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皮膚から見た膠原病

福井大学医学部感覚運動医学講座皮膚科学
長谷川　稔

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綜　説

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Key words: autoantibody —— capillaroscopy —— dermatomyositis —— dermoscopy —— peripheral vascular disorder —— systemic sclerosis

はじめに

膠原病は，多臓器の結合組織と血管の病変を主症状とし，自己抗体産生を伴う慢性難治性疾患である．この中には，関節リウマチ，全身性エリテマトーデス（SLE），全身性強皮症（SSc），皮膚筋炎・多発性筋炎，結節性多発動脈炎，シェーグレン症候群，混合性結合組織病などが含まれる．

米国の軍の学校における大規模な疫学調査[1]によれば，SLEを発症した症例はまず抗核抗体が陽性となるが，その時点（発症の平均2.3年前）ではSLEに特異的な抗体は検出されない．しかし，やがてSLEに特異的な抗体が出現すると，間もなく症状が出現する（抗Sm抗体の場合は平均0.47年）と報告されている．すなわち，膠原病に特異的な自己抗体は必ず症状に先行して出現し，早期診断を含めた膠原病の診断に最も有用な手段といえる．

また，最近の話題として，各膠原病において新しい世界的な分類基準が提唱されてきている．これらは，感度と特異性を上げるためにやや複雑なものとなっているが，これまでの分類基準と比較して，皮膚病変の項目が多く，かつ専門的なものとなっている．このことは，皮膚所見が膠原病の診断にいかに重要であるかを示しているように思われる．ここでは，膠原病の中でもSScと皮膚筋炎について皮膚症状と自己抗体を中心に解説する．

全身性強皮症をどう診断するか？

2013年に，米国リウマチ会議（ACR）と欧州リウマチ会議（EULAR）は合同で，SScの新しい分類基準案を発表した[2]（**Table 1**）．8つのカテゴリーから構成されるが，そのうち6つは皮膚所見である．指だけでなく，手背にも皮膚の肥厚や硬化が及ぶ場合，SSc類似の症状を生じうる他疾患を除外できればSScと分類できる．指の腫脹または硬化がない場合はその時点で除外されるが，いずれかがある症例では，他の項目の有無が鍵となる．この中には，内臓病変として肺動脈性肺高血圧症および/または間質性肺疾患という1項目，強皮症関連自己抗体（抗トポイソメラーゼI抗体，抗セントロメア抗体，抗RNAポリメラーゼIII抗体のいずれか）の有無に関する1項目が含まれる．皮膚に関連した6項目のうち，4項目は皮膚の血管病変に関するものである．レイノー現象をはじめとする末梢循環障害は皮膚硬化の出現に先行するため，皮膚硬化がはっきりしにくい軽症例や早期例の診断に皮膚の血管病変が有用なのである．

皮膚硬化の有無は両手の親指で皮膚を挟み込んだ場合に，皮膚が厚い（浮腫性硬化ないし軽度の硬化）あるいは皮膚が硬くて持ち上がらない（強

CLINICAL PRACTICE OF COLLAGEN DISEASES FROM A DERMATOLOGICAL STANDPOINT

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Table 1 The American College of Rheumatology/European League Against Rheumatism criteria for the classification of systemic sclerosis (SSc)

Skin thickening of the fingers of both hands extending proximal to the metacarpophalangeal joints (score 9)
Skin thickening of the fingers: Puffy fingers (score 2), Sclerodactyly of the fingers (score 4)
Fingertip lesions: digital tip ulcers (score 2), Fingertip pitting scars (score 3)
Telangiectasia (score 2)
Abnormal nailfold capillaries (score 2)
Pulmonary arterial hypertension (score 2) and/or interstitial lung disease (score 2)
Raynaud's phenomenon (score 3)
SSc-related autoantibodies (score 2): anticentromere, anti-topoisomerase I, or anti-RNA polymerases III)

The criteria are not applicable to patients with skin thickening sparing the fingers or to patients who have a scleroderma-like disorder that better explains their manifestations. The total score is determined by adding the maximum weight (score) in each category. Patients with a total score of 9 are classified as having definite SSc.

(modified the table of ref. 2)

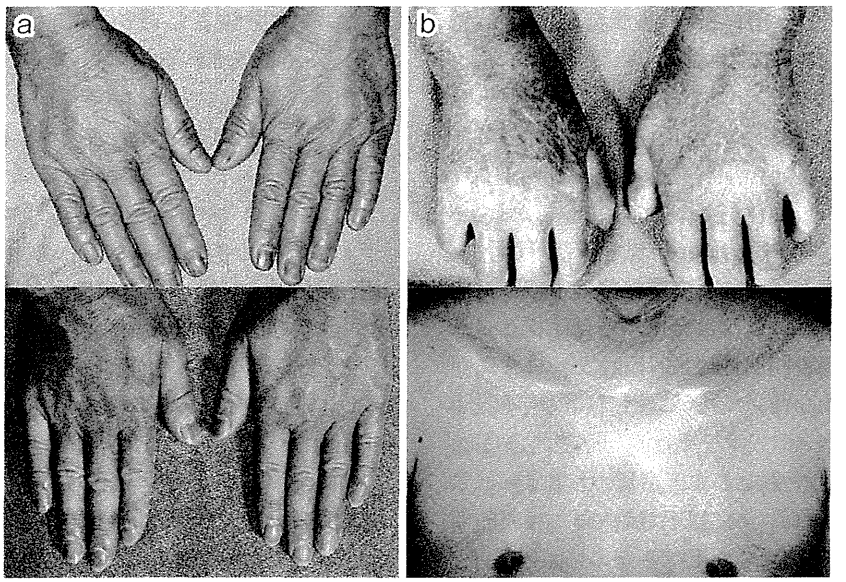

Fig. 1. a) skin sclerosis in patients with limited cutaneous systemic sclerosis (lcSSc), b) skin sclerosis in patients with diffuse cutaneous SSc (dcSSc).

い硬化）などから判断する．皮膚硬化の重症度の指標としては，modified Rodnan total skin thickness score（MRSS）が使用され，51点満点で点数が高いほど重症である[3]．病型としては，皮膚硬化が肘や膝より遠位に限局する limited cutaneous SSc（lcSSc，**Fig. 1a**）と，上腕，大腿，体幹などの近位にも拡大する diffuse cutaneous SSc（dcSSc，**Fig. 1b**）の2つに分類される．lcSScでは，長年にわたって皮膚硬化は進行しないことが多いが，dcSScでは発症5年以内の早期に皮膚硬化が急速に進行し，その後は緩徐に軽快する傾向がある．

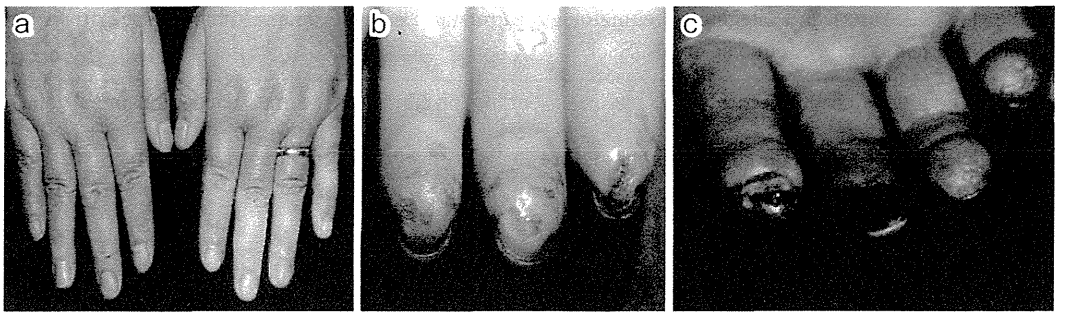

Fig. 2. a) Raynaud's phenomenon, b) fingertip pitting scars, c) digital tip ulcers.

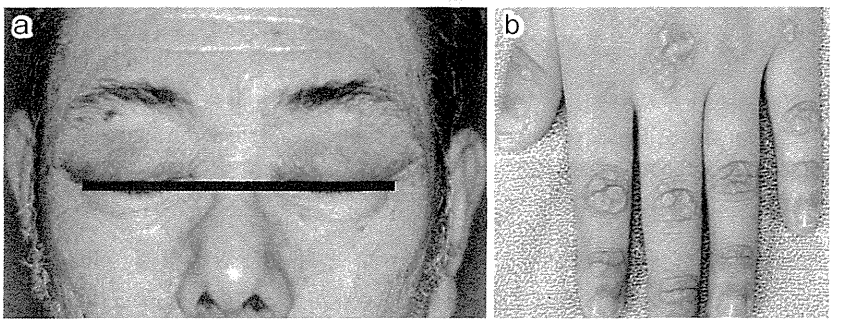

Fig. 3. a) heliotrope rash, b) Gottoron's papules/sign.

