特集　肺高血圧症診療の最前線

肺高血圧症の臨床症状と検査所見

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要　旨

肺高血圧症の代表的症状としては息切れが最も特徴的で換気量の亢進により起こる。必ずしも低酸素血症を伴わないことは他の心疾患や肺疾患との相違点となる。検査は鑑別診断，重症度判定のためのものに分類される。鑑別診断にはさまざまな検査を施行して細かい鑑別を行う必要がある。重症度判定検査は治療選択，予後判定のために必要で右心カテーテル検査，BNP，6分間歩行検査などが行われる。

Key words：特発性肺動脈性肺高血圧症，息切れ，右心カテーテル検査，6分間歩行試験/idiopathic pulmonary arterial hypertension，dyspnea，right heart catheterization，6-minute walk test

1 肺高血圧症の臨床症状

特発性肺動脈性肺高血圧症（idiopathic pulmonary arterial hypertension：IPAH）は難病に指定され医療費は主に国費で支払われている。その申請書に症状を記載する欄があり，これをまとめた報告を図1に示す。千葉大学のKasaharaらが2004年の報告書をまとめ2005年に発表している。これはIPAH患者の症状を集計したものだが肺高血圧症一般の症状と考えてよい。易疲労感，息切れ，胸痛，失神の順に出現頻度が高い。他に経験する症状としては咳嗽，血痰などがある。易疲労感は非特異的な症状でこれから肺高血圧症を鑑別診断の一つに挙げるのは難しい。

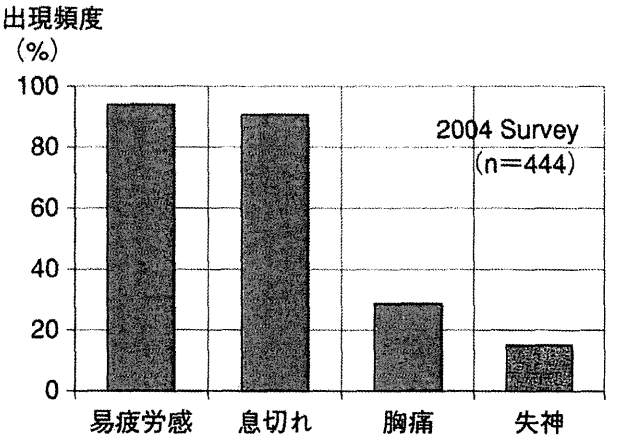

図1　特発性肺動脈性肺高血圧症の症状
〔Kasahara Y, et al. 厚労省班研究，2005より引用〕

1）息切れ

肺高血圧症の最も特徴的な症状といえる。息切れを生ずる代表的疾患は呼吸器疾患と心

Symptoms and Laboratory Findings in Pulmonary Hypertension
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$$VE = \frac{V_{CO_2} \times C}{Pa_{CO_2} \times (1 - VD/VT)}$$

図 2　肺胞換気式

VE：換気量，V_{CO_2}：二酸化炭素排泄量，
C：定数，Pa_{CO_2}：動脈血中二酸化炭素分圧，
VD/VT：死腔換気率，VD：死腔換気量，
VT：1 回換気量

臓疾患となるが，呼吸器疾患では呼吸仕事量の増加によって息切れを生じ，心臓疾患では左房圧の上昇により肺鬱血を起こし結局呼吸仕事量が増加して息切れを生ずる。また低酸素血症は，呼吸器疾患でも心臓疾患でも原病の重症度に応じて出現し，息切れの程度とも比例している。しかし肺高血圧症の息切れはこのような機序とは異なり，換気量の増加によって起こると考えられている。図 2 の肺胞換気式を使って以下のように説明できる。一定の労作をすると V_{CO_2} が決まり，Pa_{CO_2} は労作中なるべく一定値に保たれるため，換気量は VD/VT に比例することがわかる。肺高血圧症では肺血流量が減少するため生理学的死腔（換気はされているが肺血流がない領域）が増加し VD/VT が大きくなって換気量が増える。これを合目的に説明すると，「肺高血圧症では肺血流量が減少すると体内への酸素の取り込み量が減少するため換気量を増やして代償しようとする」と言える。またかなりの肺高血圧症でも低酸素血症を生じない症例もあり，重症度と酸素分圧は必ずしも関係しない。

2）胸　痛

労作時に胸痛を訴える症例があるが，右室後負荷の増加により右室の仕事量が増加し右室の相対的な虚血により生じている可能性がある。安静時に胸痛を認める患者もあり，僧帽弁狭窄症で左房の拡大により胸痛を起こすとされ，肺高血圧症でも右房の急速な拡大により胸痛を生じているのかもしれない。

3）失　神

肺高血圧症の有病率が低いため失神の鑑別疾患としてはまれとなるが，肺高血圧症の症状として出現頻度が 15%前後と少なくないので（図 1），“労作性の失神”を起こす疾患として大動脈弁狭窄症と並んで鑑別疾患として認識しておきたい。失神の存在は進行が速いことを意味しており治療を考える上で貴重な情報となるため，肺高血圧症の患者では必ず聴取すべきといえる。心疾患による労作時の失神は，労作時に心拍出量が制限される病態下で，心拍出量を代償的に増やすことが難しい状態で生じる。大動脈弁狭窄症では左室からの出口が大きく制限されており，左室肥大により代償しようとするが，狭窄の進行が肥大の程度を上回り過度の労作をすると失神を起こす。肺高血圧症では右室肥大により肺動脈における血流減少を代償しようとするが，右室は元々心筋壁が薄く右室肥大の進展には時間を要するため後負荷増加に弱く，左室も心拍出量を増やす代償機転を動員しようとするが心膜内での右室と左室の相互関係で右室負荷増加により左室は圧迫されて代償できず Adams-Stokes 失神を起こすのであろう。失神の鑑別診断のために神経内科に入院し急性肺塞栓症であったという症例を時に経験する。

4）咳　嗽

肺高血圧症で咳嗽を生ずる機序ははっきり

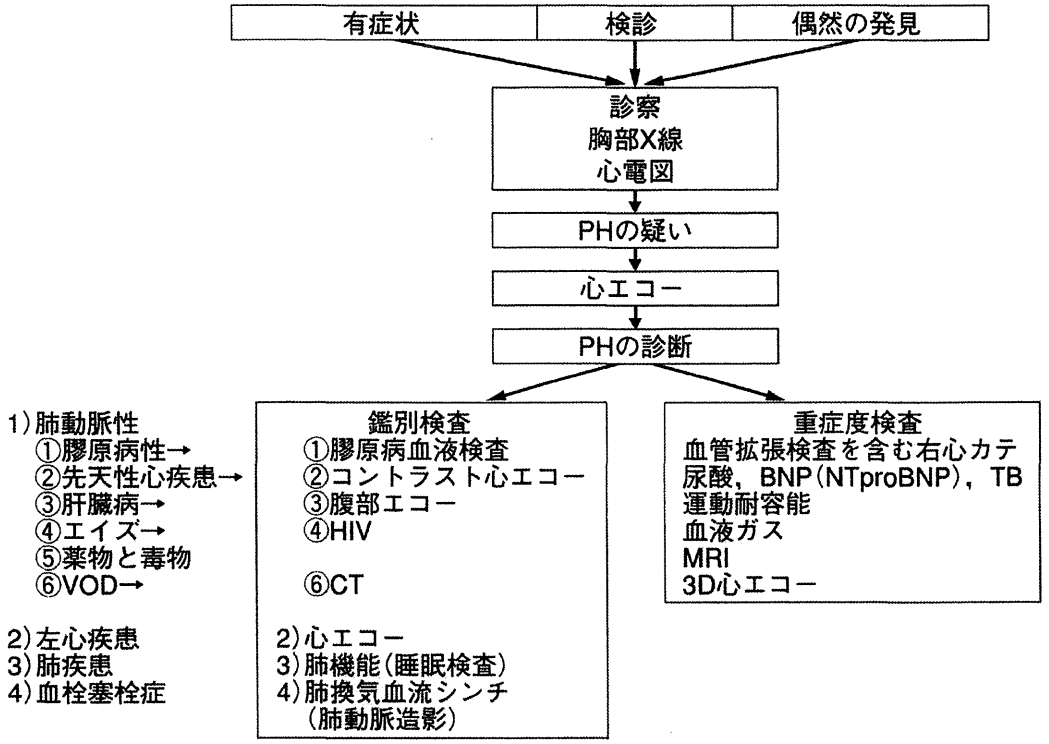

図 3　肺高血圧症の検査の展開

〔Barst RJ, McGoon M, Torbicki A, et al. Diagnosis and differential assessment of pulmonary arterial hypertension. J Am Coll Cardiol 2004；43：40S-7S. より改変引用〕

