わが国において近年急速に普及している肺動脈バルーン拡張術（BPA）とどのように組み合わせていくかが今後の検討課題である．血行動態が悪い患者ほどBPAの合併症も起こりやすいことを考えると，末梢型CTEPHもしくは外科的治療後に残存・再発したCTEPH患者に対してBPAを考慮する場合には，まずriociguatを導入して血行動態を改善させた後にBPAを行うことが，治療の安全性を高めてよりよい治療効果を得るためによいのではないかと筆者は考える．

著者のCOI（conflicts of interest）開示：本論文発表内容に関連して特に申告なし

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研究

肺動脈性肺高血圧症治療における診療実態調査*

波多野　将[1]　藤山　直人[2]　中島　康夫　早田　悟

要旨　肺動脈性肺高血圧症(PAH)の治療においては，血行動態の改善を見極めることが重要であるが，実施率は不明である．臨床現場において実施されている各種検査および治療実態についてインターネットを介したアンケート調査を行った．心臓超音波の実施率はいずれの治療経過でも9割以上と高かった．右心カテーテルは治療方針決定までは6割以上の実施率であったが，治療段階が進むにつれ3～4割程度に低下した．各検査の重要度について，心臓超音波は診断からフォローアップまでのいずれの経過においても重要であるとの回答が6割以上を占めたが，右心カテーテルは，治療段階が進むにつれて重要であるとの回答に減少傾向がみられた．仮想症例における治療方針について，重症例には経口薬を3剤併用するとの回答が14%あった．今後，医療現場での実情なども加味し，各治療段階で必要な検査を行い治療選択をすることはPAH診療において重要である．

Key word　肺動脈性肺高血圧症，血行動態，臨床調査

肺動脈性肺高血圧症(pulmonary arterial hypertension；PAH)は，進行性の疾患であり予後が不良な難治性の稀少疾患である．病態の特徴として肺動脈圧および肺血管抵抗が上昇する．病態の進行により致死的な状況を来す場合も多く，D'Alonzoらによると1980年代には無治療例における余命中央値は2.8年，5年生存率は34%[1]とされていた．近年，PAHに対する診断技術の発達や治療薬の開発も進んだことから，Benzaらによる2012年の報告では5年生存率が57～65%まで改善してきている[2]．

本邦においてPAHは国の難病指定を受けており，難病申請をする際にはこの確定診断に用いられるべき検査として，右心カテーテル，肺血流シンチグラフィが必須とされており，参考とすべき検査として心臓超音波，胸部X線像，心電図がある．これらの検査のなかでも右心カテーテルや心臓超音波は血行動態を把握するために利用されている．Hoeperらは治療目標として臨床的に安定であることに加え，WHO機能分類Ⅱ度，6分間歩行距離400～500 m以上，右房圧と心係数が正常であることを提唱している[3]．一般に肺血管病変は，肺動脈圧の上昇，心係数の低下，右房圧の上昇の順で進行すると考えられているが，治療による改善は進行の順とは逆に，右房圧の低下に次いで心係数が改善する場合が多く，さらに治療効果が得られることで肺動脈圧が低下すると考えられるため，心係数が正常化していることだけでなく肺動脈圧の低下までを目指すことが，この疾患の治療目標である[4]．このような観点から，診断時に限らず，治療開始後も血行動態の改善を見極めることが必要ではないかと考えた．われわれは，臨床現場において実施されている各種検査および診療，特に心肺血行動態に関わる検査に注目し，

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本邦におけるPAH診療の実態を明らかにするためにインターネットを介した調査を実施した.

調査方法

1. 対象

PAHを治療した経験のある医師を対象とし,条件として,最近1年間にアンブリセンタン,ボセンタン,シルデナフィル,タダラフィルの4剤のうちいずれか1剤以上をPAH治療に用いた医師とした.

調査協力を依頼した診療科は循環器内科,呼吸器内科,小児科,リウマチ・膠原病科,一般内科とした.

2. 調査方法および調査期間

2013年1月16日～1月23日を調査期間とし,アンケート調査を実施した.なお,実際の調査では調査開始から2～3日間で全回収のうち80～90%が回答され,残りの日数では少数例の回答であった.調査は市場調査会社を通じてインターネット上に調査用ホームページを作成し,医師が自ら回答した.また,情報収集および解析業務はすべて市場調査会社が行った.

3. 調査の項目と内容

1) 検査状況

PAHの診療に必要と考えられる血液検査,6分間歩行距離,心臓超音波,右心カテーテル,呼吸機能検査,心電図,胸部X線,胸部CT・MRI,肺血流シンチグラフィの実施状況を把握するために,治療段階を「鑑別・確定診断」時,「治療方針決定」時,「治療開始後の初回効果判定」時,「フォローアップ」時の4段階に設定し,各段階における検査の実施の有無について質問した.胸部X線,胸部CT・MRI,肺血流シンチグラフィは鑑別・確定診断時のみの調査とした.

2) 重要度と実施困難な理由

医師からみた各検査項目についての重要度を,「重要である」,「やや重要である」,「どちらとも言えない」,「あまり重要でない」,「重要でない」の5段階で質問した.さらに,重要と考えながら実施できていない検査項目についてはその理由を,「院内に検査設備がない」,「院内で実施できる人がいない」,「患者が拒否をする」,「非常に手間がかかる」,「検査を依頼できる施設がない」,「その他」で質問した.「その他」については自由記載で質問した.

3) 検査担当者

各検査を実施する担当者を「医師自身」,「院内の他科の医師」,「院内の技師」,「他の病院」,「その他」,「実施していない」の6項目で質問した.

4) 紹介経験

他の専門機関への紹介経験の有無について質問し,専門医への紹介を判断するために必要と考える検査項目を質問した.

5) 治療方針

各医師の薬物療法に関する方針を確認するため,2例の仮想PAH症例の検査値を提示し質問した.

①未治療の特発性PAH患者,40歳女性,平均肺動脈圧=60 mmHg,心係数=1.6 *l*/min/m^2,肺動脈楔入圧=8 mmHg,6分間歩行距離=250 m

②未治療の特発性PAH患者,40歳女性,平均肺動脈圧=39 mmHg,心係数=2.4 *l*/min/m^2,肺動脈楔入圧=8 mmHg,6分間歩行距離=460 m

さらに,各症例において初回効果判定までの薬物治療の期間を知る目的で,初回効果判定までの期間を質問した.

4. プライバシー保護

本調査の実施に際しては,無記名の調査とした.

調査結果

1. 調査対象

全国から630名に依頼し,計272名(43.2%)の医師から回答が得られた.調査対象医師属性および勤務施設の経営形態を図1に示した.診療科の内訳は循環器内科124名(45.6%),呼吸器内科65名(23.9%),リウマチ・膠原病科29名(10.7%),小児科38名(14.0%),一般内科16名(5.9%)であった.

2. 各検査の実施状況

各検査の実施状況を治療段階毎に集計し図2に示した.

右心カテーテルと呼吸機能検査は,「鑑別・確

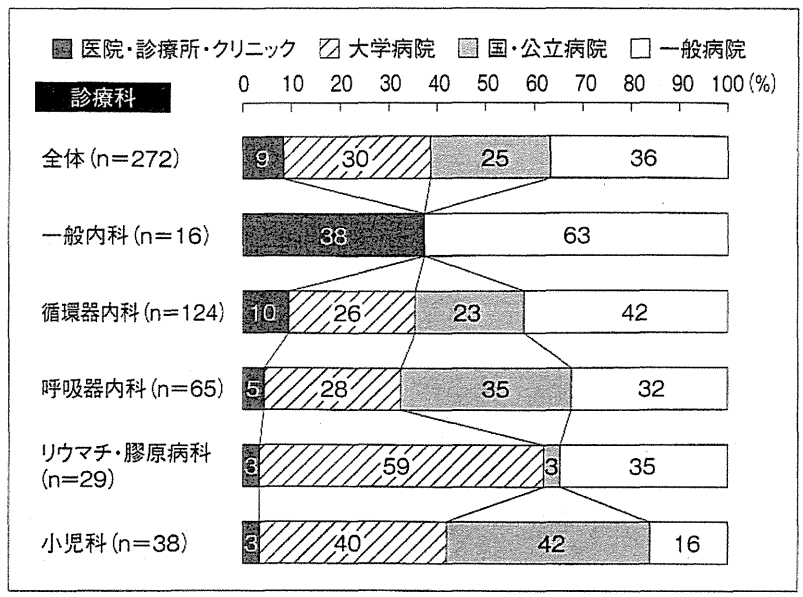

図1　調査対象医師属性および勤務施設の経営形態

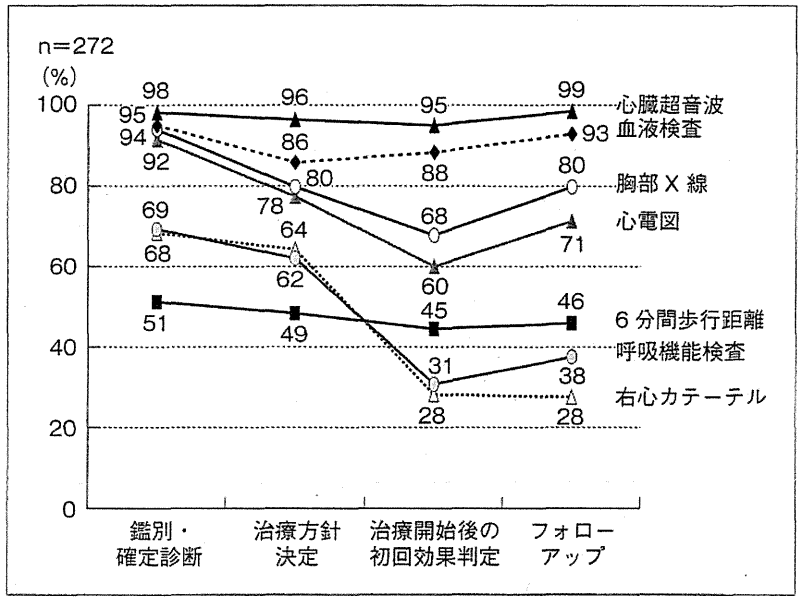

図2　治療段階毎における各検査実施状況

定診断」時ならびに「治療方針決定」時で双方とも68%，64%および69%，62%と6割以上の実施率であったが，「治療開始後の初回効果判定」時や「フォローアップ」時にはそれぞれ28%，28%および，31%，38%と3〜4割と低下していた．一方，心臓超音波と血液検査の実施率はいずれの時点においても非常に高く，心臓超音波で98%，96%，95%，99%，血液検査で95%，86%，88%，93%と約9割以上であった．6分間歩行距離検査の実施率はいずれの段階においても51%，49%，45%，46%と5割程度であった．心電図や胸部X線の実施率は4つの治療段階により変化が見られず，高い実施状況であった．鑑別・確定診断時における胸部CT・MRIおよび肺血流シンチグラフィの実施率はそれぞれ51%，74%であった．

