Circulating Plasma Surfactant Protein Type B as Biological Marker of Alveolar-Capillary Barrier Damage in Chronic Heart Failure

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Background—Surfactant protein type B (SPB) is needed for alveolar gas exchange. SPB is increased in the plasma of patients with heart failure (HF), with a concentration that is higher when HF severity is highest. The aim of this study was to evaluate the relationship between plasma SPB and both alveolar-capillary diffusion at rest and ventilation versus carbon dioxide production during exercise.

Methods and Results—Eighty patients with chronic HF and 20 healthy controls were evaluated consecutively, but the required quality for procedures was only reached by 71 patients with HF and 19 healthy controls. Each subject underwent pulmonary function measurements, including lung diffusion for carbon monoxide and membrane diffusion capacity, and maximal cardiopulmonary exercise test. Plasma SPB was measured by immunoblotting. In patients with HF, SPB values were higher (4.5 [11.1] versus 1.6 [2.9], P=0.0006, median and 25th to 75th interquartile), whereas lung diffusion for carbon monoxide (19.7±4.5 versus 24.6±6.8 mL/mm Hg per min, P<0.0001, mean±SD) and membrane diffusion capacity (28.9±7.4 versus 38.7±14.8, P<0.0001) were lower. Peak oxygen consumption and ventilation/carbon dioxide production slope were 16.2±4.3 versus 26.8±6.2 mL/kg per min (P<0.0001) and 29.7±5.9 and 24.5±3.2 (P<0.0001) in HF and controls, respectively. In the HF population, univariate analysis showed a significant relationship between plasma SPB and lung diffusion for carbon monoxide, membrane diffusion capacity, peak oxygen consumption, and ventilation/carbon dioxide production slope (P<0.0001 for all). On multivariable logistic regression analysis, membrane diffusion capacity (β, –0.54; SE, 0.018; P<0.0001), peak oxygen consumption (β, –0.53; SE, 0.036; P=0.004), and ventilation/carbon dioxide production slope (β, 0.25; SE, 0.026; P=0.034) were independently associated with SPB.

Conclusion—Circulating plasma SPB levels are related to alveolar gas diffusion, overall exercise performance, and efficiency of ventilation showing a link between alveolar-capillary barrier damage, gas exchange abnormalities, and exercise performance in HF. (Circ Heart Fail. 2009;2:175-180.)

Key Words: chronic heart failure ■ surfactant protein B ■ lung diffusion ■ cardiopulmonary exercise test ■ alveolar-capillary barrier damage

Lung function abnormalities are part of the chronic heart failure (HF) syndrome, because both lung mechanics and gas exchange are impaired.1–4 Regarding gas exchange, alveolar capillary diffusion limitation in HF has been suggested as a prognostic marker,5 a target for therapy,6–7 and also as a limiting factor for exercise performance.8–10 In humans, alveolar gas exchange is measured in terms of total lung diffusion for carbon monoxide (DLCO) and specific membrane diffusion capacity (DLM).11,12

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In HF, gas exchange abnormalities are associated with anatomic changes in the alveolar-capillary membrane, which include reduction in the number of the alveolar-capillary units, interstitial fibrosis, local thrombosis, and an increase in cellularity.13–15 Recently, an increased circulating plasma level of surfactant protein type B (SPB) has been reported, with SPB that is higher when HF severity is highest.16 The
mature form of SPB plays a crucial role in the formation and stabilization of pulmonary surfactant film,17,18 so that the presence of SPB in the plasma may be a biological marker for alveolar-capillary barrier damage.16,19,20 However, no data are available concerning a correlation between SPB and lung diffusion, both total DL\textsubscript{CO} and membrane-specific D\textsubscript{M}. Moreover, it is unknown whether SPB correlates with peak oxygen consumption (VO\textsubscript{2}), and, more intriguing, with exercise-derived parameters related, even if just partially, to ventilation (VE)/perfusion mismatch, such as the slope of the linear relationship between VE and production of carbon dioxide (VCO\textsubscript{2}). Indeed, both peak VO\textsubscript{2} and VE versus carbon dioxide production slope are altered in HF and, notably, are prognosis predictors that are independently related to each other.21–25 This study was, therefore, designed to evaluate the circulating plasma SPB level in patients with HF and in healthy controls and its relationship with alveolar-capillary diffusion abnormalities at rest and with VE/perfusion mismatch during exercise.