末梢循環障害と関連した皮膚症状の中で，レイノー現象（Fig. 2a）はほぼ全例に初発症状としてみられ，指尖部の陥凹性瘢痕（Fig. 2b）は強皮症にかなり特徴的な所見である．さらに末梢循環障害が進行すると，指尖潰瘍や壊疽に進展する（Fig. 2c）．また，顔面や手などの末端に，毛細血管拡張がしばしばみられるのも，SSc にかなり特異的な所見である．

自己抗体の種類は臨床症状をよく反映し，抗セントロメア抗体陽性例は通常 lcSSc で，内臓病変も軽症である．ただし，一部の症例では肺動脈性肺高血圧症を生じる．抗トポイソメラーゼ I 抗体陽性例の 7 割前後は dcSSc に進展し，内臓病変も重症のことが少なくない．間質性肺炎で死亡する症例が，本邦では本抗体陽性例に多い．2010 年に保険収載された抗 RNA ポリメラーゼ III 抗体の陽性例は，日本人では SSc 全体の 6% 程度に過ぎないが，ほとんどの症例が dcSSc に進行する．強皮症腎（腎クリーゼ）の頻度が高く，急な血圧上昇がみられないか注意が必要である．他には，SSc に特異的ではないが，抗 U1 RNP 抗体陽性例も SSc 全体の 5% 以上にみられる．

皮膚筋炎をどう診断するか？

皮膚筋炎は，皮膚と筋肉の炎症病変を主体とする膠原病である．症例ごとに症状や重症度は多彩だが，急速進行性間質性肺炎や合併する悪性腫瘍による死亡例も少なくない．

本疾患の皮膚病変は，内的または外的な慢性刺激によって誘発されると考えられている．皮膚筋炎に特異的な皮膚症状として，ヘリオトロープ疹と呼ばれる両上眼瞼の紅斑があげられる（Fig. 3a）．この皮膚病変の形成には，紫外線に加え，まばたきという上眼瞼の自動運動による刺激が関与すると考えられている．また，もうひとつの代表的な特異疹であるゴットロン徴候/丘疹は，手指な

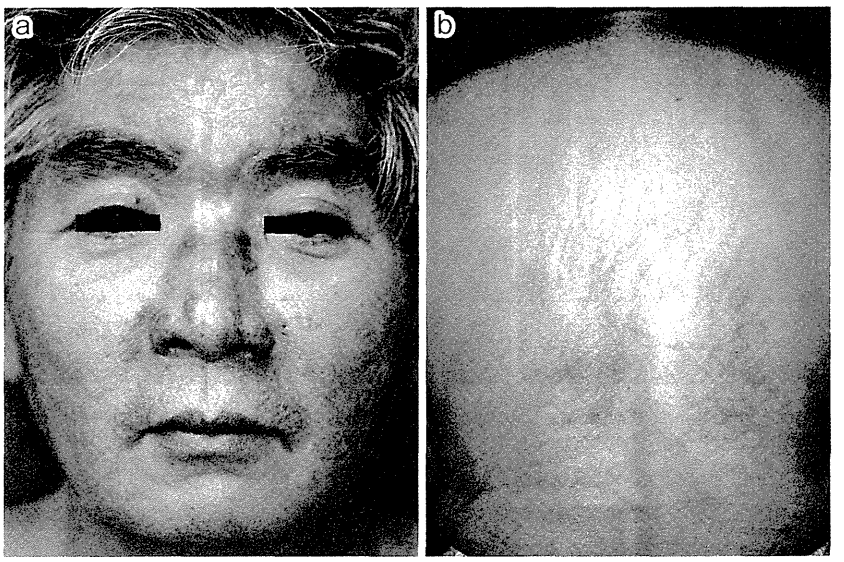

Fig. 4. a) Facial erythema that resembles seborrheic dermatitis, b) flagellate erythema.

どの関節背面にみられる紅斑や丘疹である（**Fig. 3b**）．この形成についても，関節を動かすことに伴う内的刺激や外からの刺激などの関与が指摘されている．

特異的ではないがよくみられる皮膚症状として，顔面の脂漏性皮膚炎様の紅斑（**Fig. 4a**）や体幹にみられる痒みの強い鞭で打ったような線状の紅斑（鞭打ち様紅斑，**Fig. 4b**）などがある．

近年，皮膚筋炎や多発性筋炎にみられる自己抗体に関して新たな知見が続々と報告されている[4]．これまでは，抗アミノアシルtRNA合成酵素（ARS）抗体の最も代表的なものである抗Jo-1抗体のみが保険収載されていた．しかし，2013年末に，抗Jo-1抗体，抗PL-7抗体，抗PL-12抗体，抗EJ抗体，抗KS抗体という5つの抗ARS抗体を一括して測定する抗ARS抗体という項目の測定が，皮膚筋炎と多発性筋炎の診断目的に保険収載された．抗ARS抗体陽性例は，慢性ないし亜急性の間質性肺炎がほぼ必発であるが，筋炎がみられない症例もある．典型的な皮膚筋炎の皮膚症状を示す症例は少なく，どちらかというと臨床的には皮膚筋炎よりも多発性筋炎に分類されることが多い．本抗体陽性例では，関節炎やメカニックハンドと呼ばれる手指腹の角化を伴う紅斑（**Fig. 5a**）が比較的高率にみられる．

また，皮膚筋炎に特異的な抗体として，抗Mi-2抗体，抗TIF-1抗体，抗MDA-5抗体がある．抗Mi-2抗体は典型的な皮膚筋炎の皮膚症状や筋症状を呈し，間質性肺炎や内臓悪性腫瘍の合併はみられない．抗TIF-1抗体陽性例のうち，高齢者では70–80%以上で発症とほぼ同時期に悪性腫瘍の合併が認められる．ただし，小児や若年成人での発症例には悪性腫瘍の合併がみられない．本抗体陽性例では，浮腫性紅斑が顕著で，水疱や紅皮症を生じる症例もみられる．抗MDA-5抗体陽性例では，筋炎がないかほとんどみられない症例が多く，急速性進行性間質性肺炎を高率に生じて予後不良である．本抗体陽性例では，逆ゴットロン徴候（手指の関節の指腹側にみられる鉄棒豆様の角化を伴う紅斑，**Fig. 5b**）や刺激の加わる部位に血管病変によると考えられる紫斑や潰瘍などを生じることが少なくない（**Fig. 5c**）．

レイノー現象を主訴に受診された患者さんをどう診察するか？

レイノー現象は，原発性レイノー病（レイノー

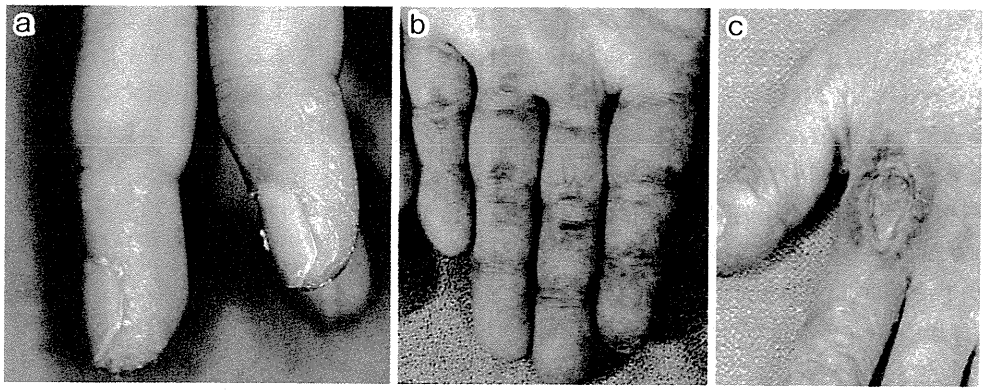

Fig. 5. a) mechanic hand, b) reverse Gottoron's sign, c) skin ulcer.

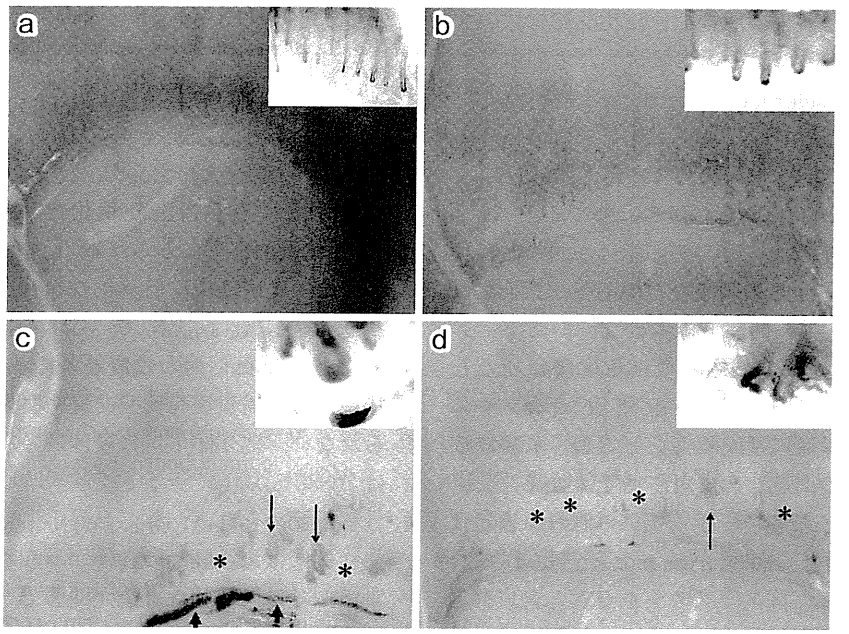

Fig. 6. capillaroscopic findings (small pictures) and dermoscopic findings (large pictures) corresponding to capillaroscopic findings. a) Normal pattern, b) Scleroderma pattern (early pattern): few enlarged/giant capillaries, few capillary hemorrhages, relatively well-preserved capillary distribution and no evident loss of capillaries. c) scleroderma pattern (active pattern): frequent giant capillaries (fine long arrows), frequent capillary hemorrhages (heavy short arrows), moderate loss of capillaries with some avascular areas (asterisks), mild disorganization of the capillary architecture and absence of ramified capillaries. d) scleroderma pattern (late pattern): irregular capillary enlargement, few or absent giant capillaries, absence of hemorrhages, severe loss of capillaries with large avascular areas (asterisks), severe disorganization of the normal capillary array and frequent ramified/bushy capillaries (fine long arrows).

