In conclusion, in our experience PEA provided immediate and substantial improvements in pulmonary hemodynamics and had sustained favorable effects on long-term survival. High PVR was a significant independent risk factor for in-hospital death. Persistence and worsening of pulmonary hypertension were associated with late death or impairment of functional class, and postoperative mPAP was shown as a risk factor for late adverse events, with an mPAP value of at least 34 mm Hg being identified as the cutoff value for the prediction of such late adverse events.

References

1. Dartevelle P, Fadel E, Mussot S, Chapelier A, Hervé P, de Perrot M, et al. Chronic thromboembolic pulmonary hypertension. *Eur Respir J*. 2004;23:637-48.
2. Hoeper MM, Mayer E, Simonneau G, Rubin LJ. Chronic thromboembolic pulmonary hypertension. *Circulation*. 2006;113:2011-20.
3. Riedel M, Stanek V, Widimsky J, Prerovsky I. Longterm follow-up of patients with pulmonary thromboembolism. Late prognosis and evolution of hemodynamic and respiratory data. *Chest*. 1982;81:151-8.
4. Jamieson SW, Kapelanski DP, Sakakibara N, Manecke GR, Thistlethwaite PA, Kerr KM, et al. Pulmonary endarterectomy: experience and lessons learned in 1,500 cases. *Ann Thorac Surg*. 2003;76:1457-64.
5. Freed DH, Thomson BM, Tsui SS, Dunning JJ, Sheares KK, Pepke-Zaba J, et al. Functional and haemodynamic outcome 1 year after pulmonary thromboendarterectomy. *Eur J Cardiothorac Surg*. 2008;34:525-30.
6. Ogino H, Ando M, Matsuda H, Minatoya K, Sasaki H, Nakanishi N, et al. Japanese single-center experience of surgery for chronic thromboembolic pulmonary hypertension. *Ann Thorac Surg*. 2006;82:630-6.
7. Saouti N, Morshuis WJ, Heijmen RH, Snijder RJ. Long-term outcome after pulmonary endarterectomy for chronic thromboembolic pulmonary hypertension: a single institution experience. *Eur J Cardiothorac Surg*. 2009;35:947-52.
8. Corsico AG, D'Armini AM, Cerveri I, Klersy C, Ansaldo E, Niniano R, et al. Long-term outcome after pulmonary endarterectomy. *Am J Respir Crit Care Med*. 2008;15(178):419-24.
9. Archibald CJ, Auger WR, Fedullo PF, Channick RN, Kerr KM, Jamieson SW, et al. Long-term outcome after pulmonary thromboendarterectomy. *Am J Respir Crit Care Med*. 1999;160:523-8.
10. Condliffe R, Kiely DG, Gibbs JS, Corris PA, Peacock AJ, Jenkins DP, et al. Improved outcomes in medically and surgically treated chronic thromboembolic pulmonary hypertension. *Am J Respir Crit Care Med*. 2008;177:1122-7.
11. Jamieson SW, Auger WR, Fedullo PF, Channick RN, Kriett JM, Tarazi RY, et al. Experience and results with 150 pulmonary thromboendarterectomy operations over a 29-month period. *J Thorac Cardiovasc Surg*. 1993;106:116-27.
12. Jamieson SW, Kapelanski DP. Pulmonary endarterectomy. *Curr Probl Surg*. 2000;37:165-252.
13. Thistlethwaite PA, Mo M, Madani MM, Deutsch R, Blanchard D, Kapelanski DP, et al. Operative classification of thromboembolic disease determines outcome after pulmonary endarterectomy. *J Thorac Cardiovasc Surg*. 2002;124(6):1203-11.
14. Tscholl D, Langer F, Wendler O, Wilkens H, Georg T, Schäfers HJ. Pulmonary thromboendarterectomy—risk factors for early survival and hemodynamic improvement. *Eur J Cardiothorac Surg*. 2001;19:771-6.
15. Bonderman D, Skoro-Sajer N, Jakowitsch J, Adlbrecht C, Dunkler D, Taghavi S, et al. Predictors of outcome in chronic thromboembolic pulmonary hypertension. *Circulation*. 2007;115:2153-8.
16. Hartz RS, Byrne JG, Levitsky S, Park J, Rich S. Predictors of mortality in pulmonary thromboendarterectomy. *Ann Thorac Surg*. 1996;62:1255-60.
17. Freed DH, Thomson BM, Berman M, Tsui SS, Dunning J, Sheares KK, et al. Survival after pulmonary thromboendarterectomy: Effect of residual pulmonary hypertension. *J Thorac Cardiovasc Surg*. 2011;141:383-7.
18. Kapitan KS, Clausen JL, Moser KM. Gas exchange in chronic thromboembolism after pulmonary thromboendarterectomy. *Chest*. 1990;98:14-9.
19. Tanabe N, Okada O, Nakagawa Y, Masuda M, Kato K, Nakajima N, et al. The efficacy of pulmonary thromboendarterectomy on long-term gas exchange. *Eur Respir J*. 1997;10:2066-72.
20. Lewczuk J, Piszko P, Jagas J, Porada A, Wójciak S, Sobkowicz B, et al. Prognostic factors in medically treated patients with chronic pulmonary embolism. *Chest*. 2001;119:818-23.
21. Moser KM, Bloor CM. Pulmonary vascular lesions occurring in patients with chronic major vessel thromboembolic pulmonary hypertension. *Chest*. 1993; 103:685-92.
22. Galiè N, Kim NH. Pulmonary microvascular disease in chronic thromboembolic pulmonary hypertension. *Proc Am Thorac Soc*. 2006;3:571-6.

●一般演題：A-11

肺動脈内に巨大壁在血栓を認め，CTEPHとの鑑別を要したEisenmenger化した心房中隔欠損症の1例

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症例は70歳，女性．19歳時に心房中隔欠損(atrial septal defect；ASD)指摘されるも，自覚症状なく本人希望で手術せずワルファリンによる抗凝固療法のみにて経過観察していた．69歳頃より，発作性心房粗細動の出現やMRCgradeの呼吸困難感出現し，本人が手術希望したため精査目的にて当院循環器内科受診．精査中施行した胸部造影CTにて肺動脈に壁在血栓を指摘されたため，慢性血栓塞栓性肺高血圧症(chronic thromboembolic pulmonary hepertension；CTEPH)の鑑別目的にて2011年6月当科に紹介となった．CT上右肺動脈主幹部から下行枝にかけて連続する，一部に石灰化を伴った壁在血栓を認めた．しかし，下肢静脈造影CTと下肢静脈エコーを施行し，深部静脈血栓(deep vein thrombosis；DVT)は認めず，また肺血流シンチグラフィでは血流欠損を認めなかった．両心カテーテル検査施行し，mPAP：53mmHg，CO：5.7L/分，PVR：659dyne･分･cm^{-5}，Qp/Qs：1.27，左右シャント率：28%，右左シャント率：2%であった．100%酸素負荷試験でPVR，PA圧の改善は認められなかった．CT上massiveな壁在血栓認めたものの，肺血流シンチグラフィで血流欠損認めなかったため，この症例はCTEPHではなく，長期間のASD放置によってEisenmenger化し，肺高血圧症ならびに*in situ*の血栓を合併したものと考えた．ASD閉鎖術の適応はないと考え，今後，在宅酸素導入および血管拡張薬による治療を予定している．CTEPHと血栓を合併したPAHの鑑別に肺血流スキャンが有用であった．ASDはじめ先天性心疾患に肺血栓症を合併した症例の報告はこれまでも散見されるが，両者の関連について文献的考察を加え報告する．

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慢性血栓塞栓性肺高血圧症の病態・診断と内科治療

——労作時の息切れを主訴とする患者で，忘れてならない慢性血栓塞栓性肺高血圧症

Pathophysiology, diagnosis and medical treatment of chronic thromboembolic pulmonary hypertension

