Assessment of endothelial dysfunction in idiopathic pulmonary fibrosis

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Abstract Background: Idiopathic pulmonary fibrosis (IPF) is defined as a specific form of chronic fibrosing interstitial pneumonia limited to the lung, with the histopathology of UIP on surgical lung biopsy. Recent epidemiological evidence indicates that patients with IPF have an increased risk of cardiovascular disease. The vascular endothelium acts to maintain vascular homeostasis through multiple mechanisms, and alteration in its function precedes the development, progression and clinical expression of atherosclerosis.

Aim of the work: To assess the prevalence of endothelial dysfunction in patients with idiopathic pulmonary fibrosis and its correlation with pulmonary hypertension.

Subjects and methods: The study included two groups. The patient group included 30 IPF patients subdivided into 2 subgroups: Subgroup I (15 IPF cases) with pulmonary hypertension; Subgroup II (15 IPF cases) without pulmonary hypertension. The control group included 10 normal healthy individuals. Patients were subjected to written informed consent, detailed history taking, thorough clinical examination, collagen profile, arterial blood gases (PaO₂, SaO₂), Pulmonary function tests (spirometry), 6 min walk test, HRCT chest scan, echocardiography, and brachial artery duplex to assess endothelial dysfunction.

Results: Subgroup (I) and Subgroup (II) showed a statistically highly significant difference in brachial artery flow mediated dilatation (BADFMD) and endothelium – reactive dilatation (ERD) which indicate endothelial dysfunction compared to the control group.

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Introduction

Idiopathic pulmonary fibrosis (IPF) is defined as a specific form of chronic fibrosing interstitial pneumonia limited to the lung, with the histopathology of usual interstitial pneumonia (UIP) on surgical (thoracoscopic or open) lung biopsy [1]. Pulmonary hypertension (PH) is frequently seen in patients with IPF and is commonly attributed to hypoxic vasoconstriction and capillary destruction. Pathology findings include endothelial proliferation and medial hypertrophy that exceed those expected in the setting of hypoxia [2–4]. Recent epidemiological evidence indicates an association between cardiovascular diseases and pulmonary fibrosis [5–7]. The vascular endothelium acts to maintain vascular homeostasis through multiple mechanisms and impaired endothelial function can contribute to the development, progression and clinical expression of atherosclerosis [8]. We hypothesized that impaired endothelial function should have an increased prevalence among IPF patients.

Subjects and methods

The present study was conducted in Chest Department, Kasr El-Aini Hospital in the period between August 2009 and August 2011. The cases were diagnosed as having IPF according to the guidelines of the international consensus statement produced as a collaborative effort from the American thoracic society and European respiratory society.

The study included 30 cases with IPF half of them with pulmonary hypertension and other half without pulmonary hypertension (Patient group) and 10 apparently healthy volunteers (Control group) after having their written consent prior to participation in the study.

All patients were subjected basically to full history taking, thorough clinical examination, routine laboratory investigations, arterial blood gases, spirometry, 6 min walk test, high resolution CT chest, trans-thoracic echocardiography with estimation of pulmonary artery systolic pressure and assessment of endothelial dysfunction with duplex imaging on right brachial artery. The vasodilatory response of the brachial artery to increased shear stress is called flow mediated dilation (FMD), and reflects the ability of vascular endothelium to produce NO. FMD of the brachial artery following transient ischemia, which is a non-invasive method for assessing endothelial function, was done according to the method defined by Celermajer et al. [9].

A high-resolution (10 MHz) linear array ultrasound transducer (GE vivid 3, SyncMaster 796 mb) was used.

Patients and control were kept in supine position and at stable room temperature. All cases abstained from vitamin C intake, fatty meals, smoking and caffeine-containing drinks for at least 12 h before testing. In order to best visualize the brachial artery, the arm was comfortably immobilized in the extended position, and the brachial artery was scanned in the longitudinal section 3-5 cm above the antecubital fossa. After baseline measurements of the brachial artery were recorded, the cuff was placed distal to the section of brachial artery and inflated to 200 mmHg for 5 min to create forearm ischemia. Subsequently, the cuff was deflated and the arterial diameter was measured at 60 s after deflation [10].

All measurements of the brachial artery internal diameter (from media-adventitia interfaces to media-adventitia interfaces) were assessed at the end of the diastole (timed by the QRS complex) to avoid any effect of arterial compliance on the measurements. Mean baseline brachial artery diameter (BAD$_{\text{basal}}$) was measured in millimeters; peak FMD measured in percentage and calculated as [[(D$_{\text{max}}$ – BAD$_{\text{basal}}$)/BAD$_{\text{basal}}$] × 100] [11].

