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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

regurgitation jet in m/s. The mean PAP was estimated according to the velocity of the pulmonary regurgitation jet in m/s. The tricuspid excursion index (Tei) (14) is defined as (A − B)/B, where A is the time interval between the end and the onset of tricuspid annular diastolic velocity, and B is the duration of tricuspid annular systolic velocity (or the RV ejection time). PA compliance for patients was calculated as the stroke volume divided by pulse pressure (systolic PAP minus diastolic PAP).

Right heart catheterization. Hemodynamic measurements and blood oxygen pressure/saturation determinations from the RA, RV, and PA were done before and immediately after the PADN procedure. These measurements were repeated at 24 h and 3 months.

Procedure. A 7-F flow-directed Swan-Ganz catheter (131HF7, Baxter Healthcare Corp., Irvine, California) was inserted into an internal jugular or subclavian vein. Measurements of resting RA pressure, RV pressure, systolic/diastolic/mean PAP, PA occlusive pressure (PAOP), cardiac output (CO) (using the thermodilution method), and mixed venous oxygen saturation were recorded. The PVR [PVR = (mean PAP − PAOP)/CO] and transpulmonary pressure gradient (TPG = mean PAP − PAOP) were then calculated. All of the measurements were recorded at the end of expiration. Five criteria (15–17) were used to evaluate whether a PAOP measurement was valid: 1) the PAOP was less than the diastolic PAP; 2) the tracing was comparable to the atrial pressure waveform; 3) the fluoroscopic image exhibited a stationary catheter following inflation; 4) free flow was present within the catheter (flush test); and 5) highly oxygenated blood (capillary) was obtained from the distal portion in the occlusion position. If the PAOP measurement was unreliable, the left ventricular end-diastolic pressure was then measured and used rather than the PAOP. The blood samples from the superior vena cava and PA were obtained for the measurements of oxygen pressure and saturation.

Equipment. A dedicated 7.5-F multiple-function (temperature sensing and ablation) catheter (PADN, patent application in progress) consisted of 2 parts: catheter shaft and handle (Fig. 1A). This catheter had a tapered (to 5-F) circular tip with 10 pre-mounted electrodes (separated from each other by 2 mm) (Fig. 1B). The circular tip had an outer diameter of 20 mm, 25 mm, 30 mm, 35 mm, 40 mm, and 45 mm, respectively. The "connect" cable linked the handle to the "connect" box (Fig. 1C). There were 3 ports (Fig. 1D) on either side of the connect box: "Catheter" was for the connection of the cable and the catheter handle, "RF" was for connecting with all kinds of radiofrequency generators used in the market, and "ECG" was for connecting with electrocardiogram monitoring equipment. On the surface of the "connect" box, there was 1 button marked by numbers 1 to 10 and "OFF" and "NULL." Numerical buttons indicated the location of each electrode on the circular tip of the catheter. When a whole system was set up (Fig. 1E), turning the numerical button on the connect box to "1" would

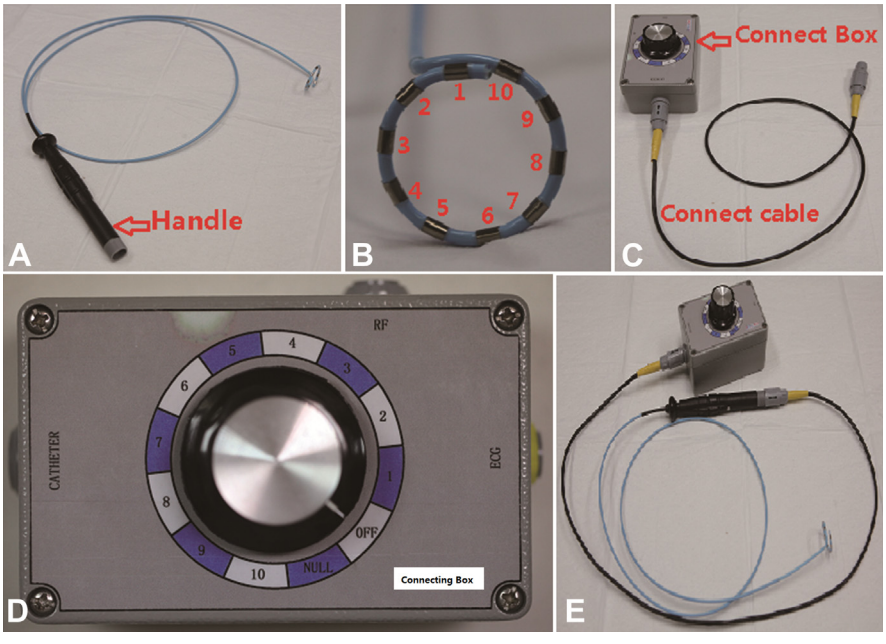

Figure 1 A Dedicated 7.5-F Triple-Function Catheter

(A) The catheter had a tapered (to 5-F) circular tip with 10 pre-mounted electrodes (each electrode has a width of 0.75mm and is separated by 2 mm **[B]**). Electrodes are connected with a connect-cable and a connect-box **(C)**. There are 10 knobs on the surface of connect-box **(D)**, and each is consistent with the electrode on the circular tip of the ablation catheter. Sequential ablation was performed by selecting the knob on the generator after the whole system is set up **(E)**.

indicate that the ablation was performed through the first electrode at the catheter tip.

