Pericardial effusion is correlated with clinical outcome after pulmonary artery denervation for pulmonary arterial hypertension

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Keywords: pulmonary arterial hypertension, pericardial effusion, pulmonary artery denervation, clinical worse event, rehospitalization

Received: October 04, 2016 Accepted: November 23, 2016 Published: December 20, 2016

ABSTRACT

Objectives: Pericardial effusion (PE) is correlated with outcomes in patients with pulmonary arterial hypertension (PAH). Pulmonary artery denervation (PADN) was used for treatment of PAH. The present study aimed to analyze the prognostic value of PE for outcomes after PADN in patients with WHO Group I, Group II and Group IV PAH.

Results: PE, frequently seen in patients with connective tissue disease, was featured by fast heart rate, decreased exercise capacity, more syncope, worsening pulmonary arterial hemodynamic and right atrium size. PADN procedure resulted in dramatic reduction of PE. After a median of 376 days follow-up, the rate of PAH-related event, all-cause death and rehospitalization increased over the PE amount and occurred in 29.8%, 19.7% and 25.2% of patients with PE, different to 3.4%, 3.4% and 6.8% of patients without PE (p = 0.034, p = 0.041 and p = 0.039, respectively). The reduction of PE during follow-up was similar among three groups.

Materials and methods: Between March 2012 and July 2014, a total of 66 consecutive patients (52 ± 16 years) who underwent PADN were stratified by no PE (n = 20), PE < 10 mm (n = 29) and PE ≥ 10 mm (n = 17) according to baseline echocardiograph. Dynamic change of PE and its correlation with PAH-related event after PADN were measured.

Conclusions: PE is associated with increased PAH-related event after PADN. PADN results in significant similar reduction of PE among patients with Group I, Group II and Group IV PAH.

INTRODUCTION

Pulmonary artery hypertension (PAH) is a debilitating condition, resulting in dyspnea and fatigue, impaired exercise capacity, and reduced survival [1]. When PAH develops, right ventricular (RV) and right atrial pressure (RAP) increased progressively, the fluid reabsorption of pericardial fluid via the venous or lymphatic channels draining into the right atrium is damaged, [2–6] leading to pericardial effusion (PE). The prevalence of PE varies from 21% to 29%, and higher in patients with connective tissue disease (CTD) [4, 6]. Pericardial fluid accumulation masks the echocardiographic findings of cardiac tamponade [6] and impairs the ventricular diastolic filling, which carries an additional risk to patients with PAH, [4, 6] particularly in PAH due to CTD [7]. As a result, PE in PAH is an indicator of right heart failure and poor prognosis.

Our group recently, reported the actual experimental [8] and short-term clinical results of pulmonary artery denervation (PADN) via significant reductions in pulmonary arterial pressure (PAP) and PE size, and improvement of 6MWD at 3-month follow-up in patients with idiopathic PAH who were unresponsive to medication [9]. We also found that the presence of PE was associated
with less reduction of PAP [9]. However, the correlation of PE with outcomes after PADN remained to be unclear. Accordingly, the present study aimed to analyze the dynamic change of PE and its predictive value for clinical outcomes in consecutive patients with idiopathic or secondary PAH or secondary PH from left ventricular dysfunction [LVD] who underwent PADN procedure.

RESULTS

Patient population

A total of 70 patients with qualifying PAH/PH were screened for this study. Four patients were excluded: 2 patients could not lie flat for 20 minutes, 1 died on the ward after consent while waiting for the procedure, and 1 died from temporary pacing catheter-induced RV perforation before the PADN procedure. The study population thus consisted of 66 patients for whom a PADN procedure was attempted: 21 idiopathic PAHs; 19 PHs due to LVD (16 due to prior myocardial infarction and 3 dilated cardiomyopathy); 10 CTDs (6 with systemic lupus erythematosus, 2 with mixed connective tissue disease and 2 with primary Sjogren’s syndrome); 9 CTEs; and CHDSR in 8 patients (5 patients with atrial septal defect and 3 patients with patent ductus arteriosus which were repaired surgically). Finally, there were 39 patients in WHO Group I, 19 in Group II and 9 in Group IV according to WHO classification.

