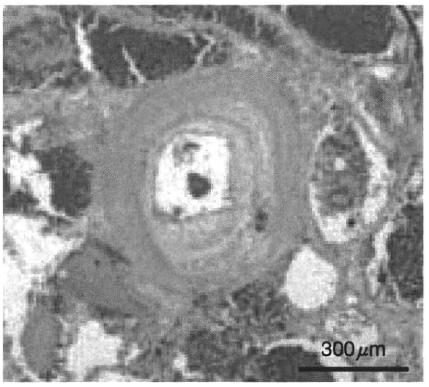

図 3　内膜および中膜肥厚
直径 500 μm 程度の動脈。細胞性内膜および中膜の肥厚を呈する（H-E 染色）。

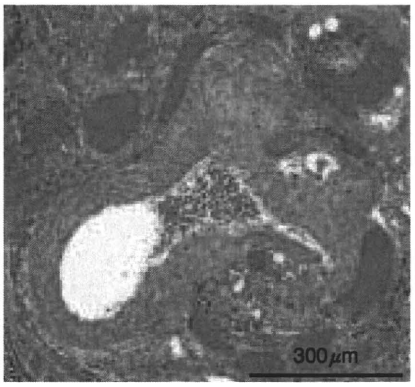

図 4　叢状病変
平滑筋細胞，内皮細胞などの部分増殖が，血管周囲結合組織に拡大。動脈壁の拡張と部分的な破壊所見がみられる（H-E 染色）。

病変であるといわれている。

b　偏心性非層状（eccentric non-laminar）および求心性非層状（concentric non-laminar）（図 3）内膜肥厚

主に線維芽細胞と結合組織基質より構成される。最近，この肥厚は血行学的ストレスにより放出される成長因子が，線維芽細胞を増殖させることで生じるといわれている。

3　外膜肥厚

膠原線維の増加を示すが，その評価は難しい。基本的に中膜肥厚に伴う非特異的変化である。

● 複合血管病変

この病変には叢状病変，血管拡張，動脈炎（フィブリノイド壊死）が含まれる。

1　叢状病変（図 4）

これは肺高血圧の重症度と急速な進行の目印として重要な変化であり，PAH の基本的な細胞異常（おそらく増殖性変化）のマーカーである[9,10]。平滑筋細胞と内皮細胞，筋線維芽細胞などの部分増殖よりなり，血管周囲結合組織が拡大することで動脈壁の拡張と部分的な破壊に関係している。

叢状病変は動脈の分岐部もしくは瘤状に突出した部位に存在し，内部にはフィブリン血栓と血小板がしばしば存在する。また，報告により差はあるが，叢状病変は肺動脈の 20～60％に認められるといわれる。また，先天的な左-右シャント疾患においては，外径で 100～200 μm の動脈で生じる傾向がある。一方，IPAH においては，100 μm 以下の動脈にも起こる。もはや PAH の特有症候であるとはいいがたい。二次性 PAH や慢性血栓塞栓性肺高血圧でさえ存在することが認められているが，出現頻度は少ない。叢状病変内の内皮細胞には血管内皮成長因子（VEGF）とそのレセプター[11]が存在し，PAH 症例においては自律的に内皮増殖や血管形成をすると考えられている[9,10]。近年では，vasculotropic なヒトヘルペスウイルス-8 と PAH の叢状病変の関連性も示されている。

2　血管拡張

拡張病変は叢状病変の末梢に生じ，静脈壁のように薄い血管壁であり肺胞出血や後の器質化，線維化の原因となりうる。

3　動脈炎

フィブリノイド壊死を伴う動脈炎の所見は PAH 初期に生じることはまれで，重症例や膠原病性肺高血圧症で生じる傾向がある。叢状病変などの複雑血管病変の前駆病変とも考えられている。動脈壁にはフィブリノイド浸出液，慢性や急性の炎症細胞が浸潤していることが多い。

● おわりに

肺高血圧症における肺動脈血管病変はさまざまな機序により中膜肥厚，内膜肥厚，叢状病変などの血管リモデリングを生じる。これらの病変が肺高血圧治療によりリバースモデリングできるか，さらに根本的 PAH の加療につながることを期待している。

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Original Article

Mortality from Pulmonary Heart Disease in Japan, 1979–2006

Masahito Sakuma, MD,[1] Norifumi Nakanishi,[1] MD, and Kunio Shirato, MD[2]

Objective: **In Japan, there have been no reports on the time-trends of mortality rates from pulmonary heart disease without pulmonary embolism (PHD). Our aim was to examine the annual changes of mortality in Japan.**

Materials and Methods: **Annual age-adjusted and age-specific PHD mortality for Japanese residents during 1979–2006 were calculated from " Vital statistics of Japan" and census data and population estimates for intercensal years.**

Results: **The number of age-adjusted deaths from PHD continued to decrease throughout the study period. The age-specific mortality from PHD increased throughout the life span except below 1 year old and decreased in recent years. Male mortality was greater at most ages. In Poisson regression analysis, the relative risk of death from PHD was increased in males and the aged except below 1 year-age, and decreased in recent years. The annual number of deaths from idiopathic pulmonary arterial hypertension/heritable pulmonary arterial hypertension (IPAH/HPAH) continued to increase throughout the study period. The number of annual new cases with IPAH/HPAH was estimated to be about 400 in a recent period of 10 years.**

Conclusion: **The annual number of deaths from PHD decreased, and those from IPAH/HPAH increased significantly during 1979–2006 in Japan.**

Keywords: mortality, pulmonary hypertension, idiopathic pulmonary arterial hypertension, pulmonary circulation

Introduction

The accumulation of evidence on the basic mechanism of occurrence of pulmonary hypertension and the appearance of new therapeutic agents has led to a revision of the classification of pulmonary hypertension and treatment strategies.[1–4] The prognosis has been dramatically improved especially in idiopathic pulmonary arterial hypertension/heritable pulmonary arterial hypertension (IPAH/HPAH).[5–8] Recently, guidelines for the treatment of pulmonary hypertension[9, 10] have been published in Japan, and concern about pulmonary hypertension is increasing.

Surveillance in Western countries has revealed that the number of deaths from PH has increased among females, and decreased among males.[11] The number of clinical cases with IPAH/HPAH is high in the third and fourth decade.[12, 13] However, age-specific mortality showed a high rate among infants below 1 year old, a low rate in childhood, and an ascending rate through the remainder of life in the United States.[14]

There have been no reports on the time-trend of mortality from pulmonary heart disease without pulmonary embolism (PHD) or IPAH/HPAH in Japan. PHD includes Group 3 (pulmonary hypertension owing to lung disease and/or hypoxia), Group 1.1 (IPAH), and Group 1.2 (HPAH) in Dana Point classification of pulmonary hypertension.[4] The causes of pulmonary hypertension in Group 3 are chronic obstructive pulmonary diseases,

[1]*Department of Cardiovascular Medicine, National Cerebral and Cardiovascular Center, Suita, Osaka, Japan*
[2]*Division of Internal Medicine, Saito Hospital, Ishinomaki, Japan*

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Corresponding author: Masahito Sakuma, MD. Department of Cardiovascular Medicine, National Cerebral and Cardiovascular Center, 5-7-1 Fujishiro-dai, Suita, Osaka 565-8565, Japan
Tel: +81-6-6833-5012, Fax: +81-6-6872-7486
E-mail: sakuma-masahito@goo.jp

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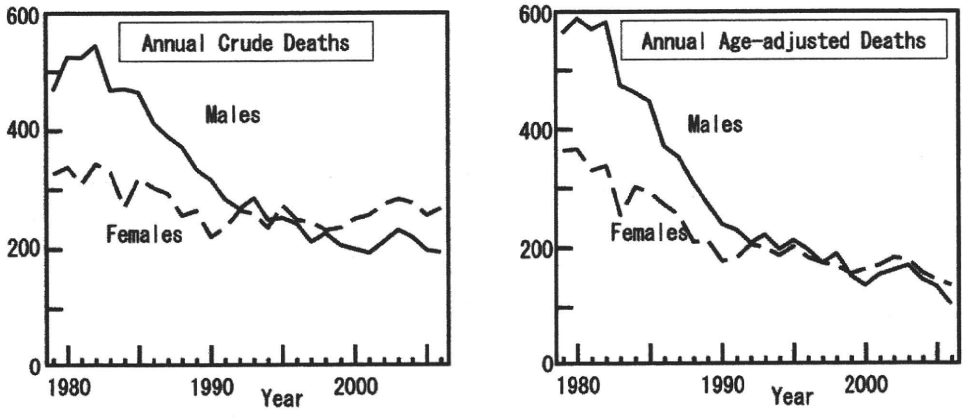

Fig. 1 Deaths from PHD by gender, 1979–2006.
PHD: pulmonary heart disease without pulmonary embolism

interstitial lung disease, other pulmonary diseases with mixed restrictive and obstructive pattern, sleep-disordered breathing, alveolar hypoventilation disorders, chronic exposure to high altitude, and developmental abnormalities.[4] Our aims were to examine the annual changes of mortality in Japan.