現象はみられるが，全身的には問題がない）と基礎疾患に伴うレイノー現象に大別できる．基礎疾患として多いのは膠原病，特にSScである．SScに特異的な自己抗体が検出されれば，SScの初発症状と考えて経過観察する必要がある．しかし，SScの中にも自己抗体が検出されない症例が1～2割存在する．その際に，新しいSScの分類基準案[2]（Table 1）にも取り上げられている爪かく部の毛細血管異常の有無が重要となる．これは肉眼だけでなく，キャピラロスコピー（毛細血管顕微鏡）かダーモスコピーを用いて確認することと記載されている．キャピラロスコピーを用いて観察すると，毛細血管の配列の乱れ，減少，拡張（典型例では巨大毛細血管），分枝状や蛇行状の病的毛細血管，出血などSScに特徴的な毛細血管所見が認められ，scleroderma patternと呼ばれる[5]（Fig. 6）．しかし，日常診療でキャピラロスコピーを用いることは決して容易ではなく，精度はかなり落ちるが，より手軽に使用できるダーモスコピーの使用が現実的である[6]（Fig. 6）．なお，皮膚筋炎ではレイノー現象は稀であるが，SScと同様の爪かく部の毛細血管異常が高率にみられ，scleroderma-like patternと呼ばれる．ただし，病態については同じではなく，SScではレイノー現象という虚血再還流障害などで血管が壊れると考えられるのに対し，皮膚筋炎では血管の炎症で障害されると想定される．SLEや他の疾患では，通常典型的なscleroderma patternは認められない．

おわりに

SSc，皮膚筋炎などの膠原病では，自己抗体と皮膚の所見，中でも血管病変と関連したものが，診断に有用である．また，キャピラロスコピーやダーモスコピーを用いて診断することで，より正確な診断が可能になるものと思われる．

利益相反（conflict of interest）に関する開示：著者は本論文の研究内容について他者との利害関係を有しません．

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Secure Combination Therapy With Low-Dose Bosentan and Ambrisentan to Treat Portopulmonary Hypertension Minimizing Each Adverse Effect

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SUMMARY

Although endothelin receptor antagonists (ERAs) including bosentan and ambrisentan are essential tools for the treatment of pulmonary arterial hypertension (PAH), each agent has a specific adverse effect with non-negligible frequency, ie, liver dysfunction for bosentan and peripheral edema for ambrisentan. These adverse effects often hinder the titration of the doses of ERAs up to the therapeutic levels. Portopulmonary hypertension, which is complicated with liver cirrhosis and successive portal hypertension, is one of the PAHs refractory to general anti-PAH agents because of the underlying progressed liver dysfunction and poor systemic condition. We here present a patient with portopulmonary hypertension, which was treated safely by combination therapy that included low-dose bosentan and ambrisentan, minimizing the adverse effects of each ERA. Combination therapy including different types of ERAs at each optimal dose may become a breakthrough to overcome portopulmonary hypertension in the future. (Int Heart J 2015; 56: 471-473)

Key words: Pulmonary artery hypertension, Endothelin receptor antagonist, Liver cirrhosis

Although portopulmonary hypertension (PoPH), which is complicated with liver cirrhosis and successive portal hypertension, is one form of pulmonary arterial hypertension (PAH), its precise mechanism remains unknown thus far.[1] It is speculated that excessive pulmonary blood flow via portosystemic shunts exerts shear stress on the PA owing to portal hypertension, which leads to proliferation and hyperplasia of PA intima and media, and then raises pulmonary vascular resistance (PVR).[2-4] While the therapeutic strategy of PoPH conforms to that of idiopathic PAH (IPAH), there is no established strategy to treat PoPH. Clinical management of PoPH is difficult because of the underlying liver dysfunction and fluid retention.

Specific attention should be paid to patients with PoPH when an endothelin receptor antagonist (ERA), one of the essential tools to treat PAH,[5-7] is administered, since its adverse effects, such as liver dysfunction or peripheral edema,[8,9] are also problematic in patients with PoPH.[1]

We here present a patient with PoPH refractory to tadalafil and beraprost, which was managed safely by the addition of 2 types of ERAs, low dose bosentan and ambrisentan, thus minimizing the adverse effects of each agent.

CASE REPORT

A 57-year-old man, who had been followed at another hospital for liver cirrhosis (Child-Pugh A) with a history of ruptured esophageal varicoses 10 years previously was admitted to our hospital on December 2011 complaining of dyspnea on effort (WHO functional class III). Chest X-rays showed dilated bilateral PA, and an electrocardiogram (ECG) indicated right heart overload (Figure 1A and B). Elevated right ventricular systolic pressure (RVSP, 124 mmHg) was estimated along with enlargement of the RV cavity by transthoracic echocardiography (Figure 2A). His plasma level of B-type natriuretic peptide (BNP) was 664 pg/mL.

We performed the first hemodynamic study at a month after the admission,[10,11] and found elevated mean PA pressure (mPAP, 62 mmHg) and decreased cardiac index (CI, 1.76 L/minute/m^2). Other differential diagnoses including connective tissue disease, adult congenital heart disease, respiratory disease, or chronic thromboembolic pulmonary hypertension were excluded by systemic inspection with blood examination, computed tomography, lung perfusion scintigraphy, and transthoracic echocardiography, and finally he was diagnosed as PoPH.[12]

Next, 125 mg of bosentan was administered as the first ERA rather than ambrisentan, considering severe bilateral leg edema and relatively reserved hepatic function. Both 180 μg of beraprost as a prostanoid and 40 mg of tadalafil as a phosphodiesterase type 5 (PDE-5) inhibitor were initiated as a 3-drug combination therapy (Figure 3).

The second hemodynamic study showed persistent eleva-

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tion of mPAP (62 versus 57 mmHg) after 2-month treatment. We could not increase the dose of bosentan up to the standard dose because of potential worsening of liver dysfunction as a side effect of bosentan.

After ambrisentan was added as the second ERA at a half dose of 2.5 mg, hemodynamic study showed a significant decrease in mPAP down to 42 mmHg while maintaining the CI level. Peak oxygen consumption increased from 10.9 to 17.8 mL/kg/minute accompanied by improved WHO functional class (from III to II). No side effect such as liver dysfunction or worsening of leg edema was observed during the treatment period.

He was then followed as an ambulatory patient and he had no complaints. After 17 months, a follow-up hemodynamic study showed a significant decrease in PVR, although mPAP increased relatively accompanied by elevated CI probably due to increased preload. Transthoracic echocardiography demonstrated amelioration of both RV dilatation and a left-side shift of the ventricular septum (Figure 2B).

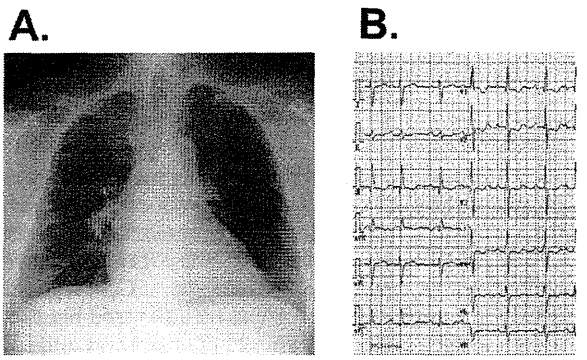

Figure 1. Chest X-ray (**A**) and electrocardiogram (**B**) obtained on admission.

Discussion

Although PoPH is one form of secondary PAH, there is no established strategy to manage it, probably because of underlying liver dysfunction and fluid retention. The prognosis of PoPH is very poor, and there are few reports describing the treatment of PoPH.[1]

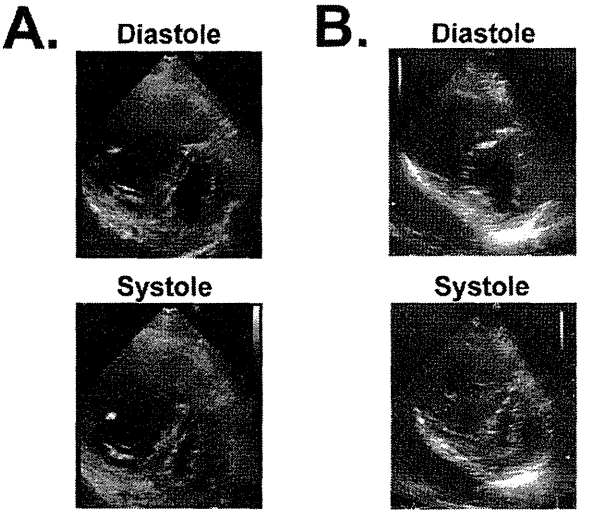

Figure 2. Transthoracic echocardiography on admission (**A**) and at 3 months after the initiation of treatment (**B**). Dilatation of the RV and left-side intraventricular septum were improved by the treatment.

