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Effect of β_2-adrenergic receptor stimulation on lung fluid in stable heart failure patients

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KEYWORDS:
albuterol;
computed tomography;
lung diffusing capacity;
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alveolar-capillary membrane conductance

BACKGROUND: The purpose of this study was to determine: (1) whether stable heart failure patients with reduced ejection fraction (HFrEF) have elevated extravascular lung water (EVLW) when compared with healthy control subjects; and (2) the effect of acute β_2-adrenergic receptor (β_2AR) agonist inhalation on lung fluid balance.

METHODS: Twenty-two stable HFrEF patients and 18 age- and gender-matched healthy subjects were studied. Lung diffusing capacity for carbon monoxide (DLCO), alveolar–capillary membrane conductance (Dm_{CO}), pulmonary capillary blood volume (V_c) (via re-breathe) and lung tissue volume (V_{tis}) (via computed tomography) were assessed before and within 30 minutes after administration of nebulized albuterol. EVLW was derived as $V_{tis} - V_c$.

RESULTS: Before administration of albuterol, V_{tis} and EVLW were higher in HFrEF vs control (998 ± 200 vs 884 ± 123 ml, $p = 0.041$; and 943 ± 202 vs 802 ± 133 ml, $p = 0.015$, respectively). Albuterol decreased V_{tis} and EVLW in HFrEF patients (–4.6 ± 7.8%, $p = 0.010$; –4.6 ± 8.8%, $p = 0.018$) and control subjects (–2.8 ± 4.9%, $p = 0.029$; –3.0 ± 5.7%, $p = 0.045$). There was an inverse relationship between pre-albuterol values and pre- to post-albuterol change for EVLW ($r^2 = -0.264$, $p = 0.015$) and Dm_{CO} ($r^2 = -0.343$, $p = 0.004$) in HFrEF only.

CONCLUSION: Lung fluid is elevated in stable HFrEF patients relative to healthy subjects. Stimulation of β_2ARs may cause fluid removal in HFrEF, especially in patients with greater evidence of increased lung water at baseline.

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Chronic heart failure (HF) is associated with an increase in pulmonary capillary pressure and wall tension secondary to the rise in left ventricle (LV) filling pressure consistent with a failing LV.[1] In addition, it has been shown that a chronic increase in adrenergic drive, as occurs with HF, elicits a downregulation of the β-receptors central to lung fluid–removal mechanisms.[2–4] In combination, it is possible that the aforementioned changes in the pulmonary system associated with HF may conspire to increase fluid flux across the pulmonary vasculature while impairing fluid clearance from the alveoli and interstitial space, thus making HF patients more susceptible lung fluid accumulation relative to their healthy counterparts. Although pulmonary congestion, a key component of which is a significant increase in lung fluid, is a hallmark of acute decompensation in HF,[5–7] it remains unclear whether stable HF patients exhibit increased extravascular lung fluid, as some studies,[8]

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but not all,[9] showed increased lung water content in HF patients. Moreover, the role of alterations in lung β-adrenoreceptor system–mediated fluid clearance mechanisms in the pulmonary edema associated with HF has not been fully elucidated. Accordingly, in this study, we aimed to determine: (1) whether stable HF patients with reduced ejection fraction (HFrEF) have elevated lung fluid compared with their healthy, age- and sex-matched counterparts; and (2) the effect of acute inhalation of a β_2-adrenergic receptor agonist on lung fluid balance in stable HFrEF patients.

Methods

Participants and ethics approval

Twenty-two adult patients with a history of HFrEF and 18 healthy, age- and sex-matched controls volunteered to participate in this study (Table 1). The patients recruited were required to meet the following criteria: (1) ≥1-year history of known HF; (2) ejection fraction of ≤40%; (3) New York Heart Association (NYHA) Functional Class I, II or III status; (4) stable symptoms (i.e., receiving optimal medication and having no change in disease status or medication) for >3 months; (5) freedom from uncontrolled systemic hypertension, anemia or other comorbidities (e.g., chronic obstructive pulmonary disease); (6) not pacemaker-dependent; and (7) body mass index (BMI) <36. The age-matched controls were recruited from the surrounding community and were current non-smokers (past 15 years) and with no history of cardiac or pulmonary disease. Each participant provided written informed consent after being given a detailed description of the study requirements. The experimental procedures were approved by the institutional review board of the Mayo Clinic and performed in accordance with the Declaration of Helsinki.

