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Pulmonary Artery Denervation to Treat Pulmonary Arterial Hypertension

The Single-Center, Prospective, First-in-Man PADN-1 Study (First-in-Man Pulmonary Artery Denervation for Treatment of Pulmonary Artery Hypertension)

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Objectives This study was designed to test the safety and efficacy of pulmonary artery (PA) denervation (PADN) for patients with idiopathic PA hypertension (IPAH) not responding optimally to medical therapy.

Background Baroreceptors and sympathetic nerve fibers are localized in or near the bifurcation area of the main PA. We previously demonstrated that PADN completely abolished the experimentally elevated PA pressure responses to occlusion of the left interlobar PA.

Methods Of a total of 21 patients with IPAH, 13 patients received the PADN procedure, and the other 8 patients who refused the PADN procedure were assigned to the control group. PADN was performed at the bifurcation of the main PA, and at the ostial right and left PA. Serial echocardiography, right heart catheterization, and a 6-min walk test (6MWT) were performed. The primary endpoints were the change of PA pressure (PAP), tricuspid excursion (Tei) index, and 6MWT at 3 months follow-up.

Results Compared with the control group, at 3 months follow-up, the patients who underwent the PADN procedure showed significant reduction of mean PAP (from 55 ± 5 mm Hg to 36 ± 5 mm Hg, $p < 0.01$), and significant improvement of the 6MWT (from 324 ± 21 m to 491 ± 38 m, $p < 0.006$) and of the Tei index (from 0.7 ± 0.04 to 0.50 ± 0.04, $p < 0.001$).

Conclusions We report for the first time the effect of PADN on functional capacity and hemodynamics in patients with IPAH not responding optimally to medical therapy. Further randomized study is required to confirm the efficacy of PADN. (First-in-Man Pulmonary Artery Denervation for Treatment of Pulmonary Artery Hypertension [PADN-1] study; chiCTR-ONC-12002085) (J Am Coll Cardiol 2013;62:1092–100) © 2013 by the American College of Cardiology Foundation

Idiopathic pulmonary arterial hypertension (IPAH) is characterized by elevations of mean pulmonary artery (PA) pressure (PAP) and pulmonary vascular resistance (PVR) (1). The pathogenesis of IPAH was believed to be due to an imbalance between locally produced vasodilators and vasoconstrictors (2). Recent studies have demonstrated that vascular wall remodeling also contributes to elevated PVR (3). Up to now, the role of neural reflex in the mediation and development of IPAH has not been specifically investigated.

In 1962, Osorio et al. (4) reported the existence of a pulmopulmonary baroreceptor reflex that originates in the large pulmonary branches, with neither the afferent nor the efferent fibers belonging to the vagus nerve. In 1980, these findings were again confirmed by Juratsch et al. (5) and Baylen et al. (6). More recently, our animal study (7) demonstrated that PA denervation (PADN) could completely abolish the increment of PAP induced by balloon occlusion at the interlobar segment but not at the basal trunk. On the basis of such findings, we designed a first-in-man study to test the safety and efficacy of PADN by inducing local injury/destruction to the baroreceptor or sympathetic nervous fibers in patients with IPAH who did not respond optimally to current medical therapy.

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Table 1 Baseline Characteristics in All Patients

	PADN Group (n = 13)	Control Group (n = 8)
Age, yrs	40 ± 16	41 ± 10
Male	9 (69)	4 (50)
Height, cm	164 ± 5	165 ± 5
Weight, kg	63 ± 6	65 ± 7
Systolic blood pressure, mm Hg	115 ± 9	114 ± 9
Diastolic blood pressure, mm Hg	68 ± 7	71 ± 5
Heart rate, beats/min	92 ± 6	90 ± 3
Time interval, yrs		
From symptom to diagnosis	3.5 ± 1.1	3.4 ± 1.2
Clinical presentation		
Dyspnea	13 (100)	8 (100)
Chest pain	10 (77)*	4 (50)
Syncope	3 (23)	2 (25)
Fatigue	13 (100)	8 (100)
From starting medication to PADN	3.3 ± 0.2	3.3 ± 0.1
Drugs used following diagnosis		
Oxygen	13 (100)	8 (100)
Monotherapy	0	0
Combination of at least 2 drugs	13 (100)	8 (100)
Diuretics	13 (100)	8 (100)
Beraprost	13 (100)	8 (100)
Bosentan	3 (23)	2 (25)
Sildenafil	11 (85)	5 (63)
Anticoagulant	13 (100)	7 (88)
Cholesterol, mml/l	2.1 ± 0.4	2.1 ± 0.3
Low-density cholesterol, mmol/l	1.1 ± 0.2	1.2 ± 0.2
Fasting blood glucose, mmol/l	3.6 ± 0.5	3.5 ± 0.5
Serum creatinine, mmol/l	63.5 ± 5.4	64.2 ± 6.8
White blood cells, × 10^9/l	4.3 ± 0.1	4.3 ± 0.2

Values are mean ± SD or n (%). *p = 0.033, compared with the control group.
PADN = pulmonary artery denervation; PAH = pulmonary artery hypertension.