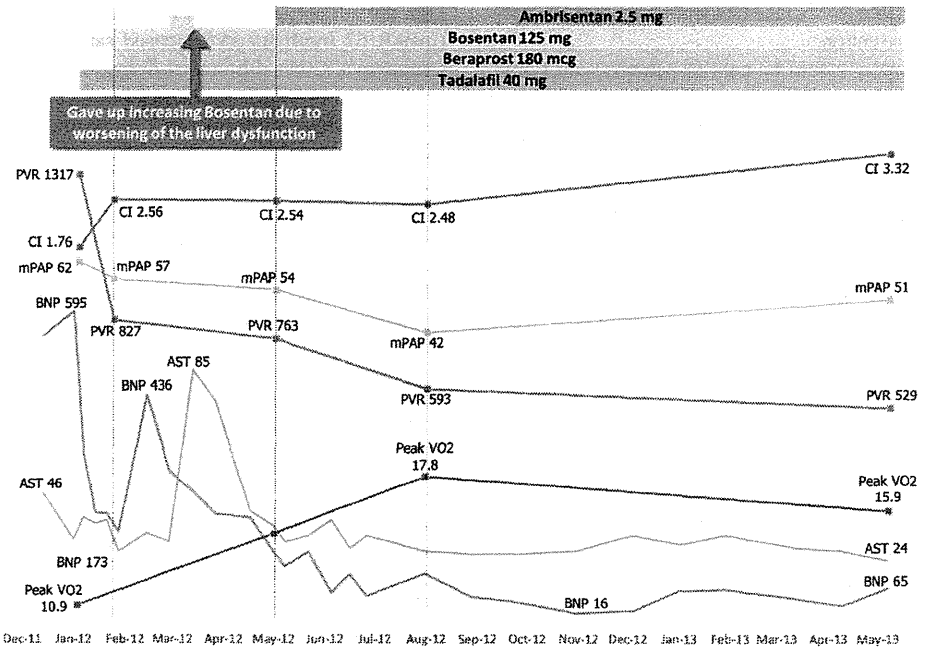

Figure 3. Time course of the treatment.

We intended from the beginning to initiate "3-drug combination therapy" consisting of (I) ERA, (II) a prostanoid, and (III) a PDE-5 inhibitor, considering the refractoriness of PoPH to any anti-PH treatments and the recently cumulating evidence supporting sequential combination therapy.[13-15]

However, we could not increase the dose of bosentan up to the standard range because of the emergence of liver dysfunction. Bosentan is accompanied by liver dysfunction with increased transaminase enzymes in 5-10% of patients, while fluid retention rarely occurs.[16,17] On the other hand, the commercially available other ERA ambrisentan frequently facilitates fluid retention while maintaining liver function,[18,19] and we could not administer the standard dose of ambrisentan instead of bosentan after taking into consideration his peripheral edema. Although little has been reported,[20] combination therapy including the 2-ERAs bosentan and ambrisentan was successfully performed by decreasing the dose of each agent within a safe range and preventing the adverse effects of the 2 drugs. Low-dose 2-ERA combination therapy may be safe, especially in patients with PAH and who are suffering from liver dysfunction or fluid retention.

Endothelin binds two opposite-effect receptors, ie, ET_AR and ET_BR. Although the precise mechanism remains unknown, ET_AR stimulation seems to cause vasoconstriction, whereas ET_BR stimulation seems to lead to vasodilation. Both receptors interact together intricately, and how this "cross-talk" contributes to the development of PAH remains unknown.[21]

Bosentan antagonizes both ET_AR and ET_BR, whereas ambrisentan antagonizes only ET_AR selectively.[22] Although there is no experimental or clinical evidence, combination therapy with the above 2 different-type antagonists may have had a synergistic vasodilation effect in the present patient.

The PAP level was probably not normalized because of the underlying untreatable portal hypertension. The establishment of combination therapy consisting of optimal doses of bosentan and ambrisentan, or including macitentan, the next generation ERA,[23] would be a future concern.

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CASE REPORT

A case of interferon-α-induced pulmonary arterial hypertension after living donor liver transplantation

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Abstract Pulmonary arterial hypertension (PAH) is a progressive and life-threatening disease characterized by elevated pulmonary vascular resistance, which results in right-heart failure. We present a case of interferon (IFN)-α-induced PAH developed after living donor liver transplantation. Although IFN is categorized as a "possible" risk factor for PAH in the current international classification, it is still under recognized. Moreover, the prognosis of IFN-induced PAH is poor in the limited number of published cases. In our case, we achieved good outcome by the withdrawal of IFN and administration of combination therapy using tadalafil, beraprost, and treprostinil. Since IFN is an important treatment option in current medical therapy, its contribution to the pathogenesis of PAH should be taken into consideration. In conclusion, our case suggests the importance of PAH screening in patients treated with IFN.

Keywords Interferon · Pulmonary arterial hypertension · Treprostinil

Introduction

Pulmonary arterial hypertension (PAH) is a severe and progressive disorder, characterized by elevated pulmonary artery pressure (PAP), and pulmonary vascular resistance (PVR) [1, 2]. It may be idiopathic, but also associated with many underlying conditions and diseases [3, 4]. Interferon (IFN) has received more attention recently as a risk factor for the development of PAH [5]. Since IFN-induced PAH is potentially lethal, it requires careful diagnosis and treatment. In this case report, we showed a case of IFN-α-induced PAH which was difficult to diagnose but eventually achieved good outcome by the withdrawal of IFN and administration of combination therapy. Prior approval and informed consent was obtained both from the institutional research ethics committee and the patient, and this study was performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments.

Case report

A 51-year-old male with a history of living donor liver transplantation (LDLT) for liver cirrhosis secondary to HCV infection was admitted to our hospital because of progressive severe hypoxemic respiratory failure. He received LDLT 2.5 years before and had been receiving IFN-α treatment after the transplantation. Prior to LDLT, he was thought to have portal hypertension since he had complications with esophageal varices, but he did not have symptoms of pulmonary hypertension at the time. (In echocardiogram prior to LDLT, the estimated right ventricular systolic pressure (RVSP) was 12 mmHg). He has had dyspnea since 15 months after LDLT. Suspecting IFN-induced interstitial pneumonia (IP), surgeons did a series of examinations. However, there were no signs of IP, and IFN therapy was continued. At the time of admission, he had WHO functional class III symptoms, and blood examination revealed markedly elevated plasma level of B-type natriuretic peptide (1264 pg/ml). Echocardiogram demonstrated severe right ventricular enlargement and elevated estimated

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Table 1 Patient's data about hemodynamic parameters and exercise capacities

	1st RHC	2nd RHC	3rd RHC	4th RHC	5th RHC
Time after 1st RHC		1 months	2 months	3 months	6 months
Medication	IFN-α (100 μg/week)	Stop IFN-α Tadalafil 40 mg DOB 2 μg/kg/min	Tadalafil 40 mg Beraprost 120 μg	Tadalafil 40 mg Beraprost 120 μg	Tadalafil 40 mg Beraprost 120 μg Treprostinil 50 ng/kg/min
HR (bpm)	69	79	61	74	57
BP (systolic/diastolic/mean: mmHg)	113/82	97/58	112/62	116/78	101/57
RAP (mmHg)	6	12	7	4	2
PAP (systolic/diastolic/mean: mmHg)	81/23/52	99/35/55	78/18/46	80/28/47	69/25/39
PCWP (mmHg)	10	9	6	6	4
CI (L/min/m^2)	2.01	3.03	2.24	2.37	2.46
PVR (WU)	12.4	8.1	10.5	10.6	8.3
SvO_2 (%)	58	65	60	69	79
6MWT (m)	280		302	413	395
BNP (pg/ml)	1264	1001	1027	340	336

RHC right-heart catheterization, *IFN* interferon, *PAH* pulmonary arterial hypertension, *DOB* dobutamine, *HR* heart rate, *BP* blood pressure, *RAP* right atrial pressure, *PAP* pulmonary arterial pressure, *PCWP* pulmonary capillary wedge pressure, *CI* cardiac index, *PVR* pulmonary vascular resistance, *SvO_2* mixed venous oxygen saturation, *6MWT* 6-min walk test, *BNP* brain natriuretic peptide

RVSP of 72 mmHg. He was referred to our department for further investigation and treatment. We conducted various examinations to rule out possible causes of PAH such as chronic thromboembolic pulmonary hypertension, IP, pulmonary tumor thrombotic microangiopathy, and pulmonary venous occlusive disease. Right-heart catheterization showed markedly elevated mean PAP and PVR as well as depressed cardiac index. Hepatic wedge pressure was within normal limit, which excluded the possibility of portopulmonary hypertension. From those examinations, he was diagnosed with IFN-α-induced PAH. Table 1 shows the change of hemodynamic parameters and exercise capacities. His clinical status partially improved by withdrawal of IFN-α and treatment with tadalafil and beraprost during the first 4 months (Table 1, 4th RHC), and then significantly improved 3 months after the addition of subcutaneous treprostinil (Table 1, 5th RHC). Since he has been taking tacrolimus for his treatment, coadministration of bosentan was contraindicated. Ambrisentan was unable to be continued because it caused severe fluid retention.

Discussion

IFN is a virally induced protein produced by activated macrophages and lymphocytes, resulting in potent immunomodulation. It has been widely used in the treatment of viral hepatitis but also in other hematological, nephrologic and dermatological malignancies [6, 7]. The role of IFN is increasingly considered as a risk factor for PAH supported by several clinical reports and experimental studies [5, 8–11]. The result of the sub-analysis of a French registry also suggests that IFN exposure may trigger PAH [5]. However, most patients diagnosed with IFN-induced PAH in the French registry and past case reports had other risk factors for PAH, such as portal hypertension by chronic hepatitis. In our case, the patient was thought to complicate portal hypertension before LDLT, which might have a latent damage on pulmonary vasculature. Therefore, IFN-α may act as a trigger to develop PAH. It was very regrettable that it took more than 1 year to diagnose him with PAH since the onset of dyspnea because adequate workup was not fully performed. Since IFN is widely used in many diseases associated with a higher risk to develop PAH, the occurrence of unexplained dyspnea and signs of right ventricular failure should be carefully screened during the period of IFN treatment.

