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ORIGINAL ARTICLE
Imaging

Safety and Efficacy of a Bolus Injection of Landiolol Hydrochloride as a Premedication for Multidetector-Row Computed Tomography Coronary Angiography

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Background: We evaluated the safety and efficacy of a bolus injection of landiolol hydrochloride, an ultrashort-acting β1-selective antagonist, as an additional treatment after premedication with an oral β-blocker to reduce heart rate prior to multidetector-row computed tomography (MDCT) coronary angiography (CAG).

Methods and Results: A total of 458 patients who underwent MDCT CAG were retrospectively enrolled. Image quality and hemodynamic parameters were compared in patients before and after approval of landiolol hydrochloride. If heart rate reduction was insufficient after premedication with an oral β-blocker, a bolus injection of landiolol hydrochloride (n=66) or other drugs (n=30) was used. The percentage of evaluable images per segment in patients after approval of landiolol (99.3%) was greater than that in patients before approval of landiolol (97.4%, P<0.01). Heart rates before scanning in patients receiving landiolol hydrochloride were similar to those receiving other drugs. Heart rate was significantly reduced approximately 5 min after injection of landiolol hydrochloride and increased shortly. No decrease in systolic blood pressure or other adverse effects was observed.

Conclusions: Bolus injection of landiolol hydrochloride sufficiently reduced heart rate without significantly reducing systolic blood pressure and produced a high percentage of evaluable images, suggesting that bolus injection of landiolol hydrochloride as an additional pretreatment is feasible in MDCT CAG. (*Circ J* 2013; **77:** 146–152)

Key Words: β-blocker; Coronary angiography; Landiolol; Multidetector-row computed tomography

Multidetector-row computed tomography (MDCT) is a promising noninvasive coronary imaging modality for visualizing coronary atherosclerosis in patients with known or suspected coronary artery disease.[1–4] However, a high heart rate (HR) can produce motion artifacts that reduce image quality.[1] Oral β-blockers have been widely used as premedication to reduce the HR to a level suitable for MDCT coronary angiography (CAG).[5] When oral β-blockers are not sufficient, intravenous β-blockers or other medications are sometimes used to further reduce the HR. However, side effects from additional premedications are common and can be life-threatening, because of prolonged pharmacologic effects.

Landiolol hydrochloride, an ultrashort-acting β1-selective antagonist, exerts a clinically relevant negative chronotropic action without negative inotropic effects when given at a low dose.[6,7] It can be used safely to reduce a patient's HR, as shown by recent clinical studies.[8–13] In addition, a previous study showed the usefulness of continuous infusion of landiolol hydrochloride for reducing HR before MDCT CAG.[14] Landiolol hydrochloride became available in Japan in September 2011 as a premedication for reducing HR for MDCT CAG, so the side effects and efficacy of landiolol hydrochloride for MDCT angiography in real clinical settings in Japan have not been fully elucidated.

To address these issues, we investigated the safety and efficacy of reducing HR with a single bolus injection of landiolol hydrochloride in combination with oral β-blocker administration prior to MDCT CAG.

Methods

Study Population

The study population included a total of 458 consecutive pa-

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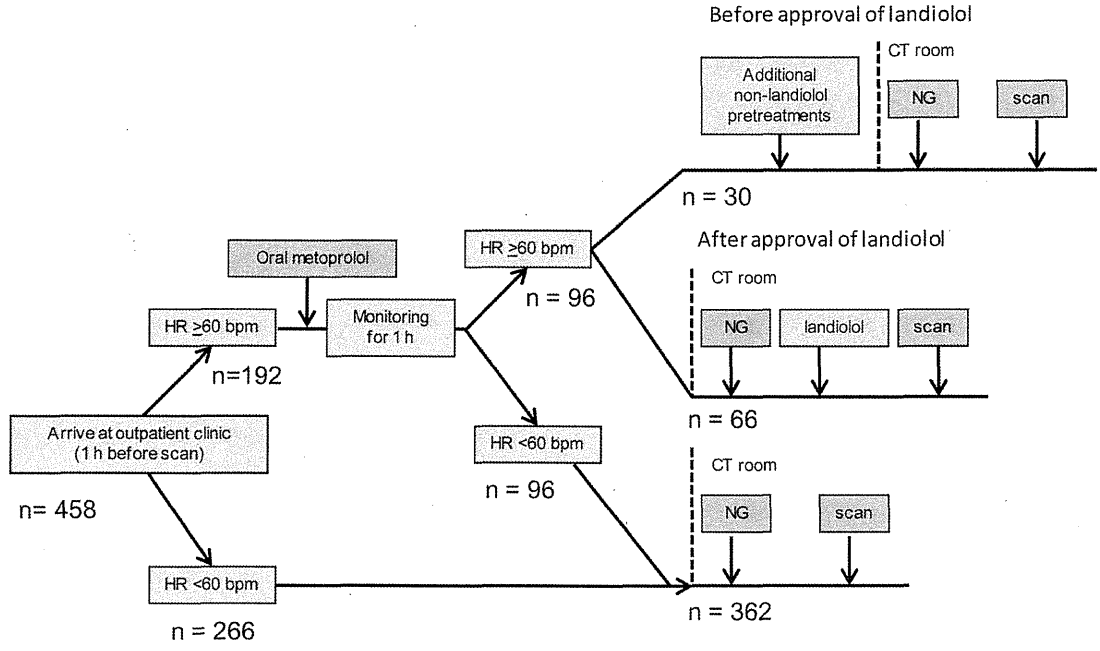

Figure 1. Diagram of steps involved in MDCT coronary angiography. All patients arrived at the hospital 1 h before the scheduled scanning time. All patients whose heart rate was ≥60 beats/min received oral metoprolol (20–40 mg). Before the approval of landiolol, if heart rate was still ≥60 beats/min, patients received an additional 20 mg oral metoprolol and/or 2 mg intravenous propranolol and/or 5 mg intravenous verapamil as additional pretreatments, repeated as needed to achieve a suitable heart rate. After approval of landiolol, patients received a bolus injection of landiolol hydrochloride (0.125 mg/kg) as additional pretreatment. HR, heart rate; bpm, beats/min; CT, computed tomography; NG, nitroglycerin.

tients who visited Okayama University Hospital or Tsuyama Central Hospital between January 2011 and February 2012 for 64-slice MDCT examination because of suspected coronary artery disease. Patients with any heart rhythm other than sinus rhythm, with any contraindication for β-blockers, or an inability to hold their breath on command were excluded. Patients with previous myocardial infarction or those with coronary stents were included, but patients who had undergone coronary artery bypass graft surgery were excluded. This study was approved by the institutional ethics committee on human research and written informed consent was given by all patients before the study.

Patient Preparation

Landiolol hydrochloride (Corebeta, Ono Pharmaceutical Co, Osaka, Japan) was approved in November 2011 for use at Okayama University Hospital and in December 2011 for use at Tsuyama Central Hospital. The study participants were divided into 2 groups: those examined before landiolol was approved (n=229) and those examined after landiolol was approved (n=229). A diagram of the study protocol is shown in Figure 1. All patients arrived at the hospital 1 h before the scheduled scanning time, and those who showed a persistently high HR of ≥60 beats/min received oral metoprolol (20–40 mg). If the HR was not sufficiently lowered (<60 beats/min) before the scheduled scanning time, patients who were treated prior to landiolol approval received additional oral metoprolol (20 mg; n=22) and/or 2 mg intravenous propranolol (n=8) and/or 5 mg intravenous verapamil (n=9) as additional pretreatments. After approval of landiolol, patients received a bolus injection of landiolol hydrochloride at a dose of 0.125 mg/kg as an additional pretreatment if the HR was not sufficiently lowered. Landiolol hydrochloride was injected intravenously 4–7 min before starting MDCT. Additional premedication was given to 30 patients before approval of landiolol and 66 patients after approval of landiolol.

