ある。

このメディカルコントロール体制とは、消防機関と医療機関との連携によって、〔1〕救急隊が現場からいつでも迅速に医師に指示、指導、助言が要請できる、〔2〕実施した救急活動の医学的判断、処置の適切性について医師による事後検証を行い、その結果を再教育に活用する、〔3〕救急救命士の資格取得後の再教育として、医療機関において定期的に病院実習を行う、という体制をいうものである。

消防機関と医療機関との協議の場である各都道府県単位及び各地域単位のメディカルコントロール協議会については、全て設置が完了しており、事後検証等により、救急業務の質的向上に積極的に取り組んでいるところである。

(4) ウツタイン様式の導入

ウツタイン様式とは、心肺停止症例をその原因別に分類するとともに、目撃の有無、バイスタンダーによる心肺蘇生の有無等に分類し、それぞれの分類における傷病者の予後を記録するためのガイドラインであり、世界的に推奨されているものである。

我が国では、平成17年1月から全国の消防本部で一斉に導入を開始する予定であるが、全国統一的な導入は各国で初めての先進的な取組みとなるものである。消防庁としては、ウツタイン様式による調査結果をオンラインで集計・分析するためのシステム整備も併せて進めており、運用が開始されると、救急救命士が行う救急救命処置の効果等の検証や諸外国との比較が客観的データに基づき可能となり、プレホスピタル・ケアの一層の充実に資するものである。

ウツタイン様式の導入に当たっては、消防機関と医療機関の連携体制の充実・強化を促進していくことが重要である。

(5) 救急隊員等による自動体外式除細動器(AED)の使用

従来、医師、救急救命士等以外の非医療従事者には心肺停止傷病者に対する除細動を実施することが認められていなかったが、平成16年7月に示された厚生労働省設置の「非医療従事者による自動体外式除細動器(AED)の使用のあり方検討会」の報告書により、非医療従事者による自動体外式除細動器(AED；Automated External Defibrillator)の使用を可能とする見解が示された。報告書では、救急隊員、一般消防職員等、業務の内容や活動領域の性格から一定の頻度で心肺停止傷病者に応急の対応をすることが期待・想定される非医療従事者には所要の講習が必要とされた。

これを受け、消防庁では、「応急手当普及啓発推進検討会」を開催し、救急隊員等のための講習のあり方を取りまとめたところであり、今後、救急隊員等に所要の講習を実施することにより、救急現場におけるより迅速な除細動が可能となり、救命効果の向上が期待される。

(6) 住民に対する応急手当の普及

救急自動車の要請から救急隊が現場に到着するまでに要する時間は、平成15年中の平均では6.3分である。この間に、救急現場に居合わせた一般市民による応急手当が適切に実施されれば、大きな救命効果が得られる。したがって、住民の間に応急手当の知識と技術が広く普及するよう、実技指導に積極的に取り組んでいくことが重要である。現在、特に心肺機能停止傷病者を救命する心肺蘇生法(CPR)技術の習得に主眼を置き、住民体験型の普及啓発活動が推進されている。

消防庁としては、「応急手当の普及啓発活動の推進に関する実施要綱」(平成5年3月制定)により、心肺蘇生法等の実技指導を中心とした住民に対する救命講習の実施や応急手当の指導者の養成、公衆の出入りする場所・事業所に勤務する管理者・従業員を対象にした応急手当の普及啓発及び学校教育を対象とした応急手当の普及啓発活動を行っている。この結果、講習受講者数は年々着実に増加しており、平成15年中の救命講習受講者数は114万人を超え、消防機関は最も代表的な応急手当普及啓発の担い手として期待されている。

消防機関においては、昭和57年に制定された「救急の日」(9月9日)及びその前後の「救急医療週間」を中心に、応急手当講習会や救急フェア等を開催し、住民に対する応急手当の普及啓発活動に努めるとともに、応急手当指導員等の養成や応急手当普及啓発用資機材の整備を推進しているところである。

また、平成16年7月から、一般市民を含めた非医療従事者による自動体外式除細動器(AED)の使用が可能となったことから、消防庁としては、「応急手当普及啓発推進検討会」の報告を受けて必要な要綱等の改正を行い、消防機関における自動体外式除細動器(AED)による除細動の内容を組み入れた救命講習の実施を促進していくこととしている。

ウツタイン様式導入に当たって

1　ウツタイン様式について

1990年6月に、ノルウェーのウツタイン修道院で開催された国際蘇生会議において、アメリカ心臓協会等の世界各国の学会の代表が、病院外心肺機能停止症例の蘇生率等について、地域間・国際間での比較が可能になるよう、記録方法に関するガイドラインを作成しました。

具体的には、心肺機能停止症例をその原因から心原性（心筋梗塞等）、非心原性（交通事故による外傷、溺水等）に分類すると共に、目撃の有無、バイスタンダーによる心肺蘇生の有無、初期心電図波形別等に分類し、それぞれの分類における傷病者の予後転帰を記録するためのガイドラインであり、その名称がウツタイン様式とされました。

2　我が国におけるウツタイン様式の導入の経緯について

ウツタイン様式は、90年代以降、心肺機能停止症例に関する記録方法として、世界的に推奨されてきました。しかし、欧米諸国においても、この様式に基づく記録が国レベルで行われている例はなく、一部の救急システムの進んだ地域での導入例があるとはいえ、現在も都市レベル、地域レベルでの導入にとどまっています。

我が国においても、東京都下や大阪府下等において、ウツタイン様式による記録、分析が行われている例や、また、救急振興財団において、平成9年から平成13年にかけて、全国10の救命救急センターと関係消防本部の協力により、ウツタイン様式による救命効果の調査が行われた例等がありますが、全国レベルでの導入は未だ行われていませでした。

しかしながら、救急救命士の処置範囲の拡大等の救急業務の質的な変化を踏まえ、救急業務高度化推進検討会において、ウツタイン様式に基づく心肺機能停止症例に関する記録様式の全国的な導入の必要性について検討が重ねられた結果、平成17年1月からウツタイン様式を導入すべきとの報告書がとりまとめられました。

3　プレホスピタル・ケアの充実に向けて

消防庁としては、ウツタイン様式の導入によって、全国的な集計、分析だけではなく、各都道府県や消防本部単位においても、集計、分析を実施し、得られる統計データを消防機関と医療機関が共有し、救命効果の客観的・医学的な評価、地域間・国際間の比較・検証を実施する予定です。そして、今後の我が国のプレホスピタル・ケアの充実に有効活用するとともに、救急救命士の処置範囲拡大を含めた、一層の救急業務の高度化を推進し、我が国の救命率の更なる向上を目指します。

Ⅶ. 資料・業績集

Exercise-Induced Hepatocyte Growth Factor Production in Patients After Acute Myocardial Infarction

—— Its Relationship to Exercise Capacity and Brain Natriuretic Peptide Levels ——

Satoshi Yasuda, MD; Yoichi Goto, MD; Hiroshi Takaki, MD; Yasuhide Asaumi, MD; Takeshi Baba, MD; Shunichi Miyazaki, MD; Hirohi Nonogi, MD

Circulation Journal
Vol. 68 No. 4 April 2004
(Pages 304–307)

Circ J 2004; **68**: 304–307

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Background The hepatocyte growth factor (HGF) is a multifunctional cytokine with cardioprotective properties and potent myogenic activity for vascular endothelium. In patients after acute myocardial infarction, exercise training has the beneficial effects on cardiovascular adaptations. We hypothesized that exercise induces HGF production in those patients. If this hypothesis is correct, HGF production may be associated with clinical parameters of cardiovascular function.

Methods and Results In 20 patients after acute myocardial infarction, HGF levels in the pulmonary artery (HGF_{PA}) and aorta (HGF_{Ao}) were determined at rest and during supine submaximal exercise, with cardiac output (CO) measured by catheterization. Exercise-induced HGF production was calculated by using the following equation: $[(HGF_{PA}-HGF_{Ao})\times CO$ during exercise$]-[(HGF_{PA}-HGF_{Ao})\times CO$ at rest]. On a separate day, peak oxygen uptake ($\dot{V}O_2$) was determined during a symptom-limited upright cardiopulmonary exercise test. Exercise increased HGF production (from 1.6±3.0 to 9.0±6.3μg/ml, $p<0.001$). Exercise-induced HGF production was inversely related to peak $\dot{V}O_2$ ($r=-0.664$, $p<0.01$) and positively related to levels of brain natriuretic peptide (BNP), a biochemical marker for post-infarction ventricular remodeling ($r=0.686$, $p<0.01$).