PADN procedure. A baseline PA angiography was performed to identify the PA bifurcation level and calculate the PA diameter (Figs. 2A to 2C). An 8-F long sheath was inserted through the femoral vein and advanced to the main PA (MPA) (Fig. 2A). The PADN catheter was advanced along this long sheath (Fig. 2B). After gently withdrawing the sheath and pushing the PADN catheter, the circular tip would be released from the sheath (Fig. 2C). Then, by slightly rotating and pushing the handle in a clockwise direction, the circular tip would be positioned at the ostium of the left PA (Level 1 of ablation, <2 mm distal to orifice, (Fig. 2D). After ablation at this level, counterclockwise rotation and withdrawing the handle would allow the circular tip to slide down to the distal bifurcation area of the MPA (Level 2 of ablation, <2 mm proximal to the bifurcation level) (Fig. 2E). Finally, continuously rotating and pushing the handle was performed until the circular tip jumped into Level 3 of ablation (<2 mm distal to the ostial right PA) (Fig. 2F).

Three criteria were used to ensure that the electrodes were tightly in contact with the endovascular surface: 1) strong manual resistance when rotating the handle; 2) inability to advance distally (Fig. 2G) or ease in, withdrawing proximally (Fig. 2H); and 3) angiographic confirmation. Following these confirmations, ablation would begin from the 1st to the 10th electrode at Level 1 and then at Levels 2 and 3. Following the first round of ablation at each level, the catheter tip was gently withdrawn, rotated, and re-advanced to ensure that the entire diameter of the vessel axis was being ablated.

The following ablation parameters were programmed at each level: temperature >50°C, energy = 10 W, and time = 60 s. The procedure would be stopped if the patient complained of intolerable chest pain. The electrocardiogram and hemodynamic pressure were monitored and continuously recorded throughout the procedure. Procedural success was defined as a reduction in the mean PAP ≥10 mm Hg (as measured by the Swan-Ganz catheter), and there were no complications. The patients were monitored in the cardiac care unit for at least 24 h after the PADN procedure.

Peri-procedural medications. An intravenous bolus of 5,000 U of heparin was given immediately following the insertion of the venous sheath. An additional approximately 2,000 to 3,000 U of heparin was added if the procedural time was greater than 1 h. Following the procedure, oral warfarin was prescribed and adjusted according to the international normalized ratio to be between 1.5 and 2.5 for all patients. If there were contraindications for warfarin, aspirin (100 mg/day) and clopidogrel (75 mg/day) were

