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ORIGINAL ARTICLE

Gender influences the relationship between lung function and cardiac remodeling in hypertensive subjects

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Hypertensive patients are predisposed to left ventricular (LV) remodeling and frequently exhibit decline in lung function as compared with the general population. Here, we investigated the association between spirometric and echocardiographic data in non-smoking hypertensive subjects and the role of gender in this regard. In a cross-sectional study, 107 hypertensive patients (60 women) enrolled from a university outpatient clinic were evaluated by clinical, hemodynamic, laboratory and echocardiographic analysis. Vital capacity, forced vital capacity (FVC), forced expired volume in 1 s (FEV1) and in 6 s (FEV6), FEV1/FVC ratio and FEV1/FEV6 ratio were estimated by spirometry. In women, higher LV mass index and E/Em ratio correlated with markers of restrictive lung alterations, such as reduced FVC ($r=-044$; $P<0.001$; $r=-0.42$; $P<0.001$, respectively) and FEV6 ($r=-0.43$; $P<0.001$; $r=-0.39$; $P<0.01$, respectively), while higher left atrial volume index correlated with markers of obstructive lung alterations, such as reduced FEV1/FVC ($r=-055$; $P<0.001$) and FEV1/FEV6 ($r=-0.45$; $P<0.001$) ratios. These relationships were further confirmed by stepwise regression analysis adjusted for potential confounders. In men, LV mass index correlated with FVC and FEV6, but these associations did not remain statistically significant after adjustment for confounding variables. Furthermore, inflammatory markers such as plasma C-reactive protein and matrix-metalloproteinases-2 and -9 levels did not influence the association between spirometric and cardiac parameters. In conclusion, these results indicate that LV remodeling is related to restrictive lung alterations while left atrial remodeling is associated with obstructive lung alterations in hypertensive women.
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INTRODUCTION

Hypertensive patients are predisposed to left ventricular (LV) remodeling[1] and usually exhibit reduced lung function as compared with the general population.[2,3] Whether this association is consequent to the coexistence of highly prevalent conditions or to direct or indirect links of pathophysiological mechanisms remains currently uncertain.

Previous studies demonstrated that subjects with chronic obstructive pulmonary disease may exhibit altered LV structure and function.[4–6] Although smoking might be a potential link between LV remodeling and pulmonary changes, similar findings have been reported in non-smokers, pointing toward the existence of additional players.[4,7] In this regard, potential mechanisms, such as obesity,[8,9] systemic inflammatory response[10,11] and activation of matrix metalloproteinases (MMPs)[12,13] have been related to both chronic pulmonary disease and LV remodeling.

The relationship between lung function and cardiovascular events was reported to be stronger in women rather than in men in some populations,[14] indicating that the association between lung and cardiovascular remodeling might be influenced by gender. Furthermore, gender-related differences in the determinants of cardiovascular remodeling were described in hypertensive subjects and other populations.[15–19] Therefore, the aim of this study was to evaluate the association between lung function and echocardiographic features in non-smoking hypertensive subjects and whether gender played a role in this regard.

METHODS

Study subjects

Hypertensive patients (60 women and 47 men) followed in a university hospital outpatient clinic were cross-sectionally evaluated by clinical, laboratory, spirometry and echocardiography analysis. Exclusion criteria were current

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smoking, age under 18 years, previous diagnosis of lung or neoplastic disease, identifiable causes of secondary hypertension and evidence of moderate or severe cardiac valve disease, hypertrophic cardiomyopathy or previous myocardial infarction. The research was carried out in accordance with the Declaration of Helsinki. This study was approved by the Human Research Ethics Committee of the State University of Campinas. All subjects gave written informed consent to participate.

