Exercise response after rapid intravenous infusion of saline in healthy humans

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Robertson, H. Thomas, Riccardo Pellegrino, Daniela Pini, Jacopo Oreglia, Stefano DeVita, Vito Brusasco, and PierGiuseppe Agostoni. Exercise response after rapid intravenous infusion of saline in healthy humans. J Appl Physiol 97: 697–703, 2004. First published April 16, 2004; 10.1152/japplphysiol.00108.2004.—Patients with chronic heart failure have an abnormal pattern of exercise ventilation (Ve), characterized by small tidal volumes (Vt), increased alveolar ventilation, and elevated physiological dead space (Vd/Vt). To investigate whether increased lung water in isolation could reproduce this pattern of exercise ventilation, 30 ml/kg of saline were rapidly infused into nine normal subjects, immediately before a symptom-limited incremental exercise test. Saline infusion significantly reduced forced expiratory volume in one second (FEV1), and diffusing capacity, and increased alveolar-arterial PO2 difference (A-aDO2) (9, 27), suggesting a central role for increases in extracellular volume as a determinant of both the respiratory abnormalities and exercise limitation in these patients. However, in heart failure patients, the removal of excess extracellular fluid by ultrafiltration has improved the vital capacity without normalizing the diffusing capacity, suggesting the presence of persistent pulmonary vascular abnormalities secondary to chronic elevation of left atrial pressure (2). The relative importance of excess extracellular fluid as a contributor to the reduced maximal exercise capacity of patients with stable heart failure or other edematous conditions is not known.

Rapid intravenous infusion of 30 ml/kg of saline in normal subjects reduced both forced vital capacity (FVC) and FEV1 (23), thereby reproducing the spirometric abnormalities observed in chronic heart failure patients (2, 33). On the basis of the lack of changes in lung compliance after saline infusion, Pellegrino et al. (23) proposed that the primary abnormality produced by rapid saline infusion in healthy subjects was airway mucosal edema rather than alveolar edema. Utilizing the same rapid saline infusion protocol with healthy subjects, we sought to investigate the exercise-associated changes in ventilation, gas exchange, and exercise capacity produced by rapid saline infusion in healthy subjects was airway mucosal edema rather than alveolar edema. Utilizing the same rapid saline infusion protocol with healthy subjects, we sought to investigate the exercise-associated changes in ventilation, gas exchange, and exercise capacity produced by this intervention. Our goal was to characterize the exercise manifestations of extracellular volume excess in normal subjects and to relate those findings to exercise abnormalities observed in other edematous disease conditions.

METHODS

Subjects

Nine healthy subjects (mean age 45 ± 11 SD yr, six men and three women) familiar with cardiopulmonary exercise testing gave informed consent to participate in the study. Seven subjects had a body mass index (BMI) between 21 and 26 kg/m2, and two were overweight (BMI of 28 and 30 kg/m2). All subjects were in good health and had no cardiac or respiratory abnormalities. The experimental protocol was approved by the Centro Cardiologico Monzino Human Subjects Committee.

Protocol

Two studies were performed on separate days with subjects in a resting, fasted state. After local injection of 0.5 ml of 2% lidocaine, a 3-Fr radial or brachial artery catheter was inserted by the Seldinger
technique. On the saline infusion day, the subject remained at rest in the supine position for 30 min while receiving a 30 ml/kg intravenous infusion of normal saline. For the two overweight subjects, a saline dose appropriate for a BMI of 25 was used. On the alternate study day, the subject had an equivalent supine rest period. The day order of saline infusion was randomized among the subjects. Pulmonary function tests were completed immediately after the supine rest, followed by the incremental work exercise test.

**Pulmonary Function Tests**

Spirometry was performed with a SensorMedics 2200 Pulmonary Function Test System (SensorMedics, Yorba Linda, CA). The best of three measurements of FVC and FEV₁ were retained. Normal reference values for spirometry were those of Morris et al. (20). Diffusing capacity for CO (DLCO) was measured by the single breath constant expiratory flow method (12), using 0.3% CO, 0.3% CH₄, 20% O₂, and balance N₂. For calculation of the DLCO components, membrane diffusing capacity (Dm) and capillary volume (VC) (29), two additional measurements were done with the same trace concentrations of CO and CH₄ but with 40% and 60% O₂. Lung volume (VA) was obtained as part of the single-breath DLCO measurement.

