呼吸器内科，21(2)：169-172，2012

話　題

肺高血圧症の治療薬
3) ET-1受容体拮抗薬*

佐　藤　　徹**

Key Words：endothelin 1(ET-1), antagonist, *Streptomyces misakiensis*

はじめに

Endothelinは血管内皮から分泌される強力な血管収縮物質として，1980年代後半に日本人研究者により発見された[1]．後にendothelin 1, 2, 3が見つかり種々の組織から分泌されることが見出されたが，血管内皮から分泌されるのはendothelin 1のみで，血管平滑筋増殖作用，線維化促進作用，血管新生作用，炎症促進作用などの有害作用を有している[2]．Endothelin受容体にはETAとETBがあるが，ETAは主に血管平滑筋に存在してendothelin 1, 2に反応し，ETBは内皮などに存在し1, 2, 3のいずれにも反応する．Endothelin 1が上記のような血管有害作用を有するため，endothelin受容体拮抗薬は，循環器疾患の治療薬となる可能性がある．放線菌の一種*Streptomyces misakiensis*の代謝産物から，endothelin 1の受容体への結合を特異的に阻害するペプチドBE-18257Bが見出された．しかし，ペプチドは半減期が短く経口投与に不適切なため，スルフォナミド骨格を有する非ペプチド系拮抗薬でETA, ETBの非選択的拮抗薬であるRo 47-0203(ボセンタン)が開発された[3]．ボセンタンは種々の循環器疾患の治療薬として検討されたが，最終的に肺高血圧に対する改善効果が証明され治療薬として使用されるようになった．その後ETAの選択的拮抗薬であるambrisentanが開発された．ETBは通常の状態では血管拡張に働くが，肺高血圧症により内皮異常が存在すると血管収縮が主体になるとされ，ETA, ETBの両者の抑制がより有用との意見もある．日本では2002年にボセンタン(商品名トラクリア®)に対する治験が施行され2005年6月に最終的に発売となり，アンブリセンタンは2010年に発売となった．

ボセンタン

1．体内薬物動態

ラットの経口投与による吸収率は69%であり，代謝は肝臓でなされ胆汁に排泄される．日本人正常人に投与した成績では2～4時間で最高血中濃度に達し，血中消失半減期は約4時間であった．

2．適　　応

肺動脈性肺高血圧症で，NYHA心機能分類のクラスII°～IV°が適応となる．肺線維症や強皮症の指尖潰瘍に有効との報告もある．

3．投 与 法

1錠62.5mgで1回1錠を朝夕食後に1日2回投与で開始する．1か月この量で投与した後，副作用の出現がなければ1回2錠を朝夕食後に1日2回投与する．1日量125mgよりも250mgの方が，効果が高いことがわかっている．二重盲検治験において，1日量250mgまでは副作用の出現率がプラセボ群と変わりなかったが，1日量500mgでは副作用の出現率が有意に高いとの結果[4]が得られており，1日投与量は250mgまでと決められた．

4．効　　果

肺高血圧症では肺動脈内皮細胞における

* ET-1 antagonist.

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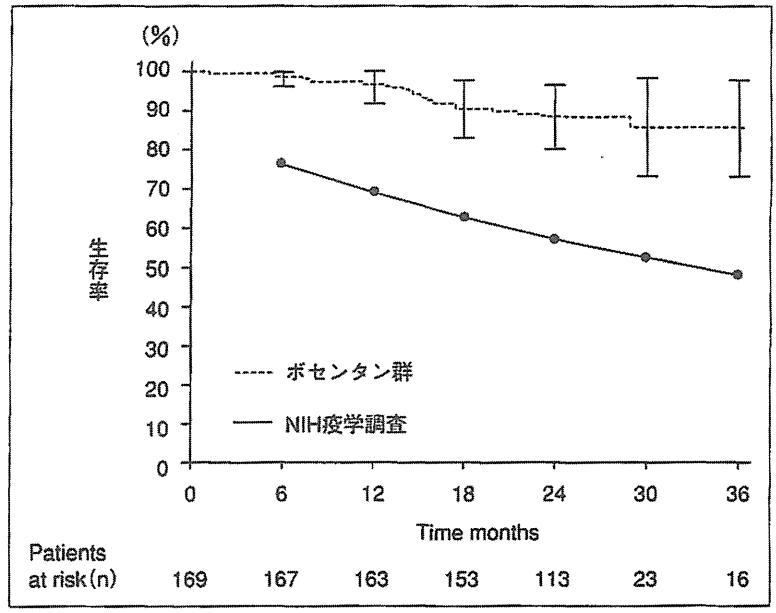

図1　ボセンタン治療とNIH疫学調査による生存率の比較(文献[5]より引用改変)

endothelin 1の産生が増加し，血管収縮，血管平滑筋肥大，細胞外マトリックス形成作用によって，肺血管抵抗が上昇することが報告されており，ボセンタンはendothelin 1を抑制することにより肺高血圧症を改善する可能性がある．そこでモノクロタリンによる肺高血圧症の実験動物に対し投与され，血行動態，右室肥大の程度，予後を改善することが示された．次いで人間への治験が行われ，肺動脈性肺高血圧症213例に対する二重盲検試験(BREATHE-1)では，4か月間の投与の後，プラセボを対象として，6分間歩行で44m歩行距離の改善，ボルグ呼吸困難指数の改善，NYHA機能分類による症状の改善が認められた[4]．その後の長期経過を観察した結果では，カプラン＝マイヤー法による2年後の予測生存率は89%であり，コントロール群の57%を大幅に上回った(図1)[5]．日本でも肺動脈性肺高血圧症21例に対して臨床治験が行われ，3か月間の投与後に，血行動態の有意な改善，6分間歩行の86mの延長，身体活動能力指数の改善などが認められた[6]．

5．副 作 用[7]

自覚的なものは，血管拡張による頭痛，めまい，筋肉痛などで他の治療薬より頻度は少ないと感じているが，肝機能障害は1割で生じ重篤なものも2～3%と報告されている．肝機能検査を1か月に一度施行する必要がある．他剤よりは少ないが，投与初期には血圧が低下することがあり血圧測定を義務づけた方がよい．3系統の血球減少も5～10%と決して少なくなく注意を要する．投与初期の方が起こりやすいが期間を経ても起こることがある．動物実験で催奇形性があり，妊産婦・授乳婦には禁忌となる．シクロスポリン，タクロリムス，グリベンクラミド，グレープジュースなどは併用禁忌となる．シルデナフィル併用で血中濃度が上昇し副作用が出やすくなる．

アンブリセンタン

1．体内薬物動態

日本人正常男性に投与した成績では2～2.5時間で最高血中濃度に達し，血中消失半減期は約10～19時間であった．主要排泄経路は糞中で一部腎臓に排泄される．

2．適　　応

WHO心機能分類のクラスII°～IV°の肺動脈性肺高血圧症が適応となる．

3．投 与 法

1錠2.5mgを，朝1回2錠から開始し適宜4錠まで増量する．

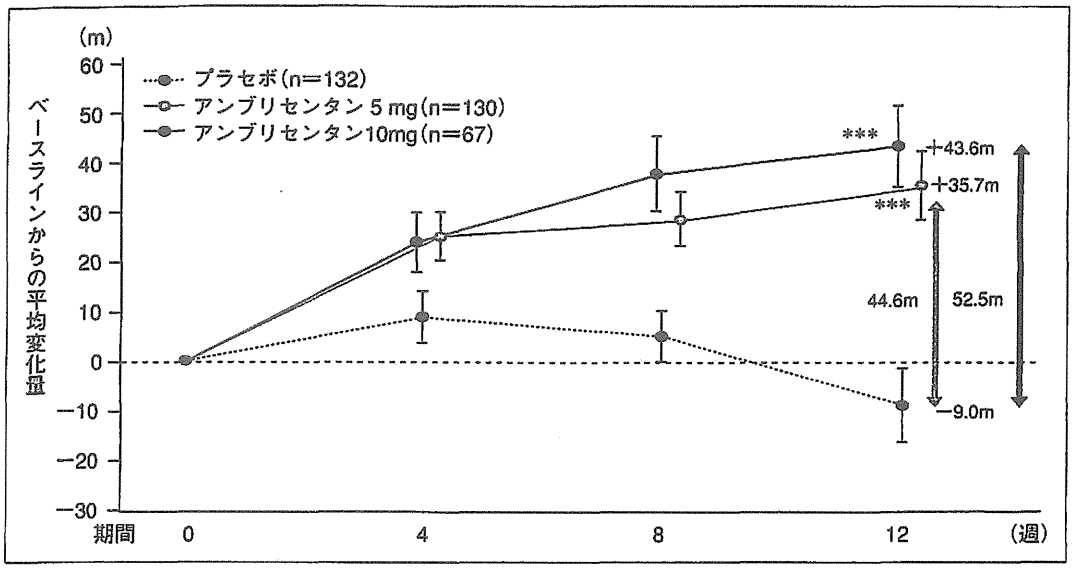

図2　アンブリセンタンによる6分間歩行距離の改善
ベースライン：プラセボ；平均342.3±79.55m，5 mg；平均347.2±80.61m，10mg；平均341.5±78.28m.
平均値±SEM　*** $P<0.001$, Wilcoxon順位和検定
PAH329例にアンブリセンタン5 mgあるいは10mgを12週間投与．プラセボ群に対して5 mg群で44.6m，10mg群で52.5mの有意な増加がみられた．　（文献[8]より引用改変）

