■膠原病性肺高血圧症は右心カテーテル検査でも高率な合併症であることが確認された。
■膠原病性肺高血圧症の基礎疾患は，欧米では強皮症が多く，日本や中国ではMCTDやSLEが多い。

未満，あるいは他で説明できないような呼吸困難がある場合には右心カテーテル検査を行った報告[4]がある。これによるとフランスでは467例中25例(5％)，イタリアでも698例中39例(6％)が右心カテーテル検査でPHと診断された。つまりgold standardの方法を用いても，SScをはじめとする膠原病ではPHが高率であることが最終的に確定されたことになる。この点においては，日本でも欧米でも違いはないと思われる。

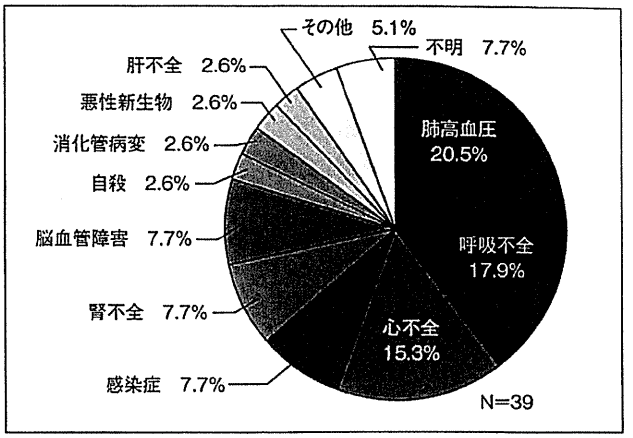

図1 MCTDの死因

欧米との相違点

1．基礎疾患の割合

ただCTD-PAHの基礎疾患を絶対数でみると，異なってくる。

全国疫学調査[1]では284例中SScが35.2%，MCTDが29.2%，SLEは28.9%であり，慶應義塾大学[5]でも70例中SScは19%と少なく，MCTDが43%，SLEが29%と多かった(図3)。さらに上海[6]でも103例中，SScは22%，MCTDが10%，SLEが38%であった。一方，欧米ではSScが6～7割と最も多く，MCTDは1割以下となっている。つまり欧米ではSScの頻度が著しく多く，日本や中国ではSLEやMCTDに多い傾向がみられる。MCTDは疾患概念が必ずしも確定しておらず，SLEやSScの亜型と捉えられることも少なくない。このため欧米ではMCTDがSScと診断されている可能性が考えられる。しかしながら欧州のdigital ulcer registry[7]ではSSc合併PHの患者数はトポイソメラーゼ1抗体陽性例が22%，抗セントロメア抗体陽性例が20%，抗U1-RNP抗体陽性例が3.2%であり(表)，抗U1-RNP抗体陽性例が少数のため，MCTD合併PHがSSc合併PHの中に組み込まれているとは考えにくい。

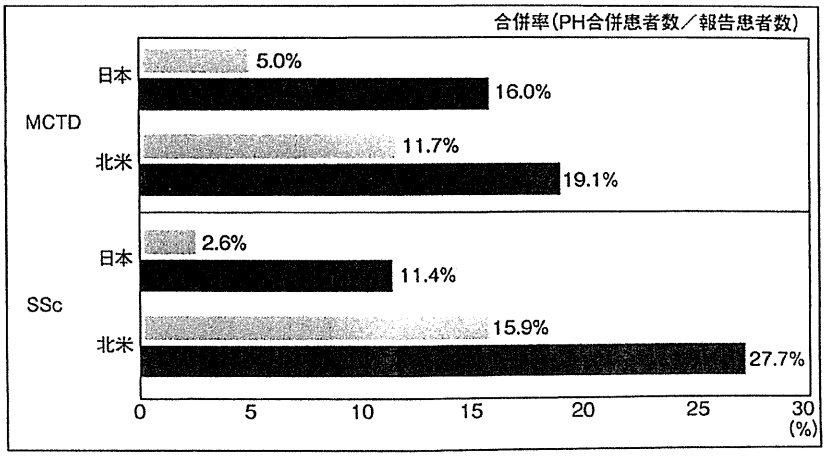

図2 膠原病に合併する肺高血圧症の割合

：主治医による　■：心エコーによる
北米：UNCOVER Study(50施設)[3] MCTD 94例，SSc 697例

2．関連する自己抗体

わが国では主に抗U1-RNP抗体陽性

■膠原病性肺高血圧症にみられる自己抗体は，欧米では抗セントロメア抗体，日本では抗U1-RNP抗体が多い。

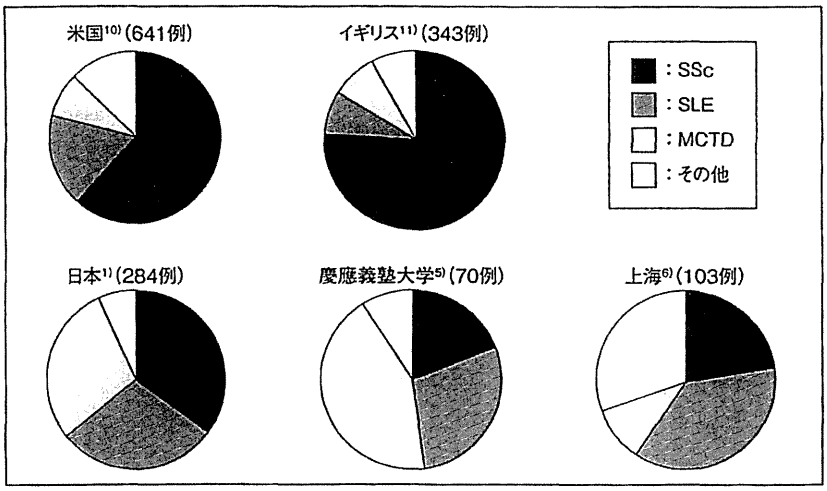

図3 膠原病合併PAHの基礎疾患の国別分布

表 強皮症性PAHの自己抗体の分布

	人数	ACA(%)	抗Topo1(%)	抗U1-RNP(%)
スペイン[8]	43	44	9.3	−
南オーストラリア[9]	18	28	17	22
欧州DUO[7]	600	20	22	3.2
慶應義塾大学[5]	13	60	8	8

例が多いのに対し，欧米では抗セントロメア抗体陽性例が多くみられる。これはわが国ではMCTDが多いのに対し，欧米ではSScが多いことから疾患構成の違いによる可能性が考えられる。SScに限ってPH患者の自己抗体を文献で検索した(表)。SScに限ってみると，必ずしも自己抗体のプロフィールが欧米とわが国とで大きく異なっているわけではなさそうである。やはり疾患構成の違いが自己抗体プロフィールに大きく影響しているものと思われる。

さいごに

CTD-PHのわが国と欧米との異同について概観してみた。この違いの原因は不明であるが，疾患構成が日本と中国，台湾で類似していることより，民族的な影響が考えられる。今後，診断や治療，予後などにおいて相互の成績の相違などを注意深く検証していく必要があると思われる。

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INTERNAL MEDICINE

□ CASE REPORT □

Pulmonary Tumor Thrombotic Microangiopathy with Circulatory Failure Treated with Imatinib

Aiko Ogawa[1], Ichiro Yamadori[2], Osamu Matsubara[3] and Hiromi Matsubara[1]

Abstract

Pulmonary tumor thrombotic microangiopathy is a lethal, yet difficult to diagnose, complication of gastrointestinal carcinoma. Even if properly diagnosed, there is no treatment, especially after a circulatory collapse. We herein report a case of pulmonary tumor thrombotic microangiopathy with circulatory failure due to pulmonary hypertension. The patient was temporarily successfully treated with imatinib, an inhibitor of the platelet-derived growth factor receptor. Pulmonary hypertension was dramatically ameliorated and the patient was able to be weaned from percutaneous cardiopulmonary support within 20 days of treatment. Imatinib may be effective for ameliorating pulmonary hypertension that is caused by pulmonary tumor thrombotic microangiopathy.

Key words: pulmonary tumor thrombotic microangiopathy, circulatory failure, treatment, imatinib

(Intern Med 52: 1927-1930, 2013)
(DOI: 10.2169/internalmedicine.52.0718)

Introduction

Pulmonary tumor thrombotic microangiopathy (PTTM) presents with rapidly progressive pulmonary hypertension related to carcinoma (1). The condition was originally reported in 1990, and since then, more than 50 cases have been pathologically diagnosed at autopsy. However, a clinical diagnosis of PTTM is difficult. In addition, there have not yet been any reported cases of patients who survived after the development of severe pulmonary hypertension with circulatory failure due to PTTM.