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◎慢性血栓塞栓性肺高血圧症(CTEPH)は，器質化した血栓により肺動脈が慢性的に閉塞を起こし，肺高血圧症を合併するものであり，厚生労働省の治療給付対象疾患に認定されている．従来，肺高血圧症の重症例では内科的治療には限界があり，予後不良とされてきたが，手術(肺血栓内膜摘除術)によりQOLや生命予後の改善が得られる症例が存在するため，その正確な診断が重要である．労作時の息切れを呈する患者をみた場合，本症を疑うことが重要であり，COPDや喘息として加療されている患者のなかに本症が隠れている可能性を考慮する必要がある．心エコーで肺高血圧症のスクリーニングを行う．肺動脈性肺高血圧症との鑑別には肺換気・血流スキャンが有用で，本症では換気に異常を認めない区域性の血流欠損を呈する．確定診断は造影CTあるいは肺動脈造影で，慢性血栓に特徴的とされる所見を呈すること，右心カテーテル検査で肺動脈楔入圧正常な肺高血圧症(平均肺動脈圧25 mmHg以上)を確認することによる．治療としては厳密な抗凝固療法が必要である．また，手術的にアプローチ可能な区域枝までの血栓を有し，中枢血栓にみあった肺血管抵抗値を示す例では肺血栓内膜摘除術が第一選択となる．末梢血栓例，高齢，合併症などで非手術適応となる患者では在宅酸素療法，右心不全対策に加えて肺血管拡張療法が用いられる．有効性の報告はみられるが，その意義は確立しておらず，現在臨床試験が進行中である．カテーテル治療の有効例の報告もみられ，治療の選択肢が広がってきている．

Key word：慢性血栓塞栓性肺高血圧症(CTEPH)，労作時息切れ，肺換気・血流スキャン，small vessel disease，肺動脈造影

慢性血栓塞栓性肺高血圧症(chronic thromoboembolic pulmonary hypertension：CTEPH)は器質化した血栓により肺動脈が慢性的に閉塞を起こし，肺高血圧症を合併するものであり，多くは労作時の息切れを主訴とする．慢性の定義としては一般に，6カ月以上にわたって肺血流分布ならびに肺循環動態の異常が大きく変化しない病態とされる[1]．その臨床経過によって，①過去に急性肺血栓塞栓症を示唆する症状が認められる反復型と，②明らかな症状のないまま病態の進行がみられる潜伏型に分けられる．従来，肺高血圧症の重症例では内科的治療には限界があり，予後不良とされてきたが[2]，近年，手術(肺血栓内膜摘除術)によりQOLや生命予後の改善が得られる症例が存在するため，その正確な診断と手術適応を考慮した重症度評価が重要である．さらに，非手術適応の本症を対象とした肺血管拡張薬やカテーテル治療の有効性の報告がみられるようになった．

CTEPHの疫学・病因・病態

わが国における急性例および慢性例を含めた肺血栓塞栓症の発生頻度は少ないとされ，剖検輯報にみる病理解剖を基礎とした検討では，その発生率は米国の約1/10とされている[3]．米国では急性肺血栓塞栓症の年間発生数が50万～60万人と推定されており，急性期の生存症例の約0.1～0.5%がCTEPHへ移行するものと考えられてきた[4]．しかし最近，急性例の3.8%が慢性化したと報告

表 1　慢性血栓塞栓性肺高血圧症の認定基準

慢性血栓塞栓性肺高血圧症は，器質化した血栓により，肺動脈が慢性的に閉塞を起こし，肺高血圧症を合併し，臨床症状として労作時の息切れなどを強く認めるものである．なお本症の診断には，右心カテーテルによる肺高血圧の診断とともに，他の肺高血圧をきたす疾患の除外診断が必要である

(1) 主要症状および臨床所見

①労作時の息切れ
②急性例にみられる臨床症状(突然の呼吸困難，胸痛，失神など)が，以前に少なくとも1回以上認められている
③下肢深部静脈血栓症を疑わせる臨床症状(下肢の腫脹及び疼痛)が以前に少なくとも1回以上認められている
④肺野にて肺血管性雑音が聴取される
⑤胸部聴診上，肺高血圧症を示唆する聴診所見の異常(Ⅱ音肺動脈成分の亢進など)がある

(2) 診断のための検査所見

①右心カテーテル検査で
　1．肺動脈圧の上昇(安静時肺動脈平均圧が25 mmHg以上，肺血管抵抗で240 dyne・s・cm^{-5}以上)
　2．肺動脈楔入圧(左心房圧)が正常(15 mmHg以下)
②肺換気・血流シンチグラム所見
　換気分布に異常のない区域性血流分布欠損(segmental defects)が，血栓溶解療法または抗凝固療法施行後も6カ月以上不変あるいは不変と推測できる．推測の場合には，6カ月後に不変の確認が必要である
③肺動脈造影
　慢性化した血栓による変化として，1)pouch defects，2)webs and bands，3)intimal irregularities，4)abrupt narrowing，5)complete obstructionの5つのうち，すくなくとも1つが証明される
④胸部造影CT所見
　造影CTにて，慢性化した血栓による変化として，1)mural defects，2)webs and bands，3)intimal irregularities，4)abrupt narrowing，5)complete obstructionの5つのうち，すくなくとも1つが証明される

(3) 参考とすべき検査所見

①心臓エコー検査にて，三尖弁収縮期圧較差40 mmHg以上で，推定肺動脈圧の著明な上昇を認め，右室肥大所見を認めること
②動脈血液ガス所見にて，低炭酸ガス血症を伴う低酸素血症を呈する
③胸部X線像で，肺動脈本幹部の拡大
④心電図で右室肥大所見

(4) 下記の除外すべき疾患を除外すること

以下の肺高血圧症を呈する病態は，慢性血栓塞栓性肺高血圧症ではなく，肺高血圧ひいては右室肥大・慢性肺性心を招来しうるので，これらを除外すること
1．特発性または遺伝性肺動脈性肺高血圧症
2．膠原病に伴う肺動脈性肺高血圧症
3．先天性シャント性心疾患に伴う肺動脈性肺高血圧症
4．門脈圧亢進症に伴う肺動脈性肺高血圧症
5．HIV感染に伴う肺動脈性肺高血圧症
6．薬剤・毒物に伴う肺動脈性肺高血圧症
7．肺静脈閉塞性疾患，肺毛細血管腫症
8．新生児遷延性肺高血圧症
9．左心性心疾患に伴う肺高血圧症
10．呼吸器疾患および/または低酸素血症に伴う肺高血圧症
11．その他の肺高血圧症(サルコイドーシス，ランゲルハンス細胞組織球症，リンパ脈管筋腫症，大動脈炎症候群，肺血管の先天性異常，肺動脈原発肉腫，肺血管の外圧迫などによる二次的肺高血圧症)

され，急性肺塞栓症例ではつねに本症への移行を念頭におくことが重要である[5]．平成18年度の治療給付対象者は800名で，うち520名の臨床調査個人票の解析ではわが国の症例は女性に多く(女2.8：男1)，年齢は62±13歳であった．40代以上では女性に多く，若年者では性差は認められなかった．また，深部静脈血栓症(deep vein thrombosis：DVT)の頻度は32.1%，急性肺塞栓症の既往は32.7%にすぎなかった[6]．

基礎疾患としては血液凝固異常(多くは抗リン脂質抗体症候群10～20%)，その他，心疾患，悪性腫瘍などが認められる．最近，海外ではassociated medical condition(脾摘，脳室-心房シャント，永久型中心静脈カテーテル，炎症性腸疾患，

