D. 考察

膠原病に伴うPAHのさらなる予後改善にスクリーニングによる早期発見が有用であることは間違いない。しかし、膠原病患者におけるPAHの併発頻度は決して高くなく、今回の検討でもリウマチ性疾患が疑われた症例のわずか1.2%、膠原病の確定診断例に限っても1.5%に過ぎなかった。そのため、PAHスクリーニングを全ての膠原病患者で繰り返し実施することは現実的でなく、費用対効果や患者への侵襲度を考慮すると、その有用性について疑問を持たざるを得ない。欧米では、膠原病に伴うPAHの基礎疾患として70%以上を占めるSScに限定したスクリーニングを推奨しているのが現状である。

今回の検討でも、日本人におけるPAHの基礎疾患は既報と同様にSSc、MCTD、SLEの3疾患であった。この点はSScが大半を占める欧米と大きく異なり、日本独自のスクリーニングプログラムの立ち上げが必要で、対象をSScだけでなくMCTDやSLEにも広げることが求められる。ただし、今回の検討では膠原病以外のリウマチ性疾患や自己免疫疾患、間質性肺疾患、レイノー現象、抗核抗体陽性のみで診断確定に至らない例でのPAH発症はなく、膠原病確定診断例のみをスクリーニング対象とすることが妥当である。

今回、診断と自己抗体を組み合わせることで膠原病の中でPAHリスクの高い6つのサブセットを同定することができた。最もリスクが高いサブセットは抗セントロメア抗体陽性SScで、次いでMCTDの順であった。SScの中でも、抗セントロメア抗体の有無で層別化することによりPAHリスクが5.6倍異なるサブセットに分類することができた。また、SLEでは抗U1RNP抗体の有無によりPAHリスクが3.5倍異なっていた。興味深いことに、SSc、MCTD、SLE以外でPAHを発症したpSS、RA、DM11例のうち10例で抗SSA抗体が検出され、SSc、MCTD、SLE以外のPAHリスク因子として抽出された。

今回の結果から、PAHリスクに基づいたスクリーニングの優先度が示された。SSc、特に抗セントロメア抗体陽性例とMCTDはPAHリスクが高く、積極的に毎年のスクリーニングを行うべきである。SLEでは抗U1RNP抗体陽性例は可能な範囲で定期的なスクリーニングの実施が好ましいが、抗U1RNP抗体陰性例では診断時、活動性上昇時、息切れを自覚した際のスクリーニングで十分かもしれない。このようなリスク層別化による効率よいPAHスクリーニングプログラムの作成が望まれるが、多施設前向き研究での検証が必要である。

E. 結論x

リウマチ性疾患が疑われた症例では、診断と自己抗体を組み合わせることでPAHリスクの層別化が可能であった。PAHリスクの高い抗セントロメア抗体陽性SScとMCTDでは毎年のスクリーニングを実施すべきだが、それ以外ではPAHリスクに基づいたスクリーニングの適応や間隔の調整が可能である。

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G. 知的財産権の出願・登録状況

1. 特許取得

なし

2. 実用新案登録

なし

3. その他

なし

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分担研究報告書

患者会を中心とした肺高血圧症の前向き症例登録研究の開発と予後調査

— 小児科領域における肺高血圧症の症例登録、予後調査および疾患発症機序に関する研究 —

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研究要旨

小児科領域における肺高血圧症の症例登録、予後調査および疾患発症機序に関する研究として、先天性心疾患に伴う肺動脈性肺高血圧症（CHD-PAH）の新たな症例登録システムを考案した。本研究班で開発された成人版登録システムをもとにして、CHDが関与するPAHの症例を幅広く登録することができ、データ解析の際には適宜条件を設定して症例を選択できるように検討した。我が国における CHD-PAH の現状を明らかにし、治療法を標準化するためにも全国的に統一化された症例登録システムが有用である。

A．研究目的

我が国における、先天性心疾患に伴う肺動脈性肺高血圧症（CHD-PAH）の生存率・生命予後を明らかにする。

B．研究方法

多施設共同の 5 年間の前方視的観察研究として、治療内容に介入しない症例登録システムを考案し、すべての CHD-PAH 患者を登録できるように検討した。

（倫理面への配慮）

本事業の基盤となる症例登録研究に関して、慶應義塾大学医学部の倫理審査委員会に申請し、認可を得ている(承認番号 2010-227)。当該分担研究項目について倫理委員会等の承認が得られた年月日を明記する。