Data Acquisition

The 64-slice CT scans were obtained using a DCT scanner (Okayama University Hospital: SOMATOM Definition Flash, Siemens Medical Solutions, Germany; Tsuyama Central Hospital: LightSpeed VCT, GE Healthcare, USA). SOMATOM Definition Flash parameters were as follows: detector collimation 64×0.6 mm, equaling a slice acquisition of 128×0.6 mm using the flying focal spot technique; table pitch adapted to HR (0.17–0.38); rotation time 275 ms; tube current time product 360 mA; and tube voltage 120 kVp. LightSpeed VCT parameters were: rotation time 350 ms; pitch 0.516 mm per gantry rotation; helical acquisition mode; detector configuration 64 rows with 0.625-mm-thick sections; and tube voltage 120 kVp. At Okayama University Hospital, a test bolus CT acquisition was performed at the level of the ascending aorta following administration of 10 ml contrast medium followed by 20 ml saline, with low-dose images obtained every 1 s. The delay before the formal scan was calculated as the time to peak enhancement in the ascending aorta plus 3 s to ensure enhancement of the distal segments of the coronary arteries. For the final scan, contrast agents (Omnipaque 350, Daiichi

Table 1. Characteristics of Patients' Undergoing MDCT CAG Before and After Approval of Landiolol Hydrochloride in Japan

	Before approval of landiolol		After approval of landiolol	
	All (n=229)	Patients receiving additional pretreatments (n=30)	All (n=229)	Patients receiving landiolol (n=66)
Age (years)	67±12	67±12	66±14	66±13
Men	117 (51%)	15 (50%)	127 (56%)	32 (49%)
BMI (kg/m^2)	22.9±3.8	22.6±3.6	22.9±3.6	22.3±3.0
Hypertension	126 (55%)	15 (50%)	140 (61%)	39 (59%)
Hyperlipidemia	138 (60%)	14 (47%)	91 (40%)*	25 (38%)
Diabetes mellitus	66 (29%)	11 (37%)	58 (25%)	21 (32%)
Angina pectoris	52 (23%)	6 (20%)	41 (18%)	12 (18%)
Prior MI	10 (4%)	1 (3%)	7 (3%)	2 (3%)
History of stent implantation	15 (7%)	1 (3%)	9 (4%)	1 (2%)
Medications				
β-blocker	26 (11%)	2 (7%)	21 (9%)	3 (4.5%)
CCB	66 (29%)	11 (37%)	79 (35%)	25 (38%)
ACEI/ARB	71 (31%)	7 (23%)	93 (41%)†	27 (41%)

Values represent mean±SD or number (%). *P<0.05 vs. all patients before approval of landiolol; †P<0.05 vs. all patients after approval of landiolol.
ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BMI, body mass index; CAG, coronary angiography; CCB, calcium-channel blocker; MDCT, multidetector-row computed tomography; MI, myocardial infarction.

Sankyo, Japan) were injected over 10 s, followed by a second bolus of 80% of the amount of contrast medium diluted 50%, and then a chaser bolus of saline. All injections were done at the same flow rate, calculated as body weight ×0.07 ml/s. At Tsuyama Central Hospital, the test bolus tracking method was performed. The amount of contrast material (Iopamiron 370, Bayer, Germany) was calculated as 330 mgI/kg. The flow time was fixed at 15 s, and the flow rate was calculated accordingly. A test bolus was performed with 5 ml contrast material followed by 20 ml saline at the same flow rate. The main injection was performed continuously at the same flow rate followed by 20 ml saline.

Axial slices were optimally reconstructed within the mid- to end-diastolic phase in each patient using retrospective ECG gating[15] and commercially available cardiac reconstruction software (AZE Inc, Tokyo, Japan). Three postprocessing techniques were applied to assess the coronary arteries: (1) maximum intensity projection, (2) curved multiplanar reconstruction, and (3) volume rendering. One senior cardiologist and 2 senior CT technicians performed the analysis, and evaluation was made on a per-segment basis. Sixteen segments were identified based on the established American Heart Association segment model[16] and consisted of the right coronary artery and distal branches (5 segments), left main trunk (1 segment), left main anterior descending artery and branches (5 segments), and circumflex artery and branches (5 segments). Segments that were absent or too small, or that contained heavy calcification or a stent, were excluded. Each segment was classified as evaluable or not evaluable as described.[17–19] Non-evaluable images were defined as those with no vessel wall definition owing to marked motion artifacts, significant structural discontinuity, or high image noise-related blurring that precluded the acquisition of diagnostic information. Segments that could be evaluated included those with excellent, good, or fair quality. Images with excellent quality were defined as those with no motion artifacts, noise-related blurring, or structural discontinuity. Images with good quality were defined as those with only minor motion artifacts or noise-related blurring and no structural discontinuity. Images with fair quality were those with some motion artifacts, noise-related blurring, or minimal structural discontinuity. Image quality was evaluated by 2 experienced observers who had no knowledge of pretreatments for reducing HR for MDCT CAG. The interobserver coefficient of variation analyzed from 20 randomly selected samples was <5%.

Evaluation of Adverse Effects of Additional Treatment

Hemodynamic parameters (systolic blood pressure (BP), diastolic BP, and HR) were evaluated for all patients upon entry into the CT room and immediately before and after scanning. For patients treated with landiolol hydrochloride, additional measurements were taken before the bolus injection. Potential adverse effects of landiolol hydrochloride (hypotension, floating sensation, dizziness, serious bradycardia, and cardiogenic shock) were also assessed by nurses.

Statistical Analysis

Continuous variables are presented as the mean±SD, and differences between the 2 groups were evaluated using an unpaired t-test. Categorical variables are presented as frequencies, and intergroup comparisons were analyzed using the χ^2 test. One-way ANOVA was performed followed by a post-hoc Bonferroni test to examine differences in the time course of hemodynamic changes. A P value <0.05 was considered statistically significant. Statistical analysis was performed using SPSS 17.0 for Windows (SPSS Inc, Chicago, IL, USA).

Results

Clinical characteristics of the 458 enrolled patients are summarized in Table 1. Our study included 244 men (53%) with a mean age of 66 years. Patients seen before approval of landiolol had a greater prevalence of dyslipidemia, but the prevalence of hypertension and of diabetes mellitus was com-

Table 2. Quality of Images Obtained Per Segment, Per Artery, and Per Patient in Patients' Undergoing MDCT CAG Before and After Approval of Landiolol Hydrochloride in Japan

	Before approval of landiolol	After approval of landiolol	P value
In all patients			
n	229	229	
Per segment	3,237/3,310 (97.8%)	3,333/3,383 (98.5%)	0.03
Per artery			
LMT	229/229 (100%)	229/229 (100%)	1
LAD	201/229 (87.8%)	217/229 (94.8%)	<0.01
LCX	213/229 (93.0%)	217/229 (94.8%)	0.44
RCA	208/229 (90.8%)	217/229 (94.8%)	0.10
Per patient	182/229 (79.4%)	203/229 (88.6%)	<0.01
In patients who received additional pretreatment			
n	30	66	
Per segment	418/429 (97.4%)	985/992 (99.3%)	<0.01
Per artery			
LMT	30/30 (100%)	66/66 (100%)	1
LAD	27/30 (90%)	66/66 (100%)	<0.01
LCX	28/30 (93.3%)	63/66 (95.5%)	0.66
RCA	26/30 (86.7%)	62/66 (93.9%)	0.23
Per patient	23/30 (76.7%)	62/66 (93.9%)	0.01

LAD, left anterior descending coronary artery; LCX, left circumflex coronary artery; LMT, left main trunk; RCA right coronary artery. Other abbreviations as in Table 1.