しないが，病勢に応じて咳嗽が消長する症例がある。

5）血　痰

血痰は肺梗塞で起こるとされている。肺の灌流は肺動脈と気管支動脈で二重に行われているが，肺の末梢は肺動脈の単独支配とされ末梢肺動脈が内膜肥厚で閉塞すると肺表面の肺梗塞を生じ血痰を生じる。Eisenmenger 症候群では多量の喀血を起こす。

6）右心不全の症状

右心不全は静脈系の鬱血を生じこれに基づく症状が出現する。下肢の静脈圧上昇は下腿浮腫を生じ，肝静脈圧の上昇は肝鬱血，さらに消化管の鬱血を起こす。肝鬱血は肝左葉に強いため，右季肋部から心窩部付近の膨満感を認める。重症の右心不全では消化管の鬱血も生ずるため消化機能が低下し，食欲は保たれるが摂取量が減少してくる。さらに腹水が貯留すると腹部全体の膨満感を自覚するようになる。

2 肺高血圧症の検査所見

図 3 に肺高血圧症の検査の流れを示す。肺高血圧症は 20〜50 代女性に多く，彼らは検診を受ける機会が少ないことや進行が比較的速いことから，検診等で無症状のうちに見つかることは少なく，症状が出現して受診する。近医を受診しても，息切れを主訴とするこの年齢の女性の鑑別として肺高血圧症が挙がることは少なく，精査が進まないことが多い。近医において胸部 X 線写真，心電図検査で異

表 1　肺高血圧症の分類

ベニス分類 2003（第 3 回世界シンポジウム，Venice, Italy, 2003）

1．肺動脈性肺高血圧症（PAH）
　1）特発性 IPAH
　2）家族性 FPAH
　3）各種疾患に伴う肺動脈性肺高血圧症 APAH
　　①膠原病性
　　②先天性心疾患
　　③肝臓病
　　④エイズ
　　⑤薬物と毒物
　　⑥その他：甲状腺疾患，糖原病，ゴーシェ病，遺伝性出血性毛細血管拡張症，異常ヘモグロビン症，骨髄増殖性疾患，脾摘出
　4）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）
　5）新生児遷延性肺高血圧症
2．左心性心疾患に伴う肺高血圧症
　1）左心の心房性，心室性心疾患
　2）左心の弁膜症
3．肺疾患および/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）睡眠障害呼吸
　4）肺胞低換気障害
　5）高所における慢性曝露
　6）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
　1）近位肺動脈の血栓塞栓性閉塞
　2）末梢肺動脈の血栓塞栓性閉塞
　3）非血栓性肺塞栓症（腫瘍，寄生虫，異物）
5．その他の肺高血圧症
　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，肺血管の圧迫（リンパ節腫脹，腫瘍，線維性縦隔炎）

常が見つかると，地域の拠点病院へ紹介され，そこで心エコー検査をされて「肺高血圧症」と診断される。胸部 X 線写真，心電図検査で異常がなく，身体診察で異常が発見されることもあるので，身体診察も重要と考えられる。心エコーで肺高血圧症が診断された後は，肺高血圧症の鑑別検査と重症度検査へと進む。

1）鑑別検査

表 1 に肺高血圧症の分類を示す。2003 年にベニスでなされた肺高血圧症の分類で，2008 年にはダナポイントで改訂されたが本質的な違いはないのでこれを示した。肺高血圧症は大きく 5 つに分類され，各大分類のなかでさらに細かく分類されている。大分類は解剖学的分類であるが，障害部位の違いは治療法の違いとも考えられ，大分類がなされれば大筋の治療方針も決まる。またさらに細かい分類は詳細な治療法の決定や予後の判定に重要となる。

a．肺動脈性肺高血圧症の鑑別

i）特発性肺動脈性肺高血圧症（IPAH）：全 IPAH の 6%に存在するとされる家族性 IPAH の遺伝子異常（BMPR II 遺伝子異常）が非家族性 IPAH でもみられることが 2000 年に発表された[1]（図 4）。これは，TGF-β 産生の細胞内シグナルを開始する膜表面レセプター（BMPR II）の遺伝子異常で，TGF-β が血管壁の増殖を調節する作用も持つサイトカインであるため，肺動脈内皮が異常に増殖する

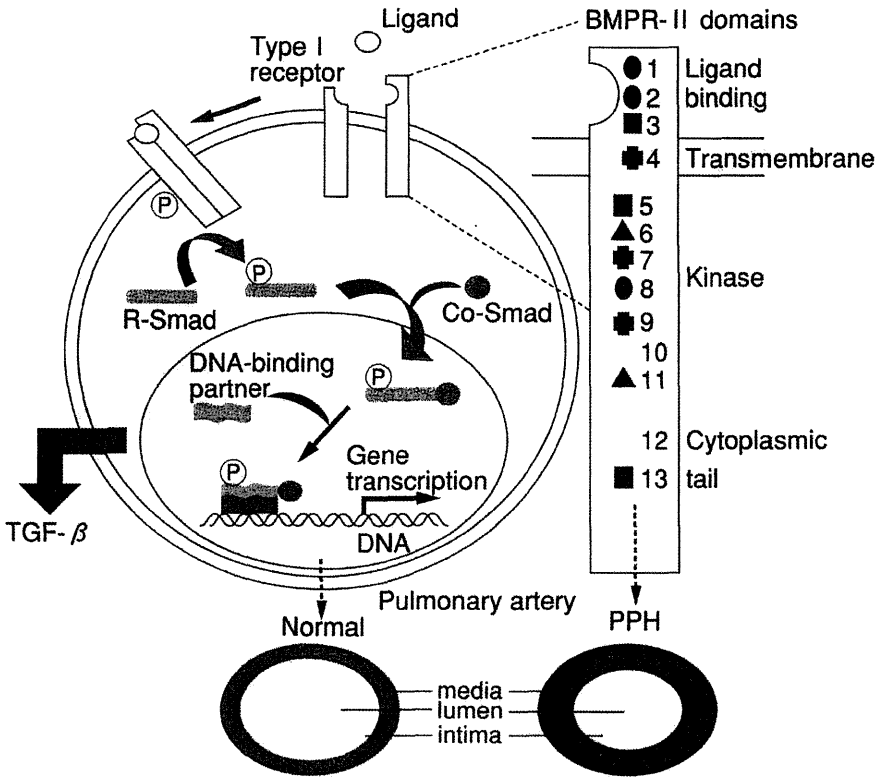

図 4　BMPR II 遺伝子異常

〔Thomson JR, Machado RD, Pauciulo MW, et al. Sporadic primary pulmonary hypertension is associated with germline mutations of the gene encoding BMPR-II, a receptor member of the TGF-beta family. J Med Genet 2000 ; 37 : 741-5. より引用〕

