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症　例

PCI後に発症した冠動脈仮性瘤に対するOn-lay patch冠動脈バイパス術の一例

合　志　桂太郎*，土　井　　潔*
大　川　和　成*，夜　久　　均*

緒　　言

経皮的冠動脈形成術(PCI)後の合併症として，冠動脈仮性瘤の報告は稀である[1~3]．その治療として，破裂および血栓閉塞の危険性から，外科的修復が要求されることが多い[3,4]．今回我々はPCI後に発症したと考えられる冠動脈仮性瘤に対し，On-lay patch冠動脈バイパス術(CABG)を施行し良好な結果を得たので報告する．

症　　例

42歳の男性が突然の胸痛を自覚し，近医を受診したところ，心電図と血液検査から急性心筋梗塞と診断された．緊急冠動脈造影の結果，左前下行枝(＃7)の閉塞を認めたため，POBA(Primary Old Balloon Angioplasty)が施行された．2週間後のfollow up冠動脈造影(CAG)で再狭窄を認めず退院となった．3ヵ月後のfollow up CAGでPOBA施行部位に90%の狭窄を認め，更に直径約8mmの嚢状冠動脈瘤も認めたため，当科に外科的治療目的に紹介入院となった．

入院時の身長175cm，体重82.5kgで，血圧は120/70mmHg，脈拍は70/minで整，心音と呼吸音は共に清であった．

胸部レントゲン写真では心胸郭比が42%であった．心電図所見では洞調律でV1～4はQSパターンを示していた．血液検査所見に特に異常は認めなかった．心臓超音波所見で心室中隔前壁～心尖部にhypokinesisを認めた．EFは72%でLVDd/Ds＝49/29mmであった．弁逆流は認めなかった．

冠動脈造影所見(前医)は＃7の第一中隔枝と第二中隔枝の間の左前下行枝に径約8mmの嚢状冠動脈瘤を認め，冠動脈瘤の前後には90%の狭窄病変も伴っていた(**図1, 2**)．

全身麻酔下に，胸骨正中切開の後，左内胸動脈を剥離した．心表面には明らかな冠動脈瘤は認められなかったが，心拍動下に左前下行枝を剥離すると，左前下行枝(＃7)に冠動脈瘤を確認できた(**図3**)．上行大動脈に送血し，右房脱血で人工心肺を開始し，上行大動脈を遮断し，大動脈基部から心筋保護液を注入し心停止を得た．冠動脈瘤を含めた左前下行枝を冠動脈瘤を起点として切開した．その内膜は瀰漫性に粥状硬化を来たしており，比較的健常な部位に至るまで切開を延長したところ，約40mmの切開口となった．冠動脈瘤は径約8mmで，第一中隔枝と第二中隔枝の間に存在しており，肉眼的には仮性瘤であった(**図4**)．冠動脈瘤が存在していた冠動脈床にはわずかながら正常内膜が存在していた．この正常内膜に縫合線を取るように(**図5**)左内胸動脈を用い約40mmにわたる側々吻合口とし，On-lay patch CABGを施行した(**図6**)．人工心肺からの離脱は特に問題を認めなかった．

術後経過は術当日に人工呼吸器から離脱し，術後3日目より一般病棟管理となった．術後8日目にfollow up CTを行い，左内胸動脈，第一・二中隔枝の良好な開存および冠動脈瘤の消失を確認した(**図7**)．その他特に合併症を認めることなく術後9日目に退院となった．

*京都府立医科大学大学院医学研究科心臓血管・呼吸器外科学

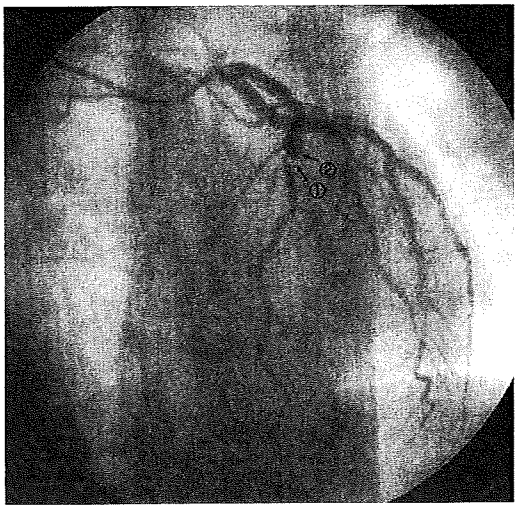

図1　術前冠動脈造影
①左前下行枝の狭窄
②冠動脈瘤

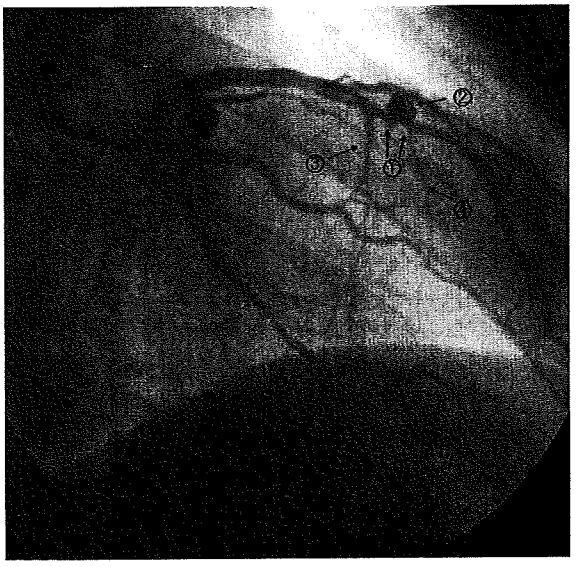

図2　術前冠動脈造影
①冠動脈瘤前後の90%狭窄
②冠動脈瘤
③第一中隔枝
④第二中隔枝

考　　察

冠動脈瘤は冠動脈造影が行われた患者の0.3～4.9%に認められ[5]，その発生部位は右冠動脈が最も多く(50%)，ついで左前下行枝，左回旋枝そして左冠動脈主幹部の順である．その成因はPahlavanら[5]の報告によると，粥状硬化によるものが50%と最も多く，次に川崎病や先天性によるものが17%，真菌・ウイルス等感染によるものが11%と続き，その他PCIなどの外傷性によるものは非常に稀である．PCI後の冠動脈瘤の成因については明確な報告は未だないが，ガイドワイヤーやバ

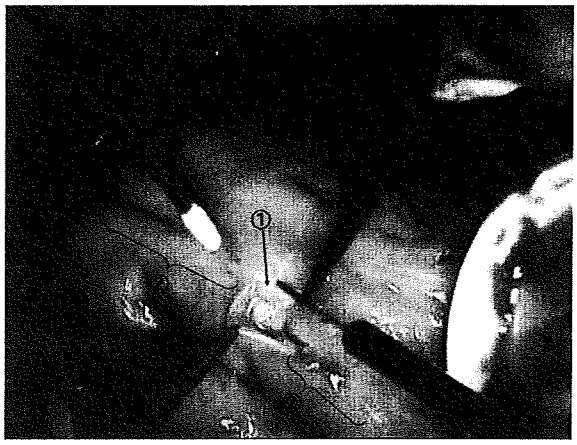

図3　左前下行枝の剥離
①冠動脈瘤
②左前下行枝

図4　左前下行枝を切開したところ
①第一中隔枝
②第二中隔枝
③冠動脈瘤

ルーンによる過度の拡張等により深部内膜損傷から冠動脈解離を来たし，内膜の脆弱部位が瘤化すると考えられている[1,2]．

冠動脈瘤はそのほとんどが無症状であり，冠動脈造影検査で偶然に発見されることが多い．巨大な冠動脈瘤では胸部レントゲンで異常陰影として認められることもある[6]．症状としては冠動脈瘤破裂による胸痛および冠動脈瘤内の血栓や粥腫による塞栓症状が主である[5]．冠動脈瘤の破裂は実際には非常に稀であり，報告された冠動脈瘤破裂症例は瘤径が11cmといった非常に大きいものであった[6]．また，冠動脈瘤は冠動脈狭窄病変を伴っていなくても比較的急速に狭窄病変が進行するとの報告もある．冠動脈瘤が一度認められると，血栓お