Table 3. Hemodynamic Parameters in Patients Who Received Additional Pretreatments Among Patients' Undergoing MDCT CAG Before and After Approval of Landiolol Hydrochloride in Japan

	Before approval of landiolol (n=30)	After approval of landiolol (n=66)	P value
At outpatient clinic			
SBP (mmHg)	144±16	135±19	0.05
DBP (mmHg)	84±12	81±13	0.33
HR (beats/min)	89±12	78±10	<0.01
Before the additional pretreatment			
SBP (mmHg)	129±16	122±19	0.09
DBP (mmHg)	78±12	72±13	0.02
HR (beats/min)	77±12	76±10	0.70
At the time of scanning			
SBP (mmHg)	137±19	120±18	<0.01
DBP (mmHg)	77±14	68±12	<0.01
HR (beats/min)	68±9	67±10	0.35
After scanning			
SBP (mmHg)	136±29	127±19	0.02
DBP (mmHg)	77±16	70±13	0.03
HR (beats/min)	66±10	70±10	0.07

DBP, diastolic blood pressure; HR, heart rate; SBP, systolic blood pressure. Other abbreviations as in Table 1.

parable between the 2 groups. Patients after approval of landiolol had a greater use of angiotensin-converting enzyme inhibitor/angiotensin receptor blockers. There were no differences in the prevalence of angina pectoris, prior myocardial infarction, or history of stent implantation between the 2 groups. The dosage of oral metoprolol as an initial pretreatment in patients before approval of landiolol (n=121) was significantly greater than that in patients after approval of landiolol (n=91) (26±10 mg vs. 22±6 mg, P<0.01). Analysis of patients who received additional pretreatment showed no differences in age, sex, body mass index, risk factors, medications, prevalence of angina pectoris, prior myocardial infarction, or history of stent implantation between patients receiving landiolol or those receiving other drugs. The dosage of oral metoprolol tended to be greater in patients receiving other drugs than in patients receiving landiolol, but there was no statistical difference (26±5 mg vs. 21±6 mg, P=0.14).

Table 2 shows the evaluation of image quality in all patients and in those who received additional pretreatments. Among all patients, the percentage of evaluable segments was

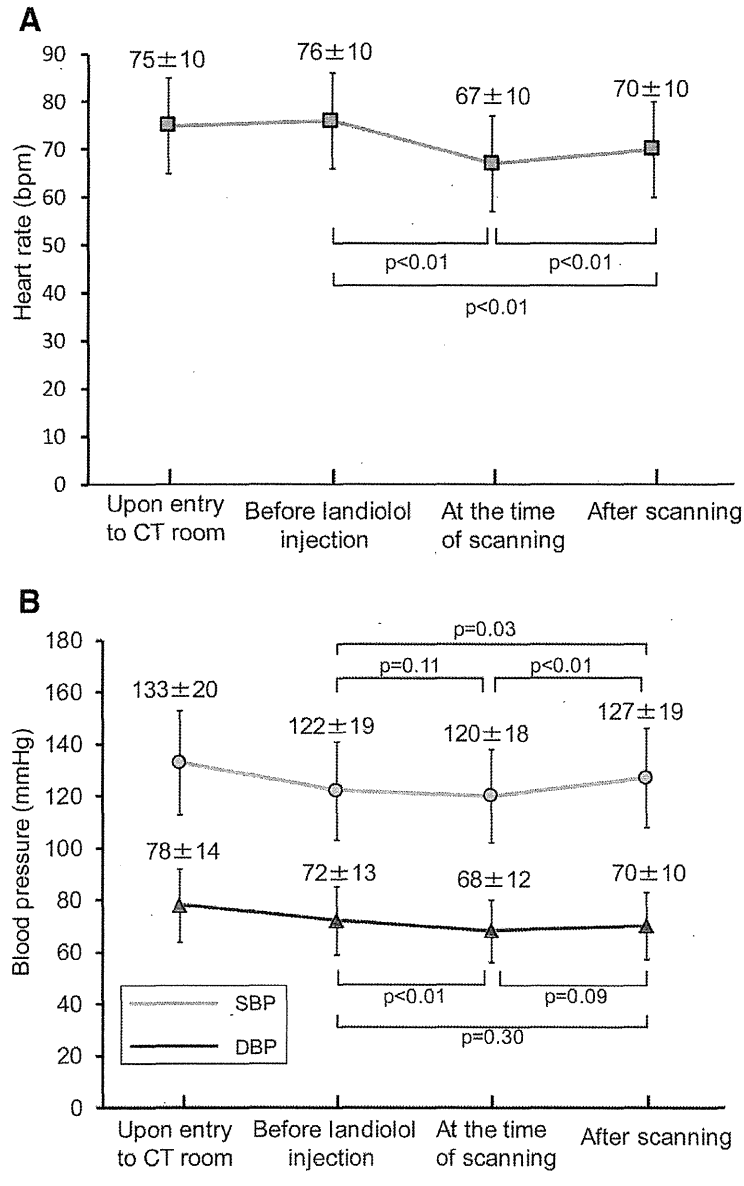

Figure 2. Graph showing the sequential changes in heart rate (A) and blood pressure (B) immediately after scanning of 66 patients given landiolol upon entry to the CT room. Data are expressed as mean±SD. SBP, systolic blood pressure; DBP, diastolic blood pressure; HR, heart rate.

significantly higher after approval of landiolol than before approval of landiolol (98.5% vs. 97.8%, respectively, P=0.03). When image qualities were analyzed according to the left main trunk, left anterior descending artery, left circumflex artery, and right coronary artery, the percentage of evaluable images in the left anterior descending artery was significantly higher after approval of landiolol than before approval of landiolol (94.8% vs. 87.8%, respectively, P<0.01). For patient-based analysis, 203 patients after approval of landiolol and 182 patients before approval of landiolol showed no motion artifacts (88.6% vs. 79.4%, respectively, P<0.01).

In patients who received additional pretreatment, the percentage of evaluable segments was significantly higher after approval of landiolol than before approval of landiolol (99.3% vs. 97.4%, respectively, P<0.01). When image quality was analyzed according to artery, the percentage of evaluable images in the left anterior descending artery was significantly higher after approval of landiolol than before approval of landiolol (100% vs. 90%, respectively, P<0.01). For patient-based analysis, the evaluable percentage was significantly higher after approval of landiolol than before approval of landiolol (93.9% vs. 76.7%, respectively, P=0.01).

Hemodynamic parameters assessed immediately before scanning and after scanning are shown in Table 3. HR was significantly higher in patients receiving other drugs than in patients receiving landiolol. HRs just before and after scanning were comparable between patients receiving landiolol and those receiving other drugs. BP just before scanning was significantly lower in patients receiving landiolol than in those receiving other drugs (P<0.01). For patients treated with landiolol (n=66), Figure 2 shows the time course of BP and HR upon entry to the CT room, before the bolus injection and immediately before and after scanning. HR was significantly decreased before scanning and then significantly increased

after scanning, but did not recover to the same level as before scanning. There were no significant decreases in systolic BP over the same time course. There were no adverse effects from landiolol hydrochloride; however, 1 patient who received 2 mg intravenous propranolol and 5 mg intravenous verapamil developed low BP for which an intravenous hypertensive agent was necessary. The amount of time from the beginning of the visit to the outpatient clinic to the end of the CT scan was significantly shorter in patients after approval of landiolol (n=229) than before approval of landiolol (n=229) (90±13 vs. 159±45 min, respectively, P<0.01).

Discussion

This study revealed that for patients who had an elevated HR after an initial metoprolol dose prior to MDCT CAG, a bolus injection of landiolol hydrochloride was safe and resulted in better image quality that with the conventional protocol without landiolol hydrochloride. This is the first study to demonstrate the clinical applicability of a bolus injection of landiolol hydrochloride as a pretreatment in combination with an oral β-blocker for MDCT CAG.