4．効　果

血管収縮に主に関与するとされるETA受容体を主に抑制し，血管拡張に関係するとされるETBへの親和性は1/4,000以下とされる．臨床的には，投与容量(2.5mg, 5 mg, 10mg)の異なる2種類の無作為前向き試験が欧米で施行され(ARIES IおよびARIES II試験)，いずれも主要評価項目とした6分間歩行試験が有意に改善し(2試験を統合したものを図2に示す)[8]，WHO心機能分類，血行動態，QOLスコアなども改善した．また，これらは長期試験に移行し，2年生存率88%と，新しい血管拡張薬が使用される以前に自然経過をアメリカで観察された予後[9]に比べて著明な改善がみられた．国内のオープン試験でも同様の結果が得られている．

5．副 作 用

最も頻度が多く問題となる副作用は浮腫で顔面，下腿などに生ずる．われわれの経験では約1/5に認めている．自覚的なものとして血管拡張による頭痛，めまい，潮紅などを生じるが，PDE5阻害剤，プロスタグラン製剤より頻度は少ない．肝機能障害はきわめて稀とされるがわれわれは30例中1例を経験した．投与初期の血圧低下には注意する．動物実験で催奇形性があり，妊産婦・授乳婦には禁忌となる．薬物相互作用のある薬剤はシクロスポリンのみとされている．

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Circulation Journal
Official Journal of the Japanese Circulation Society
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ORIGINAL ARTICLE
Pulmonary Circulation

Impact of First-Line Sildenafil Monotreatment for Pulmonary Arterial Hypertension

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Background: Sildenafil has been demonstrated as effective for the treatment of pulmonary arterial hypertension (PAH). The purpose of this study was to investigate the occurrence of clinical events after sildenafil monotreatment as a first-line therapy in patients with PAH over a long-term observation period.

Methods and Results: Sildenafil was administered as a first-line drug to 46 patients with PAH (including 24 patients with idiopathic PAH) during 2003–2010. We investigated subsequent clinical events such as the addition of epoprostenol, hospitalization for right-side heart failure, and death. All the hemodynamic parameters and the 6-min walk distance improved significantly in the enrolled patients as a whole receiving sildenafil treatment; 15 (33%) of the 46 patients required the addition of epoprostenol during follow-up. Kaplan-Meier analysis demonstrated that more than 60% of the patients receiving first-line sildenafil treatment did not require the addition of epoprostenol for a 5-year period. Furthermore, the 5-year survival rate after first-line sildenafil treatment was 81%. Finally, more than 75% of the enrolled patients did not reach the composite endpoint of hospitalization for right-side heart failure and death for a 5-year period.

Conclusions: This study describes the long-term outcome of patients with PAH receiving sildenafil monotreatment as a first-line therapy and suggests that it is a promising therapeutic strategy. (*Circ J* 2012; **76:** 1245–1252)

Key Words: Epoprostenol; Hospitalization; Prognosis; Pulmonary hypertension; Sildenafil

Pulmonary arterial hypertension (PAH) is defined as a progressive disease of increasing pulmonary vascular resistance (PVR) that leads to right-side heart failure and a grave prognosis.[1–4] Sildenafil and bosentan have been developed as new treatments for PAH during the past few years. Bosentan, an endothelial receptor antagonist, was the first oral drug shown to have an effect in patients with PAH.[5–9] Sildenafil, a phosphodiesterase-5 inhibitor, is a new effective dilator of pulmonary arteries that is also administered orally. Sildenafil has relatively few adverse effects, compared with other oral drugs for PAH, and is safe for use even in patients with mild-to-moderate renal or hepatic dysfunction; moreover, its use reportedly improves heart failure.[10] Recently, the study on Sildenafil Use in Pulmonary Arterial Hypertension (SUPER)-1 revealed that sildenafil improves exercise capacity, the World Health Organization (WHO) functional class, and the hemodynamics of patients with PAH.[11] Furthermore, SUPER-2 established the safety and tolerability of sildenafil with maintenance of the patient's functional class.[12]

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At the present time, the most powerful and effective treatment for PAH is an ambulatory continuous infusion of epoprostenol. Prior to the introduction of epoprostenol, the 5-year survival rate of patients with idiopathic PAH was 34%.[13] Epoprostenol has increased the 5-year survival rate to 67%, according to a report published in the United States in 1994.[14] However, epoprostenol therapy requires an indwelling catheter attached to an ambulatory infusion pump, limiting the patient's activities and producing the possibility of catheter infection. Thus, if oral drugs, such as bosentan and sildenafil, can be used to inhibit the progression of PAH, the introduction of epoprostenol can be delayed.

Recently, these 3 drugs, epoprostenol, bosentan, and sildenafil, have been used in combination for the treatment of PAH. However, few reports have demonstrated the long-term outcome of first-line sildenafil monotreatment or any evidence regarding the combination of these drugs. Therefore, the ob-

Received October 18, 2011; revised manuscript received December 26, 2011; accepted January 6, 2012; released online February 14, 2012
Time for primary review: 20 days

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ISSN-1346-9843 doi:10.1253/circj.CJ-11-1192

Table 1. Baseline Characteristics of Patients

	All patients (n=46)	Epo(+) group (n=15)	Epo(−) group (n=31)	P value between Epo(+) and Epo(−) groups
Age, years	42±14	35±10	46±15	<0.01
Sex, F/M	38/8	12/3	26/5	NS
NYHA FC I+II/III, n	16/30	3/12	13/18	NS
mRA, mmHg	8.0±5.5	10.1±6.1	7.0±4.9	NS
mPAP, mmHg	52±14	62±15	47±11	<0.01
PVR, Wood unit	14.6±8.7	18±8.7	13±8.2	<0.05
CO, L/min	3.7±1.6	3.4±1.2	3.9±2.9	NS
6MWD, m	349±97	332±94	364±102	NS
BNP, pg/ml	334±349	317±347	345±358	NS

All the data are expressed as the mean±standard deviation.
Epo(+) group, patients who required additional epoprostenol treatment during the observation period; Epo(−) group, patients who did not require additional epoprostenol treatment during the observation period; NS, not significant; NYHA FC, New York Heart Association functional class; mRA, mean right atrial pressure; mPAP, mean pulmonary arterial pressure; PVR, pulmonary vascular resistance; CO, cardiac output; 6MWD, 6-min walk distance; BNP, B-type natriuretic peptide.

jectives of this study were (1) to investigate the clinical efficacy of first-line sildenafil therapy during a long-term observation period, and (2) to examine the relationship of first-line sildenafil therapy and the occurrence of events such as the addition of epoprostenol, hospitalization for right-side heart failure, and death.

Methods

Study Subjects

In this study, we enrolled 57 patients with PAH who visited the Keio and Kyorin University Hospitals. The New York Heart Association functional class (NYHA FC) of enrolled patients was I, II, or III. The patients with NYHA FC IV were excluded because intravenous prostanoid should be the first-line treatment for those patients according to the algorithm proposed at the World Symposium in Venice, Italy, 2003 and revised at Dana Point, USA, in 2008.[15,16] Four patients abandoned sildenafil treatment because of the high cost of off-label use or severe, subjective adverse effects, and 7 patients with Eisenmenger syndrome were excluded because of the differences in their clinical characteristics compared with other patients with PAH. The remaining 46 patients (idiopathic PAH, n=24; secondary to connective tissue disease, n=16; associated with portal hypertension, n=6) were analyzed (age 42±14 years; 38 women, 8 men). Sildenafil was administered as a first-line drug from January 2003 to December 2010. All the patients provided informed consent, and the administration of sildenafil was approved by the institutional review boards of the hospitals.

All the patients enrolled underwent right-side heart catheterization before the administration of sildenafil and during the follow-up period. Furthermore, the 6-min walk distance (6MWD) was determined, and the B-type natriuretic peptide (BNP) level was measured before the administration of sildenafil and during the follow-up period.

Sildenafil Administration

In this study, sildenafil was administered as a first-line drug after the diagnosis of PAH. The maximum dose of sildenafil was 20 mg t.i.d. as long as the adverse effects could be tolerated. Conventional therapies, such as appropriate diuretics and oxygen therapy, were administered to all patients if such therapies were judged as being necessary based on the severity of the PAH and right-side heart failure.

Indication of Additional Epoprostenol and Bosentan

After the administration of sildenafil, the most appropriate treatment for each patient was instituted based on the algorithm.[15,16] If epoprostenol was added, the dosage was started at 1 $ng \cdot min^{-1} \cdot kg^{-1}$ and gradually increased to a dose of approximately 30 $ng \cdot min^{-1} \cdot kg^{-1}$ at 6 months.

Bosentan was administered when the efficacy of sildenafil was insufficient in terms of the clinical symptoms and objective findings or when the patient refused epoprostenol because of the need to insert an indwelling catheter and having a preference for oral treatment. The maximum dose of bosentan was 125 mg b.i.d. as long as all the adverse effects were tolerable.

Division of Patients Into 2 Groups According to the Addition of Epoprostenol

All the enrolled patients were divided into 2 groups according to the addition of epoprostenol. The patients given additional epoprostenol were designated as the Epo(+) group, and those without were designated as the Epo(−) group.