表 1 つづき

(5) 認定基準
以下の項目をすべて満たすこと
①新規申請時
1）診断のための検査所見の右心カテーテル検査所見を満たすこと
2）診断のための検査所見の肺換気・血流シンチグラム所見を満たすこと
3）診断のための検査所見の肺動脈造影所見ないしは胸部造影 CT 所見を満たすこと
4）除外すべき疾患のすべてを除外できること
②更新時
手術例と非手術例に大別をして更新をすること
1）手術例
肺血栓内膜摘除術例においては，肺高血圧症の程度は改善していても，手術日の記載があり，更新時において肺換気・血流シンチグラム所見ないしは胸部造影 CT 所見のいずれかの所見を有すること
2）非手術例
肺血管拡張療法などの治療により，肺高血圧症の程度は新規申請時よりは軽減していても，内科的治療継続が必要な場合
a）参考とすべき検査所見の中の心臓エコー検査の所見を満たすこと
b）診断のための検査所見の肺換気・血流シンチグラム所見，胸部造影 CT 所見のいずれかを有すること
なお，肺換気・血流シンチグラムないしは胸部造影 CT 検査は，新規申請時に使用した検査と同一のものでないこと
c）除外すべき疾患のすべてを除外できること

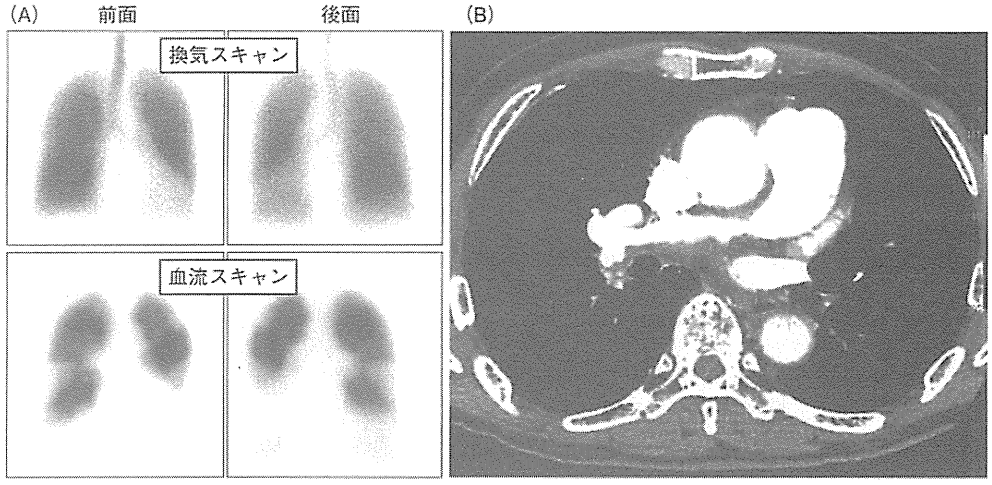


図 1 肺換気・血流スキャン(A)と造影CT(B)
A：換気に異常を認めず，区域性血流欠損を認める．
B：右肺動脈本幹に壁在血栓を認め，左下葉動脈は途絶している．

骨髄炎)や甲状腺ホルモン補充療法と本症との関連が報告され，AMC 合併例では内科治療，外科治療例ともに予後不良であることが示された[7]．また，本症の血中には溶けにくいフィブリンが存在することが報告された[8]．さらに，血栓内膜摘除標本から得られた細胞を培養すると，血小板由来増殖因子の発現が高い筋線維芽細胞様のものが分離され，増殖能が高いことも報告された[9,10]．

本症では急性肺血栓塞栓症を示唆する時期があった後，数カ月～数年の無症状期間(honeymoon period)がみられる症例もあり，この期間の肺高血圧症の進展の詳細は不明である．肺血管床は線溶能が高く，ほとんどの血栓性塞栓を処理する能力があるが，何らかの機序で処理できない場合，血栓は器質化される．血管閉塞の程度が肺高血圧症の要因として重要で，多くの症例では 40% 以上の閉塞を認めるが，肺血管の閉塞率と肺血管抵抗の相関はよいとはいえない．血栓反復，肺動

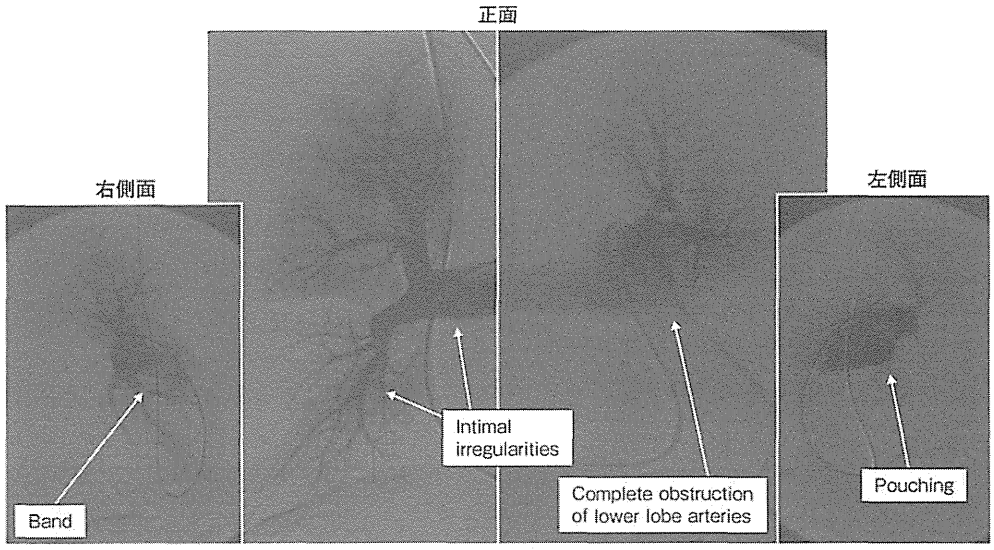


図 2　肺動脈造影

脈内での血栓の進展が関与していることも考えられており，さらに，①肺動脈性肺高血圧症でみられるような細いレベルでの血管病変，②血栓を認めない部位の増加した血流に伴う血管病変，④血栓によって閉塞した部位より，遠位における気管支動脈系との吻合を伴う血管病変など，small vessel disease の関与が示唆されている[11]．

一方，わが国においては女性に多く，DVT の頻度が低い HLA-B*5201 や HLA-DPB1*0202 と相関するタイプがみられることが報告された[12]．遺伝子マッピングの結果，DPB1*0202 ならびに，高安動脈炎の感受性遺伝子と推定される NF-κB inhibitor-like protein 1(NFKBIL1) 遺伝子プロモーターの IKBL-p*03 多型のオッズ比が高かったことから，NFKBIL1 と DPB1 が，わが国における DVT を伴わない本症の疾患感受性遺伝子である可能性が示唆されている[13]．

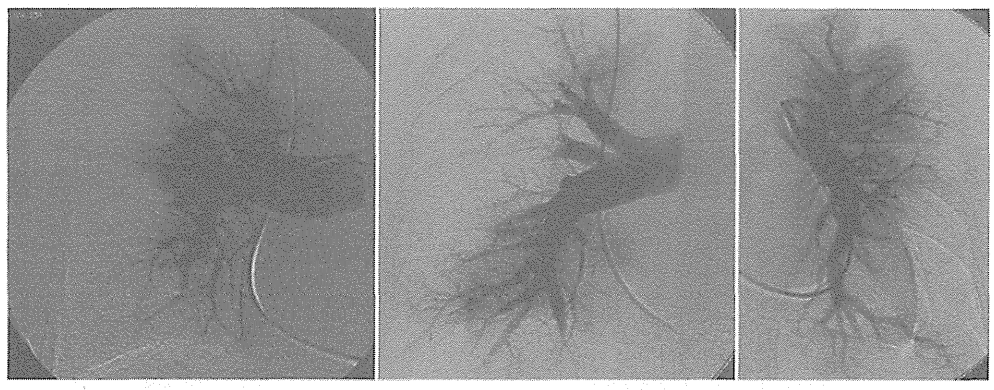
診断

労作時の息切れを主訴とする患者において本症を疑うことがもっとも重要であり，表 1 に示した症状や臨床所見を参考にしながら，動脈血ガス分析，胸部 X 線写真，心電図，心エコー検査にみられる肺高血圧症に特徴的所見の有無を検索する．その際，軽度の COPD や喘息のなかに本症が隠れている可能性を念頭におく必要がある．PAH との鑑別には肺血流スキャンが有用で，本症では区域性の血流欠損を呈し，血流スキャンが正常の場合，本症は除外される[14,15]（図 1）．確定診断は，肺動脈造影または造影 CT にて特徴的所見である①pouch defects（小袋状変化）あるいは造影 CT で