表 2　慶應義塾大学医学部における BMPR II 遺伝子異常の頻度

・異常 exon を有する IPAH	24 例
・検索した IPAH	62 例
・出現率	39%

IPAH でこの異常がみられることは納得できる。慶應大学医学部の患者で検討した結果を表 2 に示す。IPAH 以外ではほとんどみられず，IPAH では約 40%で認められる。

ii）膠原病性肺高血圧症：各種自己抗体（抗核抗体，抗 DNA 抗体，抗 RNP 抗体，抗 Scl70，抗セントロメア抗体，SSA 抗体，SSB 抗体など）の測定が有用である。最終的には膠原病専門医の診断基準の検討により診断される。

iii）Eisenmenger 症候群：先天性心疾患の診断には心エコーが有用で，PDA や VSD は診断されやすいが ASD や卵円孔開存は見逃されることがある。従って肘静脈からレボビストを静注して右左シャントの有無をみるコントラスト心エコーが必須となる。左右シャント中心の先天性心疾患が IPAH として紹介されることもある。このような症例では，心エコーでシャントが見逃されると身体診察も含め各種検査により鑑別することが難しく，心臓カテーテル検査のオキシメトリーカテーテルの通過で初めて診断されることもある。

iv）肝疾患，門脈圧亢進症：肝機能検査や腹部エコーで診断される。

v）HIV：抗体検査を全例で施行した方が

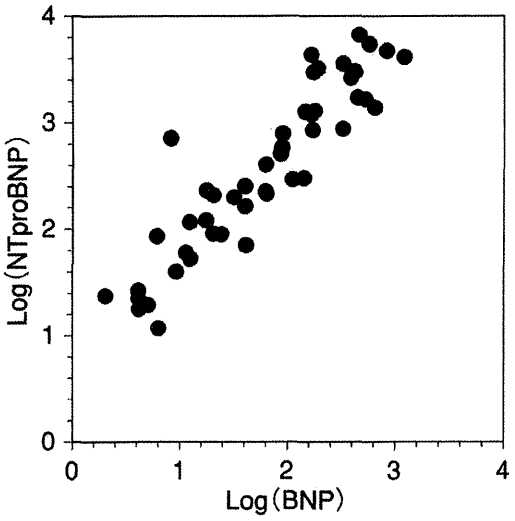

図 5　BNP と NTproBNP との関係
n＝60，R^2＝0.82

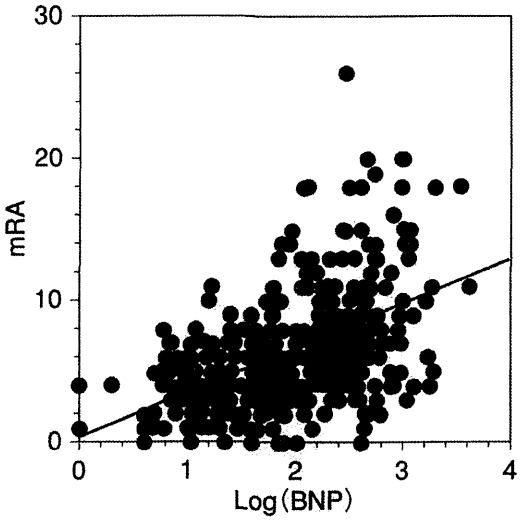

図 6　mRA と log（BNP）との関係
n＝622，R^2＝0.26

よい。

vi）薬物：薬物による肺高血圧症は意外に多いと感じている。診断には問診が中心となるが，詳しく聞くと関連を疑わせる薬剤が見い出されることがある。われわれもサリドマイドによる肺高血圧症を報告した[2]。

vii）肺静脈閉塞症：IPAH の 1/10 の頻度で認めるとされる。治療抵抗性，速い進行，肺出血（肺水腫）の合併がみられることが多いが，単純 CT 検査を施行して小葉間隔壁の肥厚を確認する。

viii）その他：PN などの血管炎は ANCA 測定，HHT（hereditary hemorrhagic telangiectagia Osler-Weber-Lendu 病）には ARC 遺伝子検索，Churg Strauss 症候群には ANCA 測定，サルコイドーシスでは ACE 測定などを施行する。

b．左心疾患の鑑別

心エコー検査で多くは鑑別できる。拘束型心筋症は中等以上の肺高血圧症を来し，心エコーで異常が見い出されにくいことから IPAH として紹介を受けることがある。心臓カテーテル検査で右房波形や右室波形により診断されるが，身体診察で頸静脈波形を十分に観察すれば診断は可能となる。

c．肺疾患の鑑別

肺機能検査で診断され，必要なら CT も有用となる。特発性間質性肺炎や LAM（肺リンパ脈管筋腫症）で重症肺高血圧症の合併が多い。

d．慢性肺血栓塞栓症

新しい血栓の生成がない症例が大部分を占めるため，CT では間接的な異常所見があるのみで診断は難しい。肺血流シンチグラムが必要となる。診断の確認，末梢性か中枢性かの鑑別，手術適応の決定のため肺動脈造影を施行する。

2）重症度検査

a．採血

i）BNP（NTproBNP）：右心室の負荷を示す指標で，右心機能障害や右心不全があると高値となる。NTproBNP の方が不活化されているため安定とされるが，われわれの検討で

は両者には高い相関がある（図 5）。BNP と右心カテーテル検査の血行動態との関係を自験例で検討すると mRA（平均右房圧）と最も関係が深く（図 6），右心不全のよいマーカー

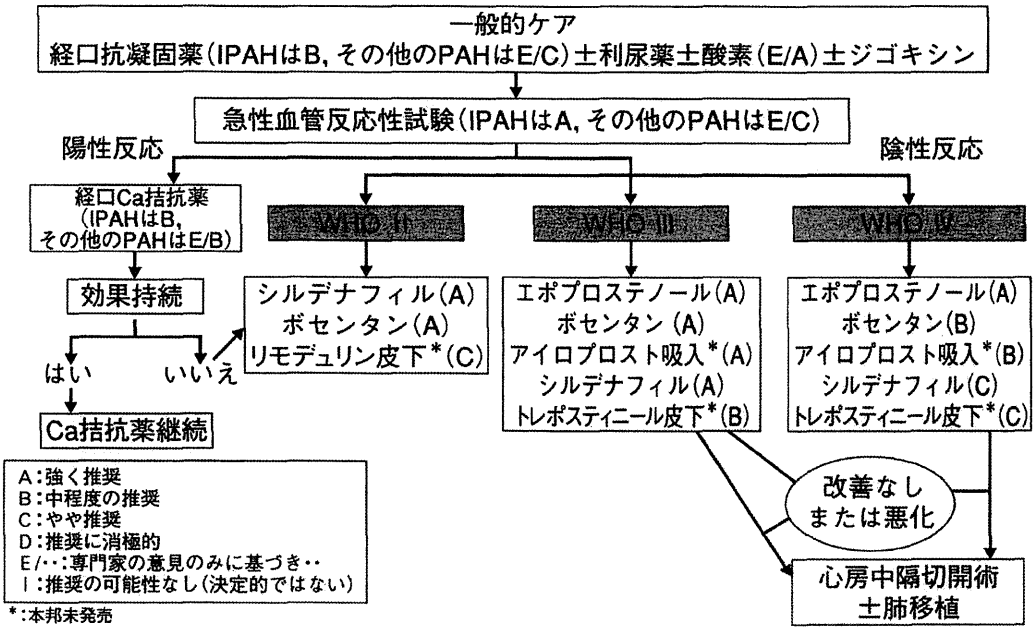

図 7　肺高血圧症治療ガイドライン
〔2007ACCP ガイドラインより一部改変引用〕

表 3　治療前と経過観察中の予後規定因子の比較

初診時-予後規定因子			Follow-up 検査-予後規定因子		
指標	施行数	p 値	指標	施行数	p 値
RVEDP	128	0.002	mRA	429	＜0.00001
mRA	135	0.003	HR	416	＜0.00001
PAR	126	0.008	PAR	405	0.00001
BNP	115	0.009	VE/Vco_2 slope	138	0.00005
CTR	72	0.018	CTR	250	0.00008
SvO_2	79	0.018	Peak Vo_2	137	0.0001
UA	126	0.037	TR	117	0.0003
			TB	397	0.001
			BNP	366	0.0019
			mPA	447	0.007

AIC：赤池の情報基準，略語は表 1，2 参照。
初診時と各検査時からの予後を Cox ハザードモデルで検討した。
HR：心拍数，nPA：平均肺動脈圧，mPAR：肺血管抵抗，mRA：平均右房圧，RVEDP：右室拡張末期圧，SvO_2：混合静脈血酸素飽和度，TB：総ビリルビン値，UA：尿酸値，BNP：Brain Natriuretic Peptide，peak Vo_2：最大酸素消費量，CTR：心胸郭比，TR：三尖弁閉鎖不全症