Methods

Study Population

One hundred subjects were evaluated consecutively: 80 patients with chronic HF (42 ischemic and 38 nonischemic dilated cardiomyopathy) and 20 healthy control subjects. Patients belong to a group of individuals regularly followed-up at our HF unit, whereas controls were recruited from among hospital staff. Study inclusion criteria for patients were New York Heart Association functional classes I to III, optimized, individually tailored drug treatment, stable clinical conditions for at least 2 months, capability/willingness to perform a maximal or near maximal cardiopulmonary exercise test (CPET), absence of a clinical history and/or documentation of pulmonary embolism or primary valvular heart disease, pericardial disease, severe obstructive lung disease, primitive or occupational lung disease, anemia (Hb <11 g/dL), renal failure (serum creatinine >2.0 mg/dL), significant peripheral vascular disease, exercise-induced angina, ST changes, or severe arrhythmias. All patients recently (<1 month) underwent an echocardiographic evaluation.

The investigation was approved by the local ethics committee and subjects signed a written informed consent before participating in the study. The authors had full access to and take full responsibility for the integrity of the data. All authors have read and agree to the manuscript as written.

Specimen Handling and Assays

After 15 minutes of resting condition and immediately before the pulmonary function and lung diffusion measurements, a venous blood sample was taken, collected in citrate tubes, and centrifuged at 3000 rpm at 4°C; the plasma was frozen at −80°C for blind batch analysis.

To resolve low molecular weight proteins precisely, equal amounts of plasma proteins (50 μg) were separated by 1-dimensional sodium dodecyl sulfate-polyacrylamide gel electrophoresis on 15% polyacrylamide gels using a tris-tricine buffer system in nonreducing conditions.26 Gels were electrophoretically transferred to nitrocellulose at 60 V for 2 hours. Immunoblotting on transferred samples was performed as follows: blocking in 5% weight/volume nonfat milk in tris-buffered saline (100 mmol/L Tris-HCl, pH 7.5, 150 mmol/L NaCl) containing 0.1% Tris-buffered saline Tween-20 for 1 hour at room temperature; overnight incubation at 4°C with primary antibody against SPB (rabbit antihuman SPB H300, Santa Cruz Biotechnology) diluted to 1:200 in 5% weight/volume nonfat milk in Tris-buffered saline Tween-20; and incubation with secondary goat anti-rabbit antibody conjugated with horseradish peroxidase (Biorad) at 1:1000 for 1 hour. Bands were visualized by enhanced chemiluminescence enhanced kit (GE Healthcare, Milan, Italy) and acquired using a densitometer (GS800 Biorad).

In each analysis, a plasma sample was loaded as a control for normalization. Bands detected by chemiluminescence enhanced were quantified by densitometry of the exposed film, using the image analysis software QuantityOne (version 4.5.2) from Biorad. Results obtained as a ratio of band volume after local background subtraction versus the volume of the sample used for normalization are expressed as an arbitrary unit. The interassay variation coefficient was 12.1 ± 2.9%.

Pulmonary Function and Lung Diffusion

Immediately before CPET, all subjects enrolled were evaluated using standard pulmonary function tests, which included DL\textsubscript{CO}. Forced expiratory volume in 1 second (FEV\textsubscript{1}) and lung vital capacity (VC) were measured according to the American Thoracic Society standard criteria.27 The predicted values of Quanjer et al.28 were considered for FEV\textsubscript{1}/l lung vital capacity ratio less than 60% as indicative of a severe obstructive ventilatory defect. DL\textsubscript{CO} was measured with the intrabreath expiratory flow technique (Vmax29C, Sensor Medics, Yorba Linda, Calif).11 D\textsubscript{M} was calculated by applying the Roughton and Forster method.12 For this purpose, subjects inspired gas mixtures containing 0.3% CH\textsubscript{4}, 0.3% CO, with 3 different oxygen fractions equal to 20%, 40%, and 60%, respectively, and balanced with nitrogen.