サイドメモ　CTEPHの肺動脈造影における胸膜下領域血流と手術成績の関連

CTEPH の手術成績の予後は肺動脈末梢血管病変の程度と関連することが推察されているが，その評価は難しい．肺動脈造影上毛細血管相の胸膜下領域の血流について，104 例で検討したところ，良好 75 例（すくなくとも 1 区域以上の胸膜下領域が造影される），不良もしくは無し 29 例（わずかに造影される，またはすべての領域で造影されない）に分けられた．不良もしくは無し群は平均肺動脈圧や肺血管抵抗が高く，また末梢血栓例が多いため，手術例の割合が少なかった（27.6% vs. 49.3%，$p=0.04$）．また，手術関連死（62.5% vs. 2.7%，$p<0.0001$）が多く，術後の肺血管抵抗が高値であった（656±668 vs. 319±223 dyn・s・cm^{-5}，$p=0.04$）．多変量解析においても不良もしくは無し群は，独立した手術成績不良因子であった．肺動脈造影上胸膜下領域の血流が不良な例は末梢病変の関与が大きく，手術成績が不良と報告された（図 3）[16]．

(A) 手術関連死例



(B) 生存例

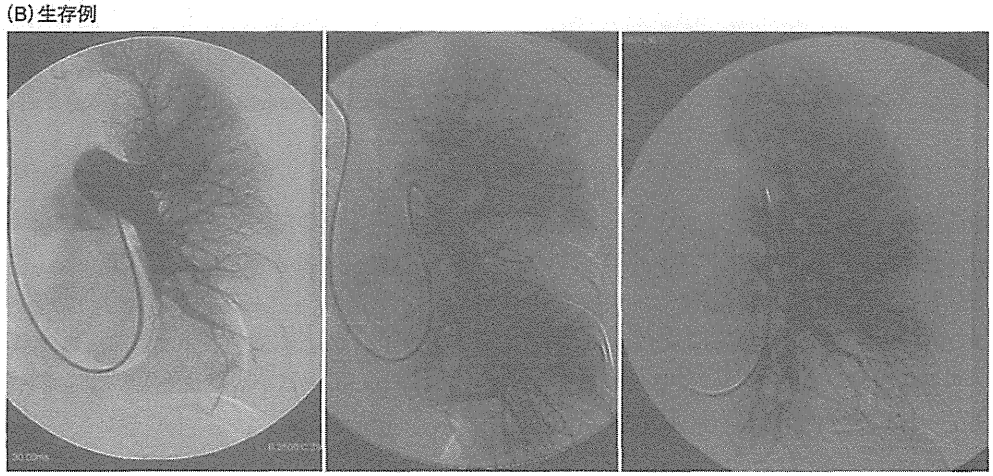


図 3　胸膜下領域血流と手術成績の関連
A：手術関連死例．胸膜下領域に血流を認めない．
B：生存例．胸膜下領域血流は良好である．

は mural defects, ②webs and bands(帯状狭窄), ③intimal irregularities, ④abrupt narrowing, ⑤complete obstruction のうちの，すくなくとも 1 つ以上を呈すること(図 2)，および右心カテーテル検査で，肺動脈圧の上昇(安静時肺動脈平均圧が 25 mmHg 以上，肺血管抵抗で 240 dyne・s・cm^{-5}以上)ならびに肺動脈楔入圧(左心房圧)が正常(15 mmHg 以下)であること，を確認する[1]．

加えて造影 CT 検査は，肺動脈区域枝レベルまでの血栓の検出と肺動脈肉腫や肺動脈炎，線維性縦隔炎などとの鑑別に有用である[14]．肺出血や肺梗塞巣の性状の評価も可能であり，非造影 CT においてもモザイクパターン(血流のある部位の肺野が高吸収領域，ない部位の肺野が低吸収領域)を呈することが本症の特徴とされる．しかし，亜区域レベルの血栓の確認や手術適応決定の際には肺動脈造影が必要とされる．最近，肺動脈造影における胸膜下領域血流と手術成績との関連についての報告もみられる[16](図 3，「サイドメモ」参照)．

治療方針

血栓再発予防と二次血栓形成予防のための抗凝固療法が第一選択となる．さらに，抗凝固療法が禁忌である場合や抗凝固療法中の再発などに対して下大静脈フィルターを挿入・留置する．本症の生命予後および QOL は，肺高血圧症の程度に大きく左右されることが知られている[2]．一般に平均肺動脈圧 30 mmHg 未満や WHO/NYHA class 2 度以下の軽症例の予後は良好とされる[17]．Class 2 以上では付着血栓の近位端が主肺動脈から区域

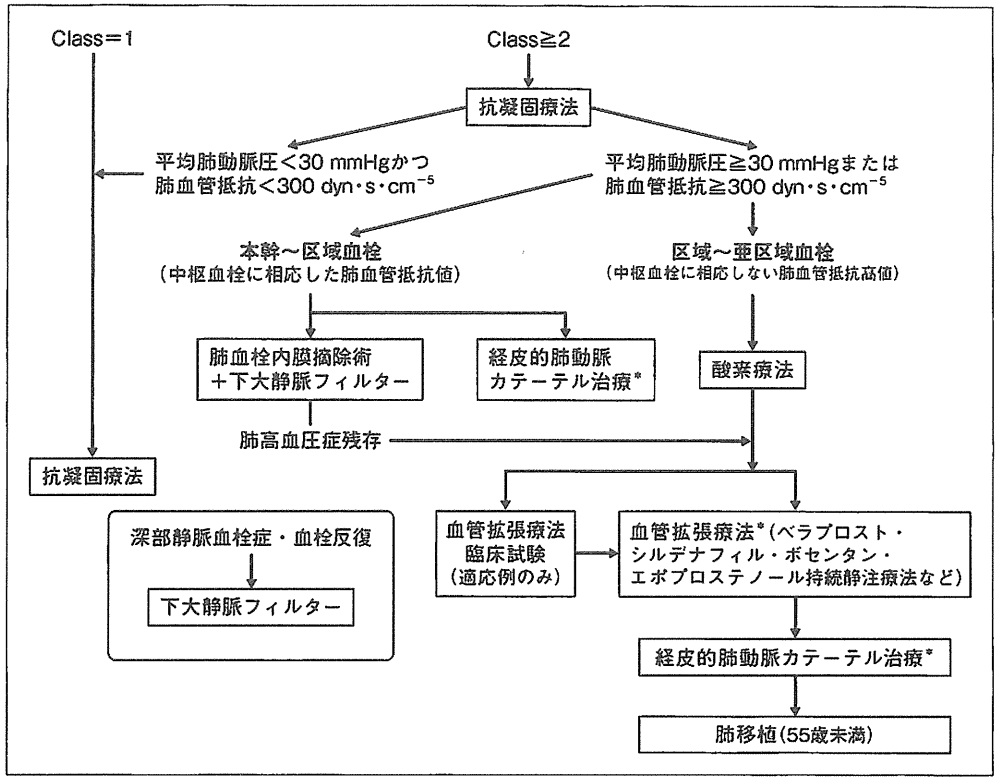


図 4　慢性血栓塞栓性肺高血圧症の治療選択指針（案）
*：評価は定まっていない．

動脈近位部にあり，中枢肺動脈血栓に相応した肺血管抵抗を示す例では外科治療が推奨される．一方，中枢血栓に相応しない著明な肺血管抵抗高値を示す，区域動脈や亜区域動脈に限局する血栓症例は手術適応外となり，肺血管拡張療法またはカテーテル治療が行われるが，その評価は定まっていない（図 4）．

