Lack of Improvement of Lung Diffusing Capacity Following Fluid Withdrawal by Ultrafiltration in Chronic Heart Failure

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OBJECTIVES
We sought to investigate the possibility that lung diffusing capacity reduction observed in chronic heart failure is reversible in the short term.

BACKGROUND
Mechanical properties of the lung usually ameliorate with antifailure treatment including drugs, ultrafiltration and heart transplantation, whereas lung diffusing rarely improves.

METHODS
We studied the mechanical properties of the lung (pulmonary function tests with determination of alveolar volume, extravascular lung fluids and lung tissue), lung diffusion for carbon monoxide (DLco), including membrane diffusing capacity (Dm), pulmonary capillary blood volume (Vc) and pulmonary hemodynamics, in 28 patients with stable chronic heart failure, before a single session of extracorporeal ultrafiltration (3973 ± 2200 ml) and four days thereafter. Lung mechanics and diffusion were also evaluated in 18 normal subjects.

RESULTS
Vital capacity, forced expiratory volume (1 s) and maximal voluntary ventilation were lower in patients when compared with normal subjects, and increased after ultrafiltration from 2.1 ± 0.7 to 2.5 ± 0.7(l)*, 1.7 ± 0.5 to 2.0 ± 0.6(l)* and 67 ± 25 to 79 ± 26 (l/min)*, respectively (* p < 0.02 vs. pre-ultrafiltration). Post-ultrafiltration alveolar volume was augmented, while lung tissue, body weight (~6 kg), chest X-ray extravascular lung water score and pulmonary vascular pressure were reduced. Heart dimensions (echocardiography) remained unchanged. DLco, Dm and Vc were 29.0 ± 5.0 ml/min/mm Hg, 47.0 ± 11.0 ml/min/mm Hg, 102 ± 20 ml in normal subjects and 17.1 ± 4.0#, 24.1 ± 6.5#, 113 ± 38 and 17.0 ± 5.0#, 24.8 ± 7.9#, 100 ± 39 in patients before and after ultrafiltration, respectively (# = p < 0.01 vs. controls).

CONCLUSIONS
In chronic heart failure, ultrafiltration improves volumes and mechanical properties of the lung by reducing lung fluids. Diffusion is unaffected by ultrafiltration, suggesting that, in chronic heart failure, the alveolar-capillary membrane abnormalities are fluid-independent. (J Am Coll Cardiol 2000;36:1600–4) © 2000 by the American College of Cardiology

In heart failure patients the mechanical properties of the lung, as well as lung diffusing capacity, are frequently altered (1–4), and pulmonary function tests often identify a restrictive pattern (2,4). Pulmonary mechanical abnormalities can be reduced, or even resolved, with different sorts of heart failure treatment, including drugs (5–7), ultrafiltration (8,9) and heart transplantation (10). On the contrary, lung diffusing capacity has been shown to improve with angiotensin-converting enzyme inhibitors (5–7), but not with other antifailure drugs, such as diuretics (11), AT1-blockers (6,7), hydralazine (5) and beta-blockers (12). Furthermore, heart transplantation, which is probably the most effective antifailure treatment, does not affect and may even worsen lung diffusing capacity. Data on lung diffusion after ultrafiltration are lacking (13–15). Raughton and Foster (16) showed that lung diffusion can be split into two subcomponents: alveolar-capillary membrane resistance and volume of pulmonary capillary blood. Indeed, 1/DLco = 1/Dm + 1/θVc, where DLco is lung diffusion capacity for carbon monoxide, Dm is alveolar-capillary membrane resistance, θ is red blood cell resistance and Vc is pulmonary capillary blood volume available for gas exchange.

From the Istituto di Cardiologia dell’Università degli Studi, Centro Cardiologico IRCCS, Centro di Studio per le Ricerche Cardiovascolari del CNR, Milan, Italy. Funded by research grants from the Istituto di Cardiologia, Centro Cardiologico, IRCCS, Università di Milano and Centro di Studio per le Ricerche Cardiovascolari del CNR.

Manuscript received January 13, 2000; revised manuscript received April 14, 2000, accepted June 15, 2000.
which has a relevant active component (19–21). Accordingly, a correlation between lung diffusing capacity decline, after heart transplant, and cyclosporine plasma levels was noted by Casan et al. (22).