Conclusions Exercise significantly increases HGF production. This phenomenon may play an important role in post-infarction patients, particularly with reduced exercise tolerance and elevated BNP levels. (*Circ J* 2004; **68**: 304–307)

Key Words: Exercise; Growth substances; Myocardial infarction; Rehabilitation

Hepatocyte growth factor (HGF), originally identified and cloned as a potent mitogen for hepatocyes, has mitogenic, motogenic, morphogenic, and anti-apoptotic activities in a variety of cells through its receptor, c-Met[1,2] HGF is a unique growth factor to act protectively against endothelial dysfunction[3–5] myocardial ischemia/infarction and remodeling[6–8] Thus, the HGF system (HGF and its receptor c-Met) is attracting increasing attention in the field of cardiovascular pathophysiology[9]

In patients with acute myocardial infarction (AMI), exercise training has the beneficial effects on cardiovascular systems[10] Cardiac effects include attenuation of post-infarction ventricular remodeling[11,12] for which brain natriuretic peptide (BNP) is a useful biochemical marker[13] Vascular effects include an increase in the density of skeletal-muscle capillaries[14] and improvement in endothelial-dependent vasodilation[15,16] which are important determinants for exercise tolerance and symptoms.

In the present study, we hypothesized that exercise induces HGF production, mediating the beneficial effects of exercise training in patients with AMI. If so, HGF production may be associated with clinical parameters of cardiovascular function.

(Received August 4, 2003; revised manuscript received December 24, 2003; accepted January 8, 2004)

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Methods

Study Patients

The study group included 20 male patients (aged 61± 12 years [mean±SD]) after AMI. The infarction site was anterior in 13 patients (65%), and inferior/lateral in 7 patients (35%). All patients underwent reperfusion therapy (percutaneous transluminal coronary angioplasty in 17 patients and intravenous administration of tissue-type plasminogen activator in 3 patients) on admission. The peak level of serum creatine kinase was 2,995±2,043 [mean± SD]U/L. The severity of heart failure ranged from New York Heart Association functional class I to II. The baseline patient characteristics are summarized in Table 1. No patients had liver (elevated levels of aminotransferases), kidney (elevated levels of creatinine or urea), or lung dysfunction (restrictive or obstructive pattern in spirometry). No patients had prior myocardial infarction. Medications remained unchanged during the entire study.

The study was approved by the institutional review committee. The protocol was fully explained, and all patients gave their written informed consent to participate in the study.

Table 1 Baseline Characteristics of Patients

NYHA, n (%)	
I	*12 (60)*
II	*8 (40)*
LVEF (%)	*43±9*
LVEDVI (ml/m²)	*70±11*
LVEDP (mmHg)	*13±6*
Coronary risk factors, n (%)	
Diabetes mellitus	*11 (55)*
Hyperlipidemia	*9 (45)*
Hypertension	*7 (35)*
Medications, n (%)	
ACE-inhibitor	*11 (55)*
Ca^{2+}-antagonist	*12 (60)*
Nitrates	*9 (45)*
Aspirin	*20 (100)*
Diuretics	*8 (40)*
Digoxin	*7 (35)*
β-blockers	*4 (20)*

NYHA, New York Heart Association classification; LVEF, left ventricular ejection fraction; LVEDVI, left ventricular end-diastolic volume index; LVEDP, left ventricular end-diastolic pressure; ACE, angiotensin-converting enzyme; Ca^{2+}, calcium.

Table 2 Changes in Hemodynamics and HGF Levels in Response to Supine Exercise

	Baseline	*Peak exercise*	*p value*
HR (beats/min)	*68±11*	*117±17*	*<0.001*
Aosyst (mmHg)	*126±17*	*169±20*	*<0.001*
PAsyst (mmHg)	*34±7*	*58±14*	*<0.001*
PAdiast (mmHg)	*11±4*	*19±5*	*<0.001*
CO (L/min)	*6.8±1.6*	*14.7±3.9*	*<0.001*
HGF_{PA} (ng/ml)	*7.72±3.50*	*7.82±3.53*	*NS*
HGF_{Ao} (ng/ml)	*7.45±3.32*	*7.14±3.14*	*NS*
ΔHGF(PA–Ao) (ng/ml)	*0.27±0.44*	*0.68±0.58*	*<0.01*
CO×ΔHGF (μg/min)	*1.6±3.0*	*9.0±6.3*	*<0.001*
$S\dot{V}O_2$ (%)	*67±4*	*34±10*	*<0.001*

HGF, hepatocyte growth factor; HR, heart rate; Ao, aorta; PA, pulmonary artery; syst, systolic pressure; diast, diastolic pressure; CO, cardiac output (by the thermodilutional method); ΔHGF (PA–Ao), the difference in HGF levels between pulmonary artery and aorta; $S\dot{V}O_2$, mixed venous O_2 saturation.
p values were assessed with the paired student t-test.

Cardiac Catheterization and Supine Exercise Test

From the right brachial artery through a 6F sheath, chronic phase coronary angiography and left ventriculography were performed according to the conventional Judkins technique, 28±7 [mean±SD] days after the onset of myocardial infarction[17] Heparin was initially administered at a dose of 5,000 IU into the distal brachial artery. For angiographic evaluation of left ventricular volumes, ventricular silhouettes in 30° right anterior oblique projections were digitized with an ANCHOR ventriculography analysis system (Siemens-Elema, Solna, Sweden). By the area-length method, the left ventricular end-systolic and end-diastolic volume indices and ejection fraction were calculated. Left ventricular pressure was measured with a 2F high-fidelity micromanometer catheter (model SPC-320; Miller Instruments, Houston, TX, USA) advanced into the left ventricle via the lumen of a 6F pig tail catheter.

A 7.5 F Swan-Ganz thermodilution catheter (Opticath®; Abbott Laboratories, North Chicago, IL, USA) was inserted through the left subclavian vein, to measure cardiac output (CO) and pulmonary artery (PA) pressure.

After sampling blood and measuring hemodynamic parameters at baseline, the supine bicycle exercise test was performed by using a Siemens Ergometry System 930B, and the mixed venous O_2 saturation ($S\dot{V}O_2$), and pressure of the PA and aorta (Ao) were monitored. We also monitored arterial blood O_2 saturation continuously using a Biox III pulse oximeter (Omeda, Louisville, KY, USA). The workload was increased at 3-min intervals in 30-W increments followed by a 0-W bicycling period for 1 min. The exercise was finished at 30 W in 2 patients, 60 W in 8 patients and 90 W in 10 patients. This final workload was the submaximal level for each patient, because the peak heart rate was approximately 80% of the maximal heart rate achieved at the symptom-limited cardiopulmonary exercise test, as described below. Before and immediately after the supine exercise test, blood samples were taken from the PA and the Ao. The samples were centrifuged at 4°C and stored at –80°C until assayed.

Cardiopulmonary Exercise Test

On a separate day (3±1 [mean±SD] days before the cardiac catheterization), patients underwent the symptom-limited cardiopulmonary exercise test (CPX), with determination of peak oxygen uptake ($\dot{V}O_2$), workload and heart rate. The exercise test was performed on a calibrated, electronically braked bicycle in an upright position (Examiner, Lode B.V., Groningen, Netherlands). Ramp protocols began at a workload of 0 W for 1 min and increased in 15-W increments at 1-min intervals. Expired gas analysis was performed by using a respiromonitor AE-280 (Minato Products, Tokyo, Japan). The $\dot{V}O_2$ was measured on a breath-by-breath basis, and was averaged over contiguous 30-s intervals, except at peak exercise, when 18-s averaging was used.

