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Optical coherence tomography for hypertensive pulmonary vasculature

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ABSTRACT

Background: Optical coherence tomography (OCT) is an intravascular imaging modality capable of providing in situ images of tissues at near histologic resolution. In this study we examine the utility of OCT in identifying vascular changes related to pulmonary arterial hypertension (PAH) and chronic thromboembolic pulmonary hypertension (CTEPH).

Methods and results: OCT of four different distal pulmonary arteries was performed during right heart catheterization in 87 patients, 64 patients with PAH and 23 patients with CTEPH. The mean luminal diameter measured by OCT for all patients was 2.26 mm. Intimal thickening was significantly increased in all PAH patients (0.26 ± 0.05 mm in idiopathic PAH, 0.24 ± 0.03 mm in connective tissue disease related PAH, 0.26 ± 0.06 mm in congenital heart disease related PAH and 0.22 ± 0.04 mm in CTEPH, respectively) compared with controls (0.13 ± 0.03 mm) (all $p < 0.05$). An intimal thickness of ≥0.176 mm had a 91% positive predictive value for pulmonary hypertension. The anatomic abnormalities revealed by OCT tended to be severe in the idiopathic PAH group and mild in the CTEPH group. Signs of intravascular webs were found in 60.9% of CTEPH patients, but no other patients. Intimal thickness was moderately correlated with pulmonary arterial pressure and pulmonary vascular resistance (r = 0.423 and 0.439, respectively, $p < 0.001$).

Conclusions: OCT provides important information for assessment of pulmonary arterial remodeling in patients with PAH and improves diagnostic capability of angiographically undetected distal-thrombotic lesions in patients with CTEPH.

1. Introduction

Pulmonary arterial hypertension (PAH) is a progressive debilitating disorder characterized by increased pulmonary arterial pressure, often leading to right-heart failure and premature death [1]. Pulmonary vascular remodeling plays an important role in the development and progression of PAH [2]. Necropsy evidence has documented the occurrence of alterations in the lumen and vessel wall of proximal and distal pulmonary arteries (PAs) in PAH. These changes have major clinical and prognostic implications [3–5]. Identification of the pathologic changes in pulmonary vasculature in PAH has been a main objective in studies related to this disorder. Assessment of pulmonary-artery morphology in PAH has been limited to pulmonary angiography and histological study of lung samples obtained from biopsies [6]. Pulmonary angiography, while providing reasonable information regarding vessel lumen, provides no information about vessel-wall abnormalities. Histological evaluation of lung biopsies provides valuable quantitative and qualitative description of changes to the pulmonary arterial wall, but requires a thoracotomy. Intravascular ultrasound (IVUS) of PAs provides useful information regarding morphology and stiffness of PAs [7–11]. However, with the maximum attainable resolution of 100 μm, which decreases linearly with distance, its ability to delineate structure is limited.

Optical coherence tomography (OCT) is a relative new, light-based, intravascular imaging technique that provides high-resolution, cross-sectional images of vessel anatomy [12,13]. Acquisition of OCT images is analogous to IVUS, except that it uses near-infrared light instead of ultrasound. This use of light gives OCT an approximate 10-fold higher resolution than IVUS (10–15 μm compared to 100–150 μm), allowing for an improved ability to visualize the anatomy of vessel walls, characterize plaque, and assist with short- and long-term changes in vessel wall following coronary interventions [13]. Recent advances in OCT technology allow faster image acquisition and improve safety and ease of use of this procedure.

Abbreviations: OCT, optical coherence tomography; mPAP, mean pulmonary artery pressure; sPAP, systolic pulmonary artery pressure; RV, right ventricle; PAH, pulmonary artery hypertension; CTEPH, chronic thromboembolic pulmonary hypertension; PA, pulmonary artery; SV, stroke volume; CO, cardiac output; RHC, right heart catheterization.

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However, limited data is available regarding the potential role of OCT imaging in evaluating patients with PAH and the corresponding anatomical changes i PAs [14–18]. The aim of our study was to examine utility of OCT in identifying anatomical changes in PAs of patients with PAH and chronic thromboembolic pulmonary hypertension (CTEPH).

