臨　牀　指　針

ワルファリン減量における プロトロンビン濃度の検討

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はじめに

ワルファリンは，本邦において抗凝固療法で使用できる唯一の薬剤であり，内服量については，個々によって異なるといわれており，現在本邦ではトロンボテスト（TT）またはプロトロンビン時間国際標準比（PT-INR）によって投与量の設定がされている。しかしながら，ワルファリンによる抗凝固療法施行時にPT-INR，高値もしくはTT低値となった場合にワルファリンの減量を余儀なくされ，減量の用量設定で問題となる場合が少なくない。そこで新しいプロトロンビン定量法であるCA-1法を用い，ワルファリン減量に対するプロトロンビン濃度（CA-1値）の関係について検討した。

Ⅰ．対　象　と　方　法

1．対　　象

対象は，ワルファリン療法施行中にワルファリンを減量した患者81例（平均年齢62.4歳，男女比42/39）とした（表1）。

2．方　　法

検体は1997年5月から1999年3月までに採取されたものを使用した。

検体採取に関しては，全てのものについて患者の同意を取っており，倫理委員会において承認されたものを使用している。

まず全検体を，カルシウム依存性プロトロンビンアクチベーターCarinactivase-1（CA-1）を用いて正常プロトロンビン濃度（CA-1値）を測定した。さらに同時期においてトロンボテスト(TT)，prothrombin time normalized ratio（PT-INR）を測定し，ワルファリンを減量したあとについても同様の検査を行い，ワルファリンの減量との相関関係について検討を行った。

次にワルファリンの減量が少量(～0.2mg/day)のものである21検体について再度同様の検討を行った。

CA-1法

CA-1法は1996年に山田らによって報告された血漿プロトロンビン濃度を測定する方法[1]で，10倍希釈した患者血漿にカルシウム，トロンビン発色合成基質（Boc-Val-Pro-Arg-pNA）を加え，37度で2分インキュベート後，CA-1を加えプロトロンビンがトロンビンに活性化したところを吸光光度計（405nm）で測定するものである。

トロンボテスト（TT），PT-INR

TTの試薬はThrombotest owren（エーザイ，東京），PT-INRはThromborel-S（Sysmex，神戸）（ISI：1.08）を使用した。また測定機器はCA-5000（Sysmex，神戸）を使用した。

3．統　計　解　析

統計学的検討は，Two groups student-t testで行った。有意差は$p<0.05$で有意差ありとした。

表1　内　　訳

	(n=81)
AVR (cases)	24
MVR (cases)	36
DVR (cases)	14
CABG (cases)	3
Af (cases)	4

AVR：Aortic valve replacement，MVR：Mitral valve replacement
DVR：Double (aortic and Mitral) valve replacement
CABG：Coronary artery bypass grafting
Af：Atrial fibrillation

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平均値は，平均値±標準偏差で表記した。

Ⅱ．結　　果

平均変化量はワルファリン0.34±0.31mg（0.05～2.0mg），PT-INR －0.53±0.58（－2.95～0.9），TT 13.28±17.65%（－55～93%），CA-1値23.69±23.4μg/ml（1.4～133.3μg/ml）であり，ワルファリン変化量，PT-INR，TT，CA-1値はいずれもワルファリン用量変化前後で有意な変化（p<0.05）を示した（図1a，b，c，d）。しかし

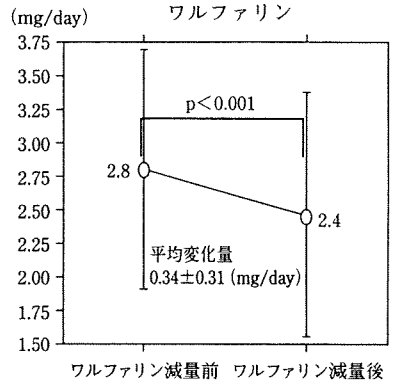

図 1a　平均変化量はワルファリンで0.34±0.31mg（0.05～2.0mg）で，ワルファリン用量変化前後で有意な変化（p<0.05）を示した。

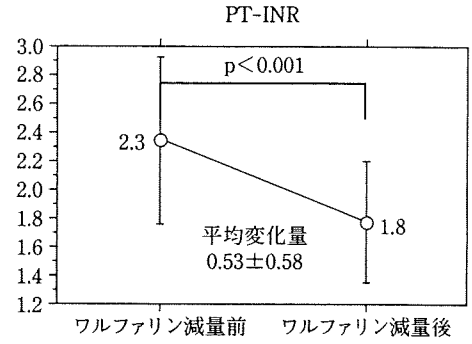

図 1b　平均変化量はPT-INRで－0.53±0.58（－2.95～0.9）であり，ワルファリン用量変化前後で有意な変化（p<0.05）を示した。

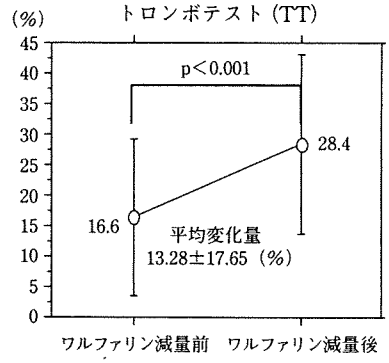

図 1c　平均変化量はTTで13.28±17.65%（－55～93%）であり，ワルファリン用量変化前後で有意な変化（p<0.05）を示した。

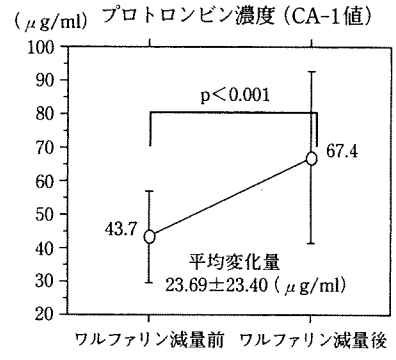

図 1d　平均変化量はCA-1値23.69±23.4μg/ml（1.4～133.3μg/ml）であり，ワルファリン用量変化前後で有意な変化（p<0.05）を示した。

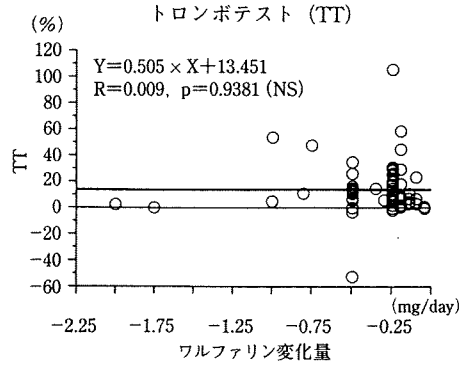

図 2a　ワルファリンの変化量との相関係数はTTでR=0.009，p=0.9381と相関しなかった。

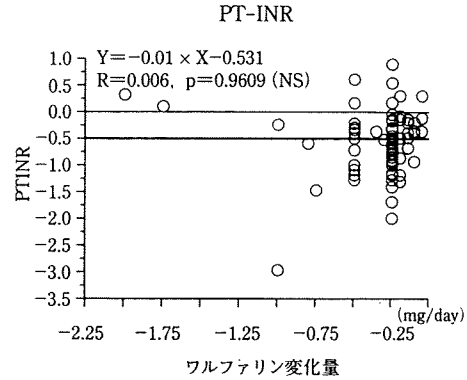

図 2b　ワルファリンの変化量との相関係数はPT-INRでR=0.006，p=0.9609と相関しなかった。

ながらワルファリンの変化量との相関係数はTT（R＝0.009，p＝0.9381）（図2a），PT-INR（R＝0.006，p＝0.9609）（図2b），CA-1値（R＝0.053，p＝0.6386）（図2c）といずれも相関しなかった。

次にワルファリンの変化量を0.05～0.2mg/dayの微量の変化で検討（21例，平均年齢61.6歳，男女比11/10）すると，平均変化量はワルファリン0.14±0.06mg（0.05～0.2mg），PT-INR 0.37±0.41（1.8～2.2），TT 17.11±17.46%（19.4～25.6%），CA-1値11.90±15.45μg/ml（42.8～59.9μg/ml）であり，TTは有意差を認めなかったが，ワルファリン変化量，PT-INR，CA-1値はいずれも有意差（p<0.05）を認めた（図3a，b，c，d）。またワルファリンの変化量との相関係数は，PT-INR（R＝0.277，p＝0.2235）（図4a)と相関しなかったが，CA-1値はR＝0.56，p＝0.083（図4b）と良い相関を示し，TT（R＝0.47，p＝0.0315）（図4c）は相関を示した。

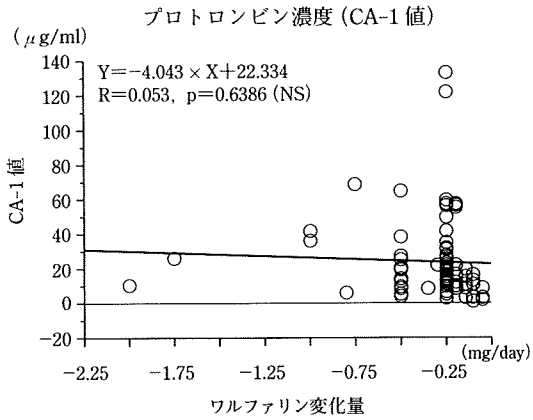

図 2c　ワルファリンの変化量との相関係数はCA-1値でR＝0.053，p＝0.6386と相関しなかった。

Ⅲ．考　　察

ワルファリンは，従来より用量依存的に効果を

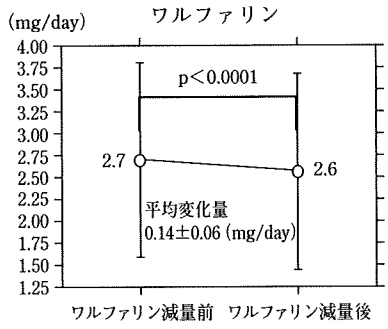

図 3a　ワルファリンの変化量を0.05～0.2mg/dayの微量の変化で検討すると，平均変化量はワルファリンで0.14±0.06mg（0.05～0.2mg）とワルファリン用量変化前後で有意差（p<0.05）を認めた。

