Intracardiac, Intravascular, Two-Dimensional, High-Frequency Ultrasound Imaging of Pulmonary Artery and Its Branches in Humans and Animals

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Intravascular ultrasound imaging is a promising new method for assessing vascular morphology. We evaluated the capability of intravascular ultrasound to quantify pulmonary artery (PA) morphology in vitro and explored the feasibility of in vivo PA imaging in animals and humans. In the in vitro study of 15 PA segments, we used a 20-MHz prototype ultrasound catheter. Intravascular ultrasound (y) provided crisp images of PA segments and demonstrated excellent correlations with anatomic measurements (x) in the estimation of luminal area (y=0.89x+2.95, r=0.99, p<0.001), luminal diameter (n=30, y=0.79x+0.96, r=0.92, p<0.001), and vessel wall thickness (n=60, y=0.65x+0.33, r=0.85, p<0.001). We subsequently introduced the probe into the PA of 10 dogs and were able to obtain real-time, two-dimensional images of the main PA, its major branches, and farther smaller branches as far as the wedge level. To evaluate the in vivo feasibility of PA imaging in conscious humans, we used a commercially available, 20-MHz intravascular ultrasound (IVUS) catheter in 22 subjects through a femoral or jugular venous sheath at the end of standard diagnostic cardiac catheterization. In 20 subjects, we acquired dynamic, high-resolution, cross-sectional images of the proximal and distal PA. Changes in shape and decreasing luminal area could be clearly recognized as the IVUS catheter reached branching points and as it passed more distally. There were no complications. We conclude that IVUS imaging can be safely performed in humans, that it provides dynamic, two-dimensional images of proximal and distal PAs, and that it has promise as a quantitative tool in studying pulmonary circulation (Circulation 1990;81:2007–2012)

Necropsy evidence has documented the occurrence of alterations in the lumen and vessel wall of proximal and distal pulmonary arteries (PAs) in primary and secondary pulmonary hypertension. These changes have major clinical and prognostic connotations. Until now, defining the structural changes in PAs and assessing their functional morphology have required indirect inference from hemodynamic studies or direct evaluation by morphometric analysis of lung biopsy material. In vivo characterization of PA abnormalities has been difficult because optimal diagnostic methods have been lacking. Pulmonary arteriography has been a primary method for evaluating PAs when information is needed about distal PAs. This technique, however, cannot directly monitor changes in the cross-sectional area of the vessel or demonstrate abnormalities in the vessel wall. Furthermore, pulmonary arteriography is associated with significant risk in patients with pulmonary hypertension. Fiberoptic angioscopy can show the interior of PAs, but this procedure is limited by the need to occlude the vessel with a balloon and by its inability to assess vessel wall architecture. Recently, a new imaging approach, catheter-based, high-frequency, intravascular ultrasound imaging, has been shown by us and others to have the in vivo capability of yielding circumferential images of peripheral and coronary arteries and of detecting arterial wall abnormalities, such as atherosclerotic lesions, intimal tears, and intravascular thrombi. In this study, we evaluated the potential of intravascular ultrasound imaging in pro-
viding quantitative data for the PA anatomy in vitro, and we explored the in vivo feasibility of imaging the PA and its branches in animals and humans.

Methods
In Vitro and In Vivo Experiments in Animals

In the in vitro experiments, we used a prototype intravascular ultrasound probe, which has been described in detail previously. Briefly, this prototype device (Summit Technology, Watertown, Massachusetts), consisted of a 110-cm-long probe core and a single 20-MHz ultrasound transducer tip inside a 6F probe sheath with a blunt tip. The probe core and transducer are rotated mechanically at 1,800 rpm within the sheath. The image is transmitted by a probe-interface unit to a calibrated display system. Using this ultrasound catheter, we examined 15 PA segments of various sizes from dogs and calves. A small wedge of arterial wall was resected in the vessel circumference for ultrasound anatomic orientation. The arterial segment was placed in a water bath, the ultrasound probe was introduced into the artery, and the images produced were recorded on videotape. The arterial segment was then photographed on a millimeter calibration grid. Ultrasound and anatomic measurements of luminal area, luminal diameter, and vessel wall thickness were made by two blinded observers. From the image of each arterial segment, one measurement was made of luminal area, two of luminal diameter, and four of vessel wall thickness (Figure 1). Similar measurements were made from enlarged photographic prints of anatomic specimens. Ultrasound measurements were then correlated with anatomic measurements.

