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Is C-Reactive Protein a Predictor of Perioperative Events Before Coronary Artery Bypass?

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The concept that "atherosclerosis is a chronic inflammatory disorder of the vessels" is widely accepted with considerable published evidence in support. Since Ridker reported that C-reactive protein (CRP), a marker of systemic inflammation, is a stronger predictor of future cardiovascular events than low-density lipoprotein-cholesterol in healthy persons[1] the predictive value of CRP in patients with coronary artery disease has undergone numerous investigations.

Article p 872

In a study of patients with acute myocardial infarction (AMI), CRP appeared a potential determinant of both death and major adverse cardiovascular events[2] As well as that study of AMI, the predictive value of preoperative CRP has been emphasized in percutaneous catheter intervention (PCI) and coronary artery bypass grafting (CABG). However, until now, studies of the predictive value of CRP have been limited to on-pump CABG[3–6]

In the past decade, off-pump CABG, which can reduce the systemic inflammatory response caused by cardiopulmonary bypass, has become popular, but there is little data about the relationship of preoperative CRP and the outcome of off-pump CABG.

In this issue of the Journal, Kim et al report an initial study concerning the predictive value of preoperative CRP in off-pump CABG[7] This information will be invaluable because they performed a prospective and observational study using a high-sensitivity nephelometric method[8] and set the cut-off point at 0.3 mg/dl according to the American Heart Association guidelines. Most previous reports have been retrospective and some were not performed with high-sensitivity CRP and had relatively high cut-off points.

Kim and colleagues demonstrate that an elevated preoperative CRP level is a significant independent predictor of major postoperative complications, especially renal dysfunction in patients undergoing off-pump CABG. Although the difference was predominant only as regards renal dysfunction, the authors conclude the predictive value of preoperative CRP is applicable to major postoperative complications from a statistical viewpoint.

This study has some notable results. First, preoperative CRP was recognized as having significant predictive value for postoperative complications, even though off-pump CABG, a less invasive procedure, eliminates the unfavorable influences of extracorporeal circulation. Second, a significant difference was observed in the immediate perioperative phase. To validate the evidence, we need to compare it with previous reports.

There are some problematic areas. Most of the previous reports have had low case numbers from a single center. Clinical outcomes of CABG, either on or off pump, have improved recently, so the incidence of postoperative complications has decreased, and a small patient number has weak statistical power. There is a controversial report that claimed that elevated preoperative CRP cannot be a marker of increased surgical risk[3] Another showed that patients with elevated preoperative CRP were exposed to higher in-hospital mortality and sepsis, but there was no difference in the incidence of renal dysfunction[5]

In the study by Biancari et al, the patient group with elevated preoperative CRP had significantly higher preoperative incidences of history of MI, diabetes, lower limb ischemia, and low left ventricular ejection fraction[4] However, the baseline patient characteristics were quite similar between the high and low CRP groups in the study by Kim et al. Biancari's group also reported long-term results: they found no significant impact on the occurrence of major immediate postoperative morbidity and mortality, against a possible impact on 12-year outcomes[6]

Another issue is the influence of preoperative medication. In Kim's study, statin and aspirin were administered to 70% of the patients. These anti-inflammatory drugs are thought to decrease the CRP level[9] so some patients could be allocated to the high or low CRP group by either being on or off this medication. Moreover, the number of patients with left main trunk disease was much less than in other reports, which might relate to the indication of CABG or the expansion of PCI, or even racial differences.

There are several inflammatory markers for atherosclerotic cardiovascular disease. In the same fashion as CRP, serum amyloid A (SAA), interleukin-6, soluble VCAM-1, soluble ICAM-1, low-density lipoprotein-cholesterol, homocysteine, and p-selectin were investigated for their predictive value of future cardiovascular events. Among these, SAA was suggested to have a similar predictive value as CRP for patients with AMI.

The mechanism of CRP is not a direct action against the arterial wall, but rather a pleiotropic action, such as activation of complement, promotion and inhibition of immune cells, or an opsonin effect on macrophages. Thus, a synergistic effect would be expected to increase the predictive value of preoperative CRP associated with any other factors.

It is very important to preoperatively assess the risks

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associated with cardiac surgery, not only for decisions about surgical indication (patient selection, timing of surgery), but also for those related to the selection of surgical procedure and risk stratification of surgical results. EuroSCORE, STS score and Parsonette score are well-known methods of evaluating surgical risk, but all the listed risk factors in those systems of calculation are macroscopic and there are no biomarkers. It might be feasible to add biomarkers into the system for calculating the risks of cardiac surgery, especially if a prospective multicenter study with large patient numbers is performed.

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心室中隔穿孔の手術：David-Komeda 法を中心に

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Ueno M, Sakata R: **Surgical repair of postinfarction ventricular septal defect.** J Jpn Coron Asssoc 2007; **13**: 251-255

I. はじめに

心室中隔穿孔(ventricular septal perforation; VSP)は，左室自由壁破裂，僧帽弁乳頭筋断裂とともに，急性心筋梗塞(acute myocardial infarction; AMI)の急性期に生じる，重篤な機械的合併症である．AMIの約2%に合併し，梗塞発症から約2～3日後に多く発症するとされるが[1]，近年の血栓溶解療法の発達で，発症時期は早まる傾向にある[2]．血行動態の急激な悪化に伴い，本症の自然予後は極めて不良であり，1カ月以上の生存は20%以下である[1,2]．したがって，早期の外科治療は必須であり，その適応はわが国のガイドラインにおいてもクラスI，レベルCのエビデンスを有する[3]．

II. 手術までに

心筋梗塞後，心不全症状が急激に進行した場合，本症を念頭に置いて注意深く聴診するべきである．続いて，bed side で心エコーを施行する．Color Doppler 法での VSP の部位，大きさの同定や shunt 率の算出は，手術適応や到達法などを決定するうえで重要である．また，Swan-Ganz カテーテルによる右室レベルでの酸素飽和度のステップアップを確認し，心拍出量と shunt 率を測定する．

Shunt 量が少量で，慢性期での手術を可能とする例がまれに存在するが，本症では心筋梗塞により左室収縮力そのものも低下しており，心原性ショックに移行し，症状が進行性に悪化する可能性も否定できない．したがって重症例のみならず，これらの症例においても IABP を挿入し，systolic unloading による後負荷軽減，shunt 量減少と，diastolic augmentation での冠血流量維持により，血行動態の安定化を図ることは有用である．しかしながら，IABP の効果のピークは24時間との報告もあり，いたずらに IABP 留置を長期化することなく，心拍出量低下，肺高血圧の進行，腎機能低下などの徴候が出現する前に，速やかに手術に踏み切るべきである[4,5]．

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VSP では，その半数に冠動脈多枝病変を伴っており，血行動態が安定している限り，責任病変の同定，他病変の確認のために，極力冠動脈造影を施行する[2,5,6]．より良い長期成績を得るためにも，体外循環時間等を考慮しながら冠血行再建術を併施すべきである[7]．

III. 手　術

1957年に Cooley らが VSP 初手術例を報告して以来，手術が本症治療手段として確立された[8]．ただし，梗塞心筋を扱うという性格上，出血と遺残短絡軽減のために，種々の術式の変遷を経て今日に至っている．そのなかで Daggett らの功績は大きく，また David-Komeda 法の開発は画期的であった[9-11]．

