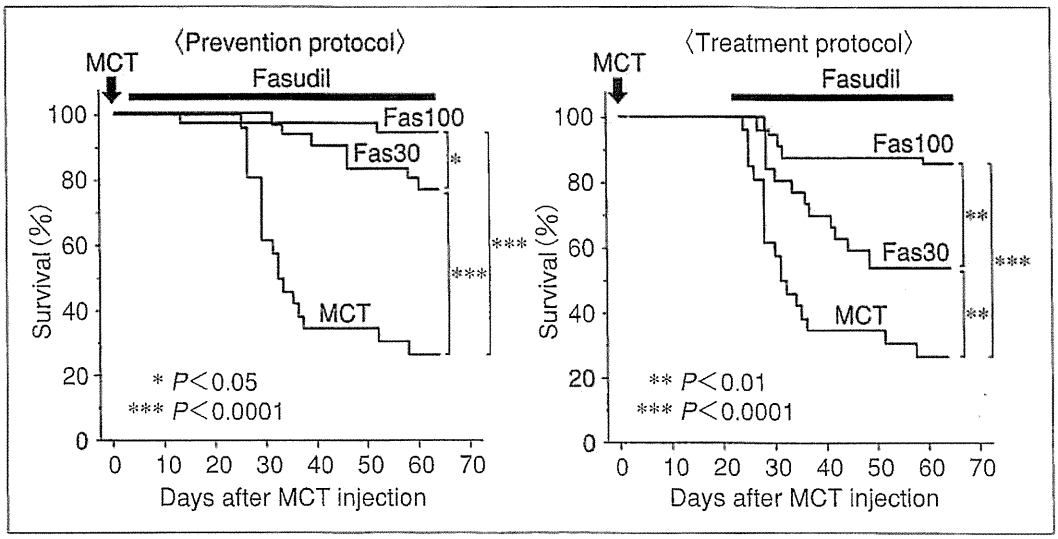

図3　動物モデルにおけるファスジルの効果
モノクロタリン誘発性ラット肺高血圧モデルにおいて，モノクロタリン投与時にファスジルの経口投与を開始する(予防プロトコール)と生存率が著明に改善し，さらに，肺高血圧症を発症させたあとにファスジル投与を開始(治療プロトコール)しても生存率が有意に改善する．
(文献[6]より引用)

作用によりイノシトール3リン酸(IP3)を生成する．IP3は細胞内のCa^{2+}貯蔵部位(筋小胞体)上のCa^{2+}チャネルを開口することによりCa^{2+}放出を惹起し，細胞内のCa^{2+}濃度を上昇させる．また，細胞膜にもCa^{2+}チャネルが存在し，さまざまな刺激に応答してチャネルが開口し，細胞外からのCa^{2+}流入がひき起こされる．筋小胞体からの放出，および細胞外からの流入により上昇した細胞内Ca^{2+}は，カルモジュリンと結合してCa^{2+}/カルモジュリン複合体を形成し，MLCKの触媒サブユニットに結合してMLCKを不活性型から活性型に変換する．活性型MLCKがMLCをリン酸化すると，ミオシン頭部に存在するMg^{2+}-ATPaseのアクチンによる活性化がひき起こされ，血管平滑筋は収縮する．その後，細胞内Ca^{2+}濃度が低下すると，Ca^{2+}はカルモジュリンから解離してMLCKは不活性化される．その結果，MLCPhが優位になり，MLCは脱リン酸化されて血管平滑筋は弛緩する(図2)．

一方，Rhoキナーゼは，細胞内Ca^{2+}濃度非依存的に血管平滑筋の収縮弛緩を制御することが知られている．すなわち，収縮性血管作動物質の刺激により，G蛋白に共役した受容体を介して低分子量G蛋白質であるRhoが活性化され，その標的蛋白の一つであるRhoキナーゼが活性化される．活性化されたRhoキナーゼは，MLCPhのミオシン結合サブユニット(MBS)をリン酸化することによりその活性を阻害する．その結果，MLCK/MLCPh活性のバランスが崩れ，MLCのリン酸化が上昇することで血管平滑筋は収縮する(図2)．

5．血管平滑筋の増殖におけるRhoキナーゼの役割

通常の生体の動脈にみられる平滑筋細胞は前述の収縮弛緩が主な働きであるが，病態や血管障害により増殖因子刺激を受けると平滑筋は形質変換を起こし増殖が誘導される．Rhoキナーゼは，トロンビンやウロテンシンII，PDGF-BB刺激による血管平滑筋細胞の増殖にも重要な役割を果たしている．また，細胞増殖において，サイクリン依存性キナーゼを阻害する働きを持つp27がその制御に重要な役割を果たしていることが知られている[2)~4)]．Rhoキナーゼは活性化するとp27の発現を低下させ，細胞増殖を亢進させる．一方，Rhoキナーゼ阻害はバルーン傷害による血管平滑筋細胞の増殖を抑制しないとの報告もあり，詳細な機序については明らかとなっていない．

6．細胞遊走におけるRhoキナーゼの役割

細胞遊走は白血球や線維芽細胞，平滑筋細胞などの細胞が持つ生理機能であり，さまざまな

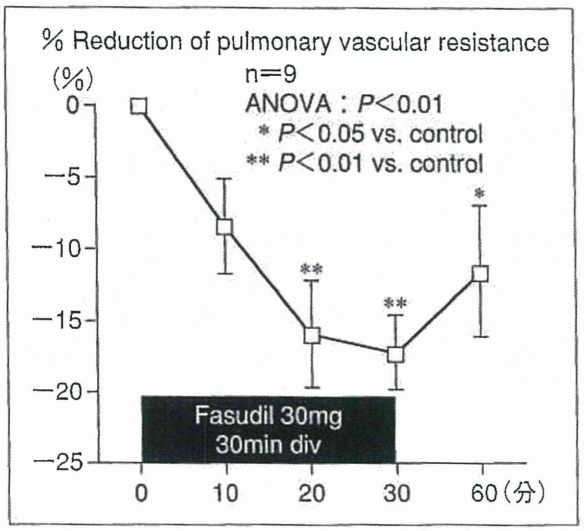

図4 重症肺高血圧症患者におけるファスジルの急性効果
重症肺高血圧症患者において，ファスジルの点滴静脈内投与は肺血管抵抗を有意に低下させる急性効果を有している． (文献[9]より引用)

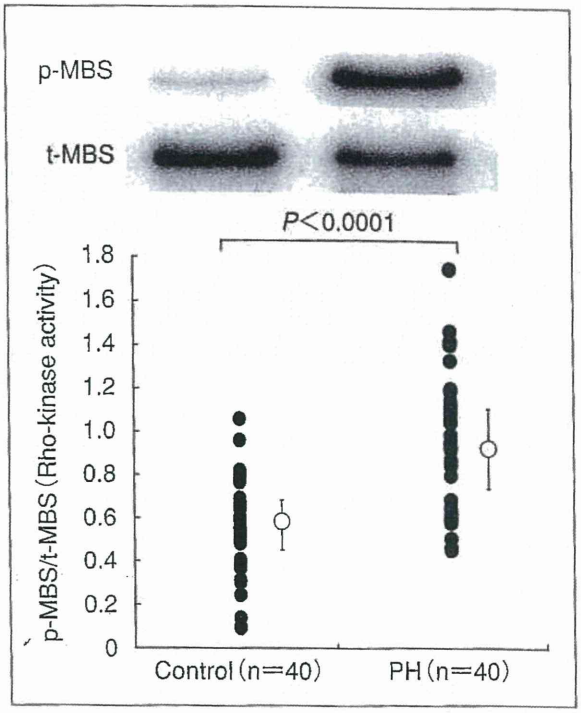

図5 肺高血圧症患者の白血球におけるRhoキナーゼ活性の亢進 (文献[10]より引用)

生理的・病的環境で重要な役割を果たしている．細胞遊走には，遊走刺激によるアクチンフィラメントの重合―脱重合(再構築)，アクチン―ミオシンによる収縮，微小管を介した細胞骨格蛋白質の輸送などが関与している．これら遊走にかかわる細胞機構の制御にRho/Rhoキナーゼが重要な役割を果たしていることが報告されている[2)~4)]．たとえば，血管平滑筋細胞においてRhoキナーゼ阻害薬はPDGFやリソフォスファチジン酸によって誘発される遊走を制御する．その機序として，遊走刺激因子などにより活性化されたRhoがRhoキナーゼを活性化してMLCPhを阻害し，MLCのリン酸化を促進して細胞の収縮性を高め，細胞遊走に関与することが考えられている．また，Rhoキナーゼはアクチンフィラメントの再構築に関与するアデューシン，ERM(ezrin/radixin/moesin)，LIMキナーゼなどの蛋白質をリン酸化することから，これらの蛋白質を介した細胞遊走の制御も考えられている．

肺高血圧症に対する新たな治療ターゲットとしてのRhoキナーゼ

1．基礎研究

下川らはモノクロタリン誘発性ラット肺高血圧モデル(MCTモデル)において[6)]，モノクロタリン投与時にファスジルの経口投与を開始する(予防プロトコール)と生存率が著明に改善することを明らかにした(図3)．次いで，MCTモデルにおいて，肺高血圧症を発症させたあとにファスジル投与を開始(治療プロトコール)しても，生存率が有意に改善することを示した(図3)．MCTモデルの肺動脈ではRhoキナーゼの活性が亢進しており，内皮機能の低下，血管平滑筋の過収縮がみられることを示した．また，組織学的検討ではMCTモデルで認められる肺動脈の中膜肥厚，微小肺動脈の筋性化がいずれもファスジル投与により抑制された．さらに下川らは，低酸素誘発性肺高血圧症マウスにおいてもファスジル経口投与が有効であることを示した[7)]．また，種々の肺高血圧症モデルにおいて，ファスジルまたはY-27632を急性吸入投与することにより肺動脈圧が低下することも報告されている[8)]．

2．臨床研究

一方，臨床的検討として，酸素，一酸化窒素，カルシウム拮抗薬の急性投与に抵抗性を示した重症肺高血圧症患者において，ファスジルの点滴が肺血管抵抗を有意に低下させたことを報告した(図4)[9)]．これらの結果から，肺高血圧症の