The treatment of IFN-induced PAH is still challenging because of the absence of evidence. In most of patients, IFN withdrawal and treatment with PAH-specific agents such as endothelin receptor antagonists (ERA) and phosphodiesterase 5 inhibitors is not sufficient to improve PAH. In French registry, repeated hemodynamic assessment was available in 13 patients exposed to IFN after the diagnosis of PAH. Among the 13 patients, 11 patients showed the increase in PVR, as well as worsening functional and exercise capacity. Among the 11 patients, 4 patients needed additional PAH-specific therapy following clinical and hemodynamic worsening while on IFN, 5 patients showed clinical and hemodynamic improvements only by IFN

withdrawal, whereas 2 patients showed no improvement by IFN withdrawal [5]. Our case is very rare in its good therapeutic course and significant hemodynamic improvement. Since clinical benefit by treprostinil was shown to be highly dose dependent, [12, 13] the higher dose of treprostinil (50 ng/kg/min) administered to our patient compared with previous studies [14] might be partially accountable for the good outcome. Treprostinil can be a better option for patients with IFN-induced PAH because epoprostenol (another strong prostanoid agent often used in the treatment of PAH) infusion has a high risk of infection for them. However, there is still no evidence to support the routine use of treprostinil in IFN-induced PAH. Although we could not use ERA because of side effects in our patient, ERA has shown preferable evidence in Japanese [15]. ERA will also be a good choice because IFN is thought to stimulate pulmonary vasculature to release endothelin-1 and mediates PAH [10, 11]. In the previous report, George PM et al. also showed that the knockout mouse of IFN receptor 1 (IFNAR1) was protected from the effects of hypoxia on the right heart, vascular remodeling, as well as raised serum endothelin 1 levels. This result supports the idea that type I IFN mediates PAH via an action of IFNAR1 [11]. Although macitentan is not available in Japan now, it will be a potential candidate medication in our patient.

In conclusion, our case suggests the importance of PAH screening in patients treated with IFN. Clinical survey of IFN-induced PAH is still insufficient, and further prospective study is needed to determine the link between IFN exposure and PAH.

Conflict of interest Masaru Hatano has a potential conflict of interest with GlaxoSmithKline Pharmaceutical and NIPPON SHINYAKU, which consists of lecture fees. The other authors have no potential conflicts of interest existing with any companies/organizations whose products or services may be discussed in this article.

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Targeted Therapy Is Required for Management of Pulmonary Arterial Hypertension After Defect Closure in Adult Patients With Atrial Septal Defect and Associated Pulmonary Arterial Hypertension

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SUMMARY

Background: Therapeutic strategies for pulmonary arterial hypertension (PAH) associated with atrial septal defect (ASD) remain a matter of debate.

Methods and Results: We identified 5 outpatients who had been diagnosed with ASD–PAH and undergone ASD closure in combination with targeted therapy with certified PAH drugs. We assessed changes in hemodynamic parameters and exercise capacity. The combination of ASD closure and targeted therapy significantly increased systemic blood flow (Qs) from the baseline (from 3.3 ± 0.6 L/minute to 4.2 ± 1.0 L/minute, $P < 0.05$) with a significant improvement in the World Health Organization Functional Class (WHO-FC; from 2.8 ± 0.4 to 1.6 ± 0.5, $P < 0.05$). The hemodynamic data before and after ASD closure without targeted therapy showed further elevation of pulmonary vascular resistance shortly after ASD closure (678 dyne·s/cm^5 to 926 dyne·s/cm^5) in 1 case, as well as after a long time since ASD closure (491.0 ± 53.7 dyne·s/cm^5 to 1045.0 ± 217.8 dyne·s/cm^5) in 2 cases. This worsening was reversed after the targeted therapy, accompanied by an increase in Qs and an improvement in WHO-FC in all cases. Conclusions: Targeted therapy should be added to ASD closure in adult patients with ASD–PAH. (Int Heart J 2015; 56: 86-93)

Key words: Adult congenital heart disease, Therapeutic strategy

A subset of adult patients with open atrial septal defect (ASD) has pulmonary arterial hypertension (PAH). Persistent exposure of the pulmonary vasculature to increased blood flow results in pulmonary obstructive arteriopathy, which leads to an increase in pulmonary vascular resistance (PVR). If PVR approaches or exceeds systemic resistance, the shunt is reversed and the patient may finally develop Eisenmenger syndrome. It has been reported that 6.1% of adult patients with septal defects have a complication of associated pulmonary hypertension (defined by echocardiography), and 3.5% have Eisenmenger syndrome.[1)] The long-term outcome after surgical repair of ASD without PAH is generally excellent; therefore, ASD closure is recommended to prevent the development of PAH, reduce the risk of right heart failure and subsequent arrhythmia, and avoid paradoxical emboli.[2,3)] In contrast, the therapeutic strategies for patients with open ASD and associated PAH (ASD–PAH) remain a matter of debate. The Guideline of the European Society of Cardiology suggests that patients with a significant shunt (signs of right ventricular volume overload) and PVR < 400 dyne·s/cm^5 should undergo ASD closure regardless of symptoms (Class I, Level B).[1)] However, the finding was based on only 1 report by Attie, *et al*[4)] and thus requires additional evidence. Recently, Beghetti, *et al* suggested that a baseline PVR index of < 480 dyne·s·m^2/cm^5 and a PVR: systemic vascular resistance (SVR) ratio of < 0.3 may be considered indicative of a favorable outcome following ASD closure.[5)] These criteria are more restrictive than those provided by the guidelines,[1,6)] but they also lack adequate supporting evidence. In contrast, Engelfriet, *et al* reported that the prognosis appeared to be worse in patients with closed ASD–PAH than in those with open ASD–PAH.[7)] In addition, Manes, *et al* recently showed that the prognosis of patients with closed congenital heart disease (CHD)-associated PAH was far worse compared with that of patients with open CHD-associated PAH.[8)] Taken together, there has been no definitive strategy for patients with ASD–PAH.

In the last decade, there have been striking advances in treatment options for PAH, including the development of new drugs, such as prostanoids, endothelin receptor antagonists, phosphodiesterase-5 inhibitors, and a soluble guanylate cyclase stimulator.[9)] Targeted therapy with these certified PAH drugs has led to the improvement of hemodynamic parameters or ex-

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ercise capacity not only in patients with idiopathic PAH[10-12] but also in those with CHD-associated PAH.[13,14] In addition, several recent reports have shown that targeted therapy with certified PAH drugs allows adult patients with uncorrected ASD–PAH to undergo successful ASD closure.[15-17] Thus, at present, the therapeutic strategy for patients with ASD–PAH needs to be revised.

The aim of this study was to determine if the targeted therapy with certified PAH drugs can improve hemodynamics and exercise capacity after defect closure in patients with ASD–PAH. We are convinced of the importance of hemodynamic correction and improvement of exercise capacity for longer survival in PAH patients. We examined outpatients at our hospital who had been preoperatively diagnosed with ASD–PAH and who had undergone ASD closure. We assessed hemodynamics and exercise capacity by consecutive catheter studies and cardiopulmonary exercise tests, respectively. Our results suggest that ASD closure alone is associated with a risk of worsening hemodynamics, although the addition of targeted therapy for PAH improves hemodynamics and exercise capacity.

Methods

Patient selection: We conducted a retrospective review of outpatients who had undergone ASD closure after being preoperatively diagnosed with ASD–PAH at our hospital in December 2013. The diagnosis for PAH was decided in accordance with the global guidelines[18] and satisfied the following criteria: mean pulmonary arterial pressure (mPAP) ≥ 25 mmHg, PVR ≥ 240 dyne·s/cm^5, and mean pulmonary capillary wedge pressure (mPCWP) ≤ 15 mmHg before surgery. We excluded patients who had other complex CHD or other possible causes of pulmonary hypertension, and those whose ASD diameters were < 15 mm. We identified 6 patients (2 males) with ASD–PAH who had undergone defect closure in our hospital. We excluded 1 female patient because of the coexistence of thromboembolism in her pulmonary artery. Thus, 5 patients were enrolled in this study. All patients underwent cardiac catheterization/hemodynamic examinations before and after ASD closure.

Hemodynamic measurements: Right heart catheterization was used to obtain all hemodynamic measurements invasively and accurately.[19,20] A Swan–Ganz catheter was introduced from the femoral or jugular vein. Next, the hemodynamic parameters, including mean right atrial pressure (mRAP), right ventricular pressure, mPCWP, mPAP, and mean left atrial pressure (mLAP, before ASD closure) were determined. Before ASD closure, the systemic blood flow (Qs or cardiac output (CO), L/minute) and pulmonary blood flow (Qp, L/minute) were calculated by the Fick method according to the following general equations:

Qs (CO) = estimated O_2 consumption (mL/minute)/arteriovenous O_2 difference (mL/L).

Qp = estimated O_2 consumption (mL/minute)/pulmonary arteriovenous O_2 difference (mL/L).