Experimental procedures

The experimental procedures were conducted during 2 separate laboratory visits separated by no longer than 1 week. At the first visit, complete blood count was assessed to rule out anemia before pulmonary function was assessed via body plethysmography (MedGraphics Elite Series Plethysmograph; Medical Graphics Corporation, St. Paul, MN) according to standard procedures.[10] During the second visit, albuterol, a short-acting β_2-adrenergic receptor agonist, was administered at a dilution of 2.5 mg per 3 ml of saline using a nebulizer for 15 minutes in each participant. Pulmonary function, lung diffusing capacity for carbon monoxide (D_{LCO}) and nitric oxide (D_{LNO}), alveolar–capillary membrane

Table 1 Participants' Characteristics, Medications and Pulmonary Function in HFrEF Patients and Healthy Control Subjects

	Control subjects	HFrEF patients	*p*-value[a]
Demographics			
Number	18	22	
Female	5 (28)	6 (27)	
Age (years)	58 ± 9	63 ± 8	0.062
Stature (cm)	174 ± 15	175 ± 10	0.754
Body mass (kg)	78.7 ± 15.2	89.9 ± 16.7	0.034
BMI, kg/m^2)	25.9 ± 4.4	29.2 ± 4.4	0.020
BSA (m^2)	1.95 ± 0.21	2.08 ± 0.23	0.069
Etiology (*n*)		10 ISC / 12 IDC	
HF duration (months)		68 ± 75	
LVEF (%)		28.5 ± 7.9	
NYHA functional class			
I		6 (27)	
II		12 (55)	
III		4 (18)	
Medications			
ACE inhibitors		22 (100)	
Aspirin		19 (86)	
β-blockers		21 (95)	
Digitalis		8 (36)	
Diuretics		16 (73)	
Pulmonary function			
FVC (% predicted)	103 ± 12	83 ± 15.8	<0.001
FEV_1 (% predicted)	106 ± 11	81 ± 18	<0.001
FEV_1/FVC (% predicted)	97 ± 7	105 ± 19	0.145
PEF (liters/s)	98 ± 11	74 ± 22	<0.001
$FEF_{25-75\%}$ (% predicted)	125 ± 32	84 ± 24	0.001
IC (liters)	109 ± 11	86 ± 21	0.002
$DLco/V_A$	10.9 ± 6.6	6.4 ± 4.6	0.015

Data are presented as group mean ± standard deviation or number (%). ACE, angiotensin-converting enzyme; BMI, body mass index; BSA, body surface area; DLco, lung diffusing capacity for carbon monoxide; $FEF_{25-75\%}$, forced expiratory flow at 25% to 75% of FVC; FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; HFrEF, heart failure with reduced ejection fraction; IC, inspiratory capacity; IDC, idiopathic dilated cardiomyopathy; ISC, ischemic; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; PEF, peak expiratory flow rate; V_A, alveolar volume.

[a]Comparison of group mean control vs group mean HFrEF.

conductance (Dm_{CO}) and pulmonary capillary blood volume (V_c) were assessed before and within 30 minutes after albuterol administration. Similarly, lung density and lung tissue volume (V_{tis}) were measured before and within 30 minutes after albuterol administration via chest computed tomography (CT) imaging.

Lung diffusing capacity

DLCO, DLNO, Dm_{CO} and V_c were assessed by simultaneously measuring the disappearance of CO and NO using a re-breathe technique, as we have described previously.[11,12] Participants sat upright and breathed through a 2-way switching valve that was connected to a pneumotachometer, a mass spectrometer (Marquette 1100 Medical Gas Analyzer; Perkin-Elmer, St. Louis, MO) and a NO analyzer (Sievers 280i NOA; Sievers, Boulder, CO). The inspiratory port of the switching valve was set to either room air or a 5-liter anesthesia bag filled with 0.3% CO ($C^{18}O$), 40 parts per million (ppm) NO (diluted in the bag immediately before each re-breathe maneuver from an 800-ppm gas mixture), 35% O_2 and N_2 balance. The total volume of gas in the anesthesia bag was determined by the resting tidal volume of each participant. For each re-breathe maneuver, the participants breathed normally on room air for 4 to 5 breaths before, at the end of a normal expiration, they were switched to the re-breathe bag and told to "nearly empty the bag" with each inspiration for 10 to 12 consecutive breaths at a breathing frequency of 32 breaths/min. Each participant performed the re-breathe maneuver in triplicate before and within 30 minutes after administration of nebulized albuterol. DLCO, DLNO, Dm_{CO} and V_c were computed using custom analysis software.

Lung tissue volume and lung density via CT

All CT scans were performed using the same scanner (GE LiteSpeed Spiral CT Scanner; GE Healthcare). Initial slices obtained for all scans were 2.5 mm thick with a 1.2-mm overlap and were then reconstructed to 1.25-mm thickness with a 0.6-mm overlap. Before the baseline scan (i.e., before albuterol administration) a scout scan was performed to determine the location and size of the lungs. The anatomic location at the start of the scan was marked on each subject using indelible ink, and the table height, field of view and number of images obtained were recorded to ensure consistency between the CT scans taken before and after albuterol administration. For each CT scan, the participants were instructed to breathe normally before inspiring fully and performing a breath-hold at total lung capacity (TLC) before the scan was initiated. During each scan, the participants breathed through a mouthpiece connected to a pneumotachometer that was integrated with a portable computer with custom analysis software, so that accurate lung volumes could be measured; this protocol ensured that all pre- and post-albuterol CT measures of lung tissue volume and lung density were made at the same lung volume.