と考えられた。

ii）TB (total bilirubin)，Alp (alkaliphosphatase)：右心不全を来すとこれらの血清値が上昇するので右心不全の判定に有用となる。

iii）尿酸：尿酸は右心不全を生じ静脈鬱血が起こると上昇することが知られている[3]。静脈鬱血により組織の核酸が分解して尿酸が上昇すると考えられる。

b．血液ガス

Pa_{O_2}に関しては重症例でも必ずしも低下しないことは「症状」の項で述べたが，$Paco_2$は重症例でより低下することが知られている。その機序は換気が亢進するからで「息切れ」の項で述べた。

c．運動耐容能

6分間歩行距離が肺高血圧症の重症度を示す指標とされ[4]また簡便で有用なため，頻用されている。予後を予測する因子としても評価され，最近の肺動脈性肺高血圧症治療薬の薬効判定に最も有用な検査法とされている。

d．血管拡張検査を含む右心カテーテル

初回の右心カテーテル検査では血管拡張負荷試験（急性血管反応性試験）を必ず施行する。これにより肺動脈スパズムによる肺高血圧症を鑑別することが可能となる。これは欧米の肺高血圧症治療ガイドラインに明示されている（図7）。肺高血圧症患者の多くは三尖弁閉鎖不全を有しているため心拍出量の測定はFick法を使用した方がよい。右房圧や肺血管抵抗などが予後と密接な関係があることが知られている[5]。

3 自験例における検査所見と予後の関係

表3に，右心カテーテル検査で慶應大学医学部へ入院時の諸検査所見と予後との関係を参考として示した。

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Circulation Journal
Official Journal of the Japanese Circulation Society
http://www.j-circ.or.jp

EDITORIAL

Medical Therapy of Chronic Thromboembolic Pulmonary Hypertension

Toru Satoh, MD

The modern surgical treatment for chronic thromboembolic pulmonary hypertension (CTEPH), the pulmonary thromboendarterectomy (PEA), has improved the symptoms and prognosis in patients with this untreatable disease.[1] In accordance with progress in the surgical treatment in CTEPH, medical treatment of pulmonary arterial hypertension (PAH), another important etiological category of pulmonary hypertension (PH), has been in progress and also considered useful for CTEPH, because CTEPH may also show high pulmonary artery pressure and the resultant damage to the pulmonary arterioles,[2,3] the same pathophysiology as in PAH. Therefore, the vasodilators used for PAH may also ameliorate the symptoms and improve prognosis in patients with CHTPH.

Article p2110

In this issue of the Journal, Dr Nishimura et al report an improvement of prognosis in patients with CTEPH after administration of the contemporary pulmonary vasodilators, sildenafil and bosentan, developed for PAH.[4] They divided their cohort into 3 chronological categories: the first group of the patients was diagnosed during 1986 to 1998 (13 years); the second group was during 1999 to 2004 (6 years); the third group was during 2005 to 2010 (6 years). The modern pulmonary vasodilators for PAH were used in 9% of the first patient group, 24% of the second group, and 70% of the third group. The 5-year survival in the third group was 89% compared with 60% in the first group with a significant difference, meaning the new pulmonary vasodilators, including sildenafil and bosentan, improve the prognosis of patients with CTEPH.

Concerning the prognosis of patients with CTEPH before the advent of contemporary vasodilators specific for PAH, there are very few reports. The most cited article is by Dr M. Riedel published in 1982, a long long time ago. Actually we have an excellent report on this published in Japan, as you may know or not. It was written in 1997, by Dr N. Nakanishi in the Cardiovascular Center, but in Japanese. If it had been written in English, it would have been a monumental paper. According to that report, prognosis had nothing to do with pulmonary arterial pressure (PAP) but was related to pulmonary vascular resistance[5] (**Figure**). Interestingly enough, the 5-year survival in these 3 reports without brand-new vasodilators was similar: in

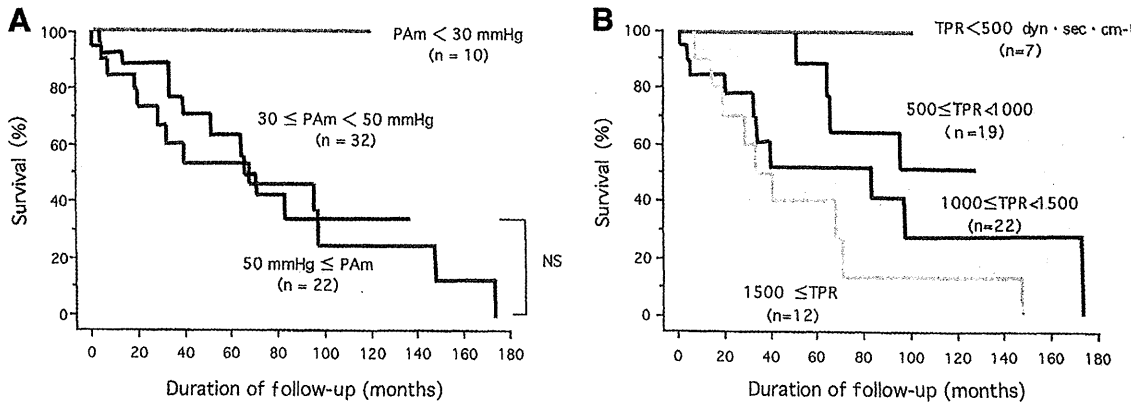

Figure. (**A**) Survival according to initial pulmonary artery pressure (PAm). Survival curves are shown according to the pulmonary artery pressures measured at diagnosis. (**B**) Survival according to initial total pulmonary resistance (TPR). Survival curves are shown according to the total pulmonary resistance measured at diagnosis (Reproduced with permission from Nakanishi et al.[5]). NS, not significant.

Received June 21, 2013; accepted June 21, 2013; released online July 12, 2013
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ISSN-1346-9843 doi:10.1253/circj.CJ-13-0775

Riedel's series approximately 60% (mean PAP: 28 mmHg, determined by my calculation based on the data reported); in Nakanishi's report, it was 58% (mean PAP: 44 mmHg); in Nishimura's paper in the first-group patients, it was 55% (mean PAP: 40 mmHg). Riedel's report included patients with acute pulmonary thromboembolism and did not demonstrate the genuine prognosis of the patients with CTEPH. You can see the very low mean PAP in the overall patient group in Riedel's report (he divided the patients into varieties of categories). I assume that Nakanishi's report shows the standard statistics on CTEPH prognosis in the era of no vasodilators. I think we should refer to his results more when we discuss the natural history of CTEPH.

Anyway, Nishimura's data indicate the improved prognosis of CTEPH patients with the newly-developed vasodilators of bosentan and sildenafil, consistent with our experiences of subjective and hemodynamic amelioration of CTEPH patients. Nowadays in Japan, PEA has been replaced by pulmonary angioplasty, more casually and noninvasively performed than PEA.[6–8] It was started in Okayama Medical Center in around 2005[6] and independently in our center in 2008.[7] Both centers have been cooperating to develop the technique into a safer and more efficient entity. Pulmonary angioplasty was first used to target peripheral lesions and now has been safely applied to more central lesions using a sophisticated technique of primary partial dilatation of the central lesion with an additional complete dilatation in 1 or 2 weeks (unpubl. data). The prognosis for pulmonary angioplasty is reported to be better than medical treatment. Concerning the difference between the 2 invasive treatments, we have compared the medium- to long-term prognoses of CTEPH between PEA and pulmonary angioplasty (unpubl. data). According to our data, the prognoses of the 2 therapies were statistically comparative. However, pulmonary angioplasty can be repeated several times and be performed in patients with prior PEA, contrary to the difficulty of repeating PEA.

When we come to treat a patient with CTEPH, we first use the new vasodilators, mostly with success, meaning that the patients' symptoms and hemodynamics improve and are maintained in a steady state for a certain period, proved by Nishimura's study.[4] But some do not respond to medical treatment and their condition is aggravated without the invasive treatment of mechanical removal of the organized thrombi. The rate of those patients seems to be 10% in 5 years according to Nishimura's data[4] and those patients have been treated with invasive methods in terms of prognosis. An indication for pulmonary angioplasty now extends to patients with less severe PAPs than the indication of PEA for its less invasiveness and easy accessibility with the same mortality, according to our unpublished data.

Nishimura's report gives us the basic statistics on the hemodynamic and prognostic changes after pulmonary vasodilators usually used for PAH. We will analyze the future data produced from the new invasive procedure, pulmonary angioplasty, based on his report.

Disclosure

T.S. receives a significant amount of fees for speaking from Actelion.