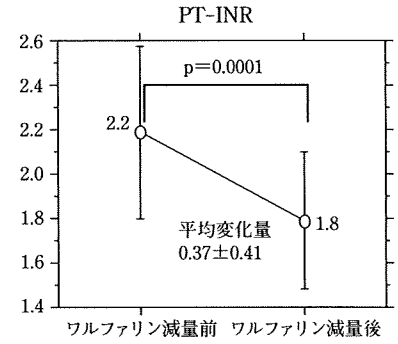

図 3b　ワルファリンの変化量を0.05～0.2mg/dayの微量の変化で検討すると，平均変化量はPT-INRで0.37±0.41（1.8～2.2）とワルファリン用量変化前後で有意差（p<0.05）を認めた。

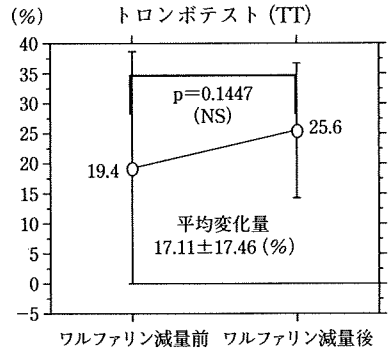

図 3c　ワルファリンの変化量を0.05～0.2mg/dayの微量の変化で検討すると，平均変化量はTTで17.11±17.46%（19.4～25.6%），とワルファリン用量変化前後で有意差を認めなかった。

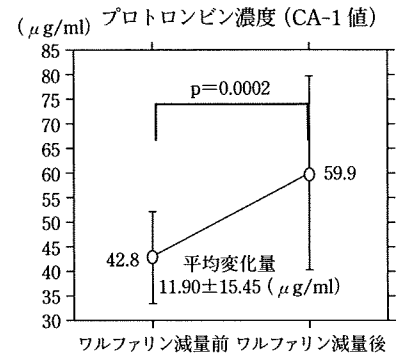

図 3d　ワルファリンの変化量を0.05～0.2mg/dayの微量の変化で検討すると，平均変化量はCA-1値11.90±15.45μg/ml（42.8～59.9μg/ml）とワルファリン用量変化前後で有意差（p<0.05）を認めた

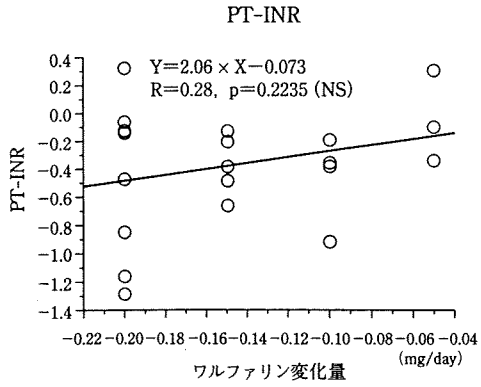

図 4a　ワルファリンの変化量との相関係数はPT-INRでR＝0.277，p＝0.2235と相関しなかった。

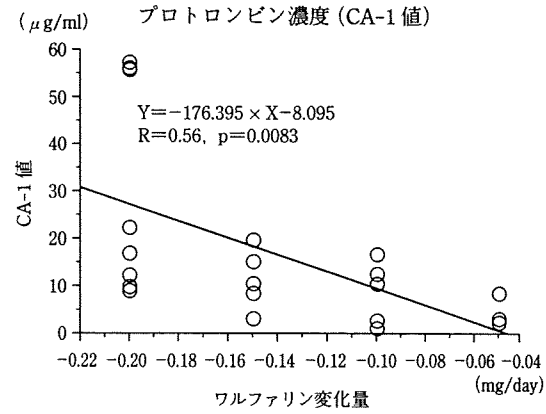

図 4b　ワルファリンの変化量との相関係数はCA-1値でR＝0.56，p＝0.083と良い相関を示した。

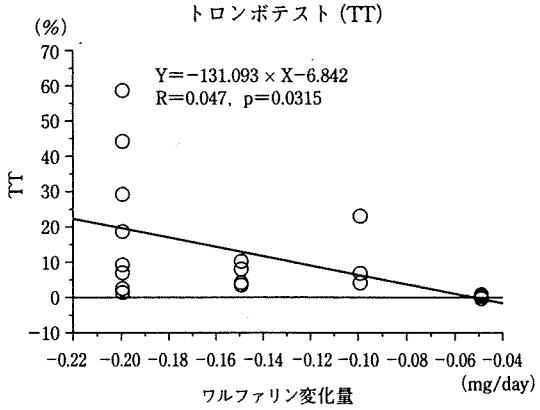

図 4c　ワルファリンの変化量との相関係数はTTでR＝0.47，p＝0.0315と相関した。

発現するものではなく，効果発現の用量は，個々によって異なるものであるとされており，コントロールの指標としてPT-INR，TTが用いられていた。しかし減量の際にはどの程度減量すべきかについて難渋することが多く，出血や梗塞などの合併症に悩まされることが少なくなかった。しかしながら，Sharmaら[2]は，TTを8～12%に保つのに必要なワルファリンの維持量は，$7.6\times\log_{10}TT(\%)-3.02$で計算できるとしている。そこで今回我々は，yamadaとmoritaによって報告されたCA-1法を用いて，ワルファリンの減量の際におけるプロトロンビン濃度の変化について検討を行った。

我々が血漿プロトロンビン（凝固第Ⅱ因子）に着目したのは，Xiら[3]が血液凝固におけるビタミンK依存因子の影響を凝固活性法にて検討した結果，他の凝固因子に比しプロトロンビンは，濃度依存的に凝固活性が直線的に上昇し，正比例の関係にあることから，ワルファリンによる抗凝固療法のモニタリングには血漿プロトロンビン濃度の測定が最適であると報告されたことによる。さらにFurieら[4][5]は，放射活性物質を用いた正常プロトロンビン測定法を開発し，プロトロンビン時間法でモニタリングするよりも，プロトロンビン濃度でモニタリングした方が血栓や出血を減少させると報告している。しかしながら，この方法は放射活性物質を用い，手技が複雑であり時間を要するため，現在実用化されていない。

今回用いたCA-1法は，Echis carinatus leucogaster毒由来のカルシウム依存性プロトロンビン活性化酵素carinactivase-1（CA-1）を用い，CA-1が正常プロトロンビンのみしか活性化しない性質を利用したプロトロンビン定量法である。測定時間は約30分であり，測定方法も簡便である。Iwahashiらは，warfarinにて抗凝固療法を行っている人工弁置換術後患者に対し，CA-1法を用いてプロトロンビン濃度を測定したところ，PT，TT，ヘパプラスチンテスト（HPT）と有意な相関をし，warfarin治療のモニタリング法として有用であると報告している[6]。

今回の検討では，warfarinを減量したもの全体で検討をすると，PT-INR，TT，CA-1法共に相関関係は得られなかったが，0.2mg/dayまでの少量の減量をさせた場合においてはCA-1法でのみ相関関係を得ることができた。ワルファリンを少量で変化させた場合にのみ，CA-1法で相関が取れた理由についてであるが，少量で変化させた場合は，プロトロンビン以外の凝固因子の変化も少ないのではないのかと考えられる。その結果，凝固機序，線容系などに及ぼす影響が少なくなり

プロトロンビンに対する他の凝固因子からの影響を少なくすることができるのではないのかと推測される。ワルファリンを少量で変化させた場合，プロトロンビン濃度との相関は，R＝0.56，p＝0.0083であり，回帰式はY＝－8.095－176.395Xで示される。この回帰式を用いるとワーファリン0.1mgの減量でプロトロンビン濃度は9.5μg/ml上昇し，0.2mgの減量では27.2μg/ml上昇することとなる。Iwahashiらの報告によると，PT-INR 2.0～3.0はプロトロンビン濃度で31.2～51.3μg/mlに相当する[7]としている。また合併症は，出血性の合併症の場合，プロトロンビン濃度は35μg/ml以下にて，血栓性の場合，プロトロンビン濃度は60μg/ml以上にて発生していたと報告している。したがってCA-1法によるモニタリングをする場合において，ワルファリンのコントロール域は35～50μg/mlくらいと推測される[8]。よってプロトロンビン濃度が30μg/ml以下になったときは，0.1mgの減量，20μg/ml以下になったときは，0.2mgのワルファリンの減量をすれば，十分ということとなる。以上より，ワルファリンの減量を少量（0.2mg/day）とした場合，ワルファリン減量によってプロトロンビン濃度は有意に減少，また用量依存的にプロトロンビン濃度は上昇をしており，有意な相関関係を示した。その回帰式は，Y＝－8.095－176.395Xで示され，ワルファリン減量に伴う，プロトロンビン濃度を予測することが今後可能になるかもしれないことが示唆された。また，ワルファリンを少量で減量した場合においても，プロトロンビン濃度，トロンボテスト，PT-INR共に有意に変化しており，ワルファリンの減量は少量より始めることが良いのではないかと思われた。

ま　と　め

ワルファリンの減量については，従来より一定の相関はないものといわれていたが，今回の検討の結果では0.2mgまでの少量の変化をさせた場合ワーファリンはプロトロンビン濃度と相関することが示唆された。

