The Application of Intravascular Ultrasound to Evaluate Pulmonary Vascular Properties and Mortality in Patients with Pulmonary Arterial Hypertension

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Background: The aim of this study was to explore the application of intravascular ultrasound (IVUS) to evaluate pulmonary vascular properties and mortality in patients with pulmonary arterial hypertension (PAH).

Methods: Patients (n = 51) with systolic pulmonary artery pressures ≥ 40 mm Hg on echocardiography were prospectively enrolled. All patients underwent right-heart catheterization and IVUS and were divided into three groups: PAH associated with connective tissue diseases (group 1, n = 25), PAH due to other causes (group 2, n = 15), and patients with connective tissue diseases without pulmonary hypertension (group 3, n = 11). PAH groups (groups 1 and 2) were divided into distal (n = 22) and proximal (n = 18) remodeling subtypes on the basis of IVUS results. All patients were followed (19 ± 10 months) to compare the differences among clinical variables, pulmonary vascular properties, and survival rates.

Results: A total of 408 segments of pulmonary arteries were studied. The PAH groups demonstrated a greater mean wall thickness than group 3 ($P < .01$ for all). Pulmonary vascular mechanical properties, including compliance, distensibility, elastic modulus, and stiffness index β, were found to be worse in the PAH groups than in group 3 ($P < .01$ for all), but they tended to be better in group 1 than in group 2. An inverse exponential association was found between pulmonary vascular mechanical properties and hemodynamics, with R^2 values ranging from 0.54 to 0.78 ($P < .001$). In the PAH groups, the mortality in group 1 was similar to that in group 2 (12% vs 13%, $P > .05$), while the distal remodeling subtype had higher mortality than the proximal remodeling subtype (23% vs 0%, $P < .05$).

Conclusions: IVUS is useful in PAH assessment by evaluating pulmonary vascular properties and predicting mortality. The classification of the proximal and distal remodeling type of PAH may be proposed to predict mortality and evaluate the prognosis of patients with PAH in clinical practice. (J Am Soc Echocardiogr 2015;■:■-■.)

Keywords: Intravascular ultrasound, Pulmonary arterial hypertension, Pulmonary vascular properties, Connective tissue diseases, Inflammation factors

Pulmonary arterial hypertension (PAH) is a common and well-known complication of connective tissue diseases (CTDs) such as systemic sclerosis (SSc), systemic lupus erythematosus (SLE), mixed CTD, and to a lesser extent rheumatoid arthritis, dermatomyositis, and Sjögren's syndrome.[1,2] PAH affects approximately 3% to 13% of patients with CTDs and is the major cause of death in this patient population.[3] Furthermore, data from registries have indicated that PAH associated with CTDs (PAH-CTDs) was the second most prevalent type of PAH after idiopathic PAH (IPAH).[4,5] There are also many other different types of PAH, such as heritable PAH, PAH associated with congenital heart diseases (CHDs), PAH associated with portal hypertension or portopulmonary hypertension, and so on. As reported in the Registry to Evaluate Early and Long-Term Pulmonary Arterial Hypertension Disease Management, survival in patients with PAH-CTDs was significantly lower than that in those with IPAH (78% vs 91%, $P < .001$).[3] But few investigations have explored if there is any difference in pulmonary vascular properties (PVPs), including pulmonary vascular morphological and mechanical properties, that contribute to the difference in prognosis between patients with PAH-CTDs and other PAH subgroups.

The pathologic changes in patients with PAH are characterized by intimal proliferative, medial hypertrophic, and fibrotic changes; adventitial thickening with moderate perivascular inflammatory infiltrates; and plexiform and thrombotic lesions.[2,6,7] These changes may induce the increase of pulmonary vascular resistance (PVR) and pulmonary arterial pressure accompanied by the abnormalities in PVPs and eventually lead to right-heart failure and death. Although right-heart catheterization (RHC) is considered the gold standard

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Abbreviations

CHD = Congenital heart disease

CO = Cardiac output

CTD = Connective tissue disease

DPAP = Diastolic pulmonary artery pressure

EM = Elastic modulus

IPAH = Idiopathic pulmonary arterial hypertension

IVUS = Intravascular ultrasound

LD = Luminal diameter

LDd = Diastolic luminal diameter

LDs = Systolic luminal diameter

mPAP = Mean pulmonary artery pressure

MWT = Mean wall thickness

PAH = Pulmonary arterial hypertension

PAWP = Pulmonary artery wedge pressure

PF-4 = Platelet factor–4

PH = Pulmonary hypertension

PPP = Pulmonary pulse pressure

PVMP = Pulmonary vascular mechanical property

PVP = Pulmonary vascular property

PVR = Pulmonary vascular resistance

RHC = Right-heart catheterization

SLE = Systemic lupus erythematosus

SPAP = Systolic pulmonary artery pressure

SSc = Systemic sclerosis

TGF-β_1 = Transforming growth factor–β_1

VAd = Diastolic total vessel area

VAs = Systolic total vessel area

VD = Vessel diameter

VDd = Diastolic vessel diameter

VDs = Systolic vessel diameter

WTP = Percentage of mean wall thickness

for evaluating and diagnosing pulmonary hypertension (PH),[8] it fails to detect PVPs and to differentiate very small changes in PVPs between different types of PAH.