Hepatocyte Growth Factor Measurements

Hepatocyte growth factor levels in the pulmonary artery (HGF_{PA}) and aorta (HGF_{Ao}) were determined with specific enzyme-linked immunosorbent assay kits (Otsuka Assay Laboratories, Tokushima, Japan). Microtiter plates coated with an anti-HGF murine monoclonal antibody were incubated with standard HGF or serum samples, and an anti-HGF rabbit polyclonal antibody was added. After adding first the anti-rabbit goat immunoglobulin G-peroxidase conjugate and then o-phenylene diamine, the absorbance was read at 492 nm using a plate reader[18] The sensitivity of the HGF kit was 0.1 ng/ml. This assay system detects only bioactive, heterodimeric (mature) forms of HGF in the blood samples[18,19] Previous studies have demonstrated that there is a strong (r=0.986) positive correlation between HGF levels measured by this assay system and those measured by bioassay (determined by stimulating DNA synthesis of rat hepatocytes in primary cultures)[18,19]

The BNP levels were determined with a specific immunoradiometirc assay kit (Shionogi Co, Osaka, Japan), as previously reported[17] The sensitivity of this BNP kit is 2 pg/ml. Brain natriuretic peptide has been considered as a biochemical marker of ventricular remodeling after myocardial infarction.

Data Analysis

Exercise-induced HGF production (μg/min) was calculated by using the following equation:

$[(HGF_{PA}-HGF_{Ao})\times CO$ at peak exercise$]-[(HGF_{PA}-HGF_{Ao})\times CO$ at rest].

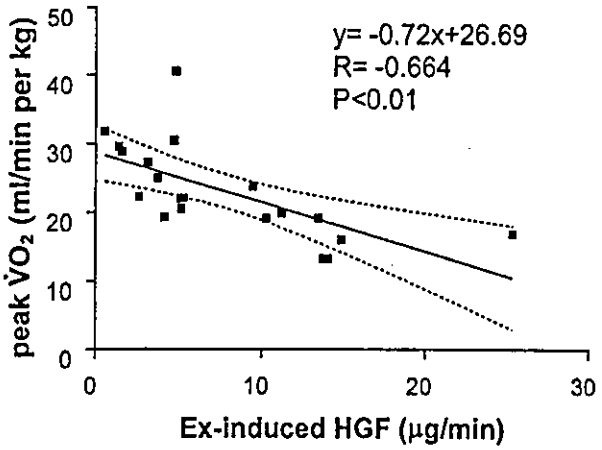

Fig 1. Correlation of the exercise (Ex)-induced hepatocyte growth factor (HGF) production with peak oxygen uptake (peak $\dot{V}O_2$) in 20 patients after acute myocardial infarction (AMI).

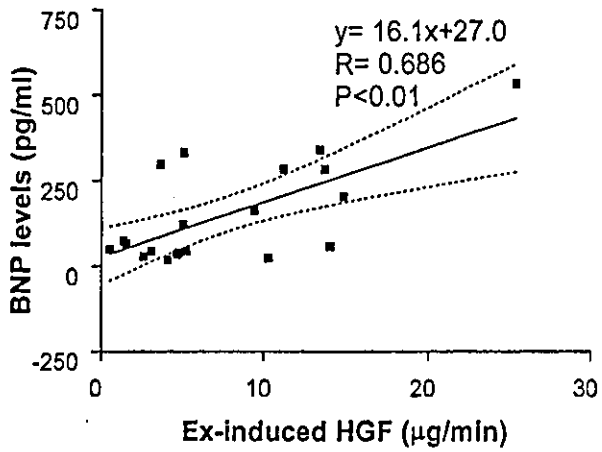

Fig 2. Correlation of the exercise Ex-induced HGF production with brain natriuretic peptide (BNP) levels.

The χ^2 test was used for comparison of categorized variables. The Student's t-test or Mann-Whitney U-test rank test was used for comparisons of mean values to determine significance of difference between the 2 groups. Linear regression curves and correlations were calculated according to the least squares method. All data are presented as mean±SD. Differences were considered significant at $p<0.05$.

Results

Changes in Hemodynamics and HGF in Response to Supine Exercise

Table 2 shows the changes in hemodynamics and HGF levels, at baseline (=before exercise) and at peak exercise during the catheterization. At baseline, there were no significant differences in HGF levels between PA and Ao. The supine exercise (74±18 W in intensity, 10±2 min in duration) significantly increased heart rate, Ao pressure, PA pressure, and CO, whereas it decreased $S\dot{V}O_2$. Although the absolute HGF levels in PA and Ao appear unchanged, the difference in HGF levels between PA and Ao (ΔHGF) significantly increased by approximately 3-fold after the exercise. When assessed based on the fold change compared with the baseline level, exercise increased the HGF_{PA} to 1.02±0.11-fold ($p<0.05$), but did not change HGF_{Ao} (0.96±0.09-fold). Finally, in the patients of the present study, exercise-induced HGF production ([ΔHGF×CO at peak exercise]−[ΔHGF×CO at baseline]) was calculated to be 7.4±6.3 μg/min, on average.

Correlations With HGF Production

Peak $\dot{V}O_2$, workload and heart rate determined during the symptom-limited upright cardiopulmonary exercise text (CPX) performed on a separate day were 23±7 ml/min per kg, 130±37 W, and 140±24 beats/min, respectively.

As shown in Fig 1, exercise-induced HGF production correlated inversely with peak $\dot{V}O_2$ ($r=-0.664$, $p<0.01$). Eight patients with peak $\dot{V}O_2<20$ ml/min per kg had greater exercise-induced HGF production (13.4±5.9 vs 3.9±2.4 μg/min, $p<0.05$) and higher prevalence of angiographically significant stenosis in major coronary arteries (>60%) (50 vs 8%, $p<0.05$) in comparison with the remaining 12 patients with $\dot{V}O_2\geq20$ ml/min per kg.

Also, as shown in Fig 2, exercise-induced HGF production correlated positively with BNP levels at baseline ($r=0.686$, $p<0.01$). However, there were no significant relations with cardiac function at rest (left ventricular end-diastolic volume index and ejection fraction), percentage increase in heart rate, Ao pressure and PA pressure in response to the submaximal supine exercise (data not shown).

Discussion

The major finding of the present study is that HGF production is induced during exercise in accordance with the severity of exercise intolerance and the increase in BNP levels.

In patients after AMI, exercise training is now emerging as an important component of the therapy[10,20] It attenuates post-infarction ventricular remodeling, which is associated with heart failure and increased mortality,[21] and is accompanied by an elevated level of BNP[13] Regular exercise training also increases the density of skeletal muscle capillaries[14] and induces repetitive increases in vascular blood flow and shear stress,[22] thereby improving endothelium-dependent vasodilation[15,16] Both central (cardiac) and peripheral (skeletal muscle and vascular) effects of exercise training may consequently improve exercise tolerance and symptoms[10] From the data obtained in the present study, a causal relationship cannot be clearly determined. However, the several effects of exercise training are potentially mediated through HGF in patients after AMI.

As shown in Table 2, exercise increases the concentration gradients of HGF levels between PA and Ao, indicating exercise-induced HGF production. The vessel wall may be a potential source of circulatory HGF[23] Fig 1 shows that exercise-induced HGF production is associated with reduced peak $\dot{V}O_2$. In particular, patients with peak $\dot{V}O_2<20$ ml/min per kg were sensitive towards the HGF response to exercise. These patients with reduced exercise capacity had a higher prevalence of coronary artery stenosis. Myocardial ischemia appears to be one of the determinants for exercise capacity and is known to induce upregulation of non-cardiac HGF systems[24] HGF promotes angiogenesis as a potent growth factor of endothelial cells[25] and promotes the functional recovery of nitric-oxide-mediated vasodila-

tion[26] thus improving myocardial blood flow. Also, as shown in Fig 2, exercise-induced HGF production is associated with increased levels of BNP. The HGF may be systemically released during exercise in response to left ventricular dysfunction and may exert wound healing and cardioprotective actions against myocardial ischemia/infarction[27,28] In a mouse myocardial infarction model, HGF gene therapy attenuated left ventricular remodeling and dysfunction[28]

The recent clinical studies also suggest a possibility that HGF may contribute to improving myocardial ischemia and dysfunction. In the CAPTURE (c7E3 Anti-Platelet Therapy in Unstable REfractory angina) trial studying the patients with acute coronary syndromes, elevated HGF levels are associated with reduced incidence of death and myocardial infarction[29] In another study in patients with coronary artery disease, elevated coronary sinus HGF levels were associated with collateral formation and with left ventricular dysfunction[30] Thus, interventions that enhance HGF levels could be beneficial in the management of those patients. Exercise is a potential approach. However, further studies are required to determine whether short-term benefits of exercise could translate into long-term effects[20]

In conclusion, the present study provides a novel aspect of exercise training as cytokine-mobilization. HGF may have a therapeutic implication in patients after AMI.