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◍オープニング・リマークス

冠疾患外科治療におけるMDCTの有用性

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2001年に米国のプライマリケア医を対象にした調査で，必須技術のランキングが報告された．全診療科が対象だが，心臓カテーテルインターベンション（PCI）が3位，抗高脂血症薬が4位，冠動脈バイパス術（CABG）が6位に入るなど，冠疾患関連が上位に挙げられた．超音波検査や消炎鎮痛剤が予想外に下位になっていたが，1位に挙げられたのは，CT，MRIであった．わが国における昨今の画像診断における両者の普及をみるとその評価が納得できる．

冠動脈の画像診断における，multidetector-row CT（MDCT）の進歩はめざましい．2002年に16列，2004年に64列のMDCTが登場し，冠動脈造影（CAG）の代替としての地位を築きつつある．

わが国において，年間20万～30万人が心臓カテーテル検査を受けている．頻回のPCIの既往を有し，CAGだけで20回以上受けたという例に遭遇することがある．心臓カテーテル検査での死亡，急性心筋梗塞，脳梗塞など重篤な合併症は0.1%以下とされ，冠動脈画像診断の標準検査であるとはいえ，侵襲的検査の性格上，血管穿刺部血腫などの合併症が存在することや，入院を要することなど被検者の負担を考えなければならない．腕頭動脈，鎖骨下動脈，腸骨動脈の蛇行や閉塞によりCAGが困難なことや，細いカテーテルを使用するために造影効果が悪いことすらある．

MDCTにも問題がないわけではない．被曝量の問題や造影剤による腎機能への影響はCAGと同様に問題である．金属アーチファクトや心房細動や期外収縮などの不整脈例，ステント内狭窄については十分な狭窄度の評価は困難である．

MDCTの魅力は非侵襲性のみでなく，3次元画像が得られる点にあるが，最近の64列のMDCTではnegative predictive valueは100%近いとされ，screeningで使用される機会は多い．PCI後の無症状例のフォローアップ，大動脈瘤手術の術前冠動脈評価，CABG術後のグラフト開存の評価などに応用すれば，患者の負担が軽減できる．CABG既往例の心臓再手術例や大動脈基部手術前での3次元画像は，従来の心臓カテーテル検査では得られない情報を提供してくれる．

本特集号は冠疾患領域におけるMDCTの利用について，外科の立場から原稿をいただいた．各施設における種々のMDCTの利用法と有用性が述べられているので，参考にしていただければ幸いである．

今後は，従来のCAGを目的とした心臓カテーテル検査が，MDCTによるscreeningの後，精査が必要な例に，血管内超音波，血管内視鏡，冠内圧などの機能評価を行うというような専門的な検査に代わっていくことが予想される．今後，128列，256列と多列化が進み高性能のMDCTが利用できる期待もあるが被曝の問題もあり，単に機器の発展にだけ期待する姿勢は慎まなければならない．本特集にあるように，造影剤を使用しないで大伏在静脈の術前評価をするなど，MDCTで得られる膨大な情報を有効に利用する工夫が重要である．

Brief Communications

Relation of waveform of transit-time flow measurement and graft patency in coronary artery bypass grafting

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Graft patency is the major factor limiting the initial clinical benefits of revascularization and patient survival; however, it is not easy to anticipate. Transit-time flow measurement (TTFM) has been the common method of assessing intraoperative coronary artery bypass grafting (CABG) patency because it is a noninvasive and easy method. TTFM provides a mean graft flow (MGF), a flow waveform, and derived values such as the pulsatility index (PI). D'Ancona and colleagues[1] reported the necessity to revise 3% of grafts on the basis of TTFM and emphasized the crucial feature of flow value interpretation as an index of graft patency. Takami and Ina[2] reported the relation between the graft flow waveform and the anastomotic quality of CABG using a fast Fourier transformation (FFT) analysis. However, there have been no reports that graft patency can be anticipated using analysis of the graft flow waveform.

We demonstrate that graft patency can be assessed with FFT analysis of TTFM waveform.

Clinical Summary

The present study included 29 patients who underwent isolated CABG with cardiopulmonary bypass and a postoperative cardiac catheterization (the term after CABG; 3–6 months). The patients received 29 saphenous vein grafts, all aortocoronary bypass grafts, including 24 patent grafts in the future and 5 occluded grafts. All anastomoses were performed by 1 surgeon (Y. O.) in the same fashion.

Graft flow tracing was obtained intraoperatively using a transit-time flowmeter (BF 1000; Medi-Stim AS, Oslo, Norway). A flow probe to fit each saphenous vein graft (3–4 mm) was placed around the graft when hemodynamic conditions were stable after weaning from CABG. On the basis of the obtained flow profile, the following variables were calculated: MGF, PI, and FFT of the flow waveform. Harmonics of FFT analysis by the flowmeter existed at frequencies that were multiplies of the frequency of the original waveform and were described in terms of an amplitude and a phase. In the present study, we defined F_0 as a power of the fundamental frequency, H_1 as a power of the first harmonic, H_2 as a power of the second harmonic, and sequentially as H_3, H_4, H_5, H_6, H_7, H_8, H_9, and H_{10}. Ha ($=H_5 + H_6 + H_7 + H_8 + H_9 + H_{10}$) was calculated.

All data were expressed as mean ± standard division. Comparison of the data between the patent and occluded grafts was performed using the Student t test.

Results

Figure 1 shows the PI and MGF of each group (patent grafts and occluded grafts). There was no significant difference between the patent grafts and occluded grafts (PI: 27.2 ± 16.6 vs 21.0 ± 10.9, respectively, $P = .181$; MGF: 3.60 ± 2.23 vs 4.91 ± 4.69, respectively, $P = .155$). Figure 2 shows the power of Ha. In the spectrum from H_5 to H_{10}, the power in the group of patent grafts was significantly higher than that in the group of occluded grafts. Ha in the group of patent grafts was significantly higher than that in the group of occluded grafts (0.352 ± 0.0517 vs 0.485 ± 0.402, respectively, $P = .04$).

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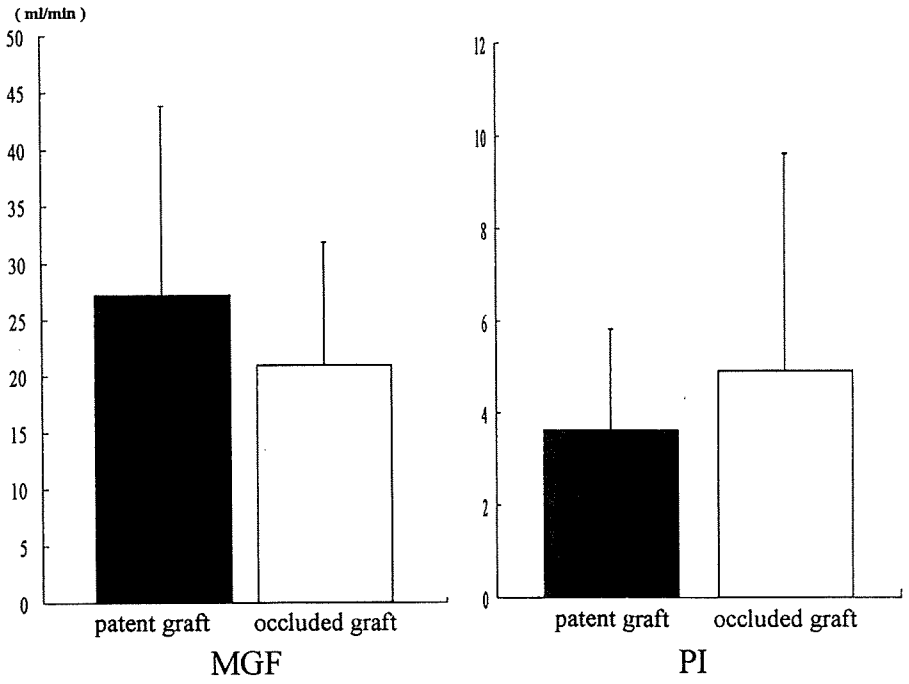

Figure 1. Comparison of PI and MGF between patent and nonpatent grafts. Bars show mean ± SD. *PI*, Pulsatility index; *MGF*, mean graft flow.

Discussion

D'Ancona and colleagues[1] emphasized the reliance on correct analysis of TTFM flow patterns to correct abnormalities and reported a predominantly systolic flow in 34 of 37 grafts, which had altered to a diastolic pattern after revision. The flow pattern was useful to confirm graft patency in conjunction with adequate MGF and PI values. In this study, MGF and PI values were not significantly different between the patent grafts and the nonpatent grafts. Some reports[3,4] demonstrated that graft flow waveform was more important in relation to graft patency than graft flow volume, because graft flow waveform affects the perfusion area of target vessels, coronary resistance, graft resistance, and quality of anastomosis. We did not consider the quality of anastomosis because our study did not include the grafts with anastomotic stenosis.

In contrast, although it was reported that the diastolic filling pattern was a good graft flow waveform,[5] no study has reported that pattern expressed as the numeric value. We demonstrated graft flow waveform expressed as the numeric value using FFT analysis, and harmonics of FFT analysis may become the parameter to express graft patency when comparing patent grafts with nonpatent grafts.

We did not report the cutoff value of the parameter including H_5, H_6, H_7, H_8, H_9, H_{10}, and Ha. Because the graft flow waveform was different in each kind of graft, including the internal thoracic artery, gastroepiploic artery, radial artery, and saphenous vein, we should investigate the parameters in each kind of graft in the future.