1. Daggett 法

Daggett らは1970年代当初，前壁中隔梗塞症例で，VSP が心尖部に限局している場合，心尖部を VSP も含めて右室，左室自由壁とともに切除し，残った中隔と自由壁を一括して閉鎖する apical amputation 法を，また，それ以外の高位の VSP には穿孔部を右室自由壁に逢着，左室切開線は直接縫合する術式をとった(図1，2)[9]．しかしながら，これらの術式では脆弱な心筋に直接糸をかける危険性や，遺残短絡の発生，さらには左室容量の減少による LOS の可能性をもたらした．そこで彼らは，Iben らの double patch repair を応用した術式を示した(図3)[9,12]．そのコンセプトは，1)梗塞部切開からの VSP へのアプローチ，2)パッチによる中隔の形成，である．本術式は前二者と異なり，縫合線は非梗塞部心筋であり，パッチの大きさを調節することで梗塞部への張力を分散でき，また左室容量の確保等の利点を有する．一方，手術手技がやや煩雑で時間を要する，左室切開線に直接左室圧がかかり出血しやすい等の問題もあるが，今日まで広く用いられている．

2. David-Komeda 法

VSP 直接閉鎖や，Daggett 法等の直接穿孔部の閉鎖をはかる術式では，中隔組織の脆弱さゆえ，遺残短絡を高頻度に合併した．そこで David，Komeda らは，直接穿孔部に侵襲を加えることなく，健常部心筋のみに心膜パッチを縫着し穿孔部を exclude する新しいコンセプトを提示した

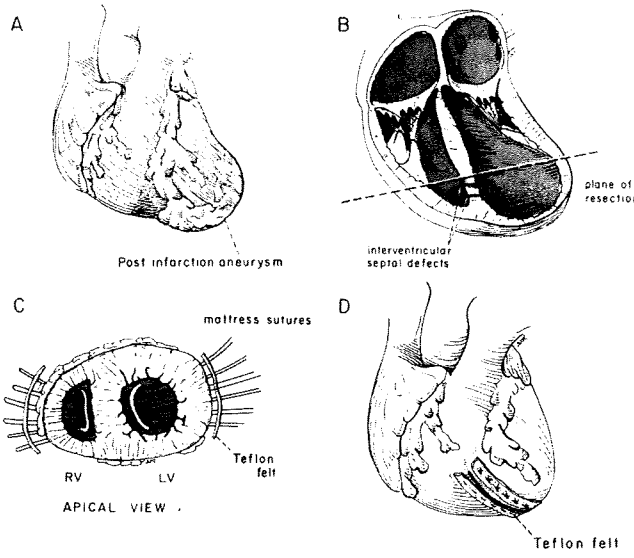

図1　Apical amputation
心尖部 VSP が適応(文献 9 より引用)

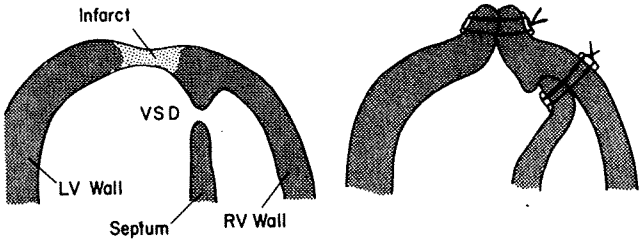

図2　心尖部以外の VSP への手術法
VSP を右室自由壁に縫着する(文献 9 より引用)

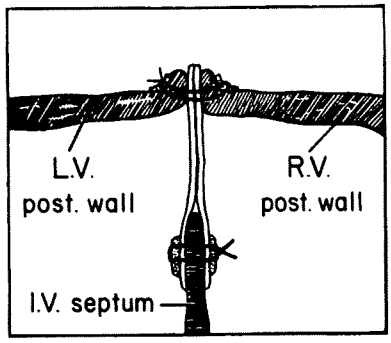

図3　Daggett 法
2 枚のパッチで中隔を形成する(文献 9 より引用)

(infarct exclusion 法)(図 4)[10,11]．本法では健常部に縫着したパッチにより，中隔穿孔部，左室切開線に左室圧がかからず，遺残短絡，出血が少ない．また，梗塞中隔，心尖部を exclude することで，遠隔期に起こる左室リモデリングの影響も回避できる．一方，特に急性期手術では健常部・梗塞部の見極めが難しく，縫合線次第では遺残短絡を生じやすくなることが欠点である．当科では，前壁中隔，下壁梗塞にかかわらず本法を用いており，その手技を後述する．

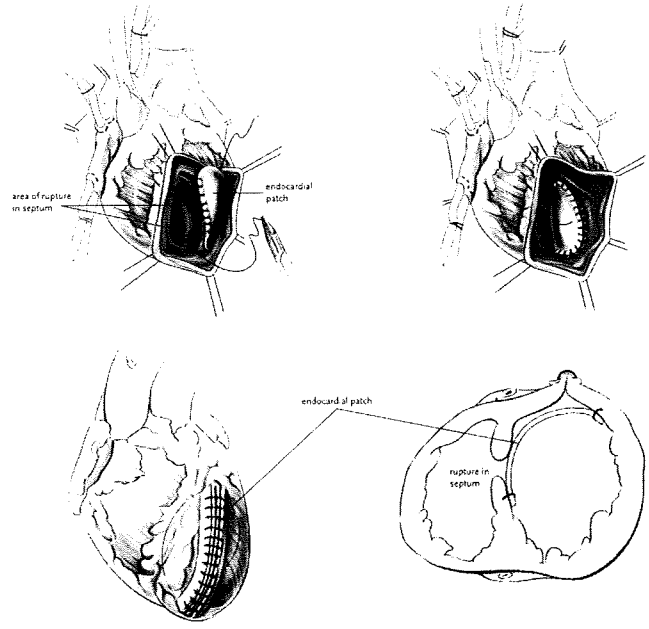

図4　David-Komeda 法
健常部中隔と自由壁にパッチを当て梗塞部中隔を exclusion する(文献 11 より引用)

3．その他の術式

Balkanay らは左室切開のみで左室，右室両側から VSP を閉鎖する術式を(図 5)，また Yamamoto らは左室切開でまず VSP に小パッチを縫着，次に大きなパッチを中隔，左室切開部に置き，パッチ間を GRF グルーで補強する術式を報告している[13,14]．いずれも基本は左室切開から VSP をパッチを用いて修復するという，Daggett 法に準ずる．

近年，Amplatzer を用いてカテーテル的に VSP を閉鎖する術式が報告されている[15,16]．部位や大きさでその適応は制限されるが，急性期に使用し，組織の器質化を待って慢性期の根治術に持ち込む，あるいは術後の遺残短絡に対しての適応等，VSP 治療の新たな展開の可能性もある．

IV．David-Komeda 法の手術手技

1．前壁中隔梗塞

左室切開は左冠動脈前下行枝から 2 cm 離し，それと平行に心尖部付近から開始する(図 6)．通常大きな対角枝が側壁に走行することが多く，これを温存するように，また内腔も確認しながら心基部側へと切開を延長する．左室壁を左右に牽引し，内腔を観察する．前述したごとく，中隔の健常部・梗塞部の見極めは非常に重要で，梗塞部に縫合線を置くと遺残短絡が，健常部を取りすぎると左室容量の減少が危惧される．われわれは通常全周性の U 字縫合を置くようにしている．少々手技は煩雑となるが，心膜パッ