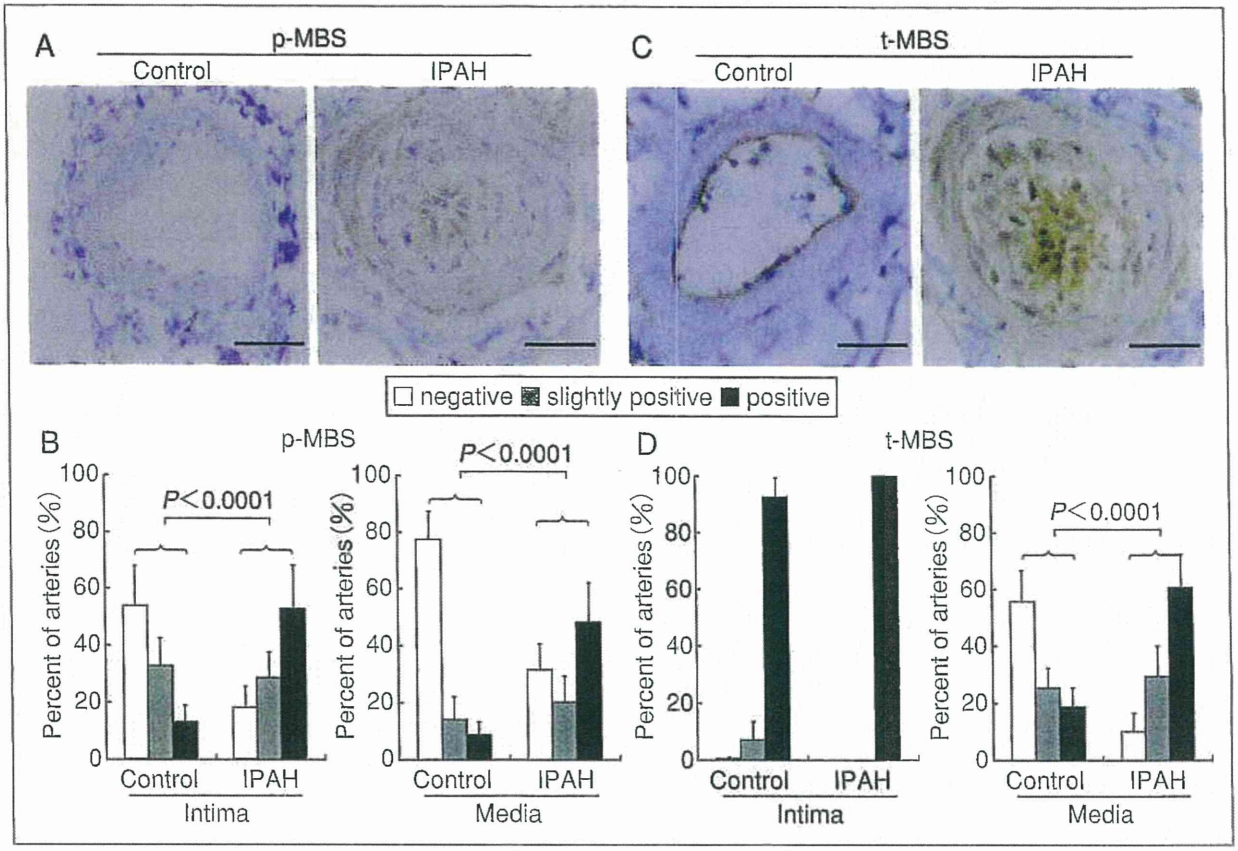

図 6　肺高血圧症患者の肺組織におけるRhoキナーゼ活性の亢進（文献[10]より引用）

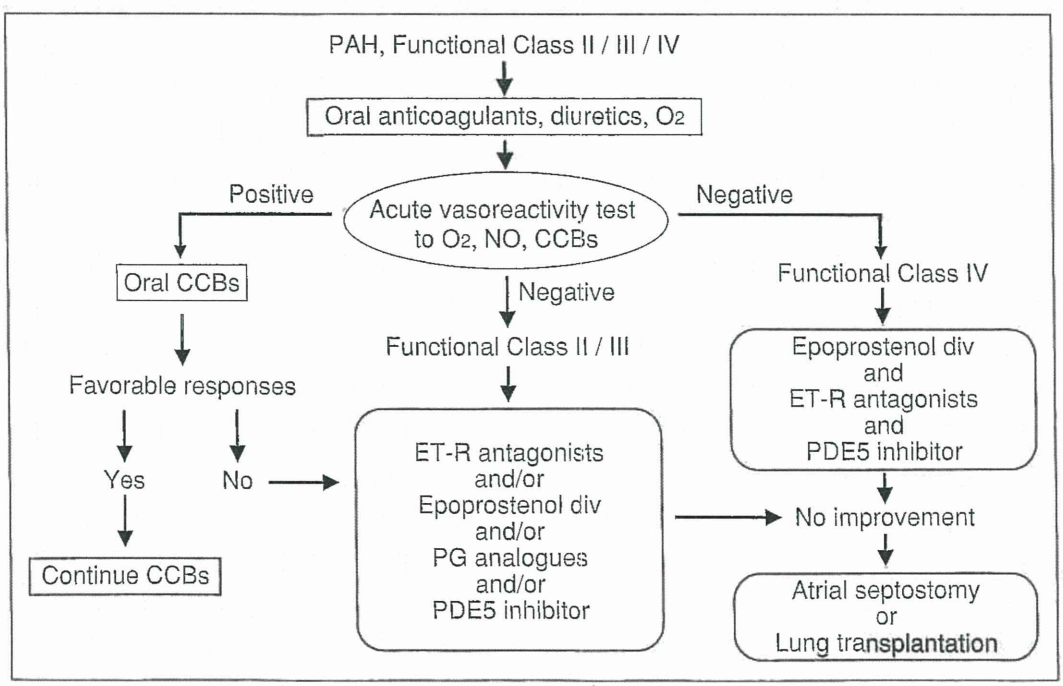

図 7　肺高血圧症の治療アルゴリズム
現時点ではベラプロスト，エポプロステノール，ボセンタン，シルデナフィルで加療しているが，Rhoキナーゼ阻害薬の有効性が示されれば重要な治療オプションとなりうる．（文献[5]より引用）

成因（内皮細胞障害，肺動脈病変形成，肺動脈持続的過収縮）にRhoキナーゼが深く関与している可能性が示唆されていたが，最近筆者らは，肺高血圧症患者の肺高血圧症患者における全身性

もしくは局所的なRhoキナーゼ活性を検討した[10]．まず肺高血圧症患者および健常者の末梢血由来多型核白血球におけるRhoキナーゼ活性の検討を行った．Western blot法によりRhoキナーゼの基質であるミオシン結合サブユニット(MBS)のリン酸化体および総MBSの比(Rhoキナーゼ活性)が，肺高血圧症患者の末梢血由来多型核白血球では健常者に比べ有意に亢進していることを認めた(図5)．次に，肺移植を受ける肺高血圧患者の肺組織およびコントロール(肺がん患者)の正常肺組織に対し，Rhoキナーゼ発現および活性を免疫組織染色法および摘出血管で検討を行ったところ，免疫組織学的にRhoキナーゼの発現および活性が，肺高血圧症患者ではコントロールと比べ有意に亢進していることが認められた(図6)．さらに肺高血圧患者の摘出肺動脈において，内皮依存的弛緩反応低下およびセロトニンに対する過収縮を認め，この平滑筋過収縮はRhoキナーゼ阻害薬によって抑制された．これらのデータから，はじめて肺高血圧症患者におけるRhoキナーゼ活性の亢進が証明され，肺高血圧症の発症，進展におけるRhoキナーゼ経路の関与が示された[10]．

おわりに

本稿では，Rhoキナーゼの基礎的知見と肺高血圧症におけるRhoキナーゼ薬の将来性について，これまでに得られてきた知見を中心に解説した．しかしながら，肺高血圧症の発症メカニズムは非常に複雑であり，Rhoキナーゼ経路の役割に関しても，まだ明らかにすべき点は多い．現在われわれは，図7に示すようなアルゴリズムで肺高血圧症の治療を行っているが[55]，今後Rhoキナーゼ阻害薬を含めた新しい薬剤の有効性が示されれば，非常に重要な併用療法オプションになると期待される．

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ORIGINAL ARTICLE
Pulmonary Circulation

Identification of New Prognostic Factors of Pulmonary Hypertension

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Background: Pulmonary hypertension (PH) still remains a serious disease, for which the plasma level of brain natriuretic peptide (BNP) and hemodynamic variables (eg, cardiac index: CI) are established prognostic factors. The aim of the present study was to identify new additional prognostic factors of the disorder to improve the management of PH.

Methods and Results: The study cohort comprised 136 consecutive PH patients admitted to hospital from 1974 to 2008, all of whom were closely followed every 6–12 months. During the follow-up period of 53.5±4.5 [SEM] months, 47 patients died of cardiopulmonary causes. The patients who were initially treated with monotherapy showed improved pulmonary hemodynamics when subsequently treated with combination therapy. Multivariate analysis showed that BNP and CI were significant and independent prognostic factors in all PH patients. However, in PH patients with low CI at diagnosis, only CI improvement by PH therapy was a significant and independent prognostic factor. Indeed, the patients with low CI at diagnosis (CI <2.5) followed by subsequent normalization in response to therapy (CI ≥2.5) showed a significantly better survival compared with those without such normalization.

Conclusions: CI normalization in response to treatment is an independent new prognostic factor of PH in patients with low CI at diagnosis, suggesting the importance of intensive therapy to achieve CI normalization. (*Circ J* 2010; **74:** 1965–1971)

Key Words: Cardiac index; Prognosis; Pulmonary hypertension; Thyroid dysfunction

Pulmonary hypertension (PH), defined as a mean pulmonary arterial pressure (PAP) greater than 25 mmHg at rest,[1,2] is a fatal disease caused by small pulmonary artery obstruction related to vascular proliferation and remodeling.[3] PH is characterized by markedly elevated PAP and increased pulmonary vascular resistance (PVR), frequently leading to right-sided heart failure and death.[3] The pathological changes of the pulmonary arteries in PH include endothelial injury, proliferation and hypercontraction of vascular smooth muscle cells and migration of inflammatory cells.[4,5] Although several vasodilators, anticoagulant agents and lung transplantation are currently used for the treatment of PH, more effective treatment needs to be developed.[6]

Identification of prognostic factors is useful for better management of PH. Possibilities include functional class, exercise capacity (eg, 6-min walking distance, cardiopulmonary exercise testing), pulmonary hemodynamics (eg, mean right atrial pressure (RAP), PVR, right ventricular end-diastolic pressure (RVEDP)), right ventricular function (eg, cardiac output (CO), clinical evidence of right ventricular failure), and plasma levels of brain natriuretic peptide (BNP), endothelin-1, uric acid, and troponin.[1,2,7–10] Among these prognostic factors, plasma BNP levels and CO are considered to be the most influential.[11] We closely follow our PH patients every 6–12 months, which includes cardiac catheterization, with the aim of identify new prognostic factors of PH. Here we report that we were able to identify that normalization of CO in response to the therapy is a significant prognostic factor of PH and probably has more significance than BNP.