フォローアップ時に実施する検査の頻度を図3に示したが，3カ月以内に実施される検査として，血液検査が93%と最も頻度が高く，右心カテーテルは5%と最も実施頻度が低かった．

3. 各検査の重視度

治療段階に応じた各検査の重視度を図4aに集計した．

心臓超音波はいずれの段階においても重要であ

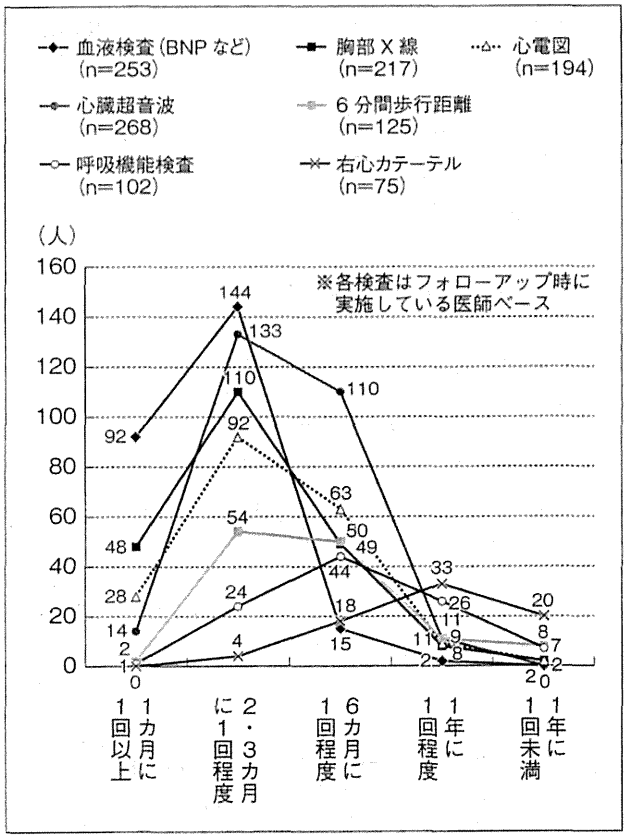

図3　フォローアップ時に実施する各検査の頻度

ると回答する医師が約7割を占めていた．右心カテーテルは治療段階が進むにつれて69%，46%，34%と重視度が減少する傾向があり，逆に6分間歩行距離は24%，31%，35%と増加する傾向がみられた．血液検査が重要であると回答した医師は「治療方針決定」時や「治療開始後の初回効果判定」時でそれぞれ35%，36%であったが，「フォローアップ」時は43%であった．呼吸機能検査，心電図検査，胸部X線検査は「治療方針決定」時には高かったが，「治療開始後の初回効果判定」時に一旦下がり，「フォローアップ」時で再度高くなっていた．

「やや重要である」，「重要である」との回答のなかでさらに実際に臨床で実施しているか否かを，治療段階毎に分類集計し**図4b**に示した．右心カテーテルは重視しているが検査は非実施と回答した医師の割合を治療段階別にみると，それぞれ「治療方針決定」時で31%，「治療開始後の初回効果判定」時で51%，「フォローアップ」時で45%であり，6分間歩行距離検査をはじめとした他の検査に比べ最も実施率が悪かった．心臓超音波と血液検査では重視はしているが検査を行っていない医師は，10%未満であった．呼吸機能検査については治療方針決定時には重要と考え実施している医師が53%であったが，それ以降は20%台であった．心電図検査，胸部X線検査はいずれの治療段階においても重要だが検査非実施と回答した医師は少なかった．

4. 重視しているが検査を実施できていない理由

図4bにおいて「治療方針決定」時，「治療開始後の初回効果判定」時，「フォローアップ」時の治療段階において検査を重視しているが検査を実施できていない医師の割合が15%以上の検査について実施できていない理由を**図5**に示す．

右心カテーテルは「手間がかかる」「院内に検査設備がない」などの理由が多くみられた．その他の回答では，「他院，他科に依頼する」という理由が挙げられ，この点は特徴的であった．また，治療開始後の初回効果判定時やフォローアップ時には「侵襲的である」，「心臓超音波で代用する」といった回答がみられた．6分間歩行距離検査ではいずれの段階においても，5割以上の医師が「非常に手間がかかる」ために実施しないと回答した．その他の回答では「鑑別診断に必要ないため」，「小児であるため」などの理由が鑑別・確定診断時に散見された．呼吸機能検査を行わない理由は「手間がかかる」が多数回答され，その他には「臨床上は必須ではない」，「有用性を感じない」といった回答が多かった．

5. 検査の実施担当者

右心カテーテルや心臓超音波の場合，調査回答医師自身が実施するとした回答はそれぞれ46%，29%であった．心臓超音波においては院内の技師による実施が56%であった．右心カテーテルの実施担当者を全診療科でみると，46%が医師自身，33%が院内の他科の医師であり，10%が他の病院だった．また，科別でみると循環器内科で医師自身が77%と多かったものの，呼吸器内科では15%，一方，リウマチ・膠原病科は医師自身による実施はないとの回答であった．

6. 他施設への紹介時の検査

他の専門施設への紹介経験と紹介前に実施する

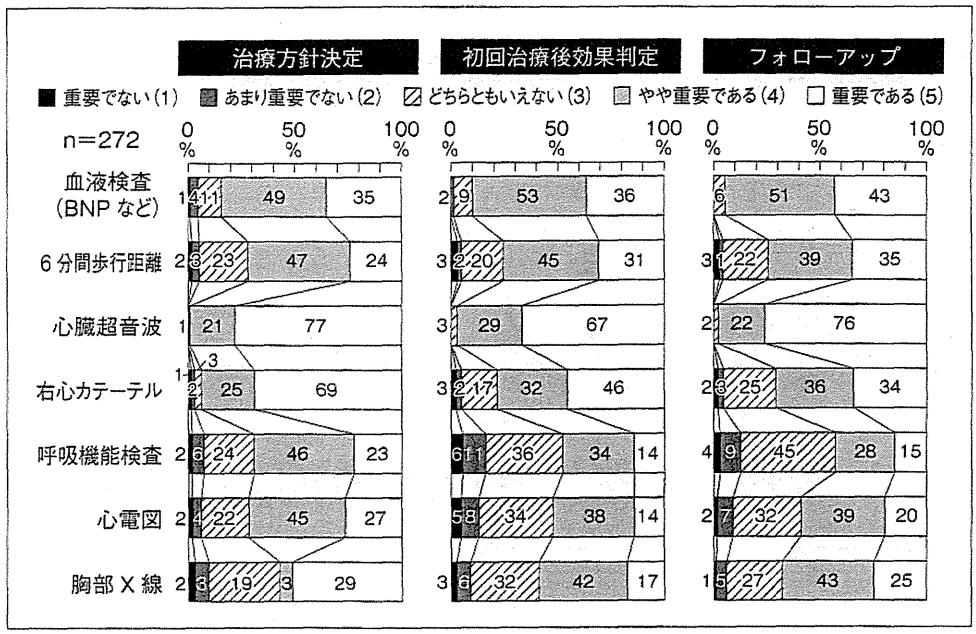

図 4a　各検査の重視度

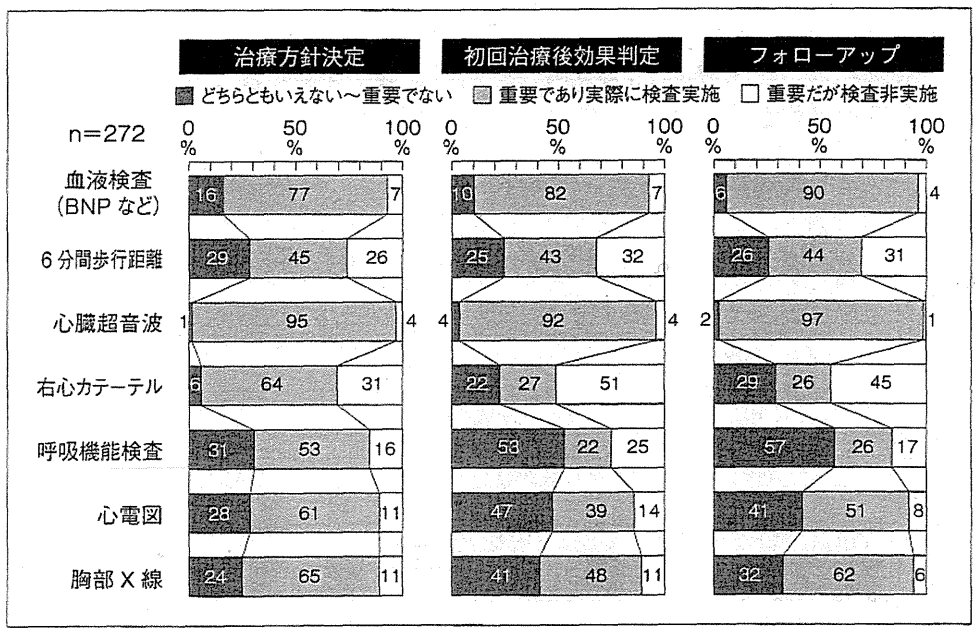

図 4b　検査を重視しているが臨床では実施していない医師の割合

検査については約半数の医師がPAH患者を他の専門施設に紹介した経験があり，その際に実施する検査として，心臓超音波が96%と最も多く，胸部X線92%，心電図90%，BNP/NT-ProBNP 88%と続いた．約8割の医師が，他の専門施設にPAH患者を紹介する理由として「症状が重篤で自施設での治療に限界があったため」と回答した．「静注用PGI2を導入するため」と回答した医師は25%であった．