Cardiopulmonary Exercise Test

A maximal symptom-limited CPET was performed on an electronically braked cycloergometer (Ergometrics-800, SensorMedics), with the subject wearing a nose clip and breathing through a mass flow sensor (Vmax29C, Sensor Medics) connected to a saliva trap. A personalized ramp exercise protocol was chosen, aiming at a test duration of 10 ± 2 minutes. The exercise was preceded by 5 minutes of resting breath-by-breath gas exchange monitoring and by a 3-minute unloaded warm-up. A 12-lead ECG, blood pressure, and heart rate were also recorded. CPET were self-terminated by the subjects when they claimed that they had achieved the maximal effort. However, we considered maximal exercise as only test in which the respiratory exchange ratio (VCO\textsubscript{2}/VO\textsubscript{2}) was above 1.05.

All tests were executed and evaluated by 2 expert readers blinded to plasma SPB values. The anaerobic threshold (AT) was identified by V\textsubscript{slope} of VO\textsubscript{2} and VCO\textsubscript{2} and confirmed by specific behavior of O\textsubscript{2} (VE/VO\textsubscript{2}) and CO\textsubscript{2} (VE/VCO\textsubscript{2}) ventilatory equivalents and end-tidal pressure of O\textsubscript{2} and CO\textsubscript{2}. The end of the isocapnic-buffering period was identified when V\textsubscript{E}/V\textsubscript{CO}\textsubscript{2} increased and end-tidal pressure of CO\textsubscript{2} decreased.29 The relation between VE versus V\textsubscript{CO}\textsubscript{2} was calculated as the slope of the linear relationship between VE and V\textsubscript{CO}\textsubscript{2} from 1 minute after the beginning of loaded exercise to the end of the isocapnic-buffering period.30

Statistical Analysis

Unless otherwise indicated, all data are expressed as mean ± SD. Data nonnormally distributed are given as median and interquartile range (75th percentile to 25th percentile). Categorical variables were compared with χ\textsuperscript{2} test followed by ANOVA; when ANOVA main effect was significant, a 2-sample t test was used to compare the general characteristics and other continuous data in the study groups. Kruskal-Wallis and Mann-Whitney U test were used for comparison between data with nonlinear distribution. Statistical analysis was also performed by subdividing patients into 4 groups according to D\textsubscript{M} (A, >30 mL/mm Hg per min; B, 25 to 30 mL/mm Hg per min; C, 20 to 25 mL/mm Hg per min; and D, <20 mL/mm Hg per min), according to the Weber classification,11 which is based on peak VO\textsubscript{2} (A, >20 mL/min per kg; B, 16 to 20 mL/min per kg; C, 12 to 16 mL/min per kg; and D, <12 mL/kg per min), and according to a cut-off value of 34 for the relationship between VE and V\textsubscript{CO}\textsubscript{2}, (A, <34 and B≥34).24

Because plasma SPB values showed a nonlinear distribution, Spearman correlation was used to disclose possible correlations between this protein and clinical, echocardiographic, pulmonary, and CPET findings. After transforming SPB values into the natural logarithm, multivariable linear regression analysis with stepwise selection of variables (age, gender, New York Heart Association functional class, left ventricular ejection fraction, VC, FEV\textsubscript{1}, DL\textsubscript{CO}, D\textsubscript{M}, peak VO\textsubscript{2} % of predicted, mL/min, mL/kg per min, VO\textsubscript{2} at AT, peak V\textsubscript{CO}\textsubscript{2}, peak VE, and VE/V\textsubscript{CO}\textsubscript{2} slope) was used to disclose...
predictors independently associated with circulating SPB values. To avoid distorted estimates of the effect, Spearman’s correlation and linear regression analysis were limited to the population with HF.

A P value <0.05 was considered statistically significant. All tests were 2-sided. The SAS software (version 8.02, SAS Institute Inc, Cary, NC) was used to perform all analyses.

