Alveolar fluid reabsorption is increased in rats with compensated heart failure

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1Department of Physiology and Biophysics, Ruth & Bruce Rappaport Faculty of Medicine, Technion, Israel Institute of Technology; 2The Rappaport Family, Institute for Research in the Medical Sciences; 3Internal Medicine B; 4Department of Vascular Surgery and Transplantation, Rambam: Human Health Care Campus, Haifa, Israel; 5Division of Pulmonary and Critical Care Medicine, Columbia University, New York, New York; and 6Division of Pulmonary and Critical Care Medicine, Northwestern University, Chicago, Illinois

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Azzam, Zaher S., Yochai Adir, Lynn Welch, Joseph Winaver, Phillip Factor, Norberto Krivoy, Aaron Hoffman, Jacob I. Sznajder, and Zaid Abassi. Alveolar fluid reabsorption is increased in rats with compensated heart failure. Am J Physiol Lung Cell Mol Physiol 291:L1094–L1100, 2006. First published June 30, 2006; doi:10.1152/ajplung.00180.2005.—Alveolar fluid reabsorption (AFR) is important in keeping the air spaces free of fluid. This process is accomplished via active transport of Na⁺ across the alveolo-capillary barrier mostly by apical Na⁺ channels and basolateral Na⁺-K⁺-ATPases. Recently, we have reported that acute elevation of left atrial pressures is associated with decreased AFR in isolated rat lungs. However, the effect of chronic elevation of pulmonary capillary pressure, such as seen in patients with congestive heart failure (CHF), on AFR is unknown. CHF was induced by creating an aorto-caval fistula (ACF) in Sprague-Dawley male rats. Seven days after the placement of the fistula, AFR was studied in the isolated perfused rat lung model. AFR in control rats was 0.49 ± 0.02 ml/h (all values are means ± SE) and increased by ~40% (0.69 ± 0.03 ml/h) in rats with chronic CHF (P < 0.001). The albumin flux from the pulmonary circulation into the air spaces did not increase in the experimental groups, indicating that lung permeability for large solutes was not increased. Na⁺-K⁺-ATPase activity and protein abundance at the plasma membrane of distal alveolar epithelial tissue were significantly increased in CHF rats compared with controls. These changes were associated with increased plasma norepinephrine levels in CHF rats compared with controls. We provide evidence that in a rat model of chronic compensated CHF, AFR is increased, possibly due to increased endogenous norepinephrine upregulating active sodium transport and protecting against alveolar flooding.

Pulmonary edema develops when fluid movement into the air space exceeds the ability of the lung to clear it (20, 37). Many in vivo and ex vivo models of normal and injured lungs have been used to determine the mechanisms by which excess air space fluid is cleared (8, 13, 26, 29, 34, 38). These studies have used models where fluid was either directly instilled into the lung or rapidly accumulated in the air space. However, there are no data regarding how the lung adapts to chronic imbalance of Starling forces as occurs in congestive heart failure (CHF). Tandon and Kasturi (40) reported that in patients with mitral stenosis, the pulmonary tissue remodels in response to chronically elevated left atrial pressure; the arterioles were muscularized with pronounced intimal proliferation. Other changes included medial hypertrophy in the veins and occasional muscularization and dilatation of the lymphatics.

Patients with CHF have chronically elevated pulmonary capillary pressures, yet they develop frank pulmonary edema only occasionally and intermittently. These clinical features thus suggest that the lung must have mechanisms to compensate for chronic elevation of pulmonary hydrostatic pressures leading to lung edema. These mechanisms have not been previously defined.

Recently, several studies have shown that exposure to acute elevation in left atrial pressures impairs alveolar fluid reabsorption (AFR) in rat lungs; however, exogenous administration of catecholamines and overexpression of genes encoding for Na⁺-K⁺-ATPase subunits resulted in the maintenance of normal AFR rates (6, 16, 35). To ascertain how the lung adapts to chronic elevation of left atrial and pulmonary venous pressure, alveolar fluid clearance was measured in a rat model of heart failure, caused by a surgical formation of an aorto-caval fistula (ACF). This model of volume overload CHF is characterized by elevated atrial and ventricular filling pressures and activation of the neurohumoral axis and as such is a model of human CHF (1).