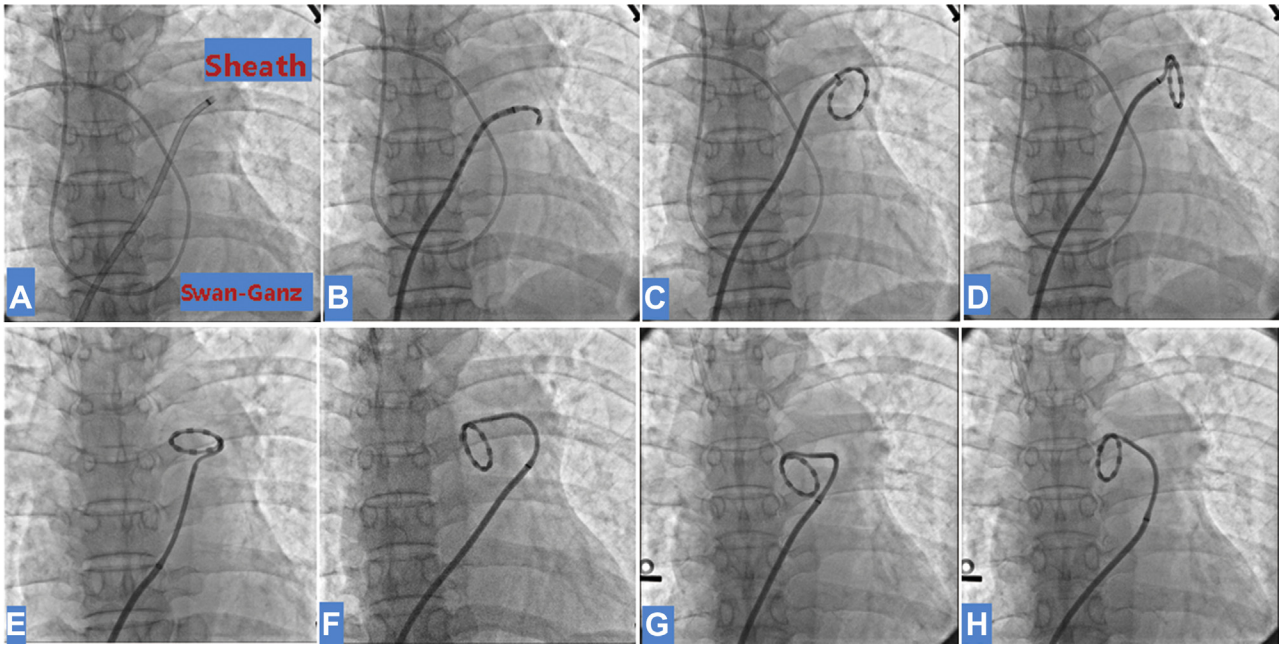

Figure 2 An 8-F Long Sheath Was Inserted Through the Femoral Vein and Advanced to the MPA

(A) The same patient as in Figure 1 is shown. The PADN catheter was advanced along this long sheath **(B)**. After gently withdrawing the sheath and pushing the PADN catheter, the circular tip would be released from the sheath **(C)**. Then, slight clockwise rotation and pushing the handle would allow the circular tip into the ostial left PA (Level 1 of ablation, <2 mm distal to orifice **[D]**). After ablation at Level 1, counterclockwise rotation and withdrawing of the handle would allow the circular tip to slide down to the distal bifurcation area of MPA (Level 2 of ablation, <2 mm proximal to the bifurcation level **[E]**). Finally, continuously rotation and pushing the handle was performed until the circular tip jumped into the Level 3 of ablation (<2 mm distal to ostial right PA **[F]**). When the electrodes tightly contacted the inner arterial surface, there existed the inability to advance distally **(G)** or to ease in withdrawing proximally **(H)**.

Table 2 Echocardiographic Measurements in 2 Groups

		Following PADN					
	Before	Post	24 H	1 Week	1 Month	2 Months	3 Months
SPAP, mm Hg							
PADN group	86 ± 5*	70 ± 4	70 ± 6	70 ± 6	69 ± 6	71 ± 6	72 ± 7
Control group	86 ± 8*	—	84 ± 9*	84 ± 8*	85 ± 9*	83 ± 7*	83 ± 9*
MPAP, mm Hg							
PADN group	38 ± 6†	24 ± 5	24 ± 4	25 ± 5	23 ± 4	26 ± 5	26 ± 6*
Control group	37 ± 7*	±	36 ± 5*	36 ± 5*	37 ± 5*	35 ± 5*	35 ± 6*
Tei							
PADN group	0.7 ± 0.04§	0.5 ± 0.04‡	0.4 ± 0.04	0.5 ± 0.04‡	0.4 ± 0.05	0.4 ± 0.04	0.5 ± 0.04‡
Control group	0.7 ± 0.04	—	0.7 ± 0.04§	0.7 ± 0.04§	0.7 ± 0.05§	0.7 ± 0.05§	0.7 ± 0.06§
Pericardial-effusion depth, mm							
PADN group	3.5 ± 0.8*	2.7 ± 0.5	2.8 ± 0.7	2.4 ± 0.5	1.4 ± 0.5	0.7 ± 0.2	0.7 ± 0.4
Control group	3.5 ± 0.7*	—	3.3 ± 0.9*	3.4 ± 0.7*	3.4 ± 0.7*	3.4 ± 0.7*	3.4 ± 0.7*
PA compliance							
PADN group	0.2 ± 0.1*	0.4 ± 0.1	0.4 ± 0.1	0.4 ± 0.1	0.4 ± 0.1	0.4 ± 0.1	0.4 ± 0.1
Control group	0.2 ± 0.1*	—	0.2 ± 0.1*	0.2 ± 0.1*	0.2 ± 0.1*	0.2 ± 0.1*	0.2 ± 0.1*

Values are mean ± SD. *$p < 0.001$, compare with following PADN. †$p < 0.04$, compared with following PADN. ‡$p < 0.001$, compared with before PADN. §$p < 0.03$, compared with following PADN at 24 h, 1 month, and 2 months.

MPAP = mean pulmonary artery pressure; PA = pulmonary artery; PADN = pulmonary artery denervation; SPAP = systolic pulmonary artery pressure; Tei = tricuspid excursion index.

prescribed indefinitely. Immediately after the PADN procedure, all medications (diuretics, sildenafil, bosentan, beraprost, and digoxin) were discontinued in the study group; the use of supplemental oxygen was left to the physician's discretion.

For patients in the control group, all medications that were previously prescribed before screening were continued. Their doses were adjusted and left to the physician's discretion.