Methods

Data on deaths and population for the period 1979–2006 were obtained from "Vital statistics of Japan",[15] census data,[16] and population estimates for intercensal years.[17, 18] The register is based on death certificates issued by doctors. PHD was diagnosed for decedents with the International Classification of Diseases, Ninth Revision (ICD-9) code 416.0 (primary pulmonary hypertension), 416.8 (other chronic pulmonary heart diseases), or 416.9 (chronic pulmonary heart disease unspecified) during 1979–1994 or ICD-10 code I27.0 (primary pulmonary hypertension), I27.8 (other specified pulmonary heart diseases), or I27.9 (pulmonary heart disease, unspecified) during 1995–2006, according to a previous report.[11] The annual age-adjusted deaths and mortality rates by gender, using the 1985 Japan population as a standard, which is a common method in Japanese epidemiology, were obtained for each year from 1979 through 2006. For these calculations, we used 5 year step populations up to 85 years old and those 85 or older as the population data in each year. The number of PHD patients (ICD-9 code 416.0, 416.8, or 416.9 or ICD-10 code I27.0, I27.8, or I27.9) was reported separately from that of kyphoscoliotic heart disease (ICD-9 code 416.1 or ICD-10 code I27.1) in total, but not by age. In order from 1979 to 2006, the number of cases of kyphoscoliotic heart disease in males was 2, 1, 1, 1, 2, 0, 0, 0, 0, 1, 0, 0, 0, 1, 1, 2, 2, 1, 1, 0, 1, 0, 1, 3, 1, 0, 2 and 2, respectively; and in females, 0, 0, 3, 6, 1, 1, 1, 2, 2, 2, 2, 0, 0, 1, 1, 2, 0, 2, 1, 3, 2, 2, 2, 1, 1, 0, 1 and 0. Therefore, the annual age-adjusted deaths and mortality rates from PHD included those from kyphoscoliotic heart disease.

The annual age-specific mortality in Japan by gender was generated using "Vital statistics of Japan",[15] census data,[16] and population estimates for intercensal years.[17, 18]

The number of patients who received the subsidy for "Intractable Diseases," which is decided by the Ministry of Health, Labour and Welfare, Japan has been reported annually during 1996–2006 by the Japan Intractable Diseases Information Center.[19] IPAH is one of the "Intractable Diseases". The numbers of annual new cases with IPAH/HPAH were estimated as the sum of the annual increment of cases and annual deaths. Annual mortality was defined as 100 times the annual deaths divided by the numbers of annual new cases.

Statistical Analysis

Statistical analysis was performed using SPSS 15.0 (SPSS Inc, Chicago, IL, USA). The results of Poisson regression analysis[20] are presented as estimated relative risks with 95% confidence intervals. Non-ordinal categorical data were analyzed by chi-square statistics.

Results

PHD

Annual deaths from pulmonary hypertension due to kyphoscoliotic heart disease ranged from 0 to 6. Most causes of death from PHD were pulmonary hypertension associated with lung diseases, hypoxemia and/or IPAH/HPAH.

The number of crude deaths and age-adjusted deaths from PHD continue to decrease both in males and in females in Japan (**Fig. 1**). The numbers of age-adjusted

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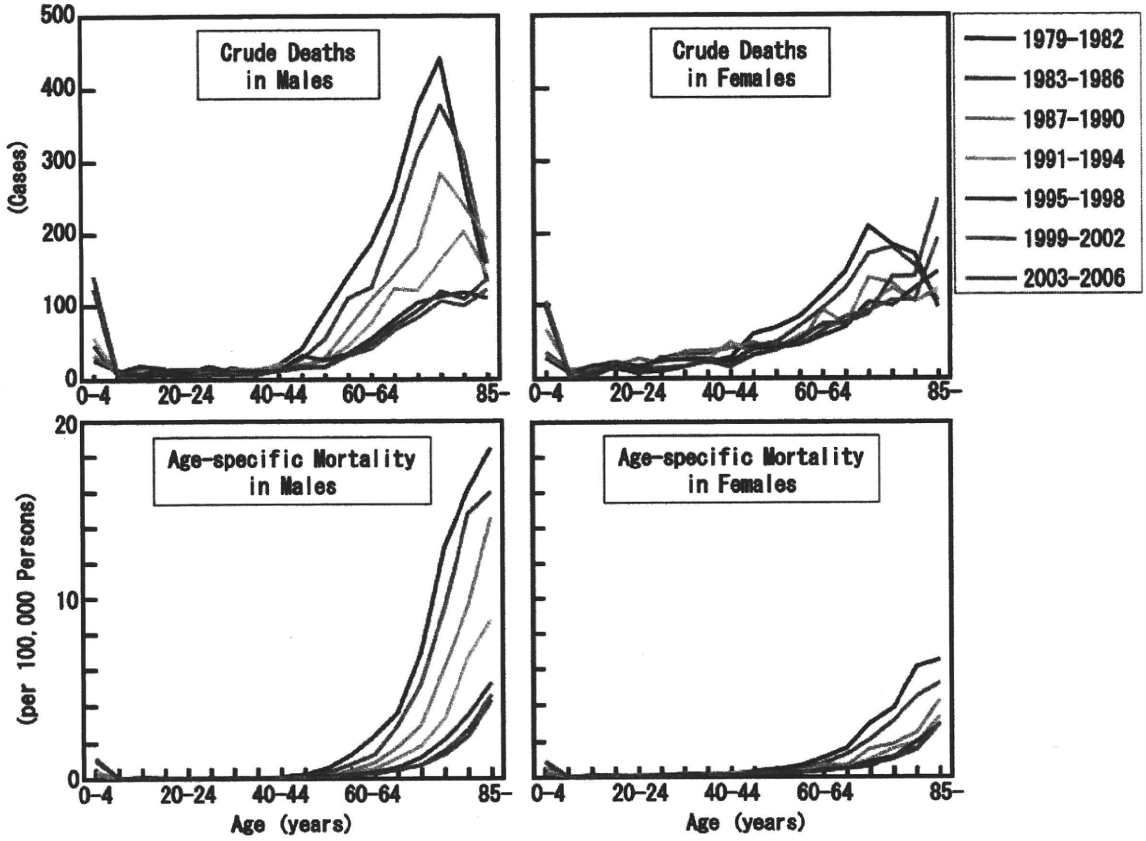

Fig. 2 Crude deaths in 5 year-age steps (upper panels) and annual age-specific mortality (lower panels) from PHD by gender. PHD: pulmonary heart disease without pulmonary embolism

deaths from PHD were higher in males than in females before the 1990s, and similar from the 1990s to 2006.

Crude deaths and age-specific mortality from PHD in Japan are shown in **Fig. 2**; generally, these indexes increased throughout the life span except below 1 year old and decreased in recent years. Male mortality was greater than that of females at most ages. In Poisson regression analysis, the relative risk of mortality from PHD was elevated in males, and the aged except below 1 year old, and decreased in recent years (**Table 1**).

IPAH/HPAH

Numbers of cases with IPAH/HPAH and annual deaths continue to increase (**Fig. 3**). Annual mortality in 2006 was 2.5 per 1,000,000 persons. The prevalence and incidence in 2006 were estimated to be 961 cases (7.5 per 1,000,000 persons) and 433 cases (3.4 per 1,000,000 persons), respectively. Annual mortality among cases with IPAH/HPAH continues to decrease (**Fig. 3**). The estimated number of IPAH/HPAH was 1.11 times (95% confidence interval, 1.03–1.20; $P = 0.007$) higher in 2003-2006 than that in 1996–1998. The relative risk of mortality from IPAH/HPAH was low in males, and increased in recent years (**Table 2**).

The ratio of deaths from IPAH/HPAH to that from pulmonary heart disease increased from 10.9% in the period between 1979 and 1982 to 69.8% in the period between 2003 and 2006 ($P<0.0001$; see **Fig. 3**).

Discussion

PHD

Age-specific mortality from PHD in Japan showed a high rate among infants <1 year old, and was elevating over 40 years old. In 2003–2006, about 70% of deaths from PHD were IPAH/HPAH. Therefore, the age-distribution in **Fig. 2** is thought to reflect that of IPAH/HPAH. This distribution pattern resembles that from IPAH/HPAH in the United States.[14]

The numbers of deaths from PHD have been declining both in males and in females in Japan. The numbers of deaths from IPAH/HPAH have been increasing.

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Table 1 Relative Risk of Mortality from PHD

	Relative Risk	95% Confidence Interval	*P*-value
Gender			
Female	1.00	-	-
Male	1.57	1.51–1.61	<0.0001
Year			
1979–1982	2.75	2.59–2.90	<0.0001
1983–1986	2.21	2.09–2.34	<0.0001
1987–1990	1.60	1.50–1.69	<0.0001
1991–1994	1.21	1.14–1.29	<0.0001
1995–1998	1.00	–	–
1999–2002	0.84	0.79–0.90	<0.0001
2003–2006	0.79	0.74–0.84	<0.0001
Age group (y.o.)			
0	6.10	5.58–6.64	<0.0001
1–9	0.29	0.26–0.32	<0.0001
10–19	0.24	0.21–0.27	<0.0001
20–29	0.25	0.22–0.27	<0.0001
30–39	0.31	0.28–0.34	<0.0001
40–49	0.49	0.45–0.53	<0.0001
50–59	1.00	–	–
60–69	2.68	2.52–2.85	<0.0001
70–79	7.35	6.93–7.79	<0.0001
80–	16.28	15.33–17.27	<0.0001

PHD: pulmonary heart disease

Therefore, the main reason for the decrease is the decrease in the number of deaths from PHD secondary to chronic obstructive pulmonary disease, fibrosing lung disease or destroyed lung from pulmonary tuberculosis. Another possible reason is that many patients with IPAH/HPAH were not diagnosed as IPAH/HPAH and were diagnosed as only pulmonary hypertension in previous years.