Baseline clinical characteristics

Compared to patients without PE, those with PE had more CTD (24.3% vs. 3.4%, \( p = 0.038 \), Table 1). Increased heart rate and WHO functional class 3–4, presentation of syncope, and decrease of 6MWD demonstrated a stepwise fashion across increasing baseline PE amount. Particularly, more prostacyclin analogues were used in overall patients (68.2%) based on non-PAH expert.

Measurements by echocardiograph and right heart catheterization

Moderate to severe PE was associated with higher PAP, RAP, RVP, PVR, Tei index, and lower CO (Table 2), compared to no or mild PE. Notably, RA area increased in a stepwise fashion across increasing the amount of PE (\( p < 0.001 \), Table 2).

As shown in Table 3, a greater mean absolute reduction of mPAP and sPAP just post-PADN was achieved in patients without PE (−12.1 mmHg and −12.3 mmHg), when compared to patients with PE ≥ 1 cm (−4.0 mmHg and −6.3 mmHg) and patients with PE < 1 cm (−4.3 mmHg and −8.8 mmHg, \( p = 0.017 \) and \( p = 0.023 \), respectively). After 24 h post-PADN, the reduction of sPAP and mPAP was comparable between three groups, a finding in consistent with the dynamic change of pericardial fluid amount (Figure 1): less reduction just post-PADN, almost 50% reduction at 24 h after PADN treatment (\( p < 0.001 \)). Since then, gradual absorption of PE over the time was associated with greater reduction of sPAP and mPAP in patients with PE (Table 3). The reduction of PE in the Group I seemed to be great but non-significant to that in Group II and Group IV (Figure 1), leading to similar improvement of hemodynamic between groups (data not showed here).

Of 37 patients with PE, complete disappearance of PE at the end of follow-up was seen in 4 patients; PE increased to near baseline level in 3 patients who had significantly reduced PE at 3 month after PADN, these 3 patients died thereafter. Of 29 patients without PE, newly appearance of PE was seen in 1 patient.

Morbidity and mortality

Median (interquartile range) follow-up was 376(307–999) days. As shown in Table 4 and Figure 2, PAH-related adverse events occurred in 10 (15.2%) patients during follow-up, including 1 patient without PE, 3 mild PE and 6 moderate/severe PE (3.3% vs. 15.0% vs. 35.3%, \( p = 0.008 \), Figure 2A). Most events occurred within one-year. There was no procedure-related complication.

All-cause mortality occurred in 8 patients (12.1%) during follow-up, with a significant different rate in those without PE (3.4%), with mild PE (10%) and with moderate to severe PE (29.4%, \( p = 0.032 \), Figure 2B). The rate of PAH-related event was comparable between patients with Group I, Group II and Group IV PAH (Data not showed here). Similarly, patients with PE had increased rate of the worsening of PAH (Figure 2C).

Univariate analysis

As shown in Table 5, univariate analysis showed that patients who had PAH-related event or all-cause death had increased PAP and systolic RVP, and RAP estimated by echo, more pericardial fluid, and decreased 6MWD.

DISCUSSION

The current study for the first time reports the correlation of baseline pericardial effusion with clinical outcome after PADN in patients with different etiologies of PAH. The major findings are: (1) the presence of PE is the mark of the severity of PAH; (2) PADN led to significant reduction of PE, with subsequent less PAH-related event, all-cause death and worsening of PAH.

