



Profound Increase of Lung Airway Resistance in Heart Failure: a Potential Important Contributor for Dyspnea

Xiaohong Liu¹ · Liuqing Yang^{2,3} · Dongmin Kwak^{2,3} · Lei Hou^{2,3} · Ruru Shang¹ · Carolyn Meyer³ · Angela Panoskaltsis-Mortari^{2,3} · Xin Xu⁴ · Edward Kenneth Weir³ · Yingjie Chen^{2,3} 

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Abstract

Dyspnea is a major symptom of heart failure (HF). Here, we have studied the lung remodeling and airway resistance in HF mice. We demonstrated that aortic banding–induced HF caused a dramatic decrease of lung compliance and an increase of lung airway resistance. The decrease of lung compliance was correlated with the increased lung weight in a linear fashion ($\gamma^2 = 0.824$). An HF-induced increase of lung airway resistance and a decrease of lung compliance were almost identical in anesthetized mice and in the isolated lungs from these mice. HF caused profound lung fibrosis in mice with increased lung weight. Moreover, HF patients of NYHA class III–IV showed increased lung density as revealed by high-resolution CT scanning. These data indicate that lung compliance and lung airway resistance may be useful in determining lung remodeling after HF, and lung structure changes may contribute to dyspnea in HF.

Keywords Heart failure · Lung fibrosis · Lung compliance · Pulmonary hypertension

Introduction

Heart failure (HF) is a complex clinical syndrome that results from any structural or functional impairment of ventricular filling or ejection of blood. The cardinal manifestations of HF are dyspnea and fatigue, which may limit exercise

tolerance, and fluid retention, which may lead to pulmonary and/or splanchnic congestion and/or peripheral edema [1]. HF can cause lung inflammation [2, 3] and WHO class-2 pulmonary hypertension (PH) [4, 5], a condition with a poor clinical outcome [4, 6, 7]. We recently demonstrated that advanced HF caused a dramatic increase of lung weight in experimental animals [2, 3], a massive lung vascular and interstitial inflammation, and severe WHO class-2 PH and right ventricular (RV) hypertrophy [2, 3, 8]. Remarkably, in some cases, we noticed that lung remodeling after HF is so extensive that the enlarged lung tissue becomes as solid as liver tissue, suggesting that lung compliance and lung airway resistance may be greatly impaired in HF animals. Importantly, the increase in lung weight was not due to an increase in lung fluid [2].

To understand the overall impact of the increased lung weight or pathological lung remodeling on lung compliance and stiffness during HF development, we studied the effect of pressure overload–induced lung airway resistance and compliance, as well as their relationships to increase of lung weight, and RV hypertrophy. We found that HF caused a similar increase of lung airway resistance and a decrease of lung compliance in both living mice during anesthesia (in vivo) and in isolated lungs (in vitro) from these mice. The increased lung

Xiaohong Liu and Liuqing Yang contributed equally to this work.

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✉ Yingjie Chen
chenx106@umn.edu

¹ Shanxi Provincial People's Hospital, Taiyuan, China

² Cardiovascular Division and Lillehei Heart Institute, University of Minnesota Medical School, Minneapolis, MN 55455, USA

³ Department of Medicine, University of Minnesota, Minneapolis, MN, USA

⁴ Department of Exercise Rehabilitation, Shanghai University of Sport, Shanghai 200438, China

airway resistance and the decreased lung compliance were significantly correlated with the increases of lung weight. We also determined the alterations of lung density in HF patients.

Materials and Methods

Experimental Mice Adult male Balb/C mice and C57B6J mice were purchased from Jackson Laboratory. The experimental study was approved by the Institutional Animal Care and Use Committee of the University of Minnesota.

Induction of HF with Transverse Aortic Constriction in Mice

Male mice at age 6–7 weeks were used for the minimally invasive transverse aortic constriction (TAC) procedure as we have previously described [2, 3, 8]. Briefly, the mice were anesthetized with a mixture of 80 mg/kg ketamine and 30 mg/kg xylazine (i.p.). The neck and upper ventral chest were shaved and the mice placed in the supine position. A horizontal incision was made at the level of the suprasternal notch to allow direct access to the transverse aorta without entering the pleural space. Aortic constriction was performed by ligating the aorta between the right innominate artery and the left carotid artery over a needle using 5.0 silk suture with the aid of a dissecting microscope. The needle was then quickly removed after the ligation. As we noticed that Balb/C mice were more sensitive to TAC-induced chronic heart failure (CHF) than C57B6J mice, a 26-gauge needle was used creating moderate pressure overload for Balb/C mice, and a 27-gauge needle was used to create more systolic pressure overload for C57B6J mice.

Echocardiography and Measurement of LV Hemodynamics

Echocardiography was performed using the high-resolution Veve 2100 or Veve 770 system during anesthesia with 1.5% isoflurane as previously reported [2, 3, 9].