Case Report

A 47-year-old woman with no previous medical history was referred to our hospital for further treatment of pulmonary hypertension in August 2007. She had a three month history of dry cough, general fatigue and dyspnea upon effort. She visited a nearby hospital, was diagnosed with pulmonary hypertension and admitted to the hospital. Two days later, she presented with syncope and was transferred to our hospital. At the time of admission, a continuous infusion of dopamine (3 μg/kg/min) and dobutamine (3 μg/kg/min) was required. Her oxygen saturation was 99% with oxygen supplementation at 5 L/min. Electrocardiography showed sinus tachycardia with an SIQIIITIII pattern and negative T wave in V2 and V3, thus suggesting acute right ventricular overload (Fig. 1A). A chest radiography showed dilated pulmonary arteries, cardiomegaly and congestion (Fig. 1B). A high-resolution computed tomography (CT) scan demonstrated a nodular shadow and septal thickening with a slight amount of pleural effusion in the lung (Fig. 1C). A contrast-enhanced CT scan showed no tumor emboli to be present in the pulmonary arteries (Fig. 1D). Due to impaired hemodynamics, we could not perform either lung perfusion scintigraphy or pulmonary angiography at the time of admission. Echocardiography showed a dilated right atrium and ventricle. A right heart catheterization revealed an elevated pulmonary arterial pressure and a reduced cardiac output (Fig. 2). We immediately started bosentan and epoprostenol therapy in order to treat pulmonary hypertension. On Day 9, despite treatment with a continuous infusion of epoprostenol (3.8 ng/kg/min) with catecholamines, the hemodynamic data deteriorated. She manifested circulatory collapse and needed percutaneous cardiopulmonary support. Imatinib, an inhibi-

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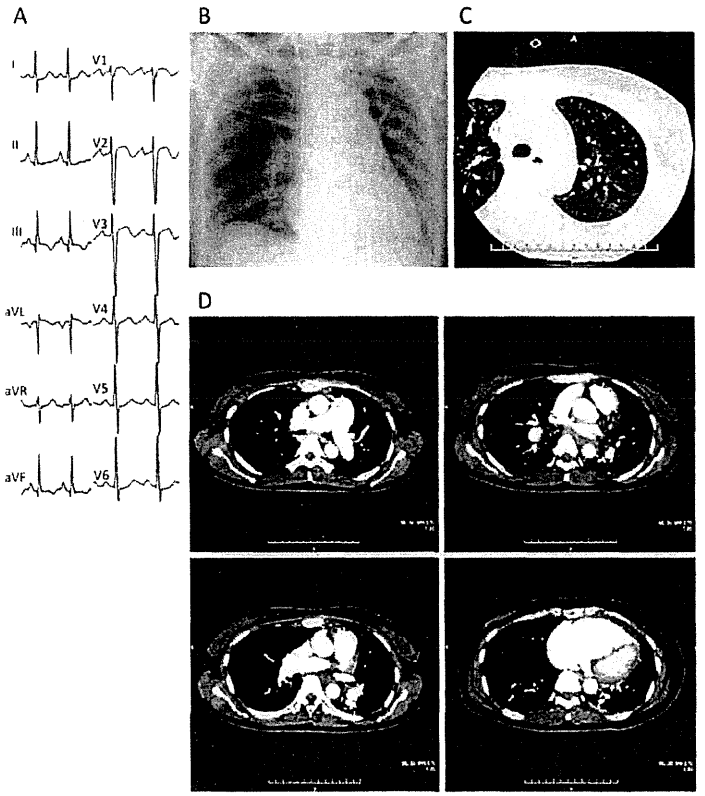

Figure 1. Images of the patient at admission. A: Electrocardiography shows sinus tachycardia with an SIQIIITIII pattern and negative T wave in V2 and V3. B: Chest radiography demonstrates dilated pulmonary arteries, cardiomegaly and congestion. C: High-resolution CT shows a nodular shadow and septal thickening with a slight amount of pleural effusion in the lung. D: A contrast-enhanced CT scan shows no tumor embolisms in the pulmonary arteries.

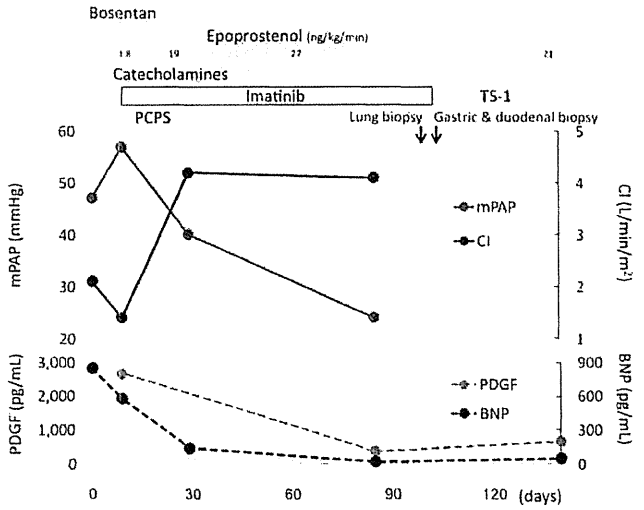

Figure 2. Time course of treatment. Mean pulmonary artery pressure (mPAP), cardiac index (CI) and plasma levels of platelet-derived growth factor (PDGF) and brain natriuretic peptide (BNP) are shown. Treatments including percutaneous cardiopulmonary support (PCPS) are also shown. The time points at which the biopsies were performed are indicated by arrows. Imatinib treatment successfully improved the hemodynamics, and PDGF decreased in parallel with the amelioration of mPAP.

tor of the tyrosine kinase receptor for platelet-derived growth factor (PDGF), was initiated (100 mg/day) and her pulmonary arterial pressure gradually decreased. She was successfully weaned from the percutaneous cardiopulmonary

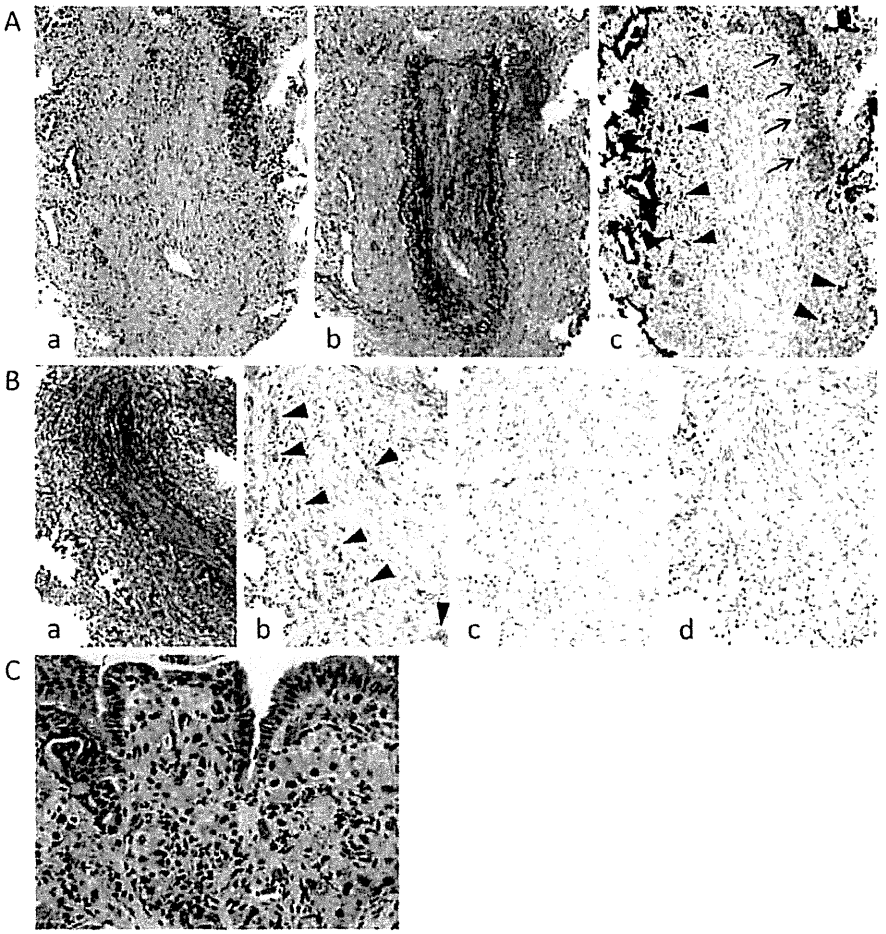

Figure 3. Histology of the lung and duodenal biopsy specimens. A: The lung biopsy specimen shows pronounced intimal thickening of a pulmonary artery (a: Hematoxylin and Eosin staining, b: elastica Masson stain). The tumor invasion can be observed in the parenchyma (arrowheads) and lymphatic vessels (arrows) (c: immunohistochemistry of cytokeratin 7). Note that the artery is stenosed, not by tumor embolism, but by a proliferation of vascular endothelial cells. B: The lung biopsy specimen shows a pulmonary artery that was stenosed by intimal thickening (a: elastica Masson stain). Vascular endothelial growth factor (b) is expressed in the tumor cells (arrowheads) that are scattered outside of the occluded vessel. PDGF-A (c) and PDGF-B (d) are not detected. C: The duodenal biopsy specimen shows the mucosa to be infiltrated by poorly differentiated adenocarcinoma.