2. Methods

2.1. Study population

This prospective study included patients with WHO group-1 PH and CTEPH from our center between July 2010 and September 2011. All selected patients had undergone an OCT procedure for PAs just after a baseline hemodynamic measurement during right-heart catheterization (RHC). No patient had received PAH-targeted therapy, such as an endothelin receptor antagonist, prostanoids, or type 5 phosphodiesterase inhibitors, when the hemodynamic and OCT images were obtained. The study protocol was approved by the Human Research Committee at our institution, and all subjects provided their informed consent.

2.2. Right-heart catheterization procedure

RHC was performed via right femoral or jugular venous access sites using a 7F Swan-Ganz catheter. Hemodynamic parameters measured and calculated included mean right atrial pressure (mRAP); systolic, diastolic, and mean pulmonary arterial pressure (sPAP, dPAP, mPAP); pulmonary capillary wedge pressure (PCWP) or left ventricular end diastolic pressure (LVEDP); heart rate (HR), mean systemic arterial pressure (mSAP); cardiac output (CO); pulmonary vascular resistance (PVR); and mixed venous oxygen saturation (SvO_2).

2.3. Acquisition of OCT images

Following measurement of the baseline hemodynamic parameters, OCT was performed with the M2CV system (Light Lab Imaging Inc., Westford, Massachusetts, USA). Briefly, a proximal occlusion balloon catheter was deployed and the imaging catheter was advanced as far as possible with the light source into the distal PAs. The occlusion balloon was inflated to a maximum of 0.5 atmos for a maximum of 30 s while the pulmonary artery was infused with lactated Ringer's solution at 1 to 2 ml (ml)/second (s) using an injector pump. A motorized pullback of 1 mm (mm)/s was performed to acquire cross-sectional images at 15 frames/s. OCT was performed in the upper and/or lower lobes, and in at least two different distal PAs in each side of the lung, in every subject.

2.4. OCT analysis

All OCT data was analyzed off-line using proprietary software (Light Lab Imaging Inc., Westford, Massachusetts, USA) by two experienced cardiologist who were blinded to the patients' group and hemodynamic data. Measurements were performed in the most distal vessels imaged in each lobe. The following measurements were made: lumen diameter, intimal thickness, relative intimal thickness, intimal thickness/lumen diameter, lumen area, intimal area, and percentage intimal area (intimal area/lumen area). Intimal thickness was the mean of four measurements made in each quadrant of the artery. Intimal area was calculated by manually tracing and subtracting the luminal areas. The degree of contraction of the vessels did not influence the measurements because ratios of surface areas and intimal thickness measurements, rather than absolute values, were measured. The average value of the measurements made in the four arteries imaged in every subject was used for analysis.

2.5. Statistical analyses

The results are presented as means with standard deviation (SD), along with the mean difference and the associated 95% confidence interval. For comparisons between the two main groups, statistical significance was determined using Student's t test. For comparisons of multiple groups, one-way ANOVA analysis, followed by Tukey's multiple-comparison test, was conducted. Spearman's rank correlation test or Pearson's correlation coefficient was used to analyze the correlation between clinical status, baseline hemodynamics, and OCT findings. The receiver-operating characteristic (ROC) curves were computed, and areas under the curves as well as 95% CIs were calculated using the Mann–Whitney statistic. Efficiency of OCT findings to predict PH was evaluated in all patients within the studied population. Sensitivity, specificity, positive, and negative predictive values were computed at maximum total sensitivity and specificity. A value of $p < 0.05$ was considered statistically significant. All statistical analyses were performed with SPSS software (version15.0; IBM, Chicago, IL, USA).