Mechanism of PE in PAH

The echocardiographic factors that adversely affect prognosis in PAH are RV dysfunction and the presence of PE [2, 3]. When PAH develops, a higher RAP that
limits the drainage of pericardial veins into the RA. On the other hand, inflammatory conditions, such as systemic lupus erythematosus and scleroderma, can independently affect the pericardium and lead to PE, [4, 6] in line with our finding that more patients with PE had CTD. Previous studies [2–6] have clearly showed that the presence or persistence of PE in PAH despite vasoactive therapy predicted worse outcomes, a result further supported by our finding that patients with PE had increased worse clinical events after PADN. Given the prognostic value of PE, the absence or resolution of PE with novel therapy should have suggested better prognosis [6].

| Table 1: Baseline clinical variables in all patients | Overall (n = 66) | No effusion (n = 29) | Effusion < 1 cm (n = 20) | Effusion ≥ 1 cm (n = 17) | P value trends |
|----------------|---------------|-------------------|------------------------|------------------------|---------------|
| Age, yr | 51.7 ± 15.7 | 50.3 ± 16.9 | 56.7 ± 12.3 | 48.3 ± 16.7 | 0.674 |
| Female, n (%) | 39(59.1) | 19(65.5) | 12(60.0) | 8(47.1) | 0.451 |
| Height, cm | 163.8 ± 7.9 | 162.9 ± 7.9 | 162.8 ± 8.5 | 166.6 ± 7.1 | 0.240 |
| Weight, kg | 60.6 ± 10.9 | 60.9 ± 10.4 | 58.6 ± 10.3 | 62.5 ± 12.8 | 0.552 |
| Blood pressure, mmHg | | | | | |
| Systolic | 125.6 ± 15.7 | 125.4 ± 13.6 | 126.7 ± 18.2 | 124.8 ± 16.7 | 0.933 |
| Diastolic | 81.3 ± 12.1 | 79.9 ± 8.6 | 80.5 ± 12.9 | 84.4 ± 15.9 | 0.463 |
| Heart rate, bpm | 77.7 ± 13.7 | 73.5 ± 12.5 | 78.5 ± 12.8 | 83.9 ± 15.0 | 0.041 |
| NT-pro BNP, pg/ml | 2206 ± 2257 | 1949 ± 3194 | 1751 ± 1838 | 3237 ± 3219 | 0.237 |
| Borg Index, scores | | | | | |
| Class stratification, n (%) | | | | | |
| ≤ Class 3 | 53(80.3) | 24(82.8) | 15(75.0) | 14(82.4) | 0.531 |
| Class 4–5 | 13(19.7) | 5(17.2) | 5(25.0) | 3(17.6) | 0.910 |
| WHO functional class, points | | | | | |
| Class stratification, n (%) | | | | | |
| Class 1–2 | 23(34.8) | 12(41.4) | 5(25.0) | 6(35.3) | 0.146 |
| Class 3–4 | 43(65.2) | 17(58.6) | 15(75.0) | 11(63.7) | 0.012 |
| 6-minute walk distance, m | 357.6 ± 117.9 | 389.3 ± 119.8 | 354.3 ± 118.3 | 307.2 ± 101.6 | 0.022 |
| Etiologies, n (%) | | | | | |
| Idiopathic PAH | 21(31.8) | 9(31.0) | 3(15.0) | 9(52.9) | 0.076 |
| Connective tissue disease | 10(15.2) | 1(3.4) | 5(25.0) | 4(23.5) | 0.038 |
| CHD surgical repair | 8(12.1) | 5(17.2) | 2(10.0) | 1(5.9) | 0.492 |
| Left heart dysfunction | 19(28.8) | 10(34.5) | 6(30.0) | 3(17.6) | 0.472 |
| CTEPH | 9(13.6) | 3(10.3) | 5(25.0) | 1(5.9) | 0.189 |
| Time to diagnosis of PAH, yr | 3.80 ± 0.65 | 4.31 ± 1.14 | 3.42 ± 1.28 | 3.38 ± 0.67 | 0.791 |
| Presentation at enrollment, n (%) | | | | | |
| Syncope | 14(21.2) | 1(3.4) | 4(20.0) | 9(52.9) | < 0.001 |
| Fatigue | 62(93.9) | 27(93.1) | 18(90.0) | 16(94.1) | 0.880 |
| Chest pain | 14(21.2) | 6(20.7) | 4(23.5) | 4(23.5) | 0.892 |
| Dyspnea | 65(98.5) | 28(96.6) | 20(100.0) | 17(100.0) | 0.877 |
| Medication before PADN, n (%) | | | | | |
| Calcium channel antagonist | 7(10.6) | 4(13.8) | 2(10.0) | 1(5.9) | 0.698 |
| ERA | 14(21.2) | 6(20.7) | 4(20.0) | 4(23.5) | 0.860 |
| Prostacyclin | 45(68.2) | 20(69.0) | 11(55.0) | 14(82.4) | 0.274 |
| 5′-PDE | 4(6.1) | 1(3.4) | 1(5.0) | 2(11.8) | 0.337 |
| Diuretics | 48(72.7) | 19(65.5) | 15(75.0) | 14(82.4) | 0.174 |
| Digoxin | 22(33.3) | 10(34.5) | 6(30.0) | 6(35.3) | 0.925 |