IPAH/HPAH

New therapeutic agents are being developed and the prognosis of IPAH/HPAH is gradually ameliorating in specialized hospitals.[5–8] When the number of diagnosed cases is unchanged and management is improved, the number of deaths should decrease at least temporally, and not increase. However, the number of deaths from IPAH/HPAH in the present data shows an unexpected increase.

The number of deaths diagnosed as a certain disease is regulated both by diagnostic power and by the results of treatment. A subtle increment of the estimated diagnostic number after 1996 may be one of the reasons for the change in the number of deaths from IPAH/HPAH. The number of deaths increases as a result of unsuccessful therapy, but also as a result of good or unchanged therapy with continuously changing the diagnosed number and/or time dependent effect of managements. Therefore, we cannot determine all the effects of new therapeutic agents in nationwide hospitals from the present study. Individual data on the duration from diagnosis to death are needed to estimate the efficacy of managements. However, the data and mortality by age have not been announced officially in Japan. The effect of newer managements on population-based mortality remains to be determined.

Recently, guidelines for the treatment of pulmonary hypertension[9, 10] have been published in Japan, and concern about pulmonary hypertension is increasing. The increment of recognition for the disease may contribute to the number of patients diagnosed as having the disease. Pulmonary hypertensions associated with human immunodeficiency virus or appetite suppressants seem not to affect the present results, because these types of pulmonary hypertension are very rare in Japan.

The ratio of deaths from IPAH/HPAH to that from pulmonary heart disease was increasing and reached about 70%. Therefore, the age distribution of deaths from pulmonary hypertension partly reflects that from IPAH/

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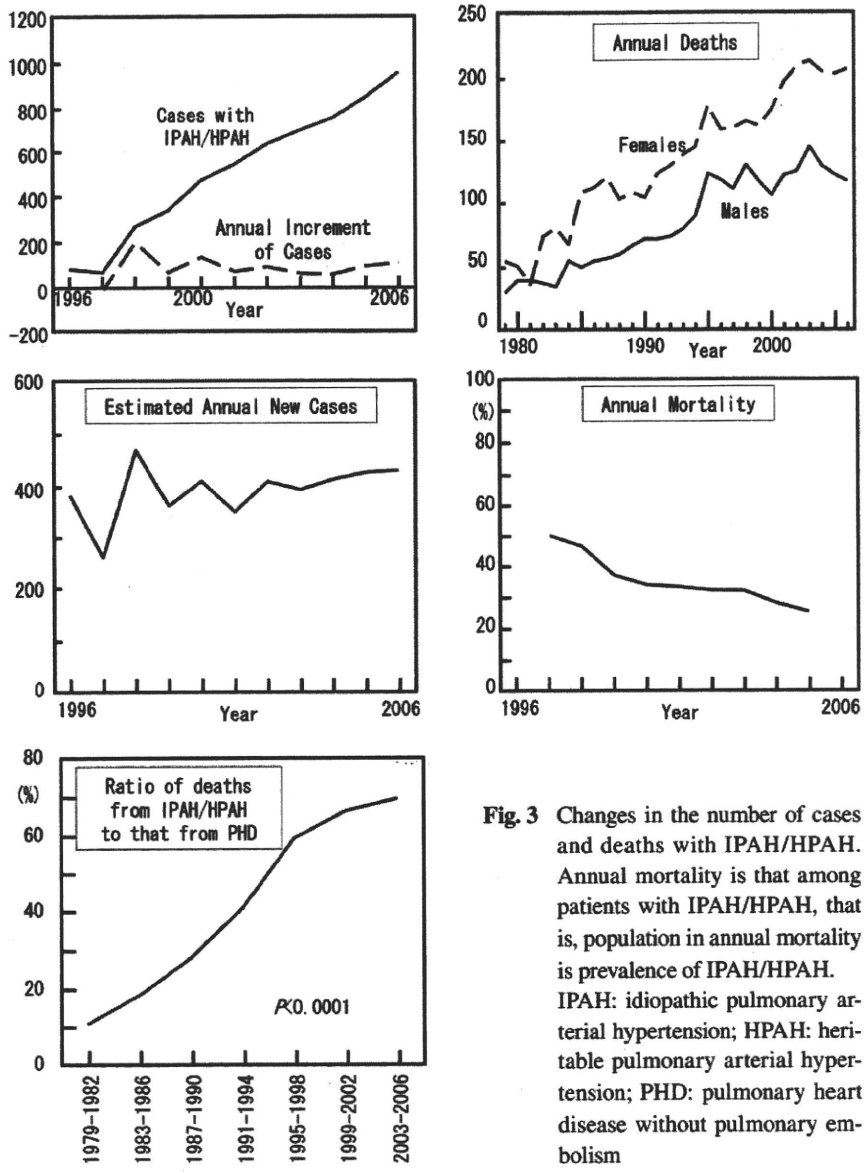

Fig. 3 Changes in the number of cases and deaths with IPAH/HPAH. Annual mortality is that among patients with IPAH/HPAH, that is, population in annual mortality is prevalence of IPAH/HPAH. IPAH: idiopathic pulmonary arterial hypertension; HPAH: heritable pulmonary arterial hypertension; PHD: pulmonary heart disease without pulmonary embolism

Table 2 Relative Risk of Mortality from IPAH

	Relative Risk	95% Confidence Interval	*P*-value
Gender			
Female	1.00	–	–
Male	0.65	0.62–0.69	<0.0001
Year			
1979–1982	0.34	0.30–0.38	<0.0001
1983–1986	0.51	0.47–0.57	<0.0001
1987–1990	0.62	0.56–0.68	<0.0001
1991–1994	0.75	0.69–0.82	<0.0001
1995–1998	1.00	–	–
1999–2002	1.05	0.97–1.14	0.24
2003–2006	1.15	1.07–1.25	0.0004

IPAH: idiopathic pulmonary arterial hypertension

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HPAH, which is considered, based on clinical studies, to appear more commonly in the young and middle-aged. However, the present results show that the crude the number of deaths from pulmonary heart disease were not higher in teens, twenties, or thirties than in other ages. The results from the U.S.A. clearly demonstrate that age-specific mortality from IPAH/HPAH is at a high rate among infants <1 year old, a low rate in childhood, and ascending rate through the remainder of life.[14]

The incidence from IPAH/HPAH was 1-2 per million people in the NIH registry,[12] and 1.7 per million population (95% coincidence interval, 1.0–2.4) in a collaborative study from France, Belgium, United Kingdom, and Netherlands.[21] The prevalence and incidence from recent reports ranged between 6.5 and 25 per million people and between 1.0 and 3.3 per million people, respectively.[22–24] The prevalence (7.5 per million people) and incidence (3.4 per million people) in the present study resembled to the findings of previous reports.

Conclusions

The annual number of deaths from PHD decreased, and those from IPAH/HPAH increased significantly during 1979–2006 in Japan.

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Three-Dimensional Structure of Pulmonary Capillary Vessels in Patients With Pulmonary Hypertension

Aya Miura, MSc*; Kazufumi Nakamura, MD, PhD*; Kengo F. Kusano, MD, PhD; Hiromi Matsubara, MD, PhD; Aiko Ogawa, MD, PhD; Satoshi Akagi, MD, PhD; Takahiro Oto, MD, PhD; Takuro Murakami, MD, PhD; Aiji Ohtsuka, MD, PhD; Chikao Yutani, MD, PhD; Tohru Ohe, MD, PhD; Hiroshi Ito, MD, PhD

Pulmonary arterial hypertension, pulmonary veno-occlusive disease, and pulmonary capillary hemangiomatosis are included in the same group (group 1) of clinical classification of pulmonary hypertension.[1] Histological changes in the small pulmonary arteries (ie, intimal fibrosis and medial hypertrophy) are similar in these 3 diseases, and clinical presentations of the 3 diseases are often indistinguishable.[1] However, it is estimated that the hemodynamics of capillary vessels are quite different in each disease. The hemodynamics of capillary vessels (ie, capillary occlusion) play an important role in cardiovascular diseases.[2] Thus, clarification of the differences in the hemodynamics is essential to understand the pathophysiology of these 3 diseases.

We obtained lung segments from patients with pulmonary hypertension who underwent living-donor lung transplantation and from patients with bronchogenic carcinoma who underwent lobectomy as described previously.[3] All experiments were performed after approval was obtained from the Human Ethics Committee of Okayama University, and written informed consent was obtained from all patients before the procedure. We succeeded in visualization of the 3-dimensional structure of the pulmonary capillary in patients with pulmonary arterial hypertension, pulmonary veno-occlusive disease, and pulmonary capillary hemangiomatosis using scanning electron microscopy of blood vascular casts.[4]

A 42-year-old man underwent lobectomy for bronchogenic carcinoma. Figure 1A shows hematoxylin-eosin staining of a normal small pulmonary artery. Blood vascular architecture in the most distal area from the carcinoma in the resected lobe shows a normal capillary network around the alveolus of the lung (Figure 1B).