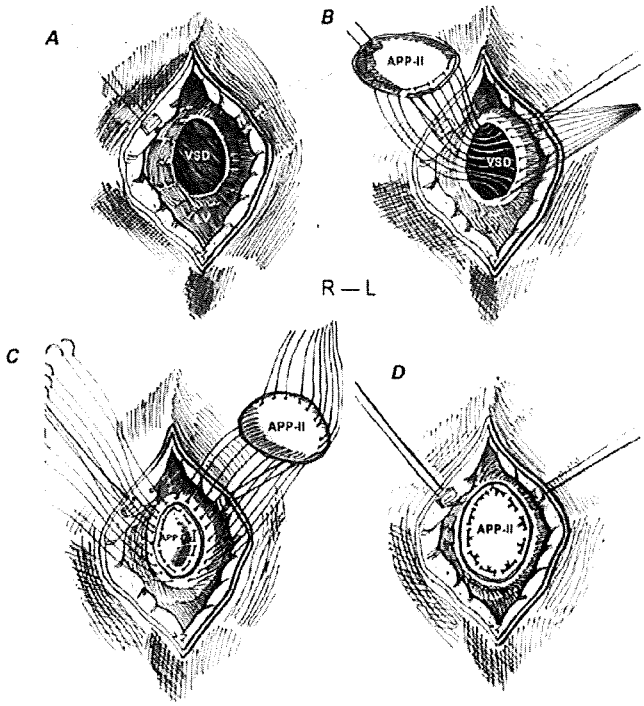

図5　Double patch repair.
左室切開のみで，右室・左室両者にパッチを当てVSPを閉鎖する(文献13より引用)

図6　左室切開
左前下行枝から2 cm離し，平行に切開する．

チの縫着は強固となり，万一遺残短絡が生じてもその範囲が最小限度ですむからである．また，かけた糸を軽く牽引することで，その部位の組織の強度もわかり，さらには次にかけるべき場所の同定や，パッチの大きさ，形状のトリミングも容易となる．

まず，心室中隔の基部寄りからフェルト付き4-0 Prolene U字縫合を開始し，随時牽引しながら中隔を上がっていく．自由壁に達する数針前で運針を中止し，逆に心尖部方向へとU字縫合を追加する．この時点で心膜パッチに

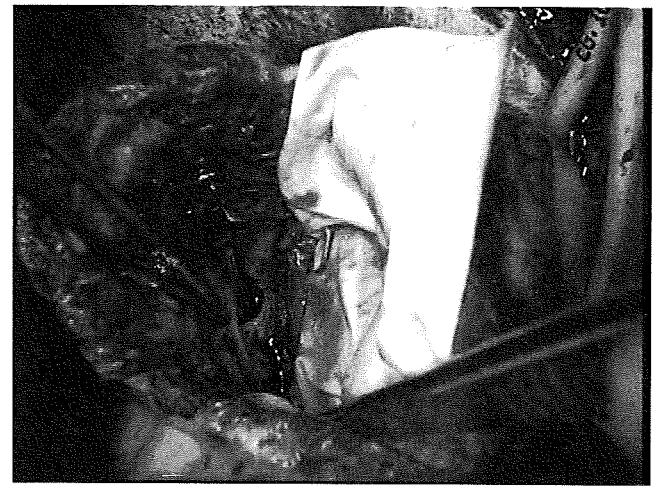

図7　中隔に心膜パッチを縫着したところ．パッチ－後乳頭筋間の健常部にかけた糸のフェルトが見える．

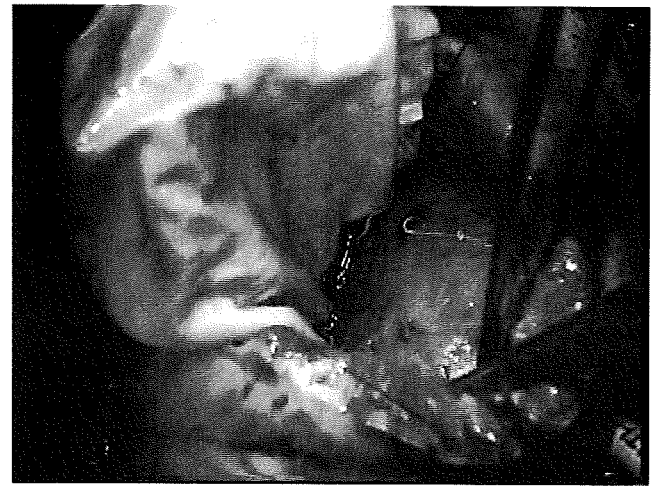

図8　中隔にパッチを縫着，反転したところ．摂子はVSPを指している．

糸をかけ，心室中隔に縫着する(図7，8)．中隔とパッチの接合が不安な部位にはZ縫合を追加すればよい．次に中隔側をさらに自由壁方向へ1針ずつ丁寧に，確実にパッチを心室壁の彎曲に沿うように縫着し，自由壁に達する．同様に心尖部でも自由壁に達するようにする．

残る自由壁側は，20 mm幅の大きな帯状のフェルトを切開線に置き，心外膜側から貫壁性に3-0 Nespolene U字縫合をかける．この際，パッチ側を徐々に縫縮するようにすれば，最後の数針で余剰したパッチのトリミング範囲がはっきりし，最終的にはパッチが心尖部側にふっくらと突出する形となる(図9)．通常1枚の心膜パッチで全周性のexclusionが可能であるが，施設によっては，あらかじめ作成した円錐状パッチの使用や，あるいは中隔側，自由壁側にそれぞれ1枚ずつ心膜パッチを縫着後，2枚のパッチを円錐状に作成する等種々の工夫も見られる．いずれにせよ，でき上がったパッチの形状は問題でなく，心室中隔に

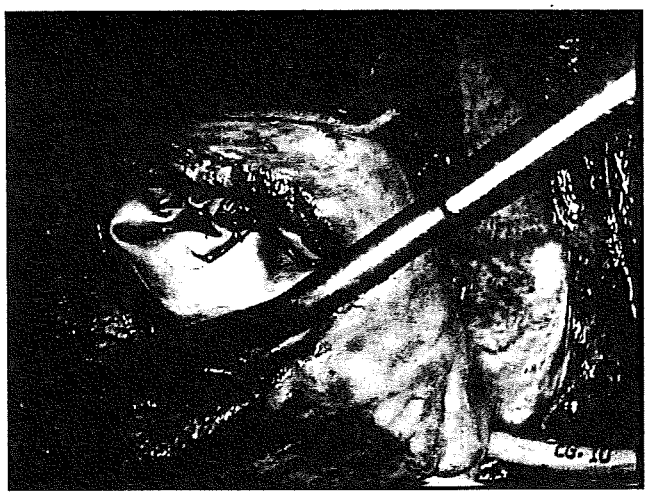

図9　全周性にパッチが縫着された時点
パッチは中隔側に突出し，左室容量の減少を防止する．吸引はVSPを指しており，梗塞部中隔は完全にexclusionされている．

