Journal of the American Society of Hypertension 8(6) (2014) 381–387

Research Article

Lung age is related to carotid structural alterations in hypertensive subjects

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Manuscript received February 15, 2014 and accepted March 15, 2014

Abstract

Hypertensive patients exhibit higher cardiovascular risk and reduced lung function compared with the general population. Whether this association stems from the coexistence of two highly prevalent diseases or from direct or indirect links of pathophysiological mechanisms is presently unclear. This study investigated the association between lung function and carotid features in non-smoking hypertensive subjects with supposed normal lung function. Hypertensive patients (n = 67) were cross-sectionally evaluated by clinical, hemodynamic, laboratory, and carotid ultrasound analysis. Forced vital capacity, forced expired volume in 1 second and in 6 seconds, and lung age were estimated by spirometry. Subjects with ventilatory abnormalities according to current guidelines were excluded. Regression analysis adjusted for age and prior smoking history showed that lung age and the percentage of predicted spirometric parameters associated with common carotid intima-media thickness, diameter, and stiffness. Further analyses, adjusted for additional potential confounders, revealed that lung age was the spirometric parameter exhibiting the most significant regression coefficients with carotid features. Conversely, plasma C-reactive protein and matrix-metalloproteinases-2/9 levels did not influence this relationship. The present findings point toward lung age as a potential marker of vascular remodeling and indicate that lung and vascular remodeling might share common pathophysiological mechanisms in hypertensive subjects. J Am Soc Hypertens 2014;8(6):381–387.

Keywords: Carotid; lung age; spirometry; systemic hypertension.

Introduction

Hypertensive patients are predisposed to a higher rate of cardiovascular events[1] and frequently exhibit decline in lung function as compared with the general population.[2,3] Whether this association stems from the coexistence of highly prevalent diseases or from direct or indirect links of pathophysiological mechanisms is presently unclear.

Several studies have associated severe pulmonary dysfunction with increased subclinical atherosclerosis.[4–8] Although smoking is certainly one of the links between the atherosclerosis and pulmonary changes, a similar association has been reported in nonsmokers, suggesting the existence of additional players.[9,10] Chronic pulmonary disease may by itself contribute to atherogenesis via persistent inflammatory stimuli.[3] Indeed, increased oxidative stress, systemic inflammatory response and activation of matrix metalloproteinases (MMPs) are strongly related to both chronic pulmonary disease and atherogenesis.[3,11–13] Hypothetically, ventilatory dysfunction may equally be associated with both systemic hypertension and atherogenesis via intermittent hypoxemia and sympathetic overflow.[14,15] Hitherto, however, it remains unknown whether

This work was supported by grants from FAPESP (2010/16252-0) and CNPq (476909/2012-0 and 304245/2013-5), Brazil.

Conflict of interest: None.

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1933-1711/$ - see front matter
http://dx.doi.org/10.1016/j.jash.2014.03.322

lung function is associated with vascular remodeling even in the absence of chronic lung disease and smoking.

In this context, this study evaluated the relationship between spirometric parameters and carotid structural/hemodynamic variables in non-smoking hypertensive subjects without obstructive or restrictive ventilatory alterations.

Methods

Study Subjects

Sixty-seven consecutive hypertensive patients followed in a university hospital outpatient clinic were cross-sectionally evaluated by clinical, laboratory, spirometric, and carotid ultrasound analysis. Exclusion criteria were current smoking, age under 18 years, neoplastic or lung disease, and identifiable causes of secondary hypertension. Subjects with forced expired volume in 1 second (FEV1)/vital capacity or forced vital capacity below the fifth percentiles of their relevant predicted values, and therefore considered to exhibit ventilatory abnormalities,[16] were also excluded. 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

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, and neck circumference was measured just below the laryngeal prominence. Fasting blood total cholesterol, lipid fractions, and glucose and C-reactive protein levels were measured using standard laboratory techniques.[17] Hypertension was defined as systolic blood pressure $\geq$140 mm Hg or diastolic blood pressure $\geq$90 mm Hg or current antihypertensive medication use. Diabetes mellitus was diagnosed if fasting blood glucose was $\geq$126 mg/dL or when participants were taking hypoglycemic medications.[18]

Systemic Hemodynamic Data

Blood pressure and heart rate were measured using a validated digital oscillometric device (HEM-705CP; Omron Healthcare, Japan). Systolic volume was generated from Doppler interrogation of transaortic flow at the aortic annular level and aortic cross-sectional area using a Vivid 3 Pro apparatus (General Electric) equipped with a 2.5-MHz transducer.[19] Cardiac output was calculated as: systolic volume $\times$ cardiac frequency, while peripheral vascular resistance was calculated as: mean blood pressure/cardiac output.

Carotid Analysis

Carotid ultrasonography was performed by a single physician using a Vivid 3 Pro apparatus equipped with a 10-MHz linear-array transducer.[20,21] A region 2 cm proximal to the carotid bifurcation was identified, and the intima-media thickness (IMT) of the far wall was evaluated as the distance between the lumen–intima interface and the media–adventitia interface. All measurements were made using an automatic border recognizer (Vivid 3 Pro IMT software analyzer). End-diastolic and peak-systolic internal common carotid artery diameters were obtained by continuous tracing of three cycles and averaged. The resistive index of internal carotid artery was calculated as follows: 1 – (minimum diastolic velocity/maximum systolic velocity). All measurements were obtained as the average from both right and left artery measurements. Carotid ultrasound and concomitant brachial blood pressure measurements were used to calculate artery compliance and stiffness index. Artery compliance measures the ability of the arteries to expand as a response to pulse pressure caused by cardiac contraction and relaxation and was calculated as: ([systolic diameter – diastolic diameter]/diastolic diameter)/(systolic blood pressure – diastolic blood pressure). Stiffness index is considered to be relatively independent of blood pressure and was calculated as: (systolic blood pressure/diastolic blood pressure)/([systolic diameter – diastolic diameter]/diastolic diameter).[20] Intraobserver and interobserver carotid IMT and diameter variabilities were $<$5%, while intraobserver and interobserver variabilities of artery compliance and stiffness index were $<$6%.

Spirometry

Spirometry was conducted in accordance with American Thoracic Society/European Respiratory Society guidelines[16] using a MicroLoop device (Micro Direct) by Dr Kiyota TA. Spirometric analysis estimated the following variables: vital capacity, forced vital capacity, FEV1 and forced expired volume in 6 seconds (FEV6), as well as the percentage of their predicted values. Lung age was estimated as previously reported.[22] The formulas used to calculate lung age were: 2.870 $\times$ height (in inches) $-$ (31.250 $\times$ observed FEV1 in liters) – 39.375 for men, and 3.560 $\times$ height (in inches) $-$ (40.000 $\times$ observed FEV1 in liters) – 77.280 for women. Intraobserver and interobserver forced vital capacity and FEV1 variabilities were $<$4%, while intraobserver and interobserver variabilities of lung age were $<$6%.

Gelatin Zymography

Gelatin zymography for assaying MMP-2 and MMP-9 activity was carried out as previously described.[20] Plasma samples were electrophoresed on a 7% polyacrylamide