Cardiac motion artifacts are a major problem in obtaining optimal coronary vessel images during MDCT, and thus HR must be adequately controlled.[20,21] Oral β-blocking agents are widely used to reduce HR, but they are not always sufficient.[22] Landiolol has similar pharmacological properties as esmolol,[23] but is short-acting and highly selective for β1 receptors, thus showing fewer side effects than other longer-acting β-blockers.[6,7] Recent studies have shown landiolol to be safe and effective in patients with perioperative atrial fibrillation or tachycardia,[9,11,13] in patients with severe ventricular arrhythmia[10] or acute decompensated heart failure,[11] and for early initiation of β-blockers in patients with acute myocardial infarction.[12] In addition, Isobe et al reported the usefulness of continuous infusion of landiolol hydrochloride for MDCT CAG.[14] Although continuous infusion of landiolol hydrochloride is reported to be safe,[14] such a procedure seems complicated in an outpatient clinic. Compared with continuous injection, the bolus injection used in this study was more practical. Furthermore, this study showed that only approximately 20% of patients who were scheduled for MDCT CAG required any premedication beyond oral β-blocker treatment. Therefore, the use of landiolol hydrochloride in selected patients may have cost-benefit advantages.

Our study assessed the effect of landiolol hydrochloride on hemodynamics during MDCT CAG. Among the patients imaged before approval of landiolol, 1 developed severe hypotension that required treatment. The protocol using a bolus injection of landiolol hydrochloride produced only a transient reduction in HR and no significant change in systolic BP. Furthermore, the amount of time from the beginning of premedication to the end of the CT scan was strikingly shorter in patients receiving landiolol hydrochloride than in those receiving other additional drugs. Thus, landiolol hydrochloride as an additional pretreatment may be useful in MDCT CAG.

Our study also compared image quality in patients before and after approval of landiolol. Although the image quality was significantly better in patients receiving landiolol hydrochloride than in those receiving other drugs, we believe that the difference was not clinically important. The overall percentage of evaluable images in both groups was 97–99%, which is sufficient for clinical use. Recent studies have shown that the percentage of evaluable images is over 90–95% when the HR is controlled appropriately.[5,21,24] Image quality with MDCT CAG is affected not only by absolute HR, but also by variability in HR.[25] However, we could not examine the difference in HR variability during CT scanning, because no data were available for patients who received additional pretreatments without landiolol. A possible explanation for the improved image quality in patients receiving landiolol hydrochloride is that it reduced HR variability during the CT scan more effectively than other drugs such as verapamil.

Study Limitations

The first limitation of our study is that among the total 458 patients enrolled, only 96 received additional premedication, including landiolol hydrochloride. Therefore, further investigation in a larger population is needed to make solid conclusions regarding the safety of landiolol hydrochloride and image quality in individual patients. Second, in this study, a greater number of patients required additional pretreatment after approval of landiolol than before approval. Although our medical staff strived to follow the protocol, additional pretreatments were not used in some cases before approval of landiolol, especially in patients whose HRs were near 60 beats/min because of concerns about adverse effects of additional β-blocker injection, delay of another scheduled CT, and extension of the patient's examination time. In similar situations after landiolol approval, however, more patients may have been given additional pretreatment because of fewer concerns. It is possible that these factors affected our results. Third, patients with heavily calcified lesions, stents, and bypass grafts were excluded from our analysis. Also, sublingual nitroglycerin was used in all patients. These factors may have affected image quality. However, every assessable arterial branch was included in our analyses, regardless of diameter.

Conclusions

Bolus injection of the ultrashort-acting β-blocker, landiolol hydrochloride, reduced HR to a level suitable for MDCT without causing a significant reduction in BP. Use of landiolol hydrochloride in combination with metoprolol for HR control shortened the total procedure time compared with the use of other secondary drugs, and high-quality images were obtained. Therefore, a bolus injection of landiolol hydrochloride is feasible as an additional premedication for MDCT CAG.

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Disclosures

Conflicts of Interest: The authors declare no conflicts of interest.

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Cardiac Dysfunction and Prolonged Hemodynamic Deterioration After Implantable Cardioverter-Defibrillator Shock in Patients With Systolic Heart Failure

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Cardiac Dysfunction and Prolonged Hemodynamic Deterioration After Implantable Cardioverter-Defibrillator Shock in Patients With Systolic Heart Failure

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Background—We investigated the acute effects of implantable cardioverter-defibrillator shock on myocardium, cardiac function, and hemodynamics in relation to left ventricular systolic function.

Methods and Results—We studied 50 patients who underwent implantable cardioverter-defibrillator implantation and defibrillation threshold (DFT) testing: 25 patients with left ventricular ejection fraction (LVEF) ≥45% and 25 patients with LVEF <45%. We measured cardiac biomarkers (creatine kinase, creatine kinase-MB, myoglobin, cardiac troponin T and I, and N-terminal probrain natriuretic peptide). Left ventricular relaxation was assessed by global longitudinal strain rate during the isovolumetric relaxation period using speckle-tracking echocardiography. Blood sampling and echocardiography were performed before, immediately after, and 5 minutes and 4 hours after DFT testing. Mean arterial pressure was measured directly during DFT testing. Cardiac biomarkers showed no significant changes in either group. LVEF was decreased until 5 minutes after DFT testing and had recovered to the baseline at 4 hours in the group with reduced LVEF (P<0.001), whereas LVEF reduction was not observed in the group with preserved LVEF (P=0.637). Global isovolumetric relaxation period was decreased until 5 minutes after DFT testing and had recovered to the baseline at 4 hours in both groups (preserved LVEF: 0.39±0.14 versus 0.23±0.13* versus 0.23±0.13* versus 0.40±0.13 s^{-1}, *P<0.001 versus baseline; reduced LVEF: 0.15±0.05 versus 0.08±0.04† versus 0.09±0.04† versus 0.15±0.05 s^{-1}, †P<0.001 versus baseline, repeated-measures ANOVA). Time to recovery of mean arterial pressure to the baseline was prolonged in the group with reduced LVEF (P<0.001).

Conclusions—Implantable cardioverter-defibrillator shock transiently impairs cardiac function and hemodynamics especially in patients with systolic dysfunction, although significant tissue injury is not observed. (***Circ Arrhythm Electrophysiol.* 2012;5:898-905.**)

Key Words: echocardiography ■ hemodynamics ■ implanted cardioverter defibrillators ■ ventricular fibrillation ■ cardiac function

Both primary and secondary preventional trials have demonstrated that implantable cardioverter-defibrillators (ICDs) reduced mortality from sudden cardiac death because of malignant ventricular arrhythmia.[1,2] Despite this survival advantage, several studies have demonstrated that ICD shock, whether it is appropriate, is associated with increased risk of mortality among patients with reduced left ventricular (LV) systolic function.[3–6] Furthermore, defibrillation threshold (DFT) testing at the time of ICD implantation sometimes invokes several critical complications, especially in patients with reduced LV contractility.[7–9] These complications include transient ischemic attack or stroke, cardiopulmonary arrest because of refractory ventricular fibrillation (VF) or pulseless electric activity, cardiogenic shock, embolic events, and death. Although ICD shock is related to short- and long-term critical complications in patients with LV systolic dysfunction, the association between electric defibrillation and cardiac function has been investigated in only a few animal experimental studies,[10–12] and there are few clinical data regarding the effect of ICD shock on cardiac function and its association with tissue damage and subsequent hemodynamic change in patients with systolic heart failure.