Statistical Analysis

The baseline characteristics, hemodynamic variables, and observation periods were compared between the 2 groups using Student's unpaired t-test. The proportion of each baseline NYHA FC was compared by the chi-square test. Comparisons of the time course of parameters between the 2 groups were made by 2-way analysis of variance for repeated measures, followed by Newman-Keuls test. The curves of the event-free rates according to the addition of epoprostenol, the event-free rates according to the composite endpoint of hospitalization for right-side heart failure and death, and the estimated survival rates were derived using the Kaplan-Meier method and compared using the log-rank test. A univariate analysis based on the proportional hazards model was used to examine the relationship between events such as death or hospitalization or the addition of epoprostenol and parameters such as the baseline characteristics and hemodynamics. The results were expressed as hazard ratios with 95% confidence intervals. A multivariate analysis based on the Cox proportional hazards regression model was used to examine the independent effect

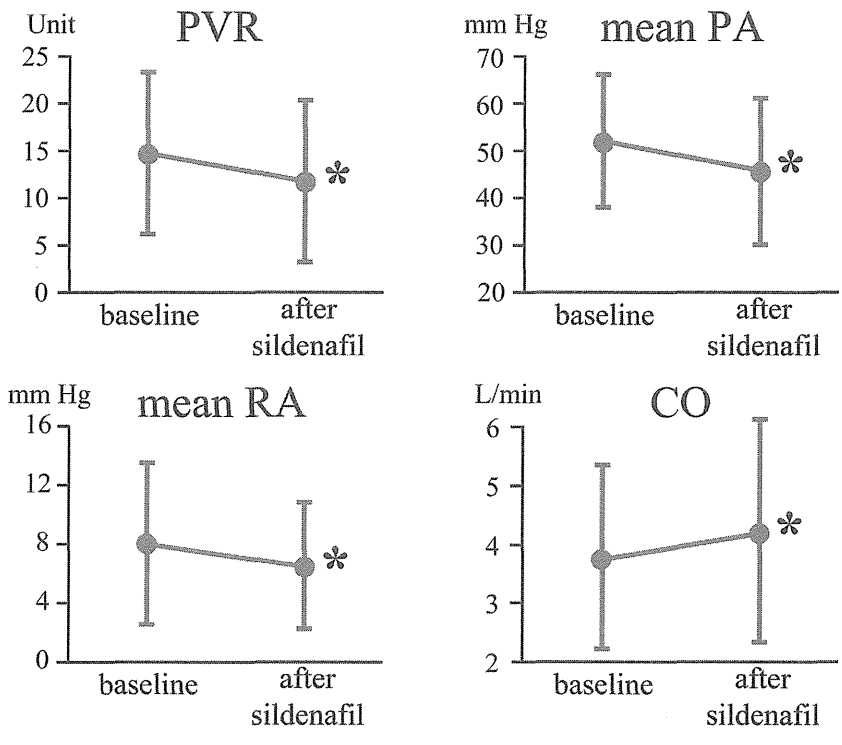

Figure 1. Hemodynamic changes during the observation period of sildenafil monotreatment in the enrolled patients as a whole. Pulmonary vascular resistance (PVR), mean pulmonary arterial pressure (mean PAP), mean right atrial pressure (mean RA), and cardiac output (CO) improved significantly with first-line sildenafil therapy. Data are the mean±standard deviation (SD). *P<0.05 vs. baseline.

of each variable on the events. The comparison of the proportion of underlying diseases between the younger group and the older group was made using chi-square test for independence. All the data are expressed as the mean±standard deviation. A value of P<0.05 was considered statistically significant.

Results

Baseline Characteristics and Changes in Hemodynamics, BNP, 6MWD, and NYHA FC in the Enrolled Patients as a Whole After Sildenafil Monotreatment

The baseline characteristics of all the patients enrolled in the study are shown in Table 1. The follow-up examinations, including right-side heart catheterization, were performed just before the addition of epoprostenol or bosentan to the treatment regimen. The patients who did not require additional treatment during the observation period were analyzed using the final follow-up data until December 2010. Therefore, our follow-up data for the hemodynamics, 6MWD, and BNP were obtained during sildenafil monotreatment. The average observation period was 21±22 months, and none of the patients were lost to follow-up.

A comparison of the hemodynamics at baseline and after sildenafil treatment is presented in Figure 1. The hemodynamic parameters, such as the PVR (14.6±8.7 vs. 11.6± 8.6 Wood units, P<0.05), mean pulmonary arterial pressure (PAP: 52.1±14.0 vs. 45.7±15.7 mmHg, P<0.01), mean right atrial pressure (RA: 8.0±5.5 vs. 6.4±4.4 mmHg, P<0.05), and cardiac output (CO: 3.7±1.6 vs. 4.2±1.9 L/min, P<0.05), improved significantly after sildenafil treatment in the enrolled patients as a whole.

Furthermore, the BNP and 6MWD at baseline and after sildenafil treatment were also compared. Some 6MWD and BNP follow-up data were missing, and some patients refused the 6MWD examination because of the presence of a gait disorder or dyspnea. The BNP (n=30) tended to be lower after sildenafil treatment, although the difference was not significant (332±362 vs. 247±382 pg/ml, P=NS). The 6MWD results (n=16) improved significantly (352±104 vs. 422±102 m, P<0.05).

During the observation period of sildenafil monotreatment, the NYHA FC either improved (n=12, 26.1%) or was maintained (n=30, 65.2%) in 42 of 46 patients, and worsened in 4 patients (8.7%) (Table 2).

Table 2. Change in NYHA FC Between Baseline and After First-Line Sildenafil Monotreatment

Change in NYHA FC	n (%)
Improved 2 classes	0 (0)
Improved 1 class	12 (26.1)
No change	30 (65.2)
Worsened 1 class	4 (8.7)

NYHA FC, New York Heart Association functional class.

Baseline Characteristics and Hemodynamic Changes in Patients Treated With or Without Epoprostenol

The patients were divided into 2 groups based on their clinical course. The Epo(−) group (n=31; 67% of all the enrolled patients) comprised patients who did not receive epoprostenol (3 of the 31 patients additionally received bosentan), and the average follow-up period was 25±23 months. The Epo(+) group (n=15; 33% of all the enrolled patients) comprised patients who were additionally treated with intravenous epoprostenol (4 of those 15 patients additionally received bosentan), and the average follow-up period was 12±18 months. The baseline characteristics of the Epo(−) and Epo(+) groups are shown in Table 1. The age of the Epo(+) group was significantly younger than that of the Epo(−) group.

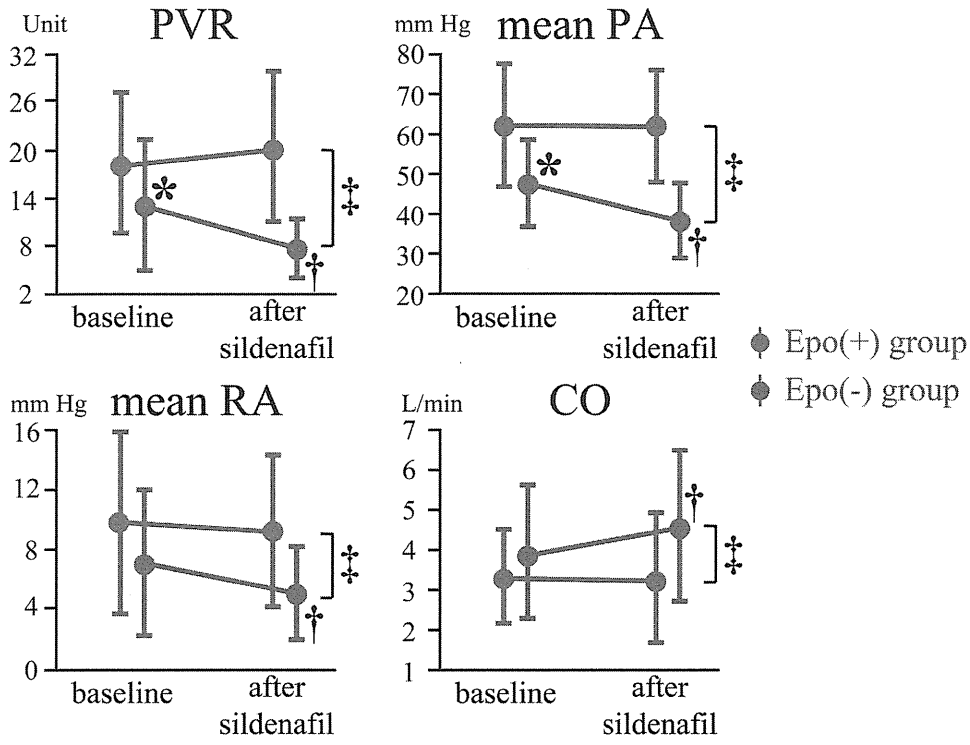

Figure 2. Hemodynamic changes during the observation period of sildenafil monotreatment among patients grouped according to the addition of epoprostenol (Epo) treatment. The red circles show the hemodynamic changes in the Epo(+) group, comprising patients treated with additional epoprostenol, and the blue circles show the hemodynamic changes in the Epo(−) group, comprising patients without additional epoprostenol treatment. At baseline, the mean PAP and PVR of the Epo(+) group were significantly higher than those of the Epo(−) group. The PVR, mean PAP, mean RA, and CO all improved significantly with sildenafil treatment in the Epo(−) group. However, these parameters did not change significantly in the Epo(+) group. The data are the mean±SD. *P<0.05 vs. baseline Epo(+) group; †P<0.05 between baseline and after sildenafil; ‡P<0.05 between the 2 groups in the time-course changes. CO, cardiac output; PAP, pulmonary arterial pressure; PVR, pulmonary vascular resistance;

The hemodynamics at baseline, before the administration of sildenafil, of the 2 groups is presented in **Figure 2**. No significant differences in the mean RA or CO were observed at baseline. However, the mean PAP and the PVR were significantly higher in the Epo(+) group than in the Epo(−) group at baseline. All the hemodynamic parameters improved significantly after sildenafil treatment, compared with the baseline values, in the Epo(−) group (mean PAP, 47.4±10.8 vs. 38.0±9.4 mmHg, P<0.01; mean RA, 7.0±4.9 vs. 5.0±3.1 mmHg, P<0.05; PVR, 12.8±8.2 vs. 7.4±3.6 Wood units, P<0.01; CO, 3.9±1.7 vs. 4.6±1.9 L/min, P<0.05). On the other hand, no significant differences in any of the hemodynamic parameters were observed after sildenafil treatment, compared with the baseline values, in the Epo(+) group (mean PAP, 61.8±15.3 vs. 61.7±13.9 mmHg, P=NS; mean RA, 10.1±6.1 vs. 9.3±5.1 mmHg, P=NS; PVR, 18.2±8.7 vs. 20.3±9.4 Wood units, P=NS; CO, 3.4±1.2 vs. 3.3±1.6 L/min, P=NS). There were significant differences between the 2 groups in the time-course of changes of all 4 parameters. However, there was a significant difference in the observation period between the 2 groups, so the possibility cannot be ruled out that this difference may have affected the statistical results.