Lung Functional Analyses The changes of lung resistance and compliance were monitored using the Flexivent system according to the manufacturer's instruction that was also reported in our previous study [10].

Detection of Lung Density in HF Patients and Controls

The data of control subjects, the HF patients, and the patients with idiopathic lung fibrosis were obtained from the medical records of Shanxi Provincial People's Hospital. The analysis for these previously recorded patients' clinical data was approved by the institutional review board of Shanxi Provincial People's Hospital.

Lung transverse CT scanning of each subject was taken when patients had maximum inspiration. The CT scanning was divided from the apex to the bottom into five zones as

illustrated in Fig. 5. For each section, the average signal intensity of 15 to 22 areas was determined from the peripheral field using NIH Image J, with an effort made to avoid the areas with large blood vessels, bronchi, and local calcification.

Data and Statistical Analysis Results were expressed as mean $\pm$ standard error. Data from two groups were compared using an unpaired *t* test. One-way ANOVA was used to test for differences for more than two groups. Post hoc pairwise comparisons were made using the Fisher least significant difference test. Linear and nonlinear regressions were performed using SigmaPlot 13.3. Statistical significance was defined as $p < 0.05$.

Results

TAC Causes Significant Increase of LV Failure and Increase of Lung Weight in Balb/C Mice

Chronic pressure overload, such as hypertension or aortic valve stenosis, causes left ventricular (LV) hypertrophy and HF. TAC is an experimental approach to mimic aortic valve stenosis and hypertension in experimental animals. Similar to previous reports, chronic pressure overload produced by TAC significantly increased the left ventricular (LV) weight, left atrial (LA) weight, lung weight, right ventricular (RV) weight, and their ratios to body weight or tibial length (Supplemental Table 1). Echocardiographic measurements showed that TAC caused a significant increase of LV end-systolic diameter, an increase of LV end-diastolic diameter, and a 48% decrease of LV ejection fraction (LV EF) (Supplemental Table 2). Overall, these data indicate that chronic pressure overload successfully resulted in LV failure and the anticipated increase of lung weight, similar to our previous studies [2, 3].

Dramatic Alterations of Lung Airway Resistance and Lung Compliance in HF Mice of Balb/C Background

To determine whether an increase of lung weight (the ratio of lung weight to body weight) can affect lung function in HF mice, we determined the lung airway resistance and lung compliance in sham mice and mice after pressure overload produced by TAC. As tested during anesthesia, TAC caused a 1.6-fold decrease of lung compliance, and a 1.8-fold increase of lung resistance in mice. TAC also caused a significant reduction of lung inspiration capacity in mice (Supplemental Table 3). The relative changes of lung airway resistance and lung compliance in HF mice are similar with or without the normalization of body weight (Supplemental Table 3).

Since the increase of lung airway resistance and the decrease of lung compliance predominantly occurred in HF mice with heavy lung, in order to highlight the role of lung weight in lung function, HF mice were further grouped according to the ratio of lung weight to body weight. When the ratio of lung

weight to body weight increased more than 50% as compared with control mice, these mice were grouped as “heavy lung,” and when the ratio of lung weight to body weight increased less than 50%, these were grouped as “light lung” group. The ratios of LV weight, lung weight, and RV weight to body weight are presented in Fig. 1a–c. The mice with a greater lung weight increase are also the mice with a greater decrease of LV ejection fraction (Fig. 1d).

Mice with heavy lungs had a 3.09-fold increase of the ratio of lung weight to body weight (Fig. 1c), a 2.1-fold decrease of lung compliance (Fig. 2a), and a 2.2-fold increase of lung resistance (Fig. 2b). The mice with light lungs showed a mild but significant decrease of lung compliance (Fig. 2a), while the lung resistance was not significantly changed (Fig. 2b). Interestingly, the ratio of lung weight to body weight significantly correlated to a TAC-induced increase of the lung compliance ($\gamma^2 = 0.824$) and a decrease of lung airway resistance ($\gamma^2 = 0.641$) in a linear fashion (Fig. 2c, d). In contrast, the decrease of lung compliance did not correlate to the decrease of LV ejection fraction in a linear fashion (Supplemental Fig. 1). The decrease of lung compliance significantly correlated to the increase of lung airway resistance (Supplemental Fig. 2). TAC-induced alterations of the lung compliance significantly correlated to the increase of the ratio of RV weight to body weight in a linear fashion (Fig. 2c, d). The data clearly showed that the increase of lung airway resistance and a decrease of lung compliance mainly occurred in HF mice with heavy lungs (Fig. 2).

Pressure Overload Causes a Significant Increase of Lung Airway Resistance in Isolated Lung from HF Mice of Balb/C Background Since an increase of lung airway resistance in mice during anesthesia could be the outcome of increased resistance in the lungs, the compression of the lungs by enlarged hearts, or structural changes in the chest wall, we further determined the lung resistance and compliance in isolated lungs from mice after TAC. Interestingly, we found that chronic TAC caused a 2.4-fold increase of the lung resistance and a

2.1-fold decrease of lung compliance in the isolated lung (Supplemental Fig. 3). The increase of lung airway resistance and the decrease of lung compliance in the isolated lung in HF mice are comparable to the data obtained from these HF mice during anesthesia.