Clinical Perspective on p 905

Recently, strain and strain rate (SR) derived from 2-dimensional speckle-tracking echocardiography have

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enabled us to quantify myocardial deformation without angle dependency,[13] and global SR during the isovolumetric relaxation period (SR_{IVR}) provides more accurate assessment of LV relaxation than conventional parameters.[14] In this study, we investigated the effects and mechanisms of ICD shock on myocardial functions by echocardiography, direct central arterial pressure measurement, and measurement of cardiac biomarkers with respect to LV systolic function.

Methods

Study Sample

The study population consisted of 50 consecutive patients who were admitted to our institution to undergo transvenous ICD implantation and DFT testing between April 2008 and December 2009. The underlying heart diseases were ischemic cardiomyopathy in 13 patients, dilated cardiomyopathy in 9 patients, hypertrophic cardiomyopathy in 6 patients, cardiac sarcoidosis in 3 patients, and idiopathic ventricular fibrillation in 19 patients. The patients were divided into 2 groups according to the preoperative LV ejection fraction (LVEF): a group of patients with preserved LVEF (LVEF ≥45%) and a group of patients with reduced LVEF (LVEF <45%).[15,16] All tests that were performed were approved by the medical ethical review committees of Okayama University Hospital. Informed consent was obtained from each patient.

Study Protocol

The study protocol is summarized in Figure 1. ICD implantation was performed using local anesthesia combined with sedation only for DFT testing. At the end of ICD implantation, we induced VF by T-wave shock after monitored anesthesia care using a bolus injection of thiopental (4 mg/kg). For minimizing change in loading condition during monitored anesthesia care, saline infusion rate was set at 0.33 mL/min. Defibrillation shock was fixed to 20 J and automatically delivered from the ICD after detection of VF. We repeated the same protocol 5 minutes after the first DFT testing and did not use a step-down protocol in any of the subjects. We performed venous blood sampling and echocardiographic examination before, immediately after, and 5 minutes and 4 hours after 2 consecutive DFT testing. Vascular access was achieved through the femoral artery, and central arterial pressure was continuously monitored in the ascending aorta during DFT testing.

Analysis of Laboratory Data

To evaluate myocardial injury by DFT testing, we measured cardiac biomarkers: serum levels of creatine kinase (CK), CK-MB fraction (CK-MB), myoglobin, cardiac troponin T, cardiac troponin I, and N-terminal probrain natriuretic peptide (NT-proBNP). CK activity was measured with CicaLiquid reagents (Kanto Chemical, Tokyo, Japan) on a Bio-Majesty analyzer (Nihondenshi, Tokyo, Japan), with upper normal limits of 287 U/L for men and 163 U/L for women. The CK-MB activity was determined using a commercially available immunoinhibition assay (CicaLiquid CK-MB; Kanto Chemical, Tokyo, Japan), with an upper normal limit of 25 U/L. Myoglobin was measured using a commercially available radioimmunoassay (Daiichi III; TFB Inc, Tokyo, Japan), with an upper normal limit of 60 ng/mL. Cardiac troponin T was assessed by an electrochemiluminescence immunoassay on an Elecsys 2010 analyzer (Roche Diagnostics, Mannheim, Germany). The lower limit of detection was 0.01 ng/mL, and the discrimination level used for myocardial injury was 0.10 ng/mL. Cardiac troponin I was determined using a 2-site immunoenzymatic assay (Access AccuTnI, Beckman Coulter, Brea, CA), with an upper normal limit of 0.50 ng/mL. NT-proBNP was measured using an electrochemiluminescence immunoassay on an Elecsys 1010 analyzer (Roche Diagnostics), with an upper normal limit of 125 pg/mL.

Analysis of Echocardiographic Data

All echocardiographic studies were performed with Vivid 7 (GE Healthcare, Milwaukee, WI). We measured LV volume and ejection fraction according to the recommendations of the American Society of Echocardiography.[17] From mitral flow velocity pattern, we measured peak mitral inflow early diastolic and atrial filling velocities and the E-wave deceleration time. Peak early diastolic mitral annular velocities were measured at septal and lateral mitral annular sites by pulsed tissue Doppler imaging, and then the average values were used for analysis (e′ velocity). The ratio of peak E velocity to e′ velocity (E/e′) was calculated as a surrogate for LV filling pressure. Longitudinal SR analysis was performed using the speckle-tracking system in an EchoPAC PC (GE Healthcare) as previously described.[14] In brief, after tracing the entire LV endocardium, the displacement of speckles of the myocardium was analyzed automatically through the cardiac cycle in the speckle-tracking system. Then the SR curve of each segment was displayed and approved. LV global SR was calculated with the use of the entire length of the LV myocardium, and peak global SR during the isovolumetric relaxation period was defined as global SR_{IVR}. The global SR_{IVR} values from the 3 apical views were averaged and used for analysis. All echocardiographic measurements and analysis were performed offline by an experienced investigator (N.T.), with no clinical information about the patients.

The following measures were taken to obtain adequate echocardiographic images for analysis promptly and maintain operative field sterility: (1) we enrolled only patients with optimal echocardiographic images, (2) the transducer position was fixed at apical impulse for minimizing loss of time and maintaining sterility because an apical

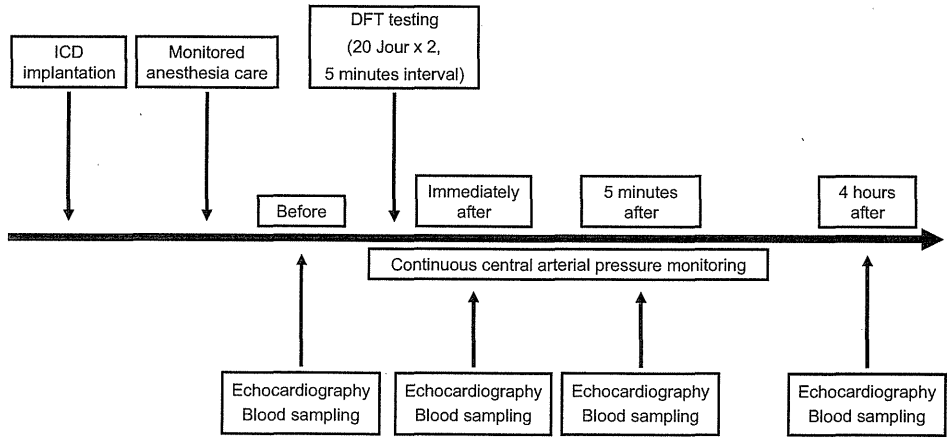

Figure 1. Outline of the clinical study protocol. ICD indicates implantable cardioverter-defibrillator; DFT, defibrillation threshold.

window was sufficient for acquiring all data as mentioned above, and (3) the operative field and catheter insertion site were carefully covered with sterile surgical drapes.

Analysis of Hemodynamic Data

Continuous measurements of systolic and diastolic arterial pressures were performed at the ascending aorta during DFT testing. Mean arterial pressure (MAP) was obtained by direct integration of the blood pressure curve. Time to reach baseline MAP was defined as the interval between the second ICD shock and the time MAP returned again.

Statistical Analysis

Data are expressed as mean±SD. Unpaired *t* test was used to detect statistical differences for continuous variables with normality of data distributions between 2 groups, and categorical data and percentage frequencies were analyzed by the Fisher exact test. Serial data (before and after the procedure) were analyzed by linear mixed-effects models, and 2-way repeated-measures ANOVA was conducted. If a significant difference between 2 groups or among 4 time points was detected by a global test, ad hoc multiple comparison was performed. Central arterial pressures before and after DFT testing were compared by paired *t* test. Ten subjects were randomly selected from each group and analyzed blindly by 2 independent investigators (N.T. and H.O.) to assess the intraclass correlation coefficient for evaluating reproducibility of longitudinal SR measurements. $P<0.05$ was considered statistically significant. All analyses were performed with JMP 9 (SAS Institute, Cary, NC).