support on Day 29. Her condition progressively improved and the hemodynamics nearly normalized by Day 85. Since we had never before observed such a rapid amelioration of pulmonary hypertension, a transbronchial lung biopsy was performed. The pathological examination revealed metastasized adenocarcinoma and PTTM (Fig. 3A). Vascular endothelial growth factor was expressed in the tumor cells, but not in the intimal cells (Fig. 3Ba and b). No expression of PDGF was detected in either type of cells (Fig. 3Bc and d). Screening for the primary focus revealed gastric and duodenal carcinoma (Fig. 3C). TS-1, an oral 5-fluorouracil derivative, was started on Day 104. Imatinib therapy was stopped because the hemodynamics had stabilized, and the patient was discharged on Day 140. A serial measurement of the plasma levels of PDGF showed a decrease in the PDGF levels in parallel with the amelioration of pulmonary hypertension (Fig. 2). She was followed up two months later, and the results of examinations suggested no evidence of pulmonary hypertension. She did not experience a recurrence of pulmonary hypertension. She died from the systemic metastasis of carcinoma approximately 9 months later. The family refused an autopsy; therefore, we could not obtain a histology sample of the lung.

Discussion

PTTM is generally related to gastrointestinal carcinoma and it triggers the development of advancing pulmonary hypertension. Pathologically, PTTM is caused by an obstruction of pulmonary arterioles by microembolisms of tumor cells, thrombus formation that is induced by the activation of thrombotic cascades on the surface of tumor embolisms and the abnormal proliferation of vascular endothelial cells caused by growth factors that are induced by tumors (2).

The clinical diagnosis of PTTM is extremely difficult (3). Even if PTTM is diagnosed, it is not treatable, and patients usually die within a couple of days.

Imatinib is a tyrosine kinase inhibitor that has been approved as an anticancer drug. The drug inhibits the phosphorylation of the PDGF receptor, and subsequently blocks many intracellular downstream signaling pathways. We originally decided to treat this patient with imatinib because of its possible efficacy in pulmonary arterial hypertension (4). However, a recent randomized study did not show significant improvement in the primary endpoint following the administration of imatinib (5) and in the present patient, the pathological diagnosis of PTTM was confirmed.

In our patient, the plasma levels of PDGF decreased in parallel with the amelioration of pulmonary hypertension following the administration of imatinib. Several tumor cells simultaneously produce PDGF and express PDGF receptors (6). The termination of the autocrine loop by imatinib may be one of the mechanisms of decreasing plasma PDGF levels. Imatinib down-regulates the expression of both PDGF and the PDGF receptor in tumor cells, thus resulting in increased apoptotic cell death and the inhibition of tumor angiogenesis, which even further decreases the production of PDGF by the tumor cells. In PTTM, PDGF and PDGF receptors are reportedly expressed in both carcinoma cells and endothelial cells (7). In the present case, PDGF was not detected in lung biopsy specimens of either the tumor cells or the initimal cells. Since the specimen was obtained only after the initiation of imatinib in this patient, we do not know whether PDGF was not expressed from the beginning or if the expression level was reduced to below detectable range following imatinib therapy. Considering the fact that the plasma PDGF levels were decreased following the imatinib treatment, it is possible that the expression level of PDGF could have been modified by imatinib therapy. Based on this limited information, it is difficult to determine which type of cells were affected by imatinib; namely, the tumor cells, the excessively-proliferated intimal cells or both.

We herein described a patient with PTTM who was at least temporarily successfully treated by imatinib. The patient's condition remarkably improved following the administration of imatinib. To the best of our knowledge, this is the first report of a case of PTTM with severe pulmonary hypertension that was successfully treated following a circulatory collapse. The findings from this case suggest that imatinib might have an ameliorative effect on pulmonary hypertension caused by PTTM, possibly by reducing the expression of PDGF. Further study is needed in order to elucidate the mechanism by which imatinib exerts its effect in PTTM.

Author's disclosure of potential Conflicts of Interest (COI).
Hiromi Matsubara: Honoraria, GlaxoSmithKline, Actelion Pharmaceuticals Japan, Nippon Shinyaku and Novartis Pharmaceuticals Corporation.

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EDITORIAL

Noninvasive and Accurate Evaluation of Cardiac Output in Patients With Pulmonary Hypertension

Kohtaro Abe, MD, PhD

Numerous methods of noninvasively measuring cardiac output (CO) have been developed,[1] but although these techniques have been used well to manage patients with cardiovascular diseases, their accuracy in patients with pulmonary hypertension (PH) has not been extensively investigated. An assessment of CO is very important in PH patients, because the severity of right ventricular dysfunction is a strong determinant of poor prognosis in these patients.[2] In particular, the hemodynamic status of patients with severe PH is often unstable and requires frequent monitoring. In recent guidelines, hemodynamic monitoring is recommended to be repeated either immediately after worsening of the clinical state or 3–6 months after the induction of a new treatment.[3,4] Therefore, reliable tools are needed to assess cardiac function. Although Doppler echocardiography is a noninvasive method that is frequently used to evaluate CO, the Doppler-derived CO is partly inaccurate in PH patients, probably because of the dependency on operator technique and the patient's enlarged heart geometry.[5,6] In addition, echocardiography is not a monitoring device. Right heart catheterization (RHC) is a direct measurement of hemodynamic parameters[7] and is a reliable tool for evaluating hemodynamic changes in PH patients. However, the frequent use of RHC is also limited by its invasiveness, infection risk, and expense.[8] Therefore, a noninvasive technique for monitoring CO is needed to help manage PH patients. This editorial provides an overview of the major methods for measuring CO, and discusses the usefulness of noninvasive CO measurement in patients with PH.

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Conventional Measurement of CO

In the 1890s, Adolph Fick presented the first method of estimating CO, which involved determining the relationship between the rate of oxygen uptake in an organ and the difference in oxy-

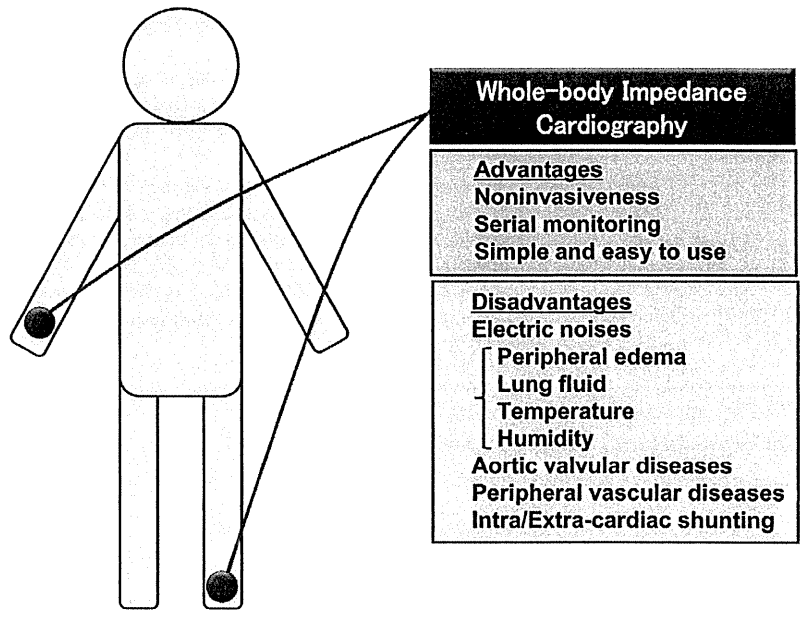

Figure. Wrist-to-ankle configuration of the electrodes, and the advantages and disadvantages of whole-body impedance cardiography (ICGWB).