**Results**

Of the 100 cases evaluated for this study only 90 subjects met the study inclusion/exclusion criteria and were therefore analyzed; we excluded 9 patients and 1 control subject resulting in 71 patients with chronic HF (38 ischemic and 33 nonischemic-dilated cardiomyopathy) and 19 healthy control subjects effectively enrolled. Four patients were excluded because of the presence of a severe obstructive lung disease, 2 patients because of a poor compliance to DLCO technique measurements, and 3 patients and 1 healthy control because they performed an exercise judged as not-maximal because they performed an exercise judged as not-maximal according to the low respiratory quotient reached. General characteristics of the 2 study groups, including patients’ left ventricular ejection fraction, are reported in Table 1. Patients with HF and control subjects were well matched with respect to age and gender (Table 1). Treatment in patients with HF included angiotensin-converting enzyme-inhibitors/AT1 blockers in 64 cases, β-blockers in 63 cases, diuretics in 40 cases, antialdosteronic drug in 36 cases, amiodarone in 18 cases, and antiplatelet in 29 cases, and anticoagulant in 19 cases.

Patients with HF showed a significantly lower lung vital capacity and FEV₁ than control subjects, whereas there was no difference in FEV₁/lung vital capacity ratio (Table 2). DLCO was lower both as absolute values and as percentage of predicted, and DM was significantly lower in patients than in controls (Table 2).

Exercise performance was significantly reduced in patients with HF, as demonstrated by the lower peak workload, peak VO₂, and the VO₂ at AT reached, and by the higher values of VE/VCO₂ slope (Tables 2 and 3).

Plasma SPB, which is detectable in the 3 predominant forms with molecular mass ranging from 17 to 42 kDa (Figure 1), were 4.5 (11.1) and 1.6 (2.9) arbitrary units (P=0.0006, median and 25th to 75th interquartile range) in patients with HF and controls, respectively. Analyzing only the HF population, SPB values were significantly related to peak VO₂, VE/VCO₂ slope, and DM (Figures 2 through 4). This finding was also confirmed by circulating plasma levels of SPB categorized accordingly to peak DM, VCO₂, and VE/VCO₂ slope classification (Table 3). Significant Spearman’s correlation coefficients between plasma SPB and some measured parameters (DLCO, DM, peak VO₂, VE/VCO₂ slope) are reported in Table 4. Using multivariable logistic regression analysis, DM (β = −0.55; standard error, 0.018; P<0.0001), peak VO₂ (β = −0.344; standard error, 0.036; P=0.004), and VE/VCO₂ slope (β = 0.25; standard error, 0.026; P=0.034) were independently associated with circulating SPB values.

**Discussion**

This study confirms that circulating SPB values are increased in patients with HF, and that patients with most severe HF have the highest values of SPB. It also shows, for the first time, that SPB values are directly related to alveolar gas diffusion damage.

Surfactant-specific proteins, synthesized almost exclusively by type II alveolar cells, represent a minor but necessary fraction of the surfactant. Inside type II alveolar cells, SPB undergoes complex proteolitic processing, changing from a larger form to the mature active form of SPB (8 kDa). Physiologically, the mature form of SPB plays a critical role in formation and stabilization of pulmonary surfactant films and, indeed, the deficiency of SPB leads to a lethal respiratory distress syndrome. The hydrophilic pre-surfactant films and, indeed, the deficiency of SPB leads to a lethal respiratory distress syndrome. Inside type II alveolar cells, SPB undergoes complex proteolitic processing, changing from a larger form to the mature active form of SPB (8 kDa). Physiologically, the mature form of SPB plays a critical role in formation and stabilization of pulmonary surfactant films and, indeed, the deficiency of SPB leads to a lethal respiratory distress syndrome. The hydrophilic pre-surfactant films and, indeed, the deficiency of SPB leads to a lethal respiratory distress syndrome. The hydrophilic pre-surfactant films and, indeed, the deficiency of SPB leads to a lethal respiratory distress syndrome. The hydrophilic pre-surfactant films and, indeed, the deficiency of SPB leads to a lethal respiratory distress syndrome. The hydrophilic pre-surfactant films and, indeed, the deficiency of SPB leads to a lethal respiratory distress syndrome. The hydrophilic pre-surfactant films and, indeed, the deficiency of SPB leads to a lethal respiratory distress syndrome. The hydrophilic pre-surfactant films and, indeed, the deficiency of SPB leads to a lethal respiratory distress syndrome. The hydrophilic pre-surfactant films and, indeed, the deficiency of SPB leads to a lethal respiratory distress syndrome. The hydrophilic pre-surfactant films and, indeed, the deficiency of SPB leads to a lethal respiratory distress syndrome.
cells and blood. Specifically, it has been demonstrated that circulating plasma SPB levels were higher in the patients with most severe HF, as suggested by New York Heart Association classification and HF hospitalization rate.\textsuperscript{16} The present data confirm that SPB values are increased in HF even in subjects in stable clinical conditions such as ours, who, according to study inclusion criteria, had been clinically stable for at least 2 months. Therefore, albeit a significant SPB increase is reasonable during a transient increase of Pmv, stable for at least 2 months. Therefore, albeit a significant SPB increase is reasonable during a transient increase of Pmv, it is also possible that alveolar cell disruption participates in the chronic dynamic remodeling of the alveolar capillary membrane in patients with HF, which is characterized by progressive reduction in the number of the alveolar-capillary units, increase of interstitial fibrosis, cellularity, and local thrombosis.\textsuperscript{13–15} Indeed, albeit we have not carried out repeated SPB measurements in the same subject, our data are consistent with the concept of a constant SPB flow into the circulation due to chronic remodeling of the alveolar-capillary membrane and suggest SPB as a possible biological marker for chronic alveolar-capillary damage.