We further analyzed the lung resistance and compliance in isolated lungs of sham mice, TAC mice with light lungs, and TAC mice with heavy lungs (Fig. 3a, b). Mice with heavy lungs were associated with a 2.8-fold reduction of lung compliance in isolated lungs from these mice (Fig. 3a). Interestingly, we found that a 3.09-fold increase of the ratio of lung weight to body weight in mice with heavy lungs was associated with an almost identical 3.02-fold increase of lung resistance in isolated lungs from these mice (Fig. 3b). These findings suggest that the increase of lung weight and the lung structure change exert a dominant role for the increased lung resistance and the decreased lung compliance. Mice with a mild increase of the ratio of lung weight to body weight showed a mild decrease of lung compliance in isolated lungs (Fig. 3). The alterations of the lung compliance and resistance in isolated lungs were significantly correlated with the increase of the ratio of lung weight to body weight in HF mice (Fig. 3c–f). Again, the data clearly showed that the increase of lung airway resistance and the decrease of the lung compliance mainly occurred in HF mice with heavy lungs (Fig. 3c–f). The data showed that pressure overload caused comparable alterations of lung resistance and lung compliance in living mice and in the isolated lungs taken from these mice.

HF-Induced Decrease of Lung Compliance Correlated with the Increase of Lung Weight in C57B6J Mice We previously observed that HF-induced increase of lung weight did not correlate to the decrease of LV ejection fraction or LV hypertrophy in C57B6J mice [2] or in Balb/C mice in a linear fashion (data not shown). The impressive linear relationship between lung weight and lung compliance in Balb/C mice motivated us to further study the above relationship in C57B6J mice, a mouse strain that generally developed LV failure and an increase of

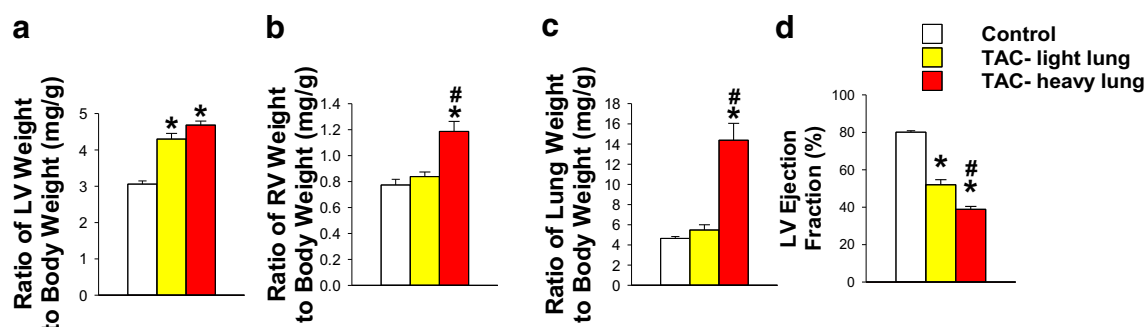


Fig. 1 The relative alterations of the ratio of LV weight to body weight, the ratio of RV weight to body weight, the ratio of lung weight to body weight, and LV ejection fraction in Balb/C mice 4 weeks after sham surgery, and in Balb/C mice with either light lungs or heavy lungs after

4 weeks TAC. The summarized data of the ratios of left ventricular (LV) weight, RV weight, and lung weight to body weight (a–c). The summarized data of the LV ejection fraction in mice during anesthesia (d)