Therefore, we decided to study the behavior of pulmonary mechanics and lung diffusing capacity in heart failure before and after a therapeutic technique that induces pulmonary hemodynamic improvement without heart volume changes, and without the confounding effects of surgery or drugs possibly interfering with lung diffusion (5,22). We aimed at knowing how much impairment is due to alveolar fluid retention and how much to nonhemodynamic and possibly nonreversible membrane damage. We used extra-corporeal ultrafiltration, which is known to reduce lung water content, right atrial and pulmonary vascular pressure, and to improve patients’ clinical condition, which includes exercise capacity as well as pulmonary mechanical properties (8,9).

METHODS

Patient population. We studied 28 patients with severe heart failure (New York Heart Association [NYHA] class III and IV) in stable clinical condition and therapeutic regimen. All patients belonged to a cohort of heart failure subjects regularly followed at the Heart Failure Unit of the Institute of Cardiology, University of Milan. Twenty-one patients were males and seven females (mean age 66 ± 8 years). Heart failure etiology was ischemic heart disease in 15 subjects, idiopathic cardiomyopathy in 9 and valvular heart disease in 4. Exclusion criteria were: left ventricular ejection fraction (by echocardiography) >35%, primary pulmonary disease, unstable angina or recent myocardial infarction, artificial pacemakers. Drug treatment included diuretics (28 cases), angiotensin-converting enzyme inhibitors (22 cases), digoxin (19 cases), nitrates (9 cases) and amiodarone (11 cases). Therapy remained unchanged throughout the study. Eighteen control subjects were also investigated (12 men and 6 women, mean age 61 ± 7 years) for pulmonary function test measurements. The study was approved by the local Ethical Committee and all patients provided informed written consent to the study.

Echocardiographic evaluation. Patients underwent echocardiographic measurement of left ventricle volumes and ejection fraction.

Pulmonary function tests. Pulmonary function tests included forced expiratory volume in 1 second (FEV₁), vital capacity (VC), and maximal voluntary ventilation (MVV) measurements. For MVV we used the greater between measured MVV over 12 s and FEV₁ × 40 (23). Alveolar volume was obtained by methane dilution technique. We also determined DLco using the single breath constant expiratory flow technique. DLco measurement was corrected for the subjects’ hemoglobin concentration, according to Coats et al. (24). We also measured the DLco subcomponents Dm and Vc (16). Lung tissue was calculated by applying the Wilson formula, which considers the decay of methane, carbon monoxide and acetylene during constant expiratory flow (25–27).

Chest X-ray. Extravascular lung fluid content was assessed with a radiographic score (28).

Hemodynamic evaluation. Hemodynamic evaluation was carried out using Swan-Ganz catheterization of the pulmonary artery (internal jugular vein approach). We measured pulmonary artery pressure, pulmonary wedge pressure, right atrial pressure and cardiac output (thermodilution, triplicate measures) after at least 30 min of complete rest.

Ultrafiltration. A single session of ultrafiltration was performed using a previously described technique (8,9). In brief, a diaphragm (D20SF Amicon) was inserted into a veno-venous extracorporeal circuit that was connected to a femoral vein through a percutaneous double-lumen Y-shaped catheter for blood withdrawal and reinfusion. Patients were treated with IV heparin. Blood was propelled by a peristaltic pump. Ultrafiltration was interrupted when right atrial pressure was reduced by 50% or red pack cell volume increased by three points.

Study design. Patients were admitted to the hospital and their clinical condition, including stability, was assessed. Thereafter, they underwent echocardiogram, chest X-ray, pulmonary function tests, lung tissue and DLco measurements, including Dm and Vc (day –1). The next day, the first hemodynamic study was performed and was followed by a single-session ultrafiltration (day 0). Four days after, clinical evaluation, hemodynamic measurements, echocardiogram, chest X-ray and the pulmonary function tests were repeated. Normal subjects underwent only pulmonary function tests.

Statistical analysis. Data are reported as mean ± 1 standard deviation. Comparisons were made by paired or unpaired t tests as, appropriate. When needed, because of multiple comparisons, the Bonferroni correction was applied. A value of p < 0.05 was considered statistically significant.