Results

Clinical Characteristics

Table 1 shows the characteristics of the study population. There were no significant differences in age, sex, and body surface area between the 2 groups. New York Heart Association functional class was higher in the group with reduced LVEF than in the group with preserved LVEF. The group with reduced LVEF more frequently included ischemic and dilated cardiomyopathies than the group with preserved LVEF. Idiopathic ventricular fibrillation was the major cause of ICD implantation in the group with preserved LVEF. Concomitant cardiovascular drug therapy was common in the group with reduced LVEF.

Serial Changes of Serum Markers Before and After DFT Testing

Serial changes of serum markers are listed in Table 2. At baseline, there were no differences in biomarkers except for NT-proBNP between the groups before DFT testing. Baseline NT-proBNP was significantly higher in the group with reduced LVEF than in the group with preserved LVEF ($P<0.002$).

All patients received 2 consecutive 20-J shocks with a 5-minute interval. All induced VFs were successfully terminated by the first 20-J shock, and shocks neither higher nor lower than 20 J were delivered. Although the response to DFT testing in CK-MB and NT-proBNP differed between the groups using repeated-measures ANOVA, DFT testing did not cause significant changes in CK, CK-MB, myoglobin, and NT-proBNP in either group. DFT testing slightly increased cardiac troponin T in the group with preserved LVEF and cardiac troponin I in the group with reduced LVEF, but these values did not exceed the normal ranges (Table 2).

Table 1. Baseline and Clinical Characteristics of the Study Population

Variable	Preserved LVEF (n=25)	Reduced LVEF (n=25)	*P* Value
Age, y	55±13	57±14	0.661
Sex, male	20 (80)	15 (60)	0.217
Body surface area, m^2	1.72±0.20	1.66±0.19	0.254
NYHA functional class			<0.001
I	19	0	
II	6	20	
III	0	5	
Cardiac disease history			
Ischemic cardiomyopathy	1 (4)	12 (48)	0.001
Dilated cardiomyopathy	0 (0)	9 (36)	0.002
Hypertrophic cardiomyopathy	5 (20)	1 (4)	0.190
Cardiac sarcoidosis	0 (0)	3 (12)	0.235
Idiopathic ventricular fibrillation	19 (76)	0 (0)	<0.001
Concomitant cardiovascular therapies			
ACE inhibitors/ARBs	6	19	0.001
β-Blockers	9	23	<0.001
Calcium channel blockers	3	1	0.609
Diuretics	3	23	<0.001
Class III antiarrhythmic agent	9	5	0.345
Statins	3	5	0.702

LVEF indicates left ventricular ejection fraction; NYHA, New York Heart Association; ACE, angiotensin-converting enzyme; ARBs, angiotensin II receptor blockers. Values are n (%) or mean±SD.

Table 2. Serial Changes of Cardiac Biomarkers Before and After DFT testing

	Before	Immediately After	5 Minutes After	4 Hours After	Preserved LVEF vs Reduced LVEF (ANOVA)
CK, U/L					
Preserved LVEF	102±59	101±56	101±56	101±50	0.154
Reduced LVEF	89±59	88±58	87±58	94±49	
CK-MB, U/L					
Preserved LVEF	8±2	8±2	8±2	8±2	0.004
Reduced LVEF	9±3	9±3	9±2	9±3	
Myoglobin, ng/mL					
Preserved LVEF	62±32	62±33	61±33	60±35	0.830
Reduced LVEF	62±22	62±19	61±19	62±19	
cTNT, ng/mL					
Preserved LVEF	0.02±0.02	0.03±0.03	0.03±0.03	0.05±0.03*	0.005
Reduced LVEF	0.04±0.03	0.04±0.03	0.04±0.03	0.05±0.03	
cTNI, ng/mL					
Preserved LVEF	0.14±0.09	0.15±0.11	0.15±0.10	0.23±0.16	0.017
Reduced LVEF	0.17±0.11	0.19±0.12	0.18±0.12	0.29±0.16*	
NT-proBNP, pg/mL					
Preserved LVEF	214±325	206±312	212±327	190±297	<0.001
Reduced LVEF	1491±1811	1519±1845	1501±1820	1531±1761	

DFT indicates defibrillation threshold; LVEF, left ventricular ejection fraction; CK, creatine kinase; cTNT, cardiac troponin T; cTNI, cardiac troponin I; NT-proBNP, N-terminal probrain natriuretic peptide.

Values are expressed as mean±SD.

*$P<0.05$ vs variables at baseline (repeated-measures ANOVA, post hoc analysis).

Serial Changes of Echocardiographic Parameters Before and After DFT Testing

Serial changes of echocardiographic parameters in both groups are demonstrated in Table 3. In baseline echocardiographic data, LV end-diastolic volume and end-systolic volume were significantly greater in the group with reduced LVEF (both $P<0.001$). Parameters of transmitral flow showed no significant differences between the 2 groups. The e′ velocity was significantly lower, and E/e′ was greater in the group with reduced LVEF than in the group with preserved LVEF ($P<0.001$ and $P=0.042$, respectively). Global SR_{IVR} was less in the group with reduced LVEF than in the group with preserved LVEF ($P<0.001$).

By repeated-measures ANOVA, the response to DFT testing differed between the groups in all echocardiographic parameters listed in Table 3. In the group with reduced LVEF, LVEF decreased immediately after DFT testing and had recovered to the baseline level 4 hours after the test, whereas it showed no significant changes after DFT testing in the group with preserved LVEF (Table 3). Among Doppler parameters, e′ velocity showed modest decreases immediately after DFT testing in both groups, but the differences were not statistically significant. Reduction of global SR_{IVR} was sustained until 5 minutes after DFT testing and had recovered to the baseline level at 4 hours in both groups (Figures 2 and 3).

Intraclass correlation coefficients of longitudinal global SR for comparison between the 2 observers and among 1 observer were 0.950 ($P<0.001$) and 0.971 ($P<0.001$), respectively.

Changes of Central Arterial Pressure Before and After DFT Testing

After monitored anesthesia care, although systolic and diastolic blood pressures were significantly decreased in both groups (group with preserved LVEF: 127±14 versus 121±13 mm Hg, $P=0.004$; 74±12 versus 67±8 mm Hg, $P=0.016$, respectively; reduced LVEF group: 112±18 versus 103±18 mm Hg, $P=0.013$; 66±8 versus 58±9 mm Hg, $P=0.005$, respectively), decrease in heart rate was not significant (group with preserved LVEF: 63±9 versus 61±8 beats per minute, $P=0.092$; group with reduced LVEF: 70±10 versus 68±13 beats per minute, $P=0.337$).

Central arterial pressures before and after DFT testing are shown in Table 4. The group with reduced LVEF had lower systolic and diastolic arterial pressures and MAP than the group with preserved LVEF before DFT testing. DFT testing caused transient, yet significant, decreases in systolic and diastolic arterial pressures and MAP in both groups. Time to recovery of MAP to the baseline level was more prolonged in the group with reduced LVEF than in the group with preserved LVEF (43±24 versus 12±10 s; $P<0.001$).