For analysis, the CT images were submitted to image analysis software (Pulmonary Analysis Software Suite; Physiological Imaging Laboratory, University of Iowa, Iowa City, IA) and all analyses were performed by a single member of the research team who was blinded to the condition (i.e., before or after albuterol) of each CT scan. The Pulmonary Analysis software was used to segment the images to separate lung tissue from surrounding structures and the mediastinum for analysis of parenchymal attenuation. In each picture element, lung density was assumed to be a linear combination of air and lung tissue, which have an attenuation of −1,000 and 0 Hounsfield units (HU), respectively. A histogram analysis of picture elements within the lung tissue was performed to obtain mean lung density (in HU) and tissue volume by summation of each voxel among all elements in the lung fields.

Estimation of extravascular lung water

The parenchymal attenuation assessed by CT (i.e., V_{tis}) includes lung tissue, blood and water. By combining our CT-derived measure of tissue volume and our measure of V_c from the lung diffusing capacity maneuvers,[12] we were able to estimate the volume of extravascular lung water as:

$$EVLW = V_{tis} - V_c$$

where EVLW is extravascular lung water (in milliliters), V_{tis} is tissue volume (in milliliters) determined via CT and V_c is pulmonary capillary blood volume (in milliliters), assessed using our CO and NO re-breathe technique.

Albuterol administration

Using a nebulizer, albuterol (a short-acting β_2AR agonist) was administered at a dilution of 2.5 mg per 3 ml of saline for ~15 minutes during tidal breathing in each participant. Heart rate (HR) and cardiac rhythm were measured via a 12-lead electrocardiogram (ECG) throughout the albuterol administration. Similarly, arterial oxygen saturation (SaO_2) was monitored continuously during albuterol administration using a pulse oximeter (Nellcor N-595; Tyco Healthcare Group, Nellcor Puritan Bennett Division, Pleasanton, CA) and a forehead sensor. Manual blood pressure and the rating of perceived dyspnea were obtained before albuterol administration and at 2-minute intervals thereafter until 5 minutes after albuterol.

Statistical analyses

Independent-samples *t*-test was used to compare subject characteristics, measures of lung function and absolute measures of lung diffusion capacity and related variables, CT-derived lung density and lung tissue volume, and extravascular lung water at equivalent time-points between the experimental groups (control vs HFrEF). Paired-samples *t*-test was used to compare absolute measures of lung diffusion capacity and related variables, CT-derived lung density and lung tissue volume, and extravascular lung water across time (before vs after albuterol administration) within each experimental group (control and HFrEF). Pearson's product-moment correlation coefficient (r) was computed to assess the relationships between baseline (i.e., before albuterol) measures of V_{tis}, EVLW and Dm_{CO} relative to pulmonary capillary blood volume and the change in these variables from before to after albuterol administration in control subjects and HFrEF patients. The acceptable Type I error was set at $p < 0.05$. Results are expressed as mean ± standard deviation, unless stated otherwise. Statistical analysis was performed using SPSS version 21.0 for Windows (SPSS, Inc, Chicago, IL).

Results

Participants' characteristics and pulmonary function measurements are shown in Table 1.

Table 2 Baseline[a] Measures of Cardiovascular Function, Lung Diffusing Capacity and Indices of Lung Fluid Balance in HFrEF Patients and Healthy Control Subjects

	Control subjects	HFrEF patients	*p*-value[b]
Cardiovascular function			
Q (liters/min)	4.14 ± 0.82	3.41 ± 1.33	0.047
CI (liters/min/m^2)	2.15 ± 0.44	1.63 ± 0.58	0.003
SV (ml)	69.7 ± 21.7	54.5 ± 19.5	0.016
HR (bpm)	61 ± 10	65 ± 9	0.049
SaO_2 (%)	98.9 ± 1.5	97.8 ± 1.7	0.032
SBP (mm Hg)	124 ± 17	120 ± 14	0.389
DBP (mm Hg)	78 ± 13	77 ± 11	0.740
MAP (mm Hg)	94 ± 11	92 ± 8	0.360
Lung diffusing capacity			
DL_{CO} (ml/mm Hg/min)	19.5 ± 3.5	16.0 ± 6.1	0.037
DL_{NO} (ml/mm Hg/min)	68.5 ± 15.1	61.4 ± 24.8	0.294
Dm_{CO} (ml/mm Hg/min)	31.1 ± 6.9	29.7 ± 11.27	0.294
V_c (ml)	81.5 ± 31.1	54.9 ± 22.1	0.003
Dm_{CO}/V_c	0.47 ± 0.26	0.57 ± 0.29	0.264
Lung fluid balance			
Lung density (HU)	−867 ± 20	−804 ± 35	<0.001
Vtis (ml)	884 ± 123	998 ± 200	0.041
EVLW (ml)	802 ± 133	943 ± 202	0.015

Data are presented as group mean ± standard deviation. CI, cardiac index; DBP, diastolic blood pressure; DL_{CO}, lung diffusing capacity for carbon monoxide; DL_{NO}; lung diffusing capacity for nitric oxide; Dm_{CO}, alveolar-capillary membrane conductance; EVLW, extravascular lung water; HFrEF, heart failure with reduced ejection fraction; HR, heart rate; MAP; mean arterial pressure; Q, cardiac output; SV, stroke volume; SaO_2, arterial oxygen saturation; SBP, systolic blood pressure; V_c, pulmonary capillary blood volume; V_{tis}; lung tissue volume.