RESULTS

Ultrafiltration was safely carried out in all patients without untoward effects. The ultrafiltrate amount was 3,973 ± 2,200 ml and ranged from 1,050 to 11,000 ml. Mean body weight was 77.2 ± 13.5 kg before ultrafiltration and 71.4 ± 12.7 kg four days after the procedure (p < 0.001). At the fourth day after ultrafiltration patients clinical conditions...
improved and NYHA functional class reduced from 3.6 ± 0.6 to 2.8 ± 0.6 (p < 0.01). Before ultrafiltration, left ventricular ejection fraction and systolic and diastolic diameters were 25.4 ± 4.3%, 54 ± 7 mm and 65 ± 8 mm, respectively, and remained unchanged four days after the procedure. Standard pulmonary function tests are reported in Table 1. An improvement in lung mechanics in all subjects was observed after ultrafiltration. In contrast, DLco, which was significantly reduced in patients compared to normal subjects, did not increase after ultrafiltration. Lack of variations in DLco was the result of an unchanged Dm with a tendency of Vc to decrease (Table 2). Patients’ alveolar volume was significantly lower than normal subjects and increased by ~10% four days after ultrafiltration. DLco, normalized for alveolar volume, decreased after the procedure, while Dm remained unchanged. Lung tissue was increased in patients with heart failure when compared with normal subjects by ~50% and, four days after ultrafiltration, reduced from 620 ± 180 ml to 550 ± 170 ml (p < 0.02). Considering the short time interval, this reduction was likely due to a decrease in lung water content. Accordingly, chest X-ray extravascular lung water score reduced from 18.4 ± 3.5 to 11.2 ± 3.0 (p < 0.01). Hemodynamic parameters before and after ultrafiltration are reported in Table 3.

**DISCUSSION**

The major result of the present study is that, in patients with chronic congestive heart failure, mechanical properties and diffusing capacity of the lung behave differently after reduction of lung fluid content, right atrial and pulmonary venous pressures by ultrafiltration. Amelioration of mechanical properties of the lung after ultrafiltration is due to reduction of lung stiffness secondary to a lowered lung fluid content (8,29). The factors that, in chronic heart failure, determine low lung diffusing capacity are the reduction of gas surface exchange and the impairment of membrane diffusing capacity. The former is inferable from reduction of vital capacity and alveolar volume, the latter from a low Dm. Lack of Dm improvement, as well as that of Dm normalized for alveolar volume after the procedure, suggests that increase in the fluid content of the alveolar capillary membrane is not the major cause of lung diffusing capacity reduction. On the other hand, membrane impairment may be due to an increase in cellularity and fibrosis. Therefore, our findings explain why Dm changes may be irreversible and not influenced by heart transplantation (13,14,18).

Ultrafiltration was safely conducted in all subjects and, as demonstrated by NYHA functional class reduction, allowed improvement of the patients’ clinical condition. The present report, however, is not intended to document the safety of ultrafiltration or its clinical efficacy, which have been previously reported in several papers (8,9,29–32). In this study, we utilized data on lung function, from patients with severe heart failure who are undergoing ultrafiltration for clinical reasons, in order to better understand the differences in the response of lung mechanics and diffusing capacity to heart failure. The response of lung mechanics and diffusing capacity to heart failure is strongly related to the degree of lung fibrosis, which in turn is probably influenced by heart transplantation (13,14,18).

**Table 1.** Standard Pulmonary Function Tests in Controls (n = 18) and in Chronic Congestive Heart Failure Patients Undergoing Ultrafiltration (n = 28)

<table>
<thead>
<tr>
<th></th>
<th>Controls Before UF</th>
<th>Four Days after UF</th>
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<tbody>
<tr>
<td>VC (L)</td>
<td>4.7 ± 1.0</td>
<td>2.1 ± 0.7$</td>
</tr>
<tr>
<td>FEV₁ (L)</td>
<td>3.9 ± 0.9</td>
<td>1.7 ± 0.5$</td>
</tr>
<tr>
<td>MVV (L/min)</td>
<td>145 ± 22</td>
<td>67 ± 25$</td>
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</tbody>
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* p < 0.01 vs. controls, § p < 0.01 vs. before ultrafiltration.