C．研究結果

対象となる CHD-PAH 症例の登録基準を以下のように設定した。

1. 年齢は問わない。
2. すでに CHD-PAH 患者と診断されている症例を初期登録する。
3. 加えて、2006 年 1 月以降の過去のデータも登録する。その際には、2013 年 1 月の時点で死亡している症例も含める。
4. 登録開始後、新たに CHD-PAH 患者と診断された症例を追加登録する。
5. PAH の診断は原則として心臓カテーテル検査データによる。ただし、個々の患者の状況により、心臓カテーテル検査を行うことができず、心エコー検査等により、総合的に PAH と診断した症例も登録する。心臓カテーテル検査の実施時期は問わない。心臓カテーテル検査における PAH の定義は以下の通り：平均肺動脈圧が 25mmHg を超え、かつ肺毛細血管楔入圧が 15mmHg 以下。心エコー等における PAH の診断の目安は以下の通り：推定右心室(肺動脈)収縮期圧が 50mmHg を超えるか、または三尖弁逆流速度が 3.4m/sec を超え、かつ肺静脈圧を上昇させる左心疾患（中等度異常の僧帽弁閉鎖不全症や肺静脈狭窄など）が否定できる。
6. CHD の種類は問わない。
7. 以下のいずれの病態も対象とする：1) 修復されていない短絡部位を有する症例（短絡部位の大小も問わない）、2) 修復されている短絡部位を有する症例（手術・カテーテル治療後）
8. PAH は 3 か月間以上持続していることを条件とする（手術後に残存する PAH についても、3 か月以上持続している場合は対象とする）。
9. 他の臨床試験（治験）に参加している症例も対象とする。
10. 特別な症例群として、以下の２つを対象に加える。ただし、これらは主要な症例群とは別個に扱い、データ解析も独立して行う：1) 肺動脈閉鎖/肺動脈狭窄に複数の主要体肺側副動脈（MAPCA）を有し、1 葉以上を支配する肺動脈の平均圧が 25mmHg を超える症例、2) Fontan 手術後で、平均肺動脈圧（中心静脈圧）18mmHg かつ肺高血圧症治療薬が用いられた症例

以下の除外基準を設定した。

1. PAH の改善に寄与する手術あるいはカテーテル治療を近い将来に計画している症例。
2. 手術あるいはカテーテル治療後、3 か月以内

の症例。
3. 肺高血圧の状態が不安定で、診断が確定できない症例。

同意の取得を以下のように定めた。
1. 書面による同意を得る（Opt-in 方式）。
2. ただし、後方視的なデータの登録については書面による個別の同意は得ない（Opt-out 方式）。

以下の方法によりデータを収集する。
1. 本研究班の成人用レジストリを CHD-PAH 用にカスタマイズした入力システムを用いる。
2. 各施設で匿名化を行い、個人情報の保護を万全にする。
3. 症例登録の際に基本的なデータを収集する。
4. 年に 4 回（3 か月毎）、定期的なデータを更新する。

D. 考察

我が国における症例登録研究の方向性として、以下の事項が重要である：1) 厚労省研究班、学会主導のデータ集積、2) データ収集法の統一、データフォーマットの統一、3) Authorship、4) 研究のデザイン、5) データの活用方法（公開および利用）、6) 適切なリサーチクエスチョン・登録項目、7) Feasibility（必要かつ十分な登録項目）。小児領域、CHD-PAH の症例登録研究については、年齢、基礎疾患のばらつき等もあり、成人の PAH 症例登録研究に比して研究のデザイン、登録項目等の統一性を確保することに困難が予測される。国際的にも発信できるデータを集積するために、Association for Pediatric Pulmonary Hypertension を母体として実施されている TOPP (Tracking Outcomes and Practice in Pediatric Pulmonary Hypertension) registry 等の症例登録システムとの整合性について検討することが重要である。

E. 結論

我が国における CHD-PAH の現状を明らかにして国際的に発信すること、また、治療法を標準化するためにも全国的に統一化され、国際的研究デザインと共通化された症例登録システムが必要である。