NT, N-terminal; BNP, brain natriuretic peptide; PAH, pulmonary arterial hypertension; CHD, congenital heart disease; CTEPH, chronic thromboembolic pulmonary hypertension; ERA, endothelin receptor antagonist; 5′-PDE, phosphodiesterase type-5 inhibitors
### Table 2: Measurements by cardiac echo and right heart catheterization in all patients

|                     | Overall \((n = 66)\) | No effusion \((n = 29)\) | Effusion < 1 cm \((n = 20)\) | Effusion ≥ 1 cm \((n = 17)\) | P value trends |
|---------------------|----------------------|--------------------------|-------------------------------|-------------------------------|---------------|
| **Echocardiographic measurements** |                       |                          |                               |                               |               |
| LADs, mm            | 41.9 ± 8.9           | 40.3 ± 7.6               | 44.9 ± 9.2                    | 40.9 ± 10.2                   | 0.188         |
| LVDD, mm            | 44.6 ± 12.2          | 46.1 ± 12.4              | 44.6 ± 10.1                   | 42.0 ± 14.2                   | 0.543         |
| LVDs, mm            | 29.9 ± 12.5          | 31.4 ± 13.3              | 29.7 ± 9.1                    | 27.5 ± 14.7                   | 0.606         |
| LVEF, %             | 62.5 ± 12.3          | 61.5 ± 14.6              | 62.2 ± 8.2                    | 64.8 ± 12.5                   | 0.672         |
| Systolic PA pressure, mmHg | 92.8 ± 30.8         | 85.5 ± 34.8              | 88.7 ± 22.3                   | 110.0 ± 26.7                  | 0.023         |
| Mean PA pressure, mmHg | 42.3 ± 15.9         | 45.3 ± 16.4              | 39.1 ± 12.9                   | 40.8 ± 13.2                   | 0.531         |
| Systolic RV pressure, mmHg | 91.8 ± 30.5         | 83.9 ± 33.4              | 87.7 ± 22.8                   | 110.0 ± 26.6                  | 0.013         |
| Mean RA pressure, mmHg | 12.0 ± 6.4          | 10.3 ± 3.5               | 11.9 ± 3.6                    | 15.0 ± 5.4                    | 0.018         |
| RA diameter, mm     | Long-axis            | 58.6 ± 11.2              | 53.2 ± 9.7                    | 61.1 ± 11.6                   | 0.001         |
|                     | Short-axis           | 49.3 ± 10.6              | 44.1 ± 7.9                    | 51.6 ± 9.8                    | 0.001         |
|                     | RA area, cm²         | 23.4 ± 9.1               | 18.8 ± 6.0                    | 25.4 ± 9.2                    | < 0.001       |
|                     | Pericardial fluid    | 2.75 ± 3.39              | 0                             | 5.49 ± 1.29                   | < 0.001       |
|                     | Tei                  | 0.63 ± 0.15              | 0.59 ± 0.16                   | 0.62 ± 0.15                   | 0.039         |
| **Measurements by RHC** |                       |                          |                               |                               |               |
| Systolic PA pressure, mmHg | 87.9 ± 29.8         | 85.4 ± 35.4              | 88.5 ± 17.9                   | 103.5 ± 25.2                  | 0.029         |
| Mean PA pressure, mmHg | 53.1 ± 19.1         | 51.7 ± 22.4              | 57.8 ± 11.6                   | 61.8 ± 17.7                   | 0.039         |
| PCWP, mmHg          | 14.8 ± 11.5          | 15.6 ± 12.7              | 13.1 ± 9.0                    | 15.4 ± 12.5                   | 0.736         |
| Mean RA pressure, mmHg | 12.6 ± 7.2          | 11.5 ± 7.9               | 11.8 ± 6.2                    | 16.5 ± 5.8                    | 0.031         |
| Systolic RV pressure, mmHg | 86.3 ± 29.0         | 82.8 ± 35.3              | 84.5 ± 17.6                   | 97.8 ± 26.1                   | 0.033         |
| PVR, Wood Units     | 13.8 ± 8.6           | 12.8 ± 6.8               | 13.3 ± 7.5                    | 18.6 ± 12.4                   | 0.036         |
| Cardiac output, L/min| 3.26 ± 1.25          | 3.26 ± 1.32              | 3.21 ± 1.15                   | 2.66 ± 1.23                   | 0.042         |