Endpoints. The primary endpoints were improvement of functional capacity by the 6MWT and mean PAP at 3 months. Clinical adverse events (including PA perforation/dissection, acute thrombus formation in the PA, all-cause death, rehospitalization due to PAH, and lung transplantation) served as secondary endpoints and were assessed by an independent event committee.

Definitions. PAH was defined as a resting mean PAP ≥25 mm Hg. Normal PAOP is between 6 and 12 mm Hg. The normal TPG is ≤12 mm Hg. Pre-capillary PAH was defined as a mean PAP ≥25 mm Hg in association with PAOP ≤15 mm Hg and PVR >3 Woods units. Post-capillary PAH was defined as a mean PAP ≥25 mm Hg in association with PAOP >15 mm Hg and a PVR ≤3 Woods unit (15,16).

Statistical analysis. Continuous variables are expressed as mean ± SD. The normality test for all of the continuous variables was performed using Kolmogorov-Smirnov and Shapiro-Wilk tests. Differences in continuous variables between different time points in the PADN group or between the PADN and control groups were analyzed using paired-sample Student *t* tests or Wilcoxon rank sum tests, as appropriate. The categorical variables were compared using the Fisher exact test. Statistical significance was defined as a 2-sided p value < 0.05. All of the analyses were performed using the statistics program SPSS version 16.0 (SPSS Institute, Chicago, Illinois).

Results

Baseline characteristics. Between March and May 2012, a total of 21 patients with PAH not responding optimally to current medical treatment were included (Table 1).

All patients presented with dyspnea and fatigue. Patients in the PADN group had more frequent chest pain (77%), compared with 50% in the control group ($p = 0.033$). The average time interval between the onset of symptom to diagnosis was 3.5 years. All patients did not respond optimally to current medical treatment after an average of 3.3 years combination of therapy using at least 2 drugs.

Echocardiographic measurements. Baseline echocardiographic variables were comparable between the 2 groups (Table 2). After 3 months treatment, there were no significant differences in echocardiographic measurements in the control group.

PADN procedure was associated with significant reduction of the systolic PAP and mean PAP through the 3 months follow-up. The size of the pericardial effusion (thickness of the fluid layer) was reduced from 3.5 ± 0.8 mm at baseline to 2.7 ± 0.5 mm ($p < 0.001$) immediately following the PADN procedure. This metric was decreased to 0.7 ± 0.4 mm at the 3-month follow-up ($p < 0.001$). Importantly, the RV Tei index was significantly improved from 0.7 ± 0.04 at baseline to 0.5 ± 0.04 ($p < 0.001$) at 3 months.

Right heart catheterization. At baseline, there were no differences in hemodynamic measurements between the PADN and control groups (Table 3). Procedural success was achieved in 12 (92.3%) patients. Procedural failure

Table 3 Hemodynamic Measurements by Right Heart Catheterization

	Before Intervention	Following PADN		
		Post	24 H	3 Months
SPAP, mm Hg				
PADN group	86 ± 8*	72 ± 5	70 ± 5	71 ± 6
Control group	86 ± 7*	—	—	86 ± 7*
MPAP, mm Hg				
PADN group	55 ± 5*	39 ± 7	36 ± 5	36 ± 5
Control group	53 ± 5*	—	—	50 ± 5*
PVR, dyne · s · cm^{-5}				
PADN group	1,883 ± 281	1,150 ± 208†	876 ± 154‡	763 ± 162§
Control group	1,877 ± 275	—	—	1,847 ± 239‖
RVP, mm Hg				
PADN group	85 ± 7‡	71 ± 6	70 ± 5	69 ± 6
Control group	86 ± 8‡	—	—	85 ± 7‡
RAP, mm Hg				
PADN group	4 ± 2	5 ± 2	5 ± 3	5 ± 2
Control group	5 ± 2	—	—	5 ± 2
PAOP, mm Hg				
PADN group	8 ± 2	8 ± 3	8 ± 4	8 ± 3
Control group	7 ± 3	—	—	7 ± 4
TPG, mm Hg				
PADN group	36 ± 6*	30 ± 5	27 ± 4	28 ± 5
Control group	42 ± 6*	—	—	34 ± 6*
Cardiac output (l/min · m^2)				
PADN group	2.0 ± 0.2	2.6 ± 0.1	2.8 ± 0.2	2.8 ± 0.3
Control group	2.1 ± 0.1	2.1 ± 0.2	2.1 ± 0.1	2.2 ± 0.2
PA O_2 saturation, %				
PADN group	42 ± 7*	51 ± 6	51 ± 6	52 ± 7
Control group	42 ± 5	43 ± 5	43 ± 5	43 ± 6

Values are mean ± SD. *$p < 0.001$, compared with following PADN. †$p < 0.05$, compared with before PADN. ‡$p < 0.003$, compared with following PADN. §$p < 0.001$, compared with before PADN. ‖$p < 0.001$, compared with 3 months in following PADN.