Clinical and laboratory data

Blood pressure and heart rate were measured using a validated digital oscillometric device (HEM-705CP; Omron Healthcare, Kyoto, Japan) with appropriate cuff sizes. Two readings were averaged, and, if blood pressure measurements differed by more than 5 mm Hg, one additional measurement was performed and then averaged. Body mass index was calculated as body weight divided by height squared. Waist circumference was measured at the midpoint between the lowest rib and the iliac crest. Low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, triglycerides, glucose, C-reactive protein and hemoglobin levels were measured using standard laboratory techniques. The creatinine clearance was measured using the plasma creatinine and a 24-h urine collection. Hypertension was defined as systolic blood pressure $\geqslant 140$ mm Hg or diastolic blood pressure $\geqslant 90$ mm Hg or current antihypertensive medication use. Diabetes mellitus was diagnosed if fasting blood glucose was $\geqslant 126$ mg dl^{-1} or when participants were taking hypoglycemic medications. Women with reported amenorrhea for more than 12 months, except for pregnancy, were identified as postmenopausal.

Spirometry

Spirometry was conducted in accordance with American Thoracic Society/European Respiratory Society guidelines[20] using a MicroLoop device (Micro Medical, Chatham, UK) by one investigator. Spirometric analysis estimated the following variables: vital capacity (VC), forced vital capacity (FVC), forced expired volume in 1 s (FEV1) and in 6 s (FEV6), the percentage of their predicted values, as well as FEV1/FVC and FEV1/FEV6 ratios. Intraobserver VC, FVC and FEV1 and FEV6 variabilities were $<5\%$.

Table 1 Clinical and laboratory features of hypertensive patients

Variable	*Women (n = 60)*	*Men (n = 47)*
Age, years	59.4 ± 1.7	59.8 ± 1.4
Body mass index, kg m^{-2}	33.1 ± 0.7	31.2 ± 0.8
Waist circumference, cm	101.1 ± 1.5	105.2 ± 1.5*
Systolic blood pressure, mm Hg	140.6 ± 3.0	138.5 ± 3.4
Diastolic blood pressure, mm Hg	77.8 ± 2.2	77.7 ± 2.8
Heart rate, b.p.m.	28	34
Diabetes mellitus, %	28	34
Former smokers, %	23	58†
Menopause, %	77	—
Hemoglobin, g dl^{-1}	13.6 ± 0.2	15.0 ± 0.2†
Creatinine clearance, ml min^{-1} per 1.73 m^2	89.8 ± 3.9	102.1 ± 5.0
Low-density lipoprotein cholesterol, mg dl^{-1}	111.0 ± 4.1	109.0 ± 6.0
High-density lipoprotein cholesterol, mg dl^{-1}	54.8 ± 2.2	44.5 ± 2.2†
Triglycerides, mg dl^{-1}	124 (74)	144 (79)
Fasting blood glucose, mg dl^{-1}	106.4 ± 4.0	124.1 ± 8.8
C-reactive protein, mg dl^{-1}	0.33 (0.55)	0.20 (0.33)*
MMP-2, U l^{-1}	0.45 ± 0.02	0.45 ± 0.03
MMP-9, U l^{-1}	0.94 ± 0.04	0.93 ± 0.07
Diuretics, %	83	83
Beta-blockers, %	47	58
Calcium-channel blockers, %	53	62
ACEI or ARB, %	90	91
Statins, %	53	62

Abbreviations: ACEI or ARB, angiotensin-converting enzyme inhibitors or angiotensin-receptor blockers; MMP, matrix metalloproteinase. *$P<0.05$; †$P<0.001$.

Echocardiography

Echocardiography studies were performed by a skilled physician on each subject with a Vivid 3 Pro apparatus (General Electric, Milwaukee, WI, USA) equipped with a 2.5-MHz transducer, as previously described.[21,22] LV dimensions were assessed from 2D guided M-mode tracings and relative wall thickness was computed as twice the posterior wall thickness divided by LV end-diastolic diameter and LV mass index was defined as LV mass/height$^{2.7}$. Left atrial volume was measured using the modified biplane area-length method and was corrected for body surface area, thus generating the left atrial volume index. Mitral inflow velocity was examined with pulsed Doppler from the 4-chamber apical view and the following indices were evaluated: peak early inflow velocity (E), peak atrial inflow velocity (A) and peak early/atrial velocity ratio (E/A). Tissue Doppler imaging evaluated the septal and lateral ventricular walls, as previously described.[23] Peak spectral longitudinal contraction (Sm) and initial (Em) diastolic velocities for three consecutive beats were analyzed. Intraobserver LV mass, Em and E/Em variabilities were <6, <7 and 7%, respectively.