Materials and Methods

Experimental model. Experiments were performed on male Sprague-Dawley rats (275–350 g; Harlan Laboratories, Jerusalem, Israel). Rats were provided water and food ad libitum. The use of animals for the present study was approved by the Technion Institutional Animal Care and Use Committee and it was according to National Institutes of Health guidelines. A 1.2-mm arterial-venous (A-V) fistula was surgically created between the inferior vena cava and abdominal aorta as previously described from our laboratory (1). These rats were compared with sham-operated rats that underwent laparotomy without fistula formation. Following recovery, rats were maintained in individual metabolic cages.

Isolated lungs. Seven days after establishing ACF and CHF development, AFR was examined using the isolated perfused liquid-filled lung model. The lungs and heart of anesthetized rats (pentobarbital, 50 mg/kg body wt ip) were removed en bloc following a 10-min ventilation with 100% O₂ and anticoagulation with heparin. The pulmonary artery and left atrium were catheterized and perfused continuously with a solution of 3% bovine serum albumin (BSA) in buffered physiological salt solution (135.5 mM Na⁺, 119.1 mM Cl⁻, 25 mM HCO₃⁻, 4.1 mM K⁺, 2.8 mM Mg²⁺, 2.5 mM Ca²⁺, 0.8 mM SO₄²⁻, and 8.3 mM glucose). Trace amounts of fluorescein-labeled (FITC)
chronic heart failure was induced in eight adrenalectomized rats; albumin were added to the perfusate. The recirculating volume of the constant pressure perfusion system was 90 ml; left atrial and pulmonary arterial pressures were set at 0 and 15 cmH2O, respectively. The lungs were immersed in a “pleural” bath (50 ml) filled with the same BSA solution. The entire system was maintained at 37°C in a water bath. Pulmonary circulation perfusate pH was maintained at 7.40 by bubbling with a gas mixture of 95% O2-5% CO2. The lungs were then instilled via the tracheal cannula with a total of 5 ml of BSA solution containing 0.1 mg/ml Evans blue dye-labeled (EBD; Sigma) albumin. Samples were taken from the instillate, perfusate, and bath solutions after an equilibration time of 10 min from the instillation and 60 min later. To ensure a homogenous sampling of the instillate, a volume of 2 ml was aspirated and reintroduced into the air spaces three times before removing each sample. All samples were centrifuged at 3,000 g for 10 min. Absorbance analysis of the supernatant or EBD albumin was performed at 620 nm in a spectrometer. Analysis of FITC-albumin (excitation 487 nm and emission 520 nm) was performed in a fluorometer.

The mathematical calculation of AFR was described elsewhere (33). Briefly:

$$V_t[EBD]_t = V_i[EBD]_0$$

$$J = (V_t - V_0)t$$

where $V_0$ is the initial known volume instilled into rat air spaces containing a known concentration of Evans blue dye-albumin [EBD]₀, $Vᵢ$ and [EBD]ᵢ are the alveolar fluid volume and EBD concentration in the instillate at time $t$, respectively. $J$ is the volume flux during a time period ($t$).

The fraction of FITC-albumin that appears in the alveolar space during the experimental protocol was used to calculate the albumin flux from the pulmonary circulation into the alveolar space.

**Experimental groups.** The experimental groups were as follows, with the number of animals in each group given in parentheses.

- Sham-operated rats that were subject to opening and closing of the abdominal wall served as a control group ($n = 8$).
- AFR was measured 7 days ($n = 7$) and 4 wk ($n = 4$) after fistula formation.

To examine the role of the apical Na⁺ channels, we instilled the lungs with $10^{-6}$ M amiloride (Na⁺-channel blocker) in both control ($n = 6$) and chronic CHF rats ($n = 4$).

The effects of the adrenergic system on AFR were investigated by treating rats with propranolol ($\beta$-adrenergic receptor antagonist). Three days after surgical creation of an A-V fistula or sham operation, propranolol (25 mg·kg⁻¹·day⁻¹) was added to the drinking water.

Upon completion of 4 days of treatment, AFR was measured in CHF ($n = 7$) and sham rats ($n = 7$) that were treated with propranolol. In addition, we instilled and perfused the lungs with $10^{-5}$ M propranolol into the lungs of sham ($n = 5$) and CHF ($n = 4$) rats. In addition, chronic heart failure was induced in eight adrenalectomized rats; however, alveolar reabsorption was measured only in two adrenalectomized CHF rats, whereas the rest of the rats did not survive for 1 wk.