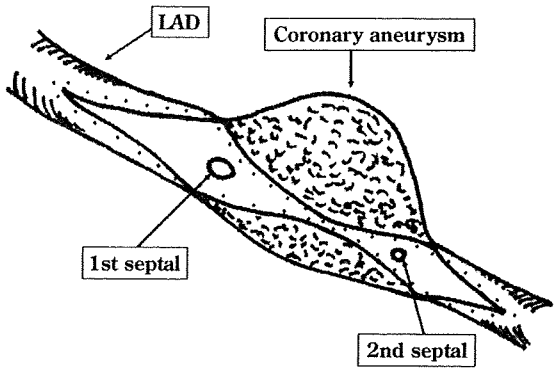

図5 手術シェーマ
点線の部位に縫合線をおいた.
LAD: 左前下行枝, 1st septal: 第一中隔枝, 2nd septal: 第二中隔枝

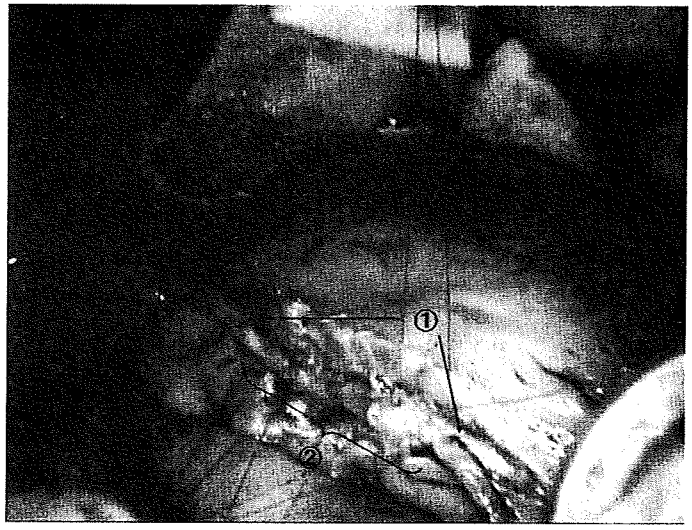

図6 On-lay patch 冠動脈バイパス術
①吻合された左内胸動脈
②左内胸動脈の On-lay patch 部分

よび塞栓予防に抗凝固療法や抗血小板療法が施行されるが, 高度冠動脈狭窄病変や塞栓症状が出現すれば必然的に PCI や外科的治療が要求される. PCI においては, ステントを留置し冠動脈瘤の縮小を認めた症例や[7], 最近では PTFE-covered, balloon-expandable stent や[8,9], self-expandable PTFE stent[10]の使用が報告されているが, 適応症例は非常に限られている.

以上のことより冠動脈瘤の治療には PCI 等を含めた内科的治療よりも外科的治療が求められることが多い.

冠動脈瘤に対する外科治療としては様々な手法が報告されている. 行われるべき処置としては, 冠動脈瘤への血行遮断と冠動脈瘤末梢領域への血行再建である. 一般的には, 冠動脈瘤を含めた冠動脈の結紮を行い, その末梢領域に CABG を行うことが多い[11~13]. しかし, この手法では, 冠動脈瘤近傍に重要分枝が存在する場合, それらを冠動脈の結紮により犠牲にする可能性が高いと考えられる. 本症例のように冠動脈瘤の近傍には比較的大きな第一・第二中隔枝が存在している場合, 結紮によりこれらを犠牲にすることが考えられた. 冠動脈瘤近傍の重要分枝を温存するには patch plasty が行われることがある[14,15]. しかし狭窄病変

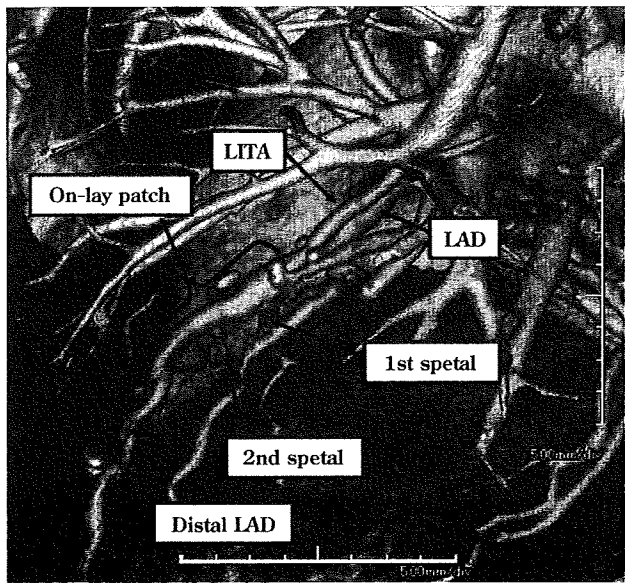

図7 術後 8 日目の follow up CT
左内胸動脈，第一および二中隔枝の良好な開存と冠動脈瘤の消失を認めた．
LITA: 左内胸動脈
LAD: 左前下行枝
Distal LAD: 吻合部末梢側の左前下行枝
1st septal: 第一中隔枝
2nd septal: 第二中隔枝

が存在している場合，冠動脈瘤は切除できても狭窄病変が残存し，また，狭窄病変への patch の吻合が困難である可能性が考えられる．本症例も冠動脈を切開すると，冠動脈瘤存在部位は高度の狭窄病変であり，さらには術前冠動脈造影では狭窄の認められなかった冠動脈瘤前後の左前下行枝は瀰漫性に粥状硬化を来たしており，patch 吻合を行うのに満足のいく血管性状に至るまでに約 40mm の冠動脈切開が必要であった．本症例では，冠動脈瘤および狭窄部位の存在していた冠動脈床には肉眼的に正常と思われる内膜が存在しており，正常内膜に左内胸動脈の吻合線をとることで，良好な吻合を行うことが可能であった．さらに，冠動脈瘤への血流の遮断および冠動脈瘤近傍の第一・二中隔枝の温存も行うことができ，さらには狭窄病変の解除も同時に行うことが可能であった．今回行った手法は，従来の冠動脈瘤に対する外科的治療目的を十分に満たす有効な手段であったと思われる．

今回の手法において，早期開存は良好なものが得られたが，今後長期成績もフォローしていく必要があると思われる．

結　論

PCI 後に発症した冠動脈瘤に対し On-lay patch CABG を施行し良好な結果を得ることができた．冠動脈瘤近傍に重要分枝や狭窄病変を有する場合，今回我々が施行した手法は冠動脈瘤に対する外科手術の一手法になり得ると考えられた．

本症例は第 12 回日本冠動脈外科学会学術大会で発表した．

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On-Lay Patch Coronary Artery Bypass Grafting for a Pseudo-Aneurysm after Percutaneous Coronary Intervention

Keitaro Koushi*, Kiyoshi Doi*, Kazunari Okawa*, Hitoshi Yaku*

*Department of Cardiovascular and Thoracic Surgery, Kyoto Prefectural University of Medicine, Kyoto, Japan

A 42-year-old man was referred to our hospital due to a coronary artery aneurysm (8mm in diameter) after percutaneous coronary intervention. He had a history of acute myocardial infarction in the left anterior descending artery (LAD) and balloon angioplasty three months previously. Coronary artery bypass grafting (CABG) was performed using cardiopulmonary bypass and cardioplegia. At the operation, a pseudo-aneurysm was found between 1st and 2nd septal branch. A longitudinal incision of 40mm length was made on the LAD across the aneurysm and stenosis. The left internal thoracic artery (LITA) was anastomosed with 8-0 prolene sutures (on-lay patch). The 3 dimension computed tomography before discharge showed disappearance of the aneurysm and good patency of the LITA graft to the LAD. Although PCI-related coronary artery aneurysm was relatively rare. Once it is found, surgical treatment was recommended due to the threat of rupture. Although plication or ligation of the coronary aneurysm and distal coronary bypass have been recommended, on-lay patch CABG may be useful and can be an option to avoid sacrifice of the major branches near by the aneurysm.

Key words : coronary aneurysm, surgical treatment, on-lay patch, CABG, PCI

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Impact of Plaque Rupture on Infarct Size in ST-Segment Elevation Anterior Acute Myocardial Infarction

Ikuyoshi Kusama, MD,* Kiyoshi Hibi, MD,* Masami Kosuge, MD,* Naoki Nozawa, MD,* Hiroyuki Ozaki, MD,* Hideto Yano, MD,* Shinnichi Sumita, MD,* Kengo Tsukahara, MD,* Jun Okuda, MD,* Toshiaki Ebina, MD,* Satoshi Umemura, MD,† Kazuo Kimura, MD*

Yokohama, Japan

Objectives We sought to assess whether coronary plaque rupture at culprit lesions is associated with infarct size in patients with anterior acute myocardial infarction (AMI).

Background Some patients with AMI have large infarcts despite early reperfusion. Whether culprit plaque morphology impacts infarct size or not remains unknown.

Methods Patients who had a first anterior AMI with reperfusion within 6 hours after onset were enrolled and divided into 2 groups according to the presence or absence of plaque rupture at the culprit lesion as defined by preintervention intravascular ultrasound (IVUS): patients with rupture (n = 54) and without rupture (n = 37).

Results Patients with plaque rupture had a higher incidence of no-reflow phenomenon (15% vs. 3%; $p = 0.08$) and a lower myocardial blush grade (1.5 vs. 2.3; $p < 0.05$) after percutaneous coronary intervention. The IVUS analysis showed that patients with plaque rupture had a higher incidence of soft plaque and positive remodeling. Peak creatine kinase levels were higher (4,707 vs. 2,309 IU/l; $p < 0.0001$) and left ventricular ejection fraction in the chronic phase was lower (54% vs. 63%; $p < 0.01$) in patients with plaque rupture. A multivariate logistic regression analysis revealed that plaque rupture and the proximal lesion site correlated with a left ventricular ejection fraction of <50% in the chronic phase (odds ratios 6.5 and 17.5, respectively; $p < 0.05$).