いかにして確実な運針を置き，遺残短絡を回避するかが重要である．

切開した左室の閉鎖は，前下行枝側にも20 mm幅の大きな帯状のフェルトを置き，先ほど使用した自由壁側のフェルトを利用しながら，4-0 Proleneのマットレス縫合で閉鎖，さらに上下端から連続縫合を追加し補強する．左室切開線には高圧はかからないため，止血は容易である．

遺残短絡の防止のために，VSPに小パッチを置き，心膜パッチとの間にGRFグルーを注入，補強する報告等もあり，大変興味深い[17]．

2．下壁梗塞

コンセプト，手技は前壁中隔梗塞とほぼ同様であるが，VSPがより基部側に存在し，梗塞範囲が下壁側に広がっていることから，左室切開線と中隔での縫着ラインが異なってくる(図10)[18]．

心尖部を頭側に挙上，心尖部を切開し，内腔を注意深く確認しながら後乳頭筋付着部が心室中隔と分離されるまで切開を進める．ここで，下壁梗塞の範囲を同定するわけであるが，思いのほか梗塞は僧帽弁輪に近いことが多い．そこで僧帽弁前尖弁輪に，左房から左室へと4-0 Prolene U字縫合を数本置き，それに続けて大動脈弁下の心室中隔に，膜様部中隔の下縁より1 cm以上離れてU字縫合を追加していく．一方，僧帽弁輪から後乳頭筋にほぼ沿うような形で，乳頭筋付着部方向へもU字縫合を追加する．ここで心膜パッチを縫着する．あとは自由壁側となるため，貫壁性の運針が可能となるが，心室中隔側でexcludeする範囲が広く，縫合線がやや平面的となり，左室容量の減少が危惧されるため，パッチの大きさは余裕をもたせたほうが望ましい．

V．手術成績

本症の手術成績は，David-Komeda法の導入で向上をみたが，未だ満足すべきものではなく，病院死が30～40%程度である[1, 5, 6, 19]．ここ数年，日本胸部外科学会によるAnnual Reportでも，急性期手術の病院死は30%前後で推移している[20-22]．術前の血行動態が大きく関与するが，各施設での症例数自体も少なく，手術経験の蓄積，習熟効果の不足に起因するところも否定できない．

一般的に，本症の手術成績を規定する危険因子として，心原性ショック，発症・手術時期，右室梗塞の合併，等が挙げられる[1]．特にAMIによる左室機能が低下した状態では，血行動態は右室機能に依存しており，右室梗塞の合併はショック，多臓器不全の誘因となり，致命的な影響をもたらす[23]．

また，遺残短絡の有無も重要な因子であり，shunt量次第では，肺うっ血が持続し，長期IABP，人工呼吸管理を要することもある．Davidらは遺残短絡は44例中1例のみと非常に優れた成績を報告しているが，最近の文献でも

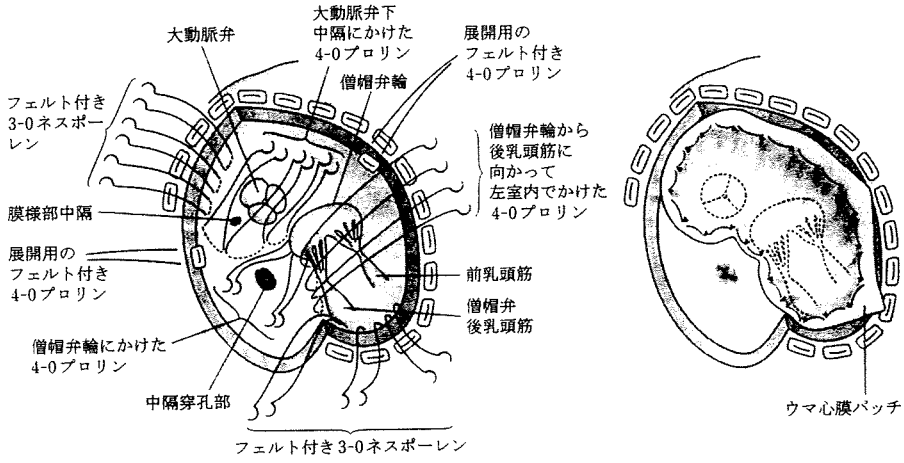

図10　下壁梗塞VSPの閉鎖法
「坂田隆造：下壁心室中隔穿孔の閉鎖法，胸部外科 **58**(9)，p. 772, 2005」より許諾を得て転載．

26～40%といまだ遺残短絡の発生率は高い[5, 6, 11, 19]．その予防には術中の中隔梗塞・健常部の見極めと，確実な運針以外方法はなく，万一遺残短絡を生じた場合は心不全症状が悪化する以前に躊躇なく再手術に踏み切るべきであろう．

VI. おわりに

VSP に対する外科手術は，多くの先達の鋭意的な努力，研究により，徐々に成績は向上している．しかし，残念ながら未だ満足すべきものとはいえず，われわれ心臓外科医が克服すべき領域の一つともいえよう．成績向上には術前循環状態の安定化を図ることはもちろんであるが，手術時期の的確な判断と，遺残短絡を生じない正確な手術手技により，少ない症例に確実に対応することが肝要である．

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Circ J 2009; **73:** 818–819

Is C-Reactive Protein a Predictor of Perioperative Events Before Coronary Artery Bypass?

Yoshitaka Okamura, MD

The concept that "atherosclerosis is a chronic inflammatory disorder of the vessels" is widely accepted with considerable published evidence in support. Since Ridker reported that C-reactive protein (CRP), a marker of systemic inflammation, is a stronger predictor of future cardiovascular events than low-density lipoprotein-cholesterol in healthy persons[1] the predictive value of CRP in patients with coronary artery disease has undergone numerous investigations.

Article p 872

In a study of patients with acute myocardial infarction (AMI), CRP appeared a potential determinant of both death and major adverse cardiovascular events[2] As well as that study of AMI, the predictive value of preoperative CRP has been emphasized in percutaneous catheter intervention (PCI) and coronary artery bypass grafting (CABG). However, until now, studies of the predictive value of CRP have been limited to on-pump CABG[3–6]

In the past decade, off-pump CABG, which can reduce the systemic inflammatory response caused by cardiopulmonary bypass, has become popular, but there is little data about the relationship of preoperative CRP and the outcome of off-pump CABG.

In this issue of the Journal, Kim et al report an initial study concerning the predictive value of preoperative CRP in off-pump CABG[7] This information will be invaluable because they performed a prospective and observational study using a high-sensitivity nephelometric method[8] and set the cut-off point at 0.3 mg/dl according to the American Heart Association guidelines. Most previous reports have been retrospective and some were not performed with high-sensitivity CRP and had relatively high cut-off points.

Kim and colleagues demonstrate that an elevated preoperative CRP level is a significant independent predictor of major postoperative complications, especially renal dysfunction in patients undergoing off-pump CABG. Although the difference was predominant only as regards renal dysfunction, the authors conclude the predictive value of preoperative CRP is applicable to major postoperative complications from a statistical viewpoint.

This study has some notable results. First, preoperative CRP was recognized as having significant predictive value for postoperative complications, even though off-pump CABG, a less invasive procedure, eliminates the unfavorable influences of extracorporeal circulation. Second, a significant difference was observed in the immediate perioperative phase. To validate the evidence, we need to compare it with previous reports.