Event-Free Rate According to the Addition of Epoprostenol

"Event" was defined as the addition of epoprostenol therapy. The Kaplan-Meier event-free curve was then determined according to the addition of epoprostenol, as shown in **Figure 3A**. The observation period was 33±27 months. The percentage of patients treated without the addition of epoprostenol was 80%, 70%, and 63% at 1, 3, and 5 years, respectively.

During the observation period, 15 patients were treated with additional epoprostenol. In 7 of them, epoprostenol was added because of right-side heart failure. In remaining 8 patients, it was added because of deterioration in NYHA FC, worsening of clinical symptoms or objective findings, and rapid progression of PAH, although without right-side heart failure.

Furthermore, we analyzed factors associated with the addition of epoprostenol. Age, mean PAP, and PVR at baseline were related to the addition of epoprostenol according to univariate analysis, and multivariate analysis demonstrated that only age at baseline was independently related to the addition of epoprostenol (**Table 3**). The median age of all the patients was 40 years. The Kaplan-Meier event-free curves according to the median age demonstrated that more of the patients aged less than 40 years required the addition of epoprostenol at an earlier stage, compared with the older patients (age >40 years) (log-rank test, P<0.05) (**Figure 3B**). In particular, at 2 years after the start of first-line sildenafil therapy, epoprostenol was added to the treatment of approximately 20% of the patients who were older than 40 years old, but 40% of the patients who were younger than 40 years required the addition of epoprostenol. Meanwhile, we compared the proportion of underlying

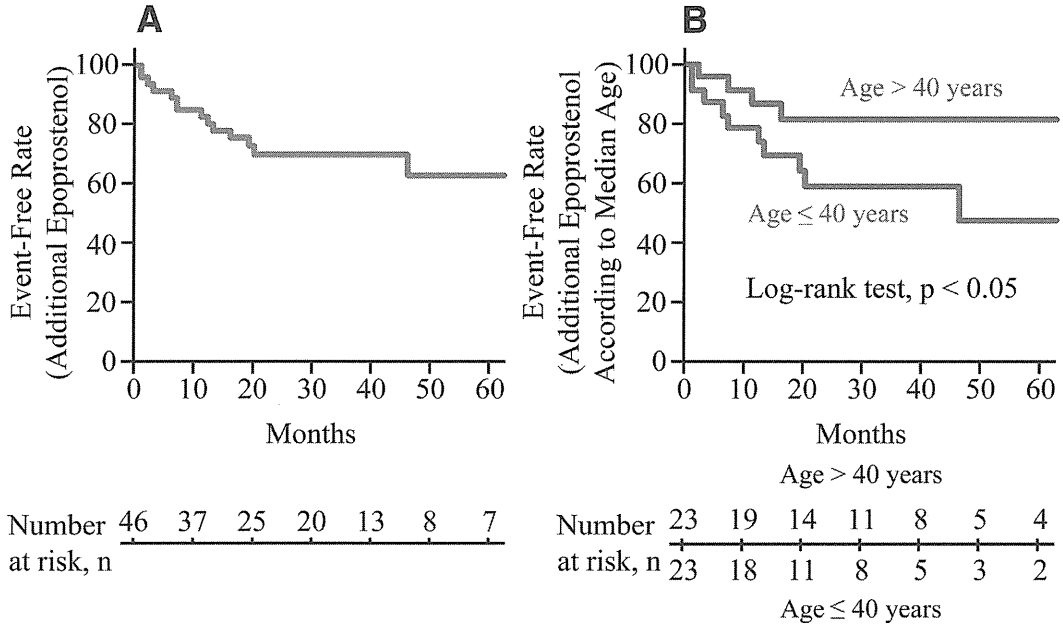

Figure 3. (A) Kaplan-Meier estimates according to the addition of epoprostenol treatment. The 1-, 3-, and 5-year rates for patients treated without the addition of epoprostenol were approximately 80%, 70%, and 63%, respectively. (B) Kaplan-Meier estimates according to the addition of epoprostenol treatment among patients grouped according to age. The overall median age was 40 years. The event-free rate among older patients (>40 years) (blue line) was significantly higher than that among younger patients (≤40 years) (red line) (P<0.05, log-rank test).

Table 3. Statistical Analysis of Variables Correlated With the Addition of Epoprostenol Treatment

	Univariate analysis		Multivariate analysis	
	HR (95%CI)	P value	HR (95%CI)	P value
Age	0.95 (0.91–0.99)	<0.05	0.94 (0.90–0.99)	<0.05
Sex	1.15 (0.32–4.12)	NS	–	–
NYHA FC I+II/III	0.38 (0.11–1.35)	NS	–	–
mRA	1.09 (0.99–1.19)	NS	–	–
mPAP	1.07 (1.03–1.12)	P<0.05	1.05 (1.00–1.10)	NS
PVR	1.06 (1.01–1.11)	P<0.05	1.05 (0.96–1.13)	NS
CO	0.78 (0.53–1.17)	NS	–	–
6MWD	0.99 (0.99–1.00)	NS	–	–
BNP	1.00 (0.99–1.00)	NS	–	–

HR, hazard ratio; CI, confidence interval. Other abbreviations see in Table 1.

diseases between the younger group (idiopathic PAH, n=15; secondary to connective tissue disease, n=5; associated with portal hypertension, n=3) and the older group (idiopathic PAH, n=9; secondary to connective tissue disease, n=11; associated with portal hypertension, n=3). There was no significant difference between the 2 groups in the proportions of the underlying diseases of PAH.

Survival Rate

In this study, 5 patients died during the observation period; 2 of them had refused epoprostenol therapy. The estimated survival rate is shown in Figure 4A. The observation period was 44±26 months. The 5-year survival rate after first-line sildenafil treatment was approximately 81%. We analyzed the factors associated with survival. Univariate analysis demonstrated that only the mean RA was related to death (Table 4). All the patients who died during the observation period were female, and their baseline NYHA FC was III. Therefore, sex and NYHA functional class were not included in the analysis.

Event-Free Rate According to the Composite Endpoint

The event-free rate for the composite endpoint of hospitalization for right-side heart failure and death is shown in Figure 4B. The observation period was 40±26 months. More than 75% of the patients had not reached the composite endpoint at 5 years. There were no significant variables related to the event in univariate analysis.

Nine of the enrolled patients needed hospitalization because of right-side heart failure; 7 needed additional epoprostenol because of right-side heart failure and the remaining 2 patients,

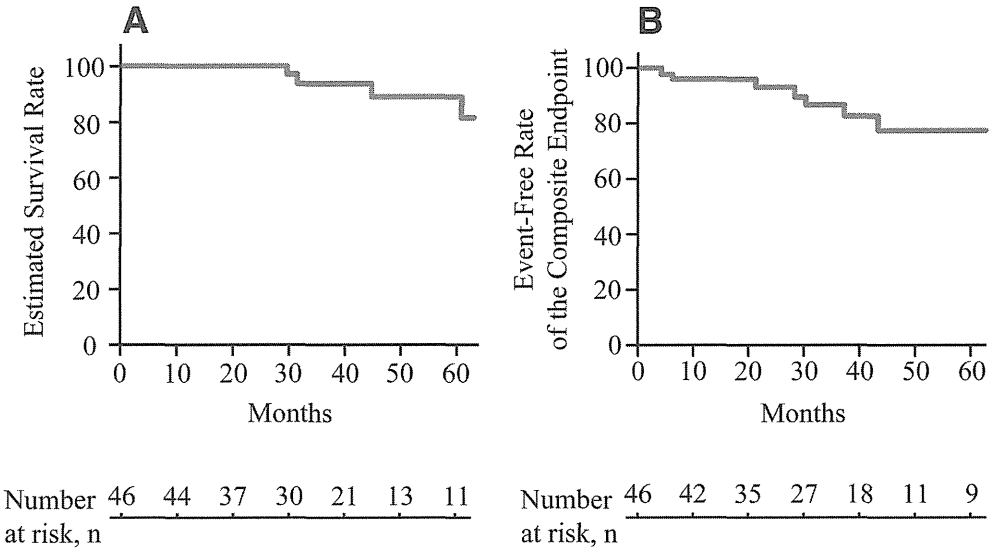

Figure 4. (A) Kaplan-Meier survival estimates for patients with pulmonary arterial hypertension (PAH) treated with first-line sildenafil therapy. (B) Kaplan-Meier estimates according to the composite endpoint of hospitalization for right-side heart failure and death.

Table 4. Statistical Analysis of Variables Correlated With Overall Survival

	HR (95%CI)	P value
Age	0.98 (0.92–1.05)	NS
mRA	1.26 (1.06–1.49)	<0.05
mPAP	1.01 (0.96–1.06)	NS
PVR	1.02 (0.92–1.13)	NS
CO	0.84 (0.32–2.18)	NS
6MWD	0.98 (0.96–1.01)	NS
BNP	1.00 (0.99–1.00)	NS

Abbreviations see in Tables 1,3.

who did not have additional epoprostenol, died because of rapid progression of right-side heart failure in the short term after hospitalization.