7. 各医師の治療法

2つの仮想症例に対し各医師が選択した処方薬を集計し**図 6a** に示した．

症例①の場合，「ホスホジエステラーゼ5(PDE5)阻害薬単剤(20%)」「エンドセリン受容体拮抗薬(ERA)単剤(19%)」，「ERA＋PDE5阻害薬(15%)」，「経口3剤併用(14%)」の回答が得られ，単剤のみならず併用療法の選択も回答された．

症例②の場合，「経口プロスタサイクリン(PGI2)単剤(23%)」，「ERA単剤(23%)」，「PDE5阻害薬単剤(20%)」の回答が得られ，単剤を選択する医師が多かった．

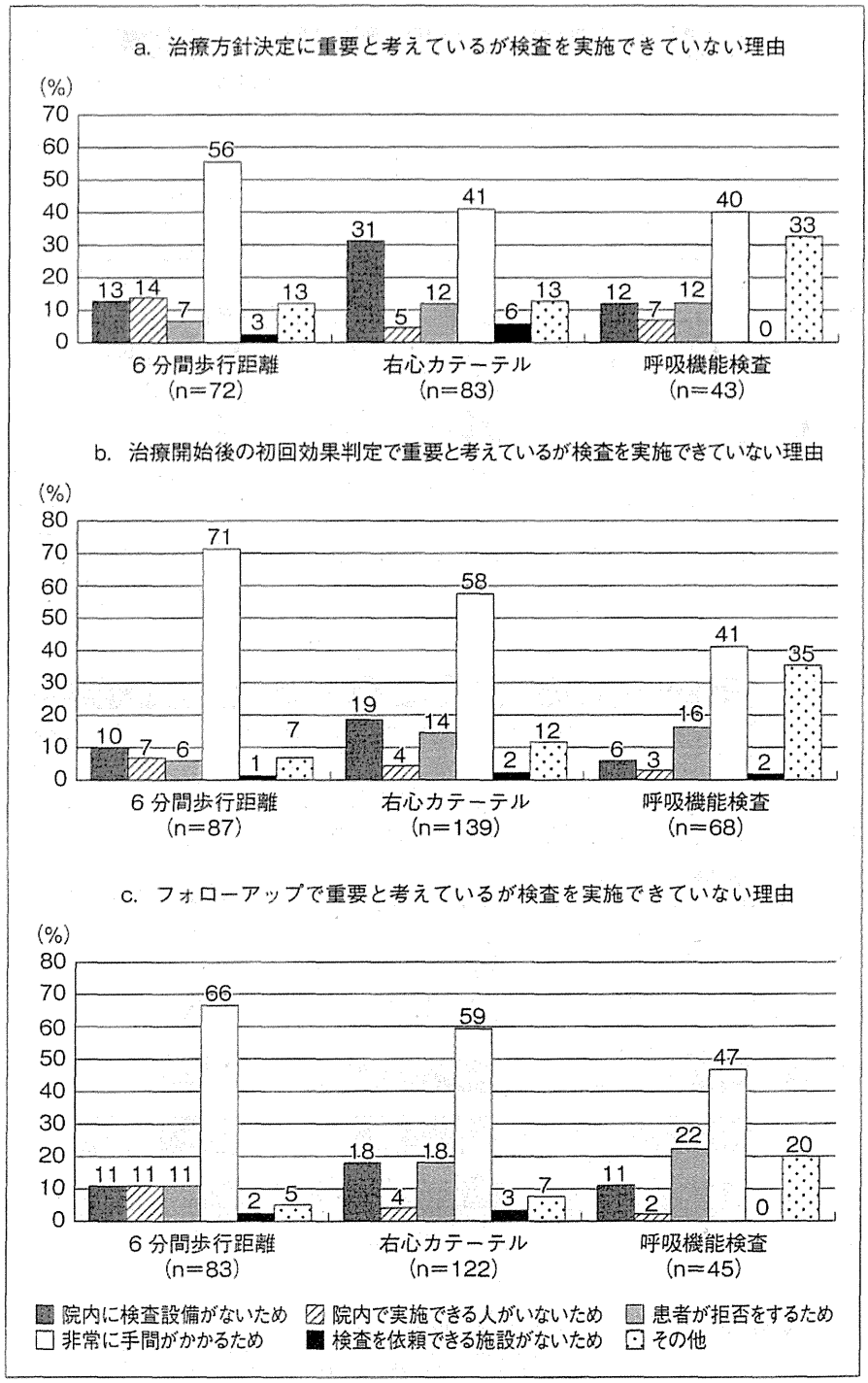

図5 重視しているが検査を実施できていない理由

さらに，初回効果判定までの期間について，その集計結果を図6bに示した．いずれの症例の場合も，1カ月以内に約60%，3カ月以内に90%以上の医師が初回効果判定を実施すると回答した．

考 察

欧州心臓病学会/欧州呼吸器学会(ESC/ERS)ガイドラインでは，特に右心カテーテルは肺高血圧症の診断，病態把握，治療効果判定には不可欠であるとしているが[5]，国内ガイドラインでは肺高血圧が存在する可能性が高い場合に右心カテーテルを用いて確定診断を行うことについてのみ記載されている[6]．今回，インターネットを用いてPAH患者に対する診療実態，特に血行動態に関する検査の実施状況を調査した結果，わが国では血行動態を測定するために用いられる右心カテー

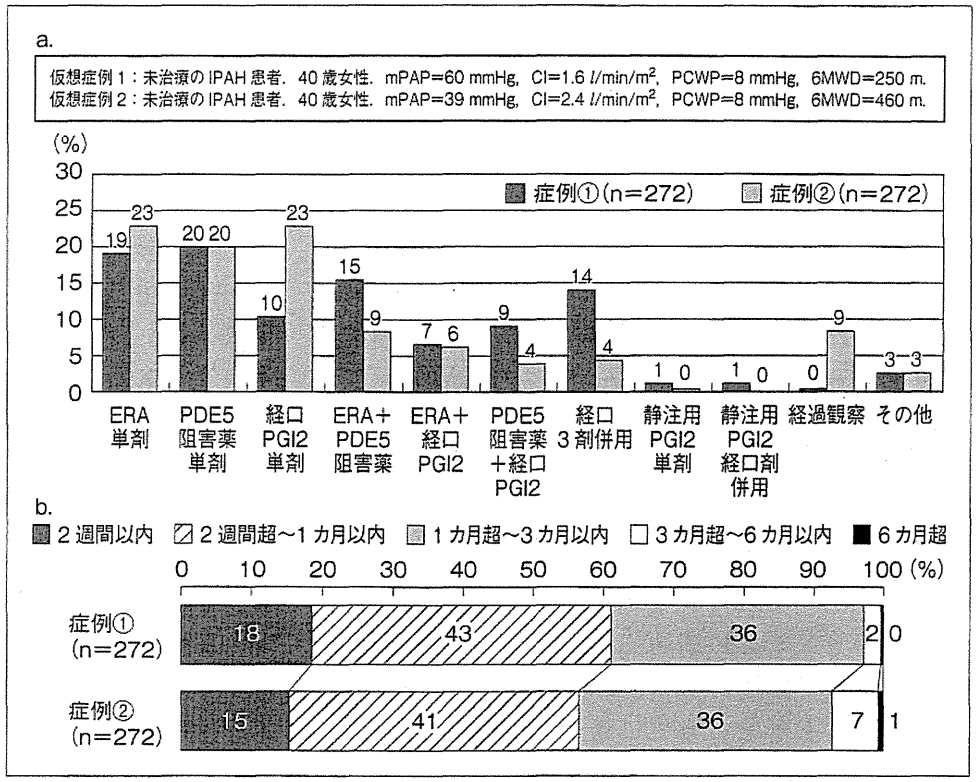

図6　仮想症例に対する治療法および治療に対する効果判定の期間

テルや心臓超音波が重要であるといった認識はあるものの，その実施頻度は心臓超音波では各時点とも8割以上であるのに対して，より正確な血行動態を反映する右心カテーテル実施頻度は各時点において3割から7割と必ずしも高くないことが明らかになった．

今回の調査では治療段階を経過別に評価したが，右心カテーテルは治療方針の決定までの段階では重要視されているものの，検査実施に要する煩雑さの問題や患者への侵襲性を意識した結果，「治療開始後の初回効果判定」や「フォローアップ」の段階ではその実施率は3割以下に低下することがわかった．院内検査設備の問題や循環器内科以外では他科への依頼が必要になることも実施に影響していたと推定された．なお，診療科別で検討したところ，循環器内科での「鑑別・確定診断」時における右心カテーテルの実施率は他の診療科と比べると約2割高く82%であったが，「治療開始後の初回効果判定」時以降は他の診療科と同様3割以下と低かった．これは他科と同様に検査に要する実施上の問題や患者への侵襲性といった問題が循環器内科でも影響していたと考えられる．一方，心臓超音波は8割以上の実施率であり，侵襲性が低いことから比較的実施しやすい検査と考えられていると推察された．また，実際に今回の調査結果においても検査実施担当者が院内の技師である割合は56%であったように技師による実施が可能であること，2012年より負荷心エコー法が診療報酬点数表に追加されたことも実施率が高い理由であると考えられる．心臓超音波はドプラ法により肺動脈収縮期圧，肺血管抵抗などの血行動態推定値を簡便に算出ができることから[7,8]PAHの推定には優れている．しかしながら，患者の体調や計測姿勢，施術者の熟練度などが結果に影響することがあるため，右心カテーテルの結果と異なる場合もあり[9]，必ずしも正確に判定できないといった問題点もある．実際，右心カテーテルと心臓超音波の両検査法を比較した場合，右心カテーテルのほうが正確かつより多くの情報をもたらす検査法であると考えられ，右房圧と心係数などの予後予測因子なども評価が可能である．フォローアップにおいても心臓超音波のみでは肺動脈圧の変化やPAHの進行をモニタリングするには不十分であることが報告されており[10]，長期的に再現性が高い検査法としても右心カテーテルが重要と考えられる．このような点