Gelatin zymography

Gelatin zymography for assaying MMP-2 and MMP-9 activity was carried out in plasma samples as previously described.[24] Plasma samples were electrophoresed on a 7% polyacrylamide gel containing 2 g l^{-1} gelatin. Gels were stained in 0.5% Coomassie blue R-250 and distained for 1 h in 40% methanol:10% acetic acid. MMP proteolytic activity was determined by densitometry analysis. MMP proteolytic activity was determined by densitometry analysis, and MMP-2 and MMP-9 were identified as bands at 72 and 92 KDa, respectively (Supplementary Figure 1).

Statistical analysis

Continuous variables with normal and non-normal distribution are presented as mean ± standard error and median (25th–75th percentile), respectively. The Kolmogorov–Smirnov test was used to test for normal distribution of the variables. A sample size of 47 participants for each gender was considered as suitable considering values of alpha error = 0.05, beta error = 0.8 and $r = 0.40$. However, we were able to extend the analysis to 60 women. Chi-squared test was used to compare categorical variables, whereas the unpaired *t*-test and Mann–Whitney test compared the parametric and non-parametric continuous variables, respectively. Bivariate correlations between variables were examined using Pearson's correlation coefficient for normally distributed data and Spearman's rank correlation coefficient for non-normal data. Given that LV mass index, E/Em ratio, relative wall thickness, ejection fraction and left atrial volume index are major echocardiographic markers of adverse cardiovascular prognosis,[1,25] we only evaluated these cardiac parameters in correlation analysis. To identify potential confounding variables, bivariate correlation analysis between cardiac parameters and clinical, laboratory and hemodynamic features of the studied subjects was also performed. Stepwise regression analysis evaluated the independent predictors of selected echocardiographic parameters. Age, prior smoking history, body mass index, menopause (solely in women), beta-blockers use, systolic blood pressure and variables that exhibited significant correlation ($P<0.05$) with echocardiography features at bivariate analysis were included as independent variables in regression models. Spirometric markers that presented highest correlation coefficients with echocardiographic parameters were selected to enter in regression analysis. Given the high collinearity among the spirometric parameters, only one spirometric variable was included at a time in each regression model. Waist circumference and body mass index were not included as independent variables in the same statistical model due to high collinearity. A *P*-value of <0.05 was considered as significant.

RESULTS

Clinical, hemodynamic and laboratory characteristics of enrolled subjects are presented in Table 1, while spirometric and echocardiography features are shown in Table 2. The results of correlation analysis between echocardiographic and spirometric variables are shown in Table 3. In women, LV mass index and E/Em showed inverse correlations particularly with FVC and FEV6, while relative wall thickness showed only a weak correlation with % of

Table 2 Echocardiographic and spirometric features of hypertensive patients

Variable	*Women (n = 60)*	*Men (n = 47)*
Echocardiographic features		
LV end-diastolic diameter, mm	48.9 ± 0.6	51.8 ± 0.8†
Interventricular septum, mm	9.7 ± 0.2	10.4 ± 0.3†
Posterior wall thickness, mm	9.6 ± 0.2	10.2 ± 0.2*
Relative wall thickness, mm	0.397 ± 0.009	0.394 ± 0.009
LV mass index, g m$^{-2.7}$	62.2 ± 2.5	60.0 ± 3.2
LV ejection fraction, %	67.1 ± 0.8	66.1 ± 0.8
Sm, cm s^{-1}	9.5 ± 0.3	9.2 ± 0.3
E/A ratio	0.97 ± 0.06	1.09 ± 0.06
E/Em ratio	11.2 ± 0.5	10.1 ± 0.6
Left atrial volume index, ml m^{-2}	40.3 ± 2.9	34.8 ± 3.2
Spirometric features		
VC, l	2.39 ± 0.06	3.37 ± 0.12‡
% Of predicted VC	82.1 ± 1.7	78.1 ± 2.5
FVC, l	2.47 ± 0.07	3.41 ± 0.11‡
% Of predicted FVC	84.8 ± 1.7	78.9 ± 2.2
FEV1, l	1.99 ± 0.07	2.70 ± 0.09‡
% Of predicted FEV1	85.0 ± 2.0	79.0 ± 2.4
FEV6, l	2.43 ± 0.07	3.34 ± 0.11‡
% Of predicted FEV6	83.8 ± 1.7	78.6 ± 2.2
FEV1/FVC ratio	0.81 ± 0.01	0.79 ± 0.01
FEV1/FEV6 ratio	0.82 ± 0.01	0.81 ± 0.01