**Preparation of basolateral membranes.** Basolateral membrane (BLM) proteins (~1.0 g net wt) were isolated from peripheral lung tissue (i.e., the distal 3–4 mm) that was harvested from sham ($n = 4$) and CHF ($n = 4$) rats. Homogenization buffer (800–1,000 µl; 300 mM mannitol in 12 mM HEPES, pH 7.4, 3 mM EGTA, pH 8.0, 1 mM EDTA, pH 8.0, 2 µg/ml leupeptin, 100 mM PMSF, and 10 mg/ml TPCK) was added to the tissue. BLM were isolated using a Percoll gradient (17, 23). Briefly, tissue was homogenized and centrifuged twice to discard the nuclear and mitochondrial pellet. Supernatant was centrifuged at 48,000 g for 30 min, BLM fraction was recovered after the membrane pellet was centrifuged in a 16% Percoll gradient at 48,000 g for 30 min, and then the ring of BLM was collected.

Na⁺-K⁺-ATPase activity in BLM. Triplet samples of BLM proteins (20 µg) from sham and chronic CHF rats ($n = 3$ each group) were resuspended in a high-Na⁺, low-K⁺ reaction buffer (50 mM/l NaCl, 5 mM/l KCl) with [γ-32P]ATP as described previously (18). Na⁺-K⁺-ATPase activity was described as the difference in liberation of 32P from ATP between the test samples (total ATPase activity) and the samples assayed with reaction buffer with 2.5 mM/l ouabain and devoid of Na⁺ and K⁺ (ouabain-insensitive ATPase activity). Results were expressed as nanomoles of inorganic phosphate per milligram of protein per hour.

**Western blot analysis.** Protein was quantified by Bradford assay (14) (Bio-Rad, Hercules, CA), and equal amounts of BLM proteins were resolved in 10% polyacrylamide gels (SDS-PAGE). Thereafter, proteins were transferred onto nitrocellulose membranes (Optitran; Schleicher & Schuell, Keene, NH) using a semi-dry transfer apparatus (Bio-Rad). Incubation with anti-Na⁺-K⁺-ATPase α1 (Upstate Biotechnology, Lake Placid, NY) was performed overnight at 4°C. Blots were developed with a chemiluminescence detection kit (PerkinElmer Life Sciences, Boston, MA) used as recommended by the manufacturer. The bands were quantified by densitometric scan (Image 1.29X, National Institutes of Health).

Histological analysis. Lung tissues were fixed in 4% paraformaldehyde overnight. Lungs were deparaffinized in xylene for 5 min (3 times) and then rehydrated in 100%, 95%, 70% ethanol and PBS. Hematoxylin and eosin staining was performed as described. Briefly, slides were stained in hematoxylin for 3 min, rinsed in tap water, dipped in acid-alcohol 8–12 times, and finally rinsed in tap water. Next, slides were stained with eosin for 30 s and then dehydrated with 95% ethanol, 100% ethanol, and xylene. Images were observed under a Nikon Eclipse E800 fluorescence microscope and were further processed by MetaMorph software.

**Table 1. Catecholamines, hemodynamic and renal characteristics of sham and compensated congestive heart failure rats**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Sham</th>
<th>CHF</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Catecholamines</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Norepinephrine, pg/ml</td>
<td>184.2±40.5</td>
<td>481.0±20.0</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Epinephrine, pg/ml</td>
<td>667±175.9</td>
<td>449.0±339.0</td>
<td>NS</td>
</tr>
<tr>
<td>CVP, mmHg</td>
<td>12.6±1.6</td>
<td>16.4±3.9</td>
<td>NS</td>
</tr>
<tr>
<td>MAP, mmHg</td>
<td>126±2</td>
<td>95±3</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>CO, ml/min</td>
<td>148.1±6.6</td>
<td>920.0±4.01</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>BW</td>
<td>302±1</td>
<td>305±22</td>
<td>NS</td>
</tr>
<tr>
<td>Wet/dry LW ratio</td>
<td>5.40±0.17</td>
<td>5.58±0.10</td>
<td>NS</td>
</tr>
<tr>
<td>%HW/BW</td>
<td>0.309±0.009</td>
<td>0.437±0.008</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Renal</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>USnV, µeq/min</td>
<td>1.810±40</td>
<td>1.570±247</td>
<td>NS</td>
</tr>
</tbody>
</table>

Values are means ± SE. CVP, central venous pressure; MAP, mean arterial pressure; CO, cardiac output; USnV, urinary sodium excretion; LW, lung weight; HW, heart weight; BW, body weight; NS, non-significant; CHF, congestive heart failure.