は，今回の調査結果でも「右心カテーテルが重要と考えているが検査をしていない」と回答した医師の割合が多いことから，十分に右心カテーテルの重要性は認識されていると考えられる．

治療目標といった観点からみた場合，心係数の正常化に留まらず，血行動態を直接反映する肺動脈圧の低下までを目指すことが望ましい．現状では「フォローアップ」時の右心カテーテルの実施率は必ずしも高いものではない．この理由として国内ガイドラインでのフォローアップ時における血行動態の把握に関する記載がないこと，循環器を専門としない診療科では循環器内科などにこの検査を継続的に依頼しなければならないことも大きな理由の一つと考えられる．また，ESC/ERSガイドラインでは短期的(3カ月)に右心カテーテルを行い血行動態に基づき薬物治療の効果を確認することが必要とされている[5]．この点については，効果判定の時期が3カ月以内とする回答が90%以上を示したことに影響していると考えられる．先述したように，治療開始後の初回効果判定時において右心カテーテルの実施率は28%と低いことから，ESC/ERSガイドラインに準じたフォローアップが必要である．さらに，検査実施担当者の調査結果からみた場合，未実施も含む全回答のうち10%で「他の病院」との回答があった．今後，PAH患者を長期的にフォローするためにも，病診連携を強化していくことは重要な課題である．

2例の仮想症例を提示し，治療薬剤および効果判定の期間について調査したところ，重症例と考えられる仮想症例①(WHO機能分類Ⅲ度と想定)において，単剤のみならず併用療法の選択も多く回答されたが，現状，医療現場では各PAH治療薬の単剤から投与を開始し，順次，他剤を追加投与する治療法が行われている．これは，2005年にHoeperらが提唱した“goal-oriented therapy”[11]の概念が広く普及し，その後ESC/ERSガイドラインにも治療経過をみながら薬剤追加するといった方針が取り入れられたためと考えられる[5,12]．しかしながら，近年ではupfront combination therapy(初期からの併用療法)の有用性を示唆する報告も増えてきており[13~15]，2013年に発表された日本循環器学会の肺高血圧症治療ガイドライン2012年改訂版でも推奨度は低いもののWHO機能分類ⅢないしⅣ度の症例に対しては，初期からの併用療法が治療選択肢として登場してきている[6]．本アンケートにおいても経口3剤併用投与との回答が14%あることから，既にupfront combination therapyが実施されつつあることが推察され，PAHの病態が進行性かつ難治性であることから初期併用療法は今後有用な治療法になると考えられる．

今回の調査から各時点において心臓超音波は高い実施率および重視度であったのに対して，初回治療効果判定時やフォローアップ時における右心カテーテルの実施率は低いものであった．しかし，PAH患者の治療経過の正確なモニタリングや治療効果の正確な判定には右心カテーテルが重要な役割を担っている．今後，医療現場での実情なども加味し，各治療段階で必要な検査を行うことはPAH診療において重要である．また，経口PAH治療薬の登場により，その治療もより簡便になってきており，血行動態によるPAHの適切な診断と治療方針の検討は重要である．

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利益相反

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Summary

Current Medical Care Status of Pulmonary Arterial Hypertension

by

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The improvement of cardiopulmonary hemodynamic is extremely important for therapy evaluation in pulmonary arterial hypertension (PAH). However, we doubted if exact hemodynamics evaluation is conducted in clinical. Thus, we have conducted a clinical survey about implementation of medical examinations and treatment strategy. Echocardiogram was used over 90% in all steps. Operation rate of right heart catheter (RHC) was over 60% till the decision of therapeutic strategy, but it decreased to 30-40% at late step. For the importance of these examinations, over 60% of doctors were answered echocardiogram is important in all steps. However the answer of the importance of RHC was decreased at late step. As the therapeutic strategy of the virtual cases 14% of doctors responded combination of three oral PAH medicine for sever case.

In conclusion, an arrangement of appropriate examinations and treatment in the each remedial step of PAH therapy is an important task.

Key words pulmonary arterial hypertension, hemodynamics, clinical survey

Case Report

Imatinib Alleviated Pulmonary Hypertension Caused by Pulmonary Tumor Thrombotic Microangiopathy in a Patient With Metastatic Breast Cancer

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Clinical Practice Points

- Pulmonary tumor thrombotic microangiopathy (PTTM) is a rare cancer-related complication leading to hypoxia, pulmonary hypertension, and heart failure.
- The standard treatment for PTTM is not established. However, imatinib, a tyrosine kinase inhibitor of platelet-derived growth factor receptor (PDGFR), may cause regression of pulmonary hypertension and pulmonary artery remodeling in PTTM.
- We report a case of a 61-year-old woman in whom PTTM developed during chemotherapy for metastatic breast cancer. Although imatinib alleviated pulmonary hypertension, she died because of progression of metastatic breast cancer 54 days after her initial admission to our hospital.
- It would be advisable to conduct a well-designed clinical trial using chemotherapy regimens combined with imatinib for PTTM.

Clinical Breast Cancer, Vol. ■, No. ■, ■-■
Keywords: Imatinib, Metastatic breast cancer, PDGFR, Pulmonary hypertension, Pulmonary tumor thrombotic microangiopathy (PTTM)

Introduction

Pulmonary tumor thrombotic microangiopathy (PTTM) is a rare cancer-related complication that causes hypoxia, pulmonary hypertension, and heart failure. We report a case of PTTM that occurred during chemotherapy for metastatic breast cancer.

Case Report

The patient was a 61-year-old woman who had undergone resection of the left breast and axillary lymph node dissection. Subsequently, she received adjuvant chemotherapy: CAF (cyclophosphamide 500 mg/m^2, doxorubicin [Adriamycin] 50 mg/m^2, and 5-fluorouracil 500 mg/m^2) followed by docetaxel and then tamoxifen followed by anastrozole for a total of 5 years. Twelve years after surgery, she experienced multiple bone and mediastinal lymph node metastases. She was treated with eribulin for 1 year. She came in with a 2-day history of progressing dyspnea and was admitted to our hospital for further medical care. On admission, her body temperature was 36.9°C, blood pressure was 117/72 mm Hg, heart rate was 74 bpm, respiratory rate was 20 breaths per minute, and oxygen saturation was 94% (room air). A chest radiograph showed normal lung fields. Results of arterial blood gas analysis in room air revealed hypoxemia: pH, 7.497; P_{CO_2}, 27.6 mm Hg; P_{O_2}, 59.7 mm Hg; and HCO^3, 20.9 mmol/L. Base excess was −0.9 (room air). Further laboratory examination showed the following: white blood cell count, 3300/mm^3 with normal differential counts; hemoglobin value,12.0 g/dL; platelet count, 75,000/mm^3; total bilirubin, 1.2 mg/dL (normal, 0.2-0.9 mg/dL); aspartate aminotransferase level, 69 IU/L (normal, 10-30 IU/L); alanine aminotransferase level, 50 IU/L (normal, 5-35 IU/L); and C-reactive protein level, 0.03 mg/dL (normal, 0-0.50 mg/dL). A blood coagulation test showed that the D-dimer was elevated to 10.67μg/mL

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(normal, < 0.49 μg/mL), and fibrin degradation products were also elevated to 44.57 μg/mL (normal, < 10 μg/mL), suggesting microthromboembolic disease.

On radiographic evaluation, enhanced computed tomography detected no pulmonary embolism (Figure 1A). However, ventilation-perfusion scintigraphy demonstrated multiple small peripheral perfusion defects in both lungs on the second day after admission (Figure 1B). A transthoracic echocardiogram showed normal left ventricular systolic function (left ventricular ejection fraction, 75%) with paradoxical movement of the interventricular septum. In addition to right ventricular and atrial enlargement, severe pulmonary hypertension was seen, with estimated right ventricular systolic pressure of 76 mm Hg.

On the fifth day after admission, she was transferred to the Department of Cardiovascular Medicine for a more precise diagnosis and intensive treatment. Subsequently, wedged pulmonary artery blood cell sampling showed histologically malignant cells, which highly suggested the diagnosis of pulmonary tumor thrombotic microangiopathy (PTTM). There were 3-dimensional clusters of atypical epithelial cells, focal glandular structures were present, and the nuclear-cytoplasm ratio was high. The cells had hyperchromatic nuclei and prominent nucleoli (Figure 2). Pulmonary artery pressure (PAP) was measured at 93/39 (60) mm Hg, and the cardiac index (CI) was 1.63 L/min/m^2. Imatinib (200 mg/d) was administered as part of a clinical trial, which was approved by the Institutional Review Board of the University of Tokyo Hospital. Nine days after administering the anti–platelet-derived growth factor (PDGF) agent imatinib, the PAP was reduced to 87/30 (50) mm Hg, and the CI was improved to 2.83 L/min/m^2. Because this suggested that imatinib might be effective for this patient, we increased the dose to 400 mg, adding tadalafil (40 mg/d). Afterward the patient was able to discontinue the use of the inotropic agent. Although the PAP was slightly elevated to 95/44 (56) mm Hg, the CI was 2.97 L/min/m^2, and it was possible to maintain hemodynamic stability. There was no worsening of the respiratory condition or right heart failure. However, the patient died of progression of breast cancer 54 days after her initial admission to our hospital.

During autopsy, an embolus of tumor cells was noted in the pulmonary artery, accompanied by intimal hyperplasia. The lumen of the pulmonary artery was severely narrowed. Tumor cells were immunohistochemically positive for PDGF-B (Figure 3).

Discussion

PTTM is a rare cancer-related pulmonary complications, leading to hypoxia, pulmonary hypertension, and heart failure. von Herbay et al reported that the incidence of PTTM was 3.3% (21 cases in 630 carcinoma autopsies).[1] They showed that all 21 cases had carcinoma with distant metastases and that 19 cases had adenocarcinomas in various organs. Among these were 2 cases of breast cancer, whereas stomach cancer was the most common. Okubo et al also reported 6 cases of PTTM in 37 gastric carcinoma autopsies, the incidence being 16.2%.[2]

No diagnostic methods for PTTM have yet been established. Generally, enhanced computed tomography shows no evidence of pulmonary embolism, but ventilation- perfusion scanning tends to be useful. Scintigraphy characteristically reveals multiple subsegmental mismatched defects. Pulmonary angiography might be expected to be the gold standard method for PTTM. However, it has been reported that its sensitivity and specificity for detecting tumor emboli were both poor.[3] For our patient, right-heart catheterization and wedged pulmonary artery blood cell sampling did confirm the clinical diagnosis of PTTM.