[a]Baseline indicates pre-albuterol.

[b]Group mean control vs group mean HFrEF.

Lung fluid balance in HFrEF patients vs healthy control subjects

Baseline pre-albuterol measures of DL_{CO}, Dm_{CO}, V_c, lung density, V_{tis} and EVLW are shown in Table 2. Before albuterol administration, group mean DLCO ($p = 0.037$) and V_c ($p = 0.003$) were greater in control subjects compared with HFrEF patients; there was no such difference in Dm_{CO} between subject groups (Table 2). Baseline pre-albuterol group mean lung density ($p < 0.001$), V_{tis} ($p = 0.041$) and EVLW ($p = 0.015$) were greater in HFrEF patients compared with healthy control subjects (Table 2). These data suggest that lung fluid is elevated in stable HFrEF patients relative to healthy subjects.

Effect of β_2AR stimulation in HFrEF and healthy controls

There was little/no change in either HR or blood pressure from before to immediately after albuterol administration in the HFrEF patients (HR: 65 ± 9 vs 69 ± 11 bpm, $p = 0.129$; MAP: 92 ± 8 vs 95 ± 7 mm Hg; $p = 0.098$). Similarly, no evidence of cardiac arrhythmia was observed in any participant during albuterol administration. Albuterol administration had no effect on forced vital capacity (FVC), but caused an increase in forced expiratory volume in 1 second (FEV_1), forced expiratory flow between 25% and 75% of FVC ($FEF_{25-75\%}$) and inspiratory capacity (IC) in both the control subjects and HFrEF patients (Table 3). DLCO, Dm_{CO}, V_c and Dm_{CO}/V_c were not different before vs after albuterol administration in either the control subjects or the HFrEF patients (Figure 1). Albuterol administration did, however, cause a significant reduction in V_{tis} in both the healthy control subjects and HFrEF patients (control: −2.8 ± 4.9%, $p = 0.029$; HFrEF: −4.6 ± 7.8%; $p = 0.010$) (Figure 2). Similarly, there was a significant reduction in EVLW from before to after albuterol administration in both control subjects and HFrEF patients (controls: −3.0

Table 3 Measures of Pulmonary Function Before and After Albuterol Administration in HFrEF Patients and Healthy Control Subjects

	Control		HFrEF	
	Pre-albuterol	Post-albuterol	Pre-albuterol	Post-albuterol
FVC (liters)	4.53 ± 0.78	4.38 ± 0.81	3.50 ± 1.14	3.37 ± 1.11
FEV_1 (liters)	3.64 ± 0.63	3.70 ± 0.69[a]	2.67 ± 1.03	2.77 ± 0.99[b]
FEV_1/FVC (%)	81 ± 6	85 ± 6[b]	75 ± 11	82 ± 7[b]
PEF (liters/s)	9.12 ± 1.63	8.97 ± 1.59	6.84 ± 2.59	6.97 ± 2.87
$FEF_{25-75\%}$ (liters/s)	3.73 ± 0.93	4.31 ± 1.02[b]	2.35 ± 1.28	2.92 ± 1.42[b]
IC (liters)	3.31 ± 0.64	3.51 ± 0.74[b]	2.61 ± 0.81	2.83 ± 0.90[a]
DL_{CO}/V_A	10.87 ± 6.60	10.93 ± 6.83	6.37 ± 4.56	6.48 ± 3.08

Data are presented as group mean ± SD. DL_{CO}, lung diffusing capacity for carbon monoxide; FEV_1, forced expiratory volume in 1 second; $FEF_{25-75\%}$, forced expiratory flow at 25% to 75% of FVC; FVC, forced vital capacity; HFrEF, heart failure patients with reduced ejection fraction; PEF; peak expiratory flow; IC, inspiratory capacity; V_A, alveolar volume.

[a]$p < 0.05$, significantly different vs pre-albuterol.

[b]$p < 0.01$, significantly different vs pre-albuterol.