Acknowledgment

This study was supported, in part, by grants from the Uehara Memorial Foundation, the Osaka Heart Club, Japan Cardiovascular Research Foundation (Dr Yasuda), and the Ministry of Health and Welfare, Japan (Dr Goto).

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Local Delivery of Argatroban for the Prevention of Restenosis After Coronary Balloon Angioplasty

—— A Prospective Randomized Pilot Study ——

Tomonori Itoh, MD; Hiroshi Nonogi, MD; Shunichi Miyazaki, MD;
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Circulation Journal
Vol. 68 No. 7 July 2004
(Pages 615–622)

Circ J 2004; 68: 615–622

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Background Effective pharmacological prevention of restenosis using the systemic administration of various drugs that were effective for the prevention of restenosis in experimental studies has not been reported. The purpose of this study was to evaluate whether the local delivery of a potent thrombin inhibitor, argatroban, using a local drug delivery device would prevent restenosis after plain old balloon angioplasty (POBA).

Methods and Results Seventy patients with chronic coronary artery disease requiring POBA were randomly assigned to wither the control group (n=35) or the argatroban group (n=35). In the argatroban group, argatroban was administered intravenously for 30 min before the POBA and intracoronarily into the dilated site using a Dispatch™ catheter immediately after the POBA, followed by a postoperative intravenous infusion for 4 h. The angiographical lesion restenosis and clinical restenosis rates at follow-up were significantly lower in the argatroban group (27% and 14%) than in the control group (56% and 37%; p=0.02 and p=0.03, respectively). There was no major complication during the procedure.

Conclusion The local delivery of argatroban is safe and effective in preventing restenosis after balloon angioplasty. (*Circ J* 2004; 68: 615–622)

Key Words: Coronary angioplasty; Direct thrombin inhibitor; Local drug delivery; Restenosis

The clinical efficacy of coronary balloon angioplasty (plain old balloon angioplasty: POBA) is limited by restenosis, which occurs in 30–50% of cases despite a successful procedure[1–4] However, in previous clinical trials[5–9] there has not been effective pharmacological prevention of restenosis using the systemic administration of various drugs that were found to be effective for the prevention of restenosis in experimental studies. One of the major factors in the failure of restenosis prevention in these clinical trials could be that the systemic administration of drugs resulted in a concentration at the site of a balloon injury that was too low. Accordingly, it has been anticipated that the local delivery of a drug at a high concentration may reduce the restenosis rate after POBA. However, the pharmacological prevention of restenosis using a local drug delivery system has not yet been tested in clinical trials except for one small-scale trial[10]

It was recently reported that the messenger RNA (mRNA) of a thrombin receptor is expressed in medial smooth muscle cells in the very early phase after a balloon catheter injury (within 6 h)[11,12] Moreover, pre-treatment with hirudin (a direct thrombin inhibitor) was found to reduce vascular lesion development after balloon injury in experimental studies[13,14] Thus, it is thought that restenosis may be prevented or minimized by the local administration of a direct thrombin inhibitor. Argatroban is a direct thrombin inhibitor that has a more potent inhibitory effect on fibrin- or clot-incorporated thrombin than other thrombin inhibitors such as heparin and hirudin[15,16] Tomaru et al reported that the local delivery of argatroban using a double-balloon catheter reduced intimal thickening after balloon injury in an experimental study[17] Accordingly, we conducted a prospective, randomized, controlled clinical trial to assess the effect of the local delivery of argatroban as a direct thrombin inhibitor using a Dispatch™ catheter system[18] (SIMED Life Systems, Inc, Maple Grove, MN, USA) in the prevention of restenosis after percutaneous coronary intervention (PCI).

Methods

Study Protocol

Between March 1995 and May 1997, 70 patients who required coronary revascularization were registered in the present trial (Drug Delivery Device in Coronary Balloon Angioplasty Trial: 3D-CAT) at the National Cardiovascular Center. The 3D-CAT is a randomized controlled pilot trial for prevention of restenosis after coronary balloon angioplasty conducted at a single center. The inclusion criterion was that the patient was scheduled for elective POBA with a balloon size equal to or larger than 2.75 mm. All of the patients had ischemic chest pain or evidence of ischemia diagnosed by a thallium-201 or treadmill exercise test. The patients were randomly assigned to 2 groups

(Received December 17, 2003; revised manuscript received April 15, 2004; accepted April 20, 2004)

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Presented at the 70th American Heart Association Scientific Sessions, November 13, 1997; Orlando, Florida, USA.

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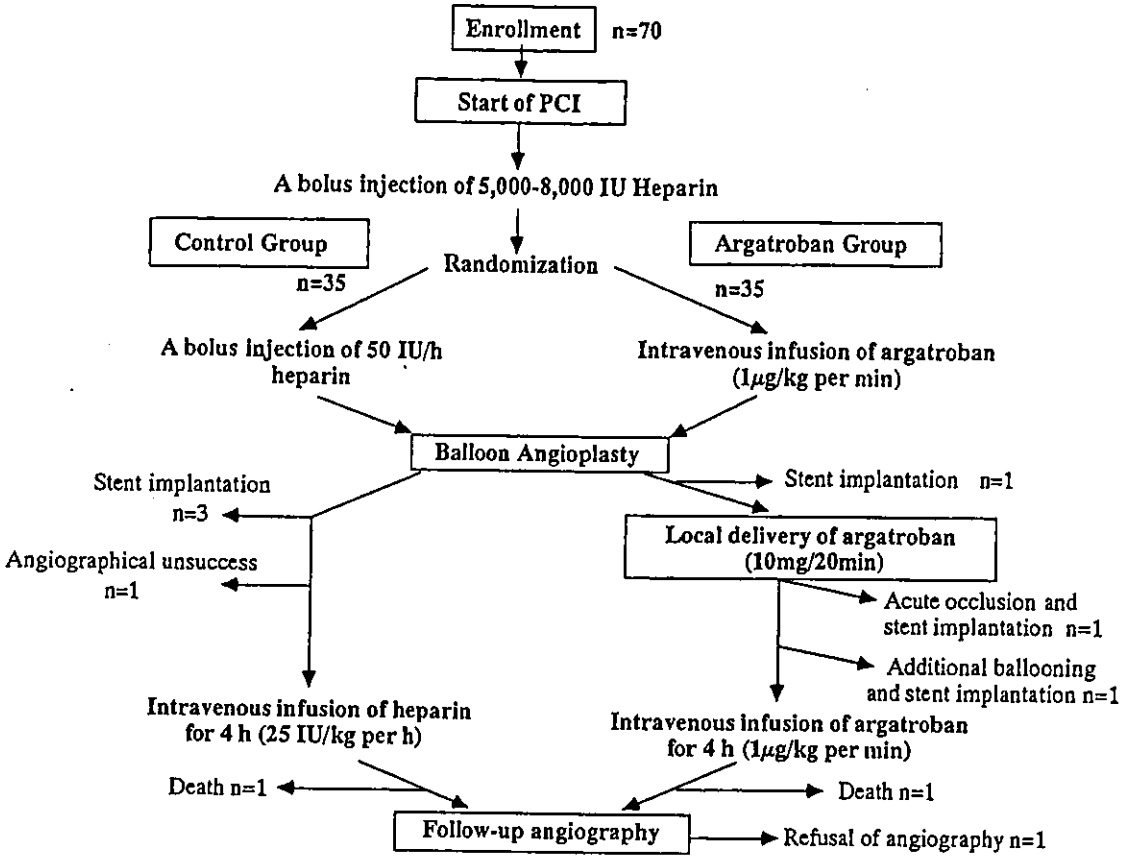