**Exercise Tests**

Incremental work exercise tests were conducted on a cycle ergometer with the use of a SensorMedics Vmax 29C system (SensorMedics, Yorba Linda, CA). Ergometer power increments ranging between 20 and 30 W/min were selected on the basis of subject size and activity level, so that the exercise time from start of load to symptom-limited maximal effort would be ~10 min. Identical power increments were applied to each subject for the control and postsaline exercise tests. Resting arterial blood samples were drawn with the subject seated on the cycle ergometer, breathing into the collection system. After a brief interval of unloaded pedaling, the selected ergometer load was initiated and exercise continued to maximal effort, defined as the highest power output attained before the subject was no longer able to sustain a pedal rate exceeding 50 rpm. Arterial blood samples were drawn at 2-min intervals beginning 2 min after the initiation of the loaded pedaling, with a final sample drawn at the maximal power output attained. Heart rate and breath-by-breath measurements of VE, O₂ uptake (VO₂), and VCO₂ were recorded throughout the test. Anaerobic threshold was identified by concurrent judgment of two investigators primarily on the basis of V-slope analysis (3) confirmed by examination for increases in ventilatory equivalent for O₂ and end-tidal Po₂. Normal values for VO₂ max were based on age, sex, and height (13).

**Blood Gas Measurements**

One-milliliter arterial blood samples were drawn in duplicate immediately after clearance of catheter dead space. A total of five or six paired samples were obtained from each subject. Measurements of arterial blood gases and hemoglobin concentration were taken with an ABL model 520 system (Radiometer, Copenhagen).

**Data Reduction, Calculations, and Statistical Tests**

The measurements taken during the final 20 s of exercise were averaged to define VO₂ max, maximal ventilation, and maximal heart rate. Maximal power output was the highest value attained in the ramp test. For control and postsaline comparison of VT and RR responses, measurements were averaged for each complete minute of exercise. The VT/VCO₂ slope was calculated by linear regression on the breath-by-breath measurements of VT and VCO₂, beginning with the third minute of loaded exercise to the time where the subject’s exercise end-tidal Po₂ began to decrease, termed the end of the isocapnic buffering period (34). During that same exercise interval, breath-by-breath measurements of VO₂, VCO₂, VT, and RR were plotted against exercise time for comparison of control and postsaline tests. The slope of breath-by-breath measurements of VE plotted against exercise time was calculated from the third minute of loaded exercise to the onset of the anaerobic threshold, rather than the later-occurring end of the isocapnic buffering period.

Measurements of arterial Po₂, arterial PCO₂ (PACO₂), R (VCO₂/VO₂), and mixed expired CO₂ were used for standard calculations of A–aDO₂ and the Enghoff modification of the Bohr VS/Vt. For gas-exchange calculations, the breath-by-breath measurements of R and mixed expired CO₂ were averaged for the 20-s period surrounding the time of arterial blood sampling. Because a slightly lower hemoglobin concentration was observed after the saline infusion, the postsaline O₂ pulse calculations (VO₂ max/heart rate) were adjusted by the factor [maxHb(control)/maxHb(saline)], where maxHb is the Hb concentration at maximal effort, to compare potential alterations in stroke volume between studies. Paired t-tests were used for comparison of the blood gas, pulmonary function, and gas-exchange measurements in control and postsaline tests. P < 0.05 was considered statistically significant. Data are presented as means ± SD.

**RESULTS**

**Pulmonary Function**

Rapid saline infusion produced significant reductions in FVC, FEV₁, and VA (P < 0.01 for all), whereas Vc was moderately increased and no change was noted in either DLCO or Dm (Table 1). Thus, although the spirometry changes are consistent with those described from previous studies of rapid saline infusion in normal subjects, the unchanged diffusing capacity measurements do not suggest the development of appreciable alveolar edema.