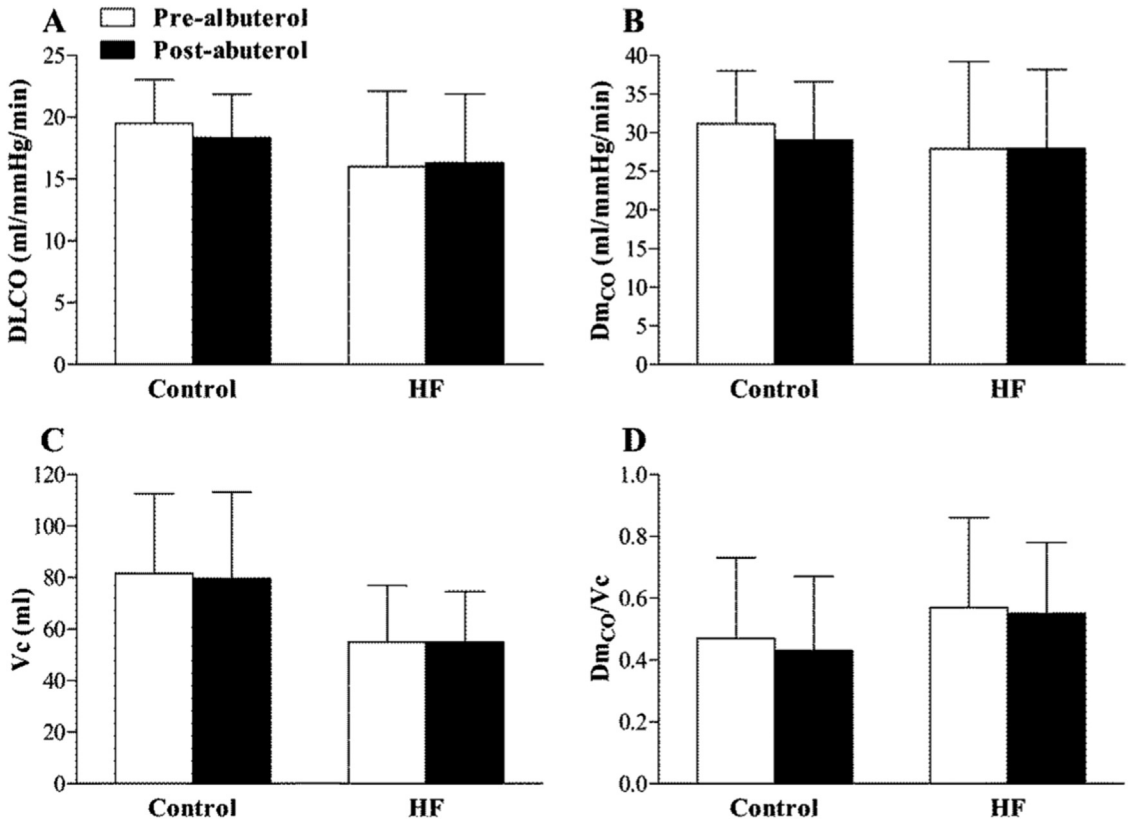

Figure 1 Group mean ± SD lung diffusing capacity for carbon monoxide (DL_{CO}) (A), alveolar–capillary membrane conductance (Dm_{CO}) (B), pulmonary capillary blood volume (V_c) (C) and the ratio of Dm_{CO} to V_c (Dm_{CO}/V_c) (D) before (white bars) and after (black bars) nebulized albuterol administration in healthy control subjects (Control) and heart failure patients with reduced ejection fraction (HF).

± 5.7%, $p = 0.045$; HFrEF: −4.6 ± 8.8%; $p = 0.018$) (Figure 2). There was a trend toward an inverse relationship between baseline values of V_{tis}, EVLW and Dm_{CO}/V_c ratio and the magnitude of the change in these variables from before to after albuterol in both the control subjects and the HFrEF patients; however, these relationships were statistically significant for EVLW and Dm_{CO}/V_c ratio in the HFrEF patients only (Figure 3). These data suggest that stimulation of the β_2ARs via nebulized albuterol administration promoted a greater degree of lung fluid clearance in individuals with the greatest evidence of lung fluid at baseline.

Discussion

Main findings

The main findings our study are as follows: (1) before albuterol administration, lung density, V_{tis} and EVLW were greater in HFrEF patients compared with healthy control subjects; (2) DLCO and V_c were greater in control subjects compared with HFrEF patients before albuterol administration; (3) albuterol administration caused a ~3% to 5% reduction in V_{tis} and EVLW in healthy control subjects and HFrEF patients; and (4) there was a trend toward an inverse relationship between baseline values of V_{tis}, EVLW and Dm_{CO}/V_c ratio and the magnitude of the change in these variables from before to after albuterol in both control subjects and HFrEF patients; however, this relationship was statistically significant for EVLW and Dm_{CO}/V_c ratio in the HFrEF patients only. Taken together, our findings suggest that: (1) lung fluid volume is elevated in stable, well-compensated HFrEF patients relative to their healthy age- and gender-matched counterparts; and (2) acute stimulation of β_2ARs appears to cause lung fluid removal in stable HFrEF patients, especially in those with evidence of elevated lung fluid volume at rest. We have shown that pharmacologic stimulation of β_2ARs may help reduce lung fluid volume in stable HFrEF patients, which lends support to the hypothesis that β_2ARs play an important role in lung fluid balance in vivo in humans, and that dysfunction of the β_2ARs may be a source of elevated lung fluid volume in stable HF patients.