Conclusions Plaque rupture is associated with morphologic characteristics of vulnerable lesions, as well as with larger infarcts and a higher incidence of no-reflow phenomenon, suggesting that plaque embolism contributes to the progression of myocardial damage in patients with anterior AMI. (J Am Coll Cardiol 2007;50:1230–7) © 2007 by the American College of Cardiology Foundation

A number of studies have suggested that plaque rupture with subsequent thrombus formation is the most frequent cause of acute coronary syndromes (1,2). Infarct size in acute myocardial infarction (AMI) is associated with prodromal angina, the duration of coronary occlusion, and collateral flow (3–5). Recent studies have indicated that stent thrombosis causes large myocardial infarctions with a significant decline in left ventricular function, despite immediate reperfusion therapy by emergency percutaneous coronary intervention (PCI) (6). These findings suggest that abrupt coronary occlusion, distal embolism, or both may promote myocardial damage. Similarly, some patients with AMI have large infarcts despite early reperfusion. The relationships among disrupted plaque morphology, infarct size, and clinical presentation remain poorly understood. To determine predictors of infarct size, we investigated the association between infarct size and the morphologic characteristics of culprit lesions by intravascular ultrasound (IVUS).

Methods

Study patients. Patients with a first ST-segment elevation anterior AMI were enrolled. All patients received coronary reperfusion within 6 h after the onset of symptoms, and infarct-related arteries were confirmed by IVUS before any PCI. Patients with malignant disease, infectious disease, or inflammatory diseases, such as collagen disease, were excluded to avoid bias. We also excluded patients with cardiogenic shock, because we performed reperfusion procedures as soon as possible, without preintervention IVUS.

From the *Division of Cardiology, Yokohama City University Medical Center, Yokohama, Japan; and the †Department of Medical Science and Cardiorenal Medicine, Yokohama City University Graduate School of Medicine, Yokohama, Japan.

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We enrolled 91 consecutive patients who met these entry criteria. Acute myocardial infarction was defined as the presence of continuous chest symptoms for more than 30 min, accompanied by ST-segment elevation of >0.2 mV on at least 2 contiguous electrocardiographic (ECG) leads and by a rise in serum creatine kinase (CK) levels to more than twice the upper limit of normal. The protocol for the study was approved by the ethics committee of the Yokohama City University Medical Center. We obtained written informed consent from all participants before initial coronary angiography.

Study protocol. On admission, all patients received 200 mg aspirin, an intravenous bolus injection of 5,000 IU heparin, and isosorbide dinitrate. In the absence of contraindications according to American College of Cardiology/American Heart Association practice guidelines (7), most patients (84%) received intravenous thrombolytic therapy. In the catheterization laboratory, coronary angiography was performed via the femoral approach. Periprocedural intravenous heparin was given to maintain an activated clotting time ≥250 s. Intracoronary isosorbide dinitrate (2.0 to 2.5 mg) was administered before angiography to prevent coronary artery spasm. After careful manipulation of the guidewire and additional intracoronary isosorbide dinitrate (2.0 to 2.5 mg), the IVUS catheter was advanced distal to the culprit lesion. After examination by IVUS, thrombus aspiration was performed in patients with obvious thrombus formation on angiography, IVUS, or both.

All IVUS studies were performed with a commercially available system (Scimed; Boston Scientific, Boston, Massachusetts) before any balloon inflation or stent implantation. A 40-MHz IVUS catheter was advanced distal to the culprit lesion, and imaging was performed in a retrograde fashion to the aorto-ostial junction at an automatic pullback speed of 0.5 mm/s, facilitating observation of the lesion. While pulling back the catheter, we manually infused contrast medium or normal saline suitable for IVUS imaging while carefully observing the lesion. This procedure enabled us to eliminate blood noise and to observe communication between the plaque and the coronary artery lumen. The IVUS images were recorded on S-VHS videotape for off-line analysis.

Cardiac enzyme measurements. 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 CK-MB and the areas under the curves (AUCs) for CK and CK-MB as calculated by the linear-trapezoidal method (8) were derived.

Electrocardiographic analysis. A 12-lead ECG was recorded on admission at a paper speed of 25 mm/s and an amplification of 10 mm/mV.

Angiographic analysis. Coronary angiograms were reviewed separately by 2 independent observers who were unaware of the IVUS findings. Coronary artery segments were identified and categorized according to the reporting system of the American Heart Association. Perfusion degree was evaluated according to the TIMI (Thrombolysis In Myocardial Infarction) criteria (9). No reflow after reperfusion was defined as postprocedural TIMI flow grade 0, 1, or 2 in the absence of mechanical obstruction on final postprocedural angiograms (10). Myocardial blush grade was graded as follows: 0, no myocardial blush or contrast density; 1, minimal myocardial blush or contrast density; 2, moderate myocardial blush or contrast density, but less than that obtained during angiography of a contralateral or ipsilateral noninfarct-related coronary artery; and 3, normal myocardial blush or contrast density, comparable to that obtained during angiography of a contralateral or ipsilateral noninfarct-related coronary artery. When myocardial blush persisted, this finding was graded as 0 (11).

Abbreviations and Acronyms

AMI = acute myocardial infarction
AUC = area under the curve
CK = creatine kinase
ECG = electrocardiography
IVUS = intravascular ultrasound
PCI = percutaneous coronary intervention

Left ventriculogram. Right anterior oblique views of left ventriculograms obtained at the chronic phase after AMI (mean 155 ± 15 days) were used to assess global and regional left ventricular function. End-diastolic and end-systolic endocardial borders were hand-traced in the frames with maximal and minimal volume, respectively. Left ventricular end-diastolic and -systolic volumes were calculated by the area-length method described by Sandler and Dodge (12) and were corrected for body surface area to determine volume index. Regional wall motion in the territory of the infarcted area was assessed by the centerline method, using 100 chords, and expressed as SD/chord. The number of contiguous chords showing >2 SD below normal wall motion by the centerline method (percent abnormally contracting segment) was used as an index of infarct size.

Analysis of IVUS images. Morphologic features on IVUS images were independently interpreted by 2 experienced observers blinded to the angiographic and clinical data. Images for which the 2 observers agreed on the diagnosis were included in subsequent analysis. Evaluation of lesion morphology and other measurements during IVUS was done according to the American College of Cardiology Clinical Expert Consensus Document on Standards for Acquisition, Measurement, and Reporting of Intravascular Ultrasound Studies (13). We defined lesions with plaque rupture on IVUS as follows: 1) lesions with fissure/dissection; or 2) lesions without fissure/dissection, but in which the injection of saline or contrast medium confirmed communication between the plaque and the coronary artery lumen (Fig. 1) (14). We defined the other lesions as nonruptured plaque. Plaque composition was assessed visually and classified as echolucent when >75% of the plaque area was less bright than the adventitia; otherwise, plaque composition was classified as fibrous.

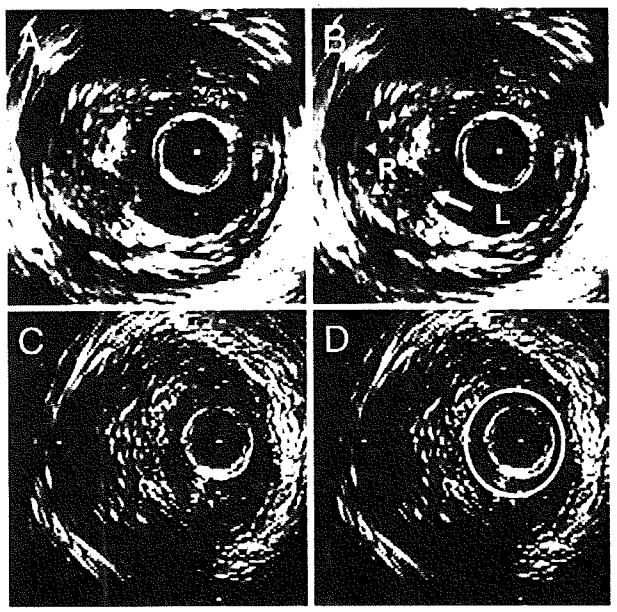

Figure 1 **Typical IVUS Images of Plaque Rupture and Nonruptured Plaque**

Typical intravascular ultrasound images of plaque rupture **(A, B)** and nonruptured plaque **(C, D)**. **(B)** Plaque ulceration with a fissure **(arrowheads)** and a communication **(arrow)** between the cavity of the rupture (R) and the lumen (L). **(D)** Lumen surface with preserved continuity. IVUS = intravascular ultrasound.

External elastic membrane (EEM) cross-sectional area (CSA) and lumen CSA (in mm^2) at the lesion site and at the proximal and distal reference sites were analyzed using planimetry software (TapeMeasure, Indec Systems, Capitola, California). The reference segments were the most normal-looking CSA within 5 mm proximal and distal to the lesion but before any side branch. Remodeling was considered positive when the lesion EEM CSA was greater than both the proximal and distal reference EEM CSA, negative when the lesion EEM CSA was less than both the proximal and distal reference EEM CSA, and intermediate when the lesion EEM CSA was intermediate between the proximal and distal reference EEM CSA (15).