Discussion

In the present study, we first found that ICD shock caused LV systolic dysfunction in patients with reduced LVEF as well as LV diastolic dysfunction, irrespective of baseline LVEF in the clinical setting. Impaired ventricular relaxation lasted at least 5 minutes after ICD shock in both groups, as demonstrated by sustained reduction of global SR_{IVR}. However, serum cardiac

Table 3. Serial Changes of Echocardiographic Parameters Before and After DFT testing

	Before	Immediately After	5 Minutes After	4 Hours After	Preserved LVEF vs Reduced LVEF (ANOVA)
LVEF, %					
Preserved LVEF	61±6	61±7	61±7	62±6	<0.001
Reduced LVEF	27±9	23±9*	22±8*	27±9	
E/A					
Preserved LVEF	1.1±0.4	1.1±0.4	1.1±0.4	1.1±0.4	<0.001
Reduced LVEF	0.9±0.8	0.8±0.6	0.8±0.6	0.8±0.6	
E-wave deceleration time, ms					
Preserved LVEF	246±54	230±48	238±50	244±53	0.030
Reduced LVEF	272±82	244±71	259±66	268±85	
Peak e′ velocity, cm/s					
Preserved LVEF	7.3±3.8	5.1±3.4	6.6±4.6	6.7±4.5	<0.001
Reduced LVEF	3.4±1.9	2.8±1.6	3.2±2.0	3.6±2.5	
E/e′					
Preserved LVEF	9.6±5.2	13.1±8.0	10.2±6.8	9.2±4.6	<0.001
Reduced LVEF	14.0±8.5	16.8±9.4	14.5±10.0	13.0±8.9	
Global SRIVR					
Preserved LVEF	0.39±0.14	0.23±0.13†	0.23±0.13†	0.40±0.13	<0.001
Reduced LVEF	0.15±0.05	0.08±0.04†	0.09±0.04†	0.15±0.05	

DFT indicates defibrillation threshold; LVEF, left ventricular ejection fraction; E/A, early diastolic and atrial filling; e′, early diastolic mitral annular velocity; SRIVR, strain rate during the isovolumetric relaxation period.

Values are expressed as mean±SD.

*$P<0.05$ vs variables at baseline (repeated-measures ANOVA, post hoc analysis).

†$P<0.01$ vs variables at baseline (repeated-measures ANOVA, post hoc analysis).

markers were unaffected or did not exceed normal values at any time point in either group, suggesting that transient ventricular dysfunction was not a result of myocardial injury. Furthermore, time to recovery of central arterial pressure to the baseline level was significantly longer in patients with reduced LVEF than in patients with preserved LVEF.

Effect of ICD Shock on Cardiac Function

The impact of internal cardioversion on LV systolic function remains controversial. Some previous echocardiographic studies showed that LV systolic function was unaffected after internal cardioversion during ICD implantation,[18,19] but LV systolic function was assessed by LVEF from the apical 4-chamber view only or the LV fractional area change from a single-plane, transgastric, short-axis view using transesophageal echocardiography. In contrast, a previous animal study demonstrated that contractile dysfunction was provoked after defibrillator shock given directly to the myocardium.[10] In the present study, LV systolic dysfunction after DFT testing was limited in patients with reduced LVEF, and this result does not contradict previous observations that cardiac output was deteriorated only in patients with low LVEF after inductions of ICD shock.[20,21]

In contrast to the effect of DFT testing on systolic function, DFT testing promoted transient diastolic dysfunction in all patients, irrespective of preoperative LVEF in the present study. Experimental studies revealed that the time constant of LV relaxation was prolonged, and LV end-diastolic pressure was increased after direct current shock even in normal hearts.[11,12] These results indicated that electric defibrillation impaired LV relaxation and deteriorated LV diastolic function. This is the first study demonstrating that defibrillation shock induced transient LV diastolic dysfunction in humans. We confirmed that reduced global SR_{IVR}, which is a new surrogate of LV relaxation, was sustained for at least 5 minutes after DFT testing and had recovered to the baseline level 4 hours after DFT testing in both groups, indicating that ICD shock impaired LV relaxation but that it was temporal in the clinical setting. Transient impairment of both systolic and diastolic LV dysfunctions by DFT testing in patients with reduced LVEF is associated with hemodyanamic instability. Prolonged recovery of central arterial pressure may have a pivotal role in the occurrence of DFT testing–related critical complications.[8]

The mechanisms of cardiac dysfunction after ICD shock remain uncertain. Serum cardiac biomarkers were not increased by DFT testing, and it was likely that significant myocardial injury did not occur. One possible explanation is abnormal Ca^{2+} transient induced by defibrillation.[22–24] It has been reported that electric shock prolonged the time decay of the Ca^{2+} transient and elevated diastolic intracellular calcium concentration even in normal myocytes[23] and that abnormal Ca^{2+} handling leads to impairment of LV relaxation.[22,25] Also, excessive intracellular Ca^{2+} overload results in contractile

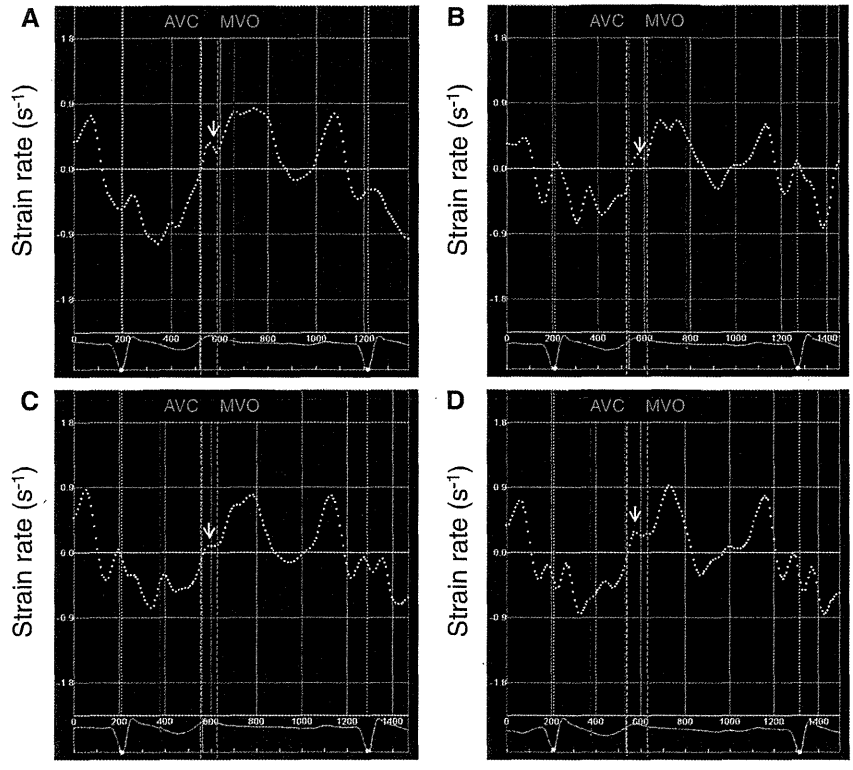

Figure 2. Serial changes of global strain rate during the isovolumetric relaxation period (SRIVR) before and after defibrillation threshold (DFT) testing in patients with preserved left ventricular ejection fraction (LVEF). A representative case of preserved LVEF. **A**, Before DFT testing, global SRIVR (**yellow arrow**) was 0.38 s^{-1} and LVEF was 71%. **B**, Immediately after DFT testing, global SRIVR was 0.20 s^{-1} and LVEF was 71%. **C**, At 5 minutes after DFT testing, global SRIVR was 0.12 s^{-1} and LVEF was 73%. **D**, At 4 hours after DFT testing, global SRIVR was 0.36 s^{-1} and LVEF was 70%. AVC indicates aortic valve closure; MVO, mitral valve opening.

dysfunction.[26] Because intracellular Ca^{2+} handling alters and diastolic intracellular Ca^{2+} concentration elevates in the failing heart,[25,27] defibrillation shock could transiently induce both diastolic and systolic dysfunctions in patients with reduced LVEF. Another possible mechanism is the occurrence of myocardial interstitial edema after defibrillation shock. Myocardial interstitial edema is a characteristic morphological change after ICD shock[12] and is associated with reduced LV distensibility and impaired relaxation.[28] However, myocardial edema is thought to be a result of thermal myocardial