A 20-year-old man underwent lung transplantation for idiopathic pulmonary arterial hypertension. The blood vascular architecture resembled dead branches. The small vessels were severely stenosed and were often occluded (Figure 2A), and the capillary was deficient (Figure 2B).

A 27-year-old man underwent lung transplantation for pulmonary veno-occlusive disease. The small pulmonary veins were stenosed (Figure 3A), and capillary vessels were swollen compared with a normal capillary (Figure 3B).

A 14-year-old boy underwent lung transplantation for pulmonary capillary hemangiomatosis. A proliferation of capillaries was seen (Figure 4A), and the capillary vessels resembled a tumorous cluster (Figure 4B).

Scanning electron microscopic study of blood vascular casts revealed the differences in the 3 diseases. Pulmonary arterial hypertension was characterized by a deficient capillary network, pulmonary veno-occlusive disease by swollen capillary vessels, and pulmonary capillary hemangiomatosis by a tumorlike outgrowth of capillaries. To the best of our knowledge, this is the first report on differences in the 3-dimensional structure of capillary vessels in normal controls, pulmonary arterial hypertension, pulmonary veno-occlusive disease, and pulmonary capillary hemangiomatosis using scanning electron microscopy of blood vascular casts. These findings provide an insight into the basic mechanism responsible for pulmonary hypertension.

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Disclosures

None.

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From the Department of Cardiovascular Medicine (A.M., K.N., K.F.K., A. Ogawa, S.A., T. Ohe, H.I.), Department of Cancer and Thoracic Surgery (T. Oto), and Department of Human Morphology (T.M., A. Ohtsuka), Okayama University Graduate School of Medicine, Dentistry, and Pharmaceutical Sciences; Division of Cardiology, National Hospital Organization, Okayama Medical Center (H.M.); and Department of Life Science (C.Y.), Okayama University of Science, Okayama, Japan.

*The first 2 authors contributed equally to this work.

Correspondence to Kazufumi Nakamura, MD, PhD, Department of Cardiovascular Medicine, Okayama University Graduate School of Medicine, Dentistry, and Pharmaceutical Sciences, 2-5-1 Shikata-cho, Okayama 700-8558, Japan. E-mail ichibun@cc.okayama-u.ac.jp

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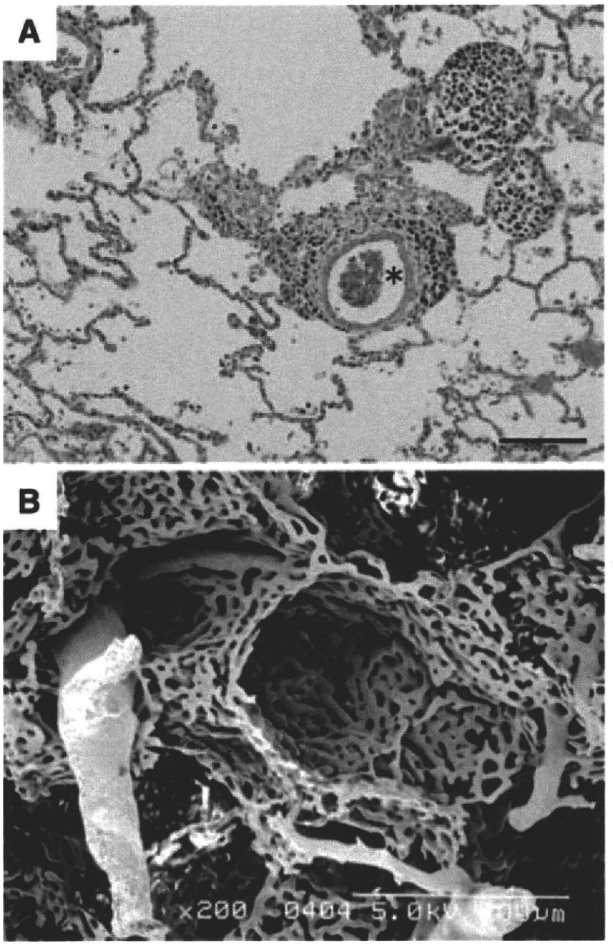

Figure 1. Images of normal control microvessels. A, Hematoxylin-eosin staining of a small pulmonary artery (*). Bar=200 μm. B, Scanning electron micrograph of blood vascular casts. Bar=200 μm.

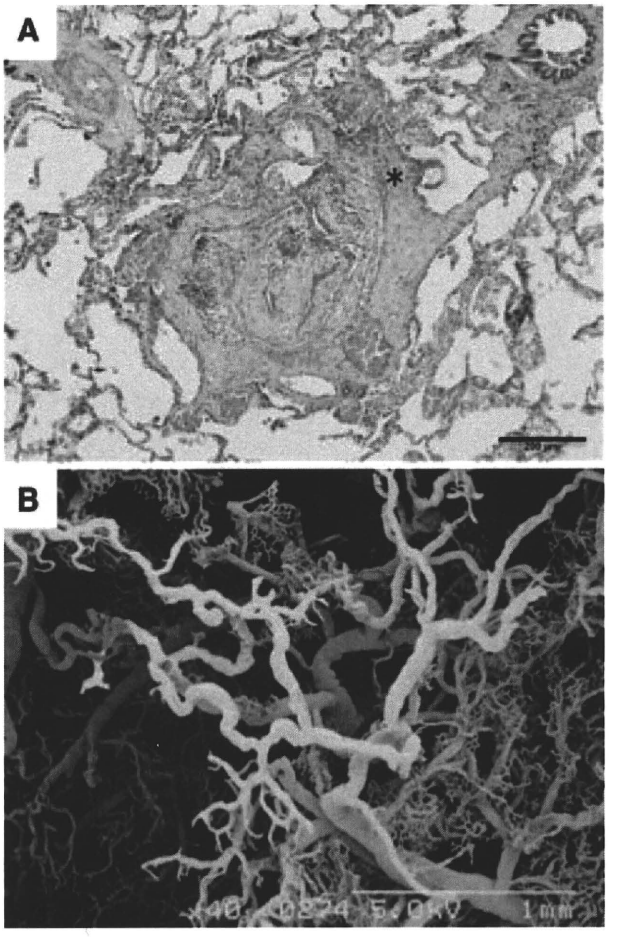

Figure 2. Images of microvessels from a patient with pulmonary arterial hypertension. A, Hematoxylin-eosin staining of small pulmonary arteries (*). Bar=200 μm. B, Scanning electron micrograph of blood vascular casts. A deficient capillary network is seen. Bar=1 mm.

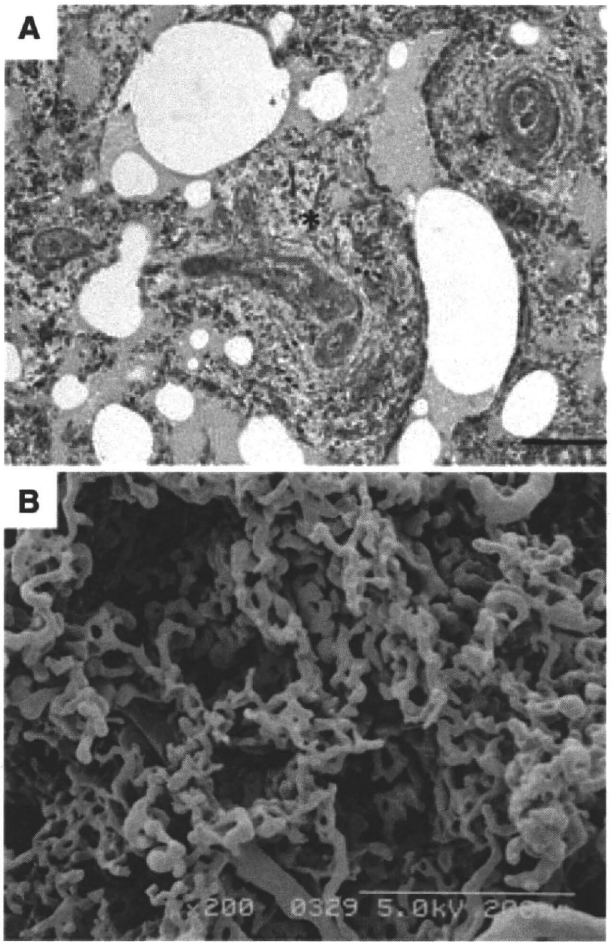

Figure 3. Images of microvessels from a patient with pulmonary veno-occlusive disease. A, Masson's trichrome staining of a small pulmonary vein (*). Bar=200 μm. B, Scanning electron micrograph of blood vascular casts. Swollen capillary vessels are seen. Bar=200 μm.