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gen concentration. The Fick formula is as follows: CO=oxygen consumption/arteriovenous oxygen difference. To calculate the Fick-derived CO, arterial and mixed venous oxygen concentrations and oxygen consumption are invasively sampled using a pulmonary artery catheter. Although this technique has been modified to be a noninvasive method using re-breathing carbon dioxide, the accuracy of indirect Fick-derived CO in PH patients remains questionable.[9] In the 1940s, Hamilton developed a method that uses a dilution technique, referred to as the thermodilution method,[10] which determines the CO from the serial change in the temperature of an indicator, such as iced glucose, injected from the right atrium. Thermodilution-derived CO remains reliable in patients without a cardiac shunt, but the disadvantages of this method are its invasiveness and the inability to collect serial measurements. In 1994, Erlanger et al reported their serial measurement of CO based on arterial pressure pulse.[1] This pulse contour method determines the CO from the arterial pulse wave through an intra-arterial catheter in the radial artery. Although several minimally invasive techniques using pulse contour have become available to continuously measure CO,[1] the usefulness of these methods in patients with PH has never been tested.

Noninvasive Measurement of CO in PH Using Impedance Cardiography (ICG)

ICG is a plethysmographic technique of estimating CO.[11] The thoracic method (ICG$_T$) applies a high-frequency electric current of known amplitude and frequency across the thorax from electrodes placed on the root of the neck and on the lower chest. Numerous studies have demonstrated the accuracy of ICG$_T$-derived CO in healthy volunteers.[11] In patients with moderate PH, the ICG$_T$-derived CO has been reported to show a good correlation with RHC-derived CO.[12]

In this issue of the Journal, Taniguchi et al report that a noninvasive cardiac system (NICaS: NI Medical, Hod-Hasharon, Israel) is an accurate tool for noninvasively and serially measuring CO in patients with moderate PH.[13] This system noninvasively determines CO based on another ICG method, whole-body impedance cardiography (ICG$_{WB}$), which involves electrodes placed on 1 wrist and on the contralateral ankle (**Figure**). The study demonstrated that NICaS-derived CO determinations correlate well with thermodilution- and Fick-derived CO measurements.

Is ICG Useful in Patients With Severe PH?

Although ICG seems to be reliable for the noninvasive measurement of CO in patients with PH, there remains a specific issue with these measurements that must be considered. Two studies have demonstrated the accuracy of ICG-derived CO in patients with moderate PH, but it remains to be demonstrated whether the technique is reliable in patients with severe PH, who require frequent monitoring. Generally, the major disadvantage of ICG is the electric noise caused by various physiological factors, such as peripheral edema, lung fluid, body motion, temperature and humidity, which may alter the electric conductivity.[14] In fact, there was a poor correlation between ICG- and RHC-derived CO in patients with congestive heart failure,[14] whereas there was good correlation in patients with non-congestive heart failure.[15] These results suggest that the accuracy of ICG-based CO measurements in patients with some physiological factors, including peripheral edema and pulmonary congestion, might be questionable. In the study reported by Taniguchi et al, most of the enrolled patients showed normal CO levels by RHC analyses. Thus, the accuracy of ICG-derived CO in patients with severe PH has not been well investigated. To confirm the usefulness of the ICG technique for measuring CO in PH patients, its reliability in patients with severe PH must be definitively demonstrated.

In conclusion, a technique for the noninvasive measurement of CO is needed to manage patients with PH. The study reported by Taniguchi et al demonstrated that whole-body ICG may provide reliable CO data in patients with moderate PH. However, a large study is still needed to investigate the accuracy of this method in severe PH patients, who require frequent monitoring.

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ORIGINAL ARTICLE

Intravenous epoprostenol treatment of patients with connective tissue disease and pulmonary arterial hypertension at a single center

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Abstract
Objective To assess the efficacy of epoprostenol treatment in Japanese patients with pulmonary arterial hypertension (PAH) associated with connective tissue disease (CTD).
Methods Sixteen patients with PAH–CTD treated with continuous intravenous epoprostenol at a single center between 2000 and 2009 were enrolled. Baseline characteristics, short-term and long-term outcomes, predictors of mortality, and safety profiles were evaluated. For survival analysis, 16 controls were selected who matched the underlying CTD, World Health Organization functional class, and use of PAH drugs, except for epoprostenol.
Results Six patients had systemic lupus erythematosus, five had mixed CTD, four had systemic sclerosis, and one had primary Sjögren's syndrome. The mean pulmonary arterial pressure (mPAP), cardiac index (CI), pulmonary vascular resistance, and functional class were significantly improved during the first 6 months of epoprostenol treatment. Cumulative survival rates at 1, 2, and 3 years in epoprostenol-treated patients were 69, 69, and 55 %, respectively, and were significantly better than those of the controls. Functional class, CI at baseline, and reduction of mPAP at 6 months were identified as predictors of survival. Adverse events, including flushing and catheter-related infection, were frequent, but all patients tolerated the treatment.
Conclusion Based on the improvements in both short-term and long-term outcomes among our patient cohort, epoprostenol is an effective treatment for CTD patients with advanced PAH.

Keywords Epoprostenol · Functional class · Pulmonary arterial hypertension · Survival

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Introduction

Pulmonary arterial hypertension (PAH) is an intractable condition in patients with connective tissue disease (CTD) [1]. Over the past decade, PAH-specific vasodilative agents, including prostanoids, endothelin receptor antagonists (ERAs), and phosphodiesterase 5 inhibitors (PDE5Is), have become available for clinical use. A large prospective cohort study recently conducted in the USA demonstrated that modern treatments have substantially improved the short-term survival of patients with PAH associated with CTD (PAH–CTD) [2]. However, the long-term survival rates remain unsatisfactory. In recently reported studies conducted in Japan (by our group) [3], USA [4], France [5], UK [6], Sweden [7], and China [8], the 3-year survival rate was 76, 64 , 56, 47, 39, and 54 %, respectively.

Epoprostenol, a synthetic prostacyclin, is a potent vasodilator and inhibitor of platelet aggregation and smooth muscle cell growth. Due to its very short half-life, epoprostenol is administered by continuous intravenous infusion via a surgically implanted central venous catheter

using a portable pump. Because of this complex procedure, epoprostenol treatment is performed only at specialized pulmonary hypertension (PH) centers. Epoprostenol has been shown to improve the exercise capacity, hemodynamics, and short-term survival of patients with idiopathic PAH (IPAH) or PAH–CTD [9, 10].

In a randomized, open-label, controlled trial involving 111 patients with systemic sclerosis (SSc) and moderate-to-severe PAH, the 6-min walk distance, hemodynamic parameters, and World Health Organization (WHO) functional class were significantly better at 12 weeks in patients treated with epoprostenol than in those treated with conventional therapy alone [10]. Short-term efficacy for hemodynamic status and exercise capacity has also been reported in open-label studies of epoprostenol involving a small number of patients with non-SSc CTDs, such as systemic lupus erythematosus (SLE) [11, 12]. Based on its short-term efficacy together with the long-term survival benefits that have been demonstrated in large cohorts of patients with IPAH [13, 14], epoprostenol is strongly recommended as the first-line treatment regimen for PAH patients in WHO functional class III or IV, in the current evidence-based treatment algorithm [15]. In particular, intravenous epoprostenol is the only therapeutic option recommended as the first-line therapy for PAH patients in WHO functional class IV.

In contrast to the numerous findings showing the short-term and long-term efficacy of epoprostenol in patients with IPAH, only limited data are available on patients with PAH–CTD in the literature [16, 17]. In addition, to date, reports on evaluations of the efficacy and safety profiles of epoprostenol in Japanese patients with PAH–CTD, who have demographic and clinical characteristics different from patients in the USA and Europe [3], are lacking. In the study reported here, we evaluated the short-term and long-term treatment effects of epoprostenol, predictors of mortality, and safety profiles in patients with PAH–CTD who were treated with epoprostenol, using a cohort of one of the major tertiary PH referral centers in Japan.