In vivo experiments were conducted in 10 anesthetized, ventilated, open-chest dogs. The animal studies conformed to the guiding principles of the American Physiological Society. The same prototype intravascular ultrasound probe used in the in vitro studies was used in the in vivo animal studies. After an anterior thoracotomy, an introducer sheath was placed in the right ventricular outflow region to guide the ultrasound catheter into the PA. Continuous imaging was performed as the probe exited the introducer sheath, entered the right ventricular outflow, and entered the main PA. Then, the blunt-tipped catheter was advanced into the PA’s proximal and distal branches. The intraluminal position of the probe in the pulmonary vasculature was verified by direct manual palpation, by conventional two-dimensional echocardiography, or by fluoroscopy.

In Vivo Intravascular Ultrasound Imaging of Pulmonary Circulation in Humans

After obtaining informed consent, we attempted PA imaging in 22 patients undergoing diagnostic cardiac catheterization. For in vivo imaging in humans, we used a commercially available intravascular ultrasound (IVUS) probe (Sonicath, Boston Scientific Corp., Watertown, Massachusetts). This device consists of a 6F disposable catheter enclosing a mechanically rotatable driveshaft with a 20-MHz ultrasound crystal at its tip. The best axial resolution is 0.3 mm, and lateral resolution is 0.5 mm. The catheter is used in conjunction with an imaging console adapted for operation at 20 MHz and 360° scans (Diasonics, Milpitas, California). The pulse-repetition frequency is 30 kHz. The number of scans per second is 15, corresponding to 900 rpm. The catheter has tracts at two locations for guidewires, a proximal tract at the distal end of the catheter and a distal tract protruding beyond the catheter tip.

IVUS imaging was performed at the end of clinically indicated diagnostic cardiac catheterization. All study patients had normal pulmonary artery pressures. Using the same introducer sheath placed in the femoral vein for diagnostic catheterization, we advanced the IVUS catheter over a 0.025-in. guidewire. In one patient who underwent myocardial biopsy via the internal jugular approach, we introduced the IVUS catheter with the same introducer sheath in the jugular vein that had been placed for biopsy. With the aid of fluoroscopy, the catheter and guidewire were first introduced into the right atrium,
and then, by standard catheter manipulation techniques, were advanced into the PAs (Figure 2). Continuous ultrasound imaging was performed from the time of introduction of the catheter into the venous system. After obtaining images of the main PA, we advanced the catheter into major PA branches and then into at least one distal branch. At the end of intravascular imaging, the catheter and sheath were removed, and hemostasis was obtained.

Results

In Vitro and In Vivo Animal Studies

IVUS provided high-resolution images of PA segments of various sizes (Figure 1). There was excellent correlation between ultrasound (y) and anatomic (x) measurements in the estimation of vessel luminal area ($y = 0.89x + 2.95$, $r = 0.99$, $p < 0.001$); similar high correlation was noted in the estimation of luminal diameter ($y = 0.79x + 0.96$, $r = 0.92$, $p < 0.001$). The correlation for vessel wall thickness measurements was significant ($y = 0.65x + 0.33$, $r = 0.85$, $p < 0.001$) (Figure 3). As reported in a previous study, interobserver and intraobserver variabilities in measurements of arterial anatomy by IVUS were negligible (interobserver correlation $r = 0.99$, 0.99, and 0.94 for luminal area, luminal diameter, and vessel wall thickness, respectively; intraobserver correlation $r = 0.99$, 0.99, and 0.97, for the same parameters, respectively).6