Statistical analysis. Statistical analysis was performed with StatView 5.0 software (SAS Institute, Cary, North Carolina). Results are expressed as mean ± SD for continuous variables. Qualitative data are presented as number (%). Continuous variables were compared by means of Student *t* test, and categoric data were compared by the chi-square test or Fisher exact test between groups. The Cochran-Mantel-Haenszel test was used for comparison of ordinal categoric variables between groups. Univariate and logistic regression analyses were used to identify predictors of left ventricular ejection fraction <50% at discharge. Covariables examined included clinical characteristics (age, gender, presence of preinfarction angina, elapsed time from symptom onset to reperfusion, and coronary risk factors), angiographic characteristics (distribution of culprit lesions, myocardial blush grade, and no-reflow phenomenon), and qualitative IVUS factors (plaque morphology and presence of plaque rupture). Univariate cariables with a value of $p < 0.2$ were entered into the multivariate models. For all analyses, values of $p < 0.05$ were considered to indicate statistical significance.

Results

Patient characteristics. Patients were classified according to the presence or absence of plaque rupture as determined by preintervention IVUS; 54 patients had plaque rupture (rupture group), and 37 did not have plaque rupture (nonrupture group). Patient characteristics are summarized in Table 1. The proportions of men (89% vs. 68%; $p < 0.05$) and current smokers (74% vs. 44%; $p < 0.01$) were higher and the incidence of preinfarction angina was lower (31% vs. 54%; $p < 0.05$) in the rupture group than in the nonrupture group. Patients older than 75 years (n = 5), patients who entered another clinical trial that prohibited thrombolysis before PCI (n = 4), and patients who had a history of ischemic stroke (n = 4) or active peptic ulcer (n = 2) did not receive thrombolytic therapy.

Angiographic findings. The angiographic findings are shown in Table 2. There were no differences between the groups in the incidence of multivessel disease or proximal lesions of the left anterior descending artery. Seventy-five patients (82%) were treated with stenting, and 10 (11%) received balloon angioplasty only. In patients (n = 6) who achieved a TIMI flow grade of 3 at initial angiography with intermediate severity of culprit lesion, PCI was not performed. Thrombus aspiration was attempted after

Table 1 **Patient Characteristics**

	Rupture	Nonrupture	p Value
Patients, n	54	37	
Age, yrs	62 ± 10	64 ± 12	0.95
Men	48 (89)	25 (68)	<0.05
Coronary risk factors			
Systemic hypertension	23 (43)	23 (62)	0.07
Diabetes mellitus	10 (19)	11 (30)	0.21
Smoking	40 (74)	16 (44)	<0.01
Hypercholesterolemia	33 (62)	23 (63)	0.95
Family history	14 (26)	11 (29)	0.78
Killip class ≥2	5 (9)	1 (3)	0.39
Thrombolysis	45 (84)	31 (83)	0.62
Preinfarction angina	17 (31)	20 (54)	<0.05
Onset to admission time, min	92 ± 61	99 ± 65	0.59
Reperfusion time, min	156 ± 77	155 ± 79	0.98
Medication after AMI			
Beta-blocker	32 (59)	19 (51)	0.45
ACE-I/ARB	41 (76)	32 (86)	0.21
Statin	27 (50)	20 (54)	0.70

Data presented are mean ± SD or number (%) of patients.
ACE-I = angiotensin-converting enzyme inhibitors; AMI = acute myocardial infarction; ARB = angiotensin receptor blockers.

Table 2 Angiographic Findings at Baseline and Left Ventriculogram Findings at Chronic Phase

	Rupture	Nonrupture	p Value
Angiographic findings			
Lesion at proximal LAD	37 (69)	22 (59)	0.37
Diseased vessel ≥2	7 (13)	5 (14)	>0.99
TIMI flow grade ≤1 at initial angiogram	18 (38)	7 (23)	0.15
No-reflow	8 (15)	1 (3)	0.08
Myocardial blush grade ≥2	29 (53)	31 (85)	<0.01
Left ventriculogram findings at chronic phase			
Ejection fraction (%)	54 ± 13	63 ± 10	<0.01
SD/chords	−2.6 ± 1.0	−1.8 ± 1.0	<0.001
LVESVI (ml/m^2)	36 ± 17	26 ± 14	<0.01
LVEDVI (ml/m^2)	77 ± 19	70 ± 18	0.10
% ACS	31 ± 18	16 ± 16	<0.001

Data presented are number (%) of patients or mean ± SD.
% ACS = percent abnormally contracting segment; LAD = left anterior descending coronary artery; LVEDVI = left ventricular end-diastolic volume index; LVESVI = left ventricular end-systolic volume index; SD/chords = regional wall motion of infarted area quantified by centerline method; TIMI = Thrombolysis in Myocardial Infarction.

IVUS interrogation and before balloon inflation in 2 patients. No distal protection device was used in this study. The incidence of no-reflow phenomenon was slightly but not significantly higher, and that of myocardial blush grade was lower in the rupture group than in the nonrupture group.

Left ventricular function in chronic phase. Sixty-five patients (71%) underwent left ventriculogram in the chronic phase. Twenty-six patients were excluded from this examination for the following reasons: 10 patients were lost to follow-up or transfered to other hospitals, 7 had renal dysfunction, 2 had allergy to contrast medium, 2 had bronchial asthma, and 5 did not give informed consent for repeat catheterization in the chronic phase. There were no differences in the number of Q waves on admission ECG, peak CK levels, or the AUC of CK levels between patients with left ventriculograms and those without left ventriculograms (data not shown). Left ventriculographic findings in the chronic phase are summarized in Table 2. Left ventricular ejection fraction and regional wall motion were lower, and left ventricular end-systolic volume and infarct size as assessed on the basis of percent abnormally contracting segment were greater in the rupture group than in the nonrupture group.

IVUS results. Coronary artery lesions were successfully observed in all patients on IVUS, without serious procedural complications. The preintervention IVUS findings are summarized in Table 3. Culprit lesions in the rupture group involved a larger vessel area and showed positive remodeling with soft plaque morphology.

Electrocardiographic findings. The number of Q waves on the admission ECG was greater in the rupture group than in the nonrupture group (2.3 ± 1.6 vs. 1.1 ± 1.2; $p < 0.05$) among patients with a reperfusion time of <120 min ($n = 39$) but did not differ between the groups (2.5 ± 1.6 vs. 2.4 ± 1.5, respectively; $p = 0.785$) among patients with a reperfusion time of ≥120 min ($n = 52$).

Table 3 Preintervention IVUS Findings

	Rupture	Nonrupture	p Value
Soft plaque morphology	46 (86)	24 (65)	<0.05
Calcium	32 (59)	20 (54)	0.62
EEM-CSA, mm^2			
Lesion	18.0 ± 4.6	13.7 ± 4.1	<0.01
Proximal reference	16.9 ± 4.0	14.9 ± 3.5	<0.05
Distal reference	12.6 ± 4.3	11.4 ± 3.3	0.23
Coronary remodeling, %*			<0.01
Positive remodeling	70	37	
Intermediate remodeling	17	29	
Negative remodeling	13	34	

Data presented are mean ± SD or number (%) of patients. *Cochran-Mantel-Haenszel test.
EEM-CSA = external elastic membrane cross-sectional area; IVUS = intravascular ultrasound.

Valuation of infarct size. Peak CK (4,707 ± 3,017 IU/l vs. 2,309 ± 1,496 IU/l; $p < 0.0001$) and CK-MB levels (383 ± 257 IU/l vs. 209 ± 135 IU/l; $p < 0.01$) as well as AUCs for CK (110,827 ± 69,297 IU/l·h vs. 58,041 ± 32,814 IU/l·h; $p < 0.0001$) and CK-MB levels (8,128 ± 4,709 IU/l·h vs. 4,889 ± 2,667 IU/l·h; $p < 0.001$) were all higher in the rupture group than in the nonrupture group (Fig. 2).

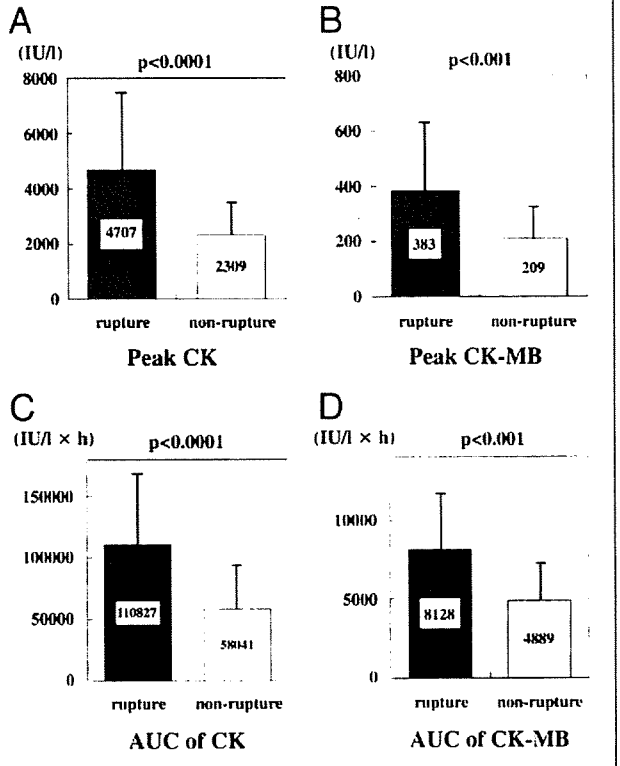

Figure 2 Comparison of Infarct Size Between the Rupture and Nonrupture Groups

Comparison of peak creatine kinase (CK) **(A)**, peak CK-MB **(B)**, area under the curve (AUC) of CK **(C)**, and AUC of CK-MB **(D)** levels between the rupture and nonrupture groups.