PVR (dyne·s/cm^5) before ASD closure was calculated according to the following equations:

PVR = 80 × (mPAP (mmHg) – mLAP (mmHg))/Qp (L/minute)

PVR after ASD closure was calculated according to the following equations:

PVR = 80 × (mPAP (mmHg) – mPCWP (mmHg))/Qp (L/minute)

SVR (dyne·s/cm^5) was calculated according to the following equations:

SVR = 80 × (mean arterial pressure (mmHg) – mRAP (mmHg))/Qs (L/minute)

For these equations, estimated O_2 consumption was calculated according to the following equation as described previously:[21]

Estimated O_2 consumption = body surface area (m^2) × [(138.1 – C × ln (age)) + 0.378 × heart rate (bpm)]

(C; 11.49 for male; 17.04 for female)

The mixed vein (MV) O_2 saturation (%) was calculated according to the following equation as described previously:[22]

MV O_2 saturation = (3 × superior vena cava O_2 saturation (%) + inferior vena cava O_2 saturation (%))/4

Then, the arteriovenous O_2 difference (mL/L) and pulmonary arteriovenous O_2 difference (mL/L) were calculated according to the following equations:

Arteriovenous O_2 difference = (arterial O_2 saturation (%) – MV O_2 saturation (%)) × Hb (g/dL) × 1.36/10

Pulmonary arteriovenous O_2 difference = (pulmonary vein O_2 saturation (%) – pulmonary arterial O_2 saturation (%)) × Hb (g/dL) × 1.36/10

After ASD closure (under the condition of no residual shunt), CO was measured by one method for each patient, the thermodilution or the Fick method. During cardiac catheterization, acute vasodilator challenge was performed by using inhaled nitric oxide (20 ppm) or oxygen (10 L/minute).

Cardiopulmonary exercise test: A cardiopulmonary exercise test (CPX) was performed on the day before the hemodynamic evaluation using an expired gas analyzer (AE-300S; Minato Ikagaku, Osaka, Japan) as described previously.[20,23] An exercise protocol was selected by the attending physician to allow a patient's individual performance to be assessed. In addition to the continuous measurement of O_2 consumption (VO_2), the peripheral arterial O_2 saturation (SpO_2) was monitored by a pulse oximeter during CPX. The peak VO_2 was expressed as a percent of the sex-, age-, body weight-, and body height-adjusted normal value for Japanese people.[24]

Therapeutic options: The most appropriate intervention was selected for each individual defect. Decisions regarding the medical therapy were made on an individual basis by the attending physician who took into account all clinical data. We defined certified PAH drugs according to the global guidelines,[18] and excluded oral beraprost because it lacks proof of chronic efficacy.

Statistical methods: Data were analyzed by a two-tailed paired *t*-test or repeated measures analysis of variance, followed by the Tukey post-hoc test; P values < 0.05 were considered significant. GraphPad Prism v5.01 (GraphPad Software, Inc.) was used to analyze the data. All results are presented as the mean ± standard deviation.

Results

Patient characteristics: The baseline data of the 5 patients are presented in Table I. The average age at the time of ASD closure was 40.4 ± 17.3 years (range, 28–70 years). The mean

Table I. Baseline Characteristics

	Case 1	Case 2	Case 3	Case 4	Case 5
Baseline clinical data					
Age at operation, years	70	36	40	28	28
Sex	F	M	F	F	M
Body surface area, m^2	1.57	1.85	1.49	1.31	1.38
Type of defect	Secondum	Secondum	Sinus venosus	Secondum	Secondum
Defect size (mm)	25 × 15	30 × 31	20 × 10	30 × 15	30 × 24
Medication for PAH	None	None	Beraprost 60 μg	None	None
Baseline hemodynamic data					
NIBP (mean), mmHg	147/75 (104)	117/66 (85)	88/56 (68)	90/57 (72)	104/70 (81)
mRAP, mmHg	5	3	2	8	5
PAP (mean), mmHg	64/19 (35)	68/27 (43)	87/28 (47)	71/33 (45)	84/20 (41)
mLAP, mmHg	7	5	5	6	5
Qp/Qs	6.0/2.3 (2.6)	7.8/3.9 (2.0)	5.0/3.5 (1.4)	5.9/3.3 (1.8)	6.4/3.7 (1.7)
PVR, dyne·s/cm^5 (PVRI, dyne·s·m^2/cm^5)	375 (589)	390 (722)	678 (1010)	529 (693)	453 (625)
SVR, dyne·s/cm^5 (SVRI, dyne·s·m^2/cm^5)	3412 (5357)	1676 (3101)	1798 (2679)	1550 (2031)	1633 (2254)
PVR/SVR	0.11	0.23	0.38	0.34	0.27
Baseline physiological data					
WHO-FC	3	3	3	3	2
Peak VO_2 (%normal)	57	81	45	N/A	N/A
Change of SpO_2 (%)	-5	-3	-12	N/A	N/A

PAH indicates pulmonary arterial hypertension; NIBP, non-invasive blood pressure; mRAP, mean right atrial pressure; PAP, pulmonary arterial pressure; mLAP, mean left atrial pressure; Qp, pulmonary blood flow; Qs, systemic blood flow; PVR, pulmonary vascular resistance; PVRI, PVR index; SVR, systemic vascular resistance; SVRI, SVR index; WHO-FC, World Health Organization Functional Class; VO_2, O_2 consumption; and SpO_2, peripheral arterial O_2 saturation.

Table II. Time Course of Catheterization and Medication After Operation

	Case 1	Case 2	Case 3	Case 4	Case 5
Operation					
Date (year)	2011	2012	2007	1993	1971
Procedure	Surgical	Percutaneous	Surgical	Surgical	Surgical
Medication for PAH	None	Bosentan 125 mg	Beraprost 120 μg	None	None
The catheter study just before the use of certified PAH drugs* (after surgical closure)					
Postoperative days	-	-	1 month	13 years	40 years
Medication for PAH	-	-	Beraprost 120 μg	None	Beraprost 120 μg
The introduction of certified PAH drugs					
Postoperative days	4 days	before closure	22 months	15 years	40 years
The latest catheter study (after the titration of medical therapy)					
Postoperative days	3 years	6 months	6 years	20 years	42 years
Medication for PAH	Bosentan 125 mg	Bosentan 125 mg	Beraprost 240 μg Sildenafil 60 mg Ambrisentan 7.5 mg	Tadarafil 40 mg Bosentan 250 mg	Beraprost 120 μg Bosentan 250 mg Riociguat 6 mg

*Certified PAH drugs do not include beraprost. PAH indicates pulmonary arterial hypertension.

values of mPAP, PVR, and Qp/Qs were 42.2 ± 4.6 mmHg, 485.0 ± 123.8 dyne·s/cm^5, and 1.9 ± 0.4, respectively. Oxygen inhalation test and the histological analysis with lung biopsy were performed in case 3, showing a substantial decrease in PVR from 678 to 454 dyne·s/cm^5 and 2.1 as an index of pulmonary vascular disease which had been defined by Yamaki, *et al*,[25] respectively, both of which indicated a possible vascular reversibility after ASD closure. On the other hand, nitric oxide inhalation (20 ppm, 10 minutes) was performed during hemodynamic measurement in cases 1 and 2, showing a small decrease in mPAP (case 1; 35 mmHg to 30 mmHg, case 2; 43 mmHg to 37 mmHg) and PVR (case 1; 375 dyne·s/cm^5 to 314 dyne·s/cm^5, case 2; 390 dyne·s/cm^5 to 314 dyne·s/cm^5). In 3 of the 5 cases (cases 1–3), CPX was performed before ASD closure and showed that the mean value of the percent peak VO_2 apparently decreased (61.0 ± 18.3%) and SpO_2 dropped at the end of the exercise by 6.7 ± 4.7% from the baseline.

Table II summarizes the information on medication. Bosentan was prescribed just after ASD closure in case 1 and before ASD closure in case 2. In case 3, the first hemodynamic evaluation following ASD closure was performed 1 month after the surgery, and sildenafil and ambrisentan were sequentially added to beraprost at 22 months after ASD closure. In case 4, tadalafil and bosentan were sequentially prescribed after the first hemodynamic evaluation, when 15 years had passed since the surgery. In case 5, beraprost was prescribed at some points between ASD closure and the first hemodynamic evaluation, and bosentan and riociguat were sequentially added after the first hemodynamic evaluation, when 40 years had passed since ASD closure.