Patients and methods

Study population

This retrospective study involved 16 patients with PAH–CTD who were treated with continuous intravenous epoprostenol. These patients were selected from the database of the specialized PH clinic of Keio University Hospital based on the following criteria: (1) initiation of treatment with continuous intravenous epoprostenol between 2000 and 2009 and (2) at least 6 months of follow-up unless the patient had died. Clinical diagnoses of SLE and SSc were made according to the American College of Rheumatology preliminary classification criteria [18, 19]. Mixed CTD (MCTD) was diagnosed according to the criteria proposed by Kasukawa and colleagues [20], and primary Sjögren's syndrome (SS) was diagnosed according to the revised criteria proposed by the American–European Consensus Group [21] without any apparent CTD. PAH was diagnosed as (1) a mean pulmonary arterial pressure (mPAP) of $\geq$25 mmHg at rest and a pulmonary capillary wedge pressure of $\leq$15 mmHg by right heart catheterization [22] and (2) PH was not attributable to left-sided heart disease, advanced interstitial lung disease (ILD) determined by a predicted forced vital capacity <70 %, or chronic thromboembolism. For survival analysis, 16 control PAH–CTD patients who matched the original patients in underlying CTD, WHO functional class, and use of PAH drugs after enrollment, but who had not received epoprostenol, were selected from our database. All clinical information and blood samples were obtained at first visit after the patients had given written informed consent; the study was approved by the Institutional Review Board.

Data collection

A complete medical history, physical examination, laboratory evaluations, and right heart catheterization were performed for each patient at the initiation of epoprostenol treatment. Hemodynamic parameters included mean pulmonary arterial pressure (mPAP), mean right atrial pressure (mRAP), cardiac output (CO), cardiac index (CI), pulmonary vascular resistance (PVR), and mixed venous oxygen saturation (SvO_2). The follow-up clinical and laboratory information was prospectively recorded in the database.

Epoprostenol was administered via a central venous catheter by an ambulatory infusion pump. Patients were started on a continuous infusion of epoprostenol at 0.5 or 1 ng/kg/min, and the dosage was gradually increased based on the patient's tolerance. Minimum target dosage at 6 months was 20 ng/kg/min. Adverse events and dosing information were recorded for all patients. Events most likely to be related to the underlying CTDs or the worsening of PAH were not considered to be drug-related. The short-term response was evaluated 6 months after the introduction of epoprostenol, based on hemodynamic parameters, WHO functional class status, and plasma brain natriuretic peptide (BNP) level. The serum antinuclear antibody (ANA) profile was obtained by an indirect immunofluorescence and immunoprecipitation assay [23]. All of the treatment regimens for PAH and the underlying CTD were recorded, and included PAH drugs (beraprost, epoprostenol, bosentan, and sildenafil) and immunosuppressive treatment, which consisted of corticosteroids

(>0.5 mg/kg prednisolone equivalent) with or without immunosuppressive agents, such as azathioprine and cyclophosphamide.

Statistical analysis

All continuous variables are shown as the mean ± standard deviation (SD). Unpaired and paired comparisons of continuous variables were made using the Mann–Whitney *U* test and Wilcoxon test, respectively. Categorical variables were compared by Fischer's exact test. Survival was analyzed using the Kaplan–Meier method, and the survival between two groups was compared using the log-rank test. The follow-up period for the analysis of survival data ended in December 2009. Univariate analysis with the Cox proportional hazards regression model was used to determine factors associated with an increased risk of mortality at 1, 3, and 5 years after the initiation of epoprostenol therapy. For this purpose, survival data in all patients were censored at year 1, 3, and 5, as described previously [3]. Twenty-two baseline characteristics were used as variables: presence or absence of Raynaud's phenomenon; ILD; underlying CTDs (SLE, MCTD, SSc, primary SS); ANA specificities (anti-U1RNP, anti-Sm, anti-SSA, anti-SSB, anticentromere, anti-topoisomerase I); WHO functional classes (II, III, and IV) as dichotomous variables; age, hemodynamic parameters (mPAP, PVR, CI, mRAP, and SvO_2), and BNP as continuous variables. Changes in hemodynamic parameters (mPAP, PVR, CI, mRAP, SvO_2) and BNP after 6 months of epoprostenol treatment were also used as continuous variables. Percent changes were calculated in comparison with the baseline values. With regard to factors selected to be associated with an increased risk of mortality by univariate analysis, cut-off values that best discriminated the favorable survival group from the poor survival group were further determined using receiver operating characteristic (ROC) curve analysis. Statistically significant results were presented as a hazard ratio (HR) with a 95 % confidence interval (95 % CI). Statistical analysis was performed using the SPSS ver. 19.0 statistical software (SPSS, Chicago, IL).

Table 1 Baseline demographic and clinical characteristics of PAH–CTD patients who were treated/not treated with epoprostenol

Demographic and clinical findings	Epoprostenol group ($n = 16$)	Control group ($n = 16$)	*P* value
Female	100 %	100 %	1.0
Age (years)	43 ± 14	36 ± 18	0.1
Raynaud's phenomenon	7 (44 %)	13 (81 %)	0.07
ILD	5 (31 %)	1 (6 %)	0.2
Underlying CTD			
SLE	6 (38 %)	6 (38 %)	1.0
MCTD	5 (31 %)	5 (31 %)	
SSc	4 (25 %)	4 (25 %)	
Primary SS	1 (6 %)	1 (6 %)	
Antinuclear antibody			
Anti-U1RNP	10 (62 %)	7 (44 %)	0.5
Anti-Sm	3 (19 %)	1 (6 %)	0.6
Anti-SSA	6 (38 %)	12 (75 %)	0.07
Anti-SSB	5 (31 %)	4 (25 %)	1.0
Anticentromere	3 (19 %)	4 (25 %)	1.0
Anti-topoisomerase I	1 (6 %)	0 (0 %)	1.0
WHO functional class (FC)			
II	1 (6 %)	1 (6 %)	1.0
III	8 (50 %)	8 (50 %)	
IV	7 (44 %)	7 (44 %)	
Hemodynamic parameters			
mPAP (mmHg)	56 ± 9	53 ± 12	0.6
mRAP (mmHg)	8.4 ± 5.0	6.3 ± 7.4	0.2
CO (L/min)	2.8 ± 1.4	3.5 ± 1.1	0.02
CI (L/min/m^2)	1.8 ± 0.7	2.4 ± 0.5	0.1
PVR (Wood units)	21 ± 9	14 ± 6	0.02
SvO_2 (%)	56 ± 12	59 ± 3	0.8
Plasma BNP (pg/ml)	1,033 ± 1,383	312 ± 286	0.2

PAH–CTD Pulmonary arterial hypertension associated with connective tissue disease, *ILD* interstitial lung disease, *SLE* systemic lupus erythematosus, *MCTD* mixed CTD, *SSc* systematic sclerosis, *SS* Sjögren's syndrome, *WHO* World Health Organization, *mPAP* mean pulmonary arterial pressure, *mRAP* mean right atrial pressure, *CO* cardiac output, *CI* cardiac index, *PVR* pulmonary vascular resistance, *SvO_2* mixed venous oxygen saturation, BNP, brain natriuretic peptide

Values are presented as the number with the percentage in parenthesis, or as the mean ± standard deviation (SD)

Results

Clinical characteristics at baseline

In our center, epoprostenol is indicated mainly for PAH patients with clinically apparent right heart failure, mPAP of ≥55 mmHg, and/or acute progression. Table 1 shows the demographic and clinical characteristics at baseline of 16 patients with PAH–CTD who were treated with epoprostenol. SLE, MCTD, and SSc were the major underlying CTDs, and this distribution was consistent with the entire cohort [3]. Anti-U1RNP antibody was the predominant ANA. All but one of the patients were classified as WHO functional class III or IV at the time of epoprostenol introduction. The hemodynamic parameters were severely impaired at epoprostenol introduction and included marked elevations of mPAP and mRAP, decreased CO and CI, a rise in PVR, and low SvO_2. The plasma BNP was also highly elevated. Prior treatment and outcomes in individual patients are listed in Table 2. Twelve patients

(75 %) had not been treated with any PAH drug or had been treated with beraprost alone. This is probably because beraprost and epoprostenol were the only drugs approved for PAH before 2005 in Japan. Epoprostenol therapy was initiated within 1 year after the diagnosis of PAH in the majority of the patients because there was no other treatment option at that time. Beraprost treatment was terminated upon the introduction of epoprostenol, but sildenafil and bosentan treatments were maintained. Thus, 12 patients received epoprostenol monotherapy, two received a combination therapy with sildenafil, and the remaining two patients received a combination therapy with sildenafil and bosentan. Seven patients had received immunosuppressive treatment in advance, but their PAH responded poorly or insufficiently to this treatment. The WHO functional class had been improved in one patient with MCTD (#15) from class III to II by treatment with high-dose prednisolone before the introduction of epoprostenol therapy. In none of the patients were the epoprostenol treatment and immunosuppressive treatment (either initiation or intensification) started simultaneously. Oxygen supplementation was started prior to the introduction of epoprostenol for all patients.