Fig 1. Study protocol and patient flow chart. A bolus of 5,000–8,000 IU heparin was injected intravenously at the start of the percutaneous coronary intervention (PCI) procedure. Patients were randomly assigned to 2 groups: the control group and the argatroban group receiving local delivery of argatroban via a Dispatch™ catheter after PCI. Control group: PCI was performed; the patients received a bolus injection of heparin during the procedure and an intravenous infusion of heparin for 4 h after angioplasty. Argatroban group: intravenous infusion of argatroban was started 30 min before the PCI, followed by local delivery of argatroban into the dilated site using a Dispatch™ catheter, and the postoperative treatment of intravenous infusion of argatroban for 4 h.

according to consecutive sealed envelopes; the control group (n=35) underwent a conventional method of POBA, and the argatroban group (n=35) had the addition of local delivery of argatroban. The exclusion criteria were (1) more than 80 years old or less than 20 years old, (2) a target lesion in a non-protected left main coronary artery, (3) a total occlusive lesion equal to TIMI 0-1 flow, (4) a severely calcified lesion, (5) a diffuse lesion, (6) a target vessel with severe proximal tortuosity, (7) a lesion that restenosed more than once, (8) a bypass graft vessel, (9) an indication for a new device (eg, directional coronary atherectomy, stent, rotational atherectomy or laser ablation), (10) poor left ventricular function (ejection fraction <40%), (11) patients receiving warfarin, (12) patients receiving an intravenous infusion of heparin, (13) a history of gastrointestinal bleeding, thrombocytopenia, or coagulopathy, (14) a history of stroke within the preceding 3 months, (15) acute myocardial infarction within the previous month, (16) patients undergoing thrombolysis within the past 24 h, (17) pregnancy, and (18) other major illness including renal failure and liver dysfunction. Informed consent was obtained from each patient.

PCI Procedure and Adjunctive Therapy

Coronary angiography was performed using the Judkins method, and a bolus of 5,000–8,000 IU heparin was given intravenously after vascular access had been established. In the control group, the POBA was performed in a standard way with a bolus injection of heparin (50 U/kg per h) during the procedure, followed by an infusion of heparin (25 U/kg per h) for 4 h after the POBA. In the argatroban group, an intravenous infusion of argatroban was given (1 μg/kg per min) 30 min before POBA, followed by the local delivery of argatroban (10 mg/20 min) into the dilated site using the Dispatch™ catheter (SIMED Life Systems) after the successful POBA. Postoperatively, the patients received an intravenous infusion of argatroban (1 μg/kg per min) for 4 h (Fig 1). All patients received both Ca antagonist and 81–162 mg of aspirin before the POBA until the follow-up angiography. In addition, β-blockers, long-acting isosorbide dinitrates or nicorandil was administered at the discretion of the treating physician before the POBA until the follow-up coronary angiography. Clinical success of the POBA was defined as angiographic success (residual stenosis <50%) without a major complication (death, myocardial infarction, or emergency coronary-artery bypass surgery) during hospitalization.

Quantitative Coronary Angiographic Analysis

All angiograms were analyzed by a computer-assisted system of quantitative coronary angiographic analysis (QCA; Cardiovascular Measurement System Ver. 3.0

Table 1 Baseline Clinical Characteristics of the Study Patients

	Control group (n=35)	Argatroban group (n=35)	p value
Age (years)	61±8	61±8	NS
M/F	29/6	27/8	NS
Risk factors			
BMI	23.6±2.0	23.5±2.6	NS
Diabetes mellitus	18	12	NS
Hypertension	19	23	NS
Total cholesterol (mg/dl)	185±32	198±36	NS
Prior MI	13	8	NS
Ejection fraction (%)	57±10	58±13	NS
Diseased coronary vessels			
1-vessel disease	23	23	NS
2-vessel disease	11	12	
3-vessel disease	1	0	
Target vessel			
LAD/LCX/RCA	18/13/4	16/16/3	NS

BMI, body mass index; MI, myocardial infarction; LAD, left anterior desending artery; LCX, left circumflex artery; RCA, right coronary artery.

Table 2 Baseline Lesion Characteristics of the Study Patients

	Control group (n=35)	Argatroban group (n=35)	p value
ACC/AHA classfication			
A	5	5	
B	29	29	NS
C	1	1	
De novo lesion	32 (94%)	28 (80%)	NS
Reference vessel diameter (mm)	2.89±0.46	2.89±0.39	NS
Minimal lumen diameter (mm)	0.86±0.24	0.83±0.19	NS
Lesion length (mm)	6.00±3.69	5.25±3.77	NS
Lesion characteristics			
Eccentricity	29 (83%)	27 (77%)	NS
Calcification	12 (34%)	16 (46%)	NS
Ostial lesion	4 (11%)	5 (14%)	NS
Proximal tortuosty	2 (6%)	1 (3%)	NS
Angled lesion	4 (11%)	4 (11%)	NS
Bifurcation	7 (20%)	6 (17%)	NS

(CMS), Medical Imaging Systems Inc, Leiden, the Netherlands). CAG was performed before, immediately after, and 3 months after the POBA (follow-up) as described in detail elsewhere![9] All angiographic analyses were performed in a blinded fashion by an experienced physician. The % diameter stenosis (%DS) and minimal lumen diameter (MLD) of the target lesion were determined quantitatively. The diameter of a Judkins catheter was measured using a precision micrometer (No. 293-421-20; precision 0.001 mm, Mitutoyo Co, Kawasaki, Japan) to obtain a calibration factor in the 'Free French' mode in the image calibration of the CMS program. The calibration factor (CF) was adjusted between 0.08 and 0.1 mm/pixel using digital zoom according to the CMS manual![20] The complex edit mode (gradient field transform: GFT) was used in the case of a complex lesion, as described in detail elsewhere?[1]

Angiographic restenosis after POBA was defined as a %DS greater than 50% on the follow-up angiogram. Clinical restenosis was defined as the recurrence of ischemia and/or target lesion revascularization within the period before the follow-up angiography.

Endpoints

The following endpoints were prospectively defined. Restenosis was the primary endpoint. Secondary endpoints included death, acute myocardial infarction (symptoms, ECG changes, and creatine kinase >twice the upper normal limit) and coronary revascularization (coronary bypass surgery, or repeated POBA and/or coronary stenting). Repeat revascularization of the target lesion (target lesion revascularization) was defined as angioplasty or bypass surgery performed because of restenosis of the target lesion in association with recurrent angina, objective evidence of myocardial ischemia, or both. The principal safety endpoints were abrupt vessel closure, stroke, major bleeding, or the need for vascular surgery. Major bleeding was defined as intracranial hemorrhage or overt bleeding associated with a decrease in hemoglobin of more than 5 g/dl.

Statistical Analyses

The data are presented as mean±SD (standard deviation). Differences in angiographical parameters (%DS and MLD) between the 2 groups before POBA, immediately after all procedure and during the follow-up were compared by unpaired t-test. Statistical comparisons of differences in categorical data between the 2 groups were performed using the chi-square test. Differences were considered significant when $p<0.05$. The clinical follow-up analyses were performed on an intention-to-treat basis and on-treatment-analyses. Moreover, angiographic follow-up analyses were performed using on-treatment-analyses.

Table 3 In-Hospital Outcomes of the Study Patients

	Control group (n=35)	Argatroban group (n=35)	p value
Stent required (%)	3 (8.6)	3 (8.6)	NS
Acute occlusion (%)	0 (0)	1 (2.8)	NS
Additional ballooning (%)	0 (0)	1 (2.8)	NS
Angiographical nonsuccess (%)	1 (2.8)	0 (0)	NS
Acute myocardial infarction (%)	0 (0)	0 (0)	NS
Emergency CABS (%)	0 (0)	0 (0)	NS
Death (%)	0 (0)	0 (0)	NS

CABS, coronary artery bypass surgery; MI, myocardial infarction.