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Histol Histopathol (2013) 28: 185-193

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Review

Crosstalk between endothelial cell and thrombus in chronic thromboembolic pulmonary hypertension: perspective

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Summary. It is generally accepted that chronic thromboembolic pulmonary hypertension (CTEPH) results from pulmonary emboli originating from deep vein thrombosis. However, this consensus opinion has been challenged, and the concept that some aspects of CTEPH exacerbation might result from a small-vessel disease leading to secondary thrombosis has been suggested.

In addition to the effect of recurrent thromboembolism, a number of lines of clinical evidence indicate that progressive worsening is contributed to by remodeling in the small pulmonary arteries. Histopathological studies of the microvascular changes in CTEPH have identified vascular lesions similar to those seen in idiopathic pulmonary arterial hypertension (IPAH). Especially in *in vitro* and *ex vivo* experiments, pulmonary artery endothelial cells (ECs) in pulmonary hypertensive diseases are suggested to exhibit an unusual hyperproliferative potential with decreased susceptibility to apoptosis, indicating that dysfunctional ECs may contribute to the progression of the diseases. Although the degree and mechanisms of EC dysfunction as a contributor to CTEPH are unclear, EC dysfunction may occur in small arteries. Indeed, the cells stimulated by the microenvironment created by the unresolved clot may release substances that induce EC dysfunction. The EC dysfunctions in CTEPH may lead to disorders of the anti-coagulation properties in ECs and may result in additional clots *in situ*. Moreover, these may lead to the progression, not only of distal thrombus, but also of proximal clotting.

This article reviews the pathobiological concepts of CTEPH and explains a crosstalk between EC dysfunction and *in situ* thrombi which may contribute to the vascular lesions of CTEPH.

Key words: Endothelial cell, Thrombus, CTEPH

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Introduction

Chronic thromboembolic pulmonary hypertension (CTEPH) has emerged as one of the leading causes of severe pulmonary hypertension. CTEPH is characterized by intraluminal thrombus formation and fibrous stenosis or complete obliteration of the pulmonary arteries (Klepetko et al., 2004). The consequence is increased pulmonary vascular resistance, resulting in pulmonary hypertension and progressive right heart failure. Pulmonary endarterectomy (PEA) is the current mainstay of therapy for CTEPH (Jamieson et al., 2003). Recently, there has been evidence suggesting that the existing consensus that the pathophysiology of CTEPH results from unresolved pulmonary emboli may have been too simplistic (Hoeper et al., 2006). Although acute pulmonary embolism is generally accepted as the main initiating event in CTEPH, small-vessel disease is believed to appear and worsen later during the course of disease, and to contribute to the progression of hemodynamic and symptomatic decline (Hoeper et al., 2006). Moreover, *in situ* thrombosis and pulmonary arteriopathy have been proposed as potential causes of CTEPH (Shure, 1996; Peacock et al., 2006).

This article reviews the pathobiological concepts of CTEPH, including pulmonary microvascular disease, the endothelial-mesenchymal transition (EnMT), EC dysfunction, and *in situ* thrombosis, which are important pathological features of pulmonary arterial hypertension (PAH) (Eisenberg et al., 1990; Welsh et al., 1996; Wolf et al., 2000; Bauer et al., 2002; Cool et al., 2004; Humbert et al., 2004; Reesink et al., 2004). Furthermore,

it explains a crosstalk between EC dysfunction and *in situ* thrombi which may contribute to the vascular lesions of CTEPH.

Microvascular lesions

In addition to the effect of recurrent thromboembolism, a number of lines of clinical evidence indicate that progressive worsening is contributed to by remodeling in the small distal pulmonary arteries in the open vascular bed (Moser and Bloor, 1993; Azarian et al., 1997; Yi et al., 2000). Indeed, the PH and right ventricular dysfunction are progressive, even in the absence of recurrent thromboemboli (Azarian et al., 1997). Moreover, there is a low degree of correlation between the extent of vascular obstruction visible on pulmonary angiography and the severity of PH (Azarian et al., 1997). There is likely a vascular stealing phenomenon, which means that there is redistribution of the pulmonary blood flow from the nonoccluded to newly endarterectomized vasculature after PEA (Moser and Bloor, 1993). There is often no hemodynamic improvement and persistent PH despite successful PEA in approximately 35% of patients (Condliffe et al., 2008).

Pulmonary microvascular disease, which is an important pathological feature of PAH, leads to increased pulmonary vascular resistance and reduced compliance, with marked proliferation of pulmonary artery smooth muscle cells (SMCs) and endothelial cells (ECs), resulting in the obstruction of blood flow in pulmonary arteries (Humbert et al., 2004). Recently, we reviewed pathogenetic concepts of pulmonary arterial hypertension (PAH) and explained the vascular lesions with EC dysfunction, i.e., apoptosis and proliferation (Sakao et al., 2009, 2010). Taraseviciene-Stewart et al. showed that a vascular endothelial growth factor (VEGF) receptor blocker induced some of the "angioproliferative" features typical of advanced PAH in a rat model, i.e., worsening of the pathological vascular remodeling, and those features were reversed by inhibitors of apoptosis, suggesting that increased apoptosis of ECs in response to loss of survival signaling provided a selection pressure that induced the emergence of actively proliferating ECs without evidence of apoptosis (Taraseviciene-Stewart et al., 2001). Moreover, our *in vitro* experiments have demonstrated that the emergence of apoptosis-resistant proliferating ECs depended on initial EC apoptosis induced by blockade of VEGF receptors and these phenotypically altered ECs expressed the tumor marker survivin and the antiapoptotic protein Bcl-$_{XL}$ (Sakao et al., 2005). Consistent with our results, Masri et al. have shown that pulmonary artery ECs isolated from patients with idiopathic PAH (IPAH) were hyperproliferative and apoptosis-resistant (Masri et al., 2007). However, these results were from an animal model and tissue culture experiments, not from human. It remains unknown whether they actually contribute to pathobiology of human PAH.

The studies of the microvascular changes in CTEPH have identified histopathological characteristics similar to those seen in IPAH and Eisenmenger's syndrome (Moser and Bloor, 1993; Azarian et al., 1997; Yi et al., 2000; Piazza and Goldhaber, 2011). Therefore, dysfunctional ECs may contribute to the progression of the microvascular changes in CTEPH as shown in PAH. Although PEA is the current mainstay of therapy for CTEPH, a recent study showed that specific vasodilative compounds, e.g., prostanoids, endothelin receptor antagonists, phosphodiesterase type 5 inhibitors or a combination, as used for PAH therapy, improved cumulative survival in the patients with inoperable CTEPH, suggesting that there may be vasodilative reactivity in the vasculature of some populations of CTEPH patients as shown in the vasculature of PAH (Seyfarth et al., 2010). Indeed, there exists evidence that patients with CTEPH show similar acute vasoreactivity to inhaled nitric oxide and iloprost (Ulrich et al., 2006; Skoro-Sajer et al., 2009).

The similarities between the microvascular changes in CTEPH and those seen in IPAH suggest that specific vasodilative compounds as used for PAH therapy may be appropriate for some populations of CTEPH, as the patients with no hemodynamic improvement and persistent PH despite successful PEA.

Endothelial-mesenchymal transition (EnMT)

EnMT is a term which has been used to describe the process through which ECs lose their endothelial characteristics and gain the expression of other mesenchymal cell characteristics (Arciniegas et al., 2007). There is the intriguing possibility that intimal SMCs may arise from ECs (Majesky and Schwartz, 1997). In the systemic circulation, Arciniegas et al. demonstrated that mesenchymal cells that existed in the intimal thickening may arise from ECs (Arciniegas et al., 2000). Indeed, the existence of "transitional cells" demonstrating features of both ECs and vascular SMCs in the plexiform lesions in the lungs from patients with IPAH has been identified (Cool et al., 2004). Our *in vitro* studies of human pulmonary microvascular endothelial cells (HPMVECs) showed that blockade of VEGF receptors generated a selection pressure that killed some ECs and expanded resident progenitor-like cells to transdifferentiate into other mesenchymal phenotypes (Sakao et al., 2007). Although there is the limitation of this study based on *in vitro* experiment, this result may support the concept that transdifferentiation of pulmonary ECs to other mesenchymal cells may contribute to the muscularization of the pulmonary arteries. Because of histopathological similarity of the microvascular changes between CTEPH and IPAH (Moser and Bloor, 1993; Azarian et al., 1997; Yi et al., 2000, Piazza and Goldhaber, 2011), EnMT may contribute to the progression of the microvascular changes in CTEPH.