Importance of the β_2AR system in control of fluid balance

β_2ARs are expressed throughout the pulmonary system, including in the airways, the alveolar spaces, the pulmonary vasculature and the pulmonary lymphatic tissue, where they appear to regulate lung fluid removal via 2 distinct mechanisms. First, it appears that stimulation of β_2ARs facilitates fluid removal from the alveolar spaces through epithelial sodium channels (ENaC) located on both Type I and II alveolar cells.[13,14] Indeed, it has been shown previously that stimulation of β_2ARs is associated with an increase in both the total number and open probability of ENaC on the apical portion of Type I and II alveolar cells

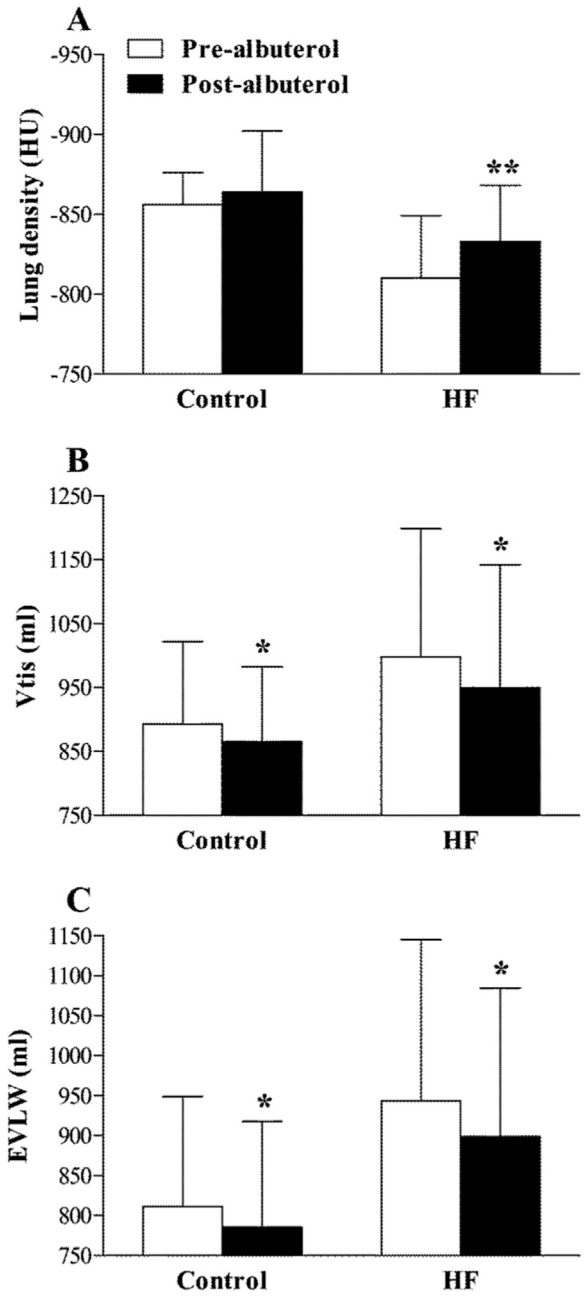

Figure 2 Group mean ± SD lung density (A), lung tissue volume (Vtis) (B) and extravascular lung water (EVLW) (C) before (white bars) and after (black bars) nebulized albuterol administration in healthy control subjects (Control) and heart failure patients with reduced ejection fraction (HF). $^{*}p < 0.05$ and $^{**}p < 0.01$, significantly different vs pre-albuterol.

secondary to an increase in the synthesis of cyclic adenosine monophosphate (cAMP) and protein kinase A (PKA).[13] Second, it has been shown that stimulation of β_2ARs on lymphatic tissue causes dilation as well as active phasic contraction of the thoracic lymphatic ducts, which acts to clear lung fluid from the perivascular spaces to the hilar lymph nodes.[15,16]

The importance of the β_2AR system in the regulation of lung fluid in both animal models and in humans has been demonstrated in a number of key studies.[17–26] For example, Tibayan et al[22] reported that administration of the non-selective β_1- and β_2-receptor agonist dobutamine, but not the selective β_1-agonist dopamine, caused a substantial increase in alveolar liquid clearance (~50%) in anesthetized, ventilated rats. In addition, it has been shown that alveolar β_2AR overexpression improves β_2AR function and maximally upregulates alveolar fluid clearance in a rat model.[21,23] In vivo, in humans, it has been demonstrated that administration of the long-acting β_2AR agonist salmeterol results in a ~50% decrease in the incidence of high-altitude pulmonary edema (HAPE) in subjects identified as HAPE-susceptible.[18] More recently, it has been shown that oral administration of the non-selective β_1- and β_2-receptor blocker carvedilol, but not the selective β_1-blocker bisoprolol, caused a significant decrease (~13%) in Dm_{CO} in healthy humans, which is indicative of an increase in extravascular lung water.[17] In combination, the findings just described clearly identify the key role for the β_2AR system in the regulation of lung fluid balance and maintenance of lung fluid homeostasis.