LADs, left atrial diameter at end-systole; LVDD, left ventricular diameter at end-diastole; LVDs, left ventricular diameter at end-systole; LVEF, left ventricular ejection fraction; PA, pulmonary artery; RV, right ventricular; RA, right atrial; PCWP, pulmonary capillary wedge pressure; PVR, pulmonary vessel resistance.

### Table 3: Dynamic change of hemodynamic parameters measured by right catheterization

|                     | Overall \((n = 66)\) | No effusion < 1 cm \((n = 29)\) | Effusion ≥ 1 cm \((n = 17)\) | P value trends |
|---------------------|----------------------|----------------------------------|-------------------------------|---------------|
| **Reduction of systolic PAP** |                       |                                  |                               |               |
| Post-PADN Absolute value, mmHg | −8 ± 10             | −12.3 ± 13.6                     | −8.8 ± 11.4                   | −6.3 ± 8.0     | 0.023         |
| Percentage, %      | −11 ± 12             | −14.8 ± 13.5                     | −10.8 ± 10.2                  | −6.2 ± 7.5     | 0.036         |
| 24 h Absolute value, mmHg | −9.6 ± 13           | −12.4 ± 18.2                    | −10.2 ± 12.7                  | −8.7 ± 11.4    | 0.070         |
| Percentage, %      | −11 ± 16             | −13.5 ± 15.8                    | −11.4 ± 18.7                  | −10.9 ± 13.5   | 0.993         |
| **End of follow-up** | Absolute value, mmHg | −17.9 ± 14.5                    | −13.5 ± 9.1                   | −18.8 ± 16.1   | 0.242         |
| Percentage, %      | −20.4 ± 13.9         | −14.6 ± 16.3                    | −20.1 ± 21.2*                 | −22.8 ± 23.1*  | 0.563         |
| **Reduction of mean PAP** |                       |                                  |                               |               |
| Post-PADN Absolute value, mmHg | −5 ± 11             | −12.1 ± 12.5                    | −4.3 ± 5.7                    | −4.0 ± 5.1     | 0.017         |
| Percentage, %      | −12 ± 19             | −22.7 ± 20.2                    | −7.7 ± 12.0                   | −6.5 ± 18.8    | 0.006         |
| 24 h Absolute value, mmHg | −6.6 ± 10           | −9.3 ± 13.1                     | −6.8 ± 7.9                    | −4.8 ± 6.4     | 0.052         |
| Percentage, %      | −13 ± 18             | −19.5 ± 21.6                    | −12.5 ± 12.4                  | −7.7 ± 17.3    | 0.048         |
| **End of follow-up** | Absolute value, mmHg | −10.5 ± 8.5                     | −9.4 ± 8.8                    | −11.6 ± 8.7    | 0.657         |
| Percentage, %      | −19.3 ± 20.6         | −19.7 ± 14.4                    | −20.3 ± 21.6*                 | −19.1 ± 20.4*  | 0.218         |

*p < 0.01, compared to the percentage of reduction post-PADN.