Short-term efficacy

We evaluated the short-term efficacy of epoprostenol after 6 months of treatment in only 12 patients because four patients had died during this period. Of the four patients who died, three patients had uncontrolled right heart failure and died within a few weeks after the initiation of epoprostenol therapy.

The dose escalation data for the first 6 months of epoprostenol treatment in the 12 patients are shown in Fig. 1. The dose was increased to 23 ± 4 (range 18–31) ng/kg/min by 6 months. The dose escalation pace was relatively slow due to some patients experiencing adverse effects, but nearly all patients were able to tolerate 20 ng/kg/min of epoprostenol, which was the minimum target dose. No PAH drug or immunosuppressive therapy was added to the therapeutic regimen during the first 6 months. The changes in hemodynamic parameters after 6 months of epoprostenol treatment are shown in Fig. 2. All the hemodynamic parameters and the BNP level showed overall trends toward improvement, but a few patients experienced worsening of these parameters. Significant improvement was observed in the mPAP (26 % reduction from baseline; $P = 0.006$), CI (36 % increase from baseline; $P = 0.02$), and PVR (41 % reduction from baseline; $P = 0.009$). In addition, the mRAP and BNP tended to decrease and SvO_2 tended to increase after 6 months of epoprostenol treatment. The distribution of WHO functional class at baseline and after 6 months of epoprostenol treatment is shown in Fig. 3. The WHO functional class improved or remained the same for all the patients. The change in functional class during the 6-month treatment period was statistically significant ($P = 0.02$).

We further evaluated potential associations between epoprostenol dosage at 6 months and changes in the hemodynamic parameters. When the 12 patients who were still alive after the first 6 months of epoprostenol were subgrouped into two groups based on epoprostenol dosage at 6 months that was higher or lower than the average dosage at this time (23 ng/kg/min), the reduction of mPAP from baseline was more prominent in patients who were able to increase the higher dosage, compared with those who were not (23 ± 6 vs. 8 ± 11 mmHg; $P = 0.02$).

Survival

All 16 patients enrolled in the study continued epoprostenol treatment during follow-up. When the four patients who died early in the course of epoprostenol treatment were excluded from the analysis (patients #1–4 in Table 2), the maximum dosage administered during follow-up was 31 ± 7 (range 22–43) ng/kg/min, and the duration of epoprostenol treatment was 52 ± 27 (range 9–90) months. Of the original 16 patients, 11 had died by 28 ± 27 (range 0.2–73) months following the initiation of epoprostenol treatment. All causes of death appeared to be related to PAH, including uncontrolled right heart failure and sudden death. During the disease course, sildenafil and bosentan were added to the epoprostenol therapeutic regimen of four patients and one patient, respectively (Table 2). The 1-, 2-, and 3-year survival rates in epoprostenol-treated patients were 69, 69, and 55 %, respectively (Fig. 4). To examine if epoprostenol treatment improved prognosis, the survival curve in epoprostenol-treated patients was compared with that of 16 control patients who matched the original patients in terms of underlying CTD, WHO functional class, and use of PAH drugs after enrollment, but who had not received epoprostenol. Comparison of the baseline characteristics of the epoprostenol versus control group revealed that the CO and PVR were worse in the epoprostenol group than in the control group ($P = 0.02$ for both comparisons), but other findings were comparable between these two groups (Table 1). In the control group, four patients and one patient were treated with sildenafil and bosentan, respectively, after enrollment. The survival rates in the control group were 56, 25, and 6 % at 1, 2, and 3 years, respectively, and the overall survival was significantly worse than that of the epoprostenol group ($P = 0.02$), even though hemodynamic parameters were worse in the control group.

Table 2 Prior treatment for PAH and outcomes in individual patients with PAH–CTD enrolled in this study

Case	Age at Epo introduction (years)	Underlying CTD	Prior treatment for PAH		WHO-FC at Epo introduction	Time between PAH diagnosis and Epo introduction (months)	Additional treatment during Epo treatment	Follow-up period (months)	Outcome
			PAH drugs	Immunosuppressive treatment					
#1	24	SLE	Ber	None	IV	12	None	1	Dead
#2	22	MCTD	Ber	PSL	IV	9	None	1	Dead
#3	68	SSc	Ber	None	IV	0	None	1	Dead
#4	27	SLE	Ber	PSL, IVCY	III	2	Sil	3	Dead
#5	47	SLE	Ber	None	III	0	Sil	9	Dead
#6	50	SLE	Ber, Sil, Bos	None	III	69	None	13	Alive
#7	48	SLE	Ber, Bos, Sil	PSL	IV	69	None	27	Dead
#8	57	MCTD	Ber	PSL	IV	9	None	32	Dead
#9	52	SSc	None	None	III	0	None	48	Dead
#10	40	SSc	Ber	None	III	0	Sil	55	Dead
#11	51	SSc	Ber, Sil	None	IV	2	None	58	Dead
#12	45	MCTD	Ber, Sil	None	III	14	None	71	Alive
#13	30	Primary SS	Ber	None	III	0	Bos	73	Alive
#14	62	MCTD	Ber	None	IV	0	Sil	73	Dead
#15	29	MCTD	Ber	PSL	II	0	None	77	Alive
#16	31	SLE	None	None	III	0	None	90	Alive

Epo epoprostenol, *Ber* beraprost, *Sil* sildenafil, *Bos* bosentan, *PSL* prednisolone, *IVCY* intravenous cyclophosphamide pulse therapy

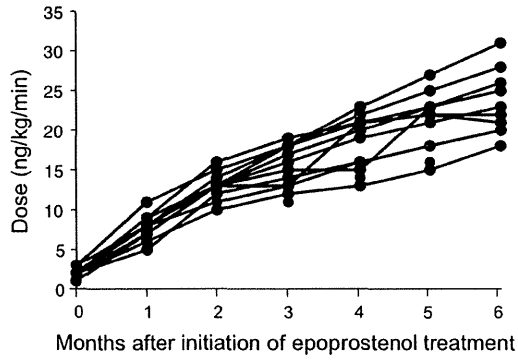

Fig. 1 Dose escalation during the first 6 months of epoprostenol treatment for the 12 patients who completed 6 months of continuous intravenous epoprostenol treatment. Epoprostenol was started at 0.5 or 1 ng/kg/min, and the dosage was increased gradually based on tolerability

Predictors of mortality

To identify variables that predict outcomes in patients with PAH–CTD who were treated with epoprostenol, we first analyzed 22 baseline parameters at the time of initiating epoprostenol therapy for all 16 patients. Since the majority of patients enrolled had low survival rates, outcomes were analyzed by setting the follow-up period at 1, 3, and 5 years, respectively, after the introduction of epoprostenol. This analysis enabled us to identify predictors of early and late mortality separately. The results of univariate analysis identified the WHO functional class and CI at baseline as sole predictors of mortality (Table 3). Patients in WHO functional class IV at baseline tended to have an increased risk for mortality throughout the disease course, but only the hazard ratio at 3 years reached statistical significance (HR 6.49; $P = 0.03$). In fact, patients in WHO functional class IV at baseline had a significantly worse survival rate than those in WHO functional classes II and III combined ($P = 0.02$) (Fig. 5a). In contrast, the baseline CI was associated with mortality 5 years after the initiation of epoprostenol treatment (HR 0.21; $P = 0.049$), but this variable showed less impact on shorter term survival, i.e., at 1 and 3 years. The cut-off value for baseline CI that best discriminated the favorable survival group from the poor survival one was determined to be 1.9 L/min/m^2 by ROC curve analysis. The cumulative survival rates were significantly different between groups stratified by a baseline CI higher and lower than 1.9 L/min/m^2 ($P = 0.01$) (Fig. 5b).