PAOP = pulmonary artery occlusive pressure; PVR = pulmonary vessel resistance; RAP = right atrial pressure; RVP = right ventricular pressure; TPG = transpulmonary pressure gradient; other abbreviations as in Table 2.

(a reduction of 6 mm Hg in the mean PAP) was recorded in 1 patient. This patient developed intolerable chest pain induced by the PADN procedure after ablation of the ostial left PA branch. The procedure was stopped for this patient.

Immediately following the PADN procedure, the systolic PAP and mean PAP significantly decreased from a baseline of 86 ± 8 mm Hg to 72 ± 5 mm Hg ($p < 0.01$) and from 55 ± 5 mm Hg to 39 ± 7 mm Hg ($p < 0.01$), respectively. These reductions were maintained through 3 months follow-up. Following the reduction of PAP, CO increased significantly (from 2.0 ± 0.2 l/min · m^2 to 2.8 ± 0.3 l/min · m^2, $p < 0.001$), leading to the significant reduction of TPG and PVR and significant increment of venous O_2 saturations in PA.

PA compliance. In the PADN group, PA compliance increased significantly from 0.20 ± 0.04 ml/mm Hg at baseline to 0.38 ± 0.06 ml/mm Hg at 3 months ($p < 0.001$), and this remained unchanged in the control group.

Assessment of functional capacity. In the PADN group, the baseline NT-BNP was 2,005 ± 442 pg/ml, which was significantly reduced to 822 ± 201 ($p = 0.003$) at 3 months following the procedure (Table 4). After 1 week, the 6MW distance increased significantly from a baseline of 324 ± 21 m to 459 ± 42 m ($p = 0.009$) at 1 month, 487 ± 47 m ($p = 0.004$) at 2 months, and 491 ± 38 m ($p = 0.004$) at 3 months. This improvement was associated with significant improvements in the World Health Organization class and BORG score. There was no improvement in either 6MW distance or functional classes in the control group.

Clinical follow-up. In the PADN group, all medications were discontinued except for the oral anticoagulant (with 1 patient also on diuretics). Three patients (23%) needed supplemental oxygen as required before the procedure. No PA perforation/dissection/aneurysm or acute thrombus formation in the PA for the PADN group was observed. There were no patients requiring lung transplantation in either group. By contrast, rehospitalization was required in 5 patients (62.5%) in the control group, and none in the PADN group ($p < 0.001$).

All patients had chest pain during the PADN procedure, with 1 patient having intolerable pain for whom the PADN procedure was not completed. There were 2 deaths during the 3-month follow-up. One patient died from septic shock 87 days following the PADN procedure. This 42-year-old

Table 4 Assessment of Functional Capacity

		Following PADN				
	Before	24 H	1 Week	1 Month	2 Months	3 Months
6MWD, m						
PADN group	324 ± 21	—	390 ± 33	459 ± 42*	487 ± 47*	491 ± 38*
Control group	358 ± 30	—	361 ± 36	365 ± 38†	362 ± 39‡	364 ± 38†
WHO class						
PADN group	3.6 ± 0.8†	—	2.3 ± 1	1.7 ± 0.9	1.6 ± 0.7	1.6 ± 0.8
Control group	3.5 ± 0.9†	—	3.5 ± 0.8†	3.5 ± 0.8†	3.5 ± 0.9†	3.2 ± 0.4†
Class ≥3						
PADN group	6 (46)†	—	1 (7.6)	1 (7.6)	1 (7.6)	1 (7.6)
Control group	4 (50)†	—	4 (50)†	4 (50)†	4 (50)†	4 (50)†
BORG index						
PADN group	3.4 ± 0.3	—	3.0 ± 0.4	3.0 ± 0.3	2.3 ± 0.4*	2.3 ± 0.4*
Control group	3.5 ± 0.4	—	3.5 ± 0.3	3.3 ± 0.4	3.2 ± 0.3†	3.3 ± 0.3†
Class ≥3						
PADN group	8 (62)†	—	3 (23)	3 (23)	3 (23)	3 (23)
Control group	4 (50)†	—	4 (50)†	4 (50)†	4 (50)†	4 (50)†
NT-BNP, pg/ml						
PADN group	2,005 ± 442‡	1,502 ± 419	1,234 ± 322	910 ± 205	837 ± 204	822 ± 201
Control group	1,993 ± 407‡	2,020 ± 435‡	1,992 ± 387‡	1,990 ± 418‡	2,001 ± 411‡	1,988 ± 422‡
All-cause death						
PADN group	—	0	0	0	1 (7.6)	1 (7.6)
Control group	—	0	0	0	1 (12.5)	1 (12.5)
Rehospitalization						
PADN group	—	0	0	0	0	0
Control group	—	0	5 (62.5)§	5 (62.5)§	5 (62.5)§	5 (62.5)§
Lung transplantation						
PADN group	—	0	0	0	0	0
Control group	—	0	0	0	0	0