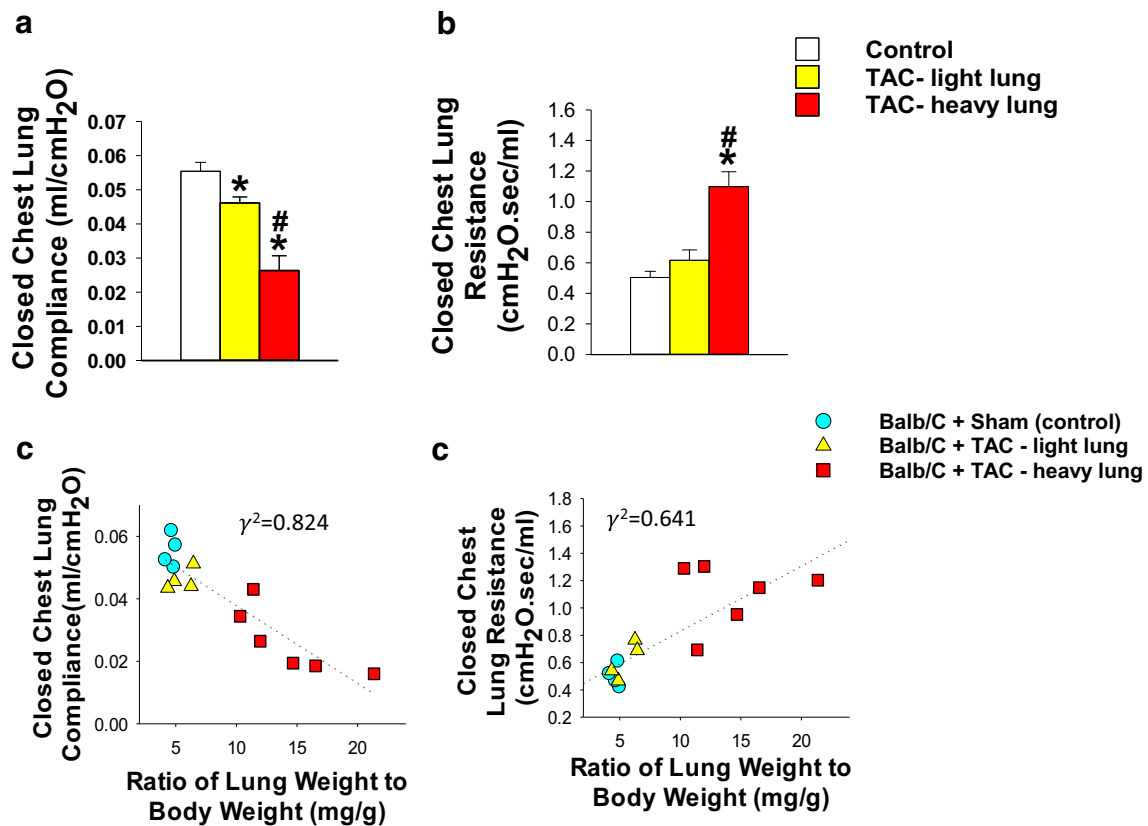


Fig. 2 TAC-induced HF caused a dramatic increase of lung resistance and a decrease of lung compliance in Balb/C mice with heavy lungs. The summarized data of the lung resistance, lung compliance, and inspiratory capacity in mice during anesthesia (a, b). The increases of lung weight

and RV weight are significantly correlated to the increase of lung resistance and the decrease of lung compliance in mice determined during anesthesia (c, d)

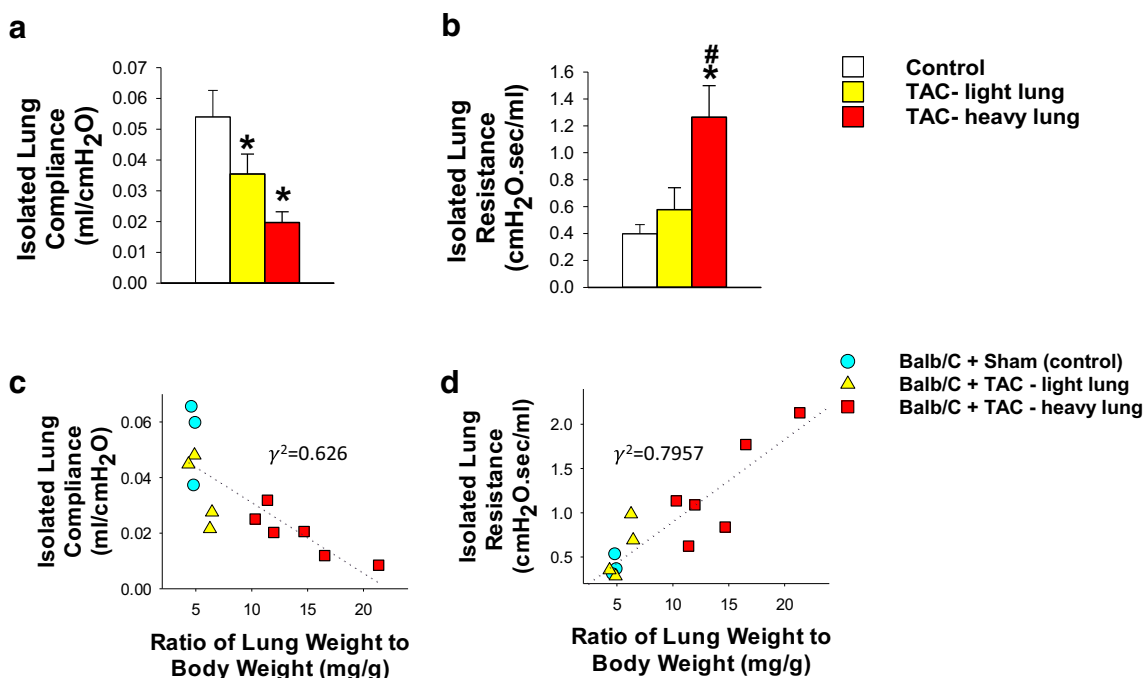


Fig. 3 TAC caused decrease of lung compliance and increase of lung resistance in isolated lungs in Balb/C mice. Summarized lung compliance and resistance in isolated lungs from mice after sham surgery, or HF mice