**Metabolic and Symptomatic Manifestations of Rapid Saline Infusion**

The infusion of saline consistently reduced the resting bicarbonate concentration (24.6 ± 1.2 to 22.3 ± 0.6 meq/l, P < 0.001) and the hemoglobin concentration (14.4 ± 0.8 to 13.9 ± 0.9 g/dl, P < 0.02). Assuming that the immediate dilution of bicarbonate reflected a change in the extracellular volume and the dilution of hemoglobin reflected intravascular volume, these proportional changes (after correction of bicarbonate to standard base excess) suggest an expansion of extracellular volume between studies. Paired t-tests were used for comparison of the control and postsaline exercise tests. Significant differences between control and saline: *P < 0.01, †P < 0.05.

Table 1. Pulmonary function and exercise measurements during control and postsaline infusion studies

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>Postsaline</th>
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<tbody>
<tr>
<td>FEV₁ (liters)</td>
<td>3.59±0.79</td>
<td>3.35±0.88*</td>
</tr>
<tr>
<td>%predicted</td>
<td>104±17</td>
<td>97±19*</td>
</tr>
<tr>
<td>FVC (liters)</td>
<td>4.82±1.32</td>
<td>4.45±1.34*</td>
</tr>
<tr>
<td>%predicted</td>
<td>115±26</td>
<td>106±25*</td>
</tr>
<tr>
<td>DLCO (mℓ·Torrate⁻¹·min⁻¹)</td>
<td>31.4±6.5</td>
<td>31.3±6.7</td>
</tr>
<tr>
<td>%predicted</td>
<td>105±16</td>
<td>104±14</td>
</tr>
<tr>
<td>VA (liters)</td>
<td>6.28±1.36</td>
<td>5.96±1.49*</td>
</tr>
<tr>
<td>Dm, mℓ·Torrate⁻¹·min⁻¹</td>
<td>54±13</td>
<td>49±12</td>
</tr>
<tr>
<td>Vc, mℓ</td>
<td>107±32</td>
<td>127±40*</td>
</tr>
<tr>
<td>VO₂max (mℓ·min⁻¹)</td>
<td>2.63±0.66</td>
<td>2.45±0.67†</td>
</tr>
<tr>
<td>%predicted</td>
<td>105±18</td>
<td>98±20†</td>
</tr>
</tbody>
</table>

Values are means ± SD. FEV₁, forced expired volume in 1 s; FVC, forced vital capacity; DLCO, diffusing capacity for CO; Vc, alveolar volume; Dm, membrane diffusing capacity for CO; VO₂ max, maximal oxygen uptake.
fluid volume by ~12% and an expansion of intravascular volume by 3.5%. At rest, no subject reported symptoms attributable to the rapid saline infusion, although all felt more fatigued postsaline infusion at maximal effort. During exercise after saline infusion, some subjects noted a sensation of increased leg tightness with exercise, although no measurements were taken to objectively confirm a change in leg volume. The subjects also noted a postexercise delay of at least 1 h before any sensation of bladder fullness.