Values are mean ± SD or n (%). *$p < 0.010$, compared with before PADN. †$p < 0.010$, compared with following PADN. ‡$p < 0.001$, compared with following PADN. §$p < 0.001$, compared with following PADN.
6 MWD = 6-min walk distance; BORG = BORG dyspnea scoring; NT-BNP = N-terminal brain natriuretic peptide; PADN = pulmonary artery denervation; WHO = World Health Organization.

lady with IPAH was first treated with bosentan for 3 months. Bosentan was stopped because of severe liver damage, then diuretics and sildenafil were prescribed for 2.2 years. This patient went for the PADN procedure and after the procedure, the mean PAP was reduced from 59 mm Hg at baseline to 23 mm Hg at 2 months follow-up. Her 6MWT increased from 134 m before, to 245 m post-PADN procedure. At 87 days after the PADN procedure, this patient developed fever and severe fatigue. Her white blood cells increased to 2.2×10^9/l. During 8-h treatment at the local hospital, a total of 2,000 ml of saline was infused, without an increase in blood pressure (systolic blood pressure was between 70 and 78 mm Hg). Immediately after being transferred to our hospital, the blood lactate level was 24.6 mmol/l, and the patient was completely cyanotic. The mean PAP by right heart catheterization was stable between 25 and 28 mm Hg. The patient died after 4 h of treatment. Another patient from the control group died from RV failure at 72 days.

Discussion

We report for the first time, to our knowledge, the safety and benefit of PADN in the treatment of IPAH. The major finding is that PADN is safe and associated with significant hemodynamic improvements, resulting in a significant increase in functional capacity.

Up to the present time, the treatment for IPAH has been directed at restoring the balance between vasodilation (e.g., prostacyclin, nitric oxide, and vasoactive intestinal peptide) and vasoconstriction (e.g., thromboxane A2, endothelin, and serotonin), growth inhibitors, mitogenic factors, and antithrombotic and prothrombotic factors (1,2). Recently, several classes of drugs have been developed. These medications have been reported to be associated with mild-to-moderate improvements in clinical symptoms, functional capacity, hemodynamics, and clinical outcomes (18–21), suggesting that diverse pathological pathways contribute to the progression of PAH and that more effective therapy is needed. However, the severe side effects are the more common reasons limiting the use of these medications.

Mechanisms of PADN. Anatomic and pathological studies have revealed marked hypertrophy of the muscular layer of the PA in patients with PAH, suggesting active vasoconstriction (1,2,22). Moreover, baroreceptor structures have been described in the PA (4,5), but the controversies regarding the

types of the afferent and efferent fibers have existed for a long time (4,5,23). Circulating catecholamine levels in PAH have been reported to be either increased (24,25) or to remain within normal limits (26,27). This discrepancy may be related to the fact that pressure overload–induced failing RV in PAH subjects via local mechanisms (28). This postulation was verified by Velez-Roa et al. (29), who reported increased sympathetic nerve traffic in advanced PAH, a finding that was further confirmed by Wensel et al. (30). Furthermore, Juratsch et al. (5) reported that the significantly increased PAP and PVR induced by balloon distension of the MPA were completely abolished by surgical denervation of the bifurcation of the MPA and chemical sympathectomy using 6-hydroxydopamine (a known mediator of adrenergic nerves). These results suggested that the efferent limb of this reflex is predominantly mediated via the adrenergic nervous system.

Before our present study in humans, the dynamic change of PA hemodynamic measurements was investigated in our animal laboratory (7). The results showed that during occlusion of left interlobar PA, PAP and PVR gradually increased and reached peak values after 5 min, and that this pressure response was completely abolished after PADN at the MPA bifurcation level rather than at sites 5 mm distal to the ostial. In this animal study, we also found that it was somewhat difficult to keep the tip of the conventional ablation catheter in tight and constant contact with the PA wall because of the movement of the PA with inspiration and expiration. So we designed a dedicated PADN catheter with a circular tip and appropriate diameter in order to improve the stability and the constant contact with the PA wall. With better and more reliable equipment, we performed this first-in-man study. The results showed that PADN performance at the bifurcation area of the MPA was associated with significant reduction of PAP and PVR, and significant improvement of 6MWT. This finding might raise concerns about the conventional pathogenesis of PAH, and might suggest the effectiveness of PADN for IPAH patients with unsatisfactory clinical response to medication, a similar new understanding on the effect of renal denervation for treatment of refractory hypertension (31).