内科治療

本症の内科治療として抗凝固療法，利尿薬や在宅酸素療法などの右心不全，呼吸不全に対する治療に加え，肺動脈性肺高血圧症に準じた血管拡張薬のベラプロストナトリウム，PGI_2 持続静注療法，ボセンタン，シルデナフィルなどの投与を行う場合があるが，その有用性についての明確なエビデンスはなく，研究段階である[6]．ボセンタンを用いた大規模比較試験ではボセンタン群で肺血管抵抗が改善したものの 6 分間歩行距離の改善はみられなかった[18]．

しかしイギリスの報告では，2003 年以後の内科治療例は 2001～2002 年の例に比較し予後が改善した．その原因としては 2003 年以後例の 90%が肺血管拡張薬で治療され，なかでもエンドセリン受容体拮抗薬とホスホジエステラーゼ-5（PDE-5）阻害薬の使用頻度が高いことが報告された[19]．自験例においても，2005 年以後の内科治療例の 5 年生存率は 87.8%で，以前に比べて改善がみられ，うち半数以上の例で PDE-5 阻害薬やボセンタンが使用されている．欧米のガイドラインでは中枢血栓に比べて PVR の高い例において，新規肺血管拡張薬の臨床試験参入が推奨されている[14,15]．さらに現在，グアニルシクラーゼ活性化薬や[20]，PGI_2 受容体アゴニストの臨床試験が行われている．

血管拡張療法の適応としては class 2 以上の症例で，末梢血栓例や重症例で手術を施行しない例，合併症を有したり本人が手術を希望しない例，手術後に肺高血圧症が残存する例，があげら

れる[14,15]．また，肺血管抵抗高値例において外科治療前の使用も試みられているが，その評価は定まっていない．

おわりに

慢性肺血栓塞栓症の血栓慢性化の原因はいまだ不明であるが，酸素やNOなどによる肺高血圧症の可逆性や，肺血管リモデリングの関与が示唆され，肺血管拡張療法のオフラベル使用や，臨床試験が進行中である．手術，カテーテル治療と治療選択肢も広がっている．なによりも労作時の息切れを呈する患者をみた場合，本症を見逃さないことが重要であることを強調したい．

文献/URL

1) 巽　浩一郎・他：日本呼吸器学会雑誌，**48**：551-564 2010.
2) Riedel, M. et al.: *Chest*, **81**：151-158, 1982.
3) 三重野龍彦・他：日本胸部疾患学会雑誌，**26**：448-456, 1988.
4) Fedullo, P. F. et al.: *N. Engl. J. Med.*, **345**：1465-1472, 2001.
5) Pengo, V. et al.: *N. Engl. J. Med.*, **350**：2257-2264, 2004.
6) 中野　趙・他：日本循環器学会，肺高血圧症治療ガイドライン改訂版．(http://www.j-circ.or.jp/guideline/)
7) Bonderman, D. et al.: *Circulation*, **115**：2153-2158, 2007.
8) Morris, T. A. et al.: *Am. J. Respir. Crit. Care Med.*, **173**：1270-1275, 2006.
9) Ogawa, A. et al.: *Am. J. Physiol. Lung Cell Mol. Physiol.*, **297**：L666-L676 2009.
10) Maruoka, M. et al.: *Int. J. Cardiol.*, 2011, Mar. 14.(Epub ahead of print)
11) Gallie, N. and Kim, N. H. S.: *Proc. Am. Thorac. Soc.*, **3**：571-576, 2006.
12) Tanabe, N. et al.: *Eur. Respir. J.*, **25**：131-138, 2005.
13) Kominami, S. et al.: *J. Hum. Genet.*, **54**：108-114, 2009.
14) Hoeper, M. M. et al.: *J. Am. Coll. Cardiol.*, **54** (Suppl. 1)：S85-S96, 2009.
15) Galie, N. et al.: *Eur. Respir. J.*, **34**：1219-1263, 2009.
16) Tanabe, N. et al.: Subpleural perfusion as a predictor for a poor surgical outcome in chronic thromboembolic pulmonary hypertension. *Chest*, 2011. (Epub ahead of print)
17) Yoshimi, S. et al.: *Circ. J.*, **72**：958-965, 2008.
18) Jaïs X. et al.: *J. Am. Coll. Cardiol.*, **52**：2127-2134, 2008.
19) Condliffe, R. et al.: *Am. J. Respir. Crit. Care Med.*, **177**：1122-1127, 2008.
20) Ghofrani, H. A. et al.: *Eur. Respir. J.*, **36**：792-799, 2010.

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Cellular and Molecular Biology

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

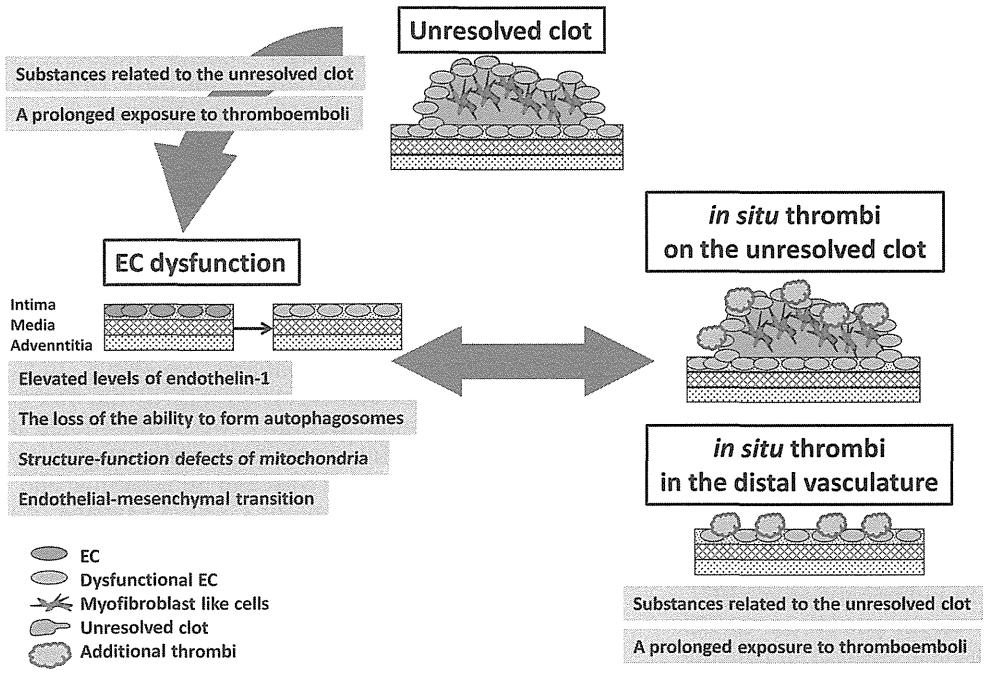

Fig. 1. Crosstalk between EC dysfunction and *in situ* thrombi in CTEPH (a hypothetical mechanism). The cells stimulated by the microenvironment created by an unresolved clot may release substances that induce EC dysfunction. The pulmonary vasculature in patients with CTEPH is subjected to prolonged 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.

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References

Ameshima S., Golpon H., Cool C.D., Chan D., Vandivier R.W., Gardai S.J., Wick M., Nemenoff R.A., Geraci M.W. and Voelkel N.F. (2003). Peroxisome proliferatoractivated receptor gamma (PPARgamma) expression is decreased in pulmonary hypertension and affects endothelial cell growth. Circ. Res. 92, 1162-1169.

Andree H.A., Stuart M.C., Hermens W.T., Reutelingsperger C.P., Hemker H.C., Frederik P.M. and Willems G.M. (1992). Clustering of lipid-bound annexin V may explain its anticoagulant effect. J. Biol. Chem. 267, 17907-17912.