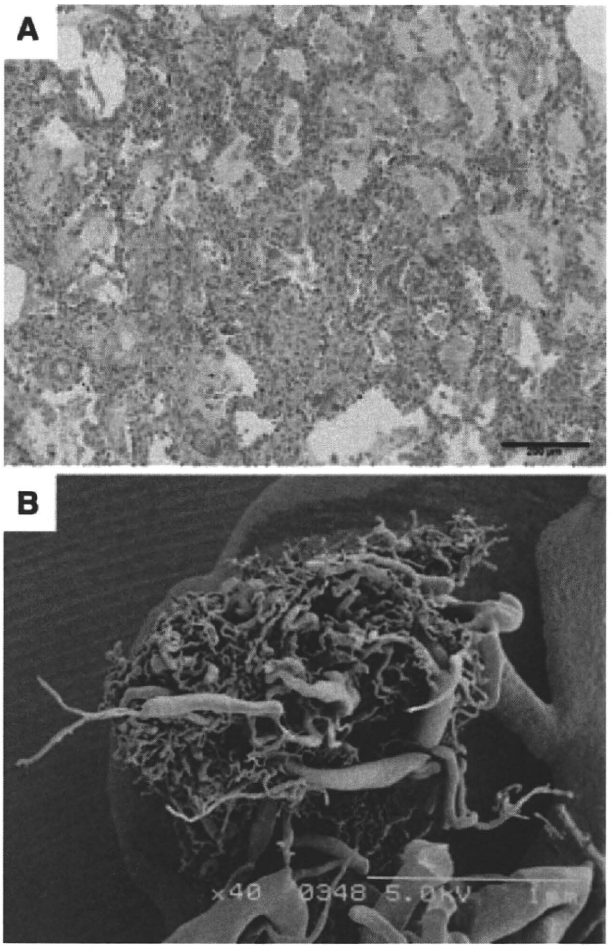

Figure 4. Images of microvessels from pulmonary capillary hemangiomatosis. A, Hematoxylin-eosin staining of small pulmonary vessels. Bar=200 μm. B, Scanning electron micrograph of blood vascular casts. Tumorlike outgrowth of capillary vessels is seen. Bar=1 mm.

肺高血圧症の概念，分類，治療戦略，予後

佐藤　徹

さとう とおる：杏林大学医学部 循環器内科

■肺高血圧症の概念

肺高血圧症の定義は，1960年にWHO（世界保健機関）主催の肺高血圧症第1回世界会議で，平均肺動脈圧25 mmHg以上とされた。2008年に米国のダナポイントで行われた第4回肺高血圧症世界会議で多くの参考文献が検討され，感度を高くするには（健康人がこの定義に入らないようにするには）やはり平均肺動脈圧25 mmHg以上とすることが確認された。しかし，特異度を上げるには（肺高血圧症の人を拾いあげるには），この定義では不十分であるため，平均肺動脈圧が20～25 mmHgは境界型肺高血圧症（borderline pulmonary hypertension）とされた。運動時の肺動脈圧上昇に基づく肺高血圧症の程度に関しては多くの報告があるが，基準値について一致した結論が得られず，今回の会議では保留とされた。まとめると，平均肺動脈圧が20 mmHgを超えると肺高血圧症の可能性が高いが，25 mmHg以下では測定誤差などから正常である可能性も否定できず，25 mmHgを超えると肺高血圧症であることは間違いないといえる。運動負荷による肺高血圧症の診断に関しては確定した基準はない。

■分　類

肺高血圧症の臨床的な分類（**表1**）は1998年にフランスのエビアンで行われた第2回世界会議で刷新された。原発性と二次性に大きく分類し，二次性をさらに細かく分類する従来の方法から，障害部位に基づいて解剖学的に4つに分類する方法にかわった。障害部位による分類は発症機序による分類ともいえ，したがって分類が決定されると大きな治療方針も決まる。4つの大分類の後，さらに細かい原因を確定することは，より詳細な治療法の選択や予後決定のために不可欠なものとなる。また，この分類表は肺高血圧症の鑑別診断をするうえで非常に便利で，分類1の肺動脈性肺高血圧症の項では頻度の多い順に原因疾患は配列されており，この表を記憶して順次鑑別疾患を検査していけばよい。2008年にはダナポイントで第4回会議が開かれ，分類がマイナーチェンジされた。

表 1　肺高血圧症の分類：ダナポイント分類 2008（第 4 回世界シンポジウム，Danapoint, USA, 2008）

1．肺動脈性肺高血圧症（PAH）
　1）特発性 PAH（IPAH）
　2）遺伝性
　3）薬物と毒物
　4）各種疾患に伴う肺動脈性肺高血圧症
　　①膠原病性
　　②先天性心疾患
　　③肝臓病
　　④エイズ
　　⑤住血吸虫
　　⑥溶血性貧血
　5）新生児遷延性肺高血圧症
1'．肺静脈および/または肺毛細管閉塞
　肺静脈閉塞性疾患（PVOD），肺毛細血管腫症（PCH）
2．左心性心疾患に伴う肺高血圧症
　1）収縮障害
　2）拡張障害
　3）弁膜症
3．呼吸器疾患および/または低酸素血症に伴う肺高血圧症
　1）慢性閉塞性肺疾患
　2）間質性肺疾患
　3）混合性障害
　4）睡眠呼吸障害
　5）肺胞低換気障害
　6）高所への慢性暴露
　7）発育障害
4．慢性血栓性および/または塞栓性疾患による肺高血圧症
5．その他の肺高血圧症
　1）血液疾患：骨髄増殖性疾患，脾摘出
　2）全身疾患：サルコイドーシス，ヒスチオサイトーシス X，リンパ管腫症，神経鞘腫，血管炎
　3）代謝疾患：甲状腺疾患，糖原病，ゴーシェ病
　4）その他：肺血管の圧迫（リンパ節腫脹，腫瘍，線維性縦隔炎）

1　肺動脈性肺高血圧症（pulmonary arterial hypertension：PAH）

肺動脈の 0.1〜0.04 mm 前後の細動脈が障害され，中膜が肥厚し内膜が増殖して内腔が狭くなる。肺動脈の血流は労作時には 4〜5 倍に増加するが，本来壁が柔軟で内腔が広がることで肺動脈圧はわずかしか上昇しないのに対し，血管壁の硬化した PAH では肺動脈圧は上昇する。肺動脈血管床の 70%前後までの障害では安静時の肺動脈圧は上昇しないが，それ以上では安静時肺動脈圧が上昇し肺高血圧症と診断される。特発性肺動脈性肺高血圧症（idiopathic pulmonary arterial hypertension：IPAH）が最も頻度が多く，膠原病性肺高血圧症（connective tissue disease pulmonary hypertension：CTDPH），先天性心疾患による肺高血圧症（congenital heart disease pulmonary hypertension：CHDPH），肝疾患による PAH が続く。外国ではこれに次いで HIV によるもの，南米で多い肺吸血虫によるもの，白人でみられる鎌形赤血球症によるものが原因となる。肺静脈の閉塞による肺静脈閉塞症（pulmonary venous occlusive disease：PVOD），肺毛細血管の閉塞による肺血管腫症（pulmonary capillary hemangiomatosis：PCH）も 1'として PAH に分類されている。PAH に対しては血管壁増殖を抑制する特異的治療が開発され，内科医の腕の見せ所と言ってよい。1991 年にプロスタサイクリ

ンであるエポプロステノールの持続点滴が開始されるまでは有効な治療法はなかったが，その後現在までに3系統の作用機序の異なる治療法が開発された。

2　左心疾患による肺高血圧症

あらゆる左心疾患はある程度重症となると肺高血圧症を生ずる。これは右心室から肺循環を通して左房に血液を還流させる driving force が約 8 mmHg とされるが，左心疾患が進行して左房圧が 18 mmHg になったとすると平均肺動脈圧は 26 mmHg（18＋8）となり，肺高血圧症の定義を満たすことになる。進行した拡張型心筋症では，肺動脈を収縮させて左心系に還流する血液量を減少させ，左房圧が高いにもかかわらず肺水腫を生じさせないような機転が働く症例がある。肺動脈性肺高血圧症を発症させて，肺水腫を回避する身体の防御作用と言える。左心疾患による肺高血圧症で最も見逃され PAH と診断されるものに，拘束型心筋症による肺高血圧症があげられる。拘束型心筋症は左室の収縮能は正常で拡張能が障害されるため，2D 心エコーで壁運動をみると左室機能は正常と判断され，同時に存在する肺高血圧症の原因を肺動脈性と考えてしまう。心エコーで左室流入パターンが E/A＞2 となり両心房の拡大がみられること，内頸静脈の拍動パターンで深い y 波が認められることなどより，診断される。治療は原病の左心疾患の治療を行う。

3　肺疾患による肺高血圧症

低酸素血症による肺動脈攣縮が肺高血圧症の主たる原因とされる。肺疾患の重症度に応じて肺動脈圧は上がるが，肺高血圧症の程度は軽く，多くは十分な酸素投与で改善がみられる。したがって，治療も原病の治療および HOT（在宅酸素療法）が適応される。“Out of proportion pulmonary hypertension”とよばれる，肺疾患の重症度を超えた高い肺動脈圧を示す症例がある。サイトカインの関与が考えられているが[1]，今後のさらなる検討が待たれる。

4　慢性肺血栓塞栓症による肺高血圧症（chronic thromboembolic pulmonary hypertension：CTEPH）

肺動脈の亜区域枝の分枝あたりまでに血栓塞栓を生じ，これが器質化して壁肥厚を起こし，狭窄・閉塞に至って肺高血圧症を生ずる。血栓塞栓の好発部位は，これらの分枝までそれより末梢側は開通していることがわかっている。したがって，これより中枢側の血栓内膜摘除術を行って狭窄・閉塞を解除することにより，肺高血圧症は改善する。これより末梢の病変が主体の症例では，手術適応からはずれる。また，血行動態が重症化すると予後も不良となるため[2]，適切な時期に手術適応の有無を決定することが必要となる。