Discussion

This study demonstrated the long-term outcome of sildenafil administration as a first-line therapy. We found that: (1) all hemodynamic parameters improved significantly after sildenafil treatment in the enrolled patients as a whole; (2) more than 60% of the enrolled patients did not require the addition of epoprostenol for 5 years; (3) the patients who required additional epoprostenol were younger and had more severe hemodynamic characteristics at baseline; and (4) more than 75% of the patients did not reach the composite endpoint of hospitalization for right-side heart failure and death for 5 years.

Previous studies have demonstrated the efficacy of sildenafil for the treatment of PAH.[11,12,17–24] In the evidence-based algorithm established at Dana Point in 2008, sildenafil was defined as a first-line drug for PAH in patients with WHO functional class II or III.[16] In the present study, all the hemodynamic parameters and exercise capacity, as evaluated using the 6MWD, improved significantly after sildenafil treatment in the enrolled patients as a whole, and the BNP level tended to decrease. These results suggest that sildenafil is effective for the treatment of PAH, even when it is administered as a first-line therapy, and are consistent with the evidence-based algorithm. Furthermore, we analyzed the changes of NYHA FC during the observation period of sildenafil monotreatment (Table 2). The SUPER-2 study reported that the majority of patients who entered the SUPER-1 trial improved or maintained their FC and 6MWD.[12] Similar to the results of SUPER-2 study, the present study demonstrated that sildenafil monotreatment resulted in maintenance or improvement of NYHA FC in the majority of all enrolled patients (91.3%). Therefore, we consider that these results demonstrate the superiority of sildenafil as a first-line drug for PAH. Moreover, we analyzed the changes in hemodynamic parameters according to the addition of epoprostenol. In our results, all the hemodynamic parameters improved significantly after sildenafil treatment in the Epo(−) group, whereas no significant differences in any of the hemodynamic parameters were observed in the Epo(+) group. The baseline PVR and mean PA were significantly higher in the Epo(+) group compared with the Epo(−) group. These results suggest that first-line sildenafil monotreatment only was not sufficient to improve hemodynamics in patients who were more severe at baseline. However, this can lead to the suggestion that any hemodynamic parameter in the Epo(+) group was not significantly worsened, meaning that sildenafil treatment contributes to maintenance of clinical stability even in the baseline severe patients. It is consistent with maintenance of NYHA FC shown in Table 2.

Furthermore, in the present study, we focused on the occurrence of events, such as the addition of epoprostenol and the composite endpoint of hospitalization for right-side heart failure and death. Epoprostenol is recognized as the most powerful and effective treatment for PAH.[25,26] However, epoprostenol requires continuous infusion via an indwelling catheter, limiting the quality of life of the patient and a risk of

catheter infection. Thus, analyzing the clinical course of additional treatment with epoprostenol after first-line sildenafil monotreatment and investigating the characteristics of high-risk patients are important. In the present study, the age of the patients who required additional treatment with epoprostenol was significantly younger than the other patients. The baseline hemodynamics suggest that the severity of PAH among the patients who required additional treatment with epoprostenol was more severe than that of other patients. Furthermore, in the multivariate analysis, age at baseline was the only variable that correlated with the addition of epoprostenol. More patients under the age of 40 years (the median age) required the addition of epoprostenol treatment at an earlier stage, compared with the older patients. Thus, the severity of the disease may progress more rapidly among younger patients. There was no significant difference in the proportions of underlying causes of PAH between the younger and older patients. These findings suggest that patients who are younger or whose severity assessment at baseline is severe have a strong possibility of requiring the addition of epoprostenol treatment, and therapeutic efficacy may need to be frequently evaluated after the start of first-line sildenafil treatment among these high-risk patients to ensure timely introduction of epoprostenol treatment. Baseline NYHA FC did not influence the requirement of additional epoprostenol therapy in the present study, which suggests that the introduction of epoprostenol is prescribed by the degree of progression of disease rather than by the baseline disease status.

In this study, more than 75% of the patients did not reach the composite endpoint of hospitalization for right-side heart failure and death for 5 years after the start of first-line sildenafil therapy. In our study, 20%, 30%, and 37% of the enrolled patients received additional treatment with epoprostenol at 1, 3, and 5 years, respectively, after the start of first-line sildenafil therapy. These findings raise the possibility that combination therapy should be considered for patients who fail to improve or whose condition deteriorates after the start of first-line sildenafil therapy and that a fairly good prognosis can be expected if the severity assessment and the timing of epoprostenol introduction are appropriate.

The estimated 5-year survival rate after the start of first-line sildenafil therapy was approximately 81%. Several studies have demonstrated the survival in patients with PAH treated in the modern management era.[27–30] Compared with the recent studies, survival in this study was relatively better and was obtained when sildenafil was used as a first-line monotherapy. Therefore, it cannot be compared simply with the survival data of recent studies in the modern management era. However, the baseline NYHA FC III/IV in our study was 65% (there were no patients with NYHA FC IV in this study), whereas that in the recent studies was approximately 80%.[27,28,30] The difference in baseline NYHA FC may explain the difference between the survival in our study and that in other recent studies. In the present study, all of the patients who died were in NYHA FC III at baseline, demonstrating that baseline NYHA FC is generally a strong prognostic factor in the mortality of PAH patients. Our statistical analysis of variables associated with overall death demonstrated that only the mean RA at baseline was related to outcome, consistent with the results of several previous reports demonstrating that the mean RA strongly correlated with the outcome of patients with PAH.[29,31] Variables arising from right-side overload, such as the mean RA, may be better prognostic indicators, even when sildenafil is used as a first-line therapy.

Study Limitations

The study limitations are the insufficient observation period and small population. A study with a longer observation period and a larger number of patients is needed to confirm the present results and to ensure their accuracy.

Conclusions

We have shown the long-term outcome of sildenafil when used as a first-line therapy for patients with PAH. Our results suggest that sildenafil is emerging as a promising first-line drug for the treatment of PAH.

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CHEST

Original Research

PULMONARY VASCULAR DISEASE

Subpleural Perfusion as a Predictor for a Poor Surgical Outcome in Chronic Thromboembolic Pulmonary Hypertension

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Background: **Small vessel disease is a major determinant of poor outcome after pulmonary endarterectomy for chronic thromboembolic pulmonary hypertension (CTEPH). Out-of-proportion pulmonary vascular resistance (PVR) may indicate the presence of small vessel disease, but it is a very subjective evaluation. We investigated poor subpleural perfusion as a marker for small vessel disease and assessed its association with disease severity and surgical outcome of CTEPH.**

Methods: **We assessed the subpleural perfused area in the capillary phase of pulmonary angiography in 104 consecutive patients, including 45 who underwent surgery, and then divided the patients into either the well-perfused group (the subpleural space in at least one segment was well perfused [n = 75]) or the poorly perfused group (subpleural spaces were either unperfused or minimally perfused in all segments [n = 29]). We compared the pulmonary hemodynamics, degree of distal thrombi, and surgical outcome between these two groups.**

Results: **The poorly perfused group had significantly higher PVR (937 ± 350 dyne/s/cm^5 vs 754 ± 373 dyne/s/cm^5, *P* = .02) and more distal thrombi, resulting in fewer surgically treated patients (27.6% vs 49.3%, *P* = .04) compared with the well-perfused group. This group showed a higher surgical mortality (62.5% vs 2.7%) and higher postoperative PVR (656 ± 668 dyne/s/cm^5 vs 319 ± 223 dyne/s/cm^5, *P* = .04). Even in a multivariate analysis, poor subpleural perfusion was associated with surgical mortality.**

Conclusions: **Poor subpleural perfusion in the capillary phase of pulmonary angiography might be related to small vessel disease and a poor surgical outcome of CTEPH.**

CHEST 2012; 141(4):929–934

Abbreviations: CTEPH = chronic thromboembolic pulmonary hypertension; DSA = digital subtraction angiography; PAP = pulmonary arterial pressure; PE = pulmonary embolism; PVR = pulmonary vascular resistance

Chronic thromboembolic pulmonary hypertension (CTEPH) is characterized by pulmonary hypertension caused by nonresolving thromboemboli of the pulmonary artery. The true incidence and prevalence of CTEPH are unknown. From 0.1% to 0.5% of patients who survive an episode of acute pulmonary embolism (PE) have been reported to develop CTEPH.[1] A prospective study that followed patients with acute PE showed that 3.8% developed CTEPH within 2 years.[2] However, up to 40% of the patients with CTEPH demonstrate no clinically apparent acute embolic

Manuscript received March 28, 2011; revision accepted September 1, 2011.

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Funding/Support: The present study was supported in part by a grant to the Respiratory Failure Research Group from the Ministry of Health, Labor and Welfare of Japan [No. 23162501 to Dr Tatsumi] and a research grant from the Ministry of Education, Culture, Sports, Science and Technology of Japan [No. 22590849 to Dr Tanabe].

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DOI: 10.1378/chest.11-0769

episodes.[3] In addition, Galiè and Kim[4] suggested that acute PE might be an initiating event and that pulmonary hypertension may result from pulmonary vascular remodeling (small vessel disease).

Although pulmonary endarterectomy is an effective modality for the treatment of CTEPH, the most important cause of mortality is the inability to reduce pulmonary arterial pressure (PAP) due to small vessel disease. A high pulmonary vascular resistance (PVR) without parallel evidence of substantial proximal obstruction suggests significant distal vasculopathy and an unsuccessful postoperative outcome,[4,5] but it is difficult to evaluate the degree of pulmonary vascular remodeling in CTEPH from the central portions of pulmonary angiograms and the degree of PVR.