Archer S.L., Gomberg-Maitland M., Maitland M.L., Rich S., Garcia J.G. and Weir E.K. (2008). Mitochondrial metabolism, redox signaling, and fusion: a mitochondria-ROS-HIF-1alpha-Kv1.5 O2-sensing pathway at the intersection of pulmonary hypertension and cancer. Am. J. Physiol. Heart. Circ. Physiol. 294, 570-578.

Arciniegas E., Ponce L., Hartt Y., Graterol A. and Carlini R.G. (2000). Intimal thickening involves transdifferentiation of embryonic endothelial cells. Anat. Rec. 258, 47-57.

Arciniegas E., Frid M.G., Douglas I.S. and Stenmark K.R. (2007). Perspectives on endothelial-to-mesenchymal transition: potential contribution to vascular remodeling in chronic pulmonary hypertension. Am. J. Physiol. Lung. Cell. Mol. Physiol. 293, L1-8.

Azarian R., Wartski M., Collignon M.A., Parent F., Herve P., Sors H. and Simonneau G. (1997). Lung perfusion scans and hemodynamics in acute and chronic pulmonary embolism. J. Nucl. Med. 38, 980-983.

Bauer M., Wilkens H., Langer F., Schneider S.O., Lausberg H. and Schafers H.J. (2002). Selective upregulation of endothelin B receptor gene expression in severe pulmonary hypertension. Circulation 105, 1034-1036.

Bonderman D., Turecek P.L., Jakowitsch J., Weltermann A., Adlbrecht C., Schneider B., Kneussl M., Rubin L.J., Kyrle P.A., Klepetko W., Maurer G. and Lang I.M. (2003). High prevalence of elevated clotting factor VIII in chronic thromboembolic pulmonary hypertension. Thromb. Haemost. 90, 372-376.

Condliffe R., Kiely D.G., Gibbs J.S, Corris P.A., Peacock A.J., Jenkins D.P., Hodgkins D., Goldsmith K., Hughes R.J., Sheares K., Tsui S.S., Armstrong I.J., Torpy C., Crackett R., Carlin C.M., Das C., Coghlan J.G. and Pepke-Zaba J. (2008). Improved outcomes in medically and surgically treated chronic thromboembolic pulmonary hypertension. Am. J. Respir. Crit. Care. Med. 177, 1122-1127.

Cool C.D., Wood K. and Voelkel N.F. (2004). Transdifferentiation of endothelial cells in primary pulmonary hypertension. Am. J. Resp. Crit. Care. Med. 167: A844.

Collen D. and Lijnen H.R. (2005). Thrombolytic agents. Thromb. Haemost. 93, 627-630.

Dartevelle P., Fadel E., Mussot S., Chapelier A., Herve P., de Perrot M., Cerrina J., Ladurie F.L., Lehouerou D., Humbert M., Sitbon O. and Simonneau G. (2004). Chronic thromboembolic pulmonary hypertension. Eur. Respir. J. 23, 637-648.

Egermayer P., Town G.I. and Peacock A.J. (1999). The role of serotonin in the pathophysiology of acute and chronic pulmonary hypertension. Thorax 54, 161-168.

Eisenberg P.R., Lucore C., Kaufman L., Sobel B.E., Jaffe A.S. and Rich S. (1990). Fibrinopeptide A levels indicative of pulmonary vascular thrombosis in patients with primary pulmonary hypertension. Circulation 82, 841-847.

Ellis C.A., Tiruppathi C., Sandoval R., Niles W.D. and Malik A.B. (1999). Time course of recovery of endothelial cell surface thrombin receptor (PAR-1) expression. Am. J. Physiol. Cell. Physiol. 276, C38-C45.

Firth A.L., Yau J., White A., Chiles P.G., Marsh J.J., Morris T.A. and Yuan J.X. (2009). Chronic exposure to fibrin and fibrinogen differentially regulates intracellular Ca2+ in human pulmonary arterial smooth muscle and endothelial cells. Am. J. Physiol. Lung Cell. Mol. Physiol. 296, L979-986.

Firth A.L., Yao W., Ogawa A., Madani M.M., Lin G.Y. and Yuan J.X. (2010). Multipotent mesenchymal progenitor cells are present in endaretectomized tissues from patients with chronic thromboembolic pulmonary hypertension. Am. J. Physiol. Cell. Physiol. 298, C1217-C1225.

Funakoshi T., Heimark R.L., Hendrickson L.E., McMullen B.A. and Fujikawa K. (1987). Human placental anticoagulant protein: isolation and characterization. Biochemistry 26, 5572-5578.

Hoeper M.M., Mayer E., Simonneau G. and Rubin L. (2006). Chronic thromboembolic pulmonary hypertension. Circulation 113, 2011-2020.

Humbert M., Morrell N.W., Archer S.L., Stenmark K.R., MacLean M.R., Lang I.M., Christman B.W., Weir E.K., Eickelberg O., Voelkel N.F. and Rabinovitch M. (2004). Cellular and molecular pathobiology of pulmonary arterial hypertension. J. Am. Coll. Cardiol. 43, 13S-24S.

Jamieson S.W., Kapelanski D.P., Sakakibara N., Manecke G.R., Thistlethwaite P.A., Kerr K.M., Channick R.N., Fedullo P.F. and Auger W.R. (2003). Pulmonary endarterectomy: experience and lessons learned in 1,500 cases. Ann. Thorac. Surg. 76, 1457-1462.

Kimura H., Okada O., Tanabe N., Tanaka Y., Terai M., Takiguchi Y., Masuda M., Nakajima N., Hiroshima K., Inadera H., Matsushima K. and Kuriyama T. (2001). Plasma monocyte chemoattractant protein-1 and pulmonary vascular resistance in chronic thromboembolic pulmonary hypertension. Am. J. Respir. Crit. Care. Med. 164, 319-324.

Klepetko W., Mayer E., Sandoval J., Trulock E.P., Vachiery J.L., Dartevelle P., Pepke-Zaba J., Jamieson S.W., Lang I. and Corris P. (2004). Interventional and surgical modalities of treatment for pulmonary arterial hypertension. J. Am. Coll. Cardiol. 43 (suppl S), 73S-80S.

Lang I.M., Marsh J.J., Olman M.A., Moser K.M., Loskutoff D.J. and

Schleef R.R. (1994a). Expression of type 1 plasminogen activator inhibitor in chronic pulmonary thromboemboli. Circulation 89, 2715-2721.

Lang I.M., Marsh J.J., Olman M.A., Moser K.M. and Schleef R.R. (1994b). Parallel analysis of tissue-type plasminogen activator and type-1 plasminogen activator inhibitor in plasma and endothelial cells derived from patients with chronic pulmonary thromboemboli. Circulation 90, 706-712.

Majesky M.W. and Schwartz S.M. (1997). An origin for smooth muscle cells from endothelium? Circ. Res. 80, 601-603.

Maruoka M., Sakao S., Kantake M., Tanabe N., Kasahara Y., Kurosu K., Takiguchi Y., Masuda M., Yoshino I., Voelkel N.F. and Tatsumi K. (2012). Characterization of myofibroblasts in chronic thromboembolic pulmonary hypertension. Int. J. Cardiol. 159, 119-127.

Masri F.A., Xu W., Comhair S.A., Asosingh K., Koo M., Vasanji A., Drazba J., Anand-Apte B. and Erzurum S.C. (2007). Hyperproliferative apoptosis-resistant endothelial cells in idiopathic pulmonary arterial hypertension. Am. J. Physiol. Lung. Cell. Mol. Physiol. 293, L548-L554.

Matsuda M. and Sugo T. (2002). Structure and function of human fibrinogen inferred from dysfibrinogens. Int. J. Hematol. 76, 352-360.

Moncada S., Palmer R.M. and Higgs E.A. (1991). Nitric oxide: physiology, pathophysiology, and pharmacology. Pharmacol. Rev. 43, 109-142.