Changes in hemodynamics and exercise capacity: Figure 1 shows the final results of the hemodynamic parameters after the combination therapy of ASD closure and targeted therapy with certified PAH drugs, which did not include beraprost. Cardiac output after ASD closure was measured by the Fick method in cases 1–3 and 5, and by the thermodilution method

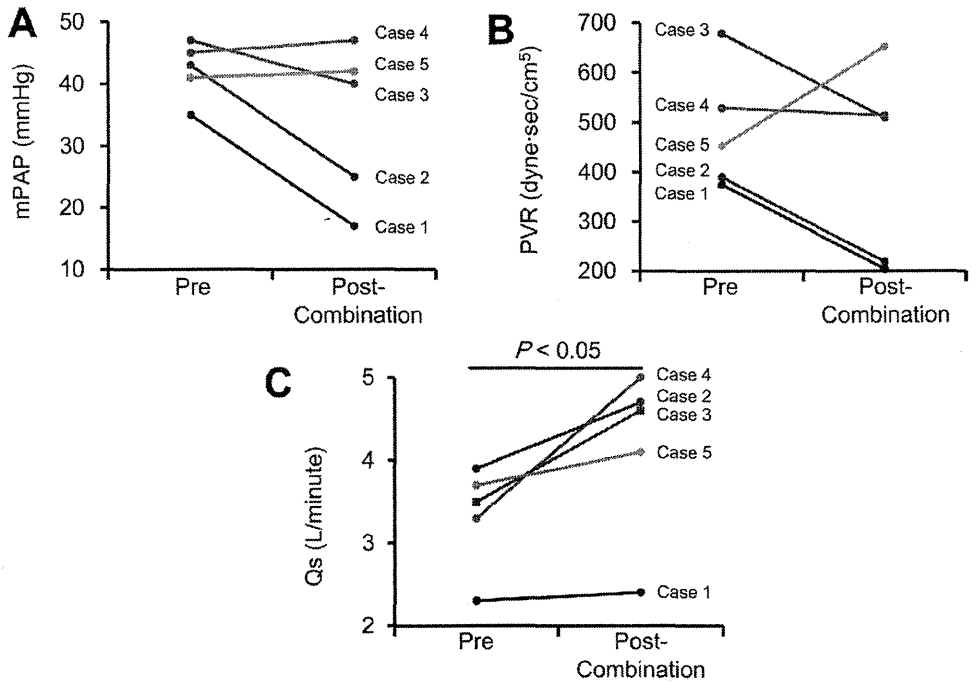

Figure 1. Hemodynamic parameters before and after the combination of ASD closure and targeted therapy. The data on mPAP (**A**), PVR (**B**), and Qs (**C**) in each patient before and after the combination therapy are presented. Qs significantly increased after the combination therapy ($P < 0.05$), whereas mPAP and PVR did not show any significant change. mPAP indicates mean pulmonary arterial pressure; PVR, pulmonary vascular resistance; Qs, systemic blood flow; Pre, baseline data before treatment; and Post-Combination, data after the combination of ASD closure and targeted therapy with certified PAH drugs.

in case 4, because in case 4 there was no data of Fick analysis in the first catheterization after ASD closure. Tricuspid regurgitation was moderate in case 4. mPAP decreased in cases 1–3 and increased in cases 4 and 5, resulting in insignificant decreases in the values of mPAP and PVR (from 42.2 ± 4.6 mmHg to 34.2 ± 12.6 mmHg and from 485.0 ± 123.8 dyne·s/cm^5 to 419.6 ± 198.5 dyne·s/cm^5, respectively). On the other hand, Qs (CO) increased in all patients, showing a statistically significant increase in Qs (from 3.3 ± 0.6 L/minute to 4.2 ± 1.0 L/minute, $P < 0.05$).

Figure 2 shows the final change in exercise capacity after the combination therapy. The World Health Organization Functional Classification (WHO-FC) was significantly improved (from 2.8 ± 0.4 to 1.6 ± 0.5, $P < 0.05$). CPX performed in cases 1–3 demonstrated that the peak VO_2 increased in all 3 patients (from 61.0 ± 18.3% to 87.0 ± 7.0% of the normal value, NS), accompanied by an improvement in desaturation at the end of the exercise (from −6.7 ± 4.7% to −2.0 ± 2.0%, NS), which is well known to be one marker for the severity of PAH.[18,26]

ASD closure alone increased PVR, which was reversed by additional targeted therapy: In cases 3–5, ASD closure was performed, followed by the hemodynamic evaluation without use of certified PAH drugs. The timing of hemodynamic evaluation and starting certified PAH drugs were different among the 3 cases (Table II). As shown in Figure 3A, in case 3, PVR was elevated at the time of the hemodynamic evaluation (1 month after ASD closure) before the use of certified PAH drugs (678 dyne·s/cm^5 to 926 dyne·s/cm^5) relative to that before ASD closure (baseline). Certified PAH drugs were introduced 22 months after ASD closure, and the latest hemodynamic evaluation revealed that the increase in PVR was reduced to a level similar to that at the baseline (926 dyne·s/cm^5 to 509 dyne·s/cm^5), suggesting that targeted therapy with certified PAH drugs exerted a beneficial effect on remodeling of the pulmonary artery. Qs (CO) increased (3.1 L/minute to 4.6 L/minute) and WHO-FC improved (from III to II) after the titration of certified PAH drugs, further confirming the beneficial effect of targeted therapy.

Also in cases 4 and 5 (Figure 3B), in which certified PAH drugs were started after a long time since ASD closure, PVR was elevated before the use of certified PAH drugs relative to the baseline (491.0 ± 53.7 dyne·s/cm^5 to 1045.0 ± 217.8 dyne·s/cm^5). The latest hemodynamic evaluation revealed that the increase in PVR was reduced to a level similar to that at the baseline (1045.0 ± 217.8 dyne·s/cm^5 to 583.0 ± 97.6 dyne·s/cm^5). Qs (CO) increased (3.5 ± 0.8 L/minute to 4.6 ± 0.6 L/minute) and WHO-FC improved after the titration of certified PAH drugs. These results suggested that certified PAH drugs had a beneficial effect even after a long period since ASD closure.

Discussion

There were several novel findings in this study. First, the targeted therapy with certified PAH drugs demonstrated improvement in the Qs (CO) and exercise capacity after ASD

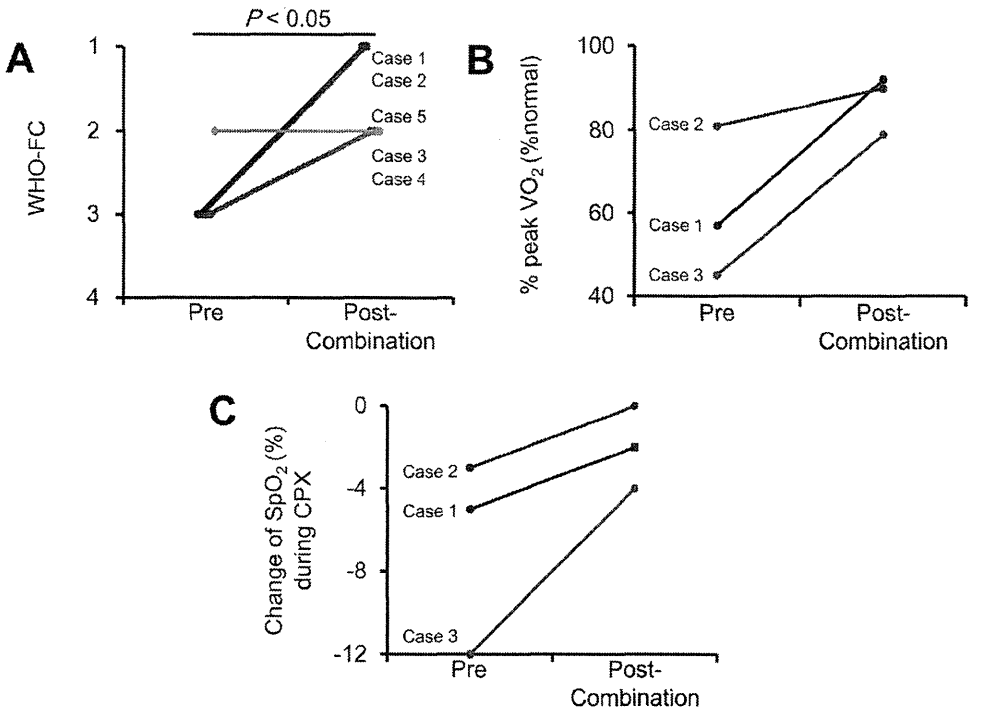

Figure 2. Physiological parameters before and after the combination of ASD closure and targeted therapy. The data on WHO-FC (**A**), %peak VO_2 (**B**), and decrease in SpO_2 during CPX (**C**) in each patient before and after the combination therapy are presented. WHO-FC improved in 4 patients ($P < 0.05$). The %peak VO_2 and desaturation during exercise improved in all patients. WHO-FC indicates World Health Organization Functional Classification; VO_2, O_2 consumption; SpO_2, arterial O_2 saturation of hemoglobin measured by pulse oximeter; CPX, cardiopulmonary exercise test; Pre, baseline data before the combination therapy; and Post-Combination, data after the combination of ASD closure and targeted therapy with certified PAH drugs.

closure, assessed by right heart catheterization and CPX, respectively (Figures 1 and 2). Second, ASD closure alone resulted in an increase in PVR in the 3 patients with ASD–PAH. In addition, targeted therapy with certified PAH drugs effectively reversed their once-worsened PVR and increased CO, even after a long period since ASD closure (Figure 3B). Taken together, we advocate the importance of using certified PAH drugs for adult patients with ASD–PAH who plan to undergo or have already undergone ASD closure.

Hemodynamic alteration after ASD closure in patients with ASD–PAH: To date, hemodynamic changes after ASD closure in patients with ASD–PAH have remained unclear. As Manes, *et al* mentioned, hemodynamic data have often been lacking or were not obtained, even before and particularly after defect closure in patients with CHD-associated PAH,[8] indicating that the decision for ASD closure had not been made properly, particularly in the era when certified PAH drugs were not available and when the medical treatment was inadequate through the following period. In this study, we demonstrated that hemodynamic changes were induced by ASD closure with or without certified PAH drugs in patients with ASD–PAH. Without use of certified PAH drugs, ASD closure alone exposes patients to the risk of PAH worsening, as indicated by an increase in PVR (Figure 3). In contrast, the concomitant use of certified PAH drugs before or just after ASD closure appeared to prevent an increase or even caused a decrease in PVR after ASD closure (cases 1 and 2), which is consistent with the findings of a recent report.[16] In addition, the combination of ASD closure and targeted therapy with certified PAH drugs improved exercise capacity and ameliorated the decrease in SpO_2 at the end of CPX in all 3 cases (cases 1–3, Figure 2). In contrast, before the targeted therapy was administered, CPXs performed 4 times did not show any improvement in peak VO_2 after ASD closure in case 3 (data not shown). This observation also suggests the necessity of using certified PAH drugs for patients with ASD–PAH who have undergone or plan to undergo ASD closure.