Comparison with drug therapy. More than 25 randomized control trials with >3,200 patients with PAH (IPAH, associated PAH, chronic thromboembolic pulmonary hypertension, and others) have been performed to test the effects of a variety of drugs (32). The average improvement of functional capacity as assessed using the 6MWT was 35.61 m, with a range of −10 to +108 m. This increase appeared to be an improvement of approximately 10.8%, which was significantly lower than the 29% (absolute increase of 101 m) observed in our study. Hemodynamic parameters were also investigated in randomized control trials with drugs. The weighted mean reduction in the mean PAP was −2.86 mm Hg, with a range of −1.00 to −9.30 mm Hg. The weighted mean reduction in the PVR was −520 dyne · s · cm^{-5}. These values are significantly different from the −13 mm Hg and −822 dyne · s · cm^{-5} improvements that were observed following PADN. On the other hand, current medications had several limitations for treatment of PAH, such as high cost, severe side effects, complex intravenous or subcutaneous injection setup, and unpredictable long-term effects. One special finding of our study was that all medications (sildenafil or bosentan) were discontinued safely for all patients except for 1 who continued to receive a diuretic after PADN. This might imply that there is a "pure" effect of PADN itself on improvements in cardiac function, hemodynamic measurements, and functional capacity. Of course, the toxic effect of medications prescribed before the enrollment could not be excluded.

Clinical relevance. NT-BNP, the precursor of BNP, may be a more sensitive measure of RV strain than BNP (32). NT-BNP levels <1,400 pg/ml (33,34) indicate the worse stage at which the PAH patients were, as in our study, unresponsive to medications. The results from the current study suggested that local sympathetic nerve activity modulates PAH, and (PADN) by inducing local injury or damage of this reflex arc localizing in the bifurcation area of the MPA was associated with significant reduction of PAP and PVR, which led to improvement of cardiac function and functional capacity. On the other hand, although there are no PA perforation in this report, the danger and the possibility of aneurysm formation should be kept in mind. Thus, a learning curve is critical in order to maintain the safety of the PADN procedure. Furthermore, taking hemodynamics and functional capacity into consideration, the benefit of the PADN procedure for IPAH patients seems to become stable after 3 months follow-up. Extended follow-up was required to assess long-term improvement. Similar to all kinds of catheter-based procedures, the PADN is possible to be repeat performed. Finally, the improvement of PA compliance might indicate the possibility of a change of pathological features in distal PA segments, 1 of the main lesions in IPAH patients (35).

Study limitations. Given the small numbers, possible bias in patient selection and the fact that this is not a placebo-controlled double-blind study, the discussion should be further moderated to indicate that much more study is required before this therapy can even be considered for treating PAH. Although the results are promising and intriguing, only carefully designed trials with controls and appropriate blinding must be done in a much larger cohort and at multiple centers before definitive conclusions about efficacy can be determined.

Conclusions

We report the effect of PADN on hemodynamics and functional capacity in patients with PAH. Future studies are needed in a randomized, multicenter setting with a larger patient population, to confirm these preliminary findings.