Morris T.A., Marsh J.J., Chiles P.G., Auger W.R., Fedullo P.F. and Woods V.L. Jr (2006). Fibrin derived from patients with chronic thromboembolic pulmonary hypertension is resistant to lysis. Am. J. Respir. Crit. Care. Med. 173, 1270-1275.

Morris T.A., Marsh J.J., Chiles P.G., Kim N.H., Noskovack K.J., Magana M.M., Gruppo R.A. and Woods V.L. Jr (2007). Abnormally sialylated fibrinogen gamma-chains in a patient with chronic thromboembolic pulmonary hypertension. Thromb. Res. 119, 257-259.

Moser K.M. and Bloor C.M. (1993). Pulmonary vascular lesions occurring in patients with chronic major vessel thromboembolic pulmonary hypertension. Chest 103, 685-692.

Peacock A., Simonneau G. and Rubin L. (2006). Controversies, uncertainties and future research on the treatment of chronic thromboembolic pulmonary hypertension. Proc. Am. Thorac. Soc. 3, 608-614.

Pi X., Yan C. and Berk B.C. (2004). Big mitogen-activated protein kinase (BMK1)/ERK5 protects endothelial cells from apoptosis. Circ. Res. 94, 362-9.

Piazza G. and Goldhaber S.Z. (2011). Chronic thromboembolic pulmonary hypertension. N. Engl. J. Med. 364, 351-360.

Reesink H.J., Lutter R., Kloek J.J., Jansen H.M. and Bresser P. (2004). Hemodynamic correlates of endothelin-1 in chronic thromboembolic pulmonary hypertension. Eur. Respir. J. 24, 110s.

Reesink H.J., Meijer R.C., Lutter R., Boomsma F., Jansen H.M., Kloek J.J. and Bresser P. (2006). Hemodynamic and clinical correlates of endothelin-1 in chronic thromboembolic pulmonary hypertension. Circ. J. 70, 1058-1063.

Robin E.D., Cross C.E., Kroetz F., Totten R.S. and Bron K. (1966). Pulmonary hypertension and unilateral pleural constriction with speculation on pulmonary vasoconstrictive substance. Arch. Intern. Med. 118, 391-400.

Sakamaki F., Kyotani S., Nagaya N., Sato N., Oya H. and Nakanishi N. (2003). Increase in thrombomodulin concentrations after pulmonary thromboendarterectomy in chronic thromboembolic pulmonary hypertension. Chest 124, 1305-1311.

Sakao S., Taraseviciene-Stewart L., Cool C.D., Tada Y., Kasahara Y., Kurosu K., Tanabe N., Takiguchi Y., Tatsumi K., Kuriyama T. and Voelkel N.F. (2007). VEGF-R blockade causes endothelial cell apoptosis, expansion of surviving CD34+ precursor cells and transdifferentiation to smooth muscle-like and neuronal-like cells. FASEB J. 21, 3640-3652.

Sakao S., Taraseviciene-Stewart L., Lee J.D., Wood K., Cool C.D. and Voelkel N.F. (2005). Initial apoptosis is followed by increased proliferation of apoptosis-resistant endothelial cells. FASEB J. 19, 1178-1180.

Sakao S., Tatsumi K. and Voelkel N.F. (2009). Endothelial cells and pulmonary arterial hypertension: apoptosis, proliferation, interaction and transdifferentiation. Respir. Res. 10, 95.

Sakao S., Tatsumi K. and Voelkel N.F. (2010). Reversible or irreversible remodeling in pulmonary arterial hypertension. Am. J. Respir. Cell. Mol. Biol. 43, 629-634.

Sakao S., Hao H., Tanabe N., Kasahara Y., Kurosu K. and Tatsumi K. (2011). Endothelial-like cells in chronic thromboembolic pulmonary hypertension: crosstalk with myofibroblast-like cells. Respir. Res. 12, 109.

Seyfarth H.J., Halank M., Wilkens H., Schäfers H.J., Ewert R., Riedel M., Schuster E., Pankau H., Hammerschmidt S. and Wirtz H. (2010). Standard PAH therapy improves long term survival in CTEPH patients. Clin. Res. Cardiol. 99, 553-556.

Shure D. (1996). Thrombendartectomy: some unanswered questions. Ann. Thorac. Surg. 62, 1253-1254.

Skoro-Sajer N., Hack N., Sadushi-Koliçi R., Bonderman D., Jakowitsch J., Klepetko W., Hoda M.A., Kneussl M..P, Fedullo P. and Lang I.M. (2009). Pulmonary vascular reactivity and prognosis in patients with chronic thromboembolic pulmonary hypertension: a pilot study. Circulation 119, 298-305.

Sofia M., Faraone S., Alifano M., Micco A., Albisinni R., Maniscalco M. and Di Minno G. (1997). Endothelin abnormalities in patients with pulmonary embolism. Chest 111, 544-549.

Suntharalingam J., Goldsmith K., van Marion V., Long L., Treacy C.M., Dudbridge F., Toshner M.R., Pepke-Zaba J., Eikenboom J.C. and Morrell N.W. (2008). Fibrinogen AThr312Ala polymorphism is associated with chronic thromboembolic pulmonary hypertension. Eur. Respir. J. 31, 736-741.

Tait J.F., Sakata M., McMullen B.A., Miao C.H., Funakoshi T., Hendrickson L.E. and Fujikawa K. (1988). Placental anticoagulant proteins: isolation and comparative characterization four members of the lipocortin family. Biochemistry 27, 6268-6276.

Tanabe N., Sugiura T., Jujo T., Sakao S., Kasahara Y., Kato H., Masuda M. and Tatsumi K. (2012). Subpleural perfusion as a predictor for a poor surgical outcome in chronic thromboembolic pulmonary hypertension. Chest 14, 929-934.

Taraseviciene-Stewart L., Kasahara Y., Alger L., Hirth P., Mc Mahon G., Waltenberger J., Voelkel N.F. and Tuder R.M. (2001). Inhibition of the VEGF receptor 2 combined with chronic hypoxia causes cell death-dependent pulmonary endothelial cell proliferation and severe pulmonary hypertension. FASEB J. 15, 427-438.

Torbicki A., Perrier A., Konstantinides S., Agnelli G., Galiè N., Pruszczyk P., Bengel F., Brady A.J., Ferreira D., Janssens U., Klepetko W., Mayer E., Remy-Jardin M. and Bassand J.P. (2008). ESC Committee for Practice Guidelines (CPG). Guidelines on the diagnosis and management of acute pulmonary embolism: the Task

Force for the Diagnosis and Management of Acute Pulmonary Embolism of the European Society of Cardiology (ESC). Eur. Heart J. 29, 2276-2315.

Ulrich S., Fischler M., Speich R., Popov V. and Maggiorini M. (2006). Chronic thromboembolic and pulmonary arterial hypertension share acute vasoreactivity properties. Chest 130, 841-846.

Voges D., Berendes R., Burger A., Demange P., Baumeister W. and Huber R. (1994). Three-dimensional structure of membrane-bound annexin V. A correlative electron microscopy-X-ray crystallography study. J. Mol. Biol. 238, 199-213.

Welsh C.H., Hassell K.L., Badesch D.B., Kressin D.C. and Marlar R.A. (1996). Coagulation and fibrinolytic profiles in patients with severe pulmonary hypertension. Chest 110, 710-717.

Wolf M., Boyer-Neumann C., Parent F., Eschwege V., Jaillet H., Meyer D. and Simonneau G. (2000). Thrombotic risk factors in pulmonary hypertension. Eur. Respir. J. 15, 395-399.