PAP, pulmonary arterial pressure; PADN, pulmonary artery denervation.
Sympathetic nerves, PE and PADN

The causality of PE and sympathetic nervous activity in the setting of PAH remains to be unknown. In general, the over activation of sympathetic nerves was evidenced by increased circulating catecholamine levels, [10, 11] abnormally high muscle sympathetic nerve activity (MSNA) [12, 13] and impaired heart rate variability [14]. PA is innervated by complex network of sympathetic nerves [15, 16] but its distribution in human body is under studied. Our unpublished experimental study showed that main trunk of sympathetic nerves was close to and paralleled to main stem of PA, an anatomic feature favors the performance of percutaneous intraluminal intervention [9].

Our finding that > 10% reduction of PAP on-treatment could be explained by the inhibitory effect of PADN on vessel constriction induced by overactivated sympathetic nerves, as PADN-induced sympathetic nerves injury could abolish the increase of PAP in an acute PH model resulted from balloon-distention.8 Furthermore, the reduction of PAP in a stepwise fashion across the crossing the baseline amount of PE implied the complicated interplay between PE and PAP. Taking together, overactivated sympathetic nerves activity played a critical role in maintaining the vicious circle involving RV failure, increased PAP and RAP, and accumulation of pericardial fluid.

Risk models for patients with PAH treated by medications have been established [7, 17]. The present univariate analysis showed that PAP, estimated RAP by medications have been established [7, 17]. The present univariate analysis showed that PAP, estimated RAP by

Table 4: Clinical outcomes during follow-up

| Follow-up (d, median [IQR]) | Overall (n = 66) | No effusion (n = 29) | Effusion < 1 cm (n = 20) | Effusion ≥ 1 cm (n = 17) | P value | trends |
|----------------------------|-----------------|---------------------|-------------------------|--------------------------|---------|--------|
| PAH-related events, n (%)  |                 |                     |                         |                          |         |        |
| Death                      | 10 (15.2)       | 1 (3.4)             | 3 (15.0)                | 6 (35.3)                 | 0.015   |        |
| Atrial septostomy          | 6 (9.1)         | 0                   | 2 (10.0)                | 4 (23.3)                 | 0.044   |        |
| In list for lung transplant| 2 (3.0)         | 0                   | 0                       | 2 (11.8)                 | 0.051   |        |
| Needing IV or SQ drugs     | 6 (9.1)         | 0                   | 1 (5.0)                 | 5 (29.4)                 | 0.003   |        |
| Worsening of PAH           | 8 (12.1)        | 1 (3.4)             | 2 (10.0)                | 5 (29.4)                 | 0.032   |        |
| 6MWD decline by > 15%      | 8 (12.1)        | 1 (3.4)             | 2 (10.0)                | 5 (29.4)                 | 0.032   |        |
| Worsening of symptoms*     | 8 (12.1)        | 1 (3.4)             | 2 (10.0)                | 5 (29.4)                 | 0.032   |        |
| Additional treatments      | 14 (21.2)       | 3 (10.3)            | 4 (20.0)                | 7 (41.2)                 | 0.047   |        |
| All-cause death, n (%)     | 8 (12.1)        | 1 (3.4)             | 2 (10.0)                | 5 (29.4)                 | 0.032   |        |
| Rehospitalization, n (%)   | 11 (16.7)       | 2 (6.8)             | 3 (15.0)                | 6 (35.3)                 | 0.037   |        |

IQR, interquartile range; PAH, pulmonary arterial hypertension; IV, intravenous; SQ, subcutaneous; 6MWD, 6-minute walk distance.

*defined as a change from baseline to a higher WHO functional class (or no change in patients who were in WHO functional class IV at baseline) plus the appearance or worsening signs of right heart failure not response to oral diuretics therapy.