**Table 2.** Lung Diffusing Capacity for Carbon Monoxide (DLco), Alveolar-Capillary Membrane Diffusing Capacity for Carbon Monoxide (Dm), Capillary Volume (Vc), Alveolar Volume (Va) and Lung Tissue (Lt) in Controls (n = 18) and in Chronic Congestive Heart Failure Patients Undergoing Ultrafiltration (n = 28)

<table>
<thead>
<tr>
<th></th>
<th>Controls Before UF</th>
<th>Four Days after UF</th>
</tr>
</thead>
<tbody>
<tr>
<td>DLco (ml/min/mm Hg)</td>
<td>29.0 ± 5.0</td>
<td>17.1 ± 4.0*</td>
</tr>
<tr>
<td>Dm (ml/min/mm Hg)</td>
<td>47.0 ± 11.0</td>
<td>24.1 ± 6.5*</td>
</tr>
<tr>
<td>Vc (ml)</td>
<td>102 ± 20</td>
<td>113 ± 38</td>
</tr>
<tr>
<td>Va (L)</td>
<td>6.3 ± 1.3</td>
<td>4.1 ± 1.6*</td>
</tr>
<tr>
<td>Lt (ml)</td>
<td>420 ± 130</td>
<td>620 ± 180§</td>
</tr>
<tr>
<td>DLco/Va (ml/min/mm Hg/L)</td>
<td>4.3 ± 4.3</td>
<td>4.3 ± 0.8</td>
</tr>
<tr>
<td>Dm/Va (ml/min/mm Hg/L)</td>
<td>7.1 ± 3.0</td>
<td>6.0 ± 2.1$</td>
</tr>
</tbody>
</table>

* p < 0.01 vs. controls, § p < 0.02 vs. before ultrafiltration.

UF = ultrafiltration.
failure treatment. Remarkably, ultrafiltration has been shown to reduce lung fluid content and, as a consequence, to improve lung mechanics (29) without changing heart dimensions (31), with no surgical trauma on the chest and without utilization of drugs possibly interfering with lung diffusing properties (22). The greater reduction in body weight four days after ultrafiltration, compared to the ultrafiltrate volume (5.8 ± 3.7 Kg vs. 3973 ± 2205 ml), is not surprising in view of the ultrafiltration capability to restore diuresis and kidney response to diuretics (32).

Vital capacity and lung tissue are inversely related to each other in relation to the amount of interstitial fluids. Both showed, before and after ultrafiltration, a significant intersubject variability in patients compared with normal subjects (Tables 1 and 2). This variability may depend on individual differences in intravascular pressures, on lung fluid drainage capacity due to the unevenly enhanced fluid removal capacity of various lung fluid drainage pathways in chronic heart failure (33,34) and on heart dimension (cardiomegaly), a major cause of lung restrictive disease in heart failure (10). Accordingly, it has been shown for many years that pulmonary wedge pressure can be predicted by chest X-ray, in acute but not in chronic heart failure, when the above reported mechanisms interplay (35). However, increase of vital capacity and reduction of lung tissue observed after ultrafiltration are as one would expect after acute lung fluid reduction. A reduction in lung fluid is suggested by lower right atrial and pulmonary wedge pressures and X-ray extravascular lung score observed four days after ultrafiltration.

In chronic heart failure, DLco is impeded mainly because Dm is reduced (17). In the present study, both overall Dm and Dm normalized for alveolar volume were low and, more importantly, remained unchanged after ultrafiltration. Because ultrafiltration reduced lung fluid, an increase in Dm would be expected if augmented lung fluid were the cause of the reduced Dm. Actually, we cannot exclude the possibility that fluid movement from the alveolar-capillary membrane is a very slow process. However, this seems unlikely because, for geometrical reasons, the gas exchange surface is highly protected by fluid overload (36) and, in all likelihood, is the first site to be fluid-free when lung fluids are reduced. Furthermore, our post-ultrafiltration study was carried out four days after the procedure, an interval that is more than enough to readjust fluid distribution in the lungs. On the other hand, while ultrafiltration-induced effects on pulmonary hemodynamics and lung fluid were appreciable, Dm remained unchanged. This suggests that, in chronic congestive heart failure, Dm reduction is not likely due to fluid accumulation but to other causes, such as fibrosis or an increase in cellularity of the alveolar-capillary membrane. This finding explains why mechanical properties and diffusing capacity of the lung behave differently after heart failure treatment, which includes drugs and heart transplantation. Furthermore, the findings of the present study are in agreement with the recently developed concept that fluid transport across the alveolar-capillary membrane is, at least in part, an active (pump-mediated) phenomenon (19–21) and that some antifailure drugs may act directly on the membrane diffusing activity (5).

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REFERENCES