Yao W., Firth A.L., Sacks R.S., Ogawa A., Auger W.R., Fedullo P.F., Madani M.M., Lin G.Y., Sakakibara N., Thistlethwaite P.A., Jamieson S.W., Rubin L.J. and Yuan J.X. (2009). Identification of putative endothelial progenitor cells (CD34+CD133+Flk-1+) in endarterectomized tissue of patients with chronic thromboembolic pulmonary hypertension. Am. J. Physiol. Lung. Cell. Mol. Physiol. 296, L870-878.

Yi E.S., Kim H., Ahn H., Strother J., Morris T., Masliah E., Hansen L.A., Park K. and Friedman P.J. (2000). Distribution of obstructive intimal lesions and their cellular phenotypes in chronic pulmonary hypertension: a morphometric and immunohistochemical study. Am. J. Respir. Crit. Care. Med. 162, 1577-1586.

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特集　肺高血圧症 ―日本から何が発信できるか

最近のトピックス

肺動脈性肺高血圧症と慢性血栓塞栓性肺高血圧症の狭間で：血管内皮細胞障害の観点から

千葉大学大学院医学研究院呼吸器内科学
坂尾誠一郎　*Sakao Seiichiro*

KEY WORD
特発性肺動脈性肺高血圧症，慢性血栓塞栓性肺高血圧症，
肺末梢血管障害，肺動脈血管内皮細胞

はじめに

特発性肺動脈性肺高血圧症(IPAH)の血管病変には，障害を受けた血管内皮細胞が関与するとの報告がある。一般的には，何らかの因子により肺動脈血管内皮細胞に障害が生じると，血管収縮因子と血管拡張因子，さらに細胞増殖因子と細胞増殖抑制因子のバランスが失われ，結果として内皮細胞の増殖，平滑筋細胞の増殖，血管収縮，閉塞性線維化，フィブリノイド壊死，叢状病変(plexiform lesion)などが形成され，病態が成立すると考えられる。そして，内皮細胞障害は同細胞の凝固線溶系調節機能にも異常を来たし，線溶系機能低下は*in situ*血栓を誘導し，病態をさらに悪化させる。さらにこれらの血管内皮細胞は高増殖能を有し，アポトーシス抵抗性であることも示されている。

近年，慢性血栓塞栓性肺高血圧症(CTEPH)の病態は器質化血栓による肺動脈中枢部の閉塞のみではなく，末梢血管障害の進展が長期経過に影響するとの報告がある。またわれわれの知見も含め，同疾患の末梢血管障害は病理学的にIPAHの血管障害に類似することが報告されている。さらに，CTEPH患者の中枢血栓組織には筋線維芽細胞が散在することが示され，われわれもまた同細胞および内皮様細胞の存在を示している。また内皮様細胞には，*in vitro*で内皮細胞と平滑筋細胞両細胞の特徴を有する移行細胞が存在することが示され，*in vivo*においても摘出血栓内に同様な移行細胞が存在することが確認された。また血栓から分離した血管内皮様細胞には，オートファジーの抑制，ミトコンドリアやSOD2の分布異常が存在した。以上のように，CTEPHにおいても中枢血管における内皮細胞障害が示された。

CTEPHにおいて，血管内皮細胞障害が実際に病態成立に関与するかはいまだ明らかではない。しかし，機能障害を示す内皮細胞が中枢肺動脈に存在することが示された。IPAHの病態主座は末梢肺動脈であり，CTEPHは中枢および末梢肺動脈である。CTEPHに存在する末梢肺動脈病変成を，併存する中枢動脈病変との関連から解明することは，IPAHの末梢病変にも共通する新たな知見の解明につながるかもしれない。今回は，両疾患における病態機序を『内皮細胞障害』の観点からレビューしたい。

■IPAHの肺動脈リモデリングは，内膜・中膜・外膜の三層からなる血管壁の肥厚と筋性化により特徴づけられる。
■血管内皮細胞障害が，肺動脈リモデリング進展のトリガーとなる可能性がある。

IPAHにおける肺動脈リモデリング

一般的に，肺動脈リモデリングは内膜，中膜，外膜の三層からなる血管壁の肥厚により特徴づけられる。これらの変化は各層を構成する細胞（内皮細胞，平滑筋細胞，線維芽細胞）の肥大や増殖，およびコラーゲン線維などを含む細胞外マトリックスの沈着により生じる[1]。また，平滑筋細胞が本来存在しない末梢血管に進展していく“muscularization（筋性化）”も重要なリモデリングである。これらの変化はおそらく，血管周囲細胞に含まれる前駆細胞[2]，外膜線維芽細胞，循環する間葉系幹細胞[3]などの平滑筋細胞への分化，あるいは内皮間葉転換（endothelial mesenchymal transition：EnMT）[4]などの関与が示唆されている。

ここで肺動脈リモデリングを内皮細胞障害の観点から考察する。何らかの因子により血管内皮細胞に障害が生じると，血管収縮因子と血管拡張因子，さらに細胞増殖因子と細胞増殖抑制因子のバランスが失われ，トロンボキサン，エンドセリン，セロトニンなどの血管収縮と細胞増殖能を有する因子が優勢となる。また一酸化窒素，プロスタサイクリンなど血管拡張と細胞増殖抑制能を有する因子は低下し，結果として内皮細胞の増殖，平滑筋細胞の増殖，血管収縮，閉塞性線維化，フィブリノイド壊死，plexiform lesionなどが形成され，その結果として肺動脈リモデリングが成立すると考えられる[5]。

さらに，内皮細胞は血液の凝固線溶系の調節に重要な役割をもつ。たとえば，内皮細胞から放出される一酸化窒素やプロスタサイクリンは血小板病週抑制能をもち，血管内における血栓形成を抑制する[6]。さらに凝固系においてフィブリノーゲンからフィブリンへの変化を阻害するTM（トロンボモジュリン）や線溶系においてプラスミノーゲンを活性化するt-PA（plasminogen activator）の発現も内皮細胞により調節される。一方で，t-PAの阻害作用をもつPAI（plasminogen activator inhibitor）-1も放出し，内皮細胞は凝固線溶系の重要な調整機能を担っている。しかし，これらの内皮細胞に障害が生じると凝固線溶系のバランスが崩れ，凝固系の亢進または線溶系の低下により*in situ*血栓を誘導する。IPAHにおいてこれらの血栓は病態をさらに悪化させる。

IPAHにおける内皮細胞増殖の機序：基礎実験から

肺動脈性肺高血圧症（PAH）の病理所見として特徴的なplexiform lesionではVEGF（vascular endothelial growth factor），VEGFR-2，HIF-1（Hypoxia Inducible Factor 1）など血管内皮新生（neointima）と関連した因子の発現が増加している[7]。これらの結果をもとに，Taraseviciene-Stewartらは長期低酸素環境下のラットにVEGF受容体阻害剤（SU5416）を投与し，PAHモデルを作成した。同モデルは内皮細胞増殖による肺動脈閉塞が主病態であり，初期には内皮細胞のアポトーシスが観察された。また初期アポトーシスを阻害すると，肺高血圧症の発症を抑制することが示された[8]。以上より，同モデルにおける内皮細胞増殖は，アポトーシスとそれに続くアポトーシス抵抗性細胞の増殖の結果ではないかと推論された。

上記仮説を証明するために，*in vitro*においてSU5416やずり応力（shear stress）がどのように細胞に影響を与えるか，アポトーシス，増殖，形質変化の観点から末梢血管障害成立機序解明を試みた。CELLMAX人工血管モデルを導入し，pulsatile shear stress下でSU5416が肺毛細血管内皮細胞にどのような影響を与えるかを調べたところ，フローサイトメトリー解析や免疫染色にて初期アポトーシス細胞とそれに続くアポトーシス抵抗性の高増殖能細胞の出現を証明した。つまり，内皮細胞の初期アポトーシスはその後の細胞形質変化に重要な役割をもち，それらアポトーシス細胞からおそらく何らかの増殖因子様物質が放出された結果，残存細胞にアポトーシス抵抗性の増殖能力の高い細胞への形質変化を誘導したと考えた[9]。さらにこ