Table 5: Univariate analysis of the associations with PAH-related event and all-cause death

| Variables by RHC             | For PAH-related event | For All-cause death |
|------------------------------|-----------------------|---------------------|
|                              | 95% CI of difference  | P value             | 95% CI of difference | P value |
| Systolic PAP                 | −40.992 to −1.191     | 0.038               | −46.248 to −2.701    | 0.021   |
| Mean PAP                     | −29.241 to −4.261     | 0.009               | −32.629 to −5.281    | 0.007   |
| Mean RAP                     | −9.590 to −0.098      | 0.055               | −9.967 to 0.746      | 0.090   |
| Systolic RV pressure         | −40.084 to −1.348     | 0.036               | −44.218 to −1.689    | 0.035   |
| Variables by echo            |                       |                     |                     |         |
| Systolic RV pressure         | −46.079 to −6.042     | 0.012               | −52.111 to −8.398    | 0.007   |
| Systolic PAP                 | −43.748 to −2.787     | 0.027               | −49.542 to −4.777    | 0.018   |
| Mean RA pressure             | −8.912 to −0.445      | 0.031               | −10.137 to −0.889    | 0.020   |
| Pericardial effusion         | −7.198 to −1.456      | 0.004               | −7.453 to −1.057     | 0.001   |
| 6-minute walk distance       | 16.154 to 172.324     | 0.019               | 3.688 to 177.097     | 0.041   |

HRC, right heart catheterization; PAP, pulmonary arterial hypertension; RAP, right atrial pressure; RV, right ventricular
Figure 1: Dynamic change of pericardial effusion (PE). PADN was associated with significant reduction of PE in three groups classified by WHO definition.

Figure 2: Kaplan-Meier survival analysis. Patients with moderate and severe pericardial effusion had lower PAH-related event-free survival rate (A) and all-cause-free survival rate (B) and worsening of PAH (C).
echo, PE, and 6MWD correlated with PAH-related event and mortality after PADN, in line with previous studies using medication [18–21]. This could be at least partially explained by the greater reduction of PAP, with resultant resolution of PE, achieved by PADN procedure.

Limitations

Small patient size was the first limitation. However, our results provided stronger evidences showing the prognostic value of PE for outcomes after PADN. Next, our results came from a single-center, and bias could be excluded. As an emerging treatment for PAH, even though PADN was only performed in several global tertiary centers, our data was recorded from real patients underwent PADN procedures. Finally, we did not analyze the correlation of PE with already established risk model. However, our data clearly showed that size of PE was the only predictor of clinical outcome after PADN.

MATERIALS AND METHODS

Patient population

Between March 2012 and July 2014, patients with either idiopathic PAH or PH arising from chronic thromboemboli (CTE) after surgery, CTD, from congenital heart disease after surgical repair (CHDSR), or secondary from left ventricular dysfunction (LVD) were considered for possible treatment with PADN, if their resting mean PAP (mPAP) ≥ 25 mmHg (for all patients) and pulmonary vascular resistance (PVR) ≥ 3 Wood Units (for PH secondary from LVD) measured by right heart catheterization (RHC).

Exclusion criteria included active infection, cancer, toxin-or anorexia-induced PH, portal hypertension, CTEPH without surgical treatment, intolerable to PADN procedure and inability to provide consent. The study was approved by the Institutional Review Board and Ethics Committee of the Nanjing First Hospital (Nanjing, China), and all patients provided written inform consent.

RHC measurements

Resting RAP, RV pressure, PAP, pulmonary artery occlusion pressure (PAOP) or left ventricular end-diastolic pressure, [1, 22, 23] and cardiac output (CO) were obtained with a 7F flow-directed Swan-Ganz catheter. PVR ([mean PAP-PAOP]/CO) was then derived. All measurements were taken at end-expiration.

PADN procedure

PADN was performed using a dedicated 7-F temperature-sensing ablation catheter. The details of the device and PADN procedure have been previously described [8, 9]. Briefly, PADN was performed only in the peri-conjunctival area between the distal main trunk and ostial left branch.