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Wet-to-dry weight ratio. The lungs of sham-operated (n = 4) and CHF rats (n = 6) were taken to calculate the wet-to-dry lung weight ratio as previously described (26).

Cardiac output, catecholamines, and sodium levels. Cardiac output was measured by Cardiomax (Columbus Instruments, Columbus, OH) interfaced with a computer, based on the thermodilution technique with a thermocouple in the thoracic aorta via the carotid artery (2, 19).

Plasma levels of norepinephrine and epinephrine were measured by HPLC on acetic acid-extracted samples (21).

Sodium concentration in the urine was measured by flame photometry (model 943, Instrumentation Laboratory) (n = 6 in each group of sham and CHF rats).

Statistical analysis. Data are presented as means ± SE; n is the number of animals in each study group. One-way analysis of variance was used when multiple comparisons were made followed by a multiple comparison test (Tukey) when the F statistic indicated significance. To analyze catecholamines, the hemodynamic and renal characteristics, we used unpaired t-test to assess the differences between the study groups. Results were considered significant when P < 0.05.

RESULTS

As shown in Table 1, the daily urinary sodium excretion (UNaV) in rats with ACF and in sham-operated controls did not differ significantly. This indicates that the CHF rats in the present study belong to the compensated CHF subgroup rather than the decompensated subgroup. The latter is characterized by a marked decrease in the excretion (UNaV < 200 μeq/24 h) (15).

AFR. AFR in isolated lungs from rats with experimental CHF was 40% higher than in sham-operated rats 1-wk post-ACF formation (0.69 ± 0.03 vs. 0.49 ± 0.02 ml/h, respectively, P < 0.001). AFR remained elevated after 4 wk from the induction of CHF (0.67 ± 0.03 ml/h, P < 0.001 compared with sham-operated controls). However, the difference between AFR at 4 wk compared with 1 wk did not reach statistical significance (P > 0.05; Fig. 1).

To evaluate the role of amiloride-sensitive Na⁺ entry pathways in this model, amiloride (10⁻⁶ M) was placed in the alveolar air spaces of 10 rats. As shown in Fig. 2, amiloride decreased AFR in CHF as well as in sham rats. However, the decrease was more prominent in CHF rats because amiloride inhibited the CHF-mediated increases in AFR. The decrease in clearance in CHF rats treated with amiloride was 61.9 ± 3.8% (mean ± SE) compared with 36.3 ± 2.2%. This difference is statistically significant (P = 0.0002).

As shown in Fig. 2, the β-adrenergic receptor antagonist, propranolol, blocked the stimulatory effects in CHF rats compared with sham rats treated with propranolol. AFR, in rats orally treated with propranolol, was 0.45 ± 0.03 and 0.44 ± 0.008 ml/h, respectively. In rats that were given propranolol directly to the lung, AFR was 0.51 ± 0.04 and 0.47 ± 0.03 ml/h, respectively.

Heart failure was induced in eight adrenalectomized CHF rats; however, only two rats survived for 7 days. The measured clearance in one rat was 0.53 ml/h, whereas, in the other rat, it was 0.34 ml/h, suggesting again that the CHF-mediated increase in AFR is due to increased endogenous norepinephrine levels.

Fig. 1. Alveolar fluid reabsorption (AFR) is increased in chronic congestive heart failure (CHF) rats 1 wk (n = 7) and 4 wk (n = 4) after operation compared with sham rats (n = 8). However, there was no significant difference between the groups of rats with CHF. The bars represent means ± SE. *P < 0.001 compared with sham rats. CT, control.