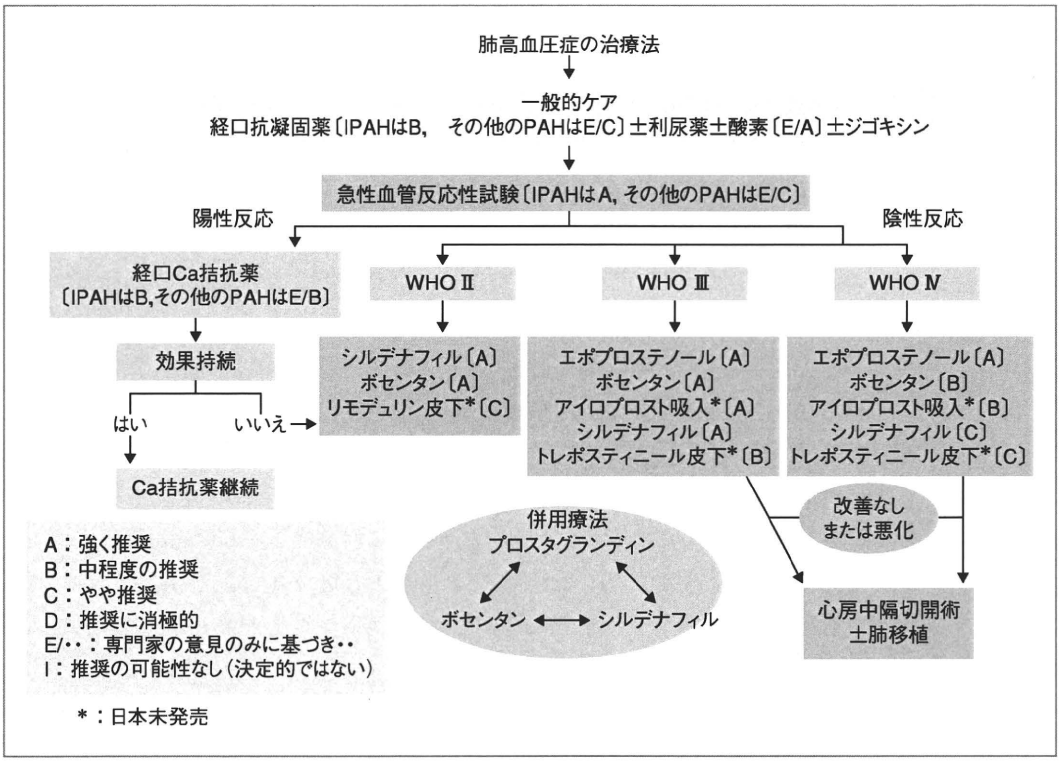

図 1　肺高血圧症の治療法（2007 ACCP ガイドラインより引用，一部改変）
PAH：肺動脈性肺高血圧症，IPAH：特発性肺動脈性肺高血圧症

■治療戦略

治療ガイドラインが，欧州心臓病学会，米国胸部疾患学会（**図 1**）より呈示されている。きわめて大ざっぱなガイドラインといえるが，症例による反応の違いが大きく，このような概略を決めておくことが最良なのであろう。まず右心不全が存在すればこの治療を行い，禁忌がなければ抗凝固薬（ワルファリン）を追加し，運動量制限などの一般的治療を開始した後，右心カテーテル検査を施行する。右心カテーテル時に血管拡張試験を行う。血管拡張法として，純酸素投与，Ca ブロッカー内服，アデノシン静注，NO 吸入，エポプロステノール静注など何でもよく，20%以上平均肺動脈圧が低下し 40 mmHg 以下となると陽性と判定される。このような症例ではひとまず Ca 拮抗薬内服で肺高血圧症の改善がみられ，しばらくはこれで肺高血圧症の進行も抑制される。問題はこのような症例の頻度が高くなく（日本人では 5%弱），またいずれは

Ca 拮抗薬のみではコントロールできなくなる症例があることにある。急性血管反応試験が陽性でも厳重に経過をみたほうが良いであろう。急性血管反応試験が陰性であれば，症状の強さに応じて治療薬を決定する。NYHA の心機能分類が予後を決める最も強い因子となることが報告されていることもあり[3]，NYHA 分類に従って治療薬を選択する。現在使用される 3 系統の治療薬（エンドセリン受容体拮抗薬，PDE-V 阻害薬，プロスタサイクリン）が種々の推奨度で記載されている。

どれから始めるかは定まったエビデンスはなく，副作用を考慮して試行錯誤をしつつ，併用療法も試みる。このなかでプロスタサイクリンは NYHA II では使用されず，NYHA IV では最も推奨度が高い。プロスタサイクリンは最も早期から PAH 治療薬として使用を開始されたが，依然最も効果の高い治療薬といえる。この薬剤をいかに使用するかが PAH の治療の鍵となる。プロスタサイクリンは持続点滴投与が必要なため，留置カテーテルの植え込みが必要で，留置カテーテルには感染という大きな合併症を伴い高温多湿の日本ではかなりの頻度で起こる。十分な感染予防が必要となる。また，患者に対しては無菌的に毎日点滴薬の調剤を行い，携帯型輸液ポンプの流量を調整し，器械のトラブルにも対処しなければいけない。慣れた施設でしっかりと在宅治療の指導を行う。さらに最近，血管壁の増殖を抑制するという作用機序を有する抗がん薬のイマチニブが PAH の第 4 の治療薬として治験が始められている。今後の展開が期待される。

■予　後

前述した新しい治療が開始される以前の，特発性肺動脈性肺高血圧症の予後は，5 年生存が 34％と 1991 年に報告された（対象 194 例）[3]。プロスタサイクリンを使用後の 3 年生存は，プロスタサイクリン使用前の 43％から 63％へと向上した（対象 18 例）[4]。さらに，3 系統の治療薬を使用されるようになってからの予後については，自験例で 76％まで改善している（対象 64 例）（**図 2**）。新しい薬剤の開発により，明らかに重症肺高血圧症の予後は改善してきている。PAH の原因別の予後をみると，Eisenmenger 症候群によるものが最も良く，IPAH，膠原病によるものが続き，HIV によるものが最も悪い[5]（**図 3**）。

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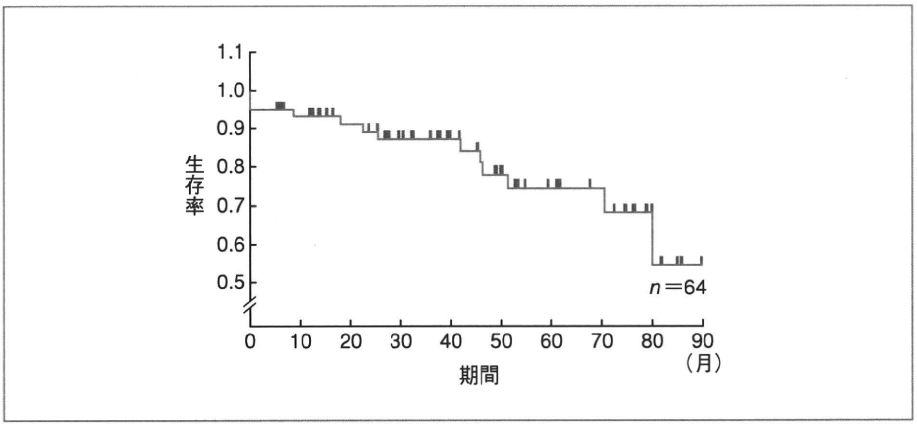

図 2　特発性肺動脈性肺高血圧症の予後（自験例）
右心カテーテル施行者のみ，1999～2006。

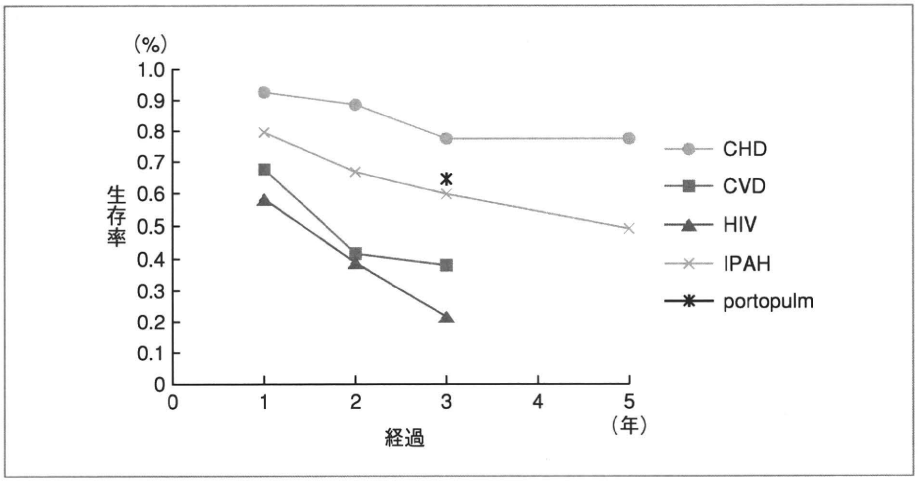

図 3　原因論に基づく肺高血圧症患者の平均生存率（文献 5 より引用）
CHD：先天性心疾患，CVD：膠原病性，IPAH：特発性肺動脈性肺高血圧症，portopulm：門脈性