Patients with severe disease may show narrowing and a complete obstruction of pulmonary arteries due to thrombi as well as the elongation and pruning of pulmonary arteries in nonobstructed areas by thrombi on pulmonary angiograms. In these cases, subpleural spaces are either unperfused or minimally perfused in all segments in the capillary phase. In other cases, the subpleural space is well perfused in at least one segment in a nonobstructed area. We hypothesized that poor subpleural perfusion in all segments indicates a severe degree of small vessel disease, resulting in a poor outcome of surgery, and we retrospectively evaluated this hypothesis.

Materials and Methods

Design and Subjects

This was a retrospective single-center cohort study involving consecutive patients. Between July 2000 and December 2009, 110 patients were diagnosed with CTEPH at Chiba University Hospital. CTEPH was defined as mean PAP $\geq$ 25 mm Hg with a normal wedge pressure in patients who had dyspnea on exertion for $>$ 6 months. Additionally, lung perfusion scans were required to demonstrate segmental or larger defects concomitant with a normal ventilation scan. Helical CT scan angiography also was performed to confirm the diagnosis and to exclude large vessel arteritis and tumors. Finally, chronic thromboembolic findings were confirmed by pulmonary angiography.[6] Adequate selective angiography was performed in 104 of these 110 patients.

In the 104 cases, there were more female patients (n = 70) than male patients (n = 34). The age at catheterization ranged from 16 to 78 years (mean $\pm$ SD, 55.3 $\pm$ 13.0). Altogether, 43 patients (41.3%) had a history of DVT, 28 (26.9%) showed abnormalities in the screening for coagulopathy, and 23 (22.1%) had antiphospholipid antibodies. The mean PAP, cardiac index, and PVR were 44.6 $\pm$ 11.9 mm Hg, 2.59 $\pm$ 0.66 L/min/m^2, and 814 $\pm$ 400 dyne/s/cm^5, respectively. Pa_{O_2} while breathing room air was 58.3 $\pm$ 10.6 mm Hg. The 6-min walk distance while breathing appropriate oxygen was 344 $\pm$ 89 m. The number of patients in each World Health Organization functional class was as follows: class 1, n = 3; class 2, n = 29; class 3, n = 67; class 4, n = 5.

Pulmonary Endarterectomy Criteria

The selection criteria for pulmonary endarterectomy were slightly modified from those defined by Moser and colleagues.[7] Our criteria were (1) a mean PAP $>$ 30 mm Hg, resulting in a calculated PVR of $>$ 300 dyne/s/cm^5, even after oral anticoagulant therapy for $>$ 6 months; (2) World Health Organization functional class of $\geq$ 2; (3) thrombi defined as accessible to current surgical techniques (ie, presence at main, lobar, or segmental arteries); and (4) the absence of severe associated disease.[8] Forty-five patients underwent pulmonary endarterectomy. Fifty-nine patients were excluded from surgery because of mild disease (mean PAP $\leq$ 30 mm Hg) (n = 12), relatively peripheral-type thrombi (n = 42), and other associated conditions (age $>$ 70 years, n = 3; COPD, n = 1; thrombocytopenia, n = 1).

Pulmonary Angiography

Informed consent was obtained regarding the performance and risk of right-sided heart catheterization and digital subtraction angiography (DSA) and the respective exposure to radiation and contrast media. Serum creatinine level never exceeded 1.5 mg/dL. Pulmonary angiography was done in conjunction with right heart catheterization. For pulmonary DSA (Infinix; Toshiba Medical Systems Corporation), the right- and left-side pulmonary arteries were selectively catheterized using a 7F Berman catheter.

Arteriograms were acquired at 2 to 3 frames/s. Posteroanterior and lateral projections of each lung were obtained. The contrast bolus consisted of 18 to ~20 mL contrast material with iodine 300 mg/mL for each of the four series. The flow rate was 9 to ~10 mL/s. DSA images were digitally recorded and printed and then analyzed at a PACS workstation (DrABLE-EX; Fujitsu Limited).

We assessed the subpleural perfused area to be $\leq$ 1.5 cm (approximately one rib width) from the lateral pleura in the capillary phase of selective pulmonary angiography in the right- and left-side posterior and anterior views followed by lateral views of the dorsal area, and then divided the patients into either the well-perfused group (subpleural space in at least one segment was well perfused) (Fig 1) or the poorly perfused group (subpleural spaces were either unperfused or minimally perfused in all segments) (Fig 2). The analysis of pulmonary angiograms was done by two trained pulmonologists blinded to the patient's identity. To fully visualize subpleural perfusion, the level and contrast needed to be adjusted on the PACS workstation by each observer. The interobserver agreement between the two investigators also was confirmed by the McNemar test for the first 50 patients ($\kappa = 0.67$, $P < .0001$, n = 50). Final evaluations were achieved by consensus.

Assessment of the Extent of Central Thrombi and Intraoperative Classification

Using the Bergin method by CT scan angiography, the central arteries were defined as vessels proximal to the segmental branches and were divided into four portions. The central disease score was quantified by adding up the number of abnormal central portions in each patient up to a maximum score of 4.[9] Thromboembolic disease was visualized during surgery, and each patient was classified into one of the following four groups as reported by Thistlethwaite et al[10] (intraoperative classification): type 1, fresh thrombus in the main lobar pulmonary arteries; type 2, intimal thickening and fibrosis proximal to the segmental arteries; type 3, disease within the distal segmental arteries only; and type 4, distal arteriolar vasculopathy without visible thromboembolic disease.

The study was approved by the ethics committee of Chiba University (approval number 826). Written informed consent was obtained from each patient before catheterization.

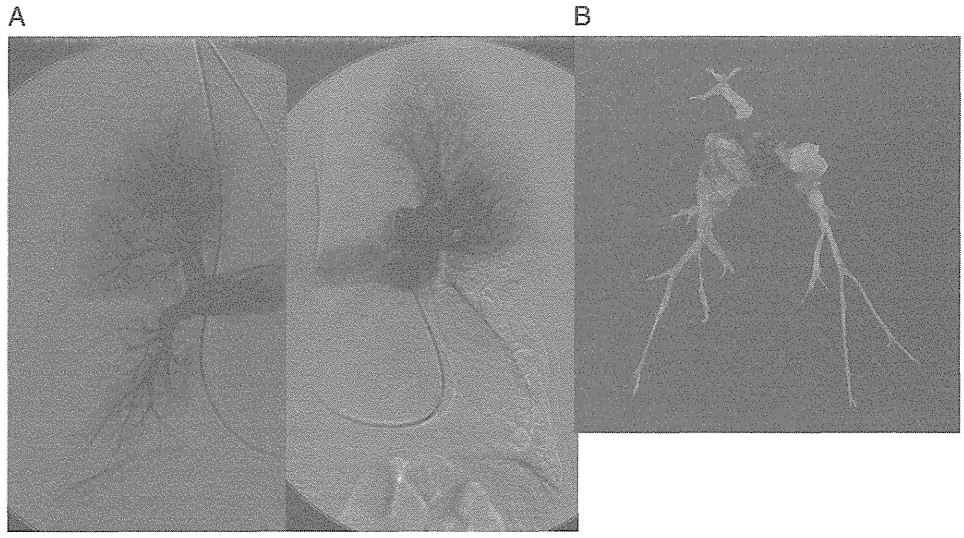

FIGURE 1. A, B, Capillary phase of pulmonary angiograms (A) and endarterectomized material (type 1) (B) in a well-perfused case (pulmonary arterial pressure, 73/23 [41] mm Hg; cardiac index, 2.1 L/min/m^2; PVR, 823 dyne/s/cm^5).

Statistical Analysis

The statistical analysis was performed using a commercially available software program (JMP 9 [Japanese version]; SAS Institute Inc). Comparisons of the well-perfused and poorly perfused groups in terms of the subpleural space were performed using the unpaired Student t test for continuous variables and by either the χ^2 test or the Wilcoxon test for categorical data, where appropriate. Risk factors for in-hospital death in the surgical group were identified using a univariate or multivariate logistic regression analyses. Correlations between postoperative PVR and preoperative parameters were analyzed by either univariate or multivariate linear regression analysis. $P < .05$ was considered to be significant.

RESULTS

Seventy-five patients comprised the well-perfused group, and 29 patients comprised the poorly perfused group. The poorly perfused group had a significantly higher mean PAP (49.5 ± 10.5 mm Hg vs 42.7 ± 11.9 mm Hg, $P = .008$) and PVR (969 ± 428 dyne/s/cm^5 vs 754 ± 367 dyne/s/cm^5, $P = .013$) and a lower central disease score compared with the well-perfused group, resulting in fewer patients meeting the operative criteria (27.6% vs 49.3%, $P = .04$) (Table 1). The overall hospital mortality after surgery

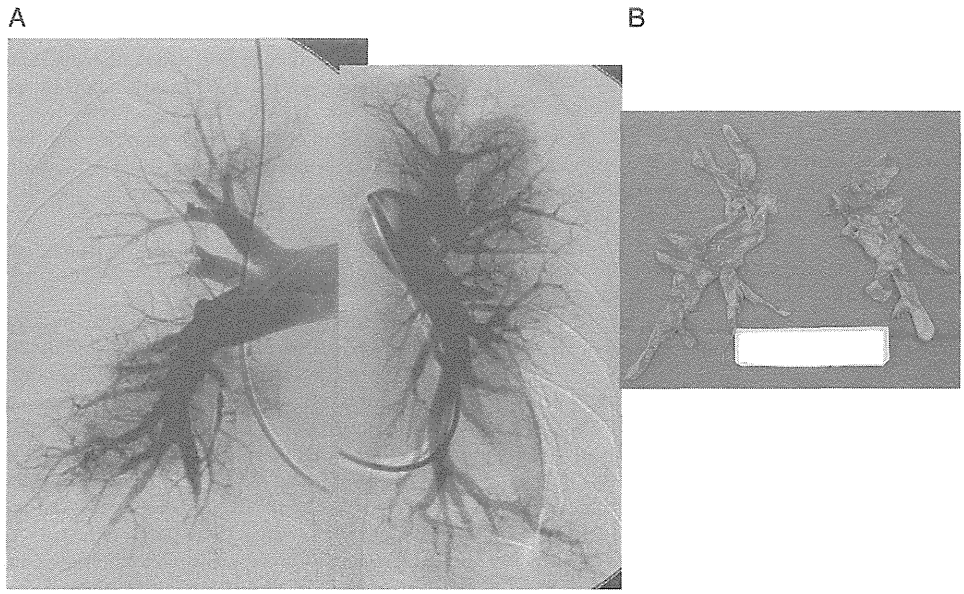

FIGURE 2. A, B, Capillary phase of pulmonary angiograms (A) and endarterectomized material (type 4) (B) in a poorly perfused case (pulmonary arterial pressure, 113/36 [62] mm Hg; cardiac index, 3.11 L/min/m^2; PVR, 1,414 dyne/s/cm^5). The picture of thrombotic material was provided with permission by Motomi Ando, MD, PhD.