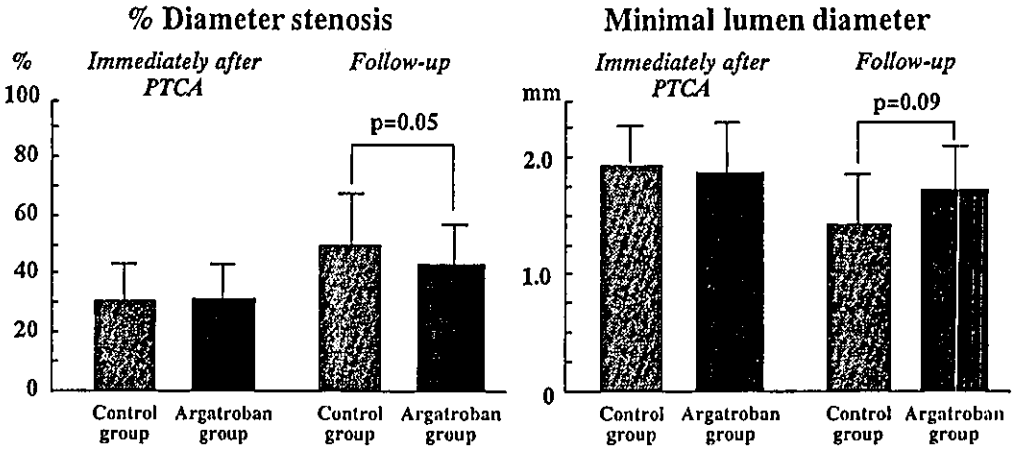

Fig 2. There were no significant differences between the 2 groups in % diameter stenosis or minimal lumen diameter immediately after PCI. Angiographic parameters including % diameter stenosis and minimal lumen diameter were marginally better in the argatroban group than in the control group at follow-up.

Results

Patient Population (Fig 1)

Four patients in the argatroban group were excluded from the follow-up CAG; 1 underwent stent implantation because of a major coronary dissection before the local delivery of argatroban, 1 had an abrupt vessel closure during the local delivery of argatroban, 1 required additional ballooning and stent implantation, and 1 refused to undergo the follow-up CAG with negative exercise thallium-201 stress imaging. Four patients in the control group were also excluded from the follow-up CAG: 3 required stent implantation because of major coronary dissection after the balloon angioplasty, and 1 had residual %DS >50% (angiographically unsuccessful). During the course of the study, 2 patients died suddenly (control 1, argatroban 1) before the follow-up angiography; the 1 in the argatroban group had cardiac sudden death after balloon angioplasty on day 60 (the patient had an old myocardial infarction with left ventricular dysfunction) and the patient in the control group died suddenly on day 60 after the balloon angioplasty (suspected rupture of a thoracic aortic aneurysm). In total, 10 patients (5 in each group) were excluded from the follow-up angiography.

Baseline Clinical and Lesion Characteristics

Tables 1 and 2 summarize the baseline clinical and lesion characteristics; there were no significant differences between the 2 groups in this study.

In-Hospital Outcome

The in-hospital outcomes are summarized in Table 3. An acute occlusion in the treated segment during the local delivery of argatroban using a Dispatch™ catheter was observed in 1 patient, requiring implantation of a Palmaz-Schatz stent. There were no major complications during the procedure in either group.

Quantitative CAG Analyses at Follow-up

Fig 2 compares the results of the angiographic analyses between the 2 groups. There were no significant differences between the 2 groups in %DS (Control group: 30.9±10.9%, Argatroban group: 31.7±9.6%) or MLD (Control group: 1.95±0.3 mm, Argatroban group: 1.92±0.35 mm) immediately after procedure. However, after 3 months, the angiographic parameters of %DS (Control group: 51.3±16.2%, Argatroban group: 43.5±14.6%) and MLD (Control group: 1.36±0.46 mm, Argatroban group: 1.57±0.47 mm) were marginally better in the argatroban group than in the control group (p=0.05 and p=0.09, respectively). The mean difference in coronary MLD (net gain) between the post-procedure and follow-up angiograms was 0.51±0.44 mm in the control group, and 0.72±0.50 mm in the argatroban group (p=0.09).

Restenosis Rates, Target Lesion Revascularization, and Clinical Follow-up Data

Fig 3 compares the restenosis rates in the 2 groups. The lesion restenosis (%DS >50%) rates were 27% in the argatroban group and 56% in the control group (p=0.02). The clinical restenosis rates were 14% in the argatroban group and 37% in the control group (intention-to-treat analysis; Table 4, p=0.03). The target lesion revascularization rates were 14% in the argatroban group and 34% in the control

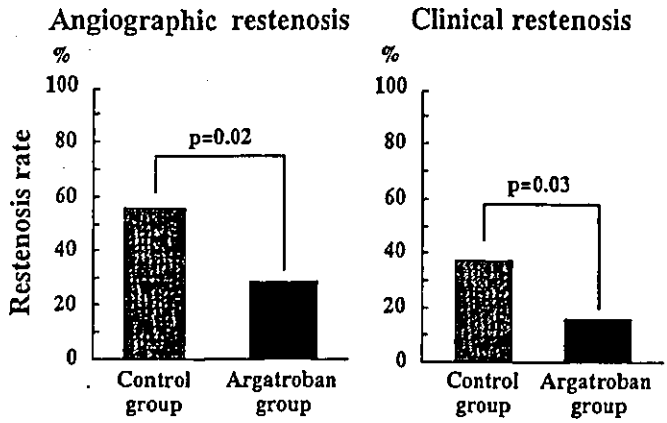

Fig3. Angiographic restenosis occurred in 5 of the 30 patients in the argatroban group (27%) and 12 of the 30 patients in the control group (56%). Clinical restenosis occurred in 5 of the 35 patients in the argatroban group (14%) and 13 of the 35 in the control group (37%).

Table 4 Clinical Outcome at Follow-up of the Study Patients

	Control group (n=35)	*Argatroban group (n=35)*	*p value*
Clinical restenosis	*13**	*5*	*0.03*
Target vessel revascularization	*12*	*5*	*0.05*
Vasospastic angina	*0*	*1*	*NS*
Myocardial infarction	*0*	*0*	*NS*
Death	*1*	*1*	*NS*
Any clinical event	*14*	*7*	*0.07*

Clinical restenosis included recurrence of ischemia and/or angina and target vessel revascularization.
**Includes one case of recurrence of ischemia (silent) without target vessel revascularization.*

Table 5 Clinical Outcome at Follow-up of the Study Patients According to on-Treatment Analysis

	Control group (n=31)	*Argatroban group (n=32)*	*p value*
Clinical restenosis	*12**	*5*	*0.03*
Target vessel revascularization	*11*	*4*	*0.06*
Vasospastic angina	*0*	*1*	*NS*
Myocardial infarction	*0*	*0*	*NS*
Death	*1*	*1*	*NS*
Any clinical event	*13*	*7*	*0.08*

Clinical restenosis included recurrence of ischemia and/or angina and target vessel revascularization.
**Includes one case of recurrence of ischemia (silent) without target vessel revascularization.*

group (intention-to-treat analysis; Table 4, p=0.05). Moreover, Table 5 shows the clinical outcome at follow-up of the study patients on-treatment-analysis. Seven cases (6 stent implantations and 1 unsuccessful procedure during initial angioplasty) were excluded in Table 5 according to on-treatment-analysis. The clinical restenosis rates at follow-up were 17% (n=5) in the argatroban group and 40% (n=12) in the control group according to on-treatment-analysis after exclusion of 10 cases (n=30, respectively; p=0.04). The details of those 10 cases are as follows: 6 stent implantations during procedure, 1 unsuccessful procedure, 2 deaths, and 1 refusal of follow-up CAG.

Discussion

Previous and Present Trials Regarding the Prevention of Restenosis

No definitively effective prevention of restenosis by systemic administration of drugs has been observed in previous clinical trials. Several types of drug therapy, such as anticoagulants (heparin, warfarin) and antiplatelet therapy (aspirin, dipyridamole, ticlopidine, prostacyclin, and thromboxane A_2 inhibitor), fish oil, and steroids have failed to reduce the restenosis rate in most clinical trials[22–24] Recently, trapidil and cholesterol-lowering agents have been shown to be promising in preventing restenosis after coronary angioplasty[25] but patients must take these drugs for several months after angioplasty.