3. Results

3.1. Demographics of the study population

Eighty-seven subjects with PAH or CTEPH (63 females; mean age 44 ± 19 years) and 17 control subjects (7 females, mean age 57 ± 14 years) all without any objective evidence of cardiovascular disease or metabolic or systemic disorders affecting the cardiovascular system underwent an OCT procedure during RHC at our center. The control subjects had been catheterized because of a resting systolic pulmonary-artery pressure of >40 mm Hg, estimated by Doppler echocardiography. Among the study population, 64 patients were clinically classified as WHO group-1 PH (including idiopathic PH (IPAH), PAH associated with connective tissue disease (CTD–PAH) and congenital heart disease (CHD–PAH)) and 23 patients were diagnosed as CTEPH by computer-tomography pulmonary angiography or pulmonary angiography during RHC. The detailed baseline demographic, clinical, and hemodynamic characteristics are listed in Table 1.

3.2. OCT findings

OCT examination was successful in all 87 PAH or CTEPH subjects without complications. Cross-sectional images obtained from different branches displayed similar shapes, which were generally circular except for bifurcation or branching sites. While intimal thickness, luminal area, and lumen diameter could be delineated clearly, because of signals caused by adjacent air-filled alveolar structures, determination of the external diameter and the vessel-wall thickness at distal and small branches was complicated. The typical OCT images of distal PAs obtained for different etiologies of PAH and patients without PAH are shown in Fig. 1.

The results of OCT measurements are summarized in Table 2. Accessible luminal diameter was similar, ranging from 1.06–3.76 mm, with a mean luminal diameter of 2.26 mm in all 104 patients. There were no differences among patients with PAH, CTEPH, and the control group regarding mean lumen diameter. In contrast, anatomical abnormalities were more severe in PAH groups than in the control group, as evidenced by a thicker pulmonary arterial intima, a larger intimal area, a higher ratio of intimal thickness to luminal diameter, and a higher ratio of intimal area to luminal area in the distal arteries. Vascular remodeling revealed by OCT also varied between different types of PAH and CTEPH. Intimal proliferation tended to be more severe and was exhibited by a thicker intimal in patients with IPAH (0.26 ± 0.05 mm) and CHD–PH (0.26 ± 0.06 mm), and was milder in patients with CTEPH (0.22 ± 0.04 mm) ($p < 0.05$), while the intimal thickness for control was 0.13 ± 0.03.

Of all the 23 patients with CTEPH, OCT imagings were successful obtained from the distal PAs of the stenostic or occluded segmental or subsegmental pulmonary branches in 14 (60.9%) patients. All those 14 patients had features of bands and webs traversing the pulmonary vascular lumen, as well as partial recanalization within the lumen. This pathology was not found in the other etiologies of PAH (Fig. 1e and f). In the rest of 9 CTEPH patients, OCT catheter could not go through the severely stenosis or completely occluded PAs. OCT images were obtained in the non-occluded PAs instead.

3.3. Relationships between OCT findings and pulmonary hemodynamics

A correlation was identified between anatomic indexes, measured with OCT imaging, of patients with PH and pulmonary hemodynamic parameters. Among all the PAH and CTEPH patients, PAP (including systolic, diastolic, and mean pressure) and PVR correlated significantly with intimal thickness and intimal area ($r = 0.423$ for sPAP and intimal thickness; $r = 0.268$ for sPAP and intimal area; $r = 0.397$ for dPAP and intimal thickness; $r = 0.284$ for dPAP and intimal area; $r = 0.391$ for mPAP and intimal thickness; $r = 0.259$ for mPAP and intimal area; $r = 0.439$ for PVR and intimal thickness; $r = 0.323$ for PVR and intimal area; $p < 0.05$ for all of these). Other hemodynamic parameters, such as mRAP, CO, and SvO_2, were not significantly correlated with the intimal thickness of PAs. The OCT findings in all PH and CTEPH patients are summarized in Table 3. The correlations between intimal thickness and pulmonary hemodynamics varied between patients with different causes of disease. Patients with higher PAP and PVR (in IPAH and CHD–PAH) had relatively better correlations with intimal thickness compared with patients with relatively lower PAP and PVR (in CTD–PAH and CTEPH).