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Translational Review

Reversible or Irreversible Remodeling in Pulmonary Arterial Hypertension

Seiichiro Sakao[1], Koichiro Tatsumi[1], and Norbert F. Voelkel[2]

[1]Department of Respirology (B2), Graduate School of Medicine, Chiba University, Chiba, Japan; and [2]Victoria Johnson Center for Obstructive Lung Diseases and Pulmonary and Critical Care Medicine Division, Virginia Commonwealth University, Richmond, Virginia

Vascular remodeling is an important pathological feature of pulmonary arterial hypertension (PAH), which leads to increased pulmonary vascular resistance, with marked proliferation of pulmonary artery smooth muscle cells (SMC) and/or endothelial cells (EC). Successful treatment of experimental PAH with a platelet-derived growth factor (PDGF) receptor tyrosine kinase inhibitor offers the perspective of "reverse remodeling" (i.e., the regression of established pulmonary vascular lesions). Here we ask the question: which forms of pulmonary vascular remodeling are reversible and can such remodeling caused by angiogenic proliferation of EC be reversed? It is important to emphasize that the report showing reduction of vascular remodeling by PDGF receptor tyrosine kinase inhibitor showed only a reduction of the pulmonary artery muscularization in chronic hypoxia and monocrotaline models, which lack the feature of clustered proliferated EC in the lumen of pulmonary arteries. The regression of vascular muscularization is an important manifestation, whereby proliferative adult SMC convert back to a nonproliferative state. In contrast, *in vitro* experiments assessing the contribution of EC to the development of PAH demonstrated that phenotypically altered EC generated as a consequence of a vascular endothelial growth factor receptor blockade did not reverse to normal EC. Whereas it is suggested that the proliferative state of SMC may be reversible, it remains unknown whether phenotypically altered EC can switch back to a normal monolayer-forming EC. This article reviews the pathogenetic concepts of severe PAH and explains the many forms in PAH with reversible or irreversible remodeling.

Keywords: remodeling; PAH; endothelial cell; smooth muscle cell

Pulmonary vascular remodeling is an important pathological feature of pulmonary arterial hypertension (PAH), which leads to increased pulmonary vascular resistance and reduced compliance, with marked proliferation of pulmonary artery smooth muscle cells (SMC) and/or endothelial cells (EC) resulting in the obstruction of blood flow in the resistance pulmonary arteries (1, 2). In a recent Perspective article, Rai and coworkers (3) characterized severe PAH as a quasi-neoplastic, angioproliferative disorder, and this concept provides a new framework for antiproliferative, antiangiogenic therapy in severe PAH.

Successful treatment with a platelet-derived growth factor (PDGF) receptor tyrosine kinase inhibitor of experimental pulmonary hypertension offers the prospect of "reverse remodeling" (i.e., the regression of established pulmonary vascular lesions) (4).

This review asks the question: which forms of pulmonary vascular remodeling are reversible and can the remodeling caused by the angiogenic proliferation of EC be reversed (5–8)? It is important to emphasize that the report showing a reduction of vascular remodeling by PDGF receptor tyrosine kinase inhibitor (4) showed only the reduction of pulmonary artery muscularization in chronic hypoxia and monocrotaline models, which lack the features of clustered proliferated EC in the lumen of pulmonary arteries (9, 10).

Further studies are necessary to characterize pulmonary vessel phenotypes to determine the reversibility of vascular remodeling and to stop angiogenesis in PAH.

SMC AND EC IN THE MANY FORMS OF PAH

Pulmonary vascular remodeling is characterized by the thickening of all three layers of the blood vessel wall (i.e., the adventitia, the media, and the intima). Such thickening is due to hypertrophy (cell growth) and/or hyperplasia (proliferation) of the predominant cell type within each of the layers, i.e., fibroblasts, SMC, and EC, as well as increased deposition of extracellular matrix components including collagen, elastin, and fibronectin (11). The thickening of the media occurs consistently in the arteries, at all levels of the pulmonary arterial tree, and less frequently in the veins (12). In addition, there is an extension of new smooth muscle into the partially muscular and nonmuscular peripheral arteries, and this is termed muscularization. This may be due to the differentiation of precursor cells (i.e., pericytes and "intermediate" cells, the latter being intermediate between pericytes and muscle cells in structure into SMC) (9). The other possibilities are the differentiation of fibroblasts and circulating mononuclear mesenchymal precursors into muscle cells (13) and the endothelial to mesenchymal transition (EMT) (14). The proliferation of pulmonary artery SMC in PAH is enhanced, whereas apoptosis is depressed (15–18). Many factors drive SMC proliferation, including bone morphogenetic protein receptor-2 (BMPR-2) mutations (19), the *de novo* expression of the anti-apoptotic protein survivin (15, 16), the increased expression/activity of the serotonin transporter (SERT) (20, 21) and the increased expression/activity of PDGF receptor. Dysfunctional voltage-sensitive potassium channels have been described in the

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This article represents a selective perusal of the pertinent literature together with a discussion of our own findings, and not a comprehensive or formal "balanced" review as outlined by a referee.

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This work is dedicated to the memory of Dr. J. T. Reeves.

Correspondence and requests for reprints should be addressed to Seiichiro Sakao, M.D., Department of Respirology (B2), Graduate School of Medicine, Chiba University, 1-8-1 Inohana, Chuo-ku, Chiba 260-8670, Japan. E-mail: sakaos@faculty.chiba-u.jp

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pulmonary artery SMC from patients with idiopathic PAH (22), and impaired K^+ channel performance has been linked to pulmonary vasoconstriction, whereas vasorelaxation due to nitric oxide and cyclic guanosine monophosphate has been linked to the activation of the Ca^{2+}-dependent K^+ channels (23). Moreover, it has been suggested that PAH has a cancer aspect because pulmonary artery SMC in PAH and cancer cells are both associated with mitochondrial disorders (24–26).

An additional feature that is seen in some forms of PAH in humans is a complex vascular lesion known as a plexiform lesion (27). These lesions contain a disorganized monoclonal EC proliferation in a stroma of myofibroblasts (28, 29). These so-called plexiform or complex vascular lesions are characterized by apoptosis-resistant (30–35), phenotypically altered EC (36–41). Recently, conclusive evidence that idiopathic PAH pulmonary artery EC have a hyperproliferative apoptosis-resistant phenotype compared with cells from control lungs has been shown using cell proliferation, DNA synthesis, and the evaluation of cell death pathways (42). Likewise, human herpes virus 8 (HHV-8) infection of pulmonary microvascular EC results in an apoptotic-resistant phenotype characteristic of severe PAH (43), although it is unclear whether HHV-8 has a pathogenetic role in idiopathic PAH (44–46). Moreover, dysfunctional endothelial progenitor cells, which are hyperproliferative with impaired ability to form vascular networks, are involved in the vascular remodeling associated with PAH (47).

An impairment of the EC function in patients with PAH leads to local thrombosis (48, 49), the interruption of which may improve the prognosis of patients with PAH. Moreover, the expression of tissue factor (TF), the membrane glycoprotein that initiates coagulation (50), facilitates angiogenesis (50), mediates arterial injury in the systemic circulation (51), and increases in the pulmonary arterioles and plexiform lesions of the rats, thus indicating that the induction of TF may contribute to the progression of PAH (52).

Xu and colleagues used an *in vitro* experiment with pulmonary artery EC from idiopathic PAH (IPAH EC) and control lungs (control EC) to show that glucose metabolism plays the primary role for energy requirements of IPAH EC based on the 3-fold greater glycolytic rate of IPAH EC compared with control EC, thus indicating that there is mitochondrial disorder in EC in idiopathic PAH, like SMC in PAH and cancer cells (53). A share of a mitochondrial disorder in SMC and EC in PAH may support the EMT hypothesis.

REVERSIBLE AND IRREVERSIBLE MODELS OF PULMONARY HYPERTENSION

In contrast to the human disease, both classical rodent models of mild to moderate pulmonary hypertension—the chronic hypoxia and monocrotaline models—lack clustered proliferated EC in the lumen of pulmonary arteries (9, 10). Pulmonary EC constitute a stable cell population with a very low turnover rate and, apparently, neither severe chronic hypoxia/hypoxemia nor monocrotaline pyrrole causes the emergence of a proliferative, dysfunctional EC phenotype (54). The defining pulmonary vascular alteration in both of these models, medial muscular thickening of proliferating SMC, is potentially reversible upon reexposure to normoxia or with the passage of time after monocrotaline injection (9, 11, 55).

Neointimal pulmonary vascular occlusive lesions that consist of proliferating SMC are found in rats after the combination of pneumonectomy with monocrotaline injection (56–60). A combination of compensatory lung growth after a pneumonectomy, hemodynamic factors, and endothelial injury by monocrotaline pyrrole may combine to produce this neointimal pulmonary vascular disease (60). Neointimal vascular occlusion is reversible with simvastatin in this rat model, through its antiproliferative and proapoptotic effects on vascular SMC (61).