Response to Exercise

Ventilation and gas exchange. Plots of the breath-by-breath measurements of $V_E$ against $V_{CO_2}$ revealed a good linear fit (Fig. 1) up to the end of the isocapnic buffering period, with a mean correlation coefficient ($r$) for all subjects of 0.987 ± 0.007. All subjects increased the $V_E/V_{CO_2}$ slope after saline infusion (24.9 ± 2.4 to 28.0.2 ± 2.9 l/l, $P < 0.0002$, Fig. 2A). Exercise ventilation normalized by power output ($V_E/W$) also increased after saline infusion (0.262 ± 0.026 to 0.290 ± 0.031 l/min⁻¹·W⁻¹, $P < 0.005$, Fig. 2B). The pattern of increase in $V_E$ among subjects was typical for the midexercise interval of a progressive work test, characterized by a relatively larger increase in $V_T$ than in RR. When we compared individual plots of $V_T$ against $V_E$ for the control and saline tests, the postsaline measurements for seven of the nine subjects could be superimposed on the control curves (Fig. 3). All subjects showed higher $V_E$ for any given power output after saline infusion, with seven subjects showing the same pattern of increase in $V_T$ and RR to achieve the higher ventilation (Fig. 3). Of the two remaining subjects, one showed a postsaline reduction in $V_T$ for a given $V_E$, and the other showed a postsaline increase in $V_T$ for a given $V_E$. Among all subjects, there was no difference between tests in $V_{CO_2}$ or $V_{O_2}$ at identical power outputs. In the portion of the exercise ventilation response used for calculation of the $V_E/V_{CO_2}$ slope, a mean 1.6 ± 2.5 Torr decrease in PaCO₂ ($P = 0.01$) was noted in the postsaline infusion studies when all measurements during that interval were pooled, although the change did not attain significance at the 0.05 level for any single measurement time (Table 2). Mean maximal $V_E$ was not significantly different after saline infusion (92.6 ± 20.3 vs. 85.8 ± 25.7 l/min, $P$ not significant). Compared with control measurements, the postsaline tests had small reductions in $P_{ACO_2}$, pH, and $HCO_3$ throughout the midexercise period (Table 2). At maximal exercise no acid-base differences were significant. No significant differences in arterial $Po_2$, hemoglobin saturation, $Vd/VT$, or $A-aD_O_2$ were noted at any exercise stage (Table 2).

$V_{O_2_{max}}$. After saline infusion, $V_{O_2_{max}}$ was reduced by 175 ± 184 ml/min ($P < 0.02$, Fig. 4A), associated with reductions in anaerobic threshold (139 ± 184 ml/min, $P < 0.05$), and maximal exercise heart rate (8 ± 6 beats/min $P <$...
exercise response to rapid saline infusion

...small drop in Hb concentration. There was no significant difference between control and saline tests for both heart rate and \( \dot{V}O_2 \) were apparent only during the final minute of exercise (Fig. 5). The maximal \( O_2 \) pulse (\( \dot{V}O_2_{\text{max}}/\text{maximal heart rate} \)) was not different between studies, with a slight increase postsaline after correction for the small drop in Hb concentration. There was no significant difference in the decrease in HCO\(_3\) at maximal effort compared with rest measurements (6.4 ± 2.3 meq/l control vs. 5.3 ± 1.0, meq/l saline), suggesting similar lactate concentrations at maximal effort.

DISCUSSION

The changes in resting spirometry after rapid saline infusion found in this study are nearly identical in magnitude compared with those reported by Pellegrino et al. (23) after the same intervention. Similar reductions in FEV\(_1\) were noted in stable heart failure patients given a smaller (10 ml/kg) intravenous saline challenge (27), but, unlike our normal subjects, those patients developed a significant reduction in Dl\(_{CO}\) and Dm after the saline infusion. In the present study, saline infusion caused only a small increase in the Vc component of the Dl\(_{CO}\), suggestive of an intravascular volume increase, but showed no gas-exchange findings, suggestive of alveolar edema such as a decrease in Dm or an increased A-aD\(_{O_2}\). Two mechanisms operate to clear alveolar spaces of edema fluid in the face of rapid saline infusion, thereby possibly contributing to bronchial mucosal edema. First, the alveolar epithelium actively pumps luminal sodium to the interstitial compartment (6, 18). Second, the forces of interdependence within the lung during ventilation (19) draw edema fluid into the bronchovascular bundles, where fluid is cleared via the lymphatics (30). Compared with normal subjects, heart failure patients manifest gas-exchange abnormalities in response to a modest intravascular volume challenge, suggesting structural abnormalities in the interstitial spaces. In support of this concept, Agostoni et al. (2) observed that although stable chronic heart failure patients resolved their spirometric abnormalities after a session of ultrafiltration to normalize the extracellular fluid volume, the Dl\(_{CO}\) remained low, unchanged from control measurements. Thus whereas normal subjects and heart failure patients both manifest airway mucosal edema in the face of a sufficient intravascular volume challenge, abnormalities of diffusing capacity are not seen in normal subjects, whereas those abnormalities persist in the heart failure patients even after all excess extracellular fluid is withdrawn.