Table 1—*Comparison of Clinical Characteristics Between the Well-Perfused and Poorly Perfused Groups*

Parameter	Well Perfused (n = 75)	Poorly Perfused (n = 29)	*P* Value
Age, y	56.9 ± 11.6	51.8 ± 11.6	.08
Female sex, No.	52	18	.48
Acute embolic episodes, %	50.7	44.8	.59
Underlying disease, %			
DVT	42.7	44.8	.84
Coagulopathy	30.7	17.2	.15
Anticardiolipin antibody	25.3	13.8	.19
Hemodynamics			
Mean right atrial pressure, mm Hg	5.0 ± 4.0	8.1 ± 5.1	.0015
Mean PAP, mm Hg	42.7 ± 11.9	49.5 ± 10.5	.008
Cardiac index, L/min/m^2	2.66 ± 0.69	2.41 ± 0.53	.08
PVR, dyne/s/cm^5	754 ± 367	969 ± 428	.013
Pao_2, mm Hg	58.6 ± 10.7	57.4 ± 10.5	.62
WHO functional class, No.			.009
I	3	0	
II	25	4	
III	46	21	
IV	1	4	
6-min walk distance, m	354 ± 87	317 ± 92	.07
Central disease score, No.			.027
0	18	16	
1	27	8	
2	18	4	
3	10	1	
4	2	0	
Surgical cases, %	49.3	27.6	.04

Data are presented as mean ± SD, unless otherwise indicated. PAP = pulmonary arterial pressure; PVR = pulmonary vascular resistance; WHO = World Health Organization.

was 13.3% (six of 45). Five patients died of residual pulmonary hypertension, whereas one patient in the poorly perfused group died of bleeding. The poorly perfused group had more patients with type 3 or 4 disease during surgery and showed a significantly higher hospital mortality (62.5% vs 2.7%, $P < 00001$) and higher postoperative PVR than the well-perfused group (Table 2). Although a univariate logistic regression analysis showed that a lower 6-min walk distance and poor subpleural perfusion to be associated with hospital death, a multiple regression analysis revealed that only poor subpleural perfusion was associated with hospital death (Table 3). The postoperative PVR was significantly correlated with the preoperative PVR, 6-min walk distance, World Health Organization functional class, and subpleural perfusion by univariate regression analysis. Multivariate regression analysis revealed poor subpleural perfusion to be an independent significant predictor for postoperative PVR (Table 4).

Discussion

Poor subpleural perfusion was found to be associated with surgical mortality as well as with a higher postoperative PVR. Even in a multivariate analysis, poor subpleural perfusion was associated with poor surgical outcome, although the poorly perfused group showed significantly more severe disease and more distal thrombi compared with the well-perfused group at baseline. To our knowledge, this report is the first to show poor subpleural perfusion to be associated with poor surgical outcome of patients with CTEPH.

Several issues still need to be considered when interpreting these results. First, we hypothesized that poor subpleural perfusion in all segments would reflect the degree of the severity of small vessel disease. As expected, the poorly perfused group showed a significantly lower central disease score, more cases of type 3 and 4 disease, and a higher PVR, suggesting a greater contribution of small vessel disease than that of the central thrombi to the severe pulmonary hemodynamic impairment in this group. In addition, poor subpleural perfusion was significantly associated with surgical mortality. Galiè and Kim[4] categorized the mechanism for small vessel disease seen in CTEPH into three processes as follows: (1) obstruction of small subsegmental elastic arteries, (2) classic pulmonary arteriopathy in small muscular arteries and arterioles distal to nonobstructed elastic pulmonary arteries, and (3) arteriopathy in small muscular arteries and arterioles distal to obstructed elastic pulmonary arteries. We excluded some cases with high PVR with respect to only subsegmental emboli or a few segmental emboli

Table 2—*Comparison of Surgical Outcome Between Well-Perfused and Poorly Perfused Groups*

Parameter	Well Perfused (n = 37)	Poorly Perfused (n = 8)	*P* Value
Preoperative mean PAP, mm Hg	46.7 ± 11.0	56.8 ± 6.2	.017
Preoperative PVR, dyne/s/cm^5	857 ± 342	1,184 ± 344	.019
Intraoperative classification			
Type, No.			< .0001
1	32	5	
2	5	0	
3	0	2	
4	0	1	
Postoperative mean PAP, mm Hg	24.8 ± 9.7	36.3 ± 18.9	.08
Postoperative PVR, dyne/s/cm^5	319 ± 223	656 ± 668	.04
Surgical mortality, No. (%)	1 (2.7)	5 (62.5)	< .0001

Data are presented as mean ± SD, unless otherwise indicated. See Table 1 for expansion of abbreviations.

from surgery. However, we had five patients with type 1 disease based on the intraoperative classification in the poorly perfused group, two of whom died of persistent pulmonary hypertension. Small vessel disease could have been present, even though the cases were classified as type 1 disease while also showing central thrombi.

Second, there have been several reports showing a higher PVR to be a significant prognostic factor for surgery.[3-5,8-12] In the present surgical series, the preoperative PVR in the surgical death cases was slightly higher than that in survivors (1,115 ± 260 dyne/s/cm^5 vs 884 ± 369 dyne/s/cm^5, $P = .15$), but it did not reach significance. Excluding the patients with a high PVR without substantial proximal obstruction may result in a smaller contribution of the PVR to the surgical outcome in our series.

Third, predicting the postoperative PVR is important because residual pulmonary hypertension correlates with surgical risk as well as with a poor quality of life at follow-up,[13,14] although a recent article reported that patients with residual pulmonary hypertension still do extremely well in the long term after surgery.[15] The presence of poor subpleural perfusion significantly correlated with postoperative PVR according to a multiple regression analysis. Thistlethwaite et al[10] reported that type 3 or type 4 diseases correlated with a higher postoperative PVR. Although the poorly perfused group included more patients with type 3 or 4 disease, the preoperative angiographic marker could be more helpful than intraoperative classification for determining the surgical indications and predicting postoperative PVR.

Fourth, we excluded 42 patients with relatively peripheral-type disease from surgery because of peripheral thrombi and out-of-proportion PVR without substantial proximal obstruction. A number of good surgical candidates may have been excluded from surgery in this series because out-of-proportion PVR is a subjective evaluation. Angiographic evaluation of the subpleural perfusion in addition to the out-of-proportion PVR may be needed to assess small vessel disease and improve patient selection for surgery.

Fifth, the use of CT scan pulmonary angiograms recently has been substituted for invasive pulmonary angiograms in the diagnosis of CTEPH. However, the present data indicate that pulmonary angiograms still play an important role in the evaluation of small vessel disease. Therefore, pulmonary angiogram remains an important tool in the preoperative evaluation of patients with CTEPH despite recent improvements in CT scan pulmonary angiograms.

Sixth, the guidelines show that the surgical mortality of 13.3% in the present series is higher than that of the current best CTEPH centers (4%-7%),[16] although it had decreased to 10% over the past 5 years. This higher mortality may be associated with inexperience in our center (fewer than five cases per year) rather than with the poor subpleural perfusion by angiographic evaluation.

Table 3—*Preoperative Parameters Associated With Surgical Death by Univariate and Multivariate Logistic Regression Analyses*

	Univariate Analysis		Multivariate Analysis	
Preoperative Assessment	OR (95% CI)	*P* Value	OR (95% CI)	*P* Value
Mean PAP	1.075 (0.99-1.185)	.10	...	...
PVR	1.007 (0.999-1.004)	.147	...	...
6-min walk distance	0.985 (0.968-0.997)	.031	0.985 (0.959-1.003)	.12
Subpleural perfusion (well vs poorly)	0.017 (0.0007-0.143)	.001	0.0197 (0.00049-0.248)	.0019

See Table 1 legend for expansion of abbreviations.

Table 4—*Correlation Between Preoperative Parameters and Postoperative PVR by Univariate and Multivariate Regression Analyses*

	Univariate Analysis		Multivariate Analysis	
Preoperative Assessment	Partial Regression Coefficient	*P* Value	Partial Regression Coefficient	*P* Value
Mean PAP	1.85	.07	...	...
PVR	2.59	.014	1.28	.21
6-min walk distance	−2.18	.037	−0.73	.35
WHO functional class	2.40	.02	1.69	.10
Central disease score	−1.64	.11		
Subpleural perfusion (well = 1, poorly = 0)	−2.86	.007	−2.39	.024

See Table 1 legend for expansion of abbreviations.