We evaluated infarct size, as represented by peak CK levels and AUC of CK, according to age, gender, established coronary risk factors, and reperfusion time (Table 4). In all subgroups, peak CK levels and AUC of CK were significantly higher in the plaque rupture group than in the nonrupture group.

Determinants of left ventricular dysfunction in chronic phase. A multivariate logistic regression analysis revealed that the presence of plaque rupture and the proximal lesion site were independent predictors of a left ventricular ejection fraction of <50% in the chronic phases (Table 5).

Table 5 Multiple Logistic Regression Analysis for LVEF <50% at Chronic Phases

Variables	Odds Ratio	95% CI	p Value
Proximal LAD	17.5	1.8–167.4	0.01
Plaque rupture	6.5	1.1–37.3	0.04
Myocardial blush grade ≤1	4.0	0.9–18.6	0.08
No-reflow phenomenon	7.9	0.3–241.4	0.23
Reperfusion time >120 min	2.6	0.6–12.0	0.23

Only univariate variables with a value of $p < 0.2$ are shown.
CI = confidence interval; LAD = left anterior descending coronary artery; LVEF = left ventricular ejection fraction.

Discussion

To our knowledge, this is the first clinical study to demonstrate that plaque rupture at culprit lesions is associated with morphologic characteristics of vulnerable lesions as well as with larger infarcts and a higher incidence of no-reflow phenomenon in patients with anterior AMI. Independent predictors of left ventricular dysfunction were plaque rupture and proximal lesion site.

Plaque rupture with subsequent thrombus formation is the most frequent cause of acute coronary syndromes (1,2). Several postmortem studies have demonstrated that about 60% of all cases of AMI are caused by plaque rupture and the other 40% by plaque erosion (16,17). In the present study, the rate of plaque rupture on IVUS was 59.3%, similar to the rates reported by Sano et al. (56%) (14) and Hong et al. (66%) (18). It is unclear whether the nonrupture plaques identified by IVUS are erosive lesions, because IVUS has a limited capability to assess the lumen surface of culprit plaque. Plaque erosions can be confirmed only by angioscopy in vivo. In a previous study by Hayashi et al. (19), culprit lesions in patients with AMI were evaluated by means of both IVUS and angioscopy. The evaluation of plaque morphology differed in only 1 (1.4%) case between the 2 modalities (19), indicating that lesions without plaque rupture on IVUS are roughly equivalent to erosive lesions.

The present study showed that proportions of men and current smokers were higher among patients with plaque rupture than among those without plaque rupture, consistent with earlier postmortem studies. Farb et al. (17) demonstrated that eroded lesions were more common in younger individuals and women. Burke et al. (20) reported that cigarette smoking was associated with coronary thrombosis in men and plaque erosion in women. Kojima et al. (21) reported that the presence of plaque

Table 4 Valuation of Infarct Size in Each Risk Factor and Subgroup

	Peak CK (IU/l)			CK AUC (IU/l·h)		
Subgroups	Rupture	Nonrupture	p Value	Rupture	Nonrupture	p Value
Hypertension						
With (n = 6)	4,945 ± 2,831	2,393 ± 1,407	<0.01	113,094 ± 60,016	58,116 ± 29,121	<0.01
Without (n = 45)	4,531 ± 3,184	2,172 ± 1,678	0.013	109,145 ± 76,390	57,909 ± 39,822	0.027
Diabetes mellitus						
With (n = 21)	4,588 ± 2,568	1,861 ± 1,150	<0.01	97,508 ± 45,738	46,448 ± 24,543	<0.01
Without (n = 10)	4,734 ± 5,137	2,499 ± 1,602	<0.01	113,854 ± 73,691	63,142 ± 35,079	<0.01
Hyperlipidemia						
With (n = 57)	4,668 ± 2,578	2,240 ± 1,578	<0.01	110,609 ± 63,651	57,329 ± 36,210	<0.01
Without (n = 34)	4,768 ± 3,672	2,497 ± 1,549	0.043	111,170 ± 79,013	59,302 ± 27,093	0.030
Smoking						
Current or ex-smoker (n = 56)	4,326 ± 2,685	2,355 ± 1,484	<0.01	100,705 ± 63,215	58,219 ± 38,860	0.019
Nonsmoker (n = 85)	5,795 ± 3,711	2,274 ± 1,540	<0.01	139,749 ± 79,832	57,914 ± 28,762	<0.01
Age, yrs						
≥65 (n = 38)	4,356 ± 2,198	2,492 ± 1,579	<0.01	103,523 ± 48,264	62,523 ± 28,248	<0.01
<65 (n = 53)	4,948 ± 3,485	2,170 ± 1,453	<0.01	115,849 ± 81,044	54,456 ± 36,375	<0.01
Gender						
Male (n = 13)	4,787 ± 3,136	2,577 ± 1,672	<0.01	111,896 ± 71,803	62,539 ± 37,493	<0.01
Female (n = 18)	4,069 ± 1,787	1,752 ± 848	<0.01	102,276 ± 48,374	49,047 ± 18,829	<0.01
Reperfusion time, min						
<120 (n = 39)	5,600 ± 3,571	2,158 ± 1,778	<0.01	131,193 ± 85,093	53,918 ± 40,329	<0.01
≥120 (n = 52)	4,045 ± 2,382	2,425 ± 1,277	<0.01	95,717 ± 51,184	60,987 ± 26,907	<0.01

Data presented are mean ± SD.
AUC = area under the curve; CK = creatine kinase.

rupture in patients with AMI is associated with current smoking. More severe damage of the endothelial cell lining and increased sympathetic discharge in smokers may heighten atherosclerotic plaque vulnerability, leading to sudden plaque rupture.

In a retrospective pathologic study, Kojima et al. (21) showed that patients with plaque rupture had a higher incidence of infarction of sudden onset than those with plaque erosion. In addition, new-onset rest angina occurred in 76% of patients with plaque rupture compared with only 24% of those with plaque erosion. Similarly, in the present study the incidence of preinfarction angina was lower in patients with plaque rupture. Although the mechanism underlying the relation between preinfarction angina and plaque morphology remains unclear, the present findings suggest that rupture of soft plaque with positive remodeling may cause abrupt coronary occlusion after sudden thrombus formation, without prodromal angina.

In patients with AMI, Tanaka et al. (10) showed that large vessels with lipid pool-like images were associated with a high risk of no reflow after primary intervention. Several studies have suggested that plaque content, rather than thrombus, may be the major determinant of microcirculatory damage (10,22). Our findings confirm and further extend these previous findings and provide evidence that ruptured plaque with echolucent plaque morphology as well as positive remodeling may cause microvascular dysfunction and no-reflow phenomenon. High thrombogenicity caused by exposure to the components of lipid-rich plaque at the rupture site may thus lead to acute coronary occlusion with large amounts of nondissolvable thrombus.

Using angioscopy, Mizote et al. (23) demonstrated that microcirculatory damage and left ventricular dysfunction after PCI are more frequent among patients with ruptured plaque than among those without ruptured plaque. Their findings suggested that plaque morphology with fibrous cap disruption as assessed by angioscopy might be a predictor of greater distal embolism. Distal protection devices were therefore suggested to be clinically useful for preventing no-reflow phenomenon and improving left ventricular function in patients with ruptured plaque. Angioscopy is a useful tool for examining the inner surface as well as intraluminal structures of coronary arteries and may have several advantages over IVUS for assessing thrombus formation. However, angioscopic procedures are troublesome and time consuming compared with IVUS procedures, because the former require low-pressure inflation of a proximal occlusive cuff or continuous flushing of normal saline solution through the irrigation channel of the angioscope. Moreover, because of its large size, advancement of an angioscopic catheter across severe coronary lesions may itself induce mechanical embolization. Therefore, in patients with AMI, IVUS procedures may be better suited for the assessment of culprit lesions, because they require less time and use smaller devices than angioscopy.

Recently, several randomized trials (24–26) assessing the value of embolic protection devices during primary PCI in patients with AMI failed to demonstrate any positive effect of "routine" embolic protection on either myocardial reperfusion or clinical outcomes. These negative results may be attributed to several factors: 1) The several extra minutes required for additional balloon occlusion may have increased infarct size and worsened clinical outcomes, offsetting the potential benefits of removing emboli; 2) embolization may have been caused by passing the device over the lesion; and 3) there may have been little chance for myocardial recovery to begin with. On the other hand, several studies have suggested that distal protection may be clinically beneficial in certain subsets of patients who have specific plaque morphology associated with an increased risk of atheroembolism (27–29). Although aspiration of atherothrombotic emboli may not improve outcomes in all patients with AMI, reliable and feasible intravascular imaging techniques are needed to identify patient subgroups that would maximally benefit from embolic protection during the "superacute phase" of AMI. We believe that IVUS might provide important information that would facilitate the identification of patients at greatest risk.