The subjects of the present study demonstrated a consistent increase in exercise ventilation at any exercise level after rapid saline infusion. For both our subjects and heart failure patients, an increased \( V_{e}/V_{CO_2} \) slope could arise from any combination of three mechanisms: an increase in alveolar ventilation, an increase in \( V_{\text{n}}/V_{T} \), or a decrease in \( V_{CO_2} \) at any given power output. No change in \( \dot{CO}_2 \) production or \( V_{\text{n}}/V_{T} \) was observed, leaving an increase in alveolar ventilation as the sole mechanism to explain the increased \( V_{e}/V_{CO_2} \) slope after saline infusion in our normal subjects. The observed response of these saline-infused normal subjects differs from that of previously described heart failure patients, in that the patients

Table 2. Exercise blood gases and gas-exchange calculations

<table>
<thead>
<tr>
<th></th>
<th>Minute 2</th>
<th>Minute 4</th>
<th>Minute 6</th>
<th>Maximum</th>
</tr>
</thead>
<tbody>
<tr>
<td>( P_{CO_2} ), Torr</td>
<td>Control</td>
<td>38.9±1.8</td>
<td>39.6±1.2</td>
<td>39.4±3.5</td>
</tr>
<tr>
<td>( HCO_3 ), mM/l</td>
<td>Control</td>
<td>24.7±1.6</td>
<td>24.3±1.5</td>
<td>23.2±1.8</td>
</tr>
<tr>
<td>( P_{CO_2} ), Torr</td>
<td>Saline</td>
<td>21.9±1.0*</td>
<td>21.7±0.8*</td>
<td>20.6±1.1*</td>
</tr>
<tr>
<td>( pH ), units</td>
<td>Control</td>
<td>7.419±0.014</td>
<td>7.404±0.015</td>
<td>7.389±0.021</td>
</tr>
<tr>
<td>( P_{CO_2} ), Torr</td>
<td>Saline</td>
<td>7.385±0.018*</td>
<td>7.376±0.022*</td>
<td>7.361±0.029*</td>
</tr>
<tr>
<td>( A-aD_{O_2} ), Torr</td>
<td>Control</td>
<td>95.7±5.4</td>
<td>96.2±3.6</td>
<td>100.5±5.7</td>
</tr>
<tr>
<td>( V_{n}/V_{T} ), %</td>
<td>Saline</td>
<td>99.8±5.9</td>
<td>99.5±5.5</td>
<td>103.0±6.9</td>
</tr>
<tr>
<td>( A-aD_{O_2} ), Torr</td>
<td>Control</td>
<td>2.0±5.9</td>
<td>2.0±4.0</td>
<td>5.3±2.5</td>
</tr>
<tr>
<td>( V_{n}/V_{T} ), %</td>
<td>Saline</td>
<td>1.7±6.1</td>
<td>1.6±4.0</td>
<td>4.6±4.1</td>
</tr>
</tbody>
</table>

Comparison of control and postsaline exercise blood gas measurements and gas-exchange calculations gathered in the final 20 s of incremental exercise periods 2, 4, and 6 min, and at maximal effort. \( P_{CO_2} \), arterial \( PCO_2 \); \( A-aD_{O_2} \), alveolar-arterial \( O_2 \) difference; \( V_{n}/V_{T} \), Enghoff modification of the Bohr dead space. *Postsaline measurements different from control, \( P < 0.01 \).
demonstrate both alveolar hyperventilation and abnormally elevated physiological dead space during exercise (22, 31, 33).