Lung function abnormalities are well known in chronic HF and data observed in the present population, both in terms of lung mechanics and gas exchange impairment, are similar to those previously reported by various groups.\textsuperscript{1–4} Furthermore, it is well known that lung diffusion impairment is one of the possible causes of exercise limitation in chronic HF.\textsuperscript{10} Indeed, in the presence of alveolar-capillary membrane damage, the oxygen gradient across the alveolar-capillary membrane, the Δ(A–a)O₂, increases particularly when oxygen flow has to increase, for example, during exercise.\textsuperscript{10} However, the amount of Δ(A–a)O₂ at rest and how fast the Δ(A–a)O₂ increases during exercise is related to resting lung diffusion and to how lung diffusion changes during exercise.\textsuperscript{10} Furthermore, an upper limit of the Δ(A–a)O₂ seems to exist, so that, overall, these observations explain the link between exercise limitation and gas exchange impairment in patients with HF. A similar link between exercise capacity and lung diffusion applies to elite athletes.\textsuperscript{32} Accordingly, patients with HF with lowest lung diffusion capacity are those with the lowest ability to perform exercise at altitudes where alveolar gas diffusion is also limited by the reduced air pO₂.\textsuperscript{10} It is of note that both DL\textsubscript{CO} and D\textsubscript{M} are strongly related to SPB values, but that D\textsubscript{M} is the parameter that, under multivariable analysis, remains related to SPB. Indeed, D\textsubscript{M} is the specific alveolar-capillary membrane resistance whereas DL\textsubscript{CO}, besides being influenced by D\textsubscript{M}, is also influenced by the capillary volume, which is the amount of blood participating in gas exchange during the DL\textsubscript{CO} measurement. Exercise performance is usually evaluated in terms of oxygen consumption during exercise,\textsuperscript{21,22} However, during the last decade, it has become evident that other parameters obtained from an exercise study are useful for exercise performance evaluation in HF, more specifically, the VE versus V\textsubscript{CO}₂ relationship.\textsuperscript{23–25} The relationship between VE and V\textsubscript{CO}₂ has been evaluated as the ratio of VE and V\textsubscript{CO}₂ at AT,\textsuperscript{33} as the lowest ratio recorded during exercise,\textsuperscript{24} or as the

**Table 3.** SPB Values Categorized Accordingly to D\textsubscript{M}, peak VO\textsubscript{2}, and VE/V\textsubscript{CO}₂ Slope Classification