In the 12 surviving patients, we further investigated whether the short-term treatment response to epoprostenol

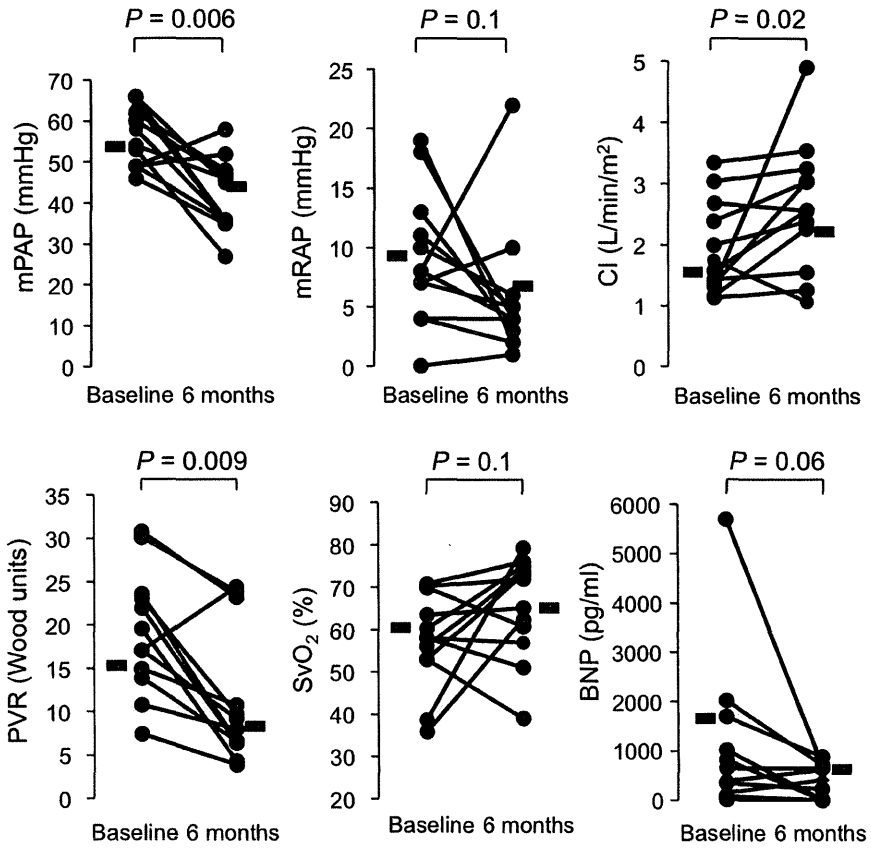

Fig. 2 Changes in hemodynamic parameters and the plasma brain natriuretic peptide (*BNP*) level after the first 6 months of epoprostenol treatment in the 12 patients who were still alive. *Bold lines* Mean of individual data. *mPAP* Mean pulmonary arterial pressure, *mRAP* mean right atrial pressure, *PVR* pulmonary vascular resistance, *CI* cardiac index, SvO_2 mixed venous oxygen saturation

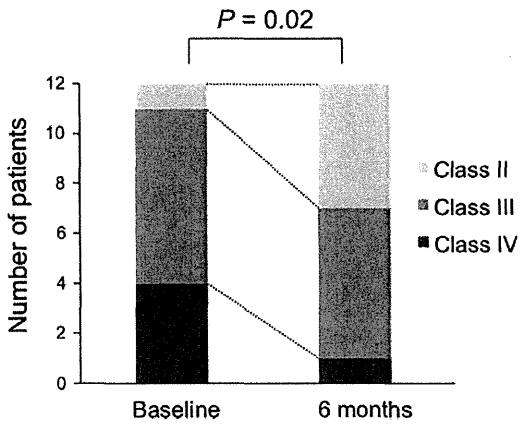

Fig. 3 Distribution of World Health Organization functional class at baseline and after 6 months of epoprostenol treatment in the 12 patients who were still alive after 6 months of treatment

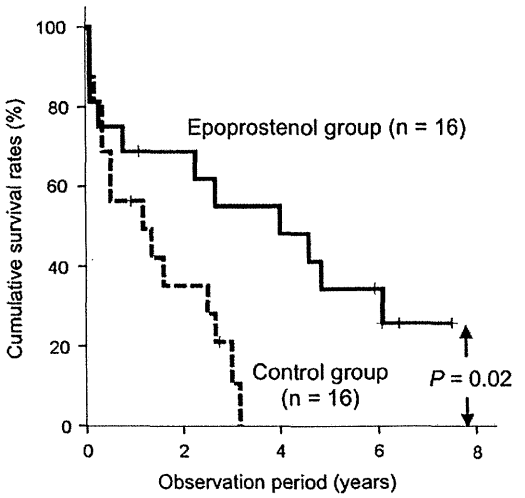

Fig. 4 Cumulative survival rates in 16 patients with PAH–CTD who were treated with epoprostenol (epoprostenol group) and 16 historical controls selected from our database that matched the patients in terms of underlying CTD, WHO functional class, and use of PAH drugs except for epoprostenol (control group). The groups were compared using the log-rank test

at 6 months was associated with subsequent outcomes. Using changes in hemodynamic parameters (mPAP, PVR, CI, mRAP, SvO_2) and BNP as variables, we identified a change in mPAP after 6 months of epoprostenol treatment as the sole predictor of mortality at 5 years (HR 0.95, 95 % CI 0.90–0.99, $P = 0.03$). The cut-off value for change in mPAP after 6 months that best discriminated the favorable survival group from the poor survival one was determined to be 25 % by the ROC curve analysis. Patients who had achieved a ≥25 % reduction of mPAP at 6 months had a

Table 3 Baseline predictors of mortality at 1, 3, and 5 years after initiation of epoprostenol treatment

Variable	Mortality					
	1 year		3 years		5 years	
	HR (95 % CI)	*P*	HR (95 % CI)	*P*	HR (95 % CI)	*P*
WHO functional class IV	8.88 (0.97–80.88)	0.053	6.49 (1.23–34.19)	0.03	3.27 (0.91–11.72)	0.07
CI (L/min/m^2)	0.40 (0.07–2.22)	0.3	0.23 (0.04–1.40)	0.1	0.21 (0.04–0.99)	0.049

HR hazard ratio, *95 % CI* 95 % confidence interval

better survival rate than those who did not ($P = 0.005$) (Fig. 6).

Safety profiles

All 16 patients reported at least one epoprostenol-related adverse event, and 46 events were recorded during 40 ± 32 months of follow-up (Table 4). The most common adverse event was flushing. Flushing, headache, and diarrhea occurred during the dose-escalating phase and were self-limiting, although these symptoms often led to a delay in the scheduled dose escalation. Seven patients (44 %) experienced a total of 25 episodes of catheter-related infection, which required hospitalization, catheter replacement, and treatment with intravenous antibiotics. Notably, the majority of patients with this event had repeated episodes, and three patients experienced more than four events. None of the patients died of this complication. Comparison of the characteristics between patients with and without catheter-related infection revealed no parameters associated with an increased risk. However, there was a trend toward an increased frequency of concomitant immunosuppressive treatment in patients with catheter-related infection than in those without (71 vs. 22 %; $P = 0.1$). Severe thrombocytopenia occurred in three patients with SLE. The platelet count in two patients partially recovered with an increased dosage of corticosteroids in combination with cyclosporin or intravenous immunoglobulin, but it did not reach the normal range while the patients were on epoprostenol treatment. The platelet count in the remaining patient was increased by reducing the epoprostenol dosage. None of the adverse events led to a discontinuation of epoprostenol.