Methods

The Ethical Committees of Tohoku University Hospital approved the study protocol and all patients provided written informed consent. Our study cohort consisted of 136 con-

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Table 1. Clinical Characteristics of Patients With PH

Total, n	136
Age (years)	45.6±1.6
Sex	
Male, n (%)	33 (24%)
Female, n (%)	103 (76%)
Survivor, n (%)	89 (65%)
Follow-up period (months)	53.5±4.5
Type of PH	
Idiopathic PAH, n (%)	43 (32%)
Heritable PAH, n (%)	3 (2%)
PAH associated with connective tissue diseases, n (%)	21 (15%)
PAH associated with congenital heart disease, n (%)	22 (16%)
PAH associated with portal hypertension, n (%)	10 (7%)
PVOD	4 (3%)
CTEPH	33 (24%)
Treatment	
Oral prostacyclin, n (%)	71 (52%)
Intravenous prostacyclin, n (%)	51 (38%)
Bosentan, n (%)	45 (33%)
Sildenafil, n (%)	8 (6%)

Values are mean±SEM.
PH, pulmonary hypertension; PAH, pulmonary arterial hypertension; PVOD, pulmonary veno-occlusive disease; CTEPH, chronic thromboembolic pulmonary hypertension.

secutive PH patients admitted to hospital between 1974 and 2008.

Study Population

The 136 patients had PH of various etiologies, including idiopathic pulmonary arterial hypertension (IPAH, n=43), heritable PAH (n=3), PAH associated with connective tissue diseases (n=21), congenital heart diseases (n=22), or portal hypertension (n=10), pulmonary veno-occlusive disease (n=4), and PH because of chronic thromboembolism (CTEPH, n=33) (**Table 1**). Besides their regular follow-up, we hospitalize patients if their symptoms or right-heart failure worsen.

Diagnosis of PH

We performed right-heart catheterization in all 136 patients, among whom we were able to perform follow-up catheterization in 88. PH was defined as a mean PAP greater than 25 mmHg at rest.[1,2] Connective tissue disease and liver disease were diagnosed clinically and by blood tests. Congenital heart disease was diagnosed by echocardiography, and CTEPH was diagnosed by ventilation–perfusion RI scans and computed tomography (CT). Pulmonary function tests, arterial blood gases, chest X-ray and CT scan were used to diagnose lung disease and hypoxia. If the aforementioned abnormalities were ruled out, the patients were diagnosed as having IPAH.[2,5] Heritable PAH was diagnosed as IPAH with a family history of PAH.[2,5,12]

Data Collection

Baseline demographic information (including age, sex, height and body weight), clinical diagnosis, comorbidities (connective tissue diseases, liver diseases, congenital heart diseases, and thyroid dysfunction) and hemodynamic data obtained during catheterization were recorded for each patient. Hyperthyroidism was defined as either an elevated level of free triiodothyronine (T3 ≥4.12 pg/ml) and/or thyroxin (T4 ≥1.5ng/dl) or reduced level of thyroid-stimulating hormone (TSH ≤0.46 μIU/ml). Hypothyroidism was defined as either elevated TSH (>3.73 μIU/ml) or a reduced level of free T3 (<2.51 pg/ml) and/or T4 (<0.88 ng/dl). Hemodynamic parameters examined included pulmonary capillary wedge pressure, pulmonary artery pressure (PAP), RVEDP, RAP, CO, cardiac index (CI), systolic and diastolic blood pressures, mean blood pressure, PVR, systolic vascular resistance, and mixed venous oxygen saturation ($S\dot{V}O_2$). Lung transplantation and death were defined as cardiopulmonary death. The CI response was evaluated at diagnosis and 1 year after treatment.

Current Medical Treatment of PH

We usually begin oral prostacyclin at a starting dose of 60 mg/day and increase it in a stepwise manner up to 240 mg/day, if tolerable. In daily practice, we usually start intravenous prostacyclin (epoprostenol) therapy during hospitalization at 0.5–1 $ng \cdot kg^{-1} \cdot min^{-1}$, which is carefully increased in a step-wise manner on the basis of symptoms and side-effects of the drug (**Figure S1**). Similarly, we usually start bosentan at 31.25 mg/day combined with dobutamine and/or milrinone in PH patients with heart failure, and at 62.5 mg/day in those without heart failure, and then carefully increase the dose in a stepwise manner every week (**Figure S2**). Regarding sildenafil, we usually start at 30 mg/day and increase the dose up to 60 mg/day if patients can tolerate it. Currently, we treat patients with PH using prostacyclin, bosentan, sildenafil as monotherapies or in combination.

Statistical Analysis

Results are expressed as mean±SEM. Unpaired t-test was used for comparison of continuous variables and chi-test for categorical variables. Survival from all-cause death and from lung transplantation was estimated by Kaplan-Meier method and differences between the curves were examined for significance using the log-rank test. Univariate and multivariate Cox proportional hazard models were used to estimate the hazard ratios and 95% confidence intervals. Statistical analyses were performed using GraphPad Prism 5.0E (GraphPad Software Inc, La Jolla, CA, USA) or SPSS (SPSS Inc, Chicago, IL, USA). P values less than 0.05 were considered to be statistically significant.

Results

Clinical Characteristics of Patients With PH

Clinical characteristics of the 136 patients are shown in **Table 1**. During the follow-up period of 53.5±4.5 months, 47 patients died of cardiovascular causes.

Current Therapies for PH

In the 136 patients with PH, 122 (90%) were treated with oral (n=71) or intravenous prostacyclin (n=51), 45 (33%) with bosentan, and 8 (6%) with sildenafil (**Table 1**). Although it has already been reported that monotherapy with intravenous epoprostenol or oral bosentan or sildenafil improves symptoms, 6-min walk distance, pulmonary hemodynamics, and survival in patients with PAH,[13–16] some of the present patients needed additional treatment. In particular, among the patients with PAH who did not respond to any monotherapy, combination therapy with oral or intravenous prostacyclin,

Table 2. Prevalence of Thyroid Dysfunction in Patients With PH

N	127
No thyroid dysfunction, n (%)	69 (54%)
Thyroid dysfunction, n (%)	58 (46%)
Hyperthyroidism, n (% of thyroid dysfunction)	11 (19%)
Hypothyroidism, n (% of thyroid dysfunction)	47 (81%)
Treatment	
Antithyroid drugs, n (% of hyperthyroidism)	5 (45%)
Thyroid hormone replacement, n (% of hypothyroidism)	3 (6%)

Abbreviation see in Table 1.

Table 3. Comparison of Thyroid Dysfunction Between PAH and CTEPH

	PAH	CTEPH	P value
N	98	29	
No thyroid dysfunction, n (%)	47 (48%)	22 (76%)	<0.05
Thyroid dysfunction, n (%)	51 (52%)	7 (24%)	
Hyperthyroidism, n (% of thyroid dysfunction)	9 (18%)	2 (29%)	NS
Hypothyroidism, n (% of thyroid dysfunction)	42 (82%)	5 (71%)	
Treatment			
Antithyroid drugs, n (% of hyperthyroidism)	3 (27%)	2 (18%)	NS
Thyroid hormone replacement, n (% of hypothyroidism)	3 (6%)	0 (0%)	

Abbreviations see in Table 1.

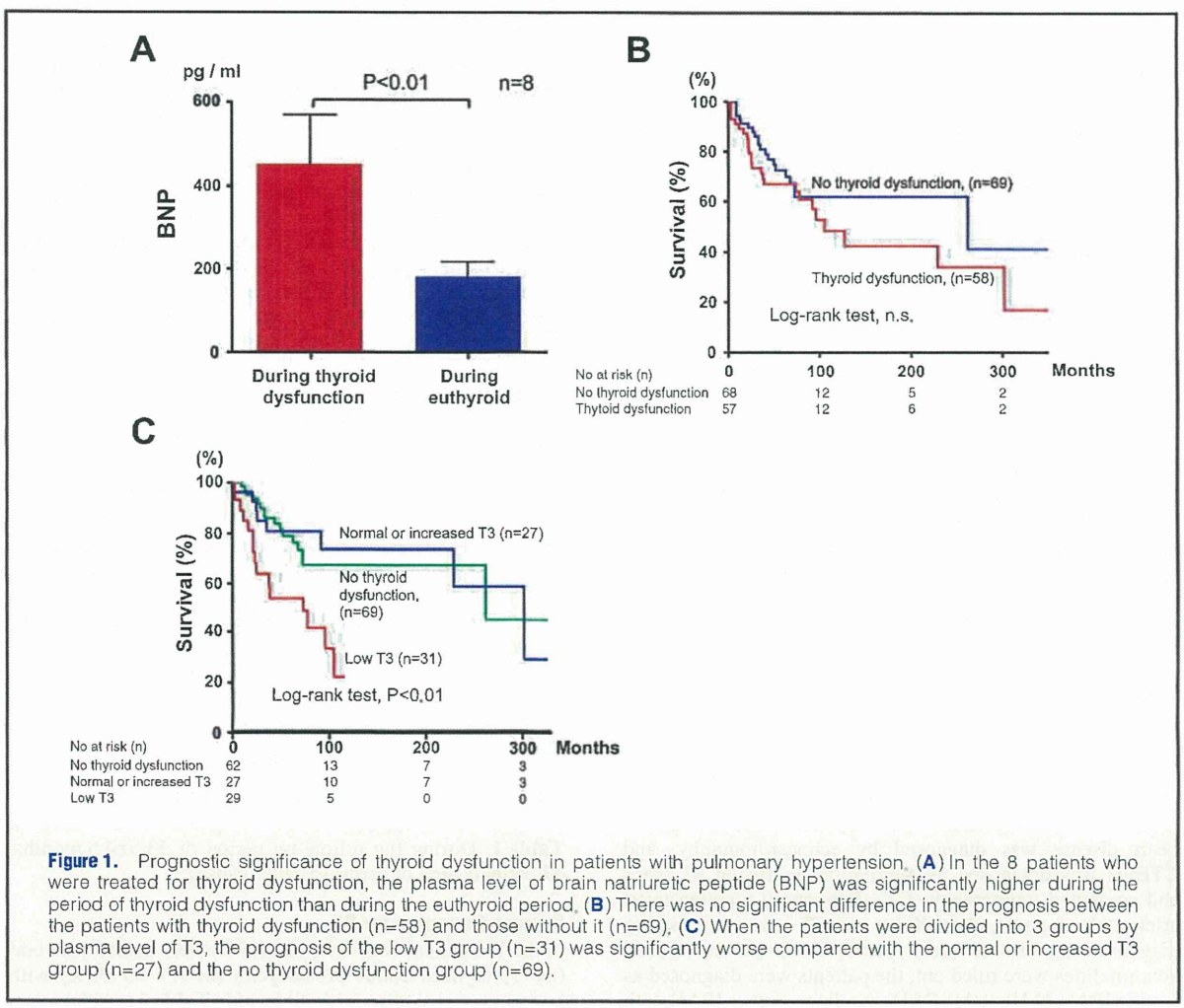

Figure 1. Prognostic significance of thyroid dysfunction in patients with pulmonary hypertension. (**A**) In the 8 patients who were treated for thyroid dysfunction, the plasma level of brain natriuretic peptide (BNP) was significantly higher during the period of thyroid dysfunction than during the euthyroid period. (**B**) There was no significant difference in the prognosis between the patients with thyroid dysfunction (n=58) and those without it (n=69). (**C**) When the patients were divided into 3 groups by plasma level of T3, the prognosis of the low T3 group (n=31) was significantly worse compared with the normal or increased T3 group (n=27) and the no thyroid dysfunction group (n=69).

bosentan, and sildenafil significantly improved pulmonary hemodynamics (**Figure S3A–D**).