Peri-procedural medication

Following the procedure, oral warfarin was prescribed and adjusted to an International Normalized Ratio (INR) of 1.5–2.5 for all patients. Aspirin (100 mg/d) and clopidogrel (75 mg/d) were indefinitely prescribed in the presence of contraindications for warfarin.

Assessment of functional capacity

Functional capacity was determined using a standard 6-minute walk distance (6MWD), [1] Borg scale, [24] and the World Health Organization (WHO) functional classification [1] by a physician blinded to the study design.

Echocardiographic measurements

Transthoracic echocardiography was performed and analyzed at the Nanjing Medical University Echocardiographic Laboratory. Measurements were performed according to American Society of Echocardiography guidelines. [25, 26] Digital echocardiographic data that contained a minimum of 3 consecutive beats (or 5 beats in cases of atrial fibrillation) were acquired and stored. Systolic RVP was set equal to systolic PAP (sPAP) in the absence of pulmonary stenosis. sPAP was calculated as the sum of RAP and the RV to RA pressure gradient during systole. RAP was estimated based on the echocardiographic features of the inferior vena cava and assigned a standard value. The RV to RA pressure gradient was calculated as 4 vt² using the modified Bernoulli equation. The mPAP was estimated according to the velocity of the pulmonary regurgitation jet in m/s. The tricuspid excision index (Tei) was defined as (A–B)/B, where A was the time interval between the end and the onset of tricuspid annular diastolic velocity, and B was the duration of tricuspid annular systolic velocity (or the RV ejection time) [26]. RA area was defined as πab, where a was the long semi-radius of RA, and b was the short semi-radius. [25, 26] Pericardial effusion severity was characterized as trace to small if the pericardial space separated by < 1 cm in diastole in any plane. Moderate or greater effusion was defined as pericardial space separation of ≥ 1 cm during diastole described previously [2].

Definitions

PAH-related clinical events, defined as those caused by worsening of PAH, initiation of treatment with intravenous or subcutaneous prostanoids, lung transplantation, atrial septostomy, or all-cause death. Worsening of PAH was defined as the occurrence of all three of the following: a decrease in 6MWD of ≥ 15% from baseline, confirmed by a second 6MWD performed on a different day within 14 days; worsening symptoms of PAH; and the need for additional treatment for PAH.
Worsening symptoms of PAH was defined as a change from baseline to a higher WHO functional class (or no change in patients who were in WHO functional class IV at baseline) plus the appearance or worsening signs of right heart failure not responsive to oral diuretic therapy. An independent clinical event committee adjudicated all deaths and reported events as to their relationship to PAH.

Statistical analysis

Continuous variables were expressed as mean ± SD. Normality was examined using Kolmogorov–Smirnov and Shapiro–Wilk tests. Differences in continuous variables between groups were analyzed using t test or Wilcoxon’s rank sum tests, as appropriate. Categorical variables were compared using Fisher’s exact test. Event-free survival was estimated using the Kaplan-Meier method and differences between groups compared with the log-rank test. Univariate analysis was performed to determine if pericardial fluid amount was the independent factor of clinical events. Statistical significance was defined as a two-sided P value < 0.05. All analyses were performed using SPSS 16.0 (SPSS Institute Inc., Chicago, Ill., USA)

CONCLUSIONS

The present study has demonstrated PE serves as a hallmark of severe progressive PAH. PADN results in significant absorption of PE with subsequent improvement of clinical outcomes. Multicenter randomized trials are warranted to determine the utility of PADN in high-risk patients with PAH.

CONFLICTS OF INTEREST

All authors have no commercial relationship with industry.

Authors’ contributions

CSL: conception and design of research. ZH, XDJ and ZL: performed right heart catheterization and follow-up. ZJ: performed cardiac echo. SGW: edited and revised manuscript. CSL, ZH, XDJ, ZJ, ZL, and SGW: approved final version of manuscript

FUNDING

This study was granted by National Natural Science Foundation of China (NSF 81270191 and NSF 91439118) and Jiangsu Provincial Special Program of Medical Science (BL2013001), Nanjing, Jiangsu, China.

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