Consistent with our findings, Hayashi et al. (19) suggested that patients with ruptured plaque on angioscopy had larger infarctions than those with eroded plaque. However, they studied not only patients with anterior AMI but also those with inferior and posterior AMI. Furthermore, they included patients treated within 24 h after the onset of AMI. Reperfusion >6 h after symptom onset has a less beneficial effect on myocardial salvage than earlier establishment of an open infarct-related artery (30). To reduce effects of confounding factors, we limited our subjects to patients who had had a first anterior AMI with reperfusion within 6 h after symptom onset, making the present study design more robust. We believe that we confirmed the association between the incidence of plaque rupture and myocardial infarct size more clearly than earlier studies.

The number of leads with abnormal Q waves on admission is an index of myocardial damage before reperfusion (31) and is not affected by myocardial damage during PCI. A greater number of Q waves implies broader transmural damage. Among patients who received reperfusion therapy within 2 h, the presence of plaque rupture was associated with a greater number of leads with abnormal Q waves on the admission ECG than was the absence of plaque rupture. Although successful reperfusion within 2 h after symptom onset can lead to myocardial salvage, the present results suggest that plaque rupture already rapidly caused myocardial damage before reperfusion, followed by greater distal embolism during reperfusion procedures.

Study limitations. The present study had several limitations. It was a single-center retrospective study with a relatively small number of patients. Individual patient characteristics were assessed on the basis of clinical histories

obtained by staff physicians, but ischemic episodes are not necessarily symptomatic. We enrolled only patients with anterior AMI, because infarct size, arterial length, and branching patterns differ among the left anterior descending, left circumflex, and right coronary arteries. Therefore, our results cannot be extrapolated to inferior or posterior infarction.

We excluded patients with cardiogenic shock, because we did not perform preintervention IVUS, thereby shortening the time to reperfusion. Obviously, patients with cardiogenic shock may represent those with the largest infarcts. Not all cases of plaque rupture present with fissure/dissection or with plaques with communications to the lumen on preintervention IVUS. Although we carefully examined lesions by flushing the surrounding region with saline or contrast medium, lesions with small ruptured plaques may be misread as nonruptured plaques. Although we used serum cardiac enzyme levels and left ventricular function in the chronic phase to assess infarct size, left ventriculograms may not accurately represent the infarct size at the time of admission. Finally, it should be emphasized that a type I error cannot be excluded, owing to the number of variables examined and the multiple comparisons performed on a fairly limited patient group.

Conclusions

Plaque rupture at culprit lesions is associated with morphologic characteristics of vulnerable lesions and with larger infarcts in patients with anterior AMI, suggesting that plaque embolism contributes to the progression of myocardial damage. Further investigations are needed to determine whether distal protection can benefit this subset of patients.

Reprint requests and correspondence: Dr. Kiyoshi Hibi, Division of Cardiology, Yokohama City University Medical Center, 4-57 Urafune-cho, Minami-ku, Yokohama 232-0024, Japan. E-mail: hibikiyo@urahp.yokohama-cu.ac.jp.

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Quantitative Coronary Angiographic Studies of Patients With Angina Pectoris and Impaired Glucose Tolerance

YU KATAOKA, MD
SATOSHI YASUDA, MD
ISAO MORII, MD
YORITAKA OTSUKA, MD
ATSUSHI KAWAMURA, MD
SHUNICHI MIYAZAKI, MD, PHD

OBJECTIVE — We investigated the morphological characteristics of coronary arteries in patients with impaired glucose tolerance (IGT) using computer-assisted quantitative coronary angiography. IGT is an independent risk factor for cardiovascular disease. However, the morphological changes developing in the coronary arteries of patients with IGT remain unknown.

RESEARCH DESIGN AND METHODS — A total of 534 patients with angina pectoris were studied. Of these, 144 patients were being treated for diabetes. The remaining 390 patients were classified as follows depending on the results of a 75-g oral glucose tolerance test: normal glucose tolerance (NGT) (n = 117), impaired fasting glucose (n = 3), IGT (n = 136), and diabetes pattern (preclinical diabetes) (n = 134). The diameters of the middle section of all major coronary artery segments were measured and averaged to determine the averaged vessel diameter (AVD). We defined segments of a diameter of ≤1.5 mm as diseased lesions and determined the averaged lesion length (ALL).

RESULTS — AVD and ALL were significantly different among patients with IGT and those with NGT. Patients with diabetes (preclinical and/or treated) had smaller AVD and longer ALL than those with IGT. By multivariate analysis, postprandial glucose levels were shown to be independently associated with an AVD <3.0 mm and an ALL >20 mm.

CONCLUSIONS — Diffuse coronary artery narrowing develops not only in patients with diabetes but also in those with IGT. This morphological change is associated with postprandial hyperglycemia.

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Artofm

Impaired glucose tolerance (IGT) has been regarded as intermediate between normal glucose tolerance (NGT) and overt diabetes. Recently, evidence has been accumulating that IGT may play a pathological role as one aspect of the metabolic syndrome. Epidemiological studies, i.e., the Funagata and DECODE (Diabetes Epidemiology: Collaborative Analysis of Diagnostic Criteria in Europe) studies (1,2), indicated that IGT characterized as postprandial hyperglycemia is an independent risk factor for cardiovascular disease. However, it is not known whether morphological changes develop in the coronary arteries of patients with IGT, as in those of diabetic patients for whom small vessel diameter and long lesion length (diffuse narrowing) are found in multiple vessels (3,4). In the present study, we assessed coronary angiographic features in patients with IGT by using computer-assisted quantitative analysis.

RESEARCH DESIGN AND METHODS

— From April 2000 to June 2002, 1,529 patients were hospitalized due to nonischemic and ischemic heart disease in our facility of the National Cardiovascular Center, a tertiary referral hospital in the northern district of Osaka, Japan. We obtained informed consent and performed quantitative coronary angiography (QCA) in patients with recurrent chest pain associated with electrocardiographic and/or echocardiographic evidence of myocardial ischemia and without contraindications to the administration of iodinated contrast agent (e.g., predialysis state of renal failure). Thus, a total of 914 patients who had organic stenosis were diagnosed with angina pectoris. Of these patients, the 112 patients who previously underwent coronary artery bypass surgery and the 126 patients with chronic total occlusion were excluded because of difficulty of QCA analysis. Among the remaining 676 patients, 144 patients in whom diabetes had previously been diagnosed and who were being treated by diet therapy alone (n = 48), oral hypoglycemic agents (n = 70), or insulin (n = 26) were defined as the treated diabetes group. The average duration of diabetes in this patient group was 17 years. Also, a 75-g oral glucose tolerance test (OGTT) was refused or could not be performed in some very old or severely ill patients who underwent urgent coronary artery bypass surgery, required mechanical circulatory support, or had refractory infectious diseases (n = 142). Finally, 390 patients with angina pectoris underwent a 75-g OGTT and were divided into the following four groups: 117 patients with normal glucose tolerance (NGT), 3 patients with impaired fasting glucose (IFG), 136 patients with IGT, and 134 patients who showed diabetes pattern (preclinical diabetes).

From the Division of Cardiology, Department of Medicine, National Cardiovascular Center, Osaka, Japan.
Address correspondence and reprint requests to Shunichi Miyazaki, MD, PhD, FACC, Division of Cardiology, Department of Medicine, National Cardiovascular Center, 5-7-1 Fujishiro-dai, Suita, Osaka 565-8565, Japan. E-mail: smiyazak@hsp.ncvc.go.jp.
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Abbreviations: ALL, averaged lesion length; AVD, averaged vessel diameter; FPG, fasting plasma glucose; IFG, impaired fasting glucose; IGT, impaired glucose tolerance; NGT, normal glucose tolerance; OGTT, oral glucose tolerance test; QCA, quantitative coronary angiography.
A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

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Table 1—*Patient characteristics*