Biochemical Prognostic Factors

Of the complications in this group of PH patients, thyroid dysfunction was most the common (n=58, 46%), comprising hyperthyroidism in 11 (19%) and hypothyroidism in 47 (81%); 5 of the 11 patients with hyperthyroidism were treated with antithyroid drugs, and 3 of the 47 patients with hypothyroidism were treated with thyroid hormone replace-

Table 4. Univariate and Multivariate Analyses of Prognostic Factors of PH

	Survivors	Deaths	P value	
			Univariate analysis	Multivariate analysis
All PH patients				
N	89	47	–	–
Follow-up (months)	61.9±5.3	37.5±7.7	–	–
Age (years)	47.3±1.9	42.3±2.7	NS	NS
Sex				
Male, n (%)	67 (75%)	36 (77%)	NS	NS
Female, n (%)	22 (25%)	11 (23%)		
mPAP (mmHg)	51.6±1.8	58.9±2.5	NS	NS
RAP (mmHg)	6.1±0.4	8.7±0.9	<0.05	NS
$S\dot{V}O_2$ (%)	67.8±1.1	62.7±1.8	<0.05	NS
Free T3 (pg/ml)	3.31±0.25	3.17±0.37	<0.05	NS
BNP (pg/ml)	260.4±36.4	517.5±65.5	<0.001	<0.05
CI at diagnosis	2.68±0.08	2.29±0.11	<0.01	<0.05
Low CI patients				
N	27	18	–	–
Follow-up (months)	60.6±8.0	30.1±4.4	–	–
Age (years)	44.0±3.2	43.5±3.9	NS	NS
Sex				
Male, n (%)	22 (82%)	13 (72%)	NS	NS
Female, n (%)	5 (19%)	5 (28%)		
mPAP (mmHg)	56.6±2.6	63±4.1	NS	NS
RAP (mmHg)	9.0±1.1	6.4±0.9	NS	NS
$S\dot{V}O_2$ (%)	61.2±2.8	62.0±1.3	NS	NS
Free T3 (pg/ml)	3.53±0.78	3.98±0.86	NS	NS
BNP response at low CI improvement (pg/ml)	368.5±82.6 to 188.5±60.7	538.1±106.5 to 305.3±85.0	0.053	NS
CI response in low CI at diagnosis ($L \cdot min^{-1} \cdot m^{-2}$)	1.98±0.06 to 2.80±0.11	2.00±0.08 to 2.55±0.13	<0.0001	<0.05

NS, not significant; mPAP, mean pulmonary artery pressure; RAP, right atrial pressure; $S\dot{V}O_2$, mixed venous oxygen saturation; T3, triiodothyronine; BNP, plasma level of brain natriuretic peptide; CI, cardiac index. Other abbreviation see in Table 1.

ment therapy (**Table 2**). In the present study, 90% of the patients were treated with oral or intravenous prostacyclin (**Table 1**), and there was no significant difference in the prevalence of thyroid dysfunction between those treated with prostacyclin (55 of 116 patients, 47%) and those without it (3 of 11 patients, 27%).

Interestingly, the prevalence of thyroid dysfunction was significantly higher in the patients with PAH than in those with CTEPH (**Table 3**). Although the patients with thyroid dysfunction had higher plasma levels of BNP than those without it (450±120 vs 177±39 pg/ml, P<0.05) (**Figure 1A**), thyroid dysfunction itself did not have a significant prognostic impact (**Figure 1B**). However, the patients with low T3 levels had a significantly poor prognosis by univariate analysis (P<0.01, hazard ratio: 2.368, 95% confidence interval: 1.221–4.593) (**Figure 1C**).

An elevated plasma level of BNP, which indicates right-heart failure, was also a significant prognostic factor in the univariate analysis (P<0.001, hazard ratio: 3.609, 95% confidence interval: 1.856–7.016), whereas multivariate analysis demonstrated that BNP was a significant independent prognostic predictor in all PH patients (**Table 4**).

Hemodynamic Prognostic Factors

Hemodynamic parameters, such as CI at diagnosis, RAP and $S\dot{V}O_2$, which are established prognostic factors, were also significant prognostic factors in our univariate analysis, whereas mean PAP was not (**Table 4**).

Low CO at diagnosis was a poor prognostic factor for death within 1 year (**Figure 2A**, **Table 4**). Importantly, in the univariate analysis patients with low CO at diagnosis (CI <2.5, n=45) followed by subsequent CI normalization in response to treatment (CI ≥2.5, n=34) survived significantly longer than those who did not respond to the treatment (CI <2.5, n=11) (**Figure 2B**, **Table 4**). However, among 43 patients with normal CI at diagnosis (CI ≥2.5), there were 37 with a subsequent normal CI (CI ≥2.5), of whom 29 survived and 8 died. Of the remaining 6 patients whose CI was reduced during the follow-up (CI <2.5), 5 survived and 1 died, indicating the insignificant difference in the CI response among patients with normal CI at the diagnosis.

Importantly, multivariate analysis demonstrated that among the significant prognostic factors in the univariate analysis, only CI improvement in response to treatment was an independent prognostic factor of PH in patients with low CI at diagnosis (**Table 4**).

Furthermore, there were no significant differences in PH treatment between survivors and those who died, except for monotherapy with intravenous prostacyclin in all PH patients (**Table 5**).

Discussion

In the present study, we aimed to identify new prognostic factors of PH in a relatively large cohort of patients with a long-term close follow-up. The results suggest that CI

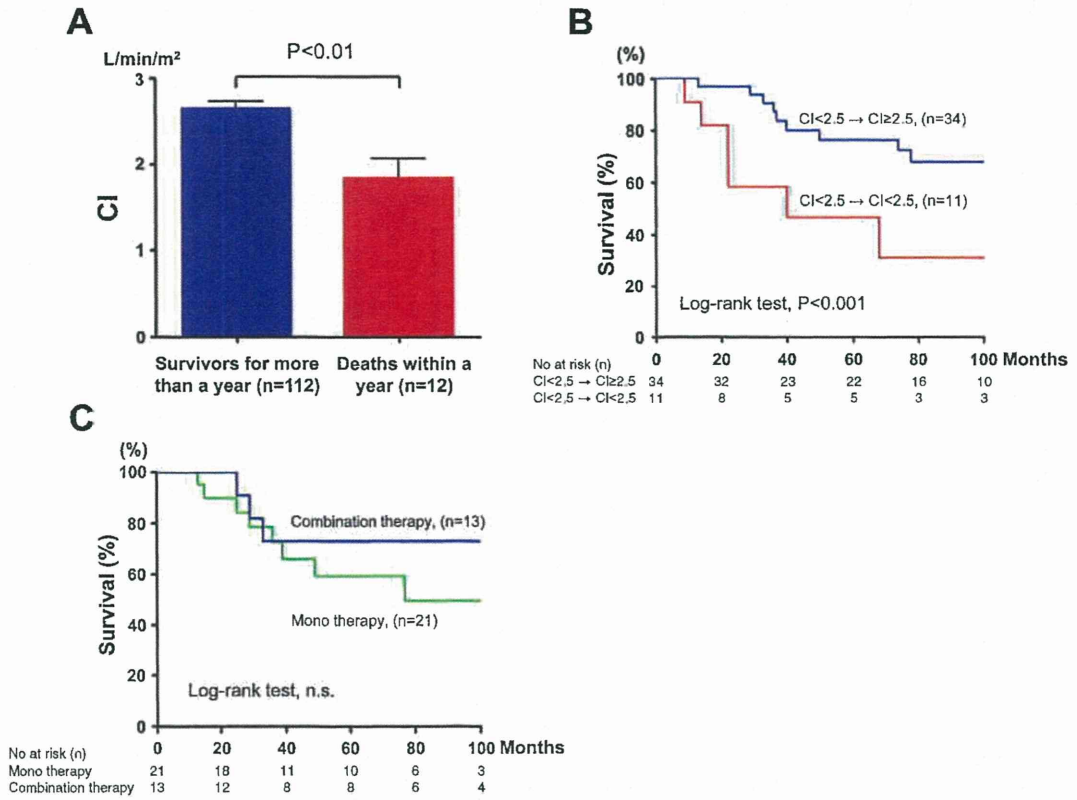

Figure 2. Prognostic significance of the cardiac index (CI) in patients with pulmonary hypertension. (**A**) Patients who survived more than 1 year had a significantly higher CI (n=112) than those who died within the year (n=12). (**B**) Patients with low cardiac output at diagnosis (CI <2.5L·min^{-1}·m^{-2}), but with subsequent normalization in response to treatment (from CI <2.5 to CI ≥2.5L·min^{-1}·m^{-2}) showed better survival than those who did not respond to the treatment (CI <2.5L·min^{-1}·m^{-2} unchanged). (**C**) Among 34 patients with low cardiac output at diagnosis (CI <2.5L·min^{-1}·m^{-2}) and subsequent normalization in response to treatment (from CI <2.5 to CI ≥2.5L·min^{-1}·m^{-2}), there was no significant difference in prognosis between the monotherapy (n=21) and combination therapy (n=13) groups.

