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Profound increase of lung airway resistance in heart failure, a potentially important contributor for dyspnea

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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 ($\gamma^2=0.824$). HF-induced increase of lung airway resistance and 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

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Clinical relevance: The HF-induced increase of lung weight is correlated with the increase of lung resistance and the decrease of lung compliance in mice. The change in lung function may be useful in the prediction of lung remodeling and HF progression.

Compliance with ethical standards: Yes

Conflict of interest: None.

can cause lung inflammation, fibrosis [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 a 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 aortic pressure overload-induced changes in 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 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 and carried out in accordance with the Guidelines for the Care and Use of Laboratory Animals.

Induction of HF with Transverse Aortic Constriction (TAC) in mice.

Male mice at age 6–7 weeks were used for the minimally invasive 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 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 the manufacture's instructions that were 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 ethics 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 5 zones as illustrated in figure 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 was 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 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, and 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.

Since we have previously shown that HF mice have markedly increased lung weight and lung fibrosis, we hypothesized that increased lung weight and lung fibrosis after HF and will cause an increase in lung airway resistance and a decrease in lung compliance. Consequently, 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 bodyweight (Supplemental Table 3).

Since the increase of lung airway resistance and decrease of lung compliance predominantly occurred in HF mice with heavy lungs, in order to highlight the role of lung weight in lung function, HF mice were further grouped according the ratio of lung weight to bodyweight. When the ratio of lung weight to bodyweight increased more than 50% as compared with control mice, these mice were grouped as “heavy lung”, and when the ratio of lung weight to bodyweight increased less than 50%, these were grouped as “light lung” group. The ratios of LV weight, lung weight, and RV weight to bodyweight are presented in Figure 1A–C. The mice with a greater lung weight increase are also the mice with a greater decrease of LV ejection fraction (Figure 1D).

Mice with heavy lungs had a 3.09 fold increase of the ratio of lung weight to bodyweight (Figure 1C), a 2.1 fold decrease of lung compliance (Figure 2A), and a 2.2 fold increase of lung resistance (Figure 2B). The mice with light lungs showed a mild but significant decrease of lung compliance (Figure 2A), while the lung resistance was not significantly changed (Figure 2B). Interestingly, the ratio of lung weight to bodyweight significantly correlated to TAC-induced increase of the lung compliance ($\gamma^2=0.824$) and decrease of lung airway resistance ($\gamma^2=0.641$) in a linear fashion (Figure 2C,D). In contrast, the decrease of lung compliance did not correlate to the decrease of LV ejection fraction in a linear fashion (Supplemental Figure 1). The decrease of lung compliance significantly correlated to the increase of lung airway resistance (Supplemental Figure 2). TAC-induced alterations of the lung compliance significantly correlated to the increase of the ratio of RV weight to bodyweight in a linear fashion (Figure 2C,D). The data clearly showed that the increase of lung airway resistance and decrease of lung compliance mainly occurred in HF mice with heavy lungs (Figure 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 2.1 fold decrease of lung compliance in isolated lung (Supplemental Figure 3). The increase of lung airway resistance and the decrease of lung compliance in 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 (Figure 3A,B). Mice with heavy lungs were associated with a 2.8 fold reduction of lung compliance in isolated lungs from these mice (Figure 3A). Interestingly, we found that a 3.09 fold increase of the ratio of lung weight to bodyweight in mice with heavy lungs was associated with an almost identical 3.02 fold increase of lung resistance in isolated lungs from these mice (Figure 3B). These

findings suggest that 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 bodyweight showed a mild decrease of lung compliance in isolated lungs (Figure 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 bodyweight in HF mice (Figure 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 (Figure 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 increase of 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 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 decrease of lung compliance significantly correlated with the ratio of lung weight to bodyweight and the ratio of RV weight to bodyweight in C57B6J mice (Figure 4, Supplemental Figure 4).

Pressure overload caused a profound increase of lung fibrosis, and lung fibroblast proliferation.

Consistent with our previous report, pressure overload caused an over 6-fold 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 Figure 3). Vimentin expression was also increased in macrophages (the mac-2 positive cells) in HF mice with heavy lungs (Supplemental Figure 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”. 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 Supplemental Table-8. 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 ($71\pm1.8\%$ in the control group vs. $39\pm3.2\%$ in the HF group), a decrease of LV fractional shortening, and significant increases of LV end diastolic volume and LV end systolic volume (Supplemental Table 8, Figure 5A). Serum BNP increased 44-fold in HF patients (Figure 5B). Meanwhile, blood high-sensitivity C-reactive protein (hs-CRP) of HF patients significantly increased 12.3 fold (Figure 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 (Supplemental Table 8), 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 5 sections (Figure 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 5 sections (Figure 5F), and increased 2.9 to 4.4 fold bilaterally in patients with idiopathic lung fibrosis (Figure 5E, F).

Discussion

Here we studied the alterations of lung airway resistance and compliance in mice after aortic pressure overload-induced heart failure. One of the major findings is that HF caused almost identical percent increases of lung weight and lung airway resistance. TAC-induced increase of the ratio of lung weight to bodyweight 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 limited value in the prediction of lung weight or lung remodeling in complicated clinical conditions. 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, 15,16], which was associated with a dramatic increase of lung weight, severe lung vascular remodeling and lung fibrosis, as well as 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 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.

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, as well as 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. Finally, the sample size used for 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.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1. The relative alterations of the ratio of LV weight to bodyweight, the ratio of RV weight to bodyweight, the ratio of lung weight to bodyweight, 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 bodyweight (A-C). The summarized data of the LV ejection fraction in mice during anesthesia (D). n = 4 to 6 each group.

Figure 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). n = 4 to 6 each group.

Figure 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 bodyweight in mice after sham and TAC (C,D). n = 4 to 6 each group.

Figure 4. The relationships between lung compliance or the lung airway resistance to the ratio of lung weight to bodyweight 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 bodyweight are significantly correlated to the lung compliance or the lung airway resistance in C57B6J mice after sham and TAC for 8 weeks (C,D). n = 5 to 8 each group.

Figure 5. Congestive heart failure (HF) causes significant increase of lung density.

The diagram of the 5 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 5 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. $n = 8$ to 11 each group.