Figure 1 (A) Enhanced Computed Tomography Revealed No Evidence of Pulmonary Embolism. (B) Ventilation-Perfusion Scanning Scintigraphy Demonstrated Multiple Small Wedged-Shaped Perfusion Defects in Bilateral Lungs

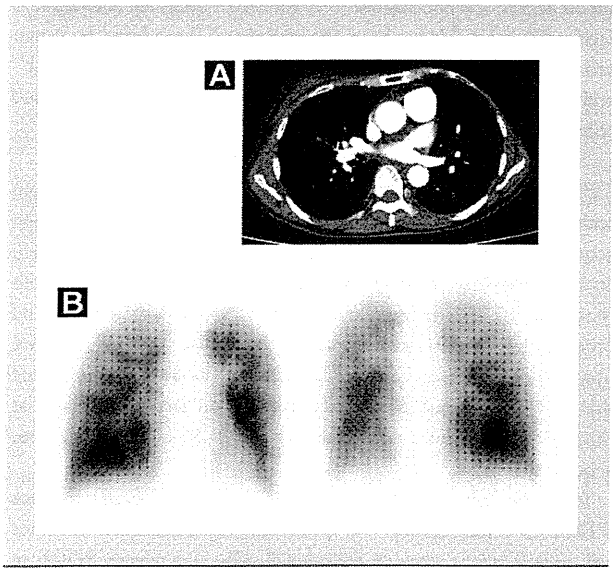


Figure 2 Cytologic Findings From Pulmonary Artery Adenocarcinoma Cells Identified by Cytologic Examination of the Blood in the Pulmonary Artery (Papanicolaou Stain). There Were 3-Dimensional Clusters of Atypical Epithelial Cells. Focal Glandular Structures Were Present, and the Nuclear-Cytoplasm Ratio Was High. The Cells Had Hyperchromatic Nuclei and Prominent Nucleoli

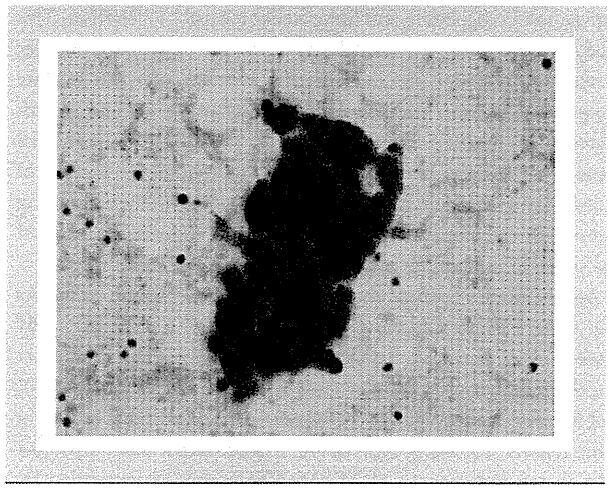
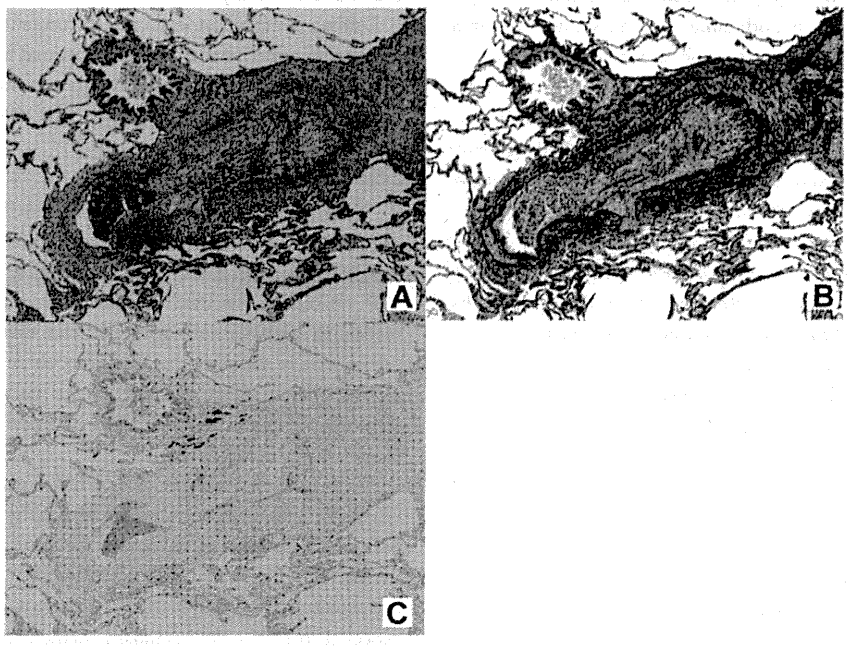


Figure 3 (A-C) Autopsy Findings. Lesion of Pulmonary Tumor Thrombotic Microangiopathy (PTTM) in the Autopsied Specimen. Embolus of Tumor Cells Was Noted in the Pulmonary Artery accompanied by Intimal Hyperplasia. The Lumen of the Pulmonary Artery Was Severely Narrowed. Tumor Cells Were Immunohistochemically Positive for PDGF-B. (A) Hematoxylin and Eosin. (B) Elastica van Gieson. (C) Immunohistochemical Findings of PDGF-B



Despite the recent development of morphometric and immunohistochemical analyses, the mechanism of PTTM is still unclear. Roberts et al presented 2 hypotheses for the development of pulmonary hypertension and right-heart failure in pulmonary tumor embolism.[4] The first is that the dysregulation of signaling pathways, which respond to the presence of an embolic cell or other intravascular insult, cause vascular remodeling.

The second hypothesis proposes that tumor emboli occlude the pulmonary artery bed and increase pulmonary vascular resistance.

von Herbay et al described the morphologic findings of PTTM in a previous report.[1] They revealed that PTTM induced both local activation of coagulation and fibrocellular intimal proliferation. This study reported that tumor cells invaded the pulmonary vascular system and occluded the small arteries and arterioles that activate coagulation systems, releasing inflammatory mediators and growth factors. This process induced fibrocellular proliferation and luminal stenosis.[5] Okubo et al also reported the morphometric analysis of pulmonary arteries and suggested that pulmonary artery remodeling induced by carcinomatous cell adhesion to the endothelium affected the status of pulmonary hypertension.[2]

Several studies revealed that cancer cells produced the molecules that cause PTTM. Okubo et al revealed that all 6 of their PTTM cases showed positive reactivity for tissue factor (TF), 5 showed positive reactivity for vascular endothelial growth factor (VEGF), and 3 showed positive reactivity for osteopontin (OPN). There were some reports suggesting that VEGF and TF might play important roles in the pathogenesis of PTTM. VEGF and TF expression by carcinoma cells has been confirmed in many cases.[5-10] VEGF has been known to be an endothelial cell–specific angiogenetic mitogen.[6] VEGF is associated with the proliferation of endothelial cells and includes angiogenesis involved in embryonic development, tumor angiogenesis, and wound healing.[11] Recently, VEGF has been reported to be involved in pulmonary hypertension.[12,13] In addition to VEGF, TF also is an important factor involved in intracellular signaling, cellular proliferation, and the development of blood vessels. TF contributes to factor VIIa–catalyzed activation of factors IX and X.[8] It has been reported that TF produced by tumor cells might play an important role in the pathogenesis of PTTM[14] and that expression of TF upregulated the *VEGF* gene and enhanced tumor angiogenesis.[15,16]

Takahashi et al reported a case of PTTM with OPN expression.[10] OPN is an arginine-glycine-aspartic acid–containing protein secreted by a variety of cells, including osteoclasts, activated T cells, activated macrophages, and various cancer cells.[17] In Takahashi et al's autopsied case of gastric adenocarcinoma, the tumor cells (both in PTTM lesions and primary gastric carcinoma) and proliferating fibromuscular intimal cells also showed positive immunoreactivity for OPN, PDGF, and VEGF. They suggested that OPN promoted fibrocellular intimal proliferation as well as thrombus formation and pulmonary hypertension in the pathogenesis of PTTM.[10]

It is also important to consider PDGF and PDGF receptor (PDGFR).[18] von Herbay et al speculated that attachment of tumor cell emboli might damage endothelial cells and release PDGF in

PTTM.[1] Yokomine et al reported an autopsied case of PTTM caused by a gastric carcinoma that expressed PDGF and PDGFR in tumor cells.[11] They also revealed that the overexpression of PDGF was detected in alveolar macrophages and PDGFR in intimal mesenchymal cells in the pulmonary artery wall, which suggested the contribution of the activated alveolar macrophages to the onset of PTTM.

The standard treatment for PTTM is not established, but it is possible that imatinib, which is a tyrosine kinase inhibitor of the PDGFR, led to regression of pulmonary hypertension and pulmonary artery remodeling in PTTM in a Japanese case report.[19]

In our patient, imatinib was administered as part of a clinical trial approved by the Institutional Review Board of the University of Tokyo Hospital. Although both PAP and the CI temporarily improved after administration of imatinib, the single-agent administration of imatinib did not suppress the disease progression of breast cancer itself. However, imatinib was efficacious in preventing the deterioration of hemodynamics and the progression of respiratory failure. The fact that tumor cells were immunohistochemically positive for PDGF-B suggested that PDGF played a role in causing PTTM and seemed to support, in this case, the efficacy of imatinib. The patient had not been able to tolerate chemotherapy at symptom onset because of her poor physical condition. It would be valuable to conduct a well-designed clinical trial to evaluate the use of chemotherapy combined with imatinib for PTTM.

Conclusion

PTTM is a cancer-related pulmonary complication that is fatal because of its extremely rapid progression. Therefore, it is important to be aware of PTTM as a differential diagnosis for patients with progressing hypoxia without pulmonary embolism. Imatinib might prove to be an effective therapy for PTTM, but further investigation will be necessary to confirm whether this is the case.

Disclosure

The authors have stated that they have no conflicts of interest.