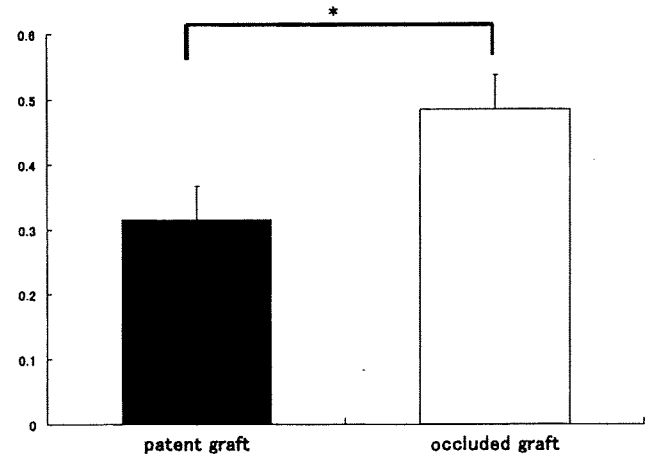

Figure 2. Comparison of Ha between patent and nonpatent grafts. Bars show mean ± SD. *P = .04.

Conclusions

We demonstrated that graft patency may be anticipated using FFT analysis of TTFM waveform.

We acknowledge the technical assistance of Ryota Tsubaki, a graduate student of Kobe University.

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Relation of Intraoperative Flow Measurement With Postoperative Quantitative Angiographic Assessment of Coronary Artery Bypass Grafting

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Background. It is critical to evaluate the anastomotic quality of coronary artery bypass grafting (CABG) in the operating room. The aim of this study is to determine the validity of intraoperative flow measurement for predicting the quality of CABG by comparison with the postoperative quantitative angiographic evaluation of the grafts.

Methods. Eighty-two grafts, including 37 internal thoracic arteries, were examined intraoperatively with a transit-time flowmeter. Coronary angiograms were performed 14 ± 5 days after CABG to quantify the diameters at the toe, heel, and anastomosis proper of the grafts.

Results. There were significant differences between patent and nonpatent grafts in all intraoperative flow parameters. However, the only cut-off value to distinguish patent from nonpatent was a fast Fourier transformation (FFT) ratio of 1.0. FFT is the ratio of powers of the fundamental frequency and its first harmonic. Postoperative quantitative angiography indicated that the stenosis was greatest at the heel of the anastomosis. The degree of stenosis at the heel of the anastomosis alone correlated significantly with intraoperative mean flow values.

Conclusions. Fast Fourier transformation analysis of flow measurement may be useful to differentiate patent grafts intraoperatively. Intraoperative flow measurement may predict the most stenotic part of the anastomosis.

(Ann Thorac Surg 2001;72:1270–4)

Coronary artery bypass grafting (CABG) has contributed to treatment of patients with ischemic heart disease to increase their survival and reduce ischemic complications [1]. Anastomotic quality of CABG is directly associated with both perioperative and long-term clinical results [2]. Therefore, it is critical for surgeons to evaluate the quality of the anastomoses of CABG in the operating room. It was traditionally common for a surgeon to determine the adequacy of the anastomosis based upon palpation of the graft pulsation, hemodynamic stability, and electrocardiographic changes, which are all unreliable and indirect. To increase reliability, several methods have been advocated for intraoperative assessment of the anastomotic quality in CABG [3–7]. Among these, transit-time flow measurement is considered to be more convenient, less invasive, more reproducible, and less time consuming [7]. The present study aimed to determine the feasibility and validity of the intraoperative transit-time flow measurement of grafts in CABG by comparing with postoperative quantitative angiographic evaluation, which has been used as the gold standard for assessing the results of coronary intervention and CABG [8–10].

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Material and Methods

Study Patients and CABG

The present study included 35 consecutive patients (28 males and 7 females; mean age, 66.4 ± 7.4 years) who underwent CABG either with cardiopulmonary bypass (n = 28) or without (n = 7). Combined procedures included mitral valve replacement (n = 4), aortic valve replacement (n = 2), abdominal aneurysmectomy (n = 2), and femoro-femoral arterial bypass (n = 1). The patients received 82 grafts, including 37 right or left internal thoracic arteries, 21 radial arteries, 18 saphenous veins, and six right gastroepiploic arteries. All anastomoses were performed by one surgeon (Y.T.) in the same fashion. Distal anastomosis was constructed with 8/0 polypropylene for arterial and 7/0 for vein grafts. Five stitches were taken around the "heel" of the graft, with two stitches to one side of the apex of the graft, one stitch through the apex, and two stitches on the opposite side. The graft was held away from the coronary artery until then. The suture loops were pulled up to approximate the graft to the coronary artery. The anastomosis was completed by placing stitches around the toe of the graft in counter-clockwise direction on the coronary artery.

Intraoperative Flow Measurement

Graft flow tracing was obtained intraoperatively using a transit-time flowmeter (BF 2000; Medi-Stim AS, Oslo, Norway). A flow probe of 3 mm or 4 mm was placed

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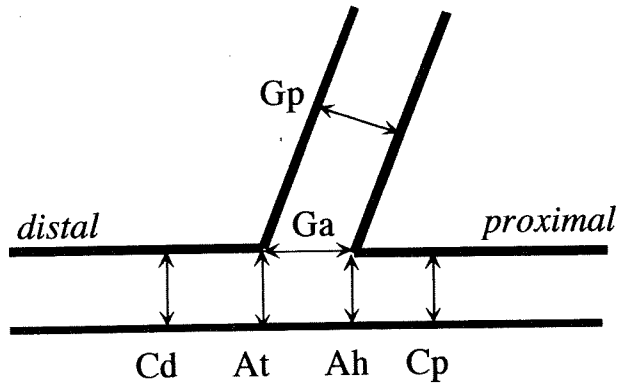

Fig 1. Parameters in the postoperative quantitative angiographic evaluation. The diameters of the native coronary artery of the proximal portion of the anastomosis (the heel, Ah), the anastomosis proper (Ga), and the coronary artery at the distal portion of the anastomosis (the toe, At) were measured. The adjacent proximal and distal native coronary (Cp and Cd) and graft segments (Gp) were also measured as references to calculate the stenosis of each portion: Ah/Cp for the heel, Ga/Gp for the anastomosis proper, and At/Cd for the toe.

around the graft when the hemodynamic condition became stable after the cardiopulmonary bypass was weaned in a standard CABG, or when an anastomotic procedure was completed in off-pump cases. Based upon the obtained flow profile, the following variables were calculated: mean graft flow (*Qm*, mL/min); pulsatility index (*PI* = [maximal flow − minimal flow]/*Qm*); percent insufficiency (% *Insuf* = volume of backward flow/volume of forward flow); and fast Fourier transformation (FFT) of the flow curve. FFT analysis is based upon the principal that all periodic waveforms can be broken down into a series of pure sine waves or harmonics [11, 12]. Harmonics exist at frequencies that are multiplies of the frequency of the original waveform ("the fundamental frequency") and are described in terms of an amplitude and phase. The pulsatile waveforms of graft flow in CABG can be considered to be periodic with a fundamental frequency (ie, the heart rate of the patient). As a parameter representing gradual decrease in power of the harmonics of the fundamental frequency, a FFT ratio (=F_0/H_1, where F_0 is a power of the fundamental frequency and H_1 is a power of the first harmonic) was calculated in the present study.

Postoperative Quantitative Angiographic Evaluation

Every patient underwent a postoperative cardiac catheterization 14 ± 5 days after CABG with a standard technique through the femoral or brachial route. A dose of 2 mg isosorbide dinitrate was injected selectively in each bypass graft. All grafts were examined from at least three different views. Each anastomotic site was analyzed quantitatively with a computer-assisted analyzing software (CCIP-310/W; Cathex Co, Tokyo, Japan). After optical magnification (2:1), an automatic edge-detection program determined the graft and coronary artery contours by assessing brightness along scan lines perpendicular to the centerlines of the vessel [8–10]. The quantitative evaluation was focused on three anastomotic sites; proximal portion of the anastomosis (heel), distal portion of the anastomosis (toe), and anastomosis proper. In addition to their diameters, the degrees of stenosis of the heel, toe, and anastomosis proper were analyzed by using the adjacent coronary or graft segments as references, as illustrated in Figure 1. A graft with stenosis more than 25% at either heel, anastomosis proper, or toe of the anastomosis was considered to be "nonpatent." The term "nonpatent" included not only occluded but also severely and moderately stenotic grafts. In contrast, a graft with stenosis less than 25% at all three portions of the anastomosis was considered to be "patent."

Statistical Analysis

All data were expressed as means ± standard deviations. Comparison of the data between the patent and nonpatent grafts were performed using the Mann-Whitney

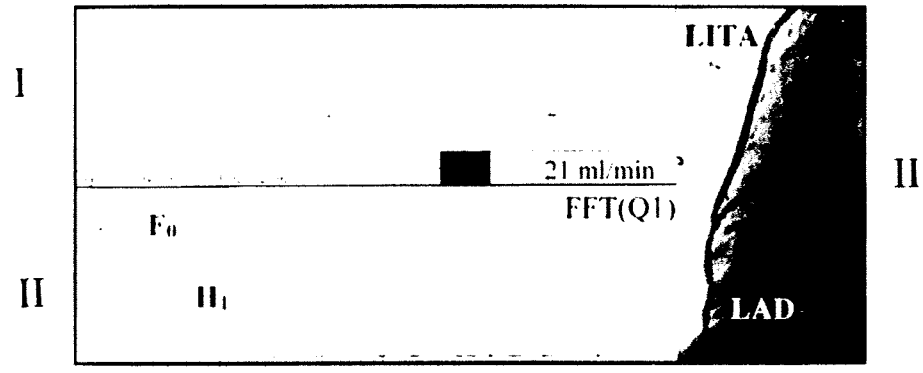

Fig 2. Data from a 73-year-old male patient who underwent an in situ grafting with a left internal thoracic artery (LITA) to left anterior descending artery (LAD). Shown are LITA flow tracing (I), fast Fourier transformation (FFT) of the flow curve (II), and postoperative angiogram of the LITA graft (III), which was patent well. (F_0 = a power of the fundamental frequency; H_1 = a power of the first harmonic.) The mean flow was 21 mL/min, the pulsatility index was 2.4, the percent insufficiency was 0 %, and the FFT ratio was 2.89.