Because we did not perform hemodynamic measurement after ASD closure before the titration of certified PAH drugs in cases 1 and 2, we cannot clarify whether ASD closure alone in the 2 cases worsened hemodynamics or not. However, we can declare the importance of applying the targeted therapy, because all 3 cases who had undergone ASD closure alone without certified PAH drugs had worsened hemodynamics (cases 3–5, Figure 3). In case 4, Qs (CO) before ASD closure was measured by the Fick method but after ASD closure we selected CO measured by the thermodilution method, because there was no data of Fick analysis in the first catheterization after ASD closure. We cannot rule out the possibility that the increase in CO after ASD closure (before the use of certified PAH drugs) in case 4 might be due to the methodological inconsistency, because under a certain amount of tricuspid regurgitation the thermodilution method usually overestimates the CO.

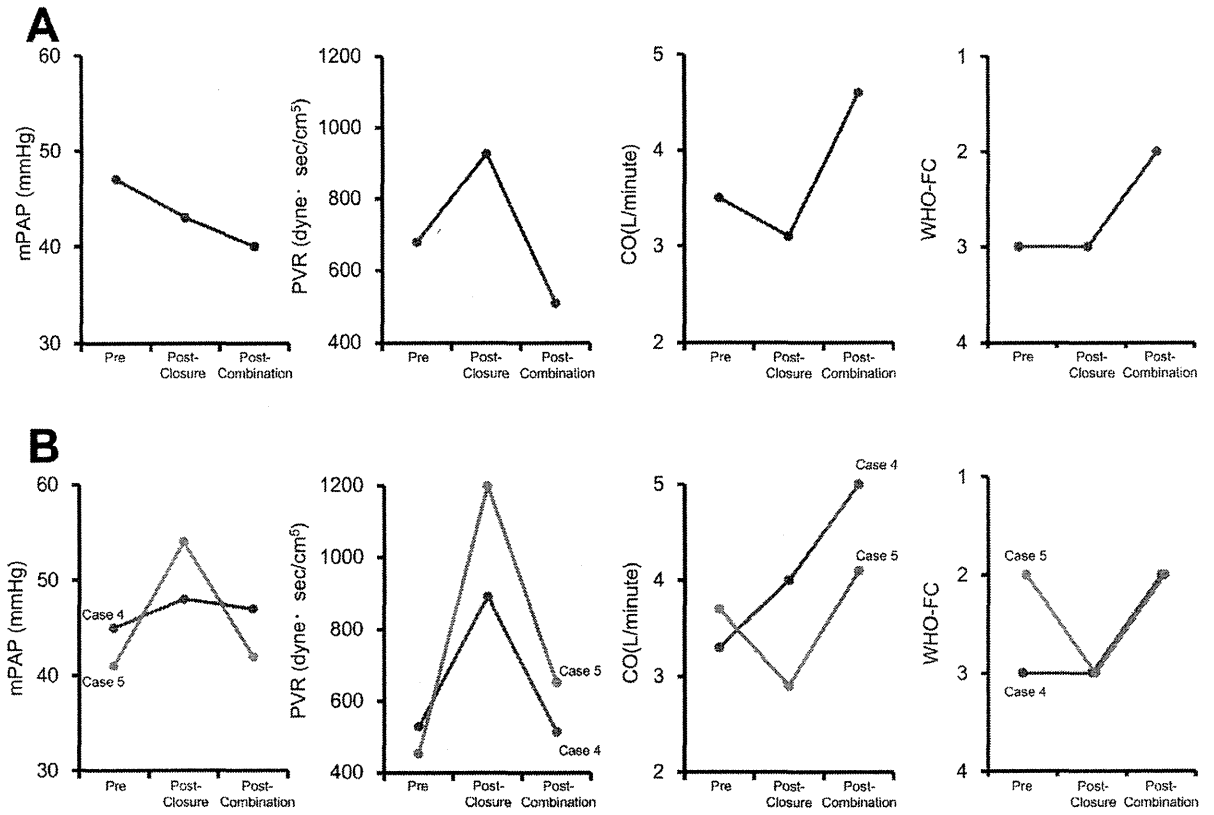

Figure 3. Consecutive hemodynamic and physiological data before surgery, after surgery without medication, and after titration of certified PAH drugs. The changes in mPAP, PVR, Qs, and WHO-FC in case 3 (**A**) and cases 4–5 (**B**) are demonstrated. In both panels, PVR increased after ASD closure alone. Then PVR decreased and Qs increased after titration of the medical therapy, and WHO-FC also improved after the medical therapy. Note that the timing of first hemodynamic evaluation after ASD closure was different between the panels. In case 3 (**A**), it was performed 1 month after the surgery, and certified PAH drugs were started 22 months after the surgery. In cases 4 and 5 (**B**), it was performed 13 years and 40 years after the surgery. mPAP indicates mean pulmonary arterial pressure; PVR, pulmonary vascular resistance; s, systemic blood flow; WHO-FC, World Health Organization Functional Classification; Pre, baseline data before treatment; Post-Closure, data after ASD closure (before administration of certified PAH drugs); and Post-Combination, data after titration of certified PAH drugs.

When and how certified PAH drugs should be used for patients with ASD–PAH?: Because several certified PAH drugs have become commercially available in Japan since 1999,[9] cases 1 and 2 were given these drugs in the perioperative period. Theoretically, shunt closure alone decreases Qp, which substantially leads to a decrease in mPAP (= Qp × PVR – mLAP or mPCWP). However, PVR may suddenly increase because of surgical stress as implied by the observation at 1 month after ASD closure in case 3 (Table II and Figure 3A); consequently, the hemodynamic status of patients may worsen relative to their preoperative status. Therefore, we believe that it is important to start the PAH drugs in the perioperative period. Furthermore, before the targeted therapy was administered 22 months after ASD closure in case 3, consecutive echocardiography did not show any apparent change in estimated right ventricular systolic pressure (data not shown), suggesting the perioperative stress may not have transiently caused the elevation of PVR, but may have induced progression of PAH vasculopathy. In addition, an apparent increase in PVR was found long after the surgery (cases 4 and 5, Figure 3B). The reason for the elevated PVR after surgical closure must be different between case 3 and cases 4–5, because the timing of postoperative assessment was highly different. In cases 4 and 5, the sustained increase in PVR may have been caused by an auto-progression due to residual PAH after ASD closure and/or from the surgical stress. Delayed introduction of targeted therapy with certified PAH drugs improved the hemodynamics and symptoms. It is important to notice that PVR reversed to a similar value before ASD closure, which would suggest that the progression of vascular remodeling after ASD closure was mostly reversible. However, we could not deny the possibility that PVR would have been reduced further if adequate medical treatment had been given from the preoperative period as seen in case 2. Therefore, we emphasize that the medication should be started as early as possible if ASD closure is to be performed in patients with ASD–PAH.

It has been reported that the prognosis of PAH after shunt closure was worse than that of PAH with uncorrected shunt flow in the era without general application of targeted therapy.[7,8] Thus, it is important to identify patients with ASD–PAH who could benefit from ASD closure without a substantial risk, even in this era with certified PAH drugs. We have not established the criteria for identification of these patients yet, but propose the use of certified PAH drugs for patients with ASD–PAH who plan to undergo or have already undergone ASD closure, even after a prolonged period.

Study limitations: Because the case series in this study consisted of outpatients at our hospital who had already undergone ASD closure, we cannot offer any suggestion about a proper method for choosing suitable candidates for ASD closure from adult patients with ASD–PAH. In patients with ASD–PAH, it is extremely important to revise the indication for ASD closure in combination with medical therapy. In addition, percutaneous ASD occlusion devices have become available that are expected to repair defects less invasively.[15,27,28] Therefore, the indication for defect closure may be different between percutaneous and surgical procedures. Thus, randomized controlled studies and/or world-scale surveys on national registries, such as the REVEAL Registry,[29] are required.

As mentioned above, there is as yet no consensus on when targeted therapy should be administered (pre- or post-operation). Further investigations are required to answer this question.

This investigation was a single-center retrospective (observational) study, and the sample size was quite small. However, we believe that the findings are sufficiently reliable to support the conclusion that targeted therapy should be administered for patients with ASD–PAH who plan to undergo or have undergone ASD closure percutaneously or surgically. To confirm our findings, randomized controlled studies and/or world-scale surveys on national registries are required.

To address all the questions associated with comparison of the prognoses of patients undergoing ASD closure and those without ASD closure will require a considerable amount of time because the long-term survival rates of patients in both groups are expected to be quite good.[7,29] It is expected that the number of adult patients with ASD–PAH will decrease, particularly in developed countries, because of early diagnosis in childhood. Therefore, we believe that we should survey past experiences with a large number of patients as soon as possible to help existing patients with ASD–PAH. Considering this, our data may be useful for decision making in other hospitals.

Conclusion: The findings in this study clearly demonstrated improvements in hemodynamics and exercise capacity by the targeted therapy with certified PAH drugs after defect closure in adult patients with ASD–PAH. Our results suggest the importance of using certified PAH drugs for patients with ASD–PAH before or after undergoing ASD closure.

Disclosure

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