Methods

Patient population. Patients with IPAH (defined as a mean PAP ≥25 mm Hg at rest) not responding optimally to current medical therapy (defined as a reduction of <5 mm Hg in the resting mean PAP during medication, or unchanged 6-min walk test (6MWT) defined as increment of 6MW distance <50 m) were eligible for the study. A total of 22 patients were screened. One patient was excluded after a positive adenosine test (defined as a decrease of the mean PAP ≥10 mm Hg to an absolute level of <40 mm Hg (8), measured by right heart catheterization). Eight patients refused to consent and were assigned to the control group. These patients continued to receive the same medical therapy as before enrollment. Thirteen patients were included in the study group.

Medical treatment before enrollment. Before enrollment, all 21 patients received a diuretic (hydrochlorothiazide at a dose of 12.5 mg to 25 mg, once daily, and/or spironolactone at a dose of 20 mg to 40 mg, once daily) and beraprost (120 mg, 4 times daily) (Table 1), with either sildenafil (20 mg, 3 times a day) or bosentan (120 mg, twice daily) or digoxin (0.125 mg, once daily).

All patients were informed that PADN was only tested previously in an animal study that showed that PADN could abolish the elevated PAP response to occlusion of the left interlobar PA by a balloon inflation (7). According to the study protocol, the risk of medications being withdrawn after the PADN procedure was described to each patient. The patients were also informed that they had the right to withdraw their consent at any time. The study protocol was presented in detail to the institutional review board and was approved by the institutional review board and ethics committee. Written consent was obtained from all patients.

Assessment of N-terminal brain natriuretic peptide level. Blood samples were obtained for N-terminal brain natriuretic peptide (NT-BNP) levels before, immediately after the PADN procedure, and at 24 h, 1 week, 1 month, 2 months, and 3 months following the PADN procedure.

Abbreviations and Acronyms

6MWT = 6-min walk test
CO = cardiac output
IPAH = idiopathic pulmonary arterial hypertension
MPA = main pulmonary artery
NT-BNP = N-terminal brain natriuretic peptide
PA = pulmonary artery
PADN = pulmonary artery denervation
PAH = pulmonary artery hypertension
PAOP = pulmonary artery occlusive pressure
PAP = pulmonary artery pressure
PVR = pulmonary vascular resistance
RA = right atrium/atrial
RV = right ventricle/ventricular
Tei = tricuspid excursion index
TPG = transpulmonary pressure gradient

Assessment of functional capacity. Functional capacity (9) was determined by the 6MWT, followed by an assessment of dyspnea using the Borg scale (10). The 6MWT was performed at 1 week, 1 month, 2 months, and 3 months following the PADN procedure. The World Health Organization classification (11) at rest and during exercise was recorded by a physician who was blinded to the study design.

Echocardiographic assessment. Echocardiography was performed at 1 week, 1 month, 2 months, and 3 months following the procedure. Echocardiographic studies were done using a Vivid 7 ultrasound system with a standard imaging transducer (General Electric Co., Easton Turnpike, Connecticut). All of the echocardiograms were performed and interpreted in the medical university's echocardiographic laboratory. All of the measurements were performed following the recommendations of the American Society of Echocardiography (12). Digital echocardiographic data that contained a minimum of 3 consecutive beats (or 5 beats in cases of atrial fibrillation) were acquired and stored. Right ventricular (RV) systolic pressure is equal to systolic PAP in the absence of pulmonary stenosis. Systolic PAP is equal to the sum of the right atrial (RA) pressure and the RV-to-RA pressure gradient during systole. RA pressure was estimated based on the echocardiographic features of the inferior vena cava and assigned a standard value (13). The RV-to-RA pressure gradient was calculated as $4v_t^2$ using the modified Bernoulli equation, where v_t is the velocity of the tricuspid