Table 5. Use of PH Drugs in Mono and Combination Therapies

	All patients			Patients with CI normalization		
	Survivors	Deaths	P value	Survivors	Deaths	P value
Monotherapy						
N	60	35		14	7	
PGI_2 oral, n (%)	36 (60.0%)	12 (34.3%)	NS	4 (28.6%)	2 (28.6%)	NS
PGI_2 intravenous, n (%)	14 (23.3%)	19 (54.3%)	<0.05	9 (64.3%)	4 (57.1%)	NS
Bosentan, n (%)	3 (5.0%)	3 (8.6%)	NS	1 (7.1%)	1 (14.3%)	NS
Sildenafil, n (%)	2 (3.3%)	0 (0%)	NS	0 (0%)	0 (0%)	–
CCB, n (%)	2 (3.3%)	1 (2.9%)	NS	0 (0%)	0 (0%)	–
No anti-PH drugs, n (%)	3 (5.0%)	0 (0%)	NS	0 (0%)	0 (0%)	–
Combination therapy						
N	33	8		11	2	
PGI_2 oral+bosentan, n (%)	16 (48.5%)	5 (62.5%)	NS	3 (27.3%)	0 (0%)	NS
PGI_2 intravenous+bosentan, n (%)	13 (39.4%)	1 (12.5%)	NS	8 (72.7%)	1 (50.0%)	NS
PGI_2 oral+sildenafil, n (%)	1 (3.0%)	0 (0%)	NS	0 (0%)	0 (0%)	–
PGI_2 intravenous+sildenafil, n (%)	0 (0%)	1 (12.5%)	NS	0 (0%)	1 (50.0%)	NS
PGI_2 oral+bosentan+sildenafil, n (%)	1 (3.0%)	0 (0%)	NS	0 (0%)	0 (0%)	–
PGI_2 intravenous+bosentan+sildenafil, n (%)	2 (6.1%)	1 (12.5%)	NS	0 (0%)	0 (0%)	–

CCB, calcium-channel blocker; PGI_2, prostaglandin I_2. Other abbreviation see in Table 1.

normalization in response to treatment is a new prognostic factor of PH and probably has more prognostic significance than BNP and other previously established prognostic factors.

Cohort of PH Patients

Our cohort of PH had more female patients with a more prevalence of PH, and most of the patients were treated with prostacyclin alone or in combination with other vasodilators, a finding consistent with previous reports.[1,17–19] Our cohort is unique because all patients were closely followed by right-heart catheterization performed every 6–12 months in order to monitor their clinical course and to adjust the doses of drugs, including epoprostenol, bosentan and/or sildenafil. All of the drugs, especially the combination with intravenous prostacyclin and other vasodilators, have already been reported to improve symptoms, 6-min walk distance, pulmonary hemodynamics, and survival.[9,20–24] Indeed, in the present study, combination therapy with intravenous prostacyclin and other vasodilators significantly improved pulmonary hemodynamics in patients with PH who were not improved by any monotherapy. However, if combination therapy is unavailable, monotherapy with intravenous prostacyclin might not be enough in patients with severe PH, as shown in **Table 5**.

Our current strategy for advanced PH is to improve quality of life and pulmonary hemodynamics (especially CI and RAP) and to prevent the development of right-heart failure, although more therapeutic progress needs to be made.[25–29]

BNP Levels in PH

Elevated BNP level is a significant prognostic factor,[10] but in the present study this was the case in the univariate analysis only, not in the multivariate analysis when we included the CI response to treatment. This result suggests that BNP and CI closely influence each other through right ventricular dysfunction and that the CI response has more prognostic significance than BNP. However, BNP should remain in use as a prognostic factor because it is easily and non-invasively measured.

Thyroid Dysfunction in PH

The present study demonstrated that 46% of the PH patients had thyroid dysfunction (hyperthyroidism in 19%; hypothyroidism in 81%). Indeed, 5 of 11 patients with hyperthyroidism were treated with antithyroid drugs, and 3 of 47 patients with hypothyroidism were treated with thyroid hormone replacement therapy, which is consistent with previous studies in which 22–49% of patients with PAH were complicated with thyroid dysfunction.[30,31]

The precise mechanisms of thyroid dysfunction in PH remain unclear; however, involvement of autoimmune mechanisms and the side-effects of prostacyclin therapy may be involved.[30] Indeed, it was reported that the treatment of thyroid dysfunction ameliorated PAP in PH patients complicated with thyroid diseases.[32–34] It also was reported that prostacyclin plays an important role in the modulation of thyroid function in patients with Graves disease, because prostacyclin therapy may cause thyrotoxicosis as a result of downregulation of prostaglandin I_2 receptors, with subsequent reduced production of cAMP.[32,33] However, in the present study, no significant influence of prostacyclin therapy was noted on the occurrence of thyroid dysfunction. Furthermore, a low plasma T3 level was a significant prognostic factor by univariate analysis but not by multivariate analysis. In contrast, a low plasma T3 level has been reported as associated with poor prognosis in patients with chronic heart failure.[35–37]

Hemodynamic Variables in PH

Although echocardiography is a non-invasive and useful tool for the follow-up of PH patients, because it can estimate systolic PAP, it alone is not enough to evaluate pulmonary hemodynamics, because RAP, $S\dot{V}O_2$ and CI are more important prognostic factors that cannot be obtained by echocardiography.[38–40] Therefore, right-heart catheterization is essential for both accurately evaluating pulmonary hemodynamics and decision making in each PH patient.[38–40] Indeed, low CO at diagnosis is a prognostic factor of PAH[41] and further, the present study demonstrated that CO normalization in response to treatment is a new prognostic factor.

During the course of the development of PAH, pulmonary arteriopathies first occur, followed by RV pressure-overload. Thus, the final goal of PH should be regression of pulmonary arteriopathies.[6] At present, because none of the available therapies is able to normalize pulmonary hemodynamics (especially during exercise), RV function (eg, CO) may determine the prognosis of PH patients.[41]

Study Limitations

Several limitations should be mentioned. First, this was an observational cohort study from a single center, so the present finding regarding the prognostic impact of CI normalization remain to be confirmed in a large, multicenter clinical study. Second, the PH patients were treated individually, but not in a randomized manner, based on their pulmonary hemodynamics and comorbidities, so some bias could be involved. However, considering the severity of the disease, such a randomized clinical study would not be appropriate from the ethical point of view.

Conclusions

In the present study, we were able to identify that CI normalization in response to treatment is a new independent prognostic factor of PH in patients with low CI at diagnosis, suggesting the importance of intensive therapy to normalize CO in PH patients.

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Disclosures

None.

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Supplementary files

Figure S1. Administration protocol for epoprostenol.

Figure S2. Administration protocol for bosentan.

Figure S3. Effects of combination therapy on pulmonary hemodynamic variables in patients with pulmonary hypertension.

Please find supplementary file(s);
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ORIGINAL ARTICLE
Ischemic Heart Disease

Prognostic Effects of Calcium Channel Blockers in Patients With Vasospastic Angina

– A Meta-Analysis –

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Background: Although calcium channel blockers (CCB) are highly effective for suppression of vasospastic angina (VSA) attacks, their prognostic effects in VSA patients remain to be examined in a large number of patients.

Methods and Results: Databases for related papers were searched and then a meta-analysis regarding the effects of CCB on major adverse cardiovascular events (MACE) in Japanese VSA patients with the 4 previous studies was performed. A total of 1,997 patients with positive coronary spasm provocation tests were evaluated. They were treated with either alone or combination of benidipine (n=320), amlodipine (n=308), nifedipine (n=182) or diltiazem (n=960). MACE were observed in 143 patients (cardiac death: 36, myocardial infarction: 51, heart failure: 26, stroke: 65, and aortic aneurysm: 11). The hazard ratio for the occurrence of MACE was significantly lower in patients treated with benidipine than in those with diltiazem. There was no significant difference in the clinical characteristics affecting the occurrence of MACE among the 4 CCB groups. Furthermore, the hazard ratio for the occurrence of MACE was significantly lower in those treated with benidipine, even after correction for patient characteristics that could have affected the occurrence of MACE (hazard ratio 0.41, P=0.016).

Conclusions: These results suggest that among the 4 major CCB that effectively suppress VSA attacks in general, benidipine showed significantly more beneficial prognostic effects than others. (*Circ J* 2010; **74:** 1943–1950)

Key Words: Calcium channel blockers; Prognosis; Vasospastic angina

The prevalence of coronary vasospasm is high in Japanese patients with ischemic heart disease[1,2] and acute myocardial infarction (AMI).[3] Therefore, the control of vasospastic angina (VSA) has been an important clinical issue in Japan.[4–7] Calcium channel blockers (CCB) have been widely used to suppress VSA attacks and to improve the outcome of VSA patients.[4,8,9] However, comparison of the prognostic effects of CCB in VSA patients remains to be performed in a large number of patients. During the past decades, several observational studies showed that the outcome of VSA patients vary, depending on the CCB used.[10–14] In the 1980s, it was shown that 80–90% of VSA patients were treated with CCB and the major adverse cardiovascular events (MACE) rate was relatively low during the 5-year follow-up.[8] Recently, the usage of CCB has further increased to 90–95% unless otherwise contraindicated. Thus, in order to compare the actual difference among the major CCB, it is necessary to perform a large-scale clinical trial. Another possible approach is to perform a meta-analysis, utilizing the database created from previously published papers that compared the prognostic effects of CCB. In the present study, we thus performed a meta-analysis in which we compared the prognostic effects of CCB in Japanese patients with VSA.

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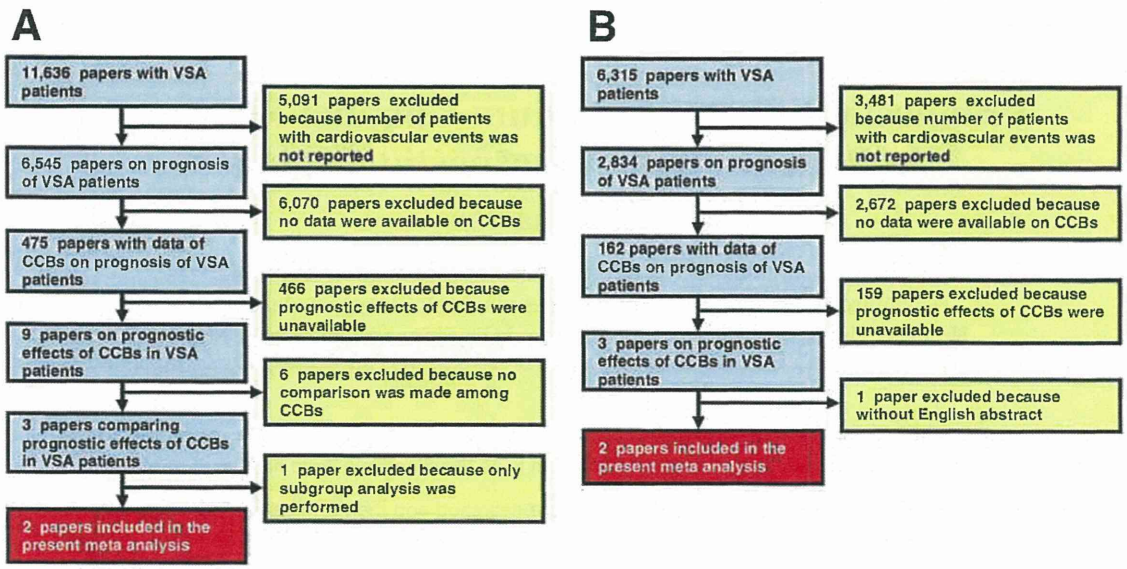

Figure 1. Summary of identification and selection of previous papers. According to the keywords, papers were systemically searched from (**A**) the database of MEDLINE® for English articles (from 1950 to 2008), and (**B**) from the database of Ichushi® (Japana centra revuo medicina) for Japanese articles with an English abstract (from 1983 to 2008). VSA, vasospastic angina; CCB, calcium channel blockers.