	NGT	IGT	Preclinical diabetes	Treated diabetes
n	117	136	134	144
Age (years)	68 ± 10	60 ± 10	69 ± 10	70 ± 8
Male	97 (83)	113 (83)	111 (83)	106 (74)
BMI (kg/m^2)	22.9 ± 2.8*	23.8 ± 2.7	24.0 ± 3.4	23.4 ± 3.1
Unstable angina pectoris	36 (31)	50 (37)	53 (39)	58 (40)
Coronary risk factors				
Hypertension	80 (68)	105 (77)	108 (81)	113 (79)
Hypercholesterolemia	80 (68)	101 (74)	97 (72)	105 (73)
Smoking	38 (33)	45 (33)	40 (30)	39 (27)
Family history of CAD	25 (22)	37 (27)	22 (16)	27 (19)
Serum creatinine ≥177 μmol/l	4 (3)	1 (1)	4 (3)	15 (11)*†
Peripheral vascular disease	9 (8)	12 (9)	22 (17)	19 (13)
Stroke	27 (23)	23 (17)	28 (21)	31 (22)
Previous MI	26 (22)	20 (15)	14 (11)	31 (22)†
Previous PCI	55 (47)	64 (47)	64 (48)	67 (46)
PCI	78 (91)	98 (72)	83 (62)	104 (72)
Stent	66 (73)	78 (80)	58 (69)	79 (76)
Glycemic status				
Fasting glucose (mmol/l)	5.02 ± 0.43	5.11 ± 0.49	6.05 ± 1.44	7.26 ± 2.00*†
Postprandial glucose (mmol/l)	6.16 ± 1.24*	9.42 ± 1.09	12.95 ± 1.87*	12.16 ± 3.41*
A1C (%)	5.3 ± 0.4	5.5 ± 0.4	6.1 ± 0.9*	7.3 ± 1.2*
Lipid profile				
Total cholesterol (mmol/l)	4.93 ± 0.88	4.93 ± 0.91	5.03 ± 0.94	4.79 ± 0.89
Triglycerides (mmol/l)	2.78 ± 1.56*†‡	3.29 ± 1.54	3.48 ± 2.09	3.53 ± 1.99
HDL cholesterol (mmol/l)	1.21 ± 0.35*†‡	1.07 ± 0.32	1.06 ± 0.29	1.03 ± 0.29
LDL cholesterol (mmol/l)	3.18 ± 0.75	3.19 ± 0.86	3.27 ± 0.86	3.06 ± 0.82
Medical treatment				
Aspirin	112 (96)	119 (88)	119 (89)	127 (88)
β-Blocker	55 (47)*†‡	95 (70)	94 (70)	87 (60)
Calcium blocker	85 (73)	88 (65)	95 (71)	97 (67)
ACE inhibitor	27 (23)	36 (27)	43 (32)	44 (31)
Statin	54 (46)	63 (46)	67 (50)	63 (44)

Data are means ± SD or *n* (%). *$P < 0.05$ vs. IGT; †$P < 0.05$ vs. preclinical diabetes; ‡$P < 0.05$ vs. treated diabetes. CAD, coronary artery disease; MI, myocardial infarction; PCI, percutaneous coronary intervention.

The 75-g OGTT

The 75-g OGTT was performed after overnight fasting. Venous blood samples were taken during fasting and at 120 min after the glucose load to measure blood glucose level. The World Health Organization criteria were used for classifying the OGTT results (5) in the present study. The NGT group was defined as having a fasting plasma glucose (FPG) level <6.1 mmol/l and a postprandial glucose level <7.8 mmol/l. The IFG group was defined as having a FPG level ≥6.1 mmol/l but <7.0 mmol/l and a postprandial glucose level <7.8 mmol/l. The IGT group was defined as having a FPG level <7.0 mmol/l and a postprandial glucose level ≥7.8 mmol/l but <11.1 mmol/l. The preclinical diabetes group was defined as having a FPG level ≥7.0 mmol/l and a postprandial glucose level ≥11.1 mmol/l.

Coronary angiography and quantitative analysis

Selective coronary angiography was performed in multiple projections after administration of intracoronary nitroglycerin (0.125–0.25 mg). Coronary angiographic measurements were performed using computer-assisted quantitative analysis (CMS-QCA version 4.0; MEDIS, Leiden, the Netherlands). In addition to the Gensini score, which has been validated previously (6), the following parameters were used for the assessment of morphological characteristics in global coronary trees. We measured the diameters of the middle section in each major coronary artery segment: segments 1, 2, and 3 of the right coronary artery; segments 6, 7, and 8 of the left anterior descending artery; and segments 11 and 13 of the left circumflex artery. For each patient, we calculated the average diameter of these segments, which was defined as averaged vessel diameter (AVD). We also defined segments narrowed to a diameter of ≤1.5 mm as diseased lesions (with the exception of the far distal portion of segments 8 and 13 showing a smooth and regular edge) and determined averaged lesion length (ALL). The data from QCA were assessed by an experienced cardiologist (I.M.), who was blind to the glucose tolerance status. The interobserver correlation coefficient and the percent error were 0.99 and 7.3 ± 4.9%

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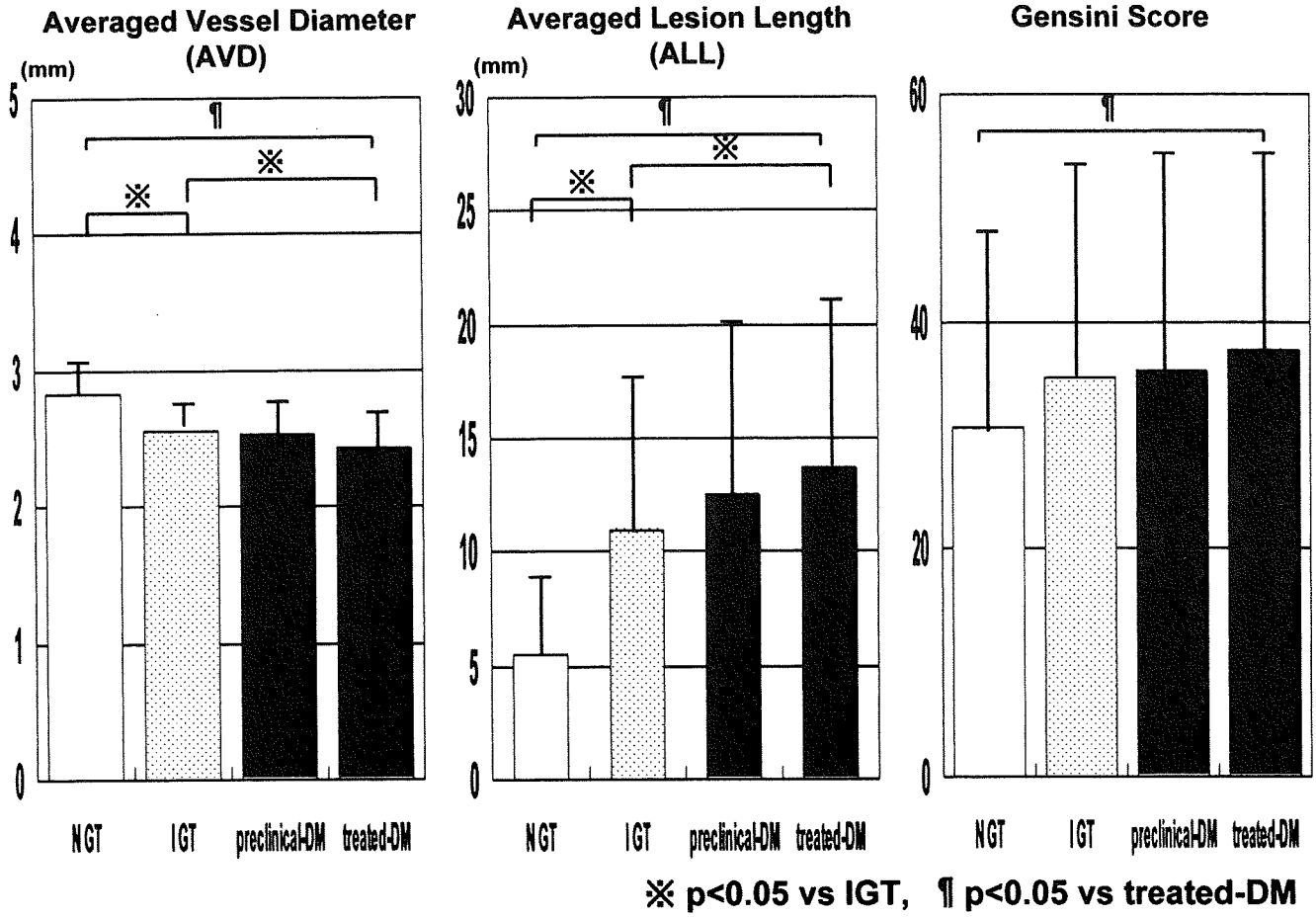

Figure 1—*Comparison of QCA results of AVD, ALL, and Gensini score among the four groups. DM, diabetes.*

for AVD and 0.93 and 7.4 ± 5.9% for ALL. The intraobserver correlation coefficient and the percent error were 0.93 and 3.6 ± 2.2% for AVD and 0.98 and 3.9 ± 2.6% for ALL.

Study design

All the patients underwent history screening, a physical examination and angiographic and laboratory analyses including HbA_{1c} (A1C), total cholesterol, triglyceride, HDL cholesterol, LDL cholesterol, and creatinine levels. In addition, patients were assessed for the prevalence of coronary risk factors, i.e., hypertension, hyperlipidemia, smoking habits, and family history, and for the presence of diabetes complications, i.e., nephropathy, a history of myocardial and cerebral infarction, and the presence of arteriosclerotic obliterance. BMI was calculated as the weight in kilograms divided by the square of height in meters (2). Blood glucose levels measured 2 h after breakfast or the 75-g OGTT were defined as those in the postprandial state in the present study. Among the four groups (NGT, IGT, preclinical diabetes, and treated diabetes), ANOVA was performed followed by Bonferroni post hoc testing. For univariate analysis, the following clinical variables and risk factors were regarded as covariates: age, sex, glycemic status (fasting, postprandial glucose level, and A1C level), lipid profiles (total cholesterol, triglyceride, HDL cholesterol, and LDL cholesterol levels), creatinine level, BMI, and the use of cardiovascular medications. On the basis of the results of univariate analysis, we performed multivariate logistic regression analysis to investigate the independent predictors of small AVD (<3.0 mm) and long ALL (>20 mm). A P value of <0.05 was considered to indicate statistical significance. All analyses were performed using Stat-View software, version 5.0 (SAS Institute, Cary, NC).