In the in vivo animal studies, we were able to obtain real-time, two-dimensional, 360° images of the right ventricular outflow and PAs in all 10 dogs (Figure 1). In all animals, we were able to pass the probe not only into the major branches of the PA but also into its distal branches and as far as the wedge level. Cross-sectional images obtained from the main PA, its major branches, bifurcation points, and wedge position displayed various shapes. When the catheter reached a bifurcation point, either the shape became elliptical, or two contiguous circular images were seen. As the ultrasound catheter was advanced further into distal branches close to the wedge position, the shape tended to become slightly irregular. Pulsation of the artery could be recognized in the images until the probe reached the wedge position. At all locations, luminal area and diameter were delineated clearly. Although the inner surface of the vessel wall was well defined in these in vivo images, defining vessel wall thickness precisely was not possible. The signals caused by adjacent air-filled alveolar structures made it difficult to determine vessel wall thickness at
distal PA branches. We did not image every branch of the PA in each dog, but we did obtain images of the main PA and its major branches and were able to image as far as the wedge position through at least one distal branch in each animal. There were no gross complications related to IVUS imaging.

**In Vivo Human Studies**

Real-time, dynamic, cross-sectional images of the main PA and its branches were obtained in 20 of 22 patients. In two, there was difficulty maneuvering the catheter from the right ventricle into the PA, and further imaging attempts were not pursued. In all other patients, we were able to pass the IVUS catheter not only into the major branches of the PA but also into its distal branches. Because the guidewire tract protruded beyond the catheter tip in this over-the-wire system, we did not attempt to advance the catheter to the wedge position; thus, PA images at the wedge position were not available. In images at all sites, the arterial lumen was crisply defined (Figures 2 and 4). A steady decrease in luminal size was observed as the IVUS catheter was advanced from the main PA into its major branches and then farther into its distal branches. The shape of the artery was generally circular except at or close to bifurcation or branch sites. Although the catheter generally tended to align itself toward the arterial wall, minor manipulation enabled coaxial positioning inside the vessel, thus allowing acquisition of circular pulsatile images of the arteries. Arterial pulsation was evident until the catheter reached the distal branches. Luminal area and diameter were well delineated clearly at all PA levels: definition of vessel wall thickness was suboptimal, however, particularly at distal sites. Patients did not experience any unusual sensation caused by mechanical rotation of the probe core inside the catheter and could not differentiate the ultrasound catheter from conventional catheters. There were no complications.

**Discussion**

This study demonstrates, for the first time, the in vivo feasibility of obtaining high-resolution, two-dimensional images of proximal and distal PAs in humans and animals with intracardiac, intravascular, high-frequency ultrasound catheters. This study also documents that the procedure can be performed safely. The in vitro experiments point to the quantitative potential of IVUS in studying PAs of various size. Recordings of the PA have been obtained with an M-mode ultrasound catheter in the past, but the images were only one-dimensional and were limited to the main PA. In another investigation, a catheter with six radial crystals was passed into the PA, but the signals obtained were coarse, incompletely circumferential, and provided only a crude estimate of cross-sectional area. In this study, we were able to obtain continuous, real-time, circumferential images of PAs from the main PA level to the distal PA level in humans and as far as the wedge level in animals. While the in vivo animal study required right ventriculotomy to advance the prototype catheter into the PA, the IVUS catheter used in the human study allowed passage of the catheter percutaneously into the right heart and into the PAs because of its easy maneuverability. Unlike other techniques, IVUS imaging provides a unique approach to study pulmonary vasculature by yielding real-time images of pulsatile PAs. With further advances in technology, improved catheter maneuverability and better image quality are likely to evolve, making PA imaging easier still. Incorporation of an inflatable balloon can render it possible to use the catheter without fluoroscopy. Blunt-tipped, smaller-sized catheters could allow imaging of distal PAs close to the wedge position in humans as well.