A vascular endothelial growth factor (VEGF) receptor blockade with the VEGF-RI/VEGF-R II antagonist SU5416 combined with chronic hypoxia results in severe angioproliferative PAH in adult rats (39). The defining pulmonary vascular alteration in this model, arterial occlusion by proliferating EC, is not reversible upon reexposure to normoxia and with passage of time after SU5416 injection (39). Together, these rat models offer the perspective that medial muscular thickening due to proliferating SMC may be reversible and arterial occlusion by proliferating EC may conversely be irreversible.

REVERSAL OF MUSCULARIZATION

Although less well studied, the shift of vascular SMC, whereby proliferative adult vascular SMC convert back to a nonproliferative state, is an important observation. This particular phenotype switch is essential for limiting SMC accumulation and for the termination of vascular remodeling. The regulatory factors that drive proliferative SMC into a nonproliferative state, and hold them in that state, are critical for effective vascular remodeling and for limiting vascular disease (62). Li and coworkers generated unique lines of nonimmortalized human vascular SMC that are capable of a conversion from proliferative to nonproliferative states (63). In the presence of serum, these SMC proliferate, migrate, and elaborate extracellular matrix similar to primary SMC. Upon withdrawal of the serum, however, they undergo a reproducible program of cellular maturation whereby they exit the cell cycle, migrate into multilayered aggregates, and then acquire the ability to rapidly contract. Li and colleagues (63) concluded that this shift to a nonproliferative and mature phenotype may be attributed to cellular plasticity, rather than the selective expansion (or loss) of distinct cell subpopulations, because the SMC are clonal. Although this plasticity of SMC has been shown in systemic arteries, the same plasticity may therefore be essential for reversing the vascular remodeling caused by proliferating SMC in PAH.

In vitro experiments conducted to assess the contribution of EC to the development of PAH have demonstrated that a VEGF receptor blockade with the VEGF-RI/VEGF-R II antagonist SU5416, under conditions of increased fluid shear stress, causes initial apoptosis followed by exuberant proliferation of the surviving EC (40). These EC are hyperproliferative and apoptosis-resistant and express the anti-apoptotic protein survivin (40). Moreover, human pulmonary microvascular EC transdifferentiated with SU5416 *in vitro* demonstrate that the shift to a transdifferentiated phenotype could be attributed to selection of distinct cell subpopulations (i.e., stem-like cells), and suggest that endothelial–mesenchymal transdifferentiation might be an important contributor to pathophysiological vascular remodeling in complex vascular lesion of PAH (41), because, although bone marrow–derived cells could participate in arterial neointimal formation after mechanical injury, they do not contribute substantially to pulmonary arterial remodeling in an experimental PAH model (64). Moreover, those EC are not capable of returning to normal EC states over 10 passages from the withdrawal of SU5416 (41). Likewise, Arciniegas and coworkers suggested that EMT was an important contributor to vascular remodeling in PAH, but might be reversible (65).

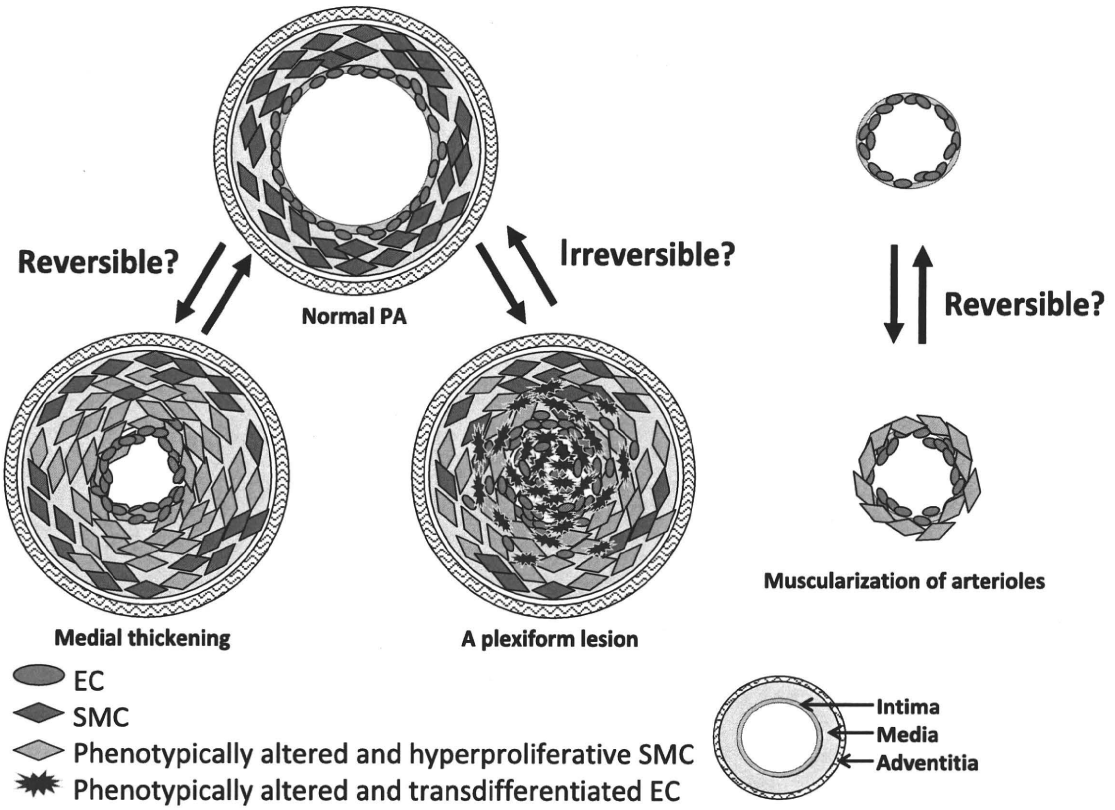

Figure 1. Reversible or irreversible remodeling in pulmonary arterial hypertension (PAH): a hypothetical mechanism. This is a hypothetical figure of a cross-section of pulmonary arteries. Pulmonary vascular remodeling in PAH is characterized by the thickening of the media, a plexiform lesion, and muscularization. Such thickening is due to hyperplasia (proliferation) of phenotypically altered smooth muscle cells (SMC). A plexiform lesion is composed of apoptosis-resistant phenotypically altered endothelial cells (EC). Muscularization is the extension of new smooth muscle into the partially muscular and nonmuscular peripheral arteries. The SMC shift between a proliferative and nonproliferative phenotype may be attributed to cellular plasticity, rather than selective expansion of distinct cell subpopulations, suggesting that this form of vascular remodeling (i.e., likely medial thickening and muscularization) may be reversible. However, irreversible PAH in congenital heart disease is strongly associated with the impaired apoptotic regulation of EC and with endothelial damage, thus suggesting that vascular remodeling, which develops because of phenotypically altered EC (i.e., likely a plexiform lesion) may therefore be irreversible.

DRUGS AND "REVERSIBLE OR IRREVERSIBLE REMODELING"

The drugs that are currently used for the treatment of PAH act not only by opposing any abnormal vasoconstriction, but also by inhibiting the growth of normal SMC: endothelin-receptor antagonists, phosphodiesterase type 5 inhibitors, and prostacyclin derivatives (66). Some patients with IPAH have been treated successfully with vasodilators with normal or nearly normal hemodynamics. It is unclear whether they have been diagnosed very early before remodeling occurred or they are a different phenotype. However, since vascular remodeling likely becomes progressively as the disease advances in patients who are resistant to these agents (67), new drugs may be developed to specifically target pulmonary vascular remodeling for these patients.

A few cases of clinical and hemodynamic improvements with the PDGF receptor tyrosine kinase inhibitors have also been reported in human PAH (68–70). Therefore, agents like these drugs may perhaps achieve reversal of remodeling, that is, the regression of established muscularized pulmonary arteries (4). A recently completed phase II clinical trial evaluating the safety and efficacy of imatinib mesylate, a tyrosine kinase inhibitor with antineoplastic activity, in PAH failed to meet the primary efficacy end point of improvement in exercise capacity; however, many secondary end points, including pulmonary hemodynamics, were significantly improved (71). However, the effects of these drugs in human PAH are currently missing and there is no data on reverse remodeling with this class of drugs in humans. It is probable that most patients with severe PAH at the time of their diagnosis have irreversible structural alterations of their microscopically small pulmonary arterioles, that is, irreversible pulmonary vascular remodeling believed to be caused by angiogenic proliferation of phenotypically altered and transdifferentiated EC (5–8, 40, 41).

Rapamycin, an antiproliferative immunosuppressor that arrests the cells in the G1 phase of the cell cycle (72), was examined in randomized, vehicle-controlled trials using a rodent model of severe PAH (57). Because of this approval for clinical practice, the potential of rapamycin for rapid translation to human PAH therapies is offered. Rapamycin is used clinically in cardiovascular medicine, as an antiproliferative agent applied to coronary stents to reduce local restenosis (73). Rapamycin inhibits hypoxia-induced activation of S6 kinase in PA adventitial fibroblasts (74), suggesting a possibility for therapeutic benefit in PAH. Rapamycin has also been shown to attenuate experimental PAH and suppress neointimal SMC proliferation in a pneumonectomy with monocrotaline-PAH model (57). In that study, however, rapamycin failed to reverse established PAH, thus suggesting that antiproliferative (rapamycin) agents were not sufficient to induce apoptosis of neointimal SMC and that additional proapoptotic agents might be needed.