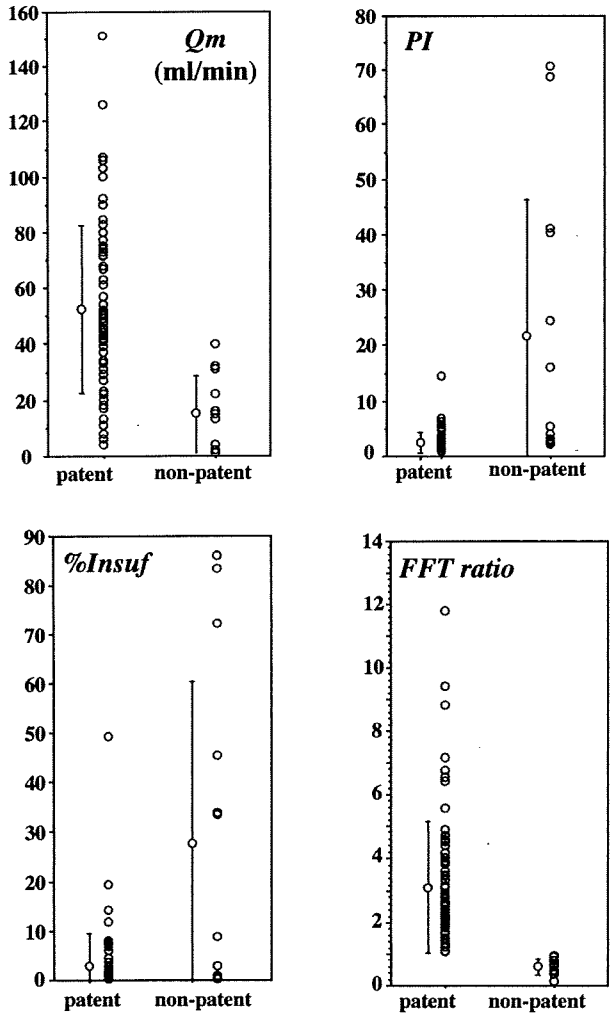

Fig 3. Results of the intraoperative flow measurement (Qm, PI, %Insuf, *and* FFT ratio). *There were significant differences in all of these parameters between the patent and nonpatent grafts.* (FFT = *fast Fourier transformation;* %Insuf = *percent insufficiency;* PI = *pulsatility index;* Qm = *mean graft flow.*)

test. Statistical correlation of variables were assessed by linear regression analysis. A p value of less than 0.05 was considered to be statistically significant.

Results

Intraoperative Flow Measurement and Patency of Grafts

Of 82 grafts, flows of five right gastroepiploic arteries could not be measured because they were too thick for the probes to be placed. Typical recordings of a left internal thoracic artery (LITA), which was revealed to be patent well in the postoperative angiograms, was demonstrated in Figure 2. The patent graft flow waveform, whether in situ or aortocoronary, showed two phases of antegrade systolic and diastolic flow. As for graft flow and derived variables, there were significant differences in *Qm, PI, %Insuf,* and FFT ratio between patent and nonpatent grafts (*Qm*: 51.2 ± 30.7 vs 13.7 ± 13.8 mL/min, $p = 0.0004$; *PI*: 2.74 ± 1.91 vs 21.8 ± 25.4, $p = 0.021$; *%Insuf*: 2.82% ± 6.98% vs 28.3% ± 33.6%, $p = 0.027$; FFT ratio: 3.20 ± 2.11 vs 0.65 ± 0.26, $p = 0.0003$), as demonstrated in Figure 3. However, it was impossible to define precisely a cut-off value to distinguish patent from nonpatent grafts in *Qm, PI,* or *%Insuf.* Only the FFT ratio appeared to have a cut-off value. While all the patent grafts had a ratio of greater than 1.0, as shown in Figure 2, all the nonpatent grafts yielded a FFT ratio of less than 1.0, as shown in Figure 4.

Postoperative Quantitative Angiographic Findings (Fig 5)

The heel portion of the CABG anastomosis was significantly inferior to the anastomotic proper and toe portion in diameter and stenosis measured on the postoperative quantitative angiography. The anastomosis proper was demonstrated to have the largest diameter and the least stenosis among the three anastomotic sites (diameter: 2.7 ± 1.3 vs 1.8 ± 0.8 and 2.1 ± 1.0 mm; stenosis: −12.5 ± 29.8% vs 6.4 ± 18.7% and 1.8 ± 14.8%).

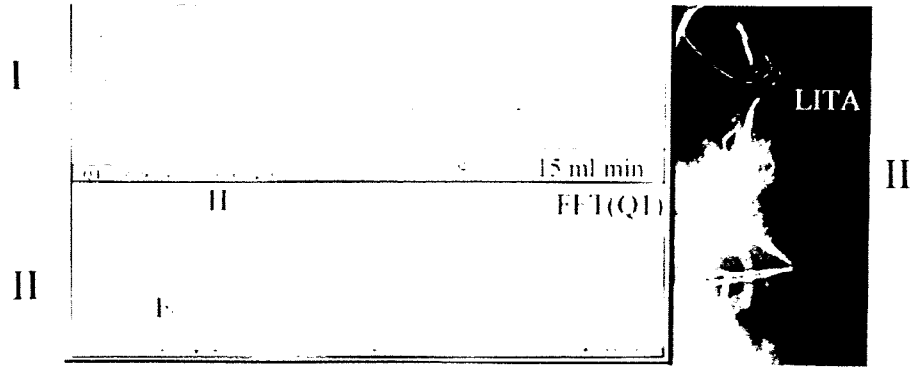

Fig 4. Data from a 62-year-old female patient who underwent in situ grafting with the left internal thoracic artery (LITA) *to the left anterior descending artery. Shown are LITA graft flow tracing* (I), *FFT of the flow curve* (II), *and a postoperative angiogram of the LITA* (III). *Note that in spite of the intraoperative flow of 15 mL/min, the LITA graft was revealed to be occluded postoperatively. The FFT ratio was 0.12.* (F_0 = *a power of the fundamental frequency;* H_1 = *a power of the first harmonic;* FFT = *fast Fourier transformation.*)

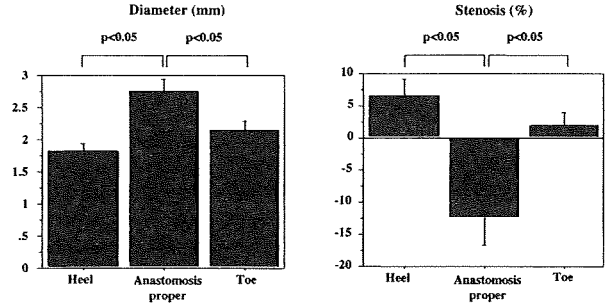

Fig 5. Results of the postoperative quantitative angiographic evaluation. The heel portion of the graft anastomosis was the most stenotic, while the anastomosis proper was the least stenotic.

Relation of Intraoperative Qm *and Postoperative Angiographic Stenosis (Fig 6)*

The intraoperative *Qm* values were significantly correlated with the degree of stenosis of the heel of the CABG anastomosis (stenosis = $-0.16Qm + 18.2$, $r = 0.38$, $p = 0.01$). However, there were no significant correlations between the *Qm* values and stenosis of both toe and anastomosis proper.

Comment

The transit-time method is based upon the principle that the time required for ultrasound to pass through blood is slightly longer upstream than downstream. Because the ultrasound beam is wider than the diameter of the vessel lumen, it is not necessary to know the vessel diameter or perform any complex calibrating procedures. Therefore, transit-time flow measurement may be the most suitable method for surgeons. Although the flow of greater than 20 mL/min is considered to be normal as patent [7], we have experienced nine cases of patent grafts less than 20 mL/min, as demonstrated in Figure 3. While surgeons can consider a graft with flow of more than 20 mL/min as patent well, they can not necessarily judge a graft with flow of less than 20 mL/min as nonpatent in the operating room. There can be a cut-off value of *Qm* to distinguish patent from stenotic or occluded grafts, because the optimal *Qm* varies with the dynamic characters, including blood pressure, heart rate, coronary resistance, and graft diameter [13]. In fact, we did not find any cut-off values of pulsatility index and percent insufficiency in this study. However, it was possible to define a cut-off value in the FFT ratio for distinguishing patent from nonpatent grafts. As shown in Figure 3, the ratios with all the patent (stenosis < 20%) grafts enrolled in this study were greater than 1.0, while the ratios with all nonpatent grafts were less than 1.0. The power spectral analysis of graft flow may reflect the flow tracing morphology. Based upon the specific physiology of coronary circulation, patent graft flow is predominantly diastolic, forming a trapezoid-shaped waveform, with a short systolic peak. In contrast, there is no diastolic flow in an occluded graft. As anastomotic stenosis increases, the predominance of the graft diastolic flow may decrease [13]. Although not fully investigated from the view point of mathematics and physics, the degree of the predominance of the graft diastolic flow may be closely associated with the distribution of power spectral in FFT analysis of the flow curve.