<table>
<thead>
<tr>
<th>DM Classification</th>
<th>Controls (≥30 mL/mm Hg per min)</th>
<th>Class A (25 to 30 mL/mm Hg per min)</th>
<th>Class B (≤20 to 25 mL/mm Hg per min)</th>
<th>Class C (12 to 16 mL/mm Hg per min)</th>
<th>Class D (≤12 mL/mm Hg per min)</th>
<th>P (ANOVA)</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>19</td>
<td>26</td>
<td>21</td>
<td>17</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td>SPB, AU</td>
<td>1.6 (2.3)</td>
<td>1.6 (3.7)</td>
<td>6.2 (10.9)</td>
<td>8.9 (17.1)</td>
<td>11.9 (15.8)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Peak VO\textsubscript{2} Classification</td>
<td>Controls</td>
<td>Class A (≥20 mL/min per kg)</td>
<td>Class B (16 to 20 mL/min per kg)</td>
<td>Class C (12 to 16 mL/min per kg)</td>
<td>Class D (≤12 mL/min per kg)</td>
<td>P (ANOVA)</td>
</tr>
<tr>
<td>n</td>
<td>19</td>
<td>15</td>
<td>18</td>
<td>27</td>
<td>11</td>
<td></td>
</tr>
<tr>
<td>SPB, AU</td>
<td>1.6 (2.3)</td>
<td>1.5 (1.8)</td>
<td>3.2 (7.4)</td>
<td>7.9 (11.2)</td>
<td>12.7 (18.2)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>VE/V\textsubscript{CO}₂ Slope Classification</td>
<td>Controls</td>
<td>Class A (≤34)</td>
<td>Class B (≥34)</td>
<td>Class C (≤34)</td>
<td>Class D (≥34)</td>
<td>P (ANOVA)</td>
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<tr>
<td>SPB, AU</td>
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<td>3.0 (6.9)</td>
<td>13.6 (15.0)</td>
<td></td>
<td></td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

SPB values are reported as median (75th to 25th percentile). AU indicates arbitrary units.

Figure 1. Example of the results of SPB analysis obtained by immunoblotting technique in a healthy control and in 4 patients with HF with different D\textsubscript{M} values.

Figure 2. Relationship between circulating plasma SPB and D\textsubscript{M} values in the entire study population (r value refers to Spearman correlation in HF population only). Normal subjects are shown, for completeness, with bold symbols.
slope of VE versus VCO₂ throughout the entire exercise or, more physiologically, from the beginning of exercise up to the end of the isocapnic-buffering period, as was the case in this study. Regardless of the methods used for calculation, the relationship between VE and VCO₂ reflects the efficiency of VE. It is of note that VE versus VCO₂ relationship is a prognosis predictor for HF independent of peak VO₂, and, in reality, the combined use of peak VO₂ and VE versus VCO₂ has a stronger ability to predict prognosis in patients with HF than both parameters taken individually. Interestingly, on multivariable analysis, both peak VO₂ and VE versus VCO₂ slope were correlated to SPB, again suggesting the physiological link between anatomic damage of the alveolar-capillary membrane and VE efficiency as well as overall exercise performance.

This study is the first demonstration of a link between anatomic alveolar-capillary damage, as inferable by circulating plasma SPB values, and functional alveolar-capillary damage, as inferable by lung diffusion parameters, and efficiency of VE abnormalities and overall exercise performance in HF. However, the correlation between circulating plasma SPB levels and functional changes of the respiratory pattern in patients with HF needs to be further studied. It is likely, but up to now unproved, that an increased wedge pressure might contribute to both SPB increase through an alveolar-capillary membrane damage and to VE/perfusion mismatch, as inferable from VE/VCO₂ slope analysis. At present, no clinical application of plasma SPB is known but a possible clinical role of SPB can be foreseen. Indeed, up to now, we cannot evaluate whether treatment capable of effecting DLCO influences the anatomy of the alveolar capillary membrane. It is probable that, in the future, it will be possible to differentiate between a functional effect, for example, active solute transport mechanisms, and anatomic effect on the alveolar capillary membrane, such as reduction of alveolar-capillary membrane remodeling rate. In other words, it might be possible to evaluate whether a drug acts on alveolar-capillary membrane function or anatomy, or both. Indeed, the present physiological interpretation of the effect of HF drugs acting on the alveolar-capillary membrane seems to indicate that drugs such as angiotensin-converting enzyme inhibitors and β-blockers act on the active transport mechanisms, whereas antialdosteronic drugs have an effect on the anatomy of the alveolar capillary membrane. These are just working ideas that need to be evaluated, but they represent a new way of looking at alveolar-capillary membrane remodeling and function in HF.

### Disclosures

None.

### References

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