Abbreviations: FEV1, forced expiratory volume in 1 s; FEV6, forced expiratory volume in 6 s; FVC, forced vital capacity; LV, left ventricular; VC, vital capacity; *$P<0.05$; †$P<0.01$; ‡$P<0.001$.

predicted FVC. Conversely, left atrial volume index showed inverse correlations mainly with FEV1/FVC and FEV1/FEV6 ratios in this gender. In men, LV mass index correlated inversely with FVC, FEV6, FEV1 and % of predicted FVC. Furthermore, spirometric variables did not correlate with E/Em ratio and relative wall thickness in men as well as with LV ejection fraction in both genders.

The correlation between cardiac parameters and clinical, laboratory and hemodynamic features is shown in Supplementary Table 1. In women, LV mass index correlated with body mass index and systolic blood pressure; E/Em ratio correlated with age, body mass index, waist circumference, diabetes mellitus and LV mass index; relative wall thickness correlated with diastolic blood pressure and LV mass index; and left atrial volume index correlated with LV mass index. In men, LV mass index showed significant correlation with body mass index, waist circumference, systolic blood pressure, C-reactive protein and use of angiotensin-converting enzyme inhibitors/angiotensin receptor blockers. It was also noteworthy that beta-blockers use, plasma C-reactive protein, MMP-2 and MMP-9 levels did not correlate with any lung parameter in both genders (data not shown).

Results of stepwise regression analysis confirmed that either FVC or FEV6 was inversely associated with LV mass and E/Em, while either FEV1/FVC ratio or FEV1/FEV6 ratio was inversely associated with left atrial volume index in women (Table 4). In men, LV mass index did not associate with any spirometric parameter after adjustment for waist circumference, systolic blood pressure, C-reactive protein and angiotensin-converting enzyme inhibitors/angiotensin receptor blockers use. At last, forced inclusion of beta-blockers use, systolic blood pressure, C-reactive protein, MMP-2 or MMP-9 as an independent variable in regression models did not change the association between spirometric and echocardiographic parameters in both genders.

Table 3 Bivariate correlation analysis between spirometric parameters and selected echocardiographic features in both genders

	Echocardiographic features			
Variable	*LV mass index*	*E/Em ratio*	*RWT*	*LAVI*
Women				
VC	−0.43‡	−0.38†	−0.13	−0.18
FVC	−0.44‡	−0.42‡	−0.15	−0.21
% Of predicted FVC	−0.26*	−0.18	−0.27*	−0.07
FEV1	−0.40†	−0.30*	−0.14	−0.40†
FEV6	−0.43‡	−0.39†	−0.13	−0.31*
FEV1/FVC ratio	−0.03	0.15	−0.02	−0.55‡
FEV1/FEV6 ratio	0.01	0.12	−0.11	−0.45‡
Men				
VC	−0.32*	−0.17	−0.02	0.22
FVC	−0.33*	−0.17	−0.12	0.19
% Of predicted FVC	−0.26	−0.13	0.04	0.21
FEV1	−0.26	−0.16	−0.15	0.17
FEV6	−0.32*	−0.17	−0.12	0.18
FEV1/FVC ratio	−0.07	−0.02	−0.09	−0.09
FEV1/FEV6 ratio	0.03	0.05	−0.10	−0.07

Abbreviations: FEV1, forced expiratory volume in 1 s; FEV6, forced expiratory volume in 6 s; FVC, forced vital capacity; LAVI, left atrial volume index; LV, left ventricular; RWT, relative wall thickness; VC, vital capacity; Spirometric variables did not correlate with LV ejection fraction in both genders. *$P<0.05$; †$P<0.01$ and ‡$P<0.001$.