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G. 知的財産権の出願・登録状況

1. 特許取得
なし

2. 実用新案登録
なし

3. その他
なし

Ⅲ. 研究成果の刊行に関する一覧表

研究成果の刊行に関する一覧表

書籍

著者氏名	論文タイトル名	書籍全体の編集者名	書　籍　名	出版社名	出版地	出版年	ページ
佐藤徹	静脈圧、循環血液量、循環時間. 容積脈波、サーモグラフィ	小川総	内科学書 Vol. 3, 改訂第８版	中山書店	東京	2013	68-70
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Letter to the Editor

Blood–injection-injury phobia: Profound sinus arrest

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A 26-year-old man was referred to our clinic for a medical check-up. During measurement of his blood pressure, the patient lost consciousness followed by persistent nausea and light-headedness. His condition deteriorated until no pulse was detected, upon which the doctors started cardiopulmonary resuscitation. Once a pulse returned, the patient was admitted to our hospital for investigation. Physical examination revealed no abnormal findings and his medical or family history was unremarkable, although he reported experiencing a similar attack of nausea in the past immediately following a venipuncture. ECG showed extreme bradycardia and a 10-second asystole, followed by junctional escape beats (Panel A). Subsequently, the patient again lost consciousness, requiring transcutaneous pacing and atropine sulfate injection for recovery. A thorough review of the patient's history revealed that he had collapsed during a vaccination as a 7-year-old, and thereafter was always on the verge of fainting during vaccination or venipuncture. Moreover, he felt nausea whenever hearing about blood, hospitals, or any medical procedures. Consequently, he had avoided medical examinations for a long time.

The current patient thus fitted a diagnosis of blood–injection-injury phobia according to the DSM-IV TR criteria. Suspecting the existence of vasovagal syncope with blood–injection-injury phobia, we also performed a tilt-table test. At 10 min of 60° tilt, he noted the onset of his usual prodromal symptoms followed by hypotension, bradycardia, and loss of consciousness. Our final diagnosis was vasovagal syncope with blood–injection-injury phobia.

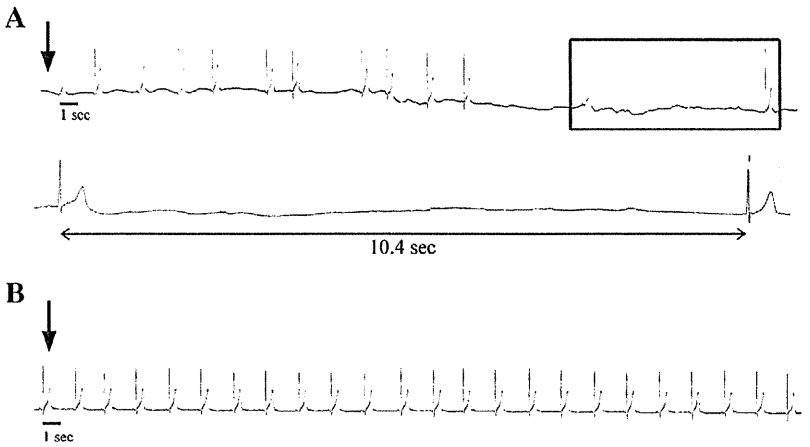

Fig. 1. Panel A: Upper ECG rhythm recorded during the asystole event. The ECG strip with a normal recording speed (25 mm/s). Panel B: ECG rhythm recorded after the cognitive behavioral therapy. The arrows indicate the time point of injection.

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Blood–injection-injury phobia is a common phobia with an estimated prevalence of 3–4% in the general population [1]. It can be triggered by seeing blood, sustaining an injury, receiving injections, or various other invasive medical procedures. It is noteworthy that blood–injection-injury phobia is the only phobia associated with syncope, and more than two thirds of patients with this condition have a history of syncope [2]. Although the etiology of syncope is poorly understood, a vasovagal mechanism has been implicated [3]. Blood–injection-injury phobia is often treated with exposure therapy, a component of cognitive behavioral therapy that involves repeated and systematic encounters with feared stimuli. A combination of applied tension and an isometric counter-pressure may significantly attenuate anxiety and avoidance behaviors [4].

Considering these facts, we instructed our patient to perform repeated physical counter-pressure maneuvers, such as leg crossing, during invasive medical procedures performed within our hospital over a few days. Subsequent tilt-table testing showed a negative result and the patient became free from any symptom or long pauses when receiving an injection (panel B). Uniquely, he remains free of further syncope after 5 years.