Quantitative coronary angiography with an edge detection algorithm plays an established role in coronary intervention [8, 9]. Although most surgeons have described the quality of the CABG anastomosis as only "patent," "stenotic," or "occluded," they should analyze the postoperative coronary angiograms quantitatively to increase the accuracy of the angiographic findings. In this study, we quantitatively examined the heel, toe, and anastomosis proper in the angiogram according to our definition. Our results, that the heel portion was the most stenotic, may have resulted from the surgical techniques of the surgeon who performed CABG for all patients enrolled in this study. The suturing bites of the stitches around the "heel" of the graft might result in these findings. In this way, quantitative angiographic evaluation may point out technical problems of the surgeons.

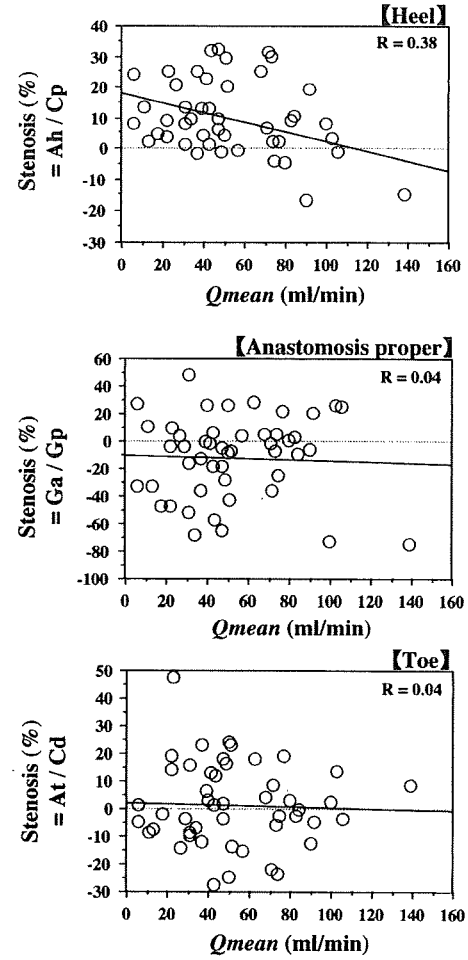

Fig 6. Correlation of the intraoperative mean flow values and the degree of stenosis on the postoperative quantitative angiograms at each portion of the graft anastomosis. Significant correlation was demonstrated for only the heel (abbreviations are the same as in Figure 1).

Quantitative angiographic evaluation also indicated in the present study that intraoperative *Qm* is closely related to the degree of the stenosis at the most stenotic portion of the CABG anastomosis. This finding suggests that intraoperative flow measurement reflects precisely the anastomotic quality of CABG. Therefore, surgeons can rely on the transit-time flow measurement in the operating room to evaluate their surgical techniques.

One limitation of this study is that we focused on only the distal anastomosis of CABG. Significant stenosis can be present proximally in cases with aortocoronary bypass. However, the proximal anastomosis is so much larger in diameter that its stenotic effect on the graft flow may be less than the distal anastomosis. The second limitation was the difficulty in obtaining intraoperative flow profiles of a right gastroepiploic artery graft by using a flow probe of 3 or 4 mm. To generalize our findings, we must collect the data of gastroepiploic artery grafts by using a larger probe or by skeletonizing the graft. The third limitation is that we did not report the parameters with which the graft flow varies. These include the perfusion area, blood pressure, heart rate, coronary resistance, and graft diameter. It is not practical to equalize these parameters strictly in the intraoperative flow measurement. These parameters might be mostly equal in this study, because flow measurement was performed in the hemodynamically stable condition.

In conclusion, FFT analysis of flow measurement might be useful to differentiate patent grafts intraoperatively. And the intraoperative flow measurement may predict the degree of the anastomosis portion that is the most stenotic.

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Branch Segment Occlusion With Acute Myocardial Infarction is a Risk for Left Ventricular Free Wall Rupture

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Background: Patients with acute myocardial infarction (AMI) whose culprit lesion lies in a branch of the 3 major coronary arteries have well-preserved cardiac function. A first MI with preserved cardiac function is a risk factor for left ventricular free wall rupture (LVFWR), so the aim of this study was to investigate the possible relationship between AMI with branch segment occlusion and LVFWR.

Methods and Results: The 439 patients with AMI were retrospectively studied. They were divided into 2 groups: group B (n=70; segments 4 atrioventricular node artery, 4 posterior descending coronary artery, 8, 9, 10, 12, 14, or 15 according to the AHA classification), and group P (n=369; segments 1, 2, 3, 5, 6, 7, 11, or 13). Primary percutaneous coronary intervention (PCI) was more often performed in group P (75% vs 57%; P=0.0018). In-hospital mortality tended to be lower in group B (1.4% vs 6.2%; P=0.105). The incidence of LVFWR was significantly higher in group B (10.0% vs 1.6%; P=0.0002). By multivariate logistic regression analysis, 1-vessel disease, absence of primary PCI, branch segment occlusion, and age were identified as independent predictors of LVFWR.

Conclusions: The incidence of LVFWR was higher in group B and branch segment occlusion was identified as an independent predictor of LVFWR. (*Circ J* 2009; **73:** 1473–1478)

Key Words: Acute myocardial infarction; Branch segment occlusion; Left ventricular free wall rupture; Primary PCI

It has been reported previously that independent predictors of prognosis after acute myocardial infarction (AMI) include age, the Killip classification, left ventricular (LV) function, enzymatic size of the infarction, and reperfusion therapy[1–10] Patients with an AMI that has the culprit lesion lying in a branch of the 3 major coronary arteries have well-preserved cardiac function with a small infarction, and usually follow a good clinical course without recourse to reperfusion therapy. However, LV free wall rupture (LVFWR) might occur more often in such patients because a first MI with preserved LV function is an independent predictor of LVFWR[10–12] Accordingly, the aim of the present study was to investigate the possible relationship between AMI with branch segment occlusion and LVFWR.

Methods

Patient Population

We retrospectively studied 439 patients admitted within 7 days of the onset of AMI, during the period January 2001 to December 2004. The clinical diagnosis of AMI was based on the concurrence of 3 criteria: (1) continuous chest pain for at least 30 min, (2) elevated myocardial enzymes (plasma creatine kinase (CK) and CK-MB fraction levels more than twice the normal value), and (3) characteristic ECG changes (ST segment elevation >1 mm, depression >0.5 mm or T-wave inversion in 2 or more contiguous leads with or

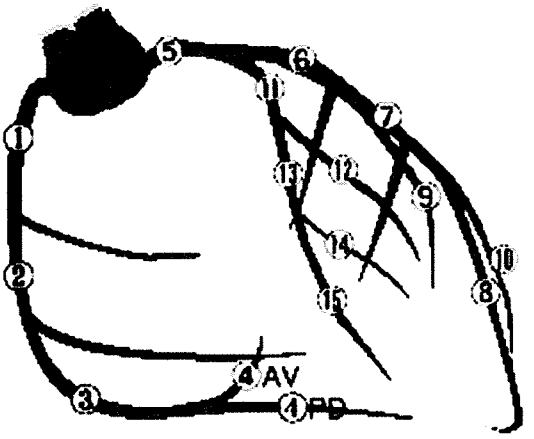

Figure 1. Segments of the coronary arteries numbered from 1 to 15 according to the AHA classification. Based on the culprit lesions identified by coronary angiography, patients were divided into 2 groups: branch segment group (group B; n=70) had culprit lesions in a minor branch of the 3 major coronary arteries (segments 4AV, 4PD, 8, 9, 10, 12, 14, or 15); proximal segment group (group P; n=369) had a culprit lesion in a proximal segment of the 3 major coronary arteries (segments 1, 2, 3, 5, 6, 7, 11, or 13). AV, atrioventricular node artery; PD, posterior descending coronary artery.

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Table 1. Clinical Characteristics, Angiographic Results, and Reperfusion Strategy

	Group B (n=70)	Group P (n=369)	P value
Age (years)	67±10	67±11	0.718
Female, n (%)	22 (31)	81 (22)	0.0863
Killip 1–3/4	66/4	343/26	0.686
HT, n (%)	50 (71)	243 (66)	0.364
Hyperlipidemia, n (%)	31 (44)	155 (42)	0.723
Diabetes mellitus, n (%)	23 (33)	128 (35)	0.768
Smoking, n (%)	37 (53)	198 (54)	0.902
Prodromal angina, n (%)	28 (40)	167 (45)	0.417
Prior MI, n (%)	8 (11)	60 (16)	0.306
Non-STEMI, n (%)	6 (8.6)	27 (7.3)	0.715
Culprit vessel, n (%)			
LAD	29 (41)	172 (47)	0.425
LCX	25 (36)	42 (11)	<0.0001
RCA	16 (23)	138 (37)	0.019
LMCA	0 (0)	17 (5)	0.067
3VD, n (%)	7 (10)	71 (19)	0.064
IABP use, n (%)	12 (17)	96 (26)	0.114
tPA use, n (%)	0 (0)	5 (1.4)	0.327
Primary PCI, n (%)	40 (57)	278 (75)	0.0018
Successful reperfusion (TIMI ≥2), n (%)	36 (51)	260 (71)	0.0018
Time from onset to reperfusion (h)	5.9±4.7	4.7±3.9	0.102
LVEF (%)	56±11	51±12	0.0017
Peak CK (IU/L)	1,910±1,293	3,618±3,065	<0.0001
Peak CK-MB (IU/L)	200±129	328±289	0.0017
Time to peak CK (h)	15.4±7.5	14.0±5.2	0.091
Medications			
β-blocker (before admission), n (%)	6 (9)	38 (10)	0.659
β-blocker (after admission), n (%)	22 (31)	132 (36)	0.485
ACEI or ARB (before admission), n (%)	20 (29)	103 (28)	0.911
ACEI or ARB (after admission), n (%)	40 (57)	246 (67)	0.125

HT, hypertension; MI, myocardial infarction; STEMI, ST elevation myocardial infarction; LAD, left anterior descending; LCX, left circumflex; RCA, right coronary artery; LMCA, left main coronary artery; VD, vessel disease; IABP, intra-aortic balloon pumping; tPA, tissue plasminogen activator; PCI, percutaneous coronary intervention; LVEF, left ventricular ejection fraction; CK, creatine kinase; ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker.

without associated abnormal Q wave). Exclusion criteria were (1) coronary angiography (CAG) not performed, and (2) cardiopulmonary arrest on arrival (CPA).