Table 1. Number of Patients, Spasm Provocation Test and Treatment With Calcium Channel Blockers in the 4 Studies Included in the Present Meta-Analysis

Study (years)	Total number of patients (n)	Follow-up rate (%)	Spasm provocation test	Calcium channel blockers			
			Positive response* (n)	Benidipine (n, %)	Amlodipine (n, %)	Nifedipine (n, %)	Diltiazem (n, %)
Ito (2004)[10]	726	92	665	148 (22)	111 (17)	106 (16)	405 (61)
Sueda (2006)[12]	194	83	161	52 (32)	35 (22)	13 (8)	46 (29)
Io (2007)[11]	1,146	91	879	42 (5)	149 (17)	39 (4)	358 (41)
Kodama (2007)[13]	389	75	292	78 (27)	13 (4)	24 (8)	151 (52)
All studies	2,455	88	1,997	320 (16)	308 (15)	182 (9)	960 (48)

*Considered positive when intracoronary administration of acetylcholine or ergonovine induced an ischemic ECG change or chest pain with 75% or greater constriction of the coronary artery.

Methods

Study Eligibility Criteria and Search Strategy

We searched the database of MEDLINE® for papers published in English from 1950 to December, 2008 and the Japana Centra Revuo Medicina (Ichushi®) for papers published in Japanese with an English abstract from 1983 to December, 2008. The keywords used were 16 CCB (nifedipine, nicardipine, nisoldipine, nitrendipine, nilvadipine, manidipine, benidipine, amlodipine, barnidipine, efonidipine, felodipine, clinidipine, aranidipine, azelnidipine, diltiazem, or verapamil), prognosis, and VSA and related terms (vasospasm, coronary VSA, rest angina, variant angina). The papers in Japanese were restricted to those with an English abstract. Among the 11,636 papers in English searched by the database of MEDLINE®, 2 papers were finally selected, in which the effects of CCB on the occurrence of MACE in VSA patients were compared (**Figure 1A**).[10,11] In addition, 2 papers in Japanese were selected[12,13] among the 6,315 papers searched by the database of Ichushi® (**Figure 1B**). Permission to perform a meta-analysis was obtained from the authors of the selected 4 papers.[10–13] We asked them to provide unlinkable, anonymous raw data (database), which we used to create a new database. This enabled us to analyze the data from 1,997 VSA patients with positive response to coronary spasm provocation tests. The coronary spasm provocation test was considered positive when an ischemic ECG changes and/or chest pain with coronary constriction was induced by intracoronary administration of acetylcholine or ergonovine, based on the 2008 Guidelines of the Japanese Circulation Society.[15] In the present study, the baseline point was defined as the day of discharge after the diagnosis of VSA, and the follow-up period was redefined from the 4 papers.

Comparison of CCB Treatments

Among the 1,997 VSA patients, 1,554 (77.8%) were treated with CCB, including benidipine (n=320), amlodipine (n=308), nifedipine (n=182) and diltiazem (n=960) (**Table 1**). Among

Table 2. Clinical Characteristics of Patients With Vasospastic Angina Treated With Each Calcium Channel Blocker

	Benidipine (n=320) (n, %)	Amlodipine (n=308) (n, %)	Nifedipine (n=182) (n, %)	Diltiazem (n=960) (n, %)	P value
Age					
Years (mean±SD)	64.6±9.8	64.4±9.5	63.4±9.9	62.6±10.3	0.015
Median (min-max)	65.4 (37–91)	65.0 (33–91)	63.0 (32–85)	62.6 (32–92)	
Sex					
Male	196 (61)	216 (70)	134 (74)	683 (71)	0.005
Female	124 (39)	92 (30)	48 (26)	277 (29)	
BMI, kg/m² (mean±SD)	23.9±3.4	23.8±3.0	23.4±2.9	23.5±3.0	0.173
Smoking	135 (42)	125 (41)	64 (35)	388 (40)	0.471
Family history of IHD	41 (13)	35 (11)	29 (16)	137 (14)	0.904
Hypertension	165 (52)	178 (58)	119 (65)	362 (38)	<0.001
Diabetes mellitus	61 (19)	46 (15)	29 (16)	141 (15)	0.343
Hyperlipidemia	150 (47)	123 (40)	58 (32)	316 (33)	<0.001
Previous MI	24 (8)	24 (8)	26 (14)	93 (10)	0.049
LVEF, % (mean±SD)	71.0±10.8	68.6±12.5	69.9±11.8	70.1±10.4	0.506
Coronary artery disease	56 (18)	56 (18)	32 (18)	163 (17)	0.952
0 VD	253 (79)	242 (79)	136 (75)	762 (79)	0.807
1 VD	39 (12)	46 (15)	24 (13)	124 (13)	
2 VD	16 (5)	9 (3)	6 (3)	32 (3)	
3 VD	1 (0)	1 (0)	2 (1)	7 (1)	
Treatment					
Nitrates	143 (45)	167 (54)	111 (61)	574 (60)	<0.001
Nicorandil	71 (22)	53 (17)	47 (26)	164 (17)	0.015
Aspirin	48 (15)	44 (14)	17 (9)	131 (14)	0.594
Statins	33 (10)	32 (10)	15 (8)	86 (9)	0.598
ARB	17 (5)	30 (10)	8 (4)	36 (4)	0.004
ACE inhibitors	33 (10)	36 (12)	15 (8)	51 (5)	0.001
β-blockers	34 (11)	33 (11)	14 (8)	67 (7)	0.076

BMI, body mass index; IHD, ischemic heart disease; MI, myocardial infarction; LVEF, left ventricular ejection fraction; VD, vessel disease; ARB, angiotensin II receptor blockers; ACE, angiotensin converting enzyme.

Table 3. The Number of Each Event Observed in Patients With Vasospastic Angina Treated With Either of 4 Calcium Channel Blockers

	Benidipine (n=320) (n, %)	Amlodipine (n=308) (n, %)	Nifedipine (n=182) (n, %)	Diltiazem (n=960) (n, %)	P value*
Overall (n=1,997)					
MACE	8 (2.5)	17 (5.5)	19 (10.4)**,‡	83 (8.6)‡	<0.001
Cardiac death	1 (0.3)	4 (1.3)	8 (4.4)**,‡	21 (2.2)†	<0.001
Myocardial infarction	4 (1.3)	4 (1.3)	5 (2.7)	31 (3.2)	0.109
Stroke	5 (1.6)	9 (2.9)	6 (3.3)	38 (4.0)†	0.213
Heart failure	4 (1.3)	6 (1.9)	3 (1.6)	17 (1.8)	0.911
Aortic aneurysm	2 (0.6)	2 (0.6)	2 (1.1)	7 (0.7)	0.937
Total death	10 (3.1)	15 (4.9)	16 (8.8)‖	65 (6.8)†	0.030

MACE, major adverse cardiovascular events.
*χ^2-test (among 4 groups) **P<0.05 (vs amlodipine), †P<0.05, ‖P<0.01, ‡P<0.001 (vs benidipine).

those treated with CCB, 1,349 patients were treated with a single CCB, including benidipine (n=219), amlodipine (n=199), nifedipine (n=143) and diltiazem (n=788). As the number of VSA patients treated with other CCB was small, these patients were excluded for comparison of the 4 CCB, although they were included in the whole meta-analysis. For patient characteristics, we examined the baseline data on age, gender, body mass index (BMI), smoking, family history of ischemic heart disease, risk factors (hypertension, diabetes mellitus, and hyperlipidemia), previous myocardial infarction (MI), left ventricular ejection fraction (LVEF), and the presence of significant coronary artery disease (CAD, 75% or greater coronary stenosis on coronary angiography). Co-treatment with other class of drugs also was examined, including nitrate preparations, nicorandil, statins, angiotensin II receptor blockers (ARB), angiotensin converting enzyme (ACE) inhibitors and β-blockers. The data for age, BMI and LVEF were handled by the use of categorization (age, 10-year intervals; BMI, ≥22.5 kg/m²; LVEF, <45%).