In the present study, we found that acute administration of the selective β_2AR agonist albuterol caused a significant reduction in lung tissue volume and extravascular lung water (~3% to 5%) in both stable HFrEF patients and healthy control subjects (Figure 2). Furthermore, there was a trend toward an inverse relationship between baseline values of V_{tis}, EVLW and Dm_{CO}/V_c ratio and the magnitude of change in these variables from before to after albuterol in both the control subjects and the HFrEF patients; however, this relationship was statistically significant for EVLW and Dm_{CO}/V_c ratio in the HFrEF patients only. These data may suggest that the greatest lung fluid clearance in response to acute albuterol administration occurs in the HFrEF patients who exhibit the greatest degree of lung fluid volume at rest. Accordingly, we have shown that acute pharmacologic stimulation of β_2ARs reduces lung fluid volume in both stable HFrEF patients and healthy control subjects, which lends support to the hypotheses that: (1) β_2ARs play a vital role in lung fluid balance in vivo in humans; and (2) dysfunction of β_2ARs may be a source of elevated lung fluid volume in stable HFrEF patients.

Why is lung fluid increased in stable HF?

It is well known that pulmonary congestion, a key component of which is a significant increase in lung fluid, is a common consequence of acute decompensation in HF.[5–7] However, it has remained somewhat controversial whether stable HF patients exhibit elevated lung fluid volume,[8,9] with chronic HF patients often appearing to "resist" pulmonary edema.[24] Indeed, in clinical practice, it is often observed that patients with severe HF lack pulmonary rales on examination or alveolar edema on chest X-ray. Theoretically, the increase in pulmonary capillary hydrostatic pressure and wall tension due to the rise in LV filling pressure consistent with a failing LV,[1] combined with downregulation of β-receptors central to lung fluid–removal mechanisms[2–4] secondary to a chronic increase in adrenergic drive, should serve to make HF patients more