RESULTS— Clinical characteristics are summarized in Table 1. Most of the parameters, with the exception of BMI, triglyceride and HDL cholesterol levels, and the prevalence of β-blocker treatment, were not different between the IGT and NGT groups. The prevalence of renal failure (serum creatinine level ≥177 μmol/l) was higher in the treated diabetes group than in the IGT group.

Glucose metabolism

As shown in Table 1, the fasting glucose and A1C levels were similar between the NGT and IGT groups. However, the postprandial glucose level was significantly different between the NGT and IGT groups ($P < 0.05$). All of these parameters relating to glucose metabolism were significantly higher in the preclinical and treated diabetes groups than in the IGT group ($P < 0.05$).

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Table 2—*Univariate and multivariate analyses*

	Univariate analysis		Multivariate analysis	
	Odds ratio (95% CI)	*P* value	Odds ratio (95% CI)	*P* value
Predictors for small vessel diameter (AVD <3.0 mm)				
Age	1.035 (1.008–1.064)	0.0117	1.028 (0.999–1.056)	0.055
Female sex	3.293 (1.288–8.419)	0.0128	2.916 (1.118–7.608)	0.0287
Fasting glucose	1.005 (0.995–1.015)	0.3712		
Postprandial glucose	1.008 (1.004–1.013)	0.0007	1.008 (1.003–1.013)	0.0016
A1C	1.181 (0.922–1.513)	0.1874		
Total cholesterol	1.001 (0.994–1.009)	0.7682		
HDL cholesterol	1.009 (0.987–1.032)	0.4166		
LDL cholesterol	0.998 (0.990–1.006)	0.6129		
Creatinine	1.145 (1.030–1.273)	0.0125	1.171 (1.031–1.331)	0.0155
Hypertension	0.883 (0.471–1.655)	0.6977		
Smoking habit	0.843 (0.486–1.461)	0.5425		
Predictors for long lesion length (ALL >20 mm)				
Age	1.041 (1.010–1.073)	0.0091	1.040 (1.007–1.074)	0.0187
Female sex	2.040 (1.115–3.735)	0.0208	2.051 (1.021–4.120)	0.0434
Fasting glucose	1.010 (1.002–1.018)	0.0106	1.002 (0.991–1.013	0.3780
Postprandial glucose	1.009 (1.005–1.014)	<0.0001	1.009 (1.002–1.015)	0.0059
A1C	1.398 (1.148–1.703)	0.0009	1.211 (0.928–1.579)	0.1584
Total cholesterol	1.000 (0.992–1.008)	0.9550		
HDL cholesterol	0.969 (0.944–0.995)	0.0206	0.969 (0.943–0.997)	0.0296
LDL cholesterol	1.005 (0.997–1.014)	0.2346		
Creatinine	1.021 (0.885–1.178	0.7762		
Hypertension	1.317 (0.660–2.628)	0.4347		
Smoking habit	0.510 (0.257–1.012)	0.0540		

QCA

The results of QCA are summarized in Fig. 1. In the IGT group, smaller AVD and longer ALL were found than in the NGT group ($P < 0.05$). These angiographic changes were more prominent in the treated diabetes group ($P < 0.05$). When assessed by the Gensini score, statistics reached significance only between the NGT and the treated diabetes groups.

Univariate and multivariate analyses

We found that the angiographic characteristics of the IGT and diabetes groups were small AVD and long ALL. Therefore, to investigate which clinical variables and risk factors were associated with these morphological changes in the coronary artery, we performed univariate and multivariate analyses (Table 2). Age, female sex, and postprandial glucose and creatinine levels were significant predictors of small AVD (<3.0 mm) by univariate analysis. By multivariate analysis, female sex and postprandial glucose and creatinine levels were independent predictors. In addition, age, female sex and fasting and postprandial glucose levels, A1C, and lower HDL cholesterol levels were significant predictors of long ALL (>20 mm) by univariate analysis. Among these parameters, age, female sex and postprandial glucose and lower HDL cholesterol levels were independent predictors by multivariate analysis.

CONCLUSIONS — The major findings of the present study using computer-assisted QCA analysis are that the morphological changes of small vessel diameter and diffuse vessel narrowing developed not only in the diabetes groups but also in the IGT group. Furthermore, these changes were associated with postprandial hyperglycemia.

High prevalence of IGT in patients with coronary artery disease

A previous study reported a high prevalence of abnormal glucose tolerance (IGT 35% and diabetes 31%) in 181 patients with acute myocardial infarction (6). In the present study of patients with angina pectoris, the prevalences of IGT and diabetes (preclinical and treated) were 24.9 and 52.5%, respectively. Also, FPG and A1C levels were similar between the IGT and NGT groups. These findings indicate that IGT plays a pathological role and its diagnosis based on a 75-g OGTT is important in patients with coronary artery diseases.

Angiographic characteristics in patients with IGT

Although IGT is a risk factor not only for the development of diabetes but also for cardiovascular morbidity and mortality (1,7–10), there have been few reports of the angiographic characteristics in patients with IGT. In a previous study of 99 patients with coronary artery disease (11), abnormal glucose tolerance (IGT and diabetes) was found in 37 patients, for whom the degree of coronary atherosclerosis, assessed by a hand-held caliper method, was the same as that for patients with NGT. Another study (12) was performed using 466 patients who were undergoing coronary angiography, including patients with chest pain syndrome (10%) and those with nonischemic cardiac disease (21%). QCA analysis could not reveal differences between the NGT group ($n = 291$) and the IFG group ($n = 82$), which would be due to the high percentage of patients without

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significant coronary artery narrowings (67–73%) in these two groups. Therefore, in the present study, we focused on patients both with angina pectoris and with angiographically documented coronary artery narrowings.

QCA analysis has the advantage of being more accurate and reproducible than visual hand-held caliper measurements (13–15). However, in particular patients with diffuse narrowings it is difficult to identify a reference segment against which diseased lesions can be compared. In these patients, there is the possibility of underestimating the severity of vascular disease when it is assessed by "percent" diameter of stenosis. In fact, as shown in Fig. 1, this could happen with the measurement of Gensini score, which enabled us to detect changes in patients with IGT. In the present study, we defined segments narrowed to a diameter of ≤1.5 mm as diseased lesions in the major proximal segment of coronary trees. Although further modification of methodology to consider left main coronary artery lesions is needed, the present study using QCA analysis, which assesses absolute values, is a novel method to assess pathological changes of diffuse and small coronary lesions.

We found that there were significant differences in AVD and ALL between the NGT and IGT groups, indicating that angiographic atherosclerotic changes (smaller vessel diameter and longer lesion length) develop in coronary arteries in patients with IGT. The degree of changes found in patients with IGT was similar to that in patients with preclinical diabetes but was less than that in treated diabetic patients in whom FPG and A1C levels were markedly elevated.

Postprandial hyperglycemia as an important determinant for coronary atherosclerosis

As seen in previous epidemiological studies, such as the DECODE study (2), the risk of cardiovascular disease is strongly associated with postprandial hyperglycemia. In the present study, multivariate analysis showed that the postprandial glucose level was an independent predictor for both small AVD (<3.0 mm) and long ALL (>20 mm) (17–22), indicating that postprandial hyperglycemia is strongly associated with diffuse and small coronary artery narrowing in patients with abnormal glucose tolerance.

Hyperglycemia promotes atherogenesis by several possible mechanisms, including increased generation of free radicals (oxidative stress), decreased production of nitric oxide, activation of the polyol pathway and the diacylglycerol–protein kinase C system, and increases in nonenzymatic glycation products and the glycosylation of certain proteins (23–28). A recent in vivo study (29) demonstrated that inflammatory cytokine levels were more affected by oscillatory than continuous hyperglycemia and that this inflammatory response to hyperglycemic spikes was attenuated by antioxidants. These findings may explain, in part, why acute hyperglycemia occurring postprandially could produce cardiovascular damage.

Limitation

Because this is a retrospective clinical investigation, we acknowledge the possibility of a selection bias for some patients. Also, a statistical association does not prove that the risk factor directly promotes coronary artery atherosclerosis. Thus, in addition to measurements of potential confounders (e.g., fat distribution, physical fitness, or inflammation), prospective studies of an interventional nature will be required to determine whether postprandial hyperglycemia has a causal role in development of coronary artery disease.

In summary, the present study using quantitative angiographic analysis demonstrates that postprandial hyperglycemia is associated with the development of diffuse coronary artery narrowings in patients with angina pectoris.

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