Endothelium – reactive dilatation was expressed as the percentage of change in the brachial artery diameter from baseline to following reactive hyperemia, i.e. percentage change = (-BAD$_{\text{FMD}}$ – BAD$_{\text{basal}}$)/BAD$_{\text{FMD}}$ × 100 [12].

Results

Table 1 shows the patients of IPF had a borderline statistically significant reduction in baseline brachial artery diameter in comparison with normal individuals (controls). But there was no statistically significant reduction in baseline brachial artery diameter in IPF patients in the presence or absence of PH.

Table 2 shows that BAD$_{\text{FMD}}$ of the IPF patients with PH ranged from 2.8 to 4.7 mm, whereas the BAD$_{\text{FMD}}$ of the IPF patients without PH ranged from 3.9 to 4.3 mm and the BAD$_{\text{FMD}}$ of the control group ranged from 4.3 to 5.1 mm.

The patients of IPF had a statistically highly significant lower dilatation response to ischemia and hypoxia in brachial artery diameter (brachial artery flow-mediated dilatation BAD$_{\text{FMD}}$) than normal individuals (controls). But there was no statistically significant low response to ischemia and hypoxia in brachial artery diameter (BAD$_{\text{FMD}}$) in IPF patients in the presence or absence of PH.

Table 3 shows that ERD of the IPF patients with PH ranged from 4.9% to 12.8%, whereas the ERD of the IPF patients without PH ranged from 4.6 to 12.8% and the ERD of the control group ranged from 11.6% to 16.3%.

The patients of IPF had a statistically highly significant reduction in endothelium–reactive dilatation (ERD)% in comparison with normal individuals (controls). But there was no statistically significant in endothelium–reactive dilatation (ERD)% in IPF patients in the presence or absence of PH.

Discussion

The aim of the current study was to assess the prevalence of endothelial dysfunction in patients with idiopathic pulmonary fibrosis and its correlation with pulmonary hypertension.
The current gold-standard method for endothelial dysfunction assessment is duplex ultrasound to measure brachial artery flow-mediated dilatation (BADFMD), which is dependent on the availability of nitric oxide released from endothelial cells. It follows that the greater the FMD the better the endothelial function. However, using duplex ultrasound is technically challenging, requires highly skilled operators, is expensive and therefore difficult to use as a readily available screening tool [11].

Despite limitations in visualization of the right heart, and operator dependence, transthoracic echocardiography (TTE) is a useful and readily available tool for evaluation of PH [13]. Tricuspid peak Doppler flow velocity correlates well with hemodynamic parameters and systolic PAP is relatively sensitive (79–100%) and specific (60–98%) for the presence of PH [14]. TTE is the recommended tool for screening and early detection of PH by the American College of Chest Physicians [15].

Table 2 shows that patients of IPF had a highly statistically significant lower response to ischemia and hypoxia in brachial artery diameter (brachial artery flow-mediated dilatation BADFMD) than normal individuals (controls). But there was no statistically significant low response to ischemia and hypoxia in brachial artery diameter (BADFMD) in IPF patients in the presence or absence of PH.

Table 3 shows that patients of IPF had a highly statistically significant reduction in endothelium–reactive dilatation (ERD)% in comparison with normal individuals (controls). But there was no statistically significant in Endothelium-reactive dilatation (ERD)% in IPF patients in the presence or absence of PAH.

These results were incompatible with the results of Hughes et al. [16], Peled et al. [17], who found that systemic component of endothelial dysfunction might be involved in PAH that is correlated with disease severity. This can be explained by that these two studies were done on idiopathic pulmonary arterial hypertension but in this study it was done on cases with PH secondary to IPF which has different pathophysiology.

The systemic involvement might be related primarily to the disease pathobiology, or mediated by a high activity of circulatory mediators such as pro-inflammatory cytokines [18], alterations in metabolic pathways of serotonin [19], prothrombotic abnormalities [20], hypoxia and sympathetic muscle nerve overactivity [21], or alteration in systemic metabolism [22]. So this finding may indicate a tight linkage between the pulmonary disease and the peripheral endothelium. However, the exact contribution of each factor to the peripheral endothelial dysfunction needs to be further investigated in longitudinal studies.

This work concluded that BADFMD and ERD were more affected in IPF patients regardless of presence or absence of PH than normal population. So, endothelial dysfunction is a possible link between IPF and cardiovascular disease.

References