There are some problematic areas. Most of the previous reports have had low case numbers from a single center. Clinical outcomes of CABG, either on or off pump, have improved recently, so the incidence of postoperative complications has decreased, and a small patient number has weak statistical power. There is a controversial report that claimed that elevated preoperative CRP cannot be a marker of increased surgical risk[3] Another showed that patients with elevated preoperative CRP were exposed to higher in-hospital mortality and sepsis, but there was no difference in the incidence of renal dysfunction[5]

In the study by Biancari et al, the patient group with elevated preoperative CRP had significantly higher preoperative incidences of history of MI, diabetes, lower limb ischemia, and low left ventricular ejection fraction[4] However, the baseline patient characteristics were quite similar between the high and low CRP groups in the study by Kim et al. Biancari's group also reported long-term results: they found no significant impact on the occurrence of major immediate postoperative morbidity and mortality, against a possible impact on 12-year outcomes[6]

Another issue is the influence of preoperative medication. In Kim's study, statin and aspirin were administered to 70% of the patients. These anti-inflammatory drugs are thought to decrease the CRP level[9] so some patients could be allocated to the high or low CRP group by either being on or off this medication. Moreover, the number of patients with left main trunk disease was much less than in other reports, which might relate to the indication of CABG or the expansion of PCI, or even racial differences.

There are several inflammatory markers for atherosclerotic cardiovascular disease. In the same fashion as CRP, serum amyloid A (SAA), interleukin-6, soluble VCAM-1, soluble ICAM-1, low-density lipoprotein-cholesterol, homocysteine, and p-selectin were investigated for their predictive value of future cardiovascular events. Among these, SAA was suggested to have a similar predictive value as CRP for patients with AMI.

The mechanism of CRP is not a direct action against the arterial wall, but rather a pleiotropic action, such as activation of complement, promotion and inhibition of immune cells, or an opsonin effect on macrophages. Thus, a synergistic effect would be expected to increase the predictive value of preoperative CRP associated with any other factors.

It is very important to preoperatively assess the risks

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associated with cardiac surgery, not only for decisions about surgical indication (patient selection, timing of surgery), but also for those related to the selection of surgical procedure and risk stratification of surgical results. EuroSCORE, STS score and Parsonette score are well-known methods of evaluating surgical risk, but all the listed risk factors in those systems of calculation are macroscopic and there are no biomarkers. It might be feasible to add biomarkers into the system for calculating the risks of cardiac surgery, especially if a prospective multicenter study with large patient numbers is performed.

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Circ J 2009; **73:** 1473–1478

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

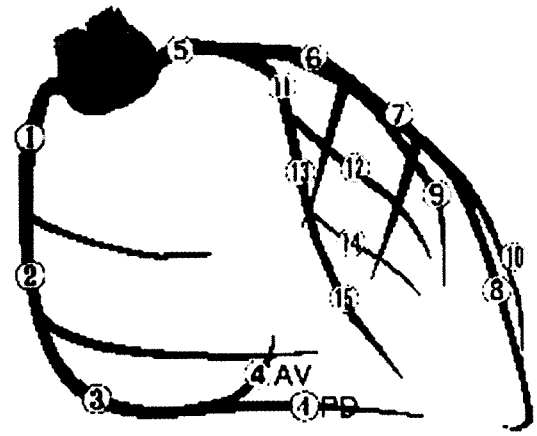

Figure 1. Segments of the coronary arteries numbered from 1 to 15 according to the AHA classification. Based on the culprit lesions identified by coronary angiography, patients were divided into 2 groups: branch segment group (group B; n=70) had culprit lesions in a minor branch of the 3 major coronary 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.

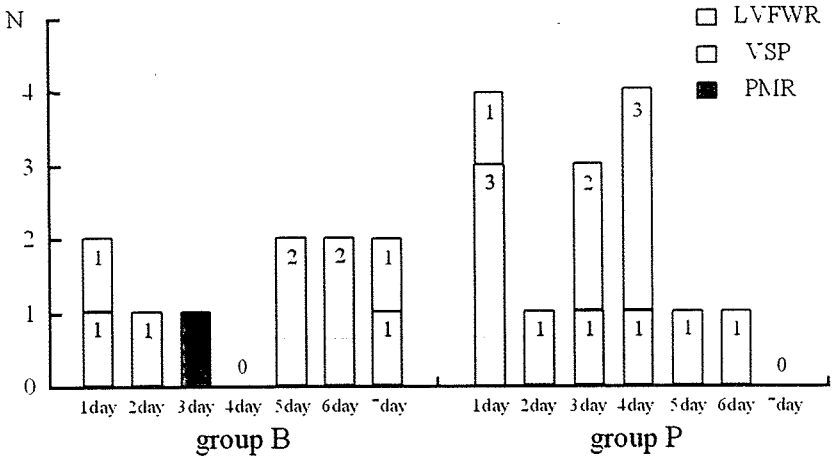

Figure 2. Timing of mechanical complications from the onset of AMI in each group. AMI, acute myocardial infarction; LVFWR, left ventricular free wall rupture; VSP, ventricular septal perforation; PMR, papillary muscle rupture.

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.

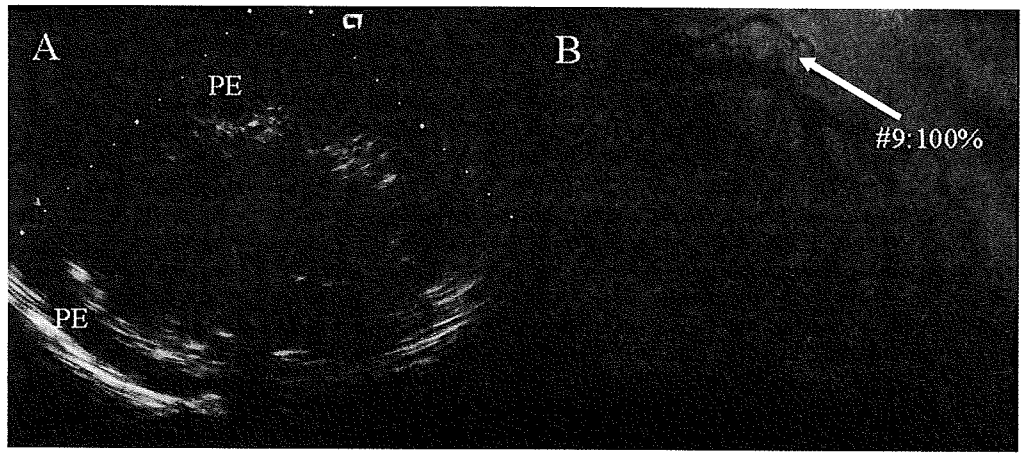

Figure 3. A 67-year-old woman was referred to hospital because of pre-shock state. (**A**) Echocardiography shows moderate pericardial effusion with cardiac tamponade. (**B**) Coronary angiography shows occlusion of the diagonal branch (#9). PE, pericardial effusion.

phase (<48h; 29%) and 5 patients in the subacute phase (>48h; 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[12,14–21] 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[12,14–19,22–24] 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%)[12,14–21] 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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Effects of Pretreatment With Statins on Infarct Size in Patients With Acute Myocardial Infarction Who Receive Fibrinolytic Therapy

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Background Experimental studies suggest that statins promote vascular fibrinolysis, so statin treatment before the onset of acute myocardial infarction (AMI) may result in a smaller infarct size.