**Critique of Study**

This study was designed primarily to evaluate the feasibility of imaging the PAs. As a first step, we...
evaluated the quantitative potential of IVUS in assessing arterial architecture in normal PA segments derived from animals, and the study indeed demonstrated excellent correlations between ultrasound and anatomic estimations of luminal area and diameter. The correlation for vessel wall thickness was significant but not as good. This may be due to some methodological problems, such as lack of precision in the ultrasound anatomic orientation or minor flaws in our technique of measuring vessel wall thickness from anatomic photographs. How well IVUS can provide such quantitative data in normal and abnormal human PA segments needs to be determined. Also, while IVUS did clearly delineate luminal size in vivo, visualizing the total vessel wall thickness of PAs and discerning the various vessel wall layers in humans were hampered by signals from adjacent structures. We have shown only the feasibility of IVUS imaging in the normal PA circulation and have not evaluated the ability of IVUS in detecting abnormalities in PAs. Further work is required in patients with pulmonary vascular disorders to determine the clinical usefulness of this technique. Our feasibility study suggests that this technique has such potential.

**Clinical Implications**

PA disease, the most important area for the potential application of IVUS in pulmonary circulation, is an end result of diverse disorders such as primary pulmonary hypertension, intracardiac and extracardiac shunt lesions, hypoxic disorders, persistent pulmonary hypertension, thromboembolic disease, granulomatous and collagen vascular diseases, and drug-related disorders. These diseases can result in a variety of pathological changes in the PAs, which include medial hypertrophy, intimal proliferation, luminal narrowing, vessel dilatation, necrotizing arteritis, and vessel occlusion. Consequent alterations in the vasoresponsive state, the degree of increase in pulmonary vascular resistance, the severity of pulmonary hypertension, and the state of reversibility or irreversibility of pulmonary hypertension have important clinical, prognostic, and therapeutic implications. Lung biopsy, pulmonary contrast arteriography, and hemodynamic measurements are the current direct and indirect methods used to evaluate the severity of the structural and functional morphology of PA changes. IVUS imaging, with its ability to provide real-time information on vessel luminal area and on vessel wall structure, appears to have the potential to provide such information in vivo. IVUS may be helpful in identifying the concentric or eccentric luminal narrowing resulting from intimal proliferation and fibrosis and from fresh and organized thrombi, which are usually present in
advanced cases of primary pulmonary hypertension. This technique could demonstrate the decrease in the arterial lumen caused by medial hypertrophy and intraluminal thrombosis in patients with pulmonary hypertension associated with severe uncorrected congenital heart lesions. In PA hypertension resulting from long-standing pulmonary venous hypertension secondary to acquired rheumatic valvular disease and ischemic cardiomyopathy, it may be possible to visualize abrupt luminal narrowing caused by intimal hyperplasia and medial hypertrophy. This technique may also be helpful in the assessment of the reversibility of pulmonary hypertension in patients considered for cardiac transplantation. Not only could the intraluminal and vessel wall architectural changes in PAs be visualized, but also the vasodilating capacity could be studied by analyzing changes in luminal area after administration of vasodilator agents. Although the inability to define vessel wall thickness in vivo in our normal subjects is a concern, it is conceivable that abnormally thickened vessel wall segments due to medial hypertrophy and intimal proliferation may be better visualized in IVUS images than normal vessel walls with a very thin intima and media. Even if precise measurements of vessel wall thickness are difficult to obtain, the changes induced in luminal configuration and size may have informative value. When these capabilities are validated in patients with various types of pulmonary hypertension, this imaging technique could possibly become an important diagnostic and prognostic tool. Further, other disorders involving the PAs, such as peripheral PA stenosis, PA hypoplasia, and acute and chronic pulmonary embolism conceivably could be diagnosed. In patients undergoing balloon pulmonary valvotomy, IVUS could be helpful in determining the balloon size required and in assessing the effects of valvuloplasty. Additionally, IVUS imaging could serve as a powerful research tool in the study of PA physiology in health and disease. Our study has demonstrated the in vivo feasibility of IVUS imaging of the PAs and its promise. With further work, its clinical and research applications and limitations can be defined.

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