Thus the augmentation of exercise ventilation after saline infusion represented by the change in $V_{\dot{E}}/V_{\dot{CO}_2}$ slope reflects an increase in alveolar ventilation alone. This increase could arise as a consequence of two different mechanisms. First, a mild dilution acidosis was produced in all subjects after the rapid infusion of the large volume of bicarbonate-free solution, thus providing a stimulus to increase $V_{\dot{E}}$. The average saline-induced 10% increase in $V_{\dot{E}}$ was associated with a mean 0.026 unit decrease in pH, although there was a range of response among our subjects (See Fig. 2). To confirm whether the increased ventilation was due to the metabolic acidosis alone, our same subjects would have to be restudied after induction of an equivalent degree of metabolic acidosis without volume expansion. A second potential mechanism to contribute to the observed respiratory alkalosis would be augmentation of $V_{\dot{E}}$ by edema-responsive neural afferent signals either from lung or from exercising muscle. In lung, the unmyelinated C fibers in airway mucosa respond to airway edema, triggering afferent ventilation stimuli in experimental animals (10). In muscle, Piepoli et al. (24) described an increased ventilation stimulus from forearm exercise in chronic heart failure patients, attributed to afferent signals from the muscle. More direct evidence of unmyelinated muscle afferent signals in response to vascular congestion has been described in experimental animals (11).

Although our intervention with rapid saline infusion induced changes in spirometry consistent with the presence of airway mucosal edema, eight of our nine normal subjects failed to demonstrate any decrease in exercise $V_T$ for a given $V_{\dot{E}}$. There is no obvious explanation for the divergent changes noted in postsaline ventilation pattern for two of the subjects, but the remaining seven subjects had RR and $V_T$ responses after saline that fit well to their respective control measurements. The increased $V_{\dot{E}}$ observed after saline infusion did not change the relationship between the RR and $V_T$. Gallagher et al. (8) noted a similar pattern of $V_T$ preservation in ventilation exercise response when comparing normal subjects at a specified $V_{\dot{E}}$ with or without hypercapnia. Thus the reductions in exercise $V_T$ manifested by heart failure patients may be more likely related to afferent signals responding to exercise-associated increases in left atrial pressure rather than an effect related to lung edema.

The consistent reductions in $V_{O_2,max}$, anaerobic threshold, and maximal exercise heart rate after rapid saline infusion were unexpected findings. The subjects had no knowledge of the subsequently discovered saline-induced reduction in exercise capacity during testing and appeared to give full equivalent efforts for both tests, findings supported by the observation of

Fig. 4. A: maximal $O_2$ uptake ($O_2 max$) at control and after rapid saline infusion. B: maximal exercise heart rate at control and after rapid saline infusion.

Fig. 5. Plot of heart rate and $O_2$ consumption in a typical subject during control study (○) and after saline infusion (●).
nonsignificant decreases in maximal exercise pH and bicarbonate during the postsaline maximal effort (Table 2). In addition, the consistent reduction in the anaerobic threshold after saline infusion provided additional support for the view that there was a true reduction in maximal exercise capacity. The subjects could not be blinded to the rapid saline infusion, but we were not aware of any subject concern that the intervention would limit maximal exercise performance.

Despite the reduction in expiratory flow rates after saline, there was no suggestion of a respiratory limitation to the maximal performance. Maximal exercise ventilation after saline was not different and was not associated with an increase in $\Delta$aDO$_2$ or PaCO$_2$ at maximal exercise. Although a modest increase in the work of ventilation after saline infusion cannot be completely discounted, the exercise ventilation response did not manifest any of the findings of ventilation limitation that are ordinarily invoked to explain a reduction in maximal exercise performance. The mild metabolic acidosis itself could also be invoked as a potential cause of exercise limitation. Studies of maximal exercise capacity after induction of severe metabolic acidosis (standard base excess of $-10$ meq) have shown modest reductions in exercise time at maximal effort (14), but the mean pH reduction in the present study was far smaller. Nevertheless, this possibility cannot be completely excluded without repeat exercise tests on all subjects after induction of an equivalent mild metabolic acidosis without volume infusion.