Recently, we have shown the existence of not only myofibroblast-like cells, but also endothelial-like cells in endarterectomized tissues from patients with CTEPH (Maruoka et al., 2012). Our experiments demonstrated that the endothelial-like cells included a few transitional cells (coexpressing both endothelial- and smooth muscle- cell markers). Moreover, experiments using commercially available HPMVECs and myofibroblast-like cells, which were isolated from the PEA tissues of CTEPH patients, demonstrated that substances associated with myofibroblast-like cells might induce the EnMT (Sakao et al., 2011). Indeed, transitional cells which co-expressed both endothelial- and smooth muscle- cell markers were identified in the PEA tissues of patients with CTEPH (Sakao et al., 2011). In support of our findings, Yao et al. showed the presence of CD34 (an endothelial marker) positive cells co-expressing α-smooth muscle actin (a smooth muscle- cell marker) in endarterectomized tissues from patients with CTEPH (Yao et al., 2009).

As shown in our experiment, Firth et al. demonstrated that a myofibroblast cell phenotype was predominant within endarterectomized tissues from patients with CTEPH, contributing extensively to the vascular lesion/clot (Firth et al., 2010). Moreover, the existence of putative endothelial progenitor cells in endarterectomized tissues of patients with CTEPH has been demonstrated (Yao et al., 2009). Firth et al. have reported the presence of multipotent mesenchymal progenitor cells within the tissues of patients with CTEPH (Firth et al., 2010). These studies suggested that the unique microenviroment created by the stabilized clot may promote these progenitor cells to differentiate into myofibloblast-like cells, and the misguided differentiation of these progenitor cells may enhance intimal remodeling (Yao et al., 2009; Firth et al., 2010). Therefore, myofibloblast-like cells may participate directly in vascular remodeling and they may induce EnMT to lead to EC dysfunction.

Indeed, it may be possible that the cells coexpressing both endothelial- and SM- cell markers in endarterectomized tissues are more likely progenitor cells rather than the cells which are differentiated by EnMT. However, in our *in vitro* experiments, there was no bone marrow-derived cell (defined as born marrow cell markers) in the cultured endothelial-like cells because *ex vivo* conditions may allow these cells to differentiate (Sakao et al., 2011).

EnMT may contribute to the development of vascular remodeling in the patients with CTEPH and interrupting this transition may provide a therapeutic target for CTEPH.

EC dysfunction

The degree and mechanisms of EC dysfunction as a contributor to CTEPH in small muscular arteries distal to nonobstructed pulmonary elastic vessels are unclear (Yi et al., 2000; Dartevelle et al., 2004; Hoeper et al., 2006). However, EC dysfunction may play a crucial role in these areas. Indeed, EC related humoral markers that have been linked to CTEPH include anticardiolipin antibodies, a known risk factor for venous thromboembolism (Torbicki et al., 2008), elevated endothelial factor VIII (Wolf et al., 2000; Bonderman et al., 2003), and monocyte chemoattractant protein 1 (Kimura et al., 2001). Moreover, markers of endothelial trauma or dysfunction, such as endothelins, regularly observed in IPAH, are also found in cases of pulmonary embolism (Sofia et al., 1997). In particular, the endothelin-1 levels in CTEPH closely correlated with the hemodynamic and clinical severity of the disease (Reesink et al., 2006). Endothelin-mediated vascular remodeling and impairment of nitric oxide function may play a crucial role in the development of vascular lesions distal to occluded vessels in CTEPH, as well as in severe PH (Bauer et al., 2002; Reesink et al., 2004). It has been observed that PH is more likely to occur following partial vascular occlusions of pulmonary artery segments than following complete occlusions (Robin et al., 1966), thus suggesting that vasoactive substances produced by the turbulent flow in CTEPH may be involved in EC dysfunction. However, it seems to be difficult to define EC dysfunction in patients with CTEPH.

Several lines of evidence indicate that autophagy has an important role in many different pathological conditions. Moreover, fewer mitochondria, the decreased expression of superoxide dismutase and normoxic decreases in reactive oxygen species have been shown to be the characteristics of mitochondrial abnormalities in PAH (Archer et al., 2008). Our recent findings demonstrated that endothelial-like cells lost their ability to form autophagosomes and had defective mitochondrial structure/function (Sakao et al., 2011), indicating that EC dysfunctions occur in the proximal lesions of patients with CTEPH. Moreover, experiments using commercially available HPMVECs and myofibroblast-like cells demonstrated that factors associated with myofibroblast-like cells might induce HPMVEC dysfunction through the inactivation of autophagy, the disruption of the mitochondrial reticulum, and the improper localization of superoxide dismutase-2 (Sakao et al., 2011). The PCR array data analysis showed that substances associated with myofibroblast-like cells induced the alterations in the endothelial cell biology of HPMVECs (Sakao et al., 2011). Although it is uncertain whether EC dysfunctions actually contribute to microvascular remodeling in patients with CTEPH, the myofibroblast-like cells in the proximal lesions may contribute to EC dysfunction in the vasculature of CTEPH. Indeed, it has been demonstrated that ECs in noninvolved pulmonary vascular beds are different from ECs in regions of organized thromboembolic material in patients with CTEPH (Lang et al., 1994a,b). In patients with CTEPH, primary ECs cultured from pulmonary arteries without thrombus had no abnormalities in the expression of fibrinolytic proteins or responses to thrombin stimulation (Lang et al., 1994a,b). However,

ECs within yellowish-white thrombi, i.e., the highly organized tissues, showed elevated type 1 plasminogen activator inhibitor (PAI-1) mRNA levels (Lang et al., 1994a). Therefore, we have to separate them to consider EC dysfunction.

The correlation between endothelins and vascular remodeling in CTEPH seems to support the possibility that pharmacological therapy using endothelin receptor antagonists are effective treatment for the patients with CTEPH.

In situ thrombosis

ECs not only facilitate the thrombotic process, but also actively inhibit thrombosis and promote fibrinolysis. The production and release of nitric oxide and prostacyclin, two potent inhibitors of platelet aggregation, by ECs are important for the prevention of intravascular thrombosis (Moncada et al., 1991). In addition, the expression of thrombomodulin (TM), a high affinity receptor for thrombin, on the surface of ECs prevents the cleavage of fibrinogen to fibrin. ECs are also a source of tissue plasminogen activator (t-PA), a key activator of plasminogen in the *fibrinolytic* cascade. On the other hand, ECs also synthesize and release plasminogen activator inhibitor (PAI)-1, an inhibitor of t-PA, highlighting the role of the endothelium in regulating the fine balance between prothrombotic and antithrombotic processes.

Indeed, the plasma concentration of soluble TM in patients with CTEPH was found to be significantly lower than that in the control group, suggesting that a

Table 1. Clinical and pathobiological features of CTEPH.