Intravascular ultrasound (IVUS) can play an important role in evaluation of PVPs, not only by investigating its functional abnormalities but also by allowing quantitative and qualitative analyses. But few studies have focused on the role of IVUS in the evaluation of PVPs in PAH-CTDs, and most only on local abnormalities of pulmonary vessels without exploring regional differences, failing to accurately analyze the changes of whole pulmonary vessels and reflect the entire scope of PVPs. In the present study, therefore, we took the regional differences into account by dividing each pulmonary vessel into two segments on the basis of IVUS, then explored the abnormalities of PVPs and determined their associations with hemodynamic measurements and prognosis.

METHODS

Ethics Statement

The present study was approved by the local ethics committee, and all enrolled subjects provided written informed consent.

Study Population

Consecutive patients ($n = 51$) with systolic pulmonary artery pressures (SPAPs) $\geq$ 40 mm Hg on echocardiography were prospectively enrolled in the study and underwent RHC and IVUS between July 2011 and March 2014. Using RHC results in combination with histories and laboratory examinations, 25 patients were confirmed as having PAH-CTDs (group 1, PAH-CTDs [$n = 25$]), and 15 were diagnosed with PAH due to other causes (group 2 [$n = 15$]), including 11 with IPAH, two with PAH associated with portal hypertension or portopulmonary hypertension, and two with PAH-CHDs, as well as another 11 patients with CTDs without PH (group 3 [$n = 11$]). Furthermore, on the basis of IVUS results, patients with PAH (whether associated with CTDs or other causes) were also divided into those with distal ($n = 22$) and proximal ($n = 18$) remodeling subtypes.

RHC and IVUS Examination

RHC procedures were performed according to the criteria from the *European Heart Journal* guidelines for the diagnosis and treatment of PH[2] using a Swan-Ganz catheter (8.5 F; Baxter Healthcare, Edwards Critical Care Division, Deerfield, IL). Right atrial pressure, right ventricular pressure, pulmonary artery pressure (SPAP, diastolic pulmonary artery pressure [DPAP], and mean pulmonary artery pressure [mPAP]), and pulmonary artery wedge pressure (PAWP) were recorded. Cardiac output (CO) was measured in triplicate using the thermodilution method or Fick method in patients in whom PAH-CHDs was suspected. PVR was calculated using the following formula: (mPAP − PAWP)/CO. Meanwhile, blood oxygen saturation in the vena cava and the right atrial, right ventricular, pulmonary, and systemic arteries was also determined.

IVUS of the pulmonary arteries was performed immediately after RHC using a 40-MHz catheter (Atlantis TM SR PRO Catheter; Boston Scientific, Natick, MA) with an axial resolution of 43 μm. As reported by Bressollette *et al.*,[9] there were no differences between the left and right lungs for all IVUS measurements, and the anatomic abnormalities were more typical and severe in the lower lobes as opposed to the upper lobes. Therefore, we measured the average from the four lobes in the lower left and right branches in each patient.

The ultrasound catheter was advanced into the distal segment of the pulmonary arteries and withdrawn to the proximal segment at a speed of 0.5 mm/sec. Good imaging quality, defined as complete circumferential demarcation of the intima and medial wall to the adventitia inner boundary (Figure 1), was achieved using an iLab system (Boston Scientific), and the real-time images were recorded using a Sony DVD recorder (DVD+R, 4.7 GB, 120 min, 16×).

Measurements of IVUS Images

Image measurements were performed independently by two experienced observers blinded to all clinical and hemodynamic data using Imap software (ImageJ version 1.44; National Institutes of Health, Bethesda, MD). Interobserver intraclass correlation coefficients were 0.991 (95% CI, 0.987–0.994) for vessel diameter (VD) and 0.993 (95% CI, 0.990–0.995) for luminal diameter (LD). Each vessel was subdivided into two segments, a distal segment with a VD $<$ 5 mm and a proximal segment with a VD $>$ 5 mm, so there were eight segments of pulmonary arteries per patient and for a total of 408 pulmonary artery segments measured (group 1, 200; group 2, 120; group 3, 88). Mean calculations were made to ensure that the data were more representative in characterizing the entire length of the vessels than just measuring one segment of the pulmonary arteries of each patient.

The following indexes were measured directly: diastolic total vessel area (VAd) and systolic total vessel area (VAs), diastolic VD (VDd) and systolic VD (VDs), diastolic and systolic luminal areas, diastolic LD