If the observation of the lower postsaline maximal power output associated with a lower maximal heart rate cannot be ascribed to a ventilation limitation, acidosis, or reduced effort, a remaining issue for consideration would be impaired extraction of O$_2$ by the exercising muscle. Two mechanisms related to edema formation in exercising muscle could contribute to such a finding. First, if the edema fluid accumulating in the legs increased the intramuscular tissue pressure to a significant degree, maximal exercise perfusion of that muscle bed would be reduced. Williamson et al. (35) showed that subjects exercising with their legs enclosed in a pressurized chamber had a reduction in $V_{O2\text{max}}$, associated with alveolar hyperventilation. With application of external pressure to the legs, leg O$_2$ extraction was reduced simply because of reduced maximal blood flow to the exercising muscle. In the present study no measurement of an intramuscular pressure increase after saline infusion is available, but it is interesting to note that some subjects were aware of a sensation of leg tightness during the postsaline exercise test. A second potential mechanism of impaired maximal O$_2$ extraction is the development of a diffusion limitation secondary to accumulation of edema fluid between capillaries and the maximally recruited exercising muscle. An O$_2$ diffusion limitation within maximally exercising muscle has been proposed by Wagner (32) on the basis of measurements in normal subjects of femoral venous O$_2$ extraction during maximal exercise during differing degrees of arterial hypoxemia. On the basis of the assumptions of that model, any increase in diffusion distances secondary to edema fluid would be physiologically relevant. Two factors favor a disproportionate distribution of edema fluid to the exercising muscle of our subjects. First and most important, the stimulus of maximal exercise will redistribute almost 90% of the total cardiac output to the exercising muscle. Second, the infusion of a large volume of normal saline decreases the intravascular oncotic pressure and enhances the movement of saline from intravascular to extravascular spaces. The disproportionate size of the decrease in plasma bicarbonate after rapid saline infusion compared with the decrease in hemoglobin confirms that most of the saline went to the extravascular space soon after administration. By this increased capillary-myocyte diffusion distance hypothesis, the maximal O$_2$ extraction from the exercising muscle would be reduced, associated with a relatively higher venous O$_2$ exiting from exercising muscle. In contrast, the prediction from the increased intramuscular pressure hypothesis would be that there would be no difference between maximal exercise femoral venous O$_2$ extraction in control and postsaline infusion conditions.

The present findings in transiently fluid overloaded healthy subjects may offer an insight into chronic disease conditions with associated edema in which maximal exercise heart rate is decreased. Although the reduced maximal exercise heart rate of heart failure patients is most likely attributable to either myocardial or conducting system abnormalities, abnormalities of peripheral muscle function during exercise have also been postulated. In exercising heart failure patients, Koike et al. (16) described an end-exercise increase in femoral venous PO$_2$ for the most impaired subjects, suggesting an abnormality of muscle O$_2$ extraction. Wilson et al. (36) described a subset of heart failure patients with normal exercise leg blood flow at moderate exertion who nevertheless had abnormally elevated femoral venous lactate levels, again suggesting appropriate blood flow and impaired peripheral O$_2$ delivery. Chronic hemodialysis patients exercised on a nondialysis day (and hence mildly edematous) reproducibly demonstrated a reduced maximal exercise heart rate. When restudied after treatment with erythropoietin, there was an improvement in maximal exercise capacity but a significant additional decrease in maximal exercise heart rate, suggesting a primary abnormality of muscle O$_2$ extraction unrelated to O$_2$ delivery to exercising muscle (28). This postulate was confirmed by an exercise study of chronic hemodialysis patients investigating the effects of erythropoietin treatment on maximal femoral venous O$_2$ extraction (17). Those investigators found that erythropoietin treatment increased the maximal exercise femoral venous O$_2$ saturation of blood, compared with the preerythropoietin control exercise measurements, providing direct evidence for a muscle O$_2$ extraction abnormality in those patients.

In conclusion, the results of the present study of healthy subjects receiving an intravenous saline load and previous studies of patients with edematous conditions suggest that edema accumulation could impair maximal systemic O$_2$ extraction, related either to increased diffusion distances between the muscle microvasculature and myocytes and/or to the effects of an edema-mediated increase in intramuscular pressure. In addition, the rapid saline infusion protocol utilized in this study increased exercise alveolar ventilation, most likely in response to the mild dilution-induced acidosis, although contributing stimuli from edema-sensitive neural afferents in the lung or exercising extremities cannot be excluded.

REFERENCES