Methods and Results The study group comprised 310 patients with AMI who received fibrinolysis within 12 h after symptom onset: 39 had received statin pretreatment (statin group) and 271 had not (non-statin group). Initial Thrombolysis In Myocardial Infarction (TIMI) flow grade did not differ between groups. Among 120 patients with initial TIMI flow grade 0/1, achievement of TIMI flow grade ≥2 after passing the guidewire through the culprit lesion was more frequent in the statin group (70% vs 35%, P=0.03). The final rate of TIMI flow grade 3 was higher in the statin group (95% vs 86%, P=0.11). Area under the curve (AUC) for creatine kinase (CK) was lower in the statin group (55,972±45,934 vs 84,195±84,276 IU·L^{-1}·h^{-1}, P=0.04). Multivariate analysis revealed statin pretreatment as an independent negative predictor of larger infarct size as defined by the upper tertile of AUC for CK (odds ratio 0.25, 95% confidence interval 0.07–0.91, P=0.035).

Conclusion Statin pretreatment may enhance fibrinolysis and reduce infarct size in patients with AMI. (*Circ J* 2009; **73:** 330–335)

Key Words: Acute myocardial infarction; Electrocardiogram; Fibrinolysis; Statins

Statins (3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors) are widely used clinically to decrease serum cholesterol levels.[1] Recent studies have focused on the pleiotropic effects of statins, which are independent of their lipid-lowering effects, such as stimulation of fibrinolysis by altering the levels and activities of tissue-plasminogen activator (t-PA) and plasminogen activator inhibitor-1.[2,3] Statins also reduce hemostasis by inhibiting platelet activation and the procoagulation cascade, and by augmenting the anticoagulation cascade.[4] Thus, statins appear to effectively enhance the fibrinolytic activity of t-PA. An experimental study in animals has shown that combination treatment with a statin and t-PA after stroke increases cerebral blood flow and reduces infarct volume as compared with fibrinolytic treatment alone;[5] however, data in humans are lacking. Prompt reperfusion of the occluded artery is crucial to limiting the size of an infarct. The present study was designed to test the hypothesis that statin treatment before the onset of acute myocardial infarction (AMI) contributes to prompt coronary artery reperfusion and smaller infarct size in patients with AMI who receive fibrinolytic therapy. We examined the relationship between statin pretreatment and the rate of coronary artery reperfusion assessed according to the Thrombolysis In Myocardial Infarction (TIMI)[6] flow grade and infarct size in patients with AMI who were given fibrinolytic therapy. The degree of myocardial damage before and after reperfusion therapy was also assessed on the basis of electrocardiographic (ECG) findings.

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Methods

Study Population

We enrolled 310 consecutive patients with ST-segment elevation AMI (mean age 60±11 years; 268 men, 42 women) who fulfilled the following criteria: (1) no history of myocardial infarction; (2) admission to Yokohama City University Medical Center within 12 h of symptom onset; (3) absence of conditions precluding the evaluation of ST-segment changes on ECG (left or right bundle-branch block, ventricular pacing); and (4) received fibrinolytic therapy. The diagnosis of AMI was based on typical chest pain lasting at least 30 min, ST-segment elevation of at least 1 mm in 2 contiguous leads, and a subsequent increase in the serum creatine kinase (CK) level to more than twice the upper limit of normal. Cardiac symptoms occurring within 48 h before the onset of AMI were defined as preinfarction angina.[7] In Yokohama City University Medical Center, in principle, patients without any contraindications for fibrinolysis were given 200 mg oral aspirin, 50 IU/kg intravenous heparin, and

800,000 units (approximately half the standard dose) intravenous monteplase, which is a mutant t-PA developed in Japan that can be given as a single-bolus intravenous injection. Glycoprotein IIb/IIIa inhibitors were not available in Japan at the time of the study. The final decision about fibrinolysis was left to the physician's discretion. In this study, we selected only patients who underwent fibrinolysis. All patients provided informed consent and the study protocol was approved by the hospital's Ethics Committee.

Definitions

We measured white blood cell and neutrophil counts, and triglycerides, total cholesterol, high-density lipoprotein-cholesterol and low-density lipoprotein-cholesterol-concentrations in serum on admission, using standard methods. Hypercholesterolemia was considered present if it had been previously diagnosed or if the total cholesterol concentration on admission was higher than 220 mg/dl or the low-density lipoprotein-cholesterol concentration on admission was higher than 140 mg/dl. Whether statins had been administered before admission was determined from detailed interviews or medical records.

Coronary Angiography (CAG)

CAG was performed as soon as possible after admission. The perfusion status of the infarct-related artery was assessed according to the TIMI study classification. The grade of collateral filling in the infarct-related artery was evaluated as described by Rentrop et al[8] and a good collateral channel was defined as grade 2 or 3. We initially evaluated TIMI flow grade in the infarct-related artery 29 min after fibrinolysis on average. If TIMI flow grade at this time was 0, 1, or 2, percutaneous coronary intervention, including stent implantation, was immediately performed. As a rule, immediate percutaneous coronary intervention was not done in patients with TIMI flow grade 3. Reperfusion time was defined as the time from symptom onset to the time when TIMI flow grade ≥2 was confirmed angiographically. In patients who had an improvement in symptoms and a decrease in ST-segment elevation before cardiac catheterization in whom TIMI flow grade ≥2 was confirmed on the first angiogram, reperfusion time was defined as the time from symptom onset until the time of confirming such clinical findings.

ECG Analysis

A 12-lead ECG was recorded on admission and 1 h after the final angiogram, at a paper speed of 25 mm/s and an amplification of 10 mm/mV. The isoelectric line was defined as the level of the preceding TP segment. ST-segment elevation was measured 80 ms after the J point by a single cardiologist who was unaware of all other clinical data. ST-segment elevation was calculated as the sum of ST-segment elevations in leads I, aV_L, and V_{1-6} for anterior AMI and leads II, III, aV_F, and V_{5-6} for non-anterior AMI[9] In addition to ST-segment measurement, we calculated the 32-point QRS score[10] which has been validated in patients with AMI and strongly correlates with infarct size[11]

Cardiac Enzyme Study

Blood samples were obtained on admission, at 3-h intervals during the first 24 h, at 6-h intervals for the next 2 days, and then daily until discharge. Peak levels of CK and the areas under the curve (AUC) for CK were calculated by the linear-trapezoidal method[12]

Statistical Analysis

Data are expressed as mean values ± standard deviation (SD) for continuous variables and as percentages for categorical variables. Analysis of variance was used to calculate P-values for continuous variables. Chi-square analysis or Fisher's exact test was used to compare categorical variables. Differences were considered statistically significant at $P<0.05$. Multivariate analysis was used to identify clinical predictors of larger infarct size, defined as the upper tertile of AUCs for CK among the variables associated ($P<0.10$) with this index on univariate analysis. Odds ratios and 95% confidence intervals were calculated. Data were analyzed with the SPSS statistical package (Release 10, SPSS Inc, Chicago, IL, USA).

Results

Among the 310 study patients, 39 had received statin treatment for at least 1 month before admission[13] (statin group: 17 [43.6%] pravastatin, 15 [38.5%] atrovastatin, 4 [10.3%] simvastatin, 2 [5.1%] fluvastatin, 1 [2.6%] pitavastatin), and 271 had not (non-statin group).