with light lungs or heavy lungs (a, b). The relationships between lung compliance or the lung airway resistance to the ratio of lung weight to body weight in mice after sham and TAC (c, d)

lung weight after a long period of TAC. Eight weeks TAC significantly increased the LV weight, lung weight, RV weight, and their ratios to body weight (Supplemental Table 5). The echocardiography data are presented in Supplemental Table 6. TAC also caused a significant increase of lung airway resistance and a decrease of lung compliance in C57B6J mice (Supplemental Table 7), indicating that the changes of lung compliance and lung airway resistance are a common phenomenon in HF mice of different strains. Most interestingly, the increase of lung airway resistance and the decrease of lung compliance significantly correlated to the ratio of lung weight to body weight and the ratio of RV weight to body weight in C57B6J mice (Fig. 4, Supplemental Fig. 4).

Pressure Overload Caused a Profound Increase of Lung Fibrosis and Lung Fibroblast Proliferation Consistent with our previous report, pressure overload caused an over sixfold increase of lung fibrosis in HF mice with heavy lungs. The lung fibrosis was broadly distributed in the lung tissues. Since fibroblasts contribute to the tissue stiffness and since vimentin is often used as a reliable marker for fibroblasts, we further determined the expression of vimentin in lung tissues in normal controls and mice with heavy lungs after TAC. Interestingly, lung vimentin expression was broadly increased in interstitial, perivascular, and vessel areas in mice with heavy lung after TAC (Supplemental Fig. 3). Vimentin expression was also increased in macrophages (the mac-2-positive cells) in HF mice with heavy lungs (Supplemental Fig. 3). Most of the macrophages (the mac-2-positive cells) were vimentin-positive cells.

Increased Lung Density in HF Patients To understand the change of lung consolidation in HF patients, we determined the relative lung densities of HF patients of NYCA class III (HF symptoms occur with regular daily activity) and IV (HF symptoms occur at rest), patients with idiopathic lung fibrosis

(as positive controls), and “normal controls” (Table 1). The latter are patients who had no history of heart or lung disease and in whom clinical examination revealed no abnormal data for heart, lung, and kidney function. The general clinical characteristics, medication, and laboratory characteristics of these groups are described in Table 1. The causes of HF in these patients include mitral valve stenosis and regurgitation after rheumatic heart disease ($n = 3$), cardiomyopathy ($n = 4$), chronic hypertension ($n = 2$), and chronic myocardial infarction ($n = 3$). The HF patients had a significant decrease of LV ejection fraction ($71 \pm 1.8\%$ in the control group vs. $39 \pm 3.2\%$ in the HF group), a decrease of LV fractional shortening, and significant increases of LV end-diastolic volume and LV end-systolic volume (Table 1, Fig. 5a). Serum BNP increased 44-fold in HF patients (Fig. 5b). Meanwhile, blood high-sensitivity C-reactive protein (hs-CRP) of HF patients significantly increased 12.3-fold (Fig. 5c), supporting an increased inflammatory status in the HF patients. Serum myoglobin, cTnI, and CK-MB were not significantly different between the HF and control groups (Table 1), reaffirming that these HF patients had no acute myocardial infarction. Lung CT scanning in the HF group showed enlarged hearts and increased lung density across all of the five sections (Fig. 5d, e). The increased lung density in HF patients presented as the typical diffuse bilateral consolidation (ground glass opacities) in a symmetrical fashion. The lung densities increased 1.9- to 2.4-fold in HF patients in these five sections (Fig. 5f) and increased 2.9- to 4.4-fold bilaterally in patients with idiopathic lung fibrosis (Fig. 5e, f).

Discussion

Here, we studied the alterations of lung airway resistance and compliance in mice after pressure overload-induced heart failure. One of the major findings is that HF caused almost

Fig. 4 The relationships between lung compliance and the lung airway resistance to the ratio of lung weight to body weight in C57B6J mice. Data were collected from C57B6J mice after sham or TAC for 8 weeks. The data showed that the increase of the ratio of lung weight to body weight are significantly correlated to the lung compliance or the lung airway resistance in C57B6J mice after sham and TAC for 8 weeks (c, d)