Despite syncope being common and severe, long-term treatments with medical insults are not established. The unique nature of the case presented herein could provide insights into the potentially permanent, positive effects of cognitive behavioral therapy in such cases (Fig. 1).

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ORIGINAL RESEARCH

Evaluation of a New Formulation of Epoprostenol Sodium in Japanese Patients with Pulmonary Arterial Hypertension (EPITOME4)

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ABSTRACT

Introduction: Pulmonary arterial hypertension (PAH) is associated with poor prognosis despite significant recent advances in its treatment. An intravenous formulation of epoprostenol sodium containing glycine and mannitol (epoprostenol GM; GlaxoSmithKline, London, UK) is widely used to treat PAH. A new formulation of epoprostenol sodium containing arginine and sucrose excipients (epoprostenol AS; Actelion Pharmaceuticals Japan Ltd., Tokyo, Japan) shows better stability at room temperature after preparing diluted solutions. The primary objective of this study was to evaluate the safety and tolerability of switching from epoprostenol GM to epoprostenol AS in Japanese patients with PAH. The authors also evaluated the efficacy and treatment satisfaction after switching formulations.

Methods: This was a two-site, open-label, single-arm, Phase 3b study. Eight adult Japanese PAH patients (seven females) treated with a stable dose of epoprostenol GM for ≥30 days were switched to epoprostenol AS and followed for 12 weeks. Outcomes included safety, changes from baseline to 12 weeks in pulmonary hemodynamic factors (pulmonary vascular resistance, mean pulmonary arterial pressure, and cardiac output), and treatment satisfaction, assessed using the Treatment Satisfaction Questionnaire for Medication (TSQM-9).

Results: The mean (range) age and time since diagnosis of PAH were 48 (25–69) years and 6.2 (0.6–13.9) years, respectively. There were no

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unexpected safety or tolerability concerns after switching formulations. The epoprostenol dose was maintained after switching formulations. There were no significant changes in pulmonary hemodynamic factors from baseline to week 12. Regarding treatment satisfaction, there was a significant improvement in convenience, which is demonstrated in the score of the domain increased from 51.40 ± 10.19 at baseline to 58.33 ± 12.96 at week 12 ($P < 0.05$).

Conclusions: Switching from epoprostenol GM to the same dose of epoprostenol AS was well tolerated over 12 weeks of treatment, and pulmonary hemodynamics were maintained. Switching to epoprostenol AS was also associated with improvements in treatment satisfaction (convenience). Clinical Trials: JapicCTI-122017.

Keywords: Efficacy; Epoprostenol; Epoprostenol formulations; Japanese patients; Prostacyclin; Pulmonary arterial hypertension; Pulmonary hemodynamic factors; Safety; Treatment satisfaction

INTRODUCTION

Pulmonary arterial hypertension (PAH) is a progressive disease with poor prognosis. It is generally characterized by constriction of pulmonary arteries and vascular remodeling. Right ventricular afterload (right ventricular hypertrophy and enlargement) is increased because of elevated pulmonary arterial pressure and pulmonary vascular resistance, which ultimately leads to right cardiac failure and death [1]. Subjective symptoms of PAH include exertional dyspnea, fatigability, palpitations, chest pain, and syncope [2].

Although the underlying mechanisms of PAH are not fully understood, vascular endothelial abnormalities cause an imbalance between vasoconstricting and vasodilating factors. In this situation, vasoconstricting factors exert a greater influence and increase shear stress. It is generally thought that remodeling of the pulmonary arterial media and narrowing of the pulmonary intravascular lumens due to increased cell proliferation are responsible for this imbalance [3–5].

Prostacyclin (PGI_2) agents with various modes of action, endothelin receptor antagonists, and phosphodiesterase-5 inhibitors are available for the treatment of PAH. Oral administration of any of these drugs is recommended for patients with PAH of World Health Organization (WHO) functional Class III or lower. For patients with Class IV PAH, continuous intravenous administration of PGI_2 is recommended. Concomitant treatment with several drugs having different modes of action is recommended if the clinical response to monotherapy is inadequate [6–8].

