**–465**
C – A	—	—	**18**	—	**–629**

Note: O_2s and CO_2s 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 ΔBE = –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, $\dot{Q}$ = cardiac output.

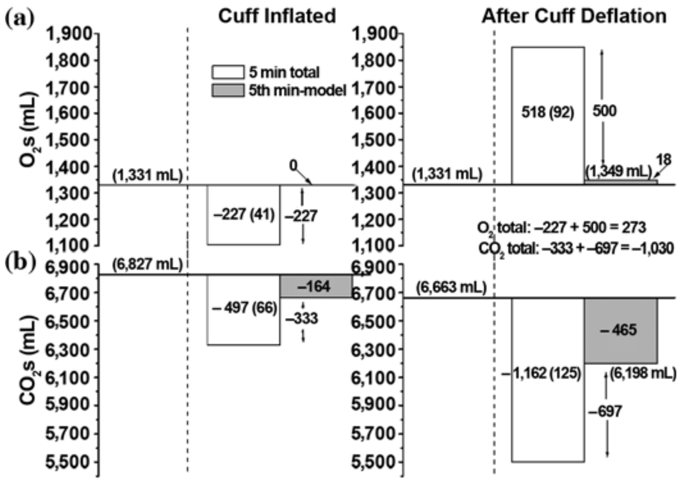

Figure 4.
Values for total gas stores from model in **Table 1** in relation to changes in gas stores from time-integrated $\dot{V}O_2$ and $\dot{V}CO_2$ shown in **Figure 2**. Standard error of the mean is shown for latter in parentheses. Total increase in **(a)** O_2s for 5 min of inflation and 5 min postinflation phase is 273 mL, and decrease in **(b)** CO_2s is 1,030 mL. CO_2 = carbon dioxide, CO_2s = CO_2 stores, O_2 = oxygen, O_2s = O_2 stores, $\dot{V}CO_2$ = CO_2 output, $\dot{V}O_2$ = O_2 uptake.

DISCUSSION

The initial increase in $\dot{V}O_2$ 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 O_2 (**Figure 2**) would reoxygenate 300 mL of venous blood having an O_2 content of 10 vol%. This rise in $\dot{V}O_2$ and the ≈30 mL significant simultaneous loss of CO_2 ($p = 0.004$) indicated a 300 mL shift of blood from the venous to arterial compartment. A redistribution of blood flow accounted for the transient reduction in $\dot{V}O_2$ during the 2nd min of ischemia, whereby cuffs restricted O_2 delivery to the legs by arterial blood, reducing $\dot{V}O_2$ temporarily and increasing O_2 content of mixed venous blood. Similar cardiovascular readjustments with breath holds during exercise have been noted to reduce $\dot{V}O_2$ [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 O_2 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 $\dot{V}O_2$ 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 CO_2 capacitance value of 1.2 $L \cdot mmHg^{-1} \cdot kg^{-1}$ 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 CO_2 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 CO_2 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 CO_2s change significantly slower than O_2s, having a half-time of 4.0 min versus 0.5 min for O_2s, based on studies on dogs by Farhi and Rahn [24]. This finding suggests that part of the loss in CO_2s following cuff deflation may be attributed to the hyperventilation during the prior ischemia.

After cuff deflation, the larger CO_2s loss relative to O_2s gain resulted from the HCO_3^- buffering of lactate entering the circulation. Correlation of lactate levels with excess $\dot{V}CO_2$ in relation to $\dot{V}O_2$ during and after heavy exercise resulted in the “anaerobic threshold” concept [32–33]. Excess $\dot{V}CO_2$ during exercise has also been used to estimate lactate accumulation in physically fit subjects [34] and cardiac patients [35]. The elevated $\dot{V}CO_2$ and CO_2s depletion is caused by carbonic acid, arising from the combination of H^+ with HCO_3^-; dissolved CO_2 from the muscle tissue being transported to the lungs once circulation is restored; and elevated $\dot{V}_E$. As shown by $\dot{V}_E/\dot{V}CO_2$ 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 PCO_2 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 HCO_3^- [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 HCO_3^- during the 5 min postinflation period, it would amount to a CO_2s 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 CO_2 loss to 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 O_2s and CO_2s to baseline levels of 1,331 and 6,827 mL, respectively. However, most of the excess CO_2 was eliminated by the time exercise stopped because $\dot{V}CO_2$ 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 CO_2s loss exceeding the O_2s gain. Qualitatively, $\dot{V}_E$ increases during exercise with cuffs inflated, depleting CO_2s, 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 O_2s, while CO_2s 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 O_2s and CO_2s 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 O_2s and CO_2s and phase differences in stores are most sensitive to values for Hb and reductions in $\dot{Q}$ during the ischemic phase. Any alveolar-arterial differences in PO_2 and PCO_2 greatly influence total stores, especially CO_2s, 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 $\dot{V}_E$ response following cuff deflation to study 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 O_2s reduction during inflation, (2) a direct relationship between workload and the increase in O_2s and reduction in CO_2s after cuff deflation, and (3) the CO_2s loss after cuff deflation exceeds the change during inflation and also exceeds the O_2s 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 O_2s is attenuated as exercise duration increases. This finding is probably associated with the increasing $\dot{V}O_2$ 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.