Patient Characteristics

The baseline characteristics of the patients in the 2 groups are summarized in **Table 1**. There were no significant differences between the 2 groups in age, smoking, preinfarction angina, heart rate, systolic blood pressure, Killip class, white blood cell count, lipid profiles on admission, time from onset to admission, time from admission to fibrinolysis, time from fibrinolysis to angiography, percutaneous coronary intervention, or stent implantation. Patients in the statin group were less likely to be male and to have anterior AMI, and were more likely to have coronary risk factors such as hypertension, hyperlipidemia, and diabetes mellitus and to have received long-term therapy with drugs such as aspirin, angiotensin-converting enzyme inhibitors, angiotensin-receptor blocker, and β-blockers before admission. There was a trend toward a lower neutrophil count on admission in the statin group, but the difference did not reach statistical significance.

ECG and CAG Findings

ECG and CAG findings are shown in **Table 2** and **Figs 1, 2**. Patients in the statin group had a smaller sum of ST-segment elevation and a lower QRS score, both on admission and 1 h later. When the analysis was limited to patients with anterior AMI, QRS scores were significantly lower in the statin group on admission and 1 h later. In addition, the sum of ST-segment elevation on admission was similar in the 2 groups, and there was a trend toward a lower ST-segment elevation 1 h later in the statin group, but the difference did not reach statistical significance.

There were no significant differences between the 2 groups in multivessel disease or collateral circulation. Initial TIMI flow grade did not differ between the 2 groups. Among the 120 patients with an initial TIMI flow grade 0 or 1, the achievement of TIMI flow grade ≥2 after passing the guidewire through the culprit lesion was more frequent in the statin group (**Fig 1**). The rate of final TIMI flow grade 3 was slightly, but not significantly, higher in the statin group.

Infarct Size and Predictors of Larger Infarct Size

Peak CK and AUC of CK were lower in the statin group (**Table 1**). When the analysis was limited to patients with an-

Table 1 Clinical Characteristics of the Patients

	Statin group (n=39)	Non-statin group (n=271)	P value
Age (years)	63±10	60±11	0.15
Men	25 (64%)	243 (90%)	<0.001
Hypertension	29 (74%)	144 (55%)	0.020
Diabetes	18 (47%)	69 (26%)	0.006
Hypercholesterolemia	39 (100%)	144 (55%)	<0.001
Current smoker	27 (71%)	203 (77%)	0.39
Preinfarction angina	12 (31%)	103 (38%)	0.38
Heart rate on admission (beats/min)	77±17	75±22	0.69
SBP on admission (mmHg)	135±31	141±33	0.29
Killip class on admission ≥2	1 (3%)	20 (8%)	0.27
WBC count on admission (/mm^3)	9,960±2,363	10,641±3,823	0.28
Neutrophil count (/mm^3)	5,977±2,199	7,036±3,687	0.08
Lipid profile on admission (mg/dl)			
Total cholesterol	205±52	212±44	0.41
LDL-cholesterol	127±44	138±39	0.11
HDL-cholesterol	49±13	44±11	0.54
Triglycerides	173±111	169±181	0.91
Anterior AMI	13 (33%)	142 (53%)	0.025
Time intervals to treatment			
Symptom onset to admission (min)	110±108	106±102	0.79
Symptom onset to recanalization (min)	147±117	158±105	0.55
Admission to fibrinolysis (min)	13±6	16±16	0.22
Fibrinolysis to first angiography (min)	32±16	29±12	0.10
Fibrinolysis to passing the guidewire* (min)	51±18	48±18	0.38
PCI	30 (79%)	190 (71%)	0.29
Stent implantation	21 (57%)	143 (53%)	0.67
Medications before admission			
Aspirin	9 (23%)	11 (4%)	<0.001
ACEI/ARB	16 (46%)	39 (15%)	<0.001
β-blocker	6 (17%)	14 (5%)	0.010
Medication in hospital			
Aspirin	39 (100%)	259 (99%)	0.70
ACEI/ARB	31 (80%)	229 (85%)	0.43
β-blocker	21 (54%)	129 (50%)	0.62
Peak CK (IU/L)	2,187±1,967	3,334±3,320	0.036
Peak CK for anterior AMI (IU/L)	2,758±2,910	4,136±3,924	0.22
AUC-CK (IU·L^{-1}·h^{-1})	55,972±45,934	84,195±84,276	0.042
AUC-CK for anterior AMI (IU·L^{-1}·h^{-1})	60,572±54,742	97,940±98,138	0.18

Data are means±SD or numbers (%) of patients.
SBP, systolic blood pressure; WBC, white blood cell; LDL, low-density lipoprotein; HDL, high-density lipoprotein; AMI, acute myocardial infarction; PCI, percutaneous coronary intervention; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin-receptor blocker; CK, creatine kinase; AUC, area under the curve.
**Passing the guidewire through the culprit lesion.*

Table 2 Electrocardiographic and Angiographic Findings

	Statin group (n=39)	Non-statin group (n=271)	P value
Sum of ST-segment elevation			
On admission (mm)	13±14	21±17	0.012
1 h later (mm)	4±6	8±8	0.004
On admission for anterior AMI (mm)	26±18	30±18	0.53
1 h later for anterior AMI (mm)	9±6	13±8	0.15
Multivessel disease	10 (26%)	72 (27%)	0.97
Initial TIMI flow grade			
0/1	16 (41%)	104 (38%)	0.66
2	10 (26%)	86 (32%)	0.44
3	13 (32%)	81 (30%)	0.99
Good collateral circulation* (%)#	5/16 (31%)	18/104 (17%)	0.19
Final TIMI flow grade			
0/1	1 (3%)	8 (3%)	0.91
2	1 (3%)	31 (11%)	0.09
3	37 (95%)	232 (86%)	0.11

Data are number (%) of patients.
**Grade 2 or 3 collateral flow to the infarct-related artery.*
#Only patients with initial TIMI flow grade 0 or 1.
TIMI, Thrombolysis In Myocardial Infarction. Other abbreviation see in Table 1.

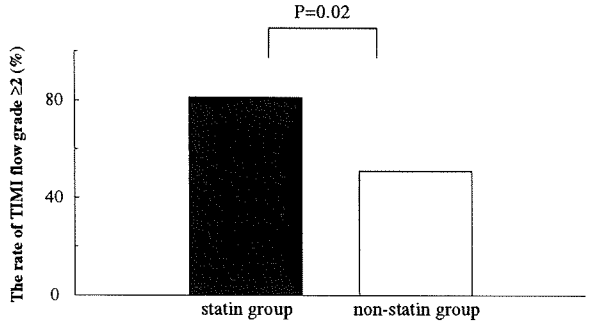

Fig 1. Comparison of the achievement of Thrombolysis In Myocardial Infarction (TIMI) flow grade ≥2 after passing the guidewire through the culprit lesion in the statin and non-statin groups. It was more frequent in patients who had initial TIMI flow grade 0 or 1 (statin group, n=16; non-statin group, n=104).

terior AMI, there were trends toward lower peak CK levels and smaller AUCs for CK in the statin group, but the differences did not reach statistical significance. In the multivariate analysis, statin pretreatment was a negative determinant, and Killip class ≥2 on admission, anterior AMI, and initial TIMI flow grade 0 or 1 were positive determinants of a larger infarct size as defined by the upper tertile of AUC for CK (**Table 3**). Other variables such as multivessel disease, final TIMI flow grade ≤2, and percutaneous coronary intervention, which were associated with a larger infarct size on univariate analysis (P<0.10), were not significant predictors of a larger infarct size.