This study complied with the Declaration of Helsinki regarding investigations in humans, and was approved by the Ethics Committee of Wakayama Medical University. All patients provided written informed consent.

CAG and Primary PCI

All patients underwent CAG during their hospital stay. Segments of the coronary arteries were numbered from 1 to 15 according to the AHA classification (**Figure 1**)[13] Based on the culprit lesions identified by CAG, patients were divided into 2 groups: those in the branch segment group (group B; n=70) had a culprit lesion in a minor branch of the 3 major coronary arteries (ie, segments 4, 8, 9, 10, 12, 14, or 15); those in the proximal segment group (group P; n=369) had a culprit lesion in a proximal segment of the 3 major coronary arteries (ie, segments 1, 2, 3, 5, 6, 7, 11, or 13). Primary PCI was performed if the patients were admitted within 12 h of the onset of symptoms, or if they were admitted 12–24 h after onset but demonstrated persistent symptoms with evidence of ongoing ischemia. However, PCI was not performed if the target vessel was judged by the operator to be unsuitable for PCI (eg, small vessel <1.5 mm in diameter, small risk area, diameter stenosis <50%, or left main lesion with TIMI 3). We analyzed the time from onset to reperfusion in cases of TIMI II or III flow after primary PCI.

Cardiac Enzymes

Infarct size was estimated by the maximum values of CK and CK-MB. These cardiac enzymes were assessed every 3 h during the first 24 h from the onset of AMI or from the time of admission. This study included 35 patients (6 patients in group B, 29 patients in group P) in whom the peak CK level could not be captured while in hospital. However, elevated CK levels (twice normal) of all such patients were confirmed by other institutions.

Diagnosis of Mechanical Complications of AMI

Diagnosis of LVFWR was based on echocardiography followed by pericardiocentesis, surgical or postmortem examination. The incidence of LVFWR included both blow-out and oozing types. Blow-out-type free wall rupture was defined as a LVFWR with pulseless electrical activity, and sudden onset of hemodynamic collapse without ECG evidence of malignant ventricular tachyarrhythmia. Oozing-type free wall rupture required surgical treatment (including pericardiodrainage) for rapidly increasing pericardial effusion, followed by cardiac tamponade. Ventricular septal perforation was initially suspected on physical examination with sudden onset of pansystolic murmur, was subsequently diagnosed on the basis of abnormal shunt-flow at the interventricular septum by color Doppler echocardiography and by a significant step-up in oxygen saturation between the right atrium and the pulmonary artery using a Swan-Ganz catheter, and finally confirmed at operation. Papillary muscle rupture was suspected on physical examination with sudden onset of pansystolic murmur, was subsequently diagnosed

Table 2. Mortality and Mechanical Complications of AMI

	Group B (n=70)	Group P (n=369)	P value
In-hospital mortality, n (%)	1 (1.4)	23 (6.2)	0.104
Mechanical complications, n (%)	10 (14)	14 (3.8)	0.0017
LVFWR, n (%)	7 (10)	6 (1.6)	0.0002
(Oozing type/blow-out type, n)	(7/0)	(4/2)	
VSP, n (%)	2 (2.8)	8 (2.2)	0.723
PMR, n (%)	1 (1.4)	0 (0)	0.768
Surgical treatment, n (LVFWR/VSP/PMR)	9 (6/2/1)	11 (4/7/0)	
In-hospital death with mechanical complications, n (LVFWR/VSP/PMR)	0 (0/0/0)	6 (2/4/0)	

AMI, acute myocardial infarction; LVFWR, left ventricular free wall rupture; PMR, papillary muscle rupture; VSP, ventricular septal perforation.

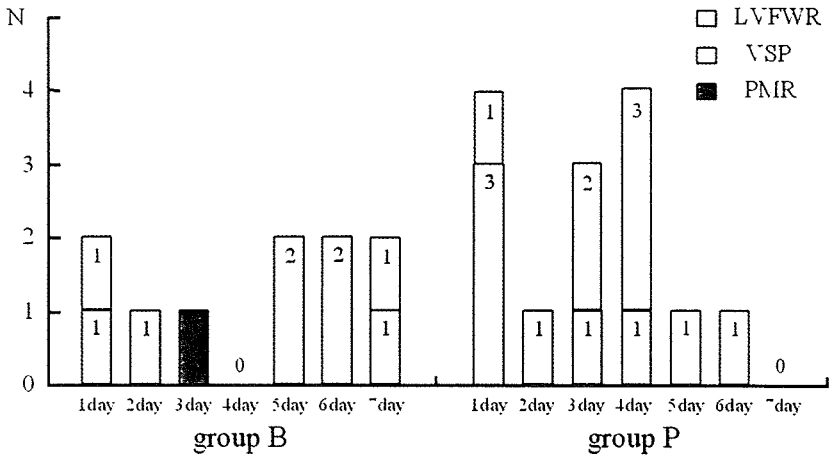

Figure 2. Timing of mechanical complications from the onset of AMI in each group. AMI, acute myocardial infarction; LVFWR, left ventricular free wall rupture; VSP, ventricular septal perforation; PMR, papillary muscle rupture.

by color Doppler echocardiography, and finally confirmed at operation.

Statistical Analysis

Statistical analysis was performed with StatView 5.0 software (SAS Institute, Cary, NC, USA). Continuous variables are expressed as mean±2 standard deviations, and compared by unpaired Student's t-test or Mann-Whitney U test. Categorical variables are presented as number (%) and compared with chi-squared statistics or Fisher's exact test. Multiple logistic regression analysis was performed in order to identify independent predictors of LVFWR in the study population. Various factors (age, gender, Killip class, history of hypertension, diabetes mellitus, hyperlipidemia, smoking, prodromal angina, and prior MI, distribution of culprit vessel, the frequency of primary PCI, ST-elevation MI, 1-vessel disease, and branch segment occlusion, LV ejection fraction (LVEF), maximum values of CK and CK-MB) were compared between patients with and without LVFWR. The multiple logistic regression analysis included the variables (ie, age, female gender, absence of prodromal angina, absence of primary PCI, 1-vessel disease, and branch segment occlusion) associated with the incidence of LVFWR in the univariate analysis (P value for selection <0.1). A probability value <0.05 was considered statistically significant.

Results

Clinical Characteristics, Angiographic Data, and Infarct Size

Table 1 shows the baseline clinical characteristics, angiographic results, reperfusion strategy and cardiac enzyme levels of the patients in each group. There were no significant differences between the groups in almost all the baseline clinical characteristics. Regarding the location of the culprit lesion, left circumflex lesions were more often seen in group B (P<0.0001) whereas right coronary artery lesions were more common in group P (P=0.019). Triple-vessel disease tended to be more often observed in group P (P=0.064). The LVEF in the acute phase was better in group B (P=0.0017). Primary PCI was more often performed in group P (75% vs 57%; P=0.0018). Peak CK and CK-MB levels were greater in group P (P<0.0001 and P=0.0017, respectively).

Incidence and Independent Predictors of LVFWR

Table 2 shows the mechanical complications of AMI occurring among the 439 patients. LVFWR occurred in 13 patients (3.0%) (including 11 patients with oozing-type free wall rupture and 2 patients with blow-out-type free wall rupture). The incidence of LVFWR was significantly higher in group B than group P (10.0% vs 1.6%; P=0.0002). On the other hand, the incidence of ventricular septal perforation and papillary muscle rupture was not significantly different between the 2 groups. Surgical treatments were performed in 9 patients of group B (including 6 of the 7 patients with LVFWR), and in 11 patients of group P (including 4 of the 6 patients with LVFWR). With respect to in-hospital deaths resulting from mechanical complications of AMI, none of 10 patients in group B died, whereas 6 of 14 patients (including 2 patients with LVFWR) died in group P (0% vs 42.9%; P=0.02).

In group B, LVFWR occurred in 2 patients in the acute

Table 3. Clinical Background of Patients With LVFWR

Case no.	Age (years)	Gender	HT	Prior MI	Killip class	Culprit vessel/lesion	No. of diseased vessel	LVEF (%)	Primary PCI	HR (beats/min)	BP (mmHg)	Symptom	ECG change
1 (group B)	75	F	+	–	2	LAD/seg.9	1VD	57	+	106	102/70	Chest pain	ST↑ in I, aVL
2 (group B)	63	F	+	–	2	RCA/seg.4	2VD	49	–	114	120/62	Fatigue	ST↑ in II, III, aVF
3 (group B)	70	F	+	–	2	LAD/seg.8	1VD	60	–	120	92/48	Chest pain	ST↑ in V1–4
4 (group B)	67	F	+	–	2	LAD/seg.9	1VD	55	–	106	116/58	Chest pain	ST↑ in I, aVL
5 (group B)	71	F	–	–	4	RCA/seg.4	2VD	52	–	86	90/60	Chest pain	ST↑ in II, III, aVF
6 (group B)	76	F	+	–	1	LAD/seg.9	1VD	49	–	98	96/62	Fatigue	ST↑ in I, aVL
7 (group B)	71	M	+	–	4	LCX/seg.14	1VD	64	–	110	70/52	Chest pain	ST↑ in aVL, V6
8 (group P)	79	M	+	–	2	LAD/seg.7	1VD	33	+	88	104/72	Chest pain	ST↑ in V2–5
9 (group P)	73	M	+	–	1	RCA/seg.1	1VD	71	+	68	106/78	None	ST↑ in II, III, aVF
10 (group P)	74	M	–	–	1	LAD/seg.6	1VD	40	+	98	104/72	Fatigue	ST↑ in I, aVL, V1–5
11 (group P)	79	M	–	–	1	LAD/seg.6	1VD	34	+	94	100/66	Fatigue	ST↑ in V1–5
12 (group P)	67	M	+	–	4	LAD/seg.7	1VD	58	–	108	72/50	Chest pain	ST↑ in V1–5
13 (group P)	79	F	+	–	4	LCX/seg.11	1VD	70	–	96	84/62	Fatigue	ST↑ in I, aVL, V5,6

HR, heart rate; BP, blood pressure. Other abbreviations see in Tables 1,2.