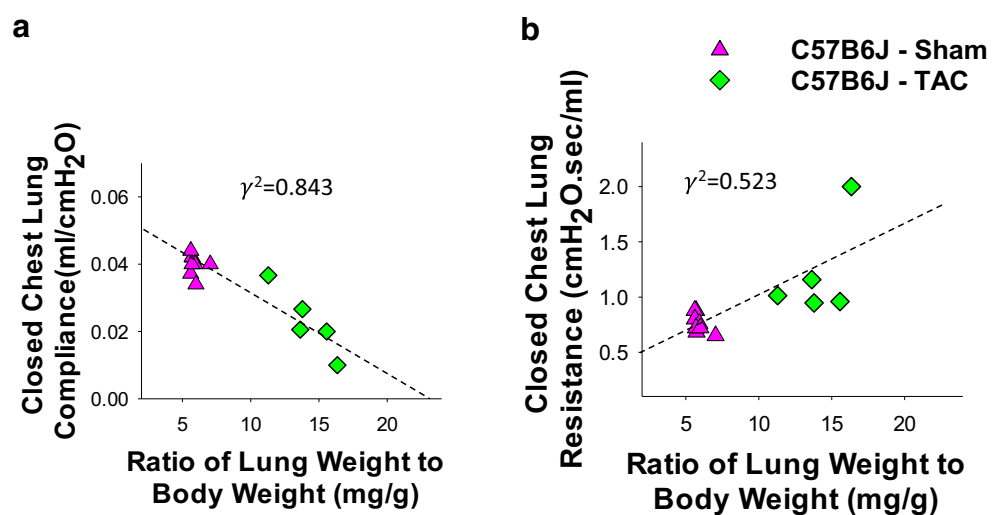


Table 1 Clinical and laboratory parameters of chronic heart failure (CHF) patients, control subjects, and idiopathic pulmonary fibrosis (IPF) patients

Parameters	CHF (<i>n</i> = 11)	Controls (<i>n</i> = 8)	IPF (<i>n</i> = 8)
Clinical characteristics			
Age (years)	68 ± 4.7	58 ± 4.9	64 ± 10
Male/female	7/3	3/5	5/3
Body mass index (kg/m ²)	23 ± 1.7	25 ± 0.4	25 ± 3.0
SBP (mmHg)	122 ± 7.7*	135 ± 6.4	130 ± 14
DBP (mmHg)	77 ± 4.3	78 ± 1.7	71 ± 7.8
Cardiac function			
NYHA class	III to IV	I	NA
LV ejection fraction (%)	39 ± 3.2*	71 ± 1.8	68 ± 7.1
LV fractional shortening (%)	23 ± 2.0*	40 ± 1.5	38 ± 4.0
LV end-diastolic volume (ml)	159 ± 21*	91 ± 9.3	95 ± 11
LV end-systolic volume (ml)	97 ± 17*	28 ± 3.7	32 ± 4.5
Medications			
Digitalis (%)	10	0	0
Diuretics (%)	100	0	0
Beta-blocker (%)	90	0	0
ACE inhibitor or ARB (%)	70	25	0
Key laboratory characteristics			
Albumin (mg/L)	38 ± 1.4	40 ± 1.2	36 ± 3.9
Serum sodium (mmol/L)	138 ± 0.8	140 ± 1.1	139 ± 15
Serum potassium (mmol/L)	4.0 ± 0.1*	3.7 ± 0.1	3.8 ± 0.4
Fasting blood-glucose (mmol/L)	5.5 ± 0.6	5.1 ± 0.5	5.8 ± 0.7
HbA1c (%)	5.8 ± 1.1	5.7 ± 0.4	6.7 ± 0.0
Total cholesterol	3.8 ± 0.3	3.8 ± 0.5	4.1 ± 0.5
Triglycerides (mmol/L)	1.3 ± 0.3	1.2 ± 0.1	1.3 ± 0.2
HDL cholesterol (mmol/L)	1.0 ± 0.1	1.3 ± 0.2	1.2 ± 0.2
LDL cholesterol (mmol/L)	2.1 ± 0.2	1.9 ± 0.3	2.2 ± 0.3
Leukocyte, WBC	6.7 ± 0.7	6.6 ± 0.3	7.5 ± 1.2
Number of neutrophils	4.6 ± 0.7	4.0 ± 0.2	4.9 ± 0.8
cTnI (ng/ml)	0.03 ± 0.01	0.02 ± 0.00	0.02 ± 0.00
Myoglobin (ng/ml)	86 ± 36	20 ± 0.5	18 ± 3.0

**p* < 0.05 as compared with control subjects

identical percent increases of lung weight and lung airway resistance. TAC-induced increase of the ratio of lung weight to body weight correlated with the increase of lung airway resistance and decrease of lung compliance in an impressive linear fashion. TAC-induced increase of lung airway resistance and decrease of lung compliance are almost identical as determined in either anesthetized animals or in isolated lungs from these animals, indicating that lung structure changes contribute to the alterations of lung airway resistance and compliance. In addition, we demonstrated that lung density was significantly increased in advanced HF patients.