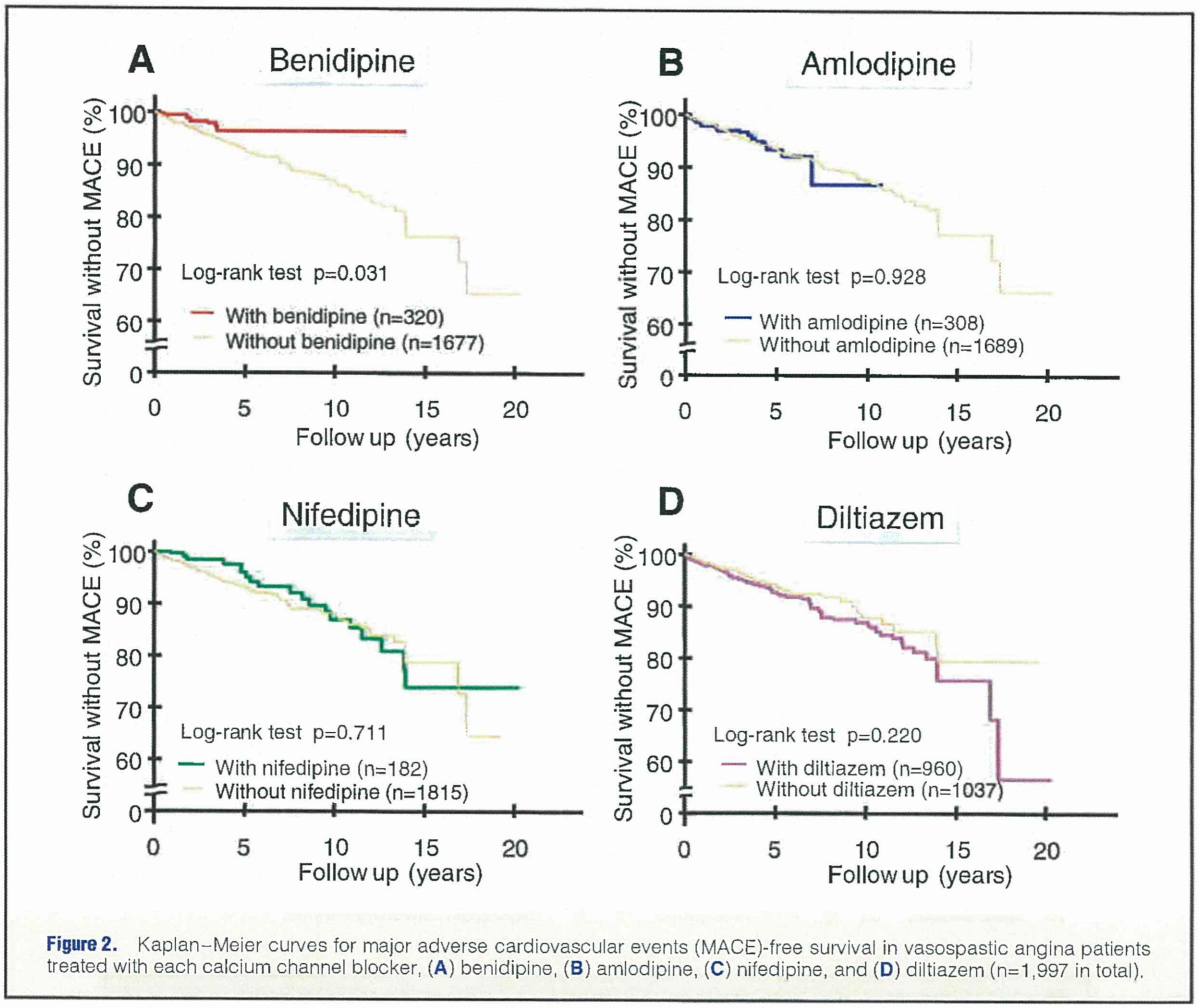

Figure 2. Kaplan–Meier curves for major adverse cardiovascular events (MACE)-free survival in vasospastic angina patients treated with each calcium channel blocker, (**A**) benidipine, (**B**) amlodipine, (**C**) nifedipine, and (**D**) diltiazem (n=1,997 in total).

Outcomes

The major outcome in this study was the occurrence of MACE, including cardiac death, MI (fatal and non-fatal), heart failure (death due to heart failure and heart failure requiring hospitalization), stroke (fatal and non-fatal), and aneurysm. The incidence of each MACE and the total number of deaths due to the event and its percentage were calculated for each CCB. We compared each MACE occurrence between the patients treated with each CCB and those without it. Because some differences were observed in the patient characteristics at baseline among the CCB groups, a search for factors (characteristics of patients and drugs used) that affected the occurrence of MACE was performed. The effect of the treatment with each CCB on the occurrence of MACE was then corrected for the factors that could have affected the occurrence of MACE.

Statistical Analysis

The major outcome of the present study was the occurrence of MACE. For each CCB, the period from the baseline day to the occurrence of MACE or the day of the last follow-up were plotted as a Kaplan–Maier curve, comparing the patients treated with each CCB and those without it. The curves were analyzed using the log-rank test. To search for factors related to the occurrence of MACE, the hazard ratio (HR) and its 95% confidence interval (CI) were calculated using Cox's regression analysis. The effect of the treatment with each CCB on the occurrence of MACE was corrected by Cox regression analysis using the factors that could affect the MACE occurrence (eg, smoking and a history of MI). In addition, in the 1,349 patients treated with a single CCB, the period until the occurrence of MACE was plotted in each CCB group as a Kaplan–Maier curve and compared using the log-rank test. All results are presented as means±SD. All statistical analyses were performed using SPSS for Windows ver. 11.0.1 (SPSS Japan Inc, Tokyo, Japan). Significance levels of 5% bilaterally and P-value less than 5% was considered to be statistically significant.

Results

Patient Characteristics

In the 4 papers used in the present meta-analysis, the diagnosis of VSA was made based on the 2008 Guidelines of the Japanese Circulation Society (**Table 1**).[15] As a result, the number of VSA patients reported by Io et al.[11] was changed from 1,047 to 879, and a total of 1,997 VSA patients with positive response to coronary spasm provocation tests were

finally analyzed. In addition, because the events used for the outcome evaluation varied slightly among the 4 papers, all of the events evaluated were handled as complex events. The follow-up period was recalculated according to the definition of MACE used in the present study, with a median follow-up period of 4.4 years (min–max: 0.2–21.9).

Table 2 shows the clinical characteristics of the VSA patients treated with each CCB. The age was higher in the benidipine group compared with other CCB groups. The prevalence of female patients was higher in the benidipine group compared with the nifedipine group. Among the major risk factors, hypertension was less frequent in the diltiazem group and hyperlipidemia was less frequent in the diltiazem or nifedipine groups compared with other CCB groups. Previous MI was observed more frequently in the nifedipine group. Regarding the concomitant drugs, nitroglycerin preparations were used less frequently in the benidipine group compared with other CCB groups, and nicorandil was more frequently used in the benidipine and nifedipine groups compared with other 2 groups. ARB were used more frequently in the amlodipine group compared with the nifedipine or diltiazem groups, while ACE inhibitors were less frequently used in the diltiazem group. Nifedipine was the long-acting form (twice a day or once a day), and diltiazem was slow-release preparation.

We also compared the reduction in the frequency of anginal attacks due to coronary spasm in the 4 CCB groups. We found that the frequencies of anginal attacks at follow up in the benidipine (0.7±1.1 attacks/month) and nifedipine (0.7± 1.6 attacks/month) groups were significantly lower than those in the amlodipine (1.4±1.6 attacks/month) and diltiazem (1.6± 5.9 attacks/month) groups (P<0.001, between each group, Mann–Whitney test).

Comparison of the Prognostic Effects of CCB

In the present study, MACE occurred in 143 patients, including cardiac death (n=36), AMI (n=51), heart failure (n=26), stroke (n=65) and aortic aneurysm (n=11). The total number of deaths was 118. Of these events, the number of each event observed in VSA patients treated with either of 4 CCB, ie, benidipine, amlodipine, nifedipine and diltiazem, was shown in **Table 3**. MACE occurred significantly less in the patients treated with benidipine compared with those without it (P= 0.031, log-rank test) (**Figure 2**). By contrast, no significant difference was noted between the patients treated with amlodipine, nifedipine or diltiazem and those without them (**Figure 2**). A search for the background factors that could have affected the occurrence of MACE showed significant differences with respect to age (10-year intervals), the presence of diabetes mellitus, the presence of CAD, and use of β-blockers (**Table 4**). The HR for the occurrence of MACE was significantly lower in the patients treated with benidipine compared to those without benidipine (HR=0.46, CI= 0.22–0.95, P=0.035) (**Figure 3**). The HR was also significantly lower in the patients treated with benidipine, even after correction for the background factors (HR=0.41, CI=0.20–0.85, P=0.016) (**Figure 3**). Again, no significant difference was noted with other 3 CCB (**Figure 3**).

Multivariate analysis showed that diabetes mellitus and CAD were independent risk factors for MACE. However, age and use of β-blockers had no significant impact on the

Table 4. Factors Influencing MACE in Patients With Vasospastic Angina (Univariate Cox Regression Analysis, n=1,997)

	HR (95%CI)	P value
Diabetes mellitus	2.02 (1.39–2.95)	<0.001
Coronary artery disease	1.97 (1.37–2.85)	<0.001
ARB	1.88 (0.91–3.89)	NS
β-blockers	1.69 (1.02–2.81)	0.043
Previous MI	1.48 (0.95–2.31)	NS
ARB/ACE inhibitors	1.48 (0.88–2.48)	NS
Nitrates	1.28 (0.90–1.82)	NS
Hypertension	1.23 (0.89–1.71)	NS
Age (every 10 years)	1.21 (1.04–1.42)	0.017
ACE inhibitors	1.17 (0.59–2.31)	NS
Nicorandil	1.13 (0.74–1.72)	NS
Smoking	1.04 (0.75–1.46)	NS
Anginal attacks (follow-up)	1.00 (0.99–1.01)	NS
Family history of IHD	0.92 (0.58–1.46)	NS
BMI, ≥22.5 kg/m²	0.85 (0.61–1.21)	NS
Hyperlipidemia	0.82 (0.57–1.18)	NS
Sex, female (vs male)	0.72 (0.48–1.07)	NS
Statins	0.65 (0.30–1.41)	NS
LVEF, <45%	0.55 (0.22–1.35)	NS

HR, hazard ratio; CI, confidence interval. Other abbreviatuions see in Tables 2,3.

	No. of pts.	MACE n	MACE (%)	Non-adjustment Hazard rate	Non-adjustment P value	Adjustment* Hazard rate	Adjustment* P value
Benidipine	320	8	(2.5)	0.46	0.035	0.41	0.016
Amlodipine	308	17	(5.5)	1.02	NS	0.98	NS
Nifedipine	182	19	(10.4)	0.91	NS	0.88	NS
Diltiazem	960	83	(8.6)	1.23	NS	1.15	NS

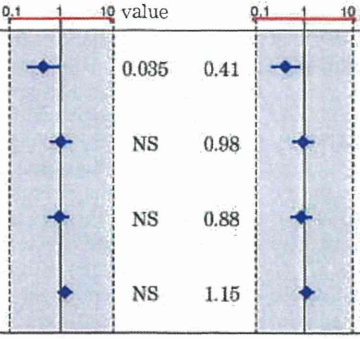

Figure 3. Influence of calcium channel blockers on major adverse cardiovascular events (MACE) in vasospastic angina patients (Cox regression analysis, n=1,997 in total). No, number; pts, patients. *The factors used for the adjustment included the established factors for MACE in general (age, diabetes, significant coronary artery disease, and β-blocker) and the factors for vasospastic angina in particular (smoking, history of previous myocardial infarction).