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ORIGINAL ARTICLE
Heart Failure

Low Blood Pressure, Low Serum Cholesterol and Anemia Predict Early Necessity of Ventricular Assist Device Implantation in Patients With Advanced Heart Failure at the Time of Referral From Non-Ventricular Assist Device Institutes

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Background: The timing of ventricular assist device (VAD) implantation is always a matter of debate, especially when a patient is referred from a non-VAD institute. We focused on objective noninvasive parameters at the time of admission to a VAD implant center and analyzed the factors predicting the necessity of early VAD.

Methods and Results: We retrospectively analyzed advanced heart failure (HF) patients referred since January 2011, including patients less than 65 years old. They all had a history of hospitalization for HF management in non-VAD institutes within 1 month before referral. We excluded patients transferred with mechanical circulatory support. We enrolled 46 patients (40 males, 39.8±13.4 years old). Among them, 26 patients had a VAD implanted or died within 120 days. By multivariable logistic analysis using admission parameters, systolic blood pressure (BP) <93 mmHg [odds ratio (OR) 13.335], hemoglobin <12.7 g/dl (OR 12.175) and serum total cholesterol <144 mg/dl (OR 8.096) were significant predictors of early VAD requirement. We constructed a scoring system according to the ORs, and the area under the receiver-operating characteristic curve was 0.913.

Conclusions: Low BP, low serum cholesterol and anemia on admission predict early VAD in advanced HF patients who have been treated in non-VAD institutes. Such patients should be promptly referred to a VAD implant center. (*Circ J* 2014; **78:** 2882–2889)

Key Words: INTERMACS profile; Seattle Heart Failure Model; Stage D heart failure

Ventricular assist device (VAD) implantation is an important therapeutic option for advanced heart failure (HF) patients. In the REMATCH trial, the use of VAD significantly improved survival in patients with advanced HF with left ventricular ejection fraction (LVEF) <25%.[1] Furthermore, continuous-flow left VAD (LVAD) is proven to accompany better prognosis and quality of life after implantation.[2]

In Japan, implantable LVADs have been approved as bridging devices to transplant since April 2011, and consequently the therapeutic strategy for advanced HF has dramatically changed.[3] However, in the clinical setting the timing of VAD implantation is always a matter of debate, especially when a patient is referred from a non-VAD institute. Indeed, some referred patients considered to be candidates for VAD implantation eventually recover with intensive medical therapy in VAD centers. In contrast, others need emergency implantation of paracorporeal VAD because their hemodynamic status has crashed before sufficient evaluation for transplant candidacy.

For the purpose of deciding this timing, profiles defined by the Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS) are useful. Because the prognosis after VAD implantation is worse for patients with profile 1 or 2 than for less sick patients, profile 3 without end-organ dysfunction is the best candidate for VAD implantation.[3,4] However, the

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Table 1. Baseline Characteristics and Clinical Course of the Enrolled Patients With Advanced HF

	Total (n=46)	Late/no-VAD group (n=20)	Early-VAD group (n=26)	P value
Baseline characteristics				
Age, years	39.8±13.4	43.7±13.0	36.8±12.5	0.084
Male, n (%)	40 (87.0)	18 (90.0)	22 (84.6)	0.468
Body height, cm	168.0±6.9	167.8±6.8	168.2±7.1	0.867
Body weight, kg	62.0±11.2	61.1±9.6	62.8±12.5	0.613
Body mass index	22.0±4.0	21.6±2.7	22.3±4.8	0.584
Body surface area, m^2	1.70±0.15	1.69±0.15	1.71±0.16	0.700
Ischemic etiology n (%)	4 (8.7)	2 (10.0)	2 (7.7)	0.590
History of HF, years	3.3±4.4	2.6±3.8	3.8±4.8	0.361
Family history of HF, n (%)	9 (19.6)	3 (15.0)	6 (23.1)	0.383
CRT/ICD, n (%)	17 (37.0)	4 (20.0)	13 (50.0)	0.036
β-blocker,* mg/day	6.0±5.8	5.6±5.8	6.3±6.0	0.677
ACEI/ARB,** mg/day	4.3±4.1	2.5±2.6	5.7±4.5	0.006
Statin, n (%)	9 (19.6)	6 (30.0)	3 (11.5)	0.117
LVEF <30%, n (%)	42 (91.3)	17 (85.0)	25 (96.2)	0.211
BNP >300pg/ml, n (%)	42 (91.3)	17 (85.0)	25 (96.2)	0.211
INTERMACS profile	–	–	–	<0.001
Profile 2, n (%)	6 (13.0)	0 (0)	6 (23.1)	–
Profile 3, n (%)	23 (50.0)	6 (30.0)	17 (65.4)	–
Profile 4 or less sick, n (%)	17 (37.0)	14 (70.0)	3 (11.5)	–
Clinical course after admission				
Paracorporeal VAD, n (%)	7 (15.2)	0	7 (26.9)	–
Implantable VAD, n (%)	21 (45.7)	3 (15.0)	18 (69.2)	–
All-cause death, n (%)	4 (8.7)	0	4 (15.4)	–

*Carvedilol equivalent; **enalapril equivalent.
ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; BNP, B-type natriuretic peptide; CRT, cardiac resynchronization therapy; HF, heart failure; ICD, implantable cardiac defibrillator; INTERMACS, Interagency Registry for Mechanically Assisted Circulatory Support; LVEF, left ventricular ejection fraction; VAD, ventricular assist device.

classification can vary according to the physician's decision, so we consider that objective parameters that can predict the early requirement for VAD in advanced HF patients are essential.

In this study, we focused on objective parameters of advanced HF patients at the time of referral from non-VAD institutes by analyzing the factors related to early necessity for VAD implantation.

Methods

Patient Selection

We retrospectively collected the data for 46 consecutive HF patients who had been referred to the University of Tokyo Hospital from non-VAD institutes for further management of HF between January 2011 and December 2013. The study period was set as described because implantable LVADs were approved in April 2011. The inclusion criteria were defined as follows: <65 years old, and history of hospitalization for HF in a non-VAD institute within 1 month before referral. Patients who were older than 65 years old were excluded because they are ineligible for heart transplantation in Japan and we excluded patients transferred with mechanical circulatory support because they usually need paracorporeal VAD immediately after transfer and thus were not primarily considered as good candidates for implantable LVAD. Patients diagnosed with acute myocarditis, transferred for the purpose of valvular or bypass surgery, or considered ineligible for VAD implantation (ie, social problems) were also excluded.

Variables Evaluated

Patients' demographic data, including vital signs and treatment on admission, were collected. To evaluate the effects of differential doses of β-blockers, angiotensin-converting enzyme inhibitors (ACEIs), and angiotensin II receptor blockers (ARBs), the doses were normalized to approximately equivalent doses of carvedilol and enalapril according to efficacy. We regarded bisoprolol 5 mg as carvedilol 20 mg, and for ACEIs/ARB, the following agents were regarded as enalapril 10 mg: imidapril 10 mg, perindopril 4 mg, losartan 50 mg, valsartan 80 mg, as previously described.[5] All laboratory data and echocardiographic parameters were obtained within several days of admission. We defined VAD implantation or death as the primary endpoint.

Follow-up After Referral

Before deciding to implant a VAD, all patients received guideline-directed medical therapy consisting of β-blockers, ACEIs/ARB, and aldosterone antagonists as tolerated. Diuretics were also titrated as needed. Cardiac resynchronization therapy (CRT) with a defibrillator was performed if indicated. Intra-aortic balloon pumping (IABP), percutaneous cardiopulmonary support, continuous hemodiafiltration, or mechanical ventilation was executed on the basis of the physician's decision. Timing of VAD implantation was determined by whether the patient developed cardiogenic shock, had progressive decline of end-organ function in spite of maximal treatment, or was considered inotrope-dependent despite optimal medical therapy.

We followed all patients from the date of their referral until

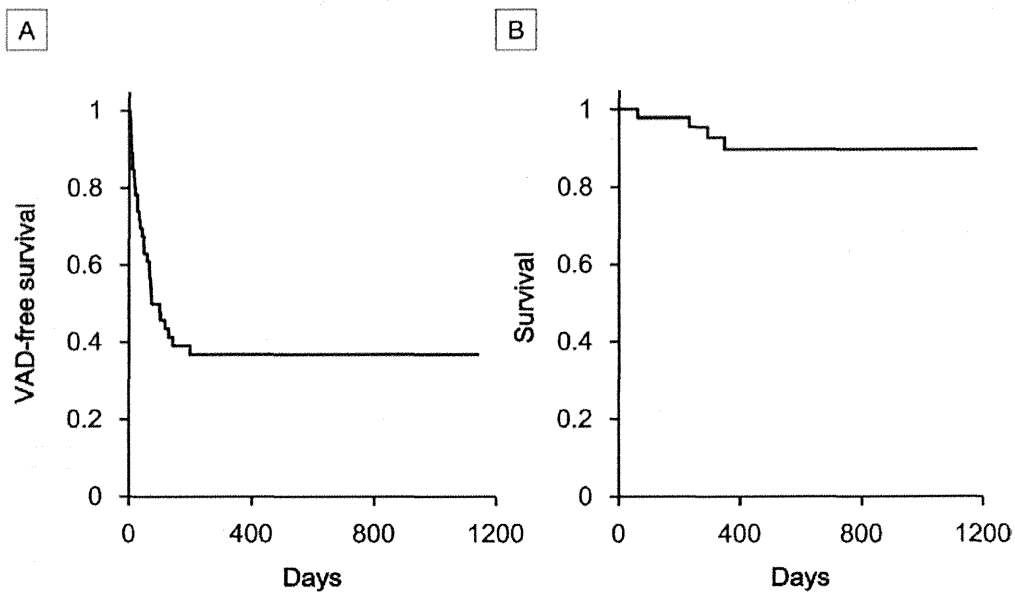


Figure 1. Kaplan-Meier curve for VAD-free survival (**A**) and survival (**B**) after admission to referral hospital of all enrolled patients (n=46) with advanced heart failure. VAD, ventricular assist device.

March 2014 or the date of their death. No patient was lost during the follow-up period unless deceased.