Variable	Value	Exercise Condition	Value Change	O_2s Difference		CO_2s Difference	
				Total* (%)†	Diff‡	Total* (%)†	Diff‡
Functional Residual Capacity (L)	4.0	A, B, C	±10%	60 (4.5)	5	21 (0.3)	3
Blood Volume (L)	5.9	A, B, C	±10%	69 (5.2)	8	263 (4.0)	19
Hb (g%)	15.0	A, B, C	±10%	118 (8.8)	2	110 (1.7)	34
Alv-Art Diff (mmHg)	PCO_2 & PO_2 = 0	A, B, C	3, 13	112 (8.4)	10	536 (8.2)	32
H^+ (nmol/L)	pHa = 7.42 at base	A, B, C	±10%	4 (0.3)	2	193 (2.9)	18
$\dot{Q}$ Decrease (L/min)	1.0	B	0 & 2	37 (2.8)	37	141 (2.1)	141
BE Decrease (mmol/L)	4.0	C	–3 & –5	2 (0.1)	2	73 (1.2)	73

Note: CO_2s 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), CO_2s = carbon dioxide stores, diff = differences, H^+ = hydrogen ion concentration, Hb = hemoglobin concentration, O_2s = oxygen stores, PCO_2 = partial pressure of carbon dioxide, pHa = arterial pH, PO_2 = partial pressure of oxygen, $\dot{Q}$ = 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.

Studies	*n*	Work (W)	Cuff Pressure (mmHg)	Work Time Before Inflation (min)	Inflation				Deflation			
					Inflation Time (min)	$\dot{V}O_2$ (mL)	$\dot{V}CO_2$ (mL)	$\dot{V}_E$ (L)	Recovery Time (min)	$\dot{V}O_2$ (mL)	$\dot{V}CO_2$ (mL)	$\dot{V}_E$ (L)
Stegemann, 1963 [1]	None given	0	250–300	0	10	–495	–387	–13	20	448	599	14
	None given	“mild”	250–300	20	6	–233	–121	0	10	228	399	17
Asmussen & Nielsen, 1964 (CO_2 added to maintain $PACO_2$) [2]	1	31	300–350	10–15	3	–358	—	—	—	—	—	—
	4	62	300–350	10–15	3	–984	—	—	—	—	—	—
	2	124	300–350	10–15	2	–1,183	—	—	—	—	—	—
Sargeant et al., 1981 [3]	5	100	250	0	2	–130	350	32	4	770	1,591	45
Stanley et al., 1985 [4]	8	49	200	6	2	–274	129	8	4	547	799	16
	8	98	200	6	2	–428	106	10	4	643	1,151	23
Roth et al., 1988 [5]	9	≈17	200	6	2	–740	—	—	4	1,440	—	—
This Study	6	75	140	5	5	282	932	55	5	654	1,283	57
					(2)	–42	167	10				

Note: See legend to **Figure 2** for “predicted” values for $\dot{V}O_2$ and $\dot{V}CO_2$ for this study; here all “predicted” values were assumed equal to baseline.
1. Stegemann J. [On the mechanism of pulse frequency regulation by metabolism. I. The influence of metabolism in a muscle group isolated from the circulation on the behavior of the pulse frequency]. Pflügers Arch Gesamte Physiol Menschen Tiere. 1963;276:481–92. German. [PMID: 13983630]
2. Asmussen E, Nielsen M. Experiments on nervous factors controlling respiration and circulation during exercise employing blocking of the blood flow. Acta Physiol Scand. 1964;60:103–11. [PMID: 14131818]
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4. Stanley WC, Lee WR, Brooks GA. Ventilation studied with circulatory occlusion during two intensities of exercise. Eur J Appl Physiol Occup Physiol. 1985;54(3): 269–77. [PMID: 3933976]
5. Roth DA, Stanley WC, Brooks GA. Induced lactacidemia does not affect postexercise O_2 consumption. J Appl Physiol. 1988;65(3):1045–49. [PMID: 3182473]
CO_2 = carbon dioxide, $PACO_2$ = partial pressure of alveolar CO_2 (mmHg).

elevated $\dot{V}_E$ and extra muscular effort and partial restoration of leg blood flow that diminish the O_2s deficit and increase the CO_2s 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 O_2s depend mainly on perfusion through lung and tissue, while CO_2s changes are primarily determined by $\dot{V}_E$, venous blood redistribution, and HCO_3^- buffering of lactate. This study estimated that the ischemia required a repayment of 273 mL of O_2 and produced 697 mL of CO_2. 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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