PGI_2 is a metabolite of arachidonic acid and plays an important role in maintaining pulmonary vascular homeostasis. It is produced by endocapillary cells, and acts as a potent vasodilator and inhibits platelet aggregation. Accordingly, the PGI_2 system plays an important role in the inhibition of vascular smooth muscle cell proliferation and helps to protect the vascular endothelium. A small decline in the function of the PGI_2 system leads to an imbalance between vasoconstrictors and vasodilators, and appears to contribute to the development of PAH [9–11].

Based on these findings, compounds that target prostacyclin receptors have been developed and are used clinically to treat PAH. One such example is intravenous epoprostenol sodium, a synthetic PGI_2 analog, which is prepared as a formulation containing glycine and mannitol as excipients (epoprostenol GM, GlaxoSmithKline, London, UK). Continuous

intravenous therapy with epoprostenol GM was reported to improve pulmonary hemodynamic factors, exercise tolerance, and the prognosis of PAH [12]. However, one limitation of this formulation is that the prepared solution is thermally unstable, and needs to be administered within 8 h at room temperature (1–30 °C) or within 24 h if cooled to 2–8 °C using frozen gel packs. Consequently, the medication cassette containing the solution has to be maintained at 2–8 °C using a frozen gel pack for the entire 24-h infusion period [13].

To overcome this limitation, another formulation of epoprostenol sodium, containing arginine and sucrose as excipients (Actelion Pharmaceuticals Japan Ltd., Tokyo, Japan; hereafter, epoprostenol AS), was developed to improve the convenience of using epoprostenol to treat PAH as the new formulation is stable for 24 h at room temperature [14].

To date, however, few studies have examined the safety, potential effects on hemodynamic factors, or treatment satisfaction associated with switching formulations of epoprostenol in patients with PAH [15]. Therefore, the authors performed a 12-week, open-label, Phase 3b study to examine the safety, efficacy, and treatment satisfaction of switching from epoprostenol GM to epoprostenol AS in Japanese patients with PAH. The authors hypothesized that switching from epoprostenol GM to epoprostenol AS would improve treatment satisfaction without increasing the incidence of adverse events or causing deteriorations in pulmonary hemodynamic factors.

METHODS

Ethics

All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2000. Informed consent was obtained from all patients for being included in the study.

Subjects

Patients aged ≥20 years at the time of informed consent and who had pulmonary hypertension classified as Group 1 using the Dana Point classification [16,17] for pulmonary hypertension were eligible if they had any of the following: idiopathic pulmonary arterial hypertension (IPAH), heritable pulmonary arterial hypertension (HPAH), PAH associated with drugs and toxins, or PAH associated with connective tissue disease. Only patients who had been treated with epoprostenol GM for ≥3 months before enrollment and at a stable dose for ≥30 days before the start of study treatment were included in the study. Females of childbearing potential had to have a negative serum pregnancy test at screening. They were also required to agree to take monthly urine/serum pregnancy tests and to use reliable contraceptives to avoid pregnancy from the time of the screening visit until 30 days after the end of the study.

Eligible patients were excluded if they met any of the exclusion criteria, such as diagnosis of respiratory or cardiovascular disorder requiring immediate surgery, presence of confirmed or suspected pulmonary vein occlusion, history of myocardial infarction, and resting pulse rate of ≥120 beats/min.

Trial Drug

Epoprostenol AS (Actelion Pharmaceuticals Japan Ltd.) was provided in 10-mL glass vials containing 0.5 mg or 1.5 mg epoprostenol

sodium. Epoprostenol AS was dissolved and diluted by adding isotonic sodium chloride solution. At the start of the 12-week treatment period, epoprostenol GM was switched to an equal dose of epoprostenol AS in the hospital. For home therapy, epoprostenol was administered via a central venous catheter by continuous drip infusion using a portable infusion pump.

Study Design

This was a two-site, open-label, single-arm, Phase 3b study. The study consisted of a 2-week pretreatment screening period, a 12-week open-label treatment period (visiting at baseline, week 1, 2, 4, 8, and 12), and a continuous treatment period until marketing of the study drug (visiting every 4 weeks). Pulmonary hemodynamic measurements and variables of clinical laboratory tests were collected at baseline and week 12. Medical interviews and checks for vital signs were performed at each visit. Females of childbearing potential received a pregnancy test every month.