Fig. 2. The sodium channel blocker amiloride, instilled into the alveolar air spaces, inhibited AFR in control (n = 6) and 1-wk CHF rats (n = 4). AFR was decreased by 61.9 ± 3.8% in CHF rats treated with amiloride compared with 36.3 ± 2.2% in amiloride-treated sham rats. This difference is statistically significant. Propranolol, either given orally (n = 7 in each group) or directly to the lungs (n = 5 in sham rats and n = 4 in CHF group), inhibited the compensatory effects seen in chronic CHF rats. This shows that the stimulatory effects were possibly achieved by the activation of β-adrenergic pathways. *P < 0.001 compared with 1-wk CHF rats that were not given amiloride or propranolol. +P < 0.001 compared with control group. **P < 0.001 compared with control rats. There was no statistical difference between the two treated propranolol CHF groups compared with control rats and sham groups treated with propranolol. The bars represent means ± SE. Ami, amiloride; IP, instilled and perfused.
Wet-to-dry weight ratio. As depicted in Table 1, the heart weight of CHF rats was significantly increased compared with sham rats \((P < 0.0001)\). The wet-to-dry lung weight ratios, a gravimetric estimate of total lung water, showed that in CHF rats, there was no significant change between CHF and sham rats.

Na\(^{+}\)-K\(^{+}\)-ATPase activity and protein abundance. Membrane-bound Na\(^{+}\)-K\(^{+}\)-ATPase activity was quantified by measurement of ouabain-sensitive ATP hydrolysis by basolateral cell membranes isolated from the peripheral lung of sham and CHF rats. Activity was measured in the presence of low-K\(^{+}\), high-Na\(^{+}\) and high ATP concentration to maximize ATPase function per molecule \((V_{\text{max}})\). These experiments revealed that Na\(^{+}\)-K\(^{+}\)-ATPase activity in rats with CHF is 35\% greater than in sham controls \((P < 0.05)\) (Fig. 3A). To test whether chronic CHF affects Na\(^{+}\)-K\(^{+}\)-ATPase abundance at the BLM, cell membrane fractions enriched for BLM were prepared from distal lung tissue of sham and CHF rats as previously described \((18)\). Western analysis of BLMs from sham and CHF rats \((n = 4 \text{ each group})\) revealed \(\sim 2.4\)-fold increase in Na\(^{+}\)-K\(^{+}\)-ATPase \(\alpha_{1}\)-subunit protein abundance in lungs of the CHF rats \((P = 0.0003)\) (Fig. 3B).

Histology and immunohistochemistry. As depicted in Fig. 4, A and B, the H&E staining did not show an increase in cellular proliferation in CHF rats compared with sham group.

Catecholamine levels and cardiac output. As shown in Table 1, rats with A-V fistula had a significant increase in the concentrations of circulating norepinephrine compared with sham controls; however, the levels of epinephrine did not differ significantly between the study groups. Thermodilution-based measurement of cardiac output indicated a biphasic pattern characterized by an initial rise in cardiac output followed by a significant reduction at 1 wk after fistula placement. Therefore, this model of CHF is considered to be a high cardiac output model in the first few days. However, after 1 wk, cardiac output was reduced by 40\% in rats with ACF compared with sham controls \((148 \pm 6.6 \text{ vs. } 90.2 \pm 4.01 \text{ ml/min}, P < 0.0001; \text{Table } 1)\). The central venous pressure was significantly increased in rats with A-V fistula compared with the control study, while the mean arterial pressure was decreased by 25\% (Table 1).

DISCUSSION

Heart failure is one of the most common problems seen in the clinical practice in adults. In hospitalized Medicare patients, heart failure is the most frequently cited diagnosis-related group \((3, 24)\). Others and we \((6, 16, 32, 35)\) have reported that the rate of AFR is decreased in acutely increased left atrial pressure. However, the effect of chronic heart failure...
on lung edema clearance has not been previously reported. Verghese et al. (41) have shown that alveolar fluid clearance in the majority of the patients with acute hydrostatic pulmonary edema was normal, and in some, clearance was increased. In the present study, we provide evidence that AFR was increased in experimental chronic left atrial hypertension (Fig. 1). This effect persisted at least for 4 wk and was associated with increased Na\(^{+}\)-K\(^{+}\)-ATPase activity and protein abundance at the BLM from peripheral lung tissues (Fig. 3, A and B, respectively). There is a large body of experimental evidence from normal animal models that suggests upregulation of the apical Na\(^{+}\) channels and Na\(^{+}\)-K\(^{+}\)-ATPase proteins increases active Na\(^{+}\) transport across the alveolar epithelium (12, 38).