Previous Risk Scores

The Seattle Heart Failure Model (SHFM) was developed by Levy et al from the data of New York Heart Association (NYHA) class IIIB or IV patients and calculated from age, vital signs, medications, laboratory measurements and utilization of CRT.[6] They also updated the SHFM score for LVAD candidates by adding variables such as usage of inotropes, IABP, or mechanical ventilation.[7] In SHFM, the therapeutic option of LVAD is available if the patients meet ACC/AHA criteria such as (1) NYHA Class IV, (2) LVEF ≤25%, and (3) mean 2 year survival ≤50%.[8] We used their website (http://depts.washington.edu/shfm) to estimate the indication for LVAD in the present group of patients.

The INTERMACS profile stratifies patients with advanced HF into 7 categories on the basis of clinical severity.[9] In this study, patients with profile 1 on admission were not enrolled because we excluded patients transferred with mechanical circulatory support.

Statistical Analysis

Continuous variables of patients who did or did not require early VAD were compared by unpaired t-test or Mann-Whitney test as appropriate. Categorical variables of patients were compared by chi-square test or Fisher's exact test as appropriate. Univariable analyses with a logistic regression model were performed to calculate odds ratio (OR) and 95% confidence interval (CI) to assess the influence of each variable on admission on early requirement for VAD. We chose 3 statistically significant variables from among the baseline characteristics, laboratory measurements and echocardiographic parameters. Cutoff points of the 3 variables were determined by receiver-operating characteristic (ROC) analysis with JMP9 (SAS Institute, Cary, NC, USA) and entered into the multivariable analysis.

Considering the results of the multivariable analysis, weighted scores were allocated to each selected variable on the basis of each OR, and we defined a summation of scores as a new risk scoring system. We then created a ROC curve for the new score, by which the area under the curve (AUC) for the score was calculated and that AUC was compared with those of previously published risk scores, including SHFM and INTERMACS profile.

Kaplan-Meier survival analysis was also performed to evaluate VAD-free survival after referral on 2 strata of the new score, and VAD-free survival among these strata was compared by log-rank test.

Unless otherwise specified, all data are expressed as mean±standard deviation. Probability was 2-tailed, with $P<0.05$ regarded as statistically significant. All statistical analyses except for the ROC analyses were calculated with PASW Statistics 18 (SPSS, Chicago, IL, USA).

Results

Baseline Characteristics

The baseline characteristics of the 46 enrolled patients are shown in **Table 1**. The mean age was 39.8±13.4 years and 87.0% were male. An ischemic etiology was found in 8.7% of the patients; 6 patients (13.0%) were considered as profile 2 and 23 (50.0%) as profile 3. LVEF was <30% in 42 patients (91.3%), and plasma levels of B-type natriuretic peptide (BNP) were >300 pg/ml in 42 patients (91.3%).

Classification of the Patients

Table 1 shows the clinical course after admission, and **Figure 1** shows the VAD-free survival and overall survival of the patients. As shown in **Figure 1A**, 28 patients (60.9%) eventually needed VAD and of them 25 had the VAD implanted within 4 months

Table 2. Demographic, Physical, Laboratory and Echocardiographic Parameters on Admission and Univariable Analysis for VAD Implantation in 46 Patients With Advanced HF

	Late/no-VAD group (n=20)	Early-VAD group (n=26)	P value	OR	95% CI
Demographic parameters					
Age, years	43.7±13.0	36.8±12.5	0.089	0.959	0.914–1.006
Male, n (%)	18 (90.0)	22 (84.6)	0.593	1.636	0.268–9.980
Body height, cm	167.8±6.8	168.2±7.1	0.863	1.008	0.925–1.097
Body weight, kg	61.1±9.6	62.8±12.5	0.605	1.014	0.962–1.069
Body mass index	21.6±2.7	22.3±4.8	0.577	1.044	0.897–1.216
Body surface area, m^2	1.69±0.15	1.71±0.16	0.693	2.166	0.047–100.583
Ischemic etiology, n (%)	2 (10.0)	2 (7.7)	0.784	0.750	0.096–5.844
History of HF, years	2.6±3.8	3.8±4.8	0.357	1.070	0.926–1.237
Family history of HF, n (%)	3 (15.0)	6 (23.1)	0.496	1.700	0.368–7.845
Physical parameters					
Heart rate, beats/min	88.8±18.0	93.4±19.8	0.413	1.013	0.982–1.046
Systolic BP, mmHg	95.9±12.8	88.0±7.8	0.024	0.924	0.862–0.989
Systolic BP <93 mmHg, n (%)	7 (35.0)	23 (88.5)	0.001	14.238	3.133–64.702
Diastolic BP, mmHg	60.2±8.8	54.6±7.8	0.040	0.916	0.842–0.996
Laboratory parameters					
White blood cell count, $\times10^3/\mu l$	7.4±2.5	7.2±2.2	0.708	0.953	0.741–1.226
Hemoglobin, g/dl	14.6±2.0	12.4±2.1	0.002	0.585	0.413–0.828
Hemoglobin <12.7 g/dl, n (%)	2 (10.0)	17 (65.4)	0.001	17.000	3.202–90.254
Platelets, $\times10^4/\mu l$	21.2±5.6	22.4±6.8	0.514	1.033	0.937–1.138
Serum sodium, mmol/L	137.1±3.9	135.3±5.4	0.219	0.920	0.805–1.051
Serum potassium, mmol/L	4.4±0.4	4.3±0.5	0.542	0.670	0.185–2.429
Serum chloride, mmol/L	101.6±4.0	99.3±6.0	0.156	0.910	0.798–1.037
Serum blood urea nitrogen, mg/dl	21.0±11.3	23.3±14.6	0.548	1.014	0.968–1.063
Serum creatinine, mg/dl	1.00±0.25	1.12±0.51	0.327	2.150	0.465–9.938
Serum uric acid, mg/dl	7.0±2.2	7.5±3.2	0.525	1.075	0.861–1.341
Serum total protein, g/dl	7.0±0.8	6.7±0.8	0.241	0.634	0.296–1.359
Serum albumin, g/dl	3.9±0.5	3.7±0.6	0.371	0.608	0.204–1.809
Serum lactate dehydrogenase, IU/L	245.3±58.5	276.4±113.5	0.287	1.004	0.996–1.013
Serum aspartate aminotransferase, IU/L	32.2±13.1	36.1±38.8	0.666	1.005	0.983–1.027
Serum alanine aminotransferase, IU/L	36.2±20.2	41.4±52.5	0.670	1.003	0.988–1.019
Serum alkaline phosphatase, IU/L	278.1±75.8	288.5±111.9	0.724	1.001	0.995–1.008
Serum γ-glutamyl transpeptidase, IU/L	117.2±104.7	107.3±88.3	0.724	0.999	0.993–1.005
Serum total bilirubin, mg/dl	1.4±0.7	1.5±0.9	0.663	1.174	0.570–2.418
Serum TC, mg/dl	181.0±43.8	146.2±46.3	0.020	0.983	0.969–0.997
Serum TC <144 mg/dl, n (%)	3 (15.0)	16 (61.5)	0.003	9.067	2.106–39.029
C-reactive protein, mg/dl	0.78±1.30	1.42±2.34	0.289	1.223	0.843–1.774
BNP, $\log_{10}$ pg/ml	2.84±0.34	2.96±0.25	0.201	3.960	0.480–32.676
Echocardiographic parameters					
LV diastolic diameter, mm	67.5±16.2	73.1±14.3	0.228	1.027	0.984–1.072
LV systolic diameter, mm	63.1±11.6	67.5±14.5	0.263	1.027	0.980–1.077
LVEF, %	21.7±10.5	20.2±6.9	0.545	0.979	0.913–1.049
Interventricular septum thickness, mm	8.3±2.3	7.8±1.8	0.416	0.884	0.657–1.189
Posterior wall thickness, mm	7.9±2.0	8.2±1.3	0.546	1.120	0.775–1.617
LA diameter, mm	50.1±6.7	48.0±7.3	0.341	0.959	0.879–1.045
AR severity	0.50±0.76	0.58±0.70	0.717	1.165	0.510–2.659
MR severity	2.55±0.69	2.31±1.01	0.355	0.725	0.367–1.433
TR severity	1.95±0.69	2.00±0.85	0.826	1.089	0.507–2.340
TR pressure gradient, mmHg	30.3±9.5	37.2±14.6	0.086	1.048	0.993–1.106

AR, aortic regurgitation; BP, blood pressure; CI, confidence interval; LA, left atrial; LV, left ventricular; MR, mitral regurgitation; OR, odds ratio; TC, total cholesterol; TR, tricuspid regurgitation. Other abbreviations as in Table 1.

Table 3. Multivariable Analysis for Early VAD Implantation Among the Variables Measured in 46 Patients With Advanced HF

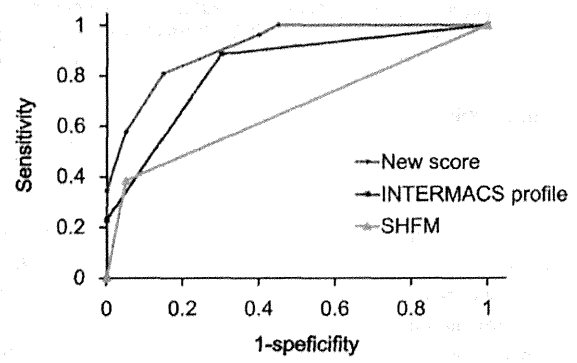
	P value	OR	95% CI
Systolic BP, <93 mmHg	0.013*	13.335	1.746–101.848
Hemoglobin, <12.7 g/dl	0.013*	12.175	1.698–87.304
Serum TC, <144 mg/dl	0.031*	8.096	1.206–54.340

Abbreviations as in Tables 1,2.