A finally limitation of the present study is related to it being retrospective and based on findings at a single institution. The results need to be confirmed prospectively in a large series from multiple institutions.

In conclusion, poor subpleural perfusion in the capillary phase of pulmonary angiography might be a useful new marker for small vessel disease. It may also be associated with a poor surgical outcome of CTEPH.

ACKNOWLEDGMENTS

Author contributions: Dr Tanabe had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Dr Tanabe: contributed to the design of the study, data analysis and interpretation, and writing and review of the entire manuscript.
Dr Sugiura: contributed to the data analysis and critical review of the manuscript.
Dr Jujo: contributed to the data analysis and critical review of the manuscript.
Dr Sakao: contributed to the data interpretation and critical review of the manuscript.
Dr Kasahara: contributed to the data interpretation and critical review of the manuscript.
Mr Kato: contributed to the imaging analysis, writing of the methods, and critical review of the manuscript.
Dr Masuda: contributed to performing the surgery, data interpretation, and critical review of the manuscript.
Dr Tatsumi: contributed to the data interpretation and critical review of the manuscript.
Financial/nonfinancial disclosures: The authors have reported to *CHEST* that no potential conflicts of interest exist with any companies/organizations whose products or services may be discussed in this article.
Role of sponsors: Neither the grant to the Respiratory Failure Research Group from the Ministry of Health, Labor and Welfare of Japan nor the research grant from the Ministry of Education, Culture, Sports,Science and Technology of Japan had a role in the design of this study nor in the decision to submit it for publication.
Other contributions: We thank Motomi Ando, MD, PhD, for his valuable surgical assistance and for providing a picture of thrombotic materials.

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INTERNAL MEDICINE

□ ORIGINAL ARTICLE □

Survival of Japanese Patients with Pulmonary Arterial Hypertension after the Introduction of Endothelin Receptor Antagonists and/or Phosphodiesterase Type-5 Inhibitors

Seiichiro Sakao, Nobuhiro Tanabe, Yasunori Kasahara and Koichiro Tatsumi

Abstract

Objective Although endothelin receptor antagonists (ERAs) and phosphodiesterase type 5 (PDE5) inhibitors have become the most commonly used treatments for pulmonary arterial hypertension (PAH) since their introduction in 2005, it remains unknown whether these medications play a significant role in the survival of Japanese patients with PAH.

Methods The cardiac catheterization and survival data of 103 PAH patients were retrospectively reviewed. A comparison of survival benefits with regard to the type of PAH was completed in PAH patients diagnosed between 2005 and 2012 and those diagnosed between 1983 and 2004 and in patients undergoing treatment with ERAs and/or PDE5 inhibitors and those being treated with conventional therapy and/or oral beraprost. Although pulmonary vascular resistance (PVR) at baseline differed, the more recent group showed better survival rates compared with those observed in the early group (5-year survival: 70.1% vs. 44.8) ($p<0.05$). In addition, the survival of PAH patients treated with ERAs and/or PDE5 inhibitors was superior to that of the patients treated without these medications (5- and 8-year survival: 77.8% and 66.7% vs. 39.0% and 37.0%, respectively) ($p<0.05$), especially in patient with idiopathic and heritable PAH.

Conclusion Superior survival rates are observed in patients with idiopathic and heritable PAH after introduction of ERAs and PDE5 inhibitors, and the use of these drugs provides benefits for survival.

Key words: pulmonary arterial hypertension (PAH), endothelin receptor antagonists (ERAs), phosphodiesterase type 5 (PDE5) inhibitors

(Intern Med 51: 2721-2726, 2012)
(DOI: 10.2169/internalmedicine.51.8162)

Introduction

An important pathological feature of pulmonary arterial hypertension (PAH) is pulmonary vascular remodeling associated with marked proliferation of pulmonary artery endothelial cells (ECs) and/or smooth muscle cells (SMCs) as well as components of the extracellular matrix that results in the obstruction of blood flow in resistant pulmonary arteries (1, 2). Moreover, it appears that all of these conditions ultimately lead to signaling imbalances between vasoconstrictive (e.g., endothelin) and vasodilatory (e.g., prostacyclin and nitric oxide) compounds (3).

There are three classes of drugs approved for the evidence-based treatment of PAH (4): prostacyclin analogues (e.g., epoprostenol, beraprost, treprostinil and iloprost [treprostinil and iloprost are approved outside Japan]), endothelin receptor antagonists (ERAs) (5, 6) (e.g., ambrisentan and bosentan) and phosphodiesterase type 5 (PDE5) inhibitors (7) (e.g., sildenafil and tadalafil). These drugs, which are currently used for the treatment of PAH, act not only by opposing any abnormal vasoconstriction, but also by inhibiting the growth of normal SMC (2). Because the drugs currently approved to treat PAH are not curative, patients require long-term therapy. In addition, long-term use of these drugs may provide sustained benefits in terms of exercise capacity and pulmonary hemodynamics in comparison to placebos or historical controls in patients with PAH (3).

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Received for publication May 14, 2012; Accepted for publication July 3, 2012
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Because of their availability and convenience, oral drugs (e.g., ambrisentan, bosentan, sildenafil and tadalafil) have recently become common treatments for PAH in Japan after being introduced in 2005. However, it remains to be elucidated whether these oral medications significantly improve survival in Japanese patients with PAH in comparison to conventional therapy.

Historically, the management of patients with PAH has been limited to conventional therapies such as anticoagulants, calcium channel blockers, diuretics, digoxin and supplemental oxygen. Beraprost was the first orally active and chemically stable prostacyclin analog to be developed and has been available for the treatment of PAH in Japan since 1992. Patients treated with beraprost demonstrate improvements in exercise capacity and symptoms within short-term durations (8). However, no beneficial effects of oral beraprost are observed on exercise capacity at nine or 12 months (9). This indicates that oral beraprost may not have sustained long-term effects. Therefore, this drug has a weak recommendation in the PAH evidence-based treatment algorithm (4) and has been approved only in Japan and Korea (10). In fact, because of its cost and availability, oral beraprost was the first-line therapy for PAH in Japan before the approval of ERAs and PDE5 inhibitors for the treatment of PAH. Therefore, in this study, the beneficial effects of ERAs and PDE5 inhibitors on survival were evaluated without regard to oral beraprost therapy.

The aim of this study was to investigate cumulative survival benefits with regard to types of PAH in patients with PAH after the introduction of ERAs and PDE5 inhibitors in comparison to those observed in patients treated with conventional therapy and/or oral beraprost.

Materials and Methods

Study subjects

From June 1983 to February 2012, 103 patients older than 15 years with PAH were treated at Chiba University Hospital. In all patients, the diagnosis of PAH was established using cardiac catheterization and based on a documented mean pulmonary arterial pressure ≥25 mmHg and a pulmonary capillary wedge pressure or left ventricular end-diastolic pressure ≤15 mmHg. All patients were classified as Group 1.1 to 1.4 on the current Dana Point classification (11). The study exclusion criteria were: 1) distal chronic thromboembolic pulmonary hypertension; 2) pulmonary veno-occlusive disease (PVOD) and/or pulmonary capillary hemangiomatosis (PCH); 3) left heart disease; and 4) chronic pulmonary disease (11). Although six of the 103 patients were classified as being in WHO function class IV, only four patients were treated with intravenous infusion of epoprostenol. Three of these patients were treated with ERAs and/or PDE5 inhibitors before the introduction of epoprostenol. According to Japanese legislation, informed consent is not required for retrospective collection of data corresponding to current practice. However, the database was anonymized and complied with the restrictive requirements of the Ministry of Health, Labor and Welfare dedicated to privacy, information technology and civil rights in Japan. The Ethics Committees of Chiba University Hospital approved the study protocol.

Efficacy measurements

The subjects were retrospectively divided into two groups: those diagnosed between 1983 and 2004 (n=66) and those diagnosed between 2005 and 2012 (n=37), since the introduction of ERAs and PDE5 inhibitors in Japan occurred in 2005. The subjects were further separated into two groups: those treated with ERAs and/or PDE5 inhibitors (n=36) and those treated with conventional therapy, including anticoagulants, calcium channel blockers, diuretics, digoxin, supplemental oxygen and/or oral beraprost and epoprostenol (n=67). In this analysis, the most recent hemodynamic data obtained before treatment were investigated. For more detailed analyses, the subjects were divided into subgroups according to types of PAH. The survival status of all patients was followed on a yearly basis and at the end of the study. Five of the 103 patients were lost to follow-up. The date of initiation of ERAs and PDE5 inhibitors was selected as the starting point to determine the survival period for assessing the effects of the drugs. The survival rates were calculated for all patients and by subgroups using Kaplan-Meier estimates. The baseline demographic and hemodynamic data were investigated in all patients and by subgroups.

Statistical analysis

The data were analyzed using JMP 9.0.0 (Japanese version, SAS Institute Inc., Tokyo, Japan) and the Excel-Toukei 2010 software program (Social Survey Research Information Co., Ltd., Tokyo, Japan). All results are expressed as the mean ± the SD for continuous variables and as the number or percentage for categorical variables. The baseline demographic and hemodynamic data were compared using unpaired Student's *t*-tests. The survival from all-cause death was estimated using the Kaplan-Meier method, and differences between groups were examined for significance using the log-rank test. Univariate and multivariate cox proportional hazards models were used to investigate the independent effects of the factors on survival. A p value of 0.05 was considered to be statistically significant.

Results

Baseline characteristics

One hundred and three patients with PAH were initially enrolled in this study (Table 1). The mean patient age was 46.9±15.0 years (range: 15 to 75) with a 4:1 female to male ratio. Forty-four patients (42.7%) were identified as having idiopathic and heritable PAH. The patients were followed for a mean period of 58.3±61.3 months and a median of