The instillation of 10\(^{-6}\) M amiloride (43) decreased AFR in both heart failure and sham rats as well; however, the decrease was more profound in the CHF group, indicating that the induction of experimental chronic CHF may increase AFR by upregulating amiloride-sensitive Na\(^{+}\) pathways in the alveolar epithelium. We reason that this upregulation of Na\(^{+}\) transport is vital for keeping the alveolar spaces free of edema in rats with chronic CHF. Andreoli (4) reviewed factors responsible for edema in chronic CHF and pointed out that one of the key elements involved in renal sodium retention is activation of apical sodium channels, ENaC, of principal cells in the cortical collecting tubule by aldosterone and by vasopressin.

Bachofen et al. (9) reported that in patients with chronic CHF, there is an increase in the number of alveolar type II cells. Notably, this finding might contribute to increased AFR. Our histology data did not show an increase in cellular proliferation (Fig. 4, A and B). However, we cannot exclude that CHF could have increased alveolar epithelial cell proliferation.

We also provide evidence that in rats with A-V fistula, Na\(^{+}\)-K\(^{+}\)-ATPase protein was increased at the plasma membrane, which resulted in increased Na\(^{+}\)-K\(^{+}\)-ATPase activity and thus edema clearance. This is consistent with our previous study that demonstrated in a rat model of acute hydrostatic pulmonary edema that Na\(^{+}\)-K\(^{+}\)-ATPase gene transfer restored AFR (6). The increase in AFR was inhibited by the nonselective β-adrenergic blocker propranolol. In addition, the A-V fistula rats that underwent adrenalectomy did not survive for more than 2 days after the operation. These experiments may suggest a role for norepinephrine in upregulating active Na\(^{+}\) transport.

The wet-to-dry lung weight ratio was not increased in CHF rats compared with sham rats. These data support our observation that increased fluid reabsorption and active sodium transport might be a defense mechanism that prevented the alveolar edema. The compensatory effects of heart failure are controlled by the neurohumoral axis with increased levels of catecholamines, renin-angiotensin system, and others (36). We found significantly elevated levels of norepinephrine in the plasma of A-V fistula rats that might have contributed to the upregulation of the active sodium system and thus keeping the alveolar spaces free of fluid. Concordant with this assumption, several studies reported the beneficial effects of adrenergic system stimulation in models of lung injury (5, 7, 18, 28). These effects are due to cAMP and protein kinase A-dependent pathway activation that recruits Na\(^{+}\)-K\(^{+}\)-ATPase subunits within 15 min of β-adrenergic receptor stimulation and MAPK/ERK-dependent pathway (25, 27, 30, 31). ACF rats are exposed to prolonged stimulation of the adrenergic system that might be correlated with increased AFR. In agreement with our observation, it has been shown recently that β-adrenergic stimulation may lead to the upregulation of Na\(^{+}\)-K\(^{+}\)-ATPase via transcriptional and posttranscriptional mechanisms (22, 39) (Fig. 5).

**Fig. 5.** Proposed pathway for increased AFR in rats with compensated chronic heart failure rats. On the basis of our data, we propose that increased levels of endogenous norepinephrine regulate Na\(^{+}\)-K\(^{+}\)-ATPase protein expression in alveolar epithelial cells (AEC).
The epithelial permeability to albumin was not different from control rats, indicating that the alveolo-capillary barrier was not grossly damaged. Our data differ somewhat with previous reports showing slightly increased permeability to tracers across the alveolo-capillary barrier with acute left atrial hypertension (10, 11, 35, 42). These differences might be attributed to the compensatory mechanisms that helped in restoring AFR and alveolo-capillary barrier integrity in this chronic model.

In summary, we report that AFR is increased in a model of chronic heart failure. We reason that these effects were correlated with the increase in norepinephrine, which via stimulation of β- and α-adrenergic receptors regulates Na+-K+-ATPase and amiloride-sensitive sodium channels in alveolar epithelial cells. We provide evidence that chronic pulmonary capillary hypertension results in physiologically significant increases in the ability of the lungs to clear excess fluid from the alveolar air space probably due to increased endogenous norepinephrine that is produced as an adaptation to CHF. This information provides new insights that are of clinical relevance to our understanding of the role of active sodium transport in keeping the alveolar spaces free of edema in patients with chronic heart failure.

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REFERENCES