DISCUSSION

In the present report, we investigated the relationship between spirometric parameters and cardiac variables in a sample of non-smoking hypertensive subjects. Our data revealed that markers of restrictive lung dysfunction, such as reduced FVC and FEV6, were associated with increased LV mass and E/Em ratio, while markers of obstructive lung alterations such as reduced FEV1/FVC and FEV1/FEV6 ratios were associated with higher left atrial volume index in women. In general, these results suggest that LV and left atrial remodeling are related to distinct lung functional alterations in hypertensive subjects and that these associations might be influenced by gender.

The knowledge regarding the relationship between lung function and cardiac remodeling in hypertensive subjects is scarce. One study evaluating 43 hypertensive subjects demonstrated that declines in lung function were associated with LV dysfunction but not with variation in LV mass.[26] In contrast to these observations, our findings revealed that reduced lung function was related not only to decreased LV function but also to increased LV mass and left atrial volume. The reasons for such discrepancies are not clear but could be explained by differences in the protocol designs, sample sizes and clinical features of the studied samples. Noticeably, the average LV mass was markedly lower in that aforementioned report, which could explain the lack of relationship between LV mass and lung function. In addition, only our study evaluated left atrial dimensions of the enrolled subjects. Conversely, we observed that reductions in lung function were independently related to LV and left atrial remodeling only in women. It must be acknowledged that the smaller sample size of men in our protocol could have contributed to explain the absence of independent association between lung and cardiac variables in these individuals. However, it was noteworthy that correlation coefficients between spirometric and echocardiographic parameters at bivariate analysis were lower among men as compared with women, which seems to

Table 4 Stepwise regression analysis for selected echocardiographic variables in women

Step	*Variable*	*Beta*	P
	Dependent: LV mass index (Model 1); $R^2 = 0.288$		
1	FVC	−0.402	<0.001
2	Systolic blood pressure	0.239	0.038
3	Body mass index	0.234	0.044
	Dependent: LV mass index (Model 2); $R^2 = 0.289$		
1	FEV6	−0.401	<0.001
2	Systolic blood pressure	0.247	0.032
3	Body mass index	0.244	0.035
	Dependent: E/Em ratio (Model 3); $R^2 = 0.181$		
1	FVC	−0.442	<0.001
	Dependent: E/Em ratio (Model 4); $R^2 = 0.206$		
1	FEV6	−0.291	0.030
2	LV mass index	−0.280	0.037
	Dependent: LAVI (Model 5); $R^2 = 0.330$		
1	FEV1/FVC ratio	−0.542	<0.001
2	LV mass index	0.245	0.033
	Dependent: LAVI (Model 6); $R^2 = 0.241$		
1	FEV1/FEV6 ratio	−0.450	<0.001
2	LV mass index	0.255	0.025

Abbreviations: FVC, forced vital capacity; FEV6, forced expiratory volume in 6 s; FEV1, forced expiratory volume in 1 s; LAVI, left atrial volume index; LV, left ventricular. Only statistically significant associations are presented in the table. Given the high collinearity among the spirometric parameters, only one spirometric variable was included at a time in each regression model. FVC was included as an independent variable in models 1 and 3, while FEV6 was included as an independent variable in models 2 and 4. FEV1/FVC ratio and FEV1/FEV6 ratio were included as independent variables in models 5 and 6, respectively. All models included age, menopause, former smoking, beta-blockers use, systolic blood pressure and body mass index, while models 3 and 4 also included diabetes mellitus and models 3, 4, 5 and 6 also included LV mass index as independent variables. Forced inclusion of C-reactive protein, MMP-2 or MMP-9 as an independent variable in regression models did not change the association between spirometric and echocardiographic parameters.

strengthen the idea that this relationship was indeed influenced by gender.

Data from the Atherosclerosis Risk in Communities study demonstrated that the association between altered lung function and cardiovascular events was stronger in women than in men,[14] thus supporting the notion that the interaction between lung and cardiovascular remodeling might be influenced by gender. Given that increased LV mass and left atrial volume as well as reduced LV diastolic function are consistent predictors of higher cardiovascular risk,[1,25] our findings seem to be in agreement with that aforementioned study. A potential explanation for such gender differences is not clear, but may include variation in sexual hormone profile. Previous data from basic research have suggested that sexual hormones might exert divergent effects on the structure and function of the heart and lungs. Androgens have been reported to exert pro-hypertrophic effects in myocardial cells and to predispose to airway reactivity,[27–29] while estrogens were shown to attenuate LV remodeling and progression to heart failure and to have bronchodilatory effects.[29–32] In turn, menopause has been coupled with reduced lung function[29] and adverse LV remodeling,[33] which might have influenced the results in our sample of hypertensive women. However, the lack of impact of menopause status on our multivariate regression analysis seems to weaken this assumption.