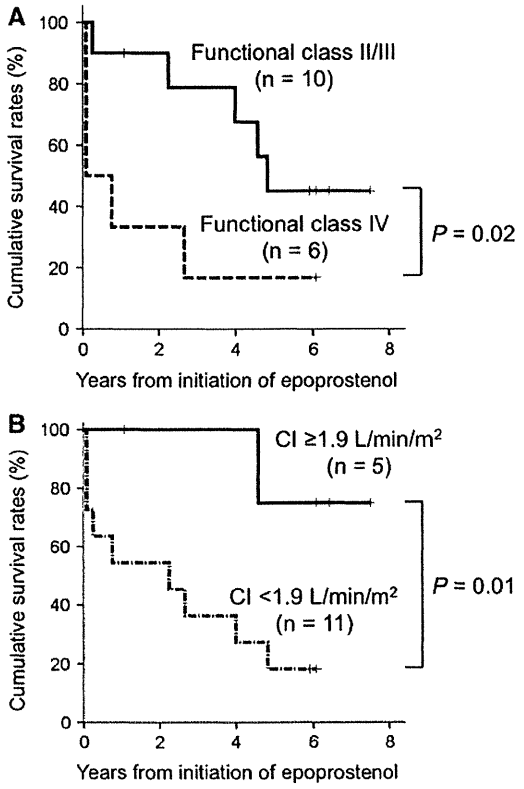

Fig. 5 Cumulative survival rates in 16 patients with PAH–CTD who were treated with epoprostenol, stratified by baseline WHO functional class (II/III vs. IV) (**a**) or baseline CI (≥1.9 vs. <1.9 L/min/m^2) (**b**). The two groups were compared using the log-rank test

Discussion

In this study, we observed a significant improvement in WHO functional class status and hemodynamic parameters, including the mPAP, CI, and PVR, after 6 months of epoprostenol treatment in CTD patients with advanced PAH who presented with severely impaired functional class and hemodynamics. Short-term hemodynamic improvement resulting from epoprostenol treatment in CTD patients with severe PAH was also reported in 111 patients with SSc at 12 weeks [10], 15 patients with various CTDs at 6 weeks [11], and four patients with SSc at 9–16 weeks [12]. In addition, we found that epoprostenol treatment prolonged the survival of patients with PAH–CTD compared with matched controls who had not received epoprostenol treatment. Adverse events related to vasodilation of the peripheral vasculature and catheter-related infection occurred frequently, but epoprostenol treatment was well tolerated in general. Our findings collectively confirm the efficacy of epoprostenol in Japanese patients with CTD and advanced PAH.

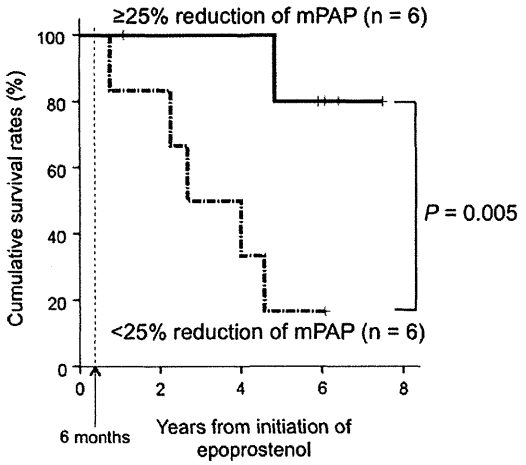

Fig. 6 Cumulative survival rates in 12 patients with PAH–CTD who had survived for 6 months after initiation of epoprostenol treatment, stratified by the change in mPAP after the first 6 months of epoprostenol treatment (≥25 % reduction vs. <25 % reduction). The two groups were compared using the log-rank test

Table 4 Adverse events related to epoprostenol treatment in 16 patients

Adverse event	Number of patients (%)	Total number of events
Flushing	13 (81)	13
Catheter-related infection	7 (44)	25
Severe thrombocytopenia (<30,000/μL)	3 (19)	3
Headache	3 (19)	3
Diarrhea	2 (13)	2

On the other hand, the long-term survival benefits in PAH–CTD patients treated with epoprostenol are less clear. In our study, the survival rates at 1, 2, and 3 years of epoprostenol treatment were 69, 69, and 55 %, respectively. These survival values are better than those of two earlier studies, which showed 1-, 2-, and 3-year survival rates of 58, 41, and 34 % [16] and 71, 52, and 48 %, respectively [17]; however, these previous results were derived solely from SSc patients, who generally have worse outcomes that patients with other forms of PAH [2, 6]. Moreover, it is notable that three of our patients died within a few weeks after the introduction of epoprostenol. Cases of early death were also reported in previous studies [10, 11, 24]. The majority of these patients died primarily of uncontrolled heart failure due to severely impaired hemodynamics, but the dilation of peripheral vasculature by epoprostenol may have contributed to the worsening circulatory insufficiency. Supportive therapies, such as catecholamine derivatives and/or percutaneous cardio-pulmonary support, should be included, especially for patients with very low CO and systemic blood pressure. It is important to recognize that the efficacy of epoprostenol is apparently limited in patients with end-stage PAH.

Our study also provided simple baseline predictors of long-term survival in epoprostenol-treated patients with PAH–CTD: WHO functional class II/III and a CI > 1.9 L/min/m^2 were associated with a favorable outcome. The WHO functional class, although it seems subjective, was a powerful predictor of survival, as also found by Kuhn and colleagues, whose study involved 91 patients with various forms of PAH, including 19 with SSc and five with SLE [16]. In addition, a ≥25 % reduction in the mPAP after the first 6 months of treatment with epoprostenol was a strong predictor of a good prognosis, suggesting that hemodynamic evaluation after 6 months of treatment provides a useful marker for stratifying the risk of death during long-term follow-up. In contrast, none of the baseline or follow-up hemodynamic parameters was selected as a predictor of future outcome in Kuhn's study [16], probably because these authors were analyzing patients with heterogeneous forms of PAH.

Our data can be readily translated into clinical practice. First, we demonstrated that in our patients with PAH–CTD long-term survival was favorable if epoprostenol was initiated when the functional status did not worsen beyond WHO functional class III and the CI was preserved. While the current treatment algorithm recommends epoprostenol, ERAs, and PDE5Is as the first-line treatment for patients in WHO functional class III [15], epoprostenol should be used in patients with severely impaired hemodynamics and/or acute progression. Second, we found that a prominent reduction in mPAP during the first 6 months of epoprostenol treatment was a predictor for favorable outcome. Thus, the dosage of epoprostenol should be escalated as sharply as possible during the first 6 months of treatment, unless the patient cannot tolerate this escalation. In this regard, epoprostenol's ability to reduce the mPAP in patients with IPAH has been shown to be dependent on its absolute dosage and dose-escalating pace [25]. Our study also showed an association between improvement of mPAP during the first 6 months of epoprostenol treatment and the dose-escalating pace of epoprostenol. Based on these findings, at our hospital we recently changed to a dose-escalating protocol for epoprostenol, i.e., dosage up to 40 ng/kg/min during the first 6 months of treatment. Finally, if the treatment response is insufficient at 6 months, even using an epoprostenol dosage that has been increased to the fullest extent possible or has not been increased due to intolerance, other PAH drugs should be readily added to the epoprostenol therapeutic regimen. A recent systematic review of combination therapy for IPAH and PAH–CTD showed that dual therapy improves multiple clinically relevant outcomes, particularly in patients

who fail to meet pre-defined clinical end-points, and that beneficial effects were observed in patients treated with epoprostenol by the sequential addition of ERA or PDE5I [26].

Epoprostenol therapy was well tolerated in general by all of our patients with PAH–CTD. Flushing, headache, and diarrhea were common and tended to be dose-dependent, but these could be managed by adjusting the dose-escalation schedule. However, particular attention should be paid to catheter-related infection. None of the patients died of this complication during the observation period of this study, but we recently experienced a patient with SLE who died of sepsis after repeated episodes of catheter-related infection. We failed to identify risk factors for this serious complication, possibly because of insufficient statistical power due to the small number of patients enrolled in this study. It is possible that an immunodeficient status and thinning of the skin due to the use of corticosteroids contribute to this complication.

Patients with advanced ILD were excluded from our study, but we generally do not use epoprostenol for patients with PH and advanced ILD because ventilation/perfusion mismatch is increased by the use of intravenous epoprostenol, thereby worsening oxygenation [27]. This unfavorable effect has, in fact, been reported in SSc patients with PH and concomitant ILD [28].

There are several limitations to our study. First, the number of patients was small, and all the patients were treated at a single PH referral center. Therefore, we acknowledge that our data on the outcomes of patients treated with epoprostenol therapy might not be representative of all patients with PAH–CTD. Second, because some of the patients received both epoprostenol and another therapy, such as PAH drugs and immunosuppressive therapy, it was not possible to attribute long-term outcomes to a specific therapeutic agent. Finally, this study included 13 patients who were diagnosed as having PAH and treated before 2005. At that time, beraprost and epoprostenol were the only PAH drugs available in Japan. Thus, the observed long-term survival rates may not reflect the current treatment environment in which a series of oral ERAs and PDE5Is are available. This also means that, in our cohort, the efficacy of epoprostenol could be assessed with minimal confounding effects from ERA and/or PDE5I.

In summary, based on our results, we conclude that epoprostenol treatment is effective for patients with advanced PAH irrespective of the underlying CTDs, but its efficacy in patients with end-stage PAH is limited. The maximum therapeutic benefit of epoprostenol is obtained when it is initiated before patients develop end-stage PAH, and its dosage is increased as rapidly as possible during the first 6 months of treatment. This strategy needs to be validated in a larger cohort.

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Conflict of interest None.

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