In contrast, coronary stenting has been shown to be effective in preventing restenosis after coronary angioplasty[26,27] and the drug eluting stent has been developed in recent years[28] Nevertheless, adjunctive anticoagulation and/or antiplatelet therapy is required for 1 month after coronary stenting, resulting in occasional bleeding complications. Accordingly, a new procedure with a low rate of adverse effects and no need for adjunctive therapy after discharge has been sought. In the present randomized, controlled study, local delivery plus intravenous infusion of argatroban reduced both the angiographic and clinical restenosis rates after coronary angioplasty. There was no increase in bleeding risk with the argatroban treatment. The restenosis rate in the argatroban group in this trial (27%) was similar to that in the stent group of the STRESS trial (32%; NS)[7] despite the fact that the reference vessel diameter was smaller (2.89±0.39 mm) than that in the STRESS trial (3.03±0.42 mm; p=0.07). The restenosis rate in the

control group in the present study was similar to that in the control group of the CAVEAT trial (56% vs 57%)[29]

Mechanism of Restenosis and Thrombin Activation

The mechanism of restenosis after PCI is considered to be a healing process after a balloon injury. Immediately after arterial injury with a balloon catheter, many factors lead to the activation of medial smooth muscle cells (SMC), but there are 3 major ones. First, elastic recoil is a pivotal factors after mechanical trauma to the abnormal vessel wall and stretching of the normal vessel wall (ie, arterial remodeling). Second, the formation of thrombus on the intimal surface and inside the disrupted plaque is an important part of the restenosis process. The intensity of thrombus formation could serve to reduce the initial gain in lumen both by adding to the plaque mass and by elaborating more growth factors[30] Third, the most intense interest has been on the impact of mitogenic factors (basic fibroblast growth factor (bFGF), platelet-derived growth factor (PDGF), transforming growth factor-beta (TGF-β), and SMC-derived growth factor (SDGF)) released by platelets, monocytes, and by components of the intact parts of the vascular wall, including the SMC. In vitro and in vivo studies have shown that injury to the endothelium and the vessel wall causes increased thrombin production[31] Thrombin, in particular, may play a significant role in the initiation of the restenosis process, because the regulation of these growth factors has been reported to be modulated by thrombin via a thrombin receptor[32,33] Moreover, thrombin activates a variety of vascular and inflammatory cell types that promote wound healing[10,32] Thus, the inhibition of the initial thrombin activation may exert a potent preventative effect on restenosis after POBA.

Direct Thrombin Inhibitors and Restenosis

The direct thrombin inhibitors, such as r-hirudin, hirulog, hirugen and D-Phe-Pro-Arg-chloromethylketone (PPACK), are expected to reduce the restenosis rate after PCI[11,34] and several relevant experimental studies have been performed in recent years. Rogasta et al reported that the 2-h systemic infusion of hirudin failed to reduce cell proliferation within the first 7 days, whereas the 2-h infusion of hirulog improved the late angiographic luminal dimensions and reduced the cross-sectional area narrowing by plaque in rabbits compared with heparin controls after angioplasty[12] They suggested that (1) hirudin inhibits cellular migration rather than proliferation, and (2) hirudin reduces mural thrombosis, resulting in less thrombus incorporation into the plaque. However, Serruys et al reported that the systemic administration of r-hirudin failed to reduce restenosis in a clinical study (HELVETICA study)[35] This discrepancy between the experimental study (Rogasta et al[12]) and the clinical study (Serruys et al[35]) may be explained by a difference in the local concentration of hirudin at the target lesion. Accordingly, it is expected that the local delivery of a high concentration of a direct thrombin inhibitor using a drug delivery device would reduce restenosis without increasing adverse effects in the clinical setting. However, there has not a previous clinical prospective randomized trial using a direct thrombin inhibitor and a local delivery device for preventing restenosis after angioplasty.

The present study has demonstrated that the intracoronary local delivery of argatroban, in addition to a 4-h intravenous infusion, prevents restenosis following POBA. Argatroban has been reported to inhibit platelet activation by fibrin- or clot-incorporated thrombin more effectively than does hirudin[16] The reason that both local delivery and continuous intravenous infusion of argatroban were used in the present study was to inhibit thrombin activity, which may increase immediately after angioplasty before the local delivery of argatroban, because there was a time delay (approximately 10 min) between the first balloon inflation and the local delivery of argatroban (thrombin receptors have been reported to appear on a SMC within a few min after balloon injury[12]). The present findings, together with the report of Rogasta et al[13] suggest that direct thrombin inhibition may successfully inhibit cell migration in the initiation of restenosis in human patients.

Local Drug Delivery Device

Several local delivery balloon catheters have been designed. The double-balloon catheter was the first percutaneous drug delivery device. Other drug delivery devices such as the Wolinsky perforated-balloon catheter, a microporous balloon, a channel catheter, and the Transport coronary angioplasty catheter have been developed since then. More recently, the drug delivery devices known as the Infusasleeve™, a hydrogel-coated balloon, and the Dispatch™ catheter have become available[36] The hydrogel-coated balloon does not have a perfusion port to support distal blood flow during balloon inflation. Imanishi et al reported that the local delivery of argatroban using a hydrogel-coated balloon reduced intimal thickening after balloon injury in an experimental study[37] The Dispatch™ catheter consists of an over-the-wire, non-dilatation catheter with a spiral inflation coil and a perfusion port on its distal tip. There are several advantages of this system for the drug delivery. First, this device allows distal coronary perfusion during balloon inflation for a sufficiently longer time compared with other drug delivery catheters. Second, this system makes it easier to deliver the drug than a hydrogel-coated balloon catheter, because in the case of the hydrogel-coated balloon, the drug must first penetrate the hydrogel-balloon surface. Third, the pharmacokinetic validity of the local delivery of argatroban using a Dispatch™ catheter has been established. Anabuki et al confirmed that the local delivery of argatroban using a Dispatch™ catheter resulted in the intramural deposition of high concentration argatroban without any arterial damage[38] This new device has been used for the prevention of reocclusion after revascularization in patients with acute myocardial infarction and unstable angina pectoris[18,39] However, there are no other clinical reports on the prevention of restenosis using the Dispatch™ catheter except for one small non-randomized trial[10] Thus, this is the first prospective randomized controlled trial using the Dispatch™ catheter and argatroban to prevent restenosis following POBA. Moreover, it is expected that these local delivery devices may be available not only for direct thrombin inhibitor but also gene therapy in the future[40]

Study Limitations

First, it is unclear whether the local delivery of argatroban using a Dispatch™ catheter is effective in patients with small vessels (<2.5 mm). Second, this study was designed as an open-label randomized trial in the light of safety concerns. Although a double-blind design may be better, it is not easy to use a specific device such as the Dispatch™ catheter in a double-blind manner. Because no

obvious benefit of long-term inflation in preventing restenosis was found in a previous study[41] the long-term inflation (20 min) with the Dispatch™ catheter is unlikely to be responsible for the significant reduction of restenosis in the present study. Third, this trial was performed at a single center, with a small number of patients. Further study is necessary with a larger number of patients in a double-blind, randomized, multicenter trial with a placebo group (local delivery of normal saline using a Dispatch™ catheter). We are now planning to conduct such a trial in Japan. Fourth, the effect of the exclusively local delivery of argatroban remains undetermined, because postoperative intravenous infusion of argatroban was combined with the intracoronary local delivery in the present study. Further study is necessary to assess the 'pure' efficacy of the local delivery of argatroban. Moreover, further study is necessary to assess the efficacy for stenting lesions in the present stenting era. Final, the present study did not evaluate local delivery direct pressure, although it is reported that high, local delivery pressure is a key determinant of vascular damage and intimal thickening[42] Further study is needed to examine the local drug delivery pressure during infusion of argatroban in the clinical setting.

Conclusions

The local delivery of argatroban using a Dispatch™ catheter was observed to be safe and effective in preventing restenosis after balloon angioplasty.

Acknowledgments

This study was supported by Drs T. Noguchi, T. Baba, Y. Miyao, T. Matsumoto MD. H. Sumida, S. Yasuda, M. Yamagishi, and A. Kawaguchi who assisted as 3D-CAT investigators.