Hallmarks	Features	Reference	Tissue Culture/ Clinical
Microvascular lesions	Progressive worsening by remodeling in the small distal pulmonary arteries	Azarian et al. (1997)	Clinical
		Moser and Bloor (1993)	Clinical
		Yi et al. (2000)	Clinical
	No hemodynamic improvement and persistent PH despite successful PEA	Condliffe et al. (2008)	Clinical
	microvascular changes in CTEPH similar to those seen in IPAH	Azarian et al. (1997)	Clinical
		Moser and Bloor (1993)	Clinical
		Yi et al. (2000)	Clinical
		Piazza and Goldhaber (2011)	Clinical
	Vasodilative reactivity in the vasculature of CTEPH	Seyfarth et al. (2010)	Clinical
EnMT	Transitional cells in endarterectomized tissues	Sakao et al. (2011)	Tissue Culture
		Yao et al. (2009)	Tissue Culture
	EnMT induced by substances associated with the cells in endarterectomized tissues	Sakao et al. (2011)	Tissue Culture
	The existence of endothelial and mesenchymal progenitor cells in endarterectomized tissues	Yao et al. (2009)	Tissue Culture
		Firth et al. (2010)	Tissue Culture
EC dysfunction	Humoral markers related with EC in CTEPH: Anticardiolipin antibodies Endothelial factor VIII Monocyte chemoattractant protein 1 Endothelins	Torbicki et al. (2008)	Clinical
		Bonderman et al. (2003)	Clinical
		Kimura et al. (2001)	Clinical
		Sofia et al. (1997)	Clinical
		Reesink et al. (2006)	Clinical
	Endothelin-mediated vascular remodeling	Reesink et al. (2006)	Clinical
	The loss of the ability to form autophagosomes	Sakao et al. (2011)	Tissue Culture
	Structure-function defects of mitochondria	Sakao et al. (2011)	Tissue Culture
	ECs with abnormalities in the expression of fibrinolytic proteins or responses to thrombin stimulation	Lang et al. (1994a,b)	Tissue Culture
		Lang et al. (1994a,b)	Tissue Culture
In situ thrombosis	A decreased plasma TM concentration	Sakamaki et al. (2003)	Clinical
	Elevated PAI-1 mRNA levels	Lang et al. (1994)	Tissue Culture
	The decreased expression of Annexin A and plasminogen activator genes in HPMVECs co-cultured with the cells from the PEA tissues	Sakao et al. (2011)	Tissue Culture

CTEPH: Chronic thromboembolic pulmonary hypertension; PH: Pulmonary arterial hypertension; PEA: Pulmonary endarterectomy; IPAH: Idiopathic pulmonary arterial hypertension; EnMT: Endothelial-mesenchymal transition; EC: endothelial cell; TM: Thrombomodulin; PAI-1: type 1 plasminogen activator inhibitor; HPMVECs: Human pulmonary microvascular endothelial cells.

decreased plasma TM concentration might reflect pulmonary vascular EC dysfunction, leading to altered anticoagulant and fibrinolytic function in CTEPH (Sakamaki et al., 2003). ECs within the highly organized tissues in CTEPH exhibited elevated PAI-1 mRNA levels in comparison to patient pulmonary artery specimens that were free of thrombus, suggesting that the prevalence of PAI-1 expression within pulmonary thromboemboli may play a role in the stabilization of vascular thrombi (Lang et al., 1994a). Moreover, there were decreases in the expression of the Annexin A5 and plasminogen activator, urokinase genes in HPMVECs co-cultured with myofibroblast-like cells from the PEA tissues of CTEPH patients (Sakao et al., 2011). Annexin A5 plays an important role in anticoagulant function and is a protein that has a high affinity for negatively-charged phospholipids (Funakoshi et al., 1987; Tait et al., 1988), over which it forms trimers (Voges et al., 1994) that become an annexin A5 shield. The formation of this shield blocks the phospholipids from phospholipid-dependent coagulation enzyme reactions (Andree et al., 1992). Plasminogen activator, urokinase, is a thrombolytic agent. Its primary physiological substrate is plasminogen, which is an inactive zymogen form of the serine protease plasmin. The activation of plasmin triggers a proteolysis cascade that, depending on the physiological environment, participates in thrombolysis or extracellular matrix degradation (Collen and Lijnen, 2005). The decreased expression of Annexin A and plasminogen activator, urokinase, may contribute to the disorder of the anti-coagulation properties in CTEPH patients. However, there is no validation of these data in an *in vivo* experiment.

There are several lines of evidence indicating that EC dysfunction might interfere with the normal balance between the pro-thrombotic and anti-thrombotic mechanisms, resulting in local thrombosis, and may contribute to the pathophysiology of PAH (Eisenberg et al., 1990; Welsh et al., 1996; Wolf et al., 2000). The EC dysfunction in CTEPH may lead to disorder of the anti-coagulation properties in ECs, i.e., may inactivate a vascular fibrinolytic system, and result in the formation of additional clots *in situ*, like PAH, because the histopathological features in the CTEPH vasculature are similar to those seen in IPAH.

Crosstalk between the unresolved clot, EC dysfunction and *in situ* thrombi

Although the first pulmonary embolism is generally accepted as the main initiating event in CTEPH, we hypothesize that the emergence of the microenvironment created by the unresolved clot may result in the local induction of substances that circulate to cause a more widespread predisposition to vascular remodeling affecting the rest of the pulmonary vascular bed, i.e., beyond the site of initial thrombosis. Our recent study suggested that myofibroblast-like cells stimulated by the microenvironment created by the unresolved clot might release substances that promote ECs to transition to other mesenchymal phenotypes and/or induce EC dysfunction, contributing not only to the proximal vasculature, but also to the distal vasculature (Sakao et al., 2011). The precise reasons for the lung-specific action of these substances in CTEPH remain unknown. One explanation may be that the pulmonary vascular

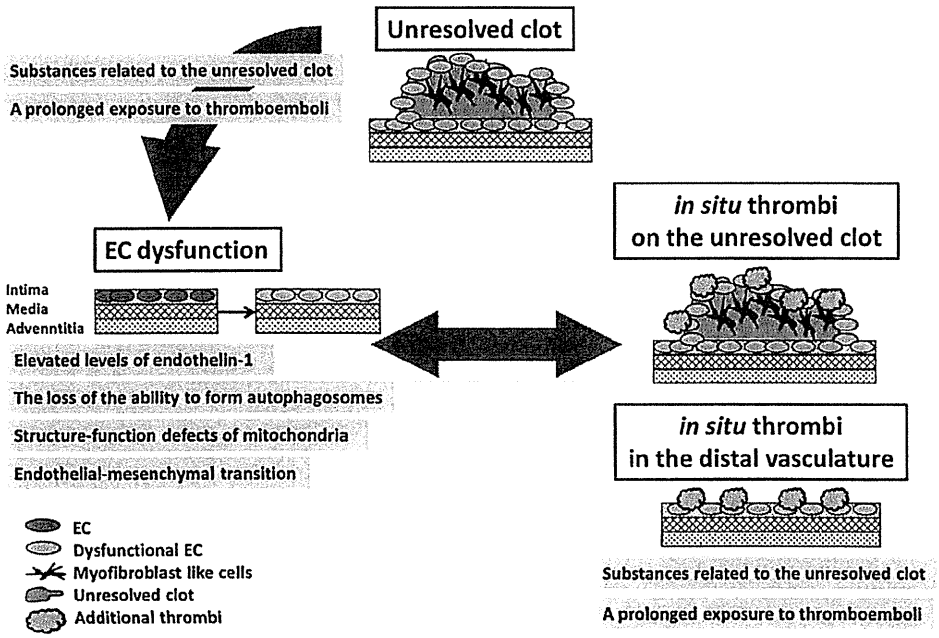

Fig. 1. Crosstalk between EC dysfunction and *in situ* thrombi in CTEPH (a hypothetical mechanism). The cells stimulated by the microenvironment created by an unresolved clot may release substances that induce EC dysfunction. The pulmonary vasculature in patients with CTEPH is subjected to prolonged exposure to thromboemboli. Indeed, thrombin is known to have potent effects on ECs, leading to endothelial barrier dysfunction due to mobilization of Ca^{2+} and rearrangement of the cytoskeleton. An impairment of the EC function in patients with CTEPH may lead to additional thrombi *in situ*, as is seen in patients with PAH, and these may lead to the progression of the proximal clot. A crosstalk between EC dysfunction and *in situ* thrombi may therefore contribute to the vascular lesions of CTEPH. CTEPH: chronic thrombo-embolic pulmonary hypertension, EC: endothelial cells.

beds, i.e., alveolar arteries, are exposed to the highest oxygen tensions in the body, which may induce the different response against substances related by an unresolved clot in comparison to systemic artery ECs. However, this explanation is not sufficient and further explanations are needed.

We fully recognize the limitation of our data interpretation which is based on *in vitro* studies of cultured cells and that this study does not confer any pathological evidence in CTEPH. Indeed, extensive small vessel disease may be a complication of a minority of CTEPH cases. Therefore, besides substances related to the microenviroment created by the stabilized clot, a second factor may be required to induce EC dysfunction which results in extensive disease. However, it remains unknown what is the second factor that is responsible for whether extensive small vessel disease occurs in a given patient.