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REFERENCES

1. Rubin LJ. Primary pulmonary hypertension. N Engl J Med 1997;336:111–7.
2. Galie N, Manes A, Negro L, et al. A meta-analysis of randomized controlled trials in pulmonary arterial hypertension. Eur Heart J 2009;30:394–403.
3. Hoeper MM, Barberia JA, Channick RN, et al. Diagnosis, assessment, and treatment of non-pulmonary arterial hypertension pulmonary hypertension. J Am Coll Cardiol 2009;54:S85–96.
4. Osorio J, Russek M. Reflex changes on the pulmonary and systemic pressures elicited by stimulation of baroreceptors in the pulmonary artery. Circ Res 1962;10:664–7.
5. Juratsch CE, Jengo JA, Castagna J, Laks MM. Experimental pulmonary hypertension produced by surgical and chemical denervation of the pulmonary vasculature. Chest 1980;77:525–30.
6. Baylen BG, Emmanouilides GC, Juratsch CE, Yoshida Y, et al. Main pulmonary artery distention: a potential mechanism for acute pulmonary hypertension in the human newborn infant. J Pediatr 1980;96:540–4.
7. Chen SL, Zhang YJ, Zhou L, et al. Percutaneous pulmonary artery denervation completely abolishes experimental pulmonary arterial hypertension in vivo. EuroIntervention 2013;9:269–76.
8. Tonelli AR, Mubarak KK, Mathai SC. Pulmonary vasodilator testing and use of calcium channel blockers in pulmonary arterial hypertension. Respir Med 2010;104:481–96.
9. Badesch DB, Champion HC, Sanchez MA, et al. Diagnosis and assessment of pulmonary arterial hypertension. J Am Coll Cardiol 2009;54:S55–66.
10. Borg GA. Psychophysical bases of perceived exertion. Med Sci Sports Exerc 1982;14:377–81.
11. Rubin LJ, American College of Chest Physicians. Diagnosis and management of pulmonary arterial hypertension: ACCP evidence-based clinical practice guidelines. Chest 2004;126 Suppl:7S–10S.
12. Lang RM, Bierig M, Deverus RB, et al. Recommendations for chamber quantification: a report from the American Society of Echocardiography's Guidelines and Standards Committee and the Chamber Quantification Writing Group. J Am Soc Echocardiogr 2005;18:1440–63.
13. Ommen SR, Nishimura RA, Hurrell DG, Klarich KW. Assessment of right atrial pressure with 2-dimensional and Doppler echocardiography: a simultaneous catheterization and cardiographic study. Mayo Clin Proc 2000;75:24–9.
14. Tei C, Nishmura RA, Seward JB, Tajik AJ. Noninvasive Doppler-derived myocardial performance index: correlation with simultaneous measurement of cardiac catheterization measurements. J Am Soc Echocardiogr 1997;10:169–78.
15. Galie N, Hoeper MM, Humbert M, et al. Guidelines for the diagnosis and treatment of pulmonary hypertension: the Task Force for the Diagnosis and Treatment of Pulmonary Hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS). Eur Heart J 2009;30:2493–537.
16. Task Force for Diagnosis and Treatment of Pulmonary Hypertension of European Society of Cardiology (ESC); European Respiratory Society (ERS); International Society of Heart and Lung Transplantation (ISHLT), Galie N, Hoeper MM, Humbert M, et al. Guidelines for the diagnosis and treatment of pulmonary hypertension. Eur Respir J 2009;34:1219–63.
17. Tonelli AR, Mubarak KK, Li N, et al. Effect of balloon inflation volume on pulmonary artery occlusion pressure in patients with and without pulmonary hypertension. Chest 2011;139:115–21.
18. Anderson JR, Nawarskas JJ. Pharmacotherapeutic management of pulmonary arterial hypertension. Cardiol Rev 2010;18:148–62.
19. Rich S. The value of approved therapies for pulmonary arterial hypertension. Am Heart J 2007;153:889–90.
20. Farber HW. The status of pulmonary arterial hypertension in 2008. Circulation 2008;117:2966–8.
21. Ghofrani HA, Wilkins MW, Rich S. Uncertainties in the diagnosis and treatment of pulmonary arterial hypertension. Circulation 2008;118:1195–201.
22. Rushmer R. Cardiac Diagnosis: Physiological Approach. Philadelphia, PA: W. B. Saunders Co; 1955:49.
23. Coleridge JC, Kidd C. Electrophysiological evidences of baroreceptors in the pulmonary artery of the dog. J Physiol 1960;150:319–23.
24. Haneda T, Nakajima T, Shirato K, et al. Effects of oxygen breathing on pulmonary vascular input impedance in patients with pulmonary hypertension. Chest 1983;83:520–7.
25. Nagaya N, Nishikimi T, Uematsu M, et al. Plasma brain natriuretic peptide as a prognostic indicator in patients with primary pulmonary hypertension. Circulation 2000;102:865–70.
26. Richards AM, Ikram H, Crozier IG, et al. Ambulatory pulmonary arterial pressure in primary pulmonary hypertension: variability, relation to systemic arterial pressure, and plasma catecholamines. Br Heart J 1990;63:103–8.
27. Nootens M, Kaufmann E, Rector T, et al. Neurohormonal activation in patients with right ventricular failure from pulmonary hypertension: relation to hemodynamic variables and endothelin levels. J Am Coll Cardiol 1995;26:1581–5.
28. Bristow MR, Minobe W, Rasmussen R, et al. β-adrenergic neuroeffector abnormalities in the failing human heart are produced by local rather than systemic mechanisms. J Clin Invest 1992;89:803–15.
29. Velez-Roa S, Ciarka A, Najem B, et al. Increased sympathetic nerve activity in pulmonary artery hypertension. Circulation 2004;110:1308–12.
30. Wensel R, Jilek C, Dorr M, et al. Impaired cardiac autonomic control relates to disease severity in pulmonary hypertension. Eur Respir J 2009;34:895–901.
31. Esler MC, Krum H, Sobotka PA, et al. Renal sympathetic denervation in patients with treatment-resistant hypertension (the Symplicity HTN-2 trial): a randomized control trial. Lancet 2012;376:1903–9.
32. Leuchte HH, El Nounou M, Tuerpe JC, et al. N-terminal pro-brain natriuretic peptide and renal insufficiency as predictors of mortality in pulmonary hypertension. Chest 2007;131:402–9.
33. Fijalkowska A, Kurzyna M, Torbicki A, et al. Serum N-terminal brain natriuretic peptide as a prognostic parameter in patients with pulmonary hypertension. Chest 2006;129:1313–21.
34. Frantz RP, Robbins IM, Durst LA, et al. Endothelin-1 and BNP plasma levels predict survival in patients with pulmonary arterial hypertension. Am J Respir Crit Care Med 2008;177:A535.
35. Galiè N, Palazzini M, Leci E, Manes A. Current therapeutic approaches to pulmonary arterial hypertension. Rev Esp Cardiol 2010;63:708–24.

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