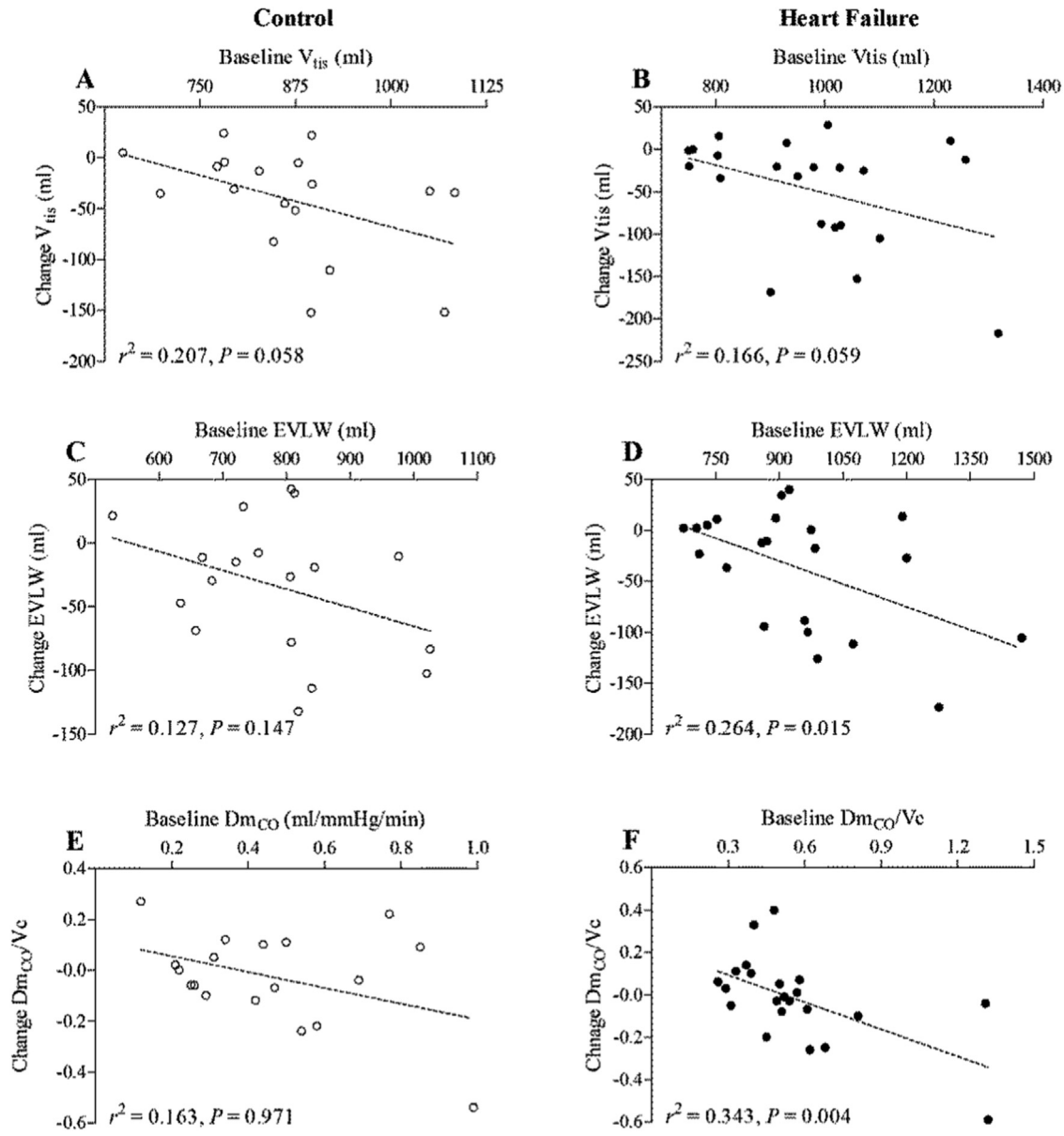

Figure 3 Scatterplots showing the relationships between the individual subject baseline values (i.e., before nebulized albuterol administration) and the before-to-after nebulized albuterol change in lung tissue volume (Vtis) (A, B), extravascular lung water (EVLW (C, D) and ratio of alveolar–capillary membrane conductance to pulmonary capillary blood volume (Dm_{CO}/V_c) (E, F) in healthy control subjects (open circles) and heart failure patients with reduced ejection fraction (filled circles).

susceptible to lung fluid accumulation relative to their healthy counterparts. However, it has also been shown that pulmonary microvascular permeability is decreased in severe HF patients, which would be expected to protect such patients from pulmonary edema.[24] In the present work, we found that lung fluid is elevated in stable HFrEF patients relative to healthy subjects (Table 2). These data may suggest that, although somewhat preventive, the reduction in pulmonary microvascular permeability often observed in stable HFrEF patients does not fully protect against an increase in extravascular lung water in this population.

Clinical implications

Recently, we reported that CT-derived measures of large airway wall thickness and luminal area are not different in healthy control subjects relative to stable HFrEF patients.[27] In combination with the findings of the present study, data from our laboratory suggest that stable, well-compensated HFrEF patients have evidence of elevated lung fluid volume, but not substantial large airway edema and/or engorgement, relative to their healthy age- and gender-matched counterparts. Although the exact clinical ramifications of such an accumulation of lung fluid in these patients are unclear, it is possible that interstitial lung edema plays a role in the abnormal pulmonary gas exchange and exaggerated ventilatory response to exercise associated with HF.

HF is a complex disease and much of the impaired pulmonary gas exchange and hyperventilatory response to exercise in HF patients has been associated with pulmonary vascular dysfunction,[28,29] skeletal muscle dysfunction,[30,31]

early onset of metabolic acidosis,[32] heightened chemosensitivity and exaggerated afferent signals from exercising muscles.[30] However, in animal models, it has been demonstrated that artificial induction of pulmonary congestion causes a rapid, shallow breathing pattern secondary to stimulation of pulmonary C fibers.[33] In addition, acute fluid loading in otherwise healthy humans has been shown to elicit a less efficient hyperventilatory response to incremental exercise.[34] Robertson et al[34] reported that rapid intravenous saline infusion (30 ml/kg over 30 minutes) caused a ~12% and a ~4% increase in extravascular fluid and intravascular fluid, respectively, with a concomitant ~12% increase in the ventilatory equivalent for carbon dioxide, a slight decrease in arterial partial pressure of carbon dioxide (PaCO2), and a reduction in aerobic exercise capacity. More recently, Paolillo et al[17] found that administration of the β_2AR antagonist carvedilol caused a ~12% increase in $\dot{V}E/\dot{V}CO_2$ slope in response to exercise that was always coincident with a ~13% decrease in Dm_{CO} (i.e., evidence of an increase in lung interstitial fluid volume).

Based on the aforementioned considerations, it is possible that lung interstitial edema provides an additional stimulus for the impaired pulmonary gas exchange and the inefficient hyperventilatory response to exercise commonly observed in HF patients. Moreover, given that a low Dm_{CO} and a high $\dot{V}E/\dot{V}CO_2$ (slope or ratio) are key prognostic predictors in HFrEF patients,[35,36] it can be suggested that elevated EVLW may be a primary target for therapeutic intervention in these patients. We found that acute, low-dose albuterol administration appears to cause lung fluid clearance (~5%) in stable HFrEF patients. Further investigation is required to determine whether such acute pharmacologic stimulation of β_2ARs may be indicated in the presence of clinical and/or radiologic signs of pulmonary edema in stable HFrEF patients.

In conclusion, lung fluid volume is elevated in stable, well-compensated HF patients with reduced ejection fraction relative to their healthy age- and sex-matched counterparts. Interestingly, stimulation of β_2ARs via acute low-dose nebulized albuterol appears to promote lung fluid removal in both healthy control subjects and HF patients, but especially in those HFrEF patients with evidence of elevated lung water at rest. Further study is needed to determine whether such acute β_2AR stimulation provides therapeutic aid in the setting of excessive lung fluid commonly observed in HFrEF.

Disclosure statement

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