In the pathogenesis of CTEPH, pulmonary microvascular lesions develop in the distal areas of unoccluded as well as occluded pulmonary arteries (Moser and Bloor, 1993; Azarian et al., 1997; Yi et al., 2000). The development of microvascular lesions distal to totally obstructed pulmonary arteries may be promoted by substances related to the microenvironment created by the unresolved clot. The development of the lesions distal to nonobstructed pulmonary arteries may be promoted not only by substances, but also by increased shear stress caused by hypoxic pulmonary vasoconstriction, because shear stress has been shown to inhibit apoptosis of ECs (Pi et al., 2004) and to stimulate EC growth (Ameshima et al., 2003; Sakao et al., 2005), contributing to vascular remodeling. However, unless the occlusion is enormous, it seems unlikely that vessel occlusion alone increases shear stress in unoccluded arteries because of the large reservoir capacity of the normal pulmonary vasculature. A more likely explanation for the lesions distal to nonobstructed pulmonary arteries may be that the pulmonary arteriopathy could be the initial pathology of the lesions in the patients with IPAH (Peacock et al., 2006). In any case, a persistent clot in the peripheral pulmonary arteries despite successful PEA may continue to create the microenvironment that induces microvascular changes. This may be the reason why there are patients who do not respond to PEA.

In the proximal lesions in patients with CTEPH, the pulmonary vasculature is subjected to a prolonged exposure to thromboemboli, i.e., components in the final common pathway of the coagulation cascade. Indeed, thrombin, a serine protease that catalyzes the conversion of fibrinogen to fibrin, is known to have potent effects on ECs, leading to endothelial barrier dysfunction due to the mobilization of Ca^{2+} and rearrangement of the cytoskeleton (Ellis et al., 1999). Moreover, chronic exposure to fibrinogen, fibrin, and thrombin caused changes in the cytosolic Ca^{2+} in pulmonary artery ECs, suggesting that such changes might contribute to EC dysfunction, thus leading to vascular changes in patients with CTEPH (Firth et al., 2009).

Based on these observations, it has been suggested that many kinds of insults to ECs of the pulmonary arteries may initiate a sequence of events which leads to the EC dysfunctions in CTEPH. Numerous factors such as hypoxia, endogenous vasoconstrictors, and inflammatory cytokines could help to sustain this process (Egermayer et al., 1999). An impairment of the EC function in patients with CTEPH may lead to additional thrombi *in situ* similar to that observed in patients with PAH, and these may also lead to the progression of the proximal clot.

It has been suggested that the core of the pathological process in CTEPH is not only related to thrombus formation, but it is also linked to disturbed thrombus resolution (Morris et al., 2006, 2007; Suntharalingam et al., 2008). An altered coagulation process may account for the pathological features of CTEPH (Wolf et al., 2000). Recently, the fibrinogen A Thr312Ala polymorphism was shown to correspond to significant differences in the genotype and allele frequencies between CTEPH and control subjects. The presence of these polymorphisms may confer resistance to fibrinolysis that subsequently contributes to the development of thrombus organization (Suntharalingam et al., 2008). The other mechanism may be the development of more fibrinolysis-resistant fibrin clots from patients with CTEPH, when compared with the fibrin clots from healthy control subjects (Morris et al., 2006). An abnormally elevated amount of disialylated fibrinogen γ-chain can render a clot resistant to plasmin, which could lead to the subsequent development of CTEPH (Morris et al., 2007). However, these explanations are not sufficient because there are many patients without known coagulation problems who have these factors, and because numerous genetic variants of human fibrinogen have been implicated in thrombotic diseases (Matsuda and Sugo, 2002). Therefore, the resistance could be ascribed to not only fibrinogen genetic polymorphisms, but also variations in the post-translational modifications.

Conclusion

Besides the altered coagulation process, a crosstalk between EC dysfunction and *in situ* thrombi may contribute to the vascular lesions of CTEPH (Fig. 1) (Table 1). Moreover, this may explain why pulmonary thromboemboli in CTEPH patients are stable. Indeed, pulmonary thromboendarterectomy may be the best way to break this crosstalk. Recently, we demonstrated that poor subpleural perfusion on pulmonary angiography might be related to distal vascular remodeling and an inadequate surgical outcome of CTEPH (Tanabe et al., 2012). No satisfactory hemodynamic improvement and persistent PH despite successful PEA in the patients with CTEPH (Condliffe et al., 2008) suggests the existence of distal vascular remodeling. Although it remains uncertain whether vascular remodeling is actually related

to the crosstalk between EC dysfunction and *in situ* thrombi, the care for these patients should be directed toward pharmacologically reducing pulmonary vascular resistance with specific vasodilative compounds as used for PAH therapy. The next step in the future is to find out new ways to define EC dysfunction and vascular remodeling in CTEPH objectively.

Acknowledgments: All authors read and approved the final manuscript. This article shows a selective perusal of the relevant literature together with a discussion of our own findings, and not a comprehensive "balanced" review as outlined by a referee.

Conflict of interest: Dr. Tatsumi has received honoraria for lectures from Glaxo Smith Kline, and Actelion Pharmaceutical Ltd. The other authors report no conflicts of interest with regard to this manuscript.

Role of the funding source: This study was supported by Research Grants for the Respiratory Failure Research Group and the Cardiovascular Diseases (19-9, 22-33) from the Ministry of Health, Labor and Welfare, Japan, a Grant-in-Aid for Scientific Research (Category C 22590851) from the Japanese Ministry of Education and Science, and Takeda Science Foundation.

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Accepted September 26, 2012

特集　肺高血圧症 ―日本から何が発信できるか

臨　床

わが国の膠原病性肺高血圧症 ―欧米例との差違

Connective tissue disease associated pulmonary arterial hypertension in Japan –Difference from that in Western countries

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KEY WORD
膠原病，肺高血圧症

膠原病性肺高血圧症(CTD-PH)の変遷と欧米との共通点

膠原病で肺高血圧症(pulmonary hypertension：PH)が注目されたのは，混合性結合組織病(mixed connective tissue disease：MCTD)における死因の分析による(図1)。つまり，従来予後良好と考えられていたMCTDの第一の死因がPHであったことによる。このため，膠原病全般におけるPHの頻度について検討がなされた。

厚生省のMCTD調査研究班が1998年に世界に先駆けて全国疫学調査を行った[1]。それによると，MCTD 1,651例中PH合併例は83例(5.02%)，全身性エリテマトーデス(systemic lupus erythematosus：SLE)で9,015例中82例(0.90%)，強皮症(systemic sclerosis：SSc)で3,778例中100例(2.64%)，多発性筋炎・皮膚筋炎(polymyositis/dermatomyositis：PM/DM)で3,349例中19例(0.56%)にみられた(図2)。特発性PAH(idiopathic pulmonary arterial hypertension：IPAH)の一般人口における有病率が100万人あたり1～5人であることを考えると，この膠原病4疾患のPH合併率は著しく高いことがわかる。これらの数字は主治医がPHと診断した例，つまり臨床所見のみられた症例である。これ以外に臨床徴候のないPHが隠れている可能性も考えられたため，2003年に厚生労働省の別の班において，症状の有無にかかわらず無作為に抽出した膠原病患者にPHの検索を行った[2]。するとMCTDで16.0%，SLEで9.3%，SScで11.4%にPHがみられ(図2)，臨床徴候のあるPHと同数かそれ以上の無症状のPHの症例がみられた。これはPHを疑う徴候のみられない膠原病患者でもその検索の必要なことを示唆している。PHに関するWHOのシンポジウムでも，SSc関連疾患(つまりSScとMCTD)では，症状の有無や変化にかかわらず毎年心エコー検査をすべきであるとしている。

わが国の上記の成績は，北米における同様の調査[3]でも裏付けられた(図2)。すなわち北米50施設の検討によると，MCTDでは主治医診断で11.7%，心エコー検査では19.1%，SScでも主治医診断で15.9%，心エコー検査で27.7%にPHがみられた。

上記は主にDoppler心エコー検査による推定肺動脈圧によるものであり，gold standardである心臓カテーテル検査によるものではない。この点に関して，フランスとイタリアでSSc患者の中で推定肺動脈圧が40mmHg以上か，ガス拡散能力(DLCO)が50%