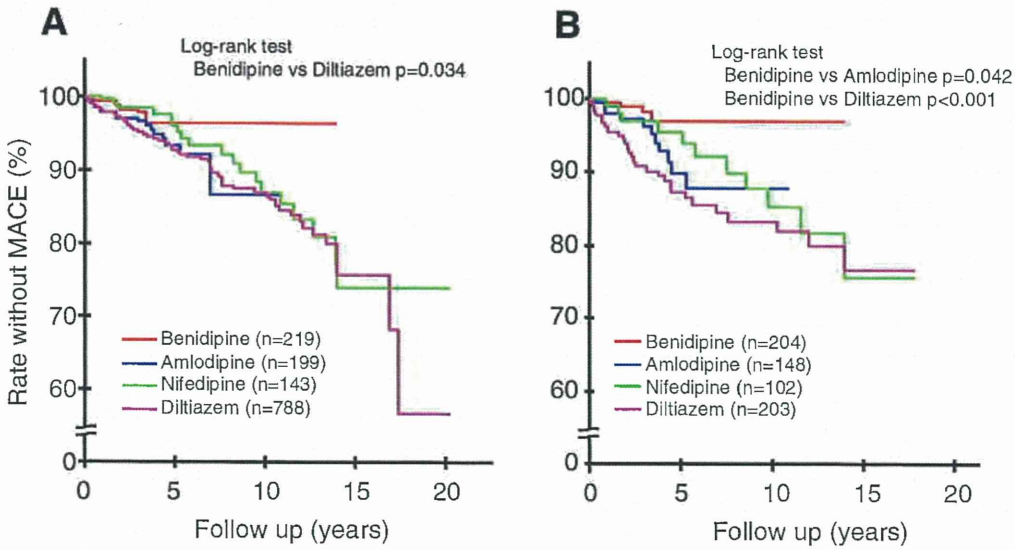

Figure 4. Kaplan–Meier curves for major adverse cardiovascular events (MACE)-free survival in vasospastic angina patients treated with each calcium channel blocker (**A**) before and (**B**) after the correction by the propensity scores.

occurrence of MACE. When the occurrence of MACE was compared among the 1,349 VSA patients treated with a single CCB, we again found that MACE occurred significantly less in the benidipine group (n=219) as compared with the diltiazem group (n=788) (P=0.034, log-rank test) (**Figure 4A**). We calculated the propensity score,[11] using the selection criteria for each agent to correct the bias of patients background. The factors of selection criteria included age, sex, hypertension, hyperlipidemia, and previous MI, and matching was performed. After correction by the propensity score, there was no significant difference in any factors among the 4 CCB groups, and again the incidence of MACE in the benidipine group (n=204) was significantly lower as compared with the diltiazem (n=203, P<0.001) and the amlodipine groups (n=148, P=0.042) (**Figure 4B**).

Discussion

The present meta-analysis with a total of 1,997 Japanese patients with VSA revealed positive coronary spasm provocation tests demonstrates that among the major CCB used for the treatment of VSA, benidipine might exert more beneficial prognostic effects as compared with other CCB. To the best of our knowledge, this is the first meta-analysis study that addresses the comparative prognostic effects of CCB in VSA patients.

Clinical Significance of Meta-Analysis for the Prognosis of VSA Patients

There have been several reports regarding the prognostic effects of CCB in patients with VSA.[8–14] However, all of these studies were retrospective in nature and therefore there could be some bias introduced when doctors chose the drugs. Nevertheless, these retrospective studies are valuable because they provide important data with VSA patients treated with different kinds of drugs. Moreover, although randomized controlled studies are considered superior to retrospective studies, one cannot exclude the bias introduced when doctors choose the patients to be enrolled. Therefore, we endeavored to evaluate the effects of CCB on the occurrence of MACE in a meta-analysis by using raw data and re-defining the study endpoint.

Prognostic Factors for the Incidence of MACE in VSA Patients

The present meta-analysis showed that diabetes mellitus, the presence of CAD, use of β-blockers and advanced age (every 10 years) were significant risk factors for MACE in VSA patients (**Table 4**). It was previously reported that the age older than 65 years was a risk factor for cardiovascular events.[10] However, in the present study, we found that advanced age, even less than 65 years, was a risk factor for MACE in VSA patients.

Diabetes mellitus is an established risk factor for cardiovascular events in VSA patients,[10,11] and insulin resistance associated with compensatory hyperinsulinemia is an independent risk factor for VSA.[16] Consistent with these findings, we found that diabetes mellitus is a risk factor for MACE. Indeed, the number of diabetic patients has been dramatically increasing in Japan,[17] indicating that special attention should be paid to diabetes mellitus in order to improve the prognosis of VSA patients.

It was repeatedly demonstrated that CAD is a prognostic factor in patients with rest angina and VSA.[1,10,11,13,18] Among these studies, Yamagishi et al emphasized that CAD is the most important prognostic factor affecting the prognosis of VSA patients, irrespective of the treatment with CCB.[18] The findings of the present study confirm that the risk of MACE is significantly increased by the presence of CAD, even in patients treated with CCB. Our findings also suggest the use of β-blockers might worsen the prognosis of VSA patients, which is consistent with an earlier report suggesting that β-blockers can worsen coronary vasospasm,[15] perhaps by

augmenting the effects of α-receptor stimulation.[19]

In the present study, multivariate analysis showed that diabetes mellitus and CAD were independent risk factors for MACE, although age and use of β-blockers had no significant impact on the occurrence of MACE. We also confirmed that the risk of cardiovascular events, such as sudden death, fatal and non-fatal MI, increased in VSA patients with significant coronary stenosis. Thus, careful observation is necessary for diagnosis and treatment of diabetes mellitus in VSA patients.

Prognostic Effects of CCB in VSA Patients

CCB are usually prescribed to VSA patients in an effort to prevent attacks of coronary vasospasm and related sudden cardiovascular death and other cardiac events.[7,9–14,18] However, only a few studies have compared the prognostic effects of CCB.[10–14] In these reports, the number of patients treated with CCB might not be high enough to draw a clear conclusion as to their prognostic effect in VSA patients. In the present study, we compared the prognostic effects of the 4 major CCB in a larger number of patients through a meta-analysis of the raw data. The result showed that benidipine had a significantly better prognostic effect as compared with amlodipine, nifedipine or diltiazem, while no differences were noted among the other 3 CCB.

Benidipine has been reported to be more selective for coronary artery smooth muscle cells compared with the other 3 CCB.[20,21] This higher selectivity of benidipine for coronary arteries might be involved not only in its inhibitory effects on coronary artery spasm, but also in its better prognostic effects. Moreover, the high affinity of benidipine for the coronary artery[22] might relate to its long-lasting effects independent of its blood concentration.[23] The beneficial prognostic effect of benidipine as compared with other CCB was first noted at sixth year, suggesting that vasculoprotective effects of but not anti-vasospastic effects of benidipine are involved (**Figure 2**). Indeed, it was recently shown that benidipine, but not diltiazem, improves vascular endothelial function assessed by flow-mediated dilation (FMD) in VSA patients[24] and that benidipine improves vascular functions, including FMD,[25] pulse wave velocity[26] and augmentation index[27] in patients with hypertension. We also previously reported that benidipine reduced MI size by increasing nitric oxide (NO) production and inhibiting free radical production in a rabbit model of MI.[28] It was reported that changing from diltiazem to benidipine reduced the frequency of anginal attacks associated with increased plasma NO levels in VSA patients.[29]

Study Limitations

The apparent limitation of the present study is that it is a meta-analysis of the retrospective cohort studies with VSA patients, where all of the patients were prescribed a CCB, at least at the time of follow-up investigation. However, we were unable to confirm treatment compliance (eg, the rate of drug cessation during the follow-up period) due to the unavailability of such data from the 4 studies.

Although the patient characteristics were corrected by propensity score matching in the present study, a prospective randomized controlled clinical trial should be conducted to compare the prognostic effects of CCB in patients with VSA. Furthermore, the information on the type of long-acting nifedipine (eg, twice a day type or once a day type) was unavailable in the present study. This point also remains to be examined in a future study.

Conclusions

The present meta-analysis with 1,997 VSA patients demonstrates that benidipine exerts more beneficial prognostic effects in Japanese patients with VSA as compared with the other 3 CCB, although this notion remain to be confirmed in future prospective randomized studies.

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Optical Coherence Tomography as a Novel Diagnostic Tool for Distal Type Chronic Thromboembolic Pulmonary Hypertension

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The new classification of pulmonary hypertension (PH) has been recently updated,[1] in which 5 major categories of the disorder have been classified. Among them, pulmonary arterial hypertension (PAH, class 1) and chronic thromboembolic PH (CTEPH, class 4) are characterized as having similar hemodynamic pulmonary circulation despite their different pathological vascular structures.

Optical coherence tomography (OCT) is an interferometer-based optical imaging modality that produces a 2-dimensional image of optical scattering from internal tissue microstructures with a high resolution of approximately 10–20 μm, 10-fold higher than that of intravascular ultrasound.[2–4] Here, we report the potential usefulness of OCT as a novel diagnostic tool for the differential diagnosis of distal type CTEPH from PAH.

The Ethics Committees of Tohoku University Hospital approved the study protocol and all patients provided written informed consent. We prospectively enrolled 31 consecutive patients with PH, including PAH (n=17), CTEPH (n=9), and normal hemodynamic subjects (control, n=5), who were

Table. Subject Characteristics

	Control	PAH	CTEPH	P value
n	6	18	9	
Age (years)	64.2±4.7	45.6±3.7	60.2±4.4	<0.05
Gender, n (%)				
Male	1 (17)	6 (33)	0 (0)	NS
Female	5 (83)	12 (67)	9 (100)	NS
Type of PH, n (%)				
IPAH	–	6 (33)	–	
CTD-PAH	–	9 (50)	–	
CHD-PAH	–	2 (11)	–	
Portal hypertension-PAH	–	1 (6)		
Hemodynamic variables				
PCWP (mmHg)	9±1	8±1	9±1	NS
Mean PAP (mmHg)	15±1	42±4	42±4	NS
CI ($L \cdot ml^{-1} \cdot m^{-2}$)	2.8±0.3	2.9±0.2	3.0±0.2	NS
Mean PVR ($dyne \cdot s^{-1} \cdot cm^{-5}$)	130±28	718±149	585±80	NS
OCT findings, n (%)				
Thrombus formation	0 (0)	0 (0)	4 (44)	<0.05
Luminal flaps	0 (0)	0 (0)	6 (67)	<0.01

Data are expressed as mean±SEM. Statistical analysis was performed between PAH and CTEPH, using unpaired t-test for continuous variables and chi-square test for categorical variables, using Stat View (SAS Institute, Cary, NC, USA).
PAH, pulmonary arterial hypertension; CTEPH, chronic thromboembolic pulmonary hypertension; PH, pulmonary hypertension; IPAH, idiopathic PAH; CTD, connective tissue disease; CHD, congenital heart disease; PCWP, pulmonary capillary wedge pressure; PAP, pulmonary arterial pressure; CI, cardiac index; PVR, pulmonary vascular resistance; OCT, optical coherence tomography.

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