Outcome Measures

Safety/Tolerability

The safety/tolerability endpoints were adverse events occurring during the 12-week treatment phase, together with changes from baseline to week 12 for vital signs (blood pressure and heart rate on the same arm in sitting or supine position), body weight, and abnormal changes from baseline to week 12 for clinical laboratory tests (general biochemistry tests, including thyroid function test and hematology test). Vital signs and body weight were assessed at each visit and clinical laboratory tests were performed at baseline and week 12 (only thyroid function was assessed every month). Adverse events reported during the 12-week evaluation period were coded according to system organ class and terms using the Medical Dictionary for Regulatory Activities/ Japanese version. The causality of adverse events in relation to the trial drug was judged by the investigators.

Efficacy Endpoints

The efficacy endpoints were changes in pulmonary hemodynamic factors, WHO functional class, and N-terminal prohormone of brain natriuretic peptide (NT-proBNP) concentrations from baseline (within 60 min before the first dose of epoprostenol AS) to immediately after switching (within 60 min after the first dose of epoprostenol AS) or week 12. Pulmonary hemodynamic factors included systolic pulmonary artery pressure, diastolic pulmonary artery pressure, mean pulmonary artery pressure, pulmonary capillary wedge pressure, cardiac output, mean right atrial pressure, mixed venous oxygen saturation, cardiac index, pulmonary vascular resistance, and pulmonary vascular resistance index. Pulmonary hemodynamics were measured by right heart catheterization, which was performed according to standard local procedures through the internal jugular, subclavian, or femoral vein by a balloon catheter placed into either the right or left pulmonary artery in a sterilized cardiac catheterization laboratory. Cardiac Output (CO) was measured using Fick's method [18].

Treatment Satisfaction

The abbreviated nine-item Treatment Satisfaction Questionnaire for Medication (TSQM-9), employed for the quality of life assessment, is a validated questionnaire that permits comparisons of patients' treatment

satisfaction across medication types and patient conditions [19]. The changes from baseline to week 12 in treatment satisfaction were assessed using the TSQM-9. This questionnaire includes three items for each of three domains: effectiveness, convenience, and global satisfaction. The scores for each domain range from 0 to 100, where higher scores indicate higher satisfaction on that domain.

Statistical Analysis

This study was an exploratory study. No hypothesis was set and no power considerations were made for this study. Patients who received at least one dose of the study drug were included in the all-treated set for analyses. Patients who had assessable data at baseline and week 12 were included in the analysis of pulmonary hemodynamics. All statistical analyses were considered to be exploratory and the significance level was set at 5% (two-sided). The efficacy variables were summarized descriptively by calculating the mean, standard deviation, standard error, median, 25th and 75th percentiles, minimum and maximum. Changes from baseline were examined using the Wilcoxon signed rank sum test. All analyses were performed using SAS (Version 9.2; SAS Inc., Cary, North Carolina, USA).

RESULTS

Patients

The study was conducted at two Japanese study sites, and started in October 2011. Eight Japanese patients (one male, seven females) with PAH were treated with the study drug and completed the 12-week evaluation period by October 2012. The characteristics of the patients are summarized in Table 1 and Supplemental Table 1. The mean (range) age

Table 1 Patient characteristics

Background factors	$N = 8$
Sex, *n* (%)	
Male	1 (12.5)
Female	7 (87.5)
Age, years	
Mean ± SD	47.6 ± 12.5
Median	46.0
[Min, Max]	[25, 69]
Age in class	
20–64 years	7 (87.5)
≥65 years	1 (12.5)
Race, *n* (%)	
Asian	8 (100.0)
Body mass index, kg/m^2	
Mean ± SD	19.94 ± 2.21
Median	20.40
[Min, Max]	[15.4, 23.0]
Etiology of PAH, *n* (%)	
IPAH	7 (87.5)
HPAH	1 (12.5)
APAH-DT	0 (0.0)
APAH-CTD	0 (0.0)
Time since PAH diagnosis, years	
Mean ± SD	6.21 ± 5.24
Median	5.26
[Min, Max]	[0.6, 13.9]
WHO functional class, *n* (%)	
I	1 (12.5)
II	5 (62.5)
III	2 (25.0)
IV	0 (0.0)

APAH-CTD associated with pulmonary arterial hypertension-connective tissue disease, *APAH-DT* associated with pulmonary arterial hypertension-drugs and toxins induced, *HPAH* heritable pulmonary arterial hypertension, *IPAH* idiopathic pulmonary arterial hypertension, *PAH* pulmonary arterial hypertension, *SD* standard deviation