While the lung remodeling is a secondary response to LV failure or the increased pulmonary venous pressure, the profound increase of lung airway resistance and decrease of lung compliance can directly cause and/or exacerbate the reduced exercise capacity and dyspnea in HF subjects. The presence of

HF-induced PH, the most common form of PH, is associated with a worse clinical prognosis [6, 7, 11, 12]. However, due to various technical issues, currently, there are no reliable simple methods to detect the lung remodeling in CHF subjects. Our previous study indicated that an increase of lung weight or RV hypertrophy does not correlate with the decrease of LV ejection fraction or LV hypertrophy in a linear fashion in the same C57B6J mouse strain, of the same age, the same gender, and the same pressure overload for the same duration [2]. The above findings were further confirmed in Balb/C mouse strain (data are not shown). In addition, the increase of lung weight poorly correlated to LV ejection fraction and LV hypertrophy in mice of different strains of the same age and gender (data not shown), suggesting that the LV ejection fraction or LV hypertrophy may have a limited value in the prediction of lung weight or lung remodeling in complicated clinical conditions.

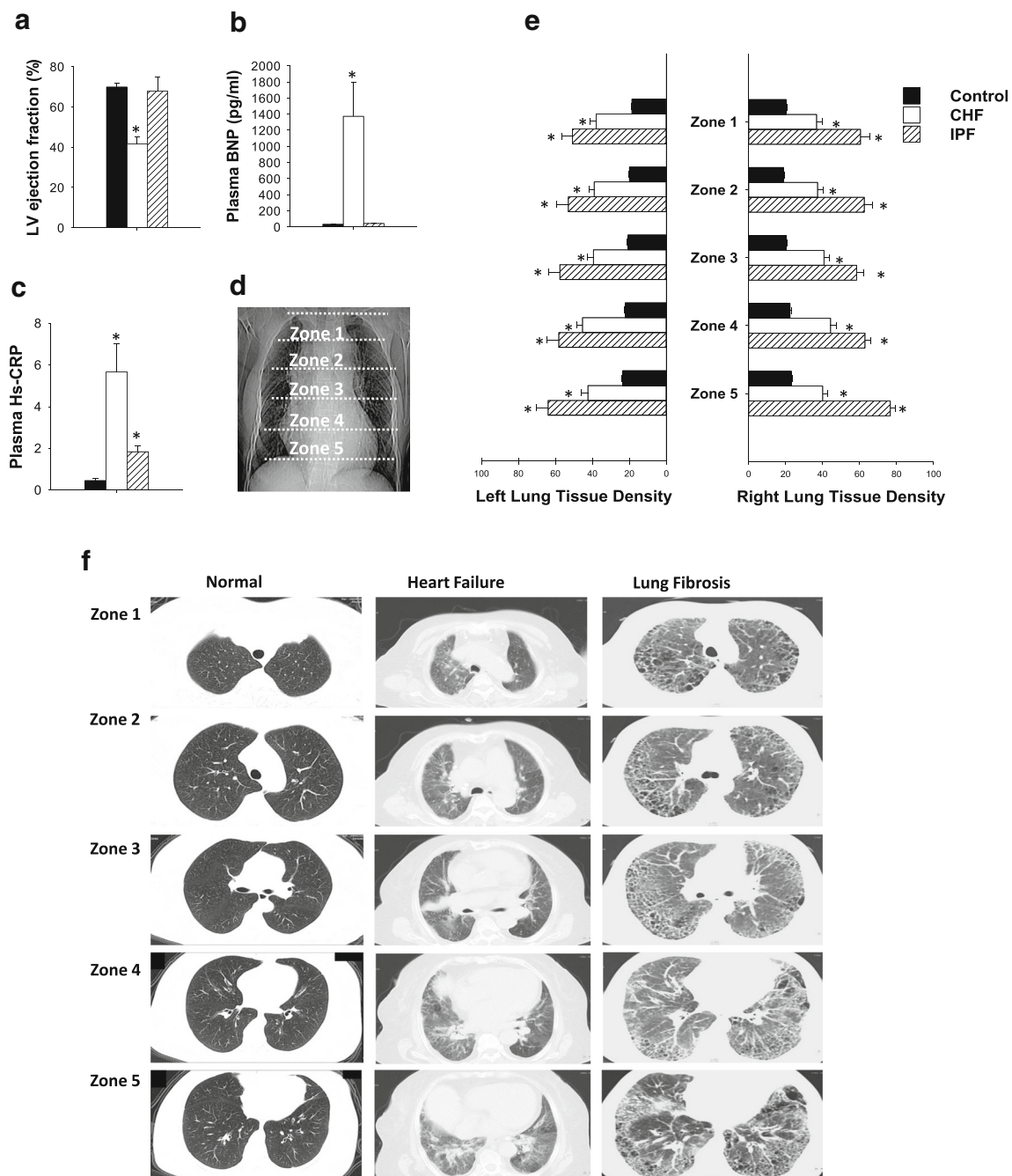


Fig. 5 Congestive heart failure (HF) causes significant increase of lung density. The diagram of the five zones used for lung density measurement (**a**). LV ejection fraction, plasma BNP content, and high-sensitivity C-reactive protein (**b–d**). Summarized lung density of five selected zones

of patients with HF or idiopathic pulmonary fibrosis (IPF) (**e**). Representative lung CT section for normal controls, HF, and IPF patients (**f**). * $p < 0.05$ vs. control group

Interestingly, the increase of lung weight is almost identical to the increase of lung resistance in HF mice. The increase of lung resistance and the decrease of lung compliance in HF mice are significantly correlated with the increase of lung weight and RV hypertrophy in a linear fashion in two different mouse strains. If the similar correlations exist in clinical conditions, lung airway resistance and lung compliance might be useful markers in predicting the lung remodeling in HF settings.