Discussion

Our study showed that statin pretreatment reduced infarct size in patients with AMI who received fibrinolytic therapy. Although statin pretreatment was not associated with restoration of TIMI flow grade ≥2 at initial angiography, among patients with initial TIMI flow grade 0 or 1, the achievement TIMI flow grade ≥2 was more frequent in the statin group. At final angiography, the rate of TIMI flow grade 3 tended to be higher in the statin group. Moreover, statin pretreatment was associated with reduced myocardial damage during ischemia and reperfusion, as assessed by ECG findings.

Table 3 Multivariate Analysis of Factors Associated With Large Infarct Size as Defined by the Upper Tertile of AUC for CK

	OR (95%CI)	*P value*
Killip class on admission ≥2	*4.13 (1.52–11.23)*	*0.005*
Anterior AMI	*2.44 (1.35–4.41)*	*0.003*
Multivessel disease	*1.74 (0.93–3.28)*	*0.086*
PCI	*1.25 (0.63–2.46)*	*0.525*
Initial TIMI flow grade 0/1	*2.59 (1.45–4.62)*	*0.001*
Final TIMI flow grade ≤2	*2.02 (0.92–4.42)*	*0.078*
Statin pretreatment	*0.25 (0.07–0.91)*	*0.035*

Only univariate variables with a value of P<0.10 are shown.
OR, odds ratio; CI, confidence interval. Other abbreviations see in Tables 1,2.

Statins and Fibrinolysis

An experimental study in animals has shown beneficial effects of combination treatment with a statin and t-PA on cerebrovascular patency after stroke[5] Following plaque disruption, statins promote vascular fibrinolysis by exerting various inhibitory actions on platelet deposition and aggregation, coagulation factors, and rheology![14,15] However, our study found no significant difference in the coronary artery reperfusion rate as assessed by initial TIMI flow grade after fibrinolytic therapy between patients with and without statin pretreatment. Susceptibility to coronary fibrinolytic treatment is influenced by a number of related factors, including the age of the thrombus, its composition, the characteristics of the surrounding plasma, and the temporal evolution of the occluding thrombosis![16,17] Perhaps the small dose of t-PA (approximately half the standard dose) used in our study was inadequate and the timing of initial coronary angiography (mean, 29min from fibrinolysis) was too early to demonstrate an effect of statin pretreatment on coronary artery reperfusion after fibrinolytic therapy. When the analysis was limited to patients with an occluded infarct-related artery

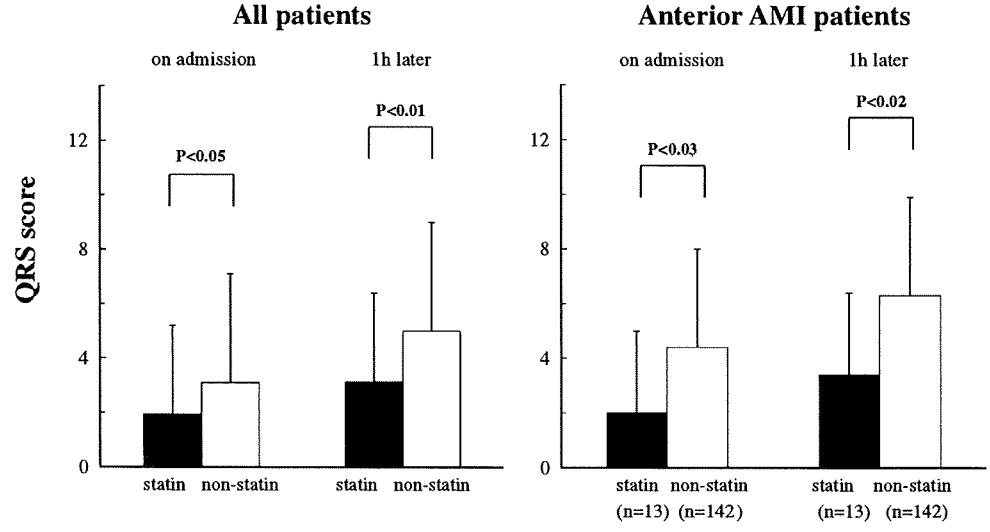

Fig 2. Comparisons of QRS scores on ECG at admission and 1h later in the statin and non-statin groups. AMI, acute myocardial infarction.

on the initial angiogram, coronary artery reperfusion with TIMI flow grade ≥2 after passing the guidewire through the culprit lesion was more frequently associated with statin pretreatment, suggesting that the thrombus was more fragile. This finding may imply that statins partially enhance the efficacy of t-PA.

Statins and Myocardial Damage

In the early stages of AMI, the degree of ST-segment elevation and the evolution of abnormal Q waves may reflect the severity of myocardial damage[18–20] Greater ST-segment elevation implies ongoing severe myocardial injury, and higher QRS scores imply broader transmural myocardial damage. In our study, patients who received statin pretreatment had a smaller magnitude of ST-segment elevation and lower QRS scores on admission as well as after reperfusion. The ECG findings on admission are not affected by myocardial damage occurring after reperfusion therapy, such as reperfusion injury or distal embolization, which suggests that statin pretreatment was associated with less myocardial damage during ischemia and reperfusion, resulting in a smaller infarct size as assessed by peak CK levels and AUC for CK. Although the precise mechanisms underlying the protective effects of statins against ischemia–reperfusion injury are unclear, statins have shown vasculoprotective and cardioprotective effects in experimental studies. Statins may improve endothelial function by decreasing expression of endothelial adhesion molecules, increasing nitric oxide bioavailability, and attenuating the production of reactive oxygen species[2,21,22] In addition, statins are thought to stabilize plaque by decreasing lipid oxidation, inflammation, matrix metalloproteinase-2, and cell death and by increasing the content of tissue inhibitor of metalloproteinase-1 and collagen; these effects might reduce distal embolization?[23] Furthermore, statins have been shown to open mitochondrial adenosine triphosphate-sensitive potassium channels, suggesting pharmacological ischemic preconditioning effects?[24,25] These effects might contribute to reduced myocardial damage during ischemia–reperfusion. Several studies have demonstrated that statin pretreatment reduces microvascular and myocardial damage after coronary intervention in patients with AMI[13,26]

Study Limitations

First, this was a single-center retrospective study performed in a relatively small number of patients. Second, we could not precisely assess the effects of the pretreatment period or the dose of statins. Furthermore, we could not analyze the effects of differences in statin type because of the small number of patients. Third, patients with statin pretreatment were more likely to have received drugs such as aspirin, angiotensin-converting enzyme inhibitors, angiotensin-receptor blocker, and β-blockers before admission. Although these medications may affect clinical outcomes, they were not found to be associated with larger infarct size. In addition, patients with statin pretreatment were more likely to have hypertension, hyperlipidemia, and diabetes mellitus. Patients given statin pretreatment may thus have been more aggressively treated in terms of diet, exercise, or other lifestyle interventions.

Conclusions

The present study shows that statin pretreatment is associated with a smaller infarct size in patients with AMI who receive fibrinolytic therapy. Our results provide evidence that statins have cardioprotective effects and enhance the effectiveness of t-PA.

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