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臨床研修プラクティス
Practical Training Magazine for Residents
2004年9月号－1巻6号

特集 胸痛にどう対応するか？

Ⅲ. 胸痛を診断手技でどう鑑別していくか，各診断機器の適応を学ぶ

6. アンギオでみる胸痛

野々木宏

6 アンギオでみる胸痛

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救急医療における胸痛患者の診療のポイントは，時間の遅れにより致死的となり得る疾患群を的確に診断し，専門治療のコントロール下に置くことである．そのうち緊急造影検査を必要とするのは，急性心筋梗塞症をはじめとする急性冠症候群である．したがって胸痛診断には，緊急冠動脈造影(CAG)の実施を念頭に鑑別や合併症のチェックを時間の遅れなく行うことが必要である．

緊急CAGを念頭においた胸痛診断のポイント

1．鑑別診断には注意深い問診が必要であり，それにより虚血性心疾患と大部分の非虚血性心疾患を鑑別することができるか，または疾患を絞り込むことが可能となる(Ⅱ章参照)．

2．**理学的所見**：すばやく問診しながら全身状態を短時間で把握する．緊急冠動脈造影を念頭に禁忌となる事項がないか確認する．特に四肢動脈の触れ，血圧左右差，呼吸左右差，胸郭動き，ラ音の有無，頸動脈(血管雑音)，圧痛，腹痛の併存，深呼吸や体位変換での増悪，腹部筋性防御，動脈瘤，大腿動脈触知を行う(Ⅱ章参照)．

3．**検査**：すべての症例で心電図モニター，静脈路確保，酸素吸入(O_2，モニター，ivと覚える)を行いながら，トリアージを行い，救急室で早期に評価を行う．12誘導心電図，胸部X線撮影(心拡大の有無，肺うっ血の有無，気胸の有無，縦隔拡大の有無)，緊急採血：血算，心筋逸脱酵素，血液ガス分析，生化学一般検査，血液型とクロス用血液確保がある．特に12誘導心電図は，急性冠症候群の診断のみならず重症度判定，また急性期治療法の選択に重要である．来院時に胸痛の有無を問わずST変化が生じている例はリスクが高く，ST上昇例では緊急再灌流療法の適用を検討する(Ⅲ章心電図参照)．

冠動脈造影の適応時期をいかに考えるか?

急性心筋梗塞症が疑われたときの救急外来あるいは入院直後の初期対応は，一般的な治療，救命に必要な処置，緊急冠動脈造影や再灌流療法の準備である．そのためには上記にあげた診断に10分以上かけない迅速な対応が必要である[1, 2](図1)．

(1) **急性心筋梗塞症**：ST上昇型心筋梗塞症の急性期治療の目的は，急性期死亡率の減少のみならず長期予後の改善にある．そのためには梗塞サイズを縮小させることが必須である．したがって，でき得る限り早期に閉塞血管を再灌流させることが急性期治療の目標となる．ST上昇型の急性心筋梗塞症に対して，発症から1時間前後であれば，救急室から血栓溶解療法の使用が勧められる．これで再灌流が得られれば，梗塞サイ

▶鑑別診断には注意深い問診が必要.

▶緊急冠動脈造影を念頭に禁忌となる事項がないか確認する.

▶12誘導心電図は，急性冠症候群の診断のみならず重症度判定，また急性期治療法の選択に重要！

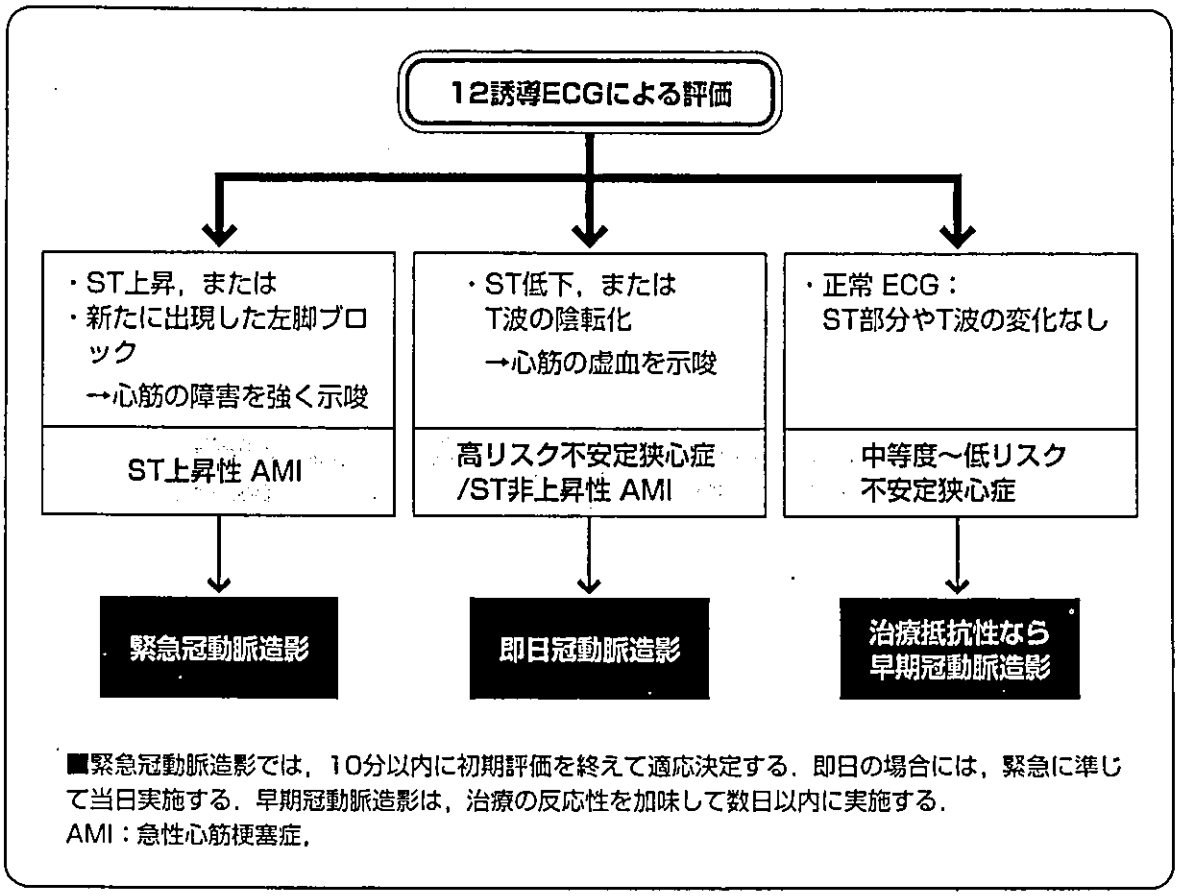

図1：急性冠症候群の12誘導心電図（ECG）所見と冠動脈造影実施時期（文献2を改変）

ズの縮小効果が最大限に活かされ，予後の改善につながる．PTCAは血栓溶解療法と同等に扱われているため，熟練した医師が緊急PTCA施行可能な状況では，PTCAを適用してよい．ただし，PTCA実施までに1時間以上必要な場合には，血栓溶解療法の適用を考えるべきである．また，重症例（心原性ショックなど）には確実な再灌流が必要であるため，血栓溶解療法よりもPTCAが勧められる．これにはPTCAの施行可能な施設へ短時間で転送可能な体制が必要である．非ST上昇型で入院時に胸痛が持続していて，硝酸薬を使用しても，胸痛が15分以上遷延しているような場合は，緊急造影を行う決定的な因子であり，禁忌がない限り緊急冠動脈造影の適応である．

(2) **不安定狭心症**：入院時に胸痛がない，あるいは胸痛が速やかに消失した例では，緊急冠動脈造影を行うか否かについては，議論のあるところである．この場合には，重症度評価が役立つ．Braunwaldは，重症度分類に薬物治療状態を加味してさらに3段階の分類を付加している[3]．最も重症と考えられる病態は，48時間以内に安静時胸痛が生じ（Ⅲ型），最大薬物治療でも発作が生じている群である．心筋逸脱酵素であるトロ