Table 4. Independent Predictors of LVFWR in Multivariate Logistic Regression Analysis

	OR	95%CI	P value
1VD	5.915	1.163–30.08	0.032
Absence of primary PCI	5.711	1.578–20.67	0.0079
Branch segment occlusion	5.451	1.572–18.90	0.0075
Absence of prodromal angina	3.433	0.682–17.28	0.135
Female	1.631	0.458–5.81	0.45
Age (every 1-year increment)	1.077	1.001–1.157	0.046

OR, odds ratio; CI, confidence interval. Other abbreviations see in Tables 1,2.

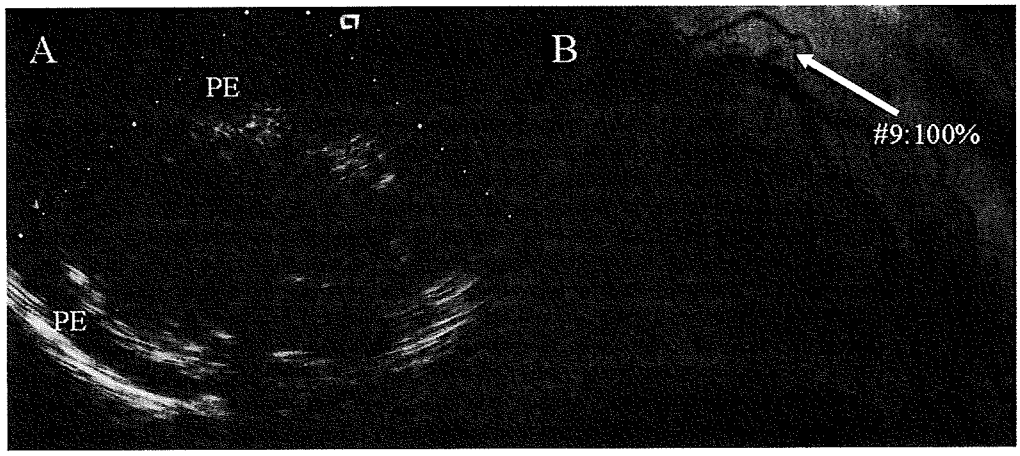

Figure 3. A 67-year-old woman was referred to hospital because of pre-shock state. (**A**) Echocardiography shows moderate pericardial effusion with cardiac tamponade. (**B**) Coronary angiography shows occlusion of the diagonal branch (#9). PE, pericardial effusion.

phase (<48 h; 29%) and 5 patients in the subacute phase (>48 h; 71%). On the other hand, in group P, LVFWR occurred in 4 patients in the acute phase (67%) and in 2 patients in the subacute phase (33%) (**Figure 2**).

Table 3 shows the clinical background of the patients with LVFWR, including angiographic findings and the clinical course in the intensive care unit. These patients had advanced age (73±3 years old) and less prior MI compared with the others; 6 of 7 patients in group B were female compared with only 1 of 6 patients in group P. Primary PCI was performed in only 1 of 7 patients in group B compared with 4 of 6 patients in group P. In 4 of 7 patients of group B, the culprit lesions were diagonal or a branch of the left circumflex artery with ST elevation in lead I and/or aVL.

Table 4 shows the independent predictors of LVFWR in multivariate logistic regression analysis. 1-vessel disease (P=0.032), absence of primary PCI (P=0.0079), branch segment occlusion (P=0.0075), and age (P=0.046) were identified as independent predictors of LVFWR. **Figure 3** is a representative case of LVFWR in group B.

Discussion

The main important findings in the present study are (1) in-hospital mortality tended to be lower in group B than in group P; (2) the incidence of LVFWR was significantly higher in group B than group P; and (3) branch segment occlusion was an independent predictor of LVFWR.

It has been reported previously that LV function and the enzymatic size of infarction are independent predictors of prognosis after AMI[3–6] Patients in group B had better preserved cardiac function with a smaller infarct than those in group P. Therefore, it was thought that in-hospital mortality in group B would tend to be lower despite the lower rate of primary PCI.

LVFWR is a catastrophic complication, estimated from previous reports to occur in between 0.96 and 2.6% of patients with AMI![2,14–21] It has been previously reported that independent predictors of LVFWR include advanced age, female gender, history of hypertension, 1-vessel disease with preserved LV function, first MI, absence of reperfusion therapy, and delayed admission![2,14–19,22–24] Figueras et al reported that undue in-hospital physical activity appears to increase the risk of mechanical complications of AMI, including LVFWR[23] We suggest 3 reasons why LVFWR occurred more often in group B. Firstly, LV function in group B was better, and therefore LV wall stress in the infarct zone might have been greater. Secondly, the rate of primary PCI was lower in group B. In 6 of 7 patients with LVFWR in group B, LVFWR occurred prior to hospital admission. All 6 patients were admitted over 24 h after AMI onset and thus lost the opportunity for reperfusion therapy, including primary PCI. Thirdly, 15 of 70 patients in group B did not undergo strict blood pressure control, and their delayed admission meant they were not cautioned against undue physical effort to avoid excessive strain on the infarcted wall, particularly during the 48 h after the onset of AMI.

Concerning the mechanism of LVFWR, Becker et al have classified it into 3 types[25] Type I rupture is characterized as an abrupt, slit-like myocardial tear. Type II rupture has an area of myocardial erosion, indicative of a slowly progressing tear. Type III rupture comprises a tear occurring where an aneurysm has formed. Nakamura et al[26] and Nakatsuchi et al[27] each reported that rupture in the early phase (<24 h) correlates with type I, whereas rupture in the late phase correlates with type III. In the present study, 3 of 6 cases of rupture in group P, but only 1 of 7 ruptures in group B, occurred in the early phase. Remarkably, 5 of 7 ruptures in group B occurred in the late phase (>5 days). Moreover, 5 ruptures in group B occurred without aneurysmal formation. These findings suggest that many of the cases of LVFWR in group B were type II ruptures, characterized as oozing-type ruptures.

With respect to the timing of LVFWR, it has previously been reported that LVFWR with reperfusion often occurred in the early phase (within 24 h), while those without reperfusion often occurred in the late phase![5,22,28–30] In group B, 6 of 7 patients with ruptures did not undergo reperfusion therapy. Therefore, we considered that LVFWR in group B often occurred in the late phase.

It has been reported that LV function and absence of cardiogenic shock are predictive factors for the prognosis of surgical treatment in mechanical complications of AMI![31–33] In the present study, it is considered that the cases of mechanical complications of AMI in group B had a good prognosis for preserved LV function and stable hemodynamic status upon cardiac drainage and/or intra-aortic balloon pump insertion.

It is reported that in recent times the in-hospital mortality among patients with AMI has decreased from 15–20% to 2–7% because of reperfusion therapy, including primary PCI![1–5,7,34–37] The GUSTO-I study reported that the major cause of in-hospital deaths among AMI patients was cardiogenic shock with a large degree of myocardial damage and multivessel disease, while a less common cause (≈10%) was LVFWR[37] The present study showed that LVFWR often occurs in AMI patients with a culprit lesion in branches of the 3 major coronary arteries.

Study Limitations

Firstly, this study enrolled selected patients who were admitted to hospital and underwent CAG. Therefore, the selection bias of the study population cannot be excluded entirely. It is also possible that patients complicated with LVFWR in group P were not admitted because of pre-hospital death following a larger infarct. However, the hospital in question is 1 of only 2 advanced lifesaving first-aid centers in this medical community, and the incidence of LVFWR in group P was 1.6%, in agreement with previous reports (between 0.96 and 2.6%)![2,14–21] Secondly, this study included patients who were admitted after 24 h from symptom onset. The groups differed with respect to clinical characteristics, such as bed rest level and therapeutic course, and this might affect the difference in the incidence of LVFWR. Recently, Figueras et al reported the relationship between admission delay >24 h and LVFWR[23,24] In the present study, admission delay was often seen in group B and so those patients lost the chance for reperfusion therapy, including primary PCI, and this is 1 of the reasons why LVFWR occurred more often in group B. Finally, this was a retrospective single-center study, and the overall number of patients with LVFWR was small. Therefore, the results should be viewed as preliminary and need to be confirmed by larger clinical trials.

Conclusions

In the era of primary PCI, patients with AMI whose culprit lesions lie in branches of the 3 major coronary arteries demonstrate LVFWR more frequently than those whose lesions lie in proximal segments. Branch segment occlusion was identified as an independent predictor of LVFWR. These patients are less likely to receive acute phase treatment, including primary PCI, and so better care of these patients should been taken to reduce the mortality of AMI.

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