While the role and the underlying mechanism of lung remodeling during HF progression are not totally clear, we have demonstrated that advanced HF causes a profound lung inflammation [2, 3, 14–16], which was associated with a dramatic increase of lung weight, severe lung vascular remodeling and lung fibrosis, and RV hypertrophy in mice [2]. Lung inflammation and fibrosis have also been reported in HF patients [13]. We have further demonstrated that induction of

endogenous Tregs, a group of anti-inflammatory T cells, significantly attenuated lung inflammation and the transition from left heart failure to RV hypertrophy in mice with existing LV failure [3]. Moreover, studies from our group and others have demonstrated that conventional T cell activation occurs during HF development and that inhibition of T cell activation with an FDA-approved drug, abatacept, can attenuate T cell activation and HF development [16, 17]. We have further demonstrated that the depletion of CD11c⁺ antigen-presenting cells is effective in attenuating TAC-induced T cell activation and TAC-induced HF [18]. Since macrophages play an important role in lung inflammation and fibrosis, and since vimentin gene deficiency attenuated LPS or bleomycin-induced lung inflammation and fibrosis [19], the increased macrophages and vimentin expression might promote the lung inflammation and fibrosis, as well as the increased lung resistance in HF mice. These data indicate that advanced HF could cause lung inflammation and lung remodeling, and the lung inflammation could additionally exacerbate HF progression on the right side of the heart.

The marked increase of lung resistance and the decrease of lung compliance were predominantly observed in TAC mice with heavy lungs. The dramatic increase of lung resistance and the decrease of lung compliance are likely a collective outcome of lung fibrosis (secondary to fibroblast proliferation), inflammation, and other lung vessel and interstitial remodeling. Based on the profound lung consolidation and alteration of lung airway resistance, it is reasonable to believe that lung structure changes (particular the lung fibrosis, inflammation, and lung vessel muscularization) might also directly contribute to the clinical symptoms such as shortness of breath, the poor gas exchange capacity, and reduced arterial oxygen saturation in HF patients. HF-induced “lung congestion” or “lung edema” could theoretically contribute to the increased lung weight and HF-induced dyspnea; however, our previous study showed that the percentage of lung water content was unchanged in HF mice [2], a finding that has been independently confirmed by others [20]. Thus, lung congestion or lung edema might not be the major contributor for the increased lung weight or decreased lung compliance in HF mice. In addition, the same TAC often causes a different degree of increase of lung weight in mice as demonstrated in the current study and previous reports [3, 8, 21]. While the underlying mechanism for the disparity in lung weight in heart failure mice remains unknown, we postulate that a different adaptive response to the pressure overload by these mice is a culprit.

The present study has several limitations. First, the mouse TAC-induced lung consolidation is relatively acute compared with the more chronic course observed in patients with mitral stenosis or chronic hypertension-induced HF. Therefore, the mouse model may not fully mimic the clinical conditions in HF patients. Second, the increased lung density in HF patients by CT scanning might not be equivalent to the increased lung

weight in HF mice. Thus, an additional method to accurately estimate the lung weight in HF patients is needed. Third, the increase of lung resistance and the decrease of lung compliance are likely to be a collective outcome of lung collagen deposition, increased proliferation of lung fibroblasts and myofibroblasts, increased smooth muscle cells, and the diffuse lung inflammation. The present study could not differentiate the relative contribution of each of the above changes to the increased lung airway resistance or the decreased lung compliance in HF mice. Fourth, while the study provides a solid evidence of an increase of lung airway resistance and the relationships among various parameters, the intriguing relationships between the increase in lung weight and other changes in HF mice still could not reveal the causal relationships between these parameters. Fifth, the small sample size in human subjects limited the impact in the study analysis. An additional independent study using a large sample size by other group is needed. Finally, the sample size used for the correlation analysis was fairly small. Nevertheless, defining an important and largely unknown phenomenon that directly affects HF symptoms can reveal an important new direction for further mechanistic studies.

In summary, we found that TAC-induced HF is associated with a dramatic increase of lung weight and an equally dramatic increase of lung resistance and decrease of lung compliance in mice. The increase of lung weight significantly correlated with the increase of lung airway resistance and the decrease of lung compliance in a linear fashion. These findings support an important role of lung consolidation in HF development and progression.

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Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

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