Smoking and obesity could also account for the association between lung and heart parameters. Nevertheless, only non-smokers were enrolled in our study and adjustment for former smoking in regression analysis did not change the association between spirometric and LV variables in studied women. Likewise, previous data from other group showed that former or current smoking did not affect the relationship between LV and lung functions in hypertensive subjects,[26] thus strengthening the idea that smoking status may not be a major determinant of the association between cardiac and pulmonary parameters. Obesity and higher body mass index have been also consistently associated with adverse LV remodeling and altered lung function in several populations.[8,9] In the present report, the enrolled subjects were mostly obese, and, therefore, more predisposed to exhibit both LV and lung alterations. Nevertheless, results of regression analysis showed that the relationship between lung and echocardiographic parameters was independent of body mass index in hypertensive women, which indicates that variation in body mass *per se* did not explain the association in this gender.

The link between increased cardiac remodeling and obstructive pulmonary disease might be also mediated by persistent low-grade systemic inflammation and activation of MMPs. This assumption is supported by elevated circulating levels of C-reactive protein and MMPs, especially the gelatinases MMP-2 and MMP-9, observed in subjects with chronic obstructive pulmonary disease[10,34] or LV hypertrophy and dysfunction.[11,35,36] In our sample of hypertensive women, however, C-reactive protein, MMP-2 and MMP-9 levels did not correlate with echocardiographic and spirometric variables and did not influence the association between spirometric and echocardiographic parameters at regression analysis. Although we did not measure other markers of inflammatory status or alternative MMPs, the present findings suggest that low-grade inflammation and activation of MMPs might not be a major link between lung function and LV remodeling, at least in our sample.

The fact that increased LV mass and E/Em ratio were related to restrictive lung dysfunction also raises the hypothesis that reductions in lung function were actually a consequence of hypertensive cardiac remodeling. Restrictive lung alterations may be a manifestation of pulmonary congestion,[37] which is in turn an acknowledged complication of LV hypertrophy and dysfunction. Curiously, we found that increased left atrial volume was related to obstructive rather than to restrictive lung alterations. At a first glance this result may seem paradoxical, since subjects with chronic obstructive pulmonary disease are reported to exhibit reduced pulmonary vein dimensions suggestive of low left atrial preload.[38] Conversely, obstructive lung alterations may be also a manifestation of pulmonary congestion,[39] which could offer a plausible explanation for the association between increased left atrial volume and decreased FEV1/FVC and FEV1/FEV6 ratios. Despite the lack of a precise mechanistic explanation, the present data may be clinically relevant, because the results of regression analysis showed that spirometric parameters were the variables that exhibited the most significant associations with LV mass index, E/Em ratio and left atrial volume index in hypertensive women. Therefore, it can be suggested that spirometry may be used as a potential tool to predict LV remodeling in that population. However, further studies are necessary to confirm this hypothesis.

Some potential limitations of this study should be acknowledged. First, the majority of hypertensive patients were on medications. Some findings might be, therefore, attributable to differential effect of various therapy regimens. However, no significant correlation between anti-hypertensive medications or statins use and echocardiographic parameters was detected, except for a significant relationship between angiotensin-converting enzyme inhibitors or angiotensin-receptor blockers and LV mass index in men. Second, the cross-sectional design may limit our ability to infer a causal relationship between lung function and echocardiographic alterations. In this context, further longitudinal studies are necessary to address this issue.

In conclusion, this study showed that markers of reduced lung function were associated with increased LV mass and left atrial volume and worse diastolic function in hypertensive women. These findings raise the possibility that gender modulates the interaction between lung and cardiac remodeling in patients with systemic hypertension.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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Supplementary Information accompanies the paper on Hypertension Research website (http://www.nature.com/hr)