Table 4. AUC of the New Scoring System and Other Scoring Systems for Early-VAD Necessity

	AUC (95% CI)	P value
New score	0.913 (0.798–0.965)	–
INTERMACS profile	0.827 (0.694–0.910)	0.195
SHFM	0.667 (0.553–0.765)	<0.001

AUC, area under the curve;SHFM, Seattle Heart Failure Model. Other abbreviations as in Tables 1,2.



	cutoff	sensitivity	specificity
New score	3	0.81	0.85
INTERMACS profile	3	0.88	0.70
SHFM	1	0.38	0.95

Figure 2. ROC analysis of the new score, the INTERMACS profile and SHFM for the prediction of VAD necessity within 120 days, with the sensitivity and specificity of each score at the cutoff point. ROC, receiver-operating characteristics; INTERMACS, Interagency Registry for Mechanically Assisted Circulatory Support; SHFM, Seattle Heart Failure Model; VAD, ventricular assist device.

of admission; 1 patient died within the 4 months, before VAD implantation. Next, we classified the patients who had a VAD implanted or died before day 120 into an early-VAD group (n=26), and a late/no-VAD group (n=20). Status on admission and the clinical course of both groups are also shown in **Table 1**. Patients in the early-VAD group tended to be younger than those in the late/no-VAD group, though statistically insignificant (36.8±12.5 vs. 43.7±13.0 years, P=0.084). The initial dose of β-blockers on admission was comparable between groups (6.3±6.0 mg/day in early-VAD group vs. 5.6±5.8 mg/day in late/no-VAD group, P=0.677) but the doses of ACEIs/ARB were significantly higher in the early-VAD group (5.7±4.5 mg/day vs 2.5±2.6 mg/day, P=0.006). CRT/implantable cardiac defibrillator implantation was performed in 13 patients (50.0%) in the early-VAD group and in 4 patients (20.0%) from the late/no-VAD group (P=0.036).

In the early-VAD group, a paracorporeal VAD was implanted in 7 patients as an emergency life-saving procedure in all cases, and an implantable VAD in 18 patients. One patient died before VAD implantation. In the late/no-VAD group, 3 patient had a VAD implanted after day 120. In the follow-up period until March 2014, 3 patients in the early-VAD group died after VAD implantation (all of them had received an implantable VAD), whereas no patients died in the late/no-VAD group.

Univariable Logistic Analysis

We performed univariable logistic analysis to find predictors for early VAD. **Table 2** shows the demographic and physical parameters on admission. Low systolic blood pressure (BP; P=0.024, OR 0.924, 95% CI 0.862–0.989) was a significant factor related to the necessity for VAD. Of the laboratory data (**Table 2**), low hemoglobin level (P=0.002, OR 0.585, 95% CI 0.413–0.828) and low serum total cholesterol level (P=0.020, OR 0.983, 95% CI 0.969–0.997) predicted the early necessity for VAD. Serum bilirubin and creatinine levels, which are the well-known markers of end-organ dysfunction, or the plasma BNP level on admission were not significantly related to early VAD necessity. Of the echocardiographic parameters (**Table 2**), none of the variables, including left ventricular diastolic diameter and LVEF, were significantly related to early VAD necessity.

Multivariable Logistic Analysis

Because 26 primary events were observed in the early-VAD group, we chose all 3 statistically significant variables for the multivariable analysis. Systolic BP <93 mmHg (P=0.001, OR 14.238, 95% CI 3.133–64.702), hemoglobin <12.7 g/dl (P=0.001, OR 17.000, 95% CI 3.202–90.254) and serum total cholesterol <144 mg/dl (P=0.003, OR 9.067, 95% CI 2.106–39.029) were selected (**Table 2**) and entered into the multivariable analysis, which found that all of them were independent predictors for early VAD necessity (**Table 3**).

Scoring System

We created a new scoring system using these 3 factors (**Table 3**). We assigned 2 points to systolic BP <93 mmHg, 2 points to hemoglobin <12.7 g/dl and 1 point to serum total cholesterol <144 mg/dl, based on the ORs in the multivariable analysis. A ROC curve of the score was drawn, and the AUC for the score was 0.913 (**Figure 2, Table 4**). With a cutoff of 3 points, the sensitivity for VAD necessity within 120 days was 0.81 and the specificity was 0.85. We also compared the predictability of this score with other risk scores. The AUC of INTERMACS profile was 0.827, and with a cutoff of profile 3 the sensitivity was 0.88 and the specificity was 0.70. The AUC of SHFM was 0.667, and the sensitivity and specificity were 0.38 and 0.95, respectively. Our new scoring had a significantly better predictability for the early necessity of VAD over SHFM (**Table 4**).

We also classified the patients into 2 strata according to the new score (score 0–2 or 3–5), and performed Kaplan-Meier analysis. **Figure 3A** shows that the VAD-free survival was significantly different between the 2 strata (P<0.001, by log-rank test). We also compared VAD-free survival after stratification with the INTERMACS profile and SHFM (**Figures 3B,C**). VAD-free survival after admission was also significantly different between the 2 strata according to INTERMACS profile (profile 2–3 and profile 4 or less sick, P<0.001) and SHFM (LVAD criteria (+) and (–), P<0.001).

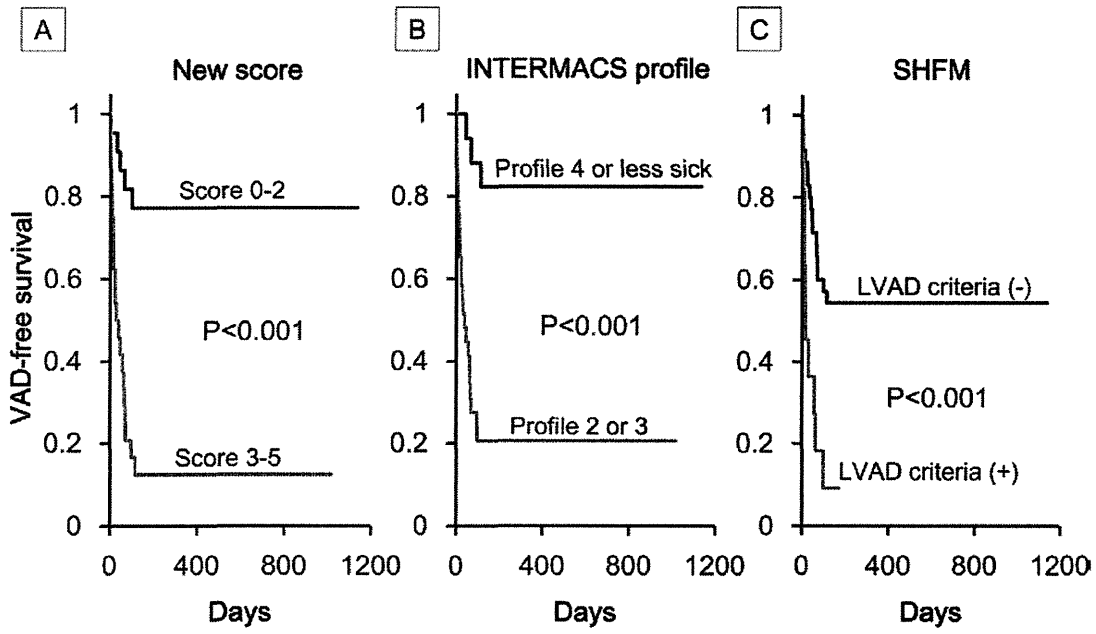


Figure 3. Kaplan-Meier analysis of VAD-free survival according to the new score system (**A**), profile 2 or 3 and profile 4 or less sick in INTERMACS (**B**), and LVAD criteria (–) and (+) in SHFM (**C**). VAD-free survival was compared by log-rank test and each P value is shown. INTERMACS, Interagency Registry for Mechanically Assisted Circulatory Support; LVAD, left ventricular assist device; SHFM, Seattle Heart Failure Model.

Discussion

This study demonstrated that low systolic BP, and low levels of hemoglobin and low serum total cholesterol on admission were independent predictors of subsequent VAD implantation in the not too distant future for advanced HF patients referred from non-VAD institutes. For the purpose of deciding the timing of VAD implantation, it has been suggested that profiles defined by INTERMACS are useful,[3,4] but the decision is physician-dependent. We emphasize that the combination of 3 objectively defined parameters was similarly predictive to INTERMACS profile. There have been several risk scores proposed for predicitng prognosis after VAD implantation,[7,10–12] but to our knowledge, this is the first report to focus on the early necessity for VAD using objective parameters. We also underscore that we selected noninvasive variables. Hemodynamic parameters obtained invasively may be useful for determining the timing, but are often unavailable at the time of referral from non-VAD institutes.

In this report, we use the term "at the time of referral". In reality, we collected the data at the time of admission to the referral hospital, and so to be exact, we use the term "at the time of admission to the referral hospital". However, we consider it was easier to understand the meaning and importance of this report by using the term "at the time of referral".

Clinical Course of Advanced HF Patients Referred to Hospital

According to our results, VAD-free survival was only 43.5% at 4 month after admission (**Figure 1**). Furthermore, the existence of 2 of the 3 factors (systolic BP <93 mmHg, hemoglobin <12.7 g/dl and serum total cholesterol <144 mg/dl) predicted early VAD implantation after admission (**Figure 2**). Kaplan-Meier analysis showed these patients had extremely poor VAD-free survival (**Figure 3**), which was comparable with the VAD-free survival of status 1 patients after being listed for heart transplantation as we reported recently.[13]

Effect of Each Parameter on Patients' Outcomes

It has been previously shown that low BP,[14,15] anemia[16,17] and low serum total cholesterol[18,19] are predictors of higher mortality in HF patients, which is consistent with our results, because patients who needed VAD were expected to have poor prognosis without VAD implantation.

Patients presenting with low systolic BP may have low cardiac output and impaired organ perfusion,[20] so it is reasonable that low systolic BP predicts HF severity and the patient's outcome. In this study, the dose of ACEIs/ARB in early-VAD patients was higher than that in late/non-VAD patients (**Table 1**), which could be related to the duration of HF treatment, and could be a cause of the lower BP in early-VAD patients.

BP is an objective, but fluctuating parameter. We used BP measured noninvasively after admission with the patient in a stable condition and supine position. Although the difference in systolic BP between early-VAD and late/no-VAD patients was small, we consider the cutoff value of 93 mmHg as clinically reasonable, considering that systolic BP <90 mmHg is commonly regarded as a state of shock.

Low serum total cholesterol is a novel predictor of survival in chronic HF, but the mechanism is not fully understood.[18] In our study the dose of statin was not statistically different, but tended to be higher in the patients in the late/no-VAD group than in those in early-VAD group, although the total cholesterol level was significantly lower in the early-VAD group (**Tables 1,2**). The protective role of lipoproteins in downregu-