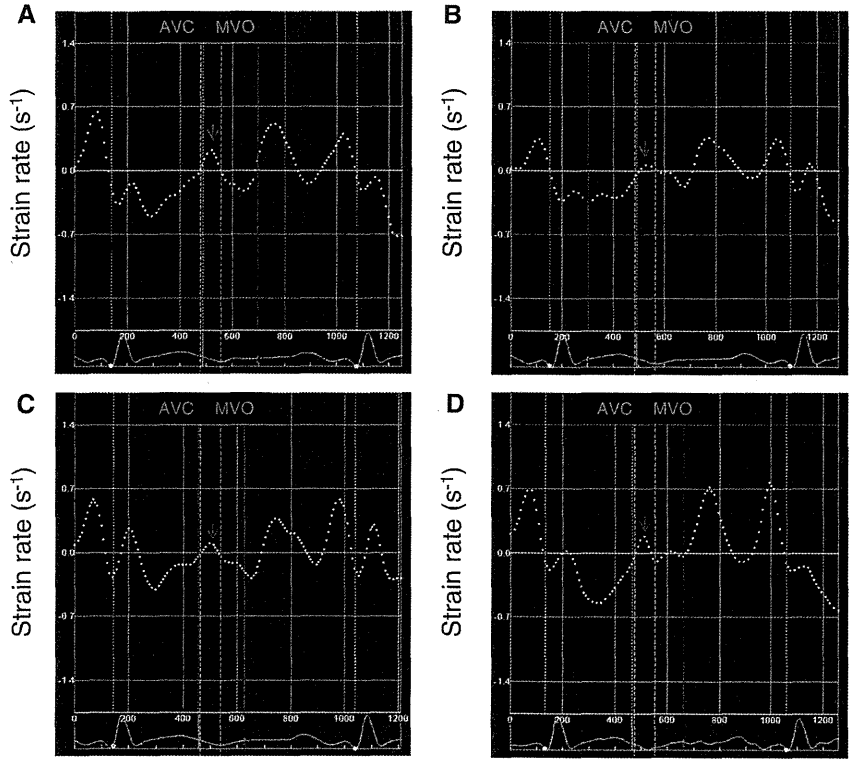

Figure 3. Serial changes of global strain rate during the isovolumetric relaxation period (SRIVR) before and after defibrillation threshold (DFT) testing in patients with reduced left ventricular ejection fraction (LVEF). A representative case of reduced LVEF. **A**, Before DFT testing, global SRIVR (**red arrow**) was 0.23 s^{-1} and LVEF was 39%. **B**, Immediately after DFT testing, global SRIVR was 0.08 s^{-1} and LVEF was 34%. **C**, At 5 minutes after DFT testing, global SRIVR was 0.08 s^{-1} and LVEF was 33%. **D**, At 4 hours after DFT testing, global SRIVR was 0.23 s^{-1} and LVEF was 37%. AVC indicates aortic valve closure; MVO, mitral valve opening.

Table 4. Central Arterial Pressure Measurements and Recovery Time of MAP After DFT testing

	Preserved LVEF	Reduced LVEF
Baseline systolic arterial pressure, mm Hg	121±13	103±18*
Baseline diastolic arterial pressure, mm Hg	67±8	58±9*
Baseline MAP, mm Hg	85±10	73±11*
Systolic arterial pressure immediately after DFT testing, mm Hg	87±15†	67±22*†
Diastolic arterial pressure immediately after DFT testing, mm Hg	39±8†	33±7*†
MAP immediately after DFT testing, mm Hg	55±9†	44±11*†
Time to reach baseline MAP, s	12±10	43±24*

MAP indicates mean arterial pressure; DFT, defibrillation threshold; LVEF, left ventricular ejection fraction.
Values are expressed as mean±SD.
*$P<0.01$ vs preserved LVEF.
†$P<0.01$ vs variables at baseline.

injury after ICD shock,[12] and we could not demonstrate either myocardial edema by echocardiography or tissue injury determined by biological markers in this study. Thus, the impact of myocardial interstitial edema on cardiac dysfunction remains obscure.

Implications of Echocardiographic Parameters

Although both global SR_{IVR} and e′ velocity reflect the property of LV relaxation, statistically significant reduction of e′ velocity was not observed after DFT testing, and decreased global SR_{IVR} was sustained for 5 minutes after DFT testing. This discrepancy may result from the fact that global SR_{IVR} is a measurement of whole heart motion, whereas e′ velocity is a localized measurement of mitral annular movement. The present results also support the superiority of global SR_{IVR} to e′ velocity for assessing LV relaxation.

Study Limitations

First, because the number of subjects in this study was limited, further research is needed to obtain a definitive conclusion regarding the association of ICD shock and subsequent cardiac dysfunction. Second, we cannot exclude the possibility of an effect of VF itself on cardiac dysfunction. Even though the duration of VF is short, VF causes cardiac dysfunction as a result of reduced blood flow and tissue perfusion. However, previous experimental studies have demonstrated that electric defibrillation itself also impaired intracellular Ca^{2+} dynamics and that it was associated with cardiac dysfunction,[22–24] and a previous clinical study has proved that ICD shock strength, not VF, was most relevant to reduction in cardiac index.[29] Thus, we believe that DFT testing after induced VF played a crucial role in cardiac dysfunction observed in this study. Third, all patients were receiving monitored anesthesia care during DFT testing and awakened during postprocedural investigation. However, the effect of anesthesia on the results might be small because echocardiographic parameters before DFT testing were comparable to those at 4 hours after DFT testing even though these data were acquired during sedated and waking periods, respectively. Central arterial pressure measurements were performed during the sedated period in all subjects. Fundamentally, it is impossible to deliver appropriate ICD shock during the waking period of patients. Fourth, because DFT testing is required in all patients undergoing ICD implantation at our institution, we were not able to include a control group with monitored anesthesia care and without DFT testing in this study, although the inclusion of such a control group would be helpful for assessing the impact of anesthesia on cardiac function and hemodynamics. Fifth, we cannot foreclose the possibility that the high prevalence of antihypertensive agent usage was associated with prolonged recovery of central arterial pressure in patients with reduced LVEF. Last, it is uncertain whether the current results can properly explain the mechanism of the adverse effect on long-term outcome after ICD shock. However, these results showed that ICD shock caused cardiac dysfunction at least temporarily and that subsequent hemodynamic instability, especially in patients with reduced LVEF, has the potential for worsening the clinical outcome after ICD shock in patients with heart failure.

Conclusions

ICD shock caused LV systolic dysfunction in patients with reduced LVEF and LV diastolic dysfunction irrespective of LVEF, although tissue injury determined by serum cardiac biomarkers was not observed. Furthermore, in patients with reduced LVEF, hemodynamic instability was prolonged. Therefore, even though the effects of ICD shock on cardiac function and hemodynamics are transient, clinicians should select an optimal medical therapy for avoiding ICD shock, and the necessity of DFT testing should be reconsidered, especially in patients with reduced LVEF.

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Disclosures

None.

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CLINICAL PERSPECTIVE

The benefit of the implantable cardioverter-defibrillator (ICD) in sudden cardiac death has been demonstrated in several trials. Although ICD shocks themselves are related to short- and long-term serious complications, especially in patients with left ventricular (LV) systolic dysfunction, the effect of ICD shocks on cardiac function and their association with tissue damage and subsequent hemodynamic change in patients with systolic heart failure have not been well understood. In the present study, using echocardiography, we demonstrated that ICD shocks caused LV systolic dysfunction in patients with reduced LV ejection fraction (LVEF) and LV diastolic dysfunction and both in patients with reduced and preserved LVEF in the clinical setting. Impaired ventricular relaxation lasted at least 5 minutes after ICD shocks in both groups, as demonstrated by sustained reduction of global strain rate during the isovolumetric relaxation period from 2-dimensional speckle-tracking echocardiography, which provides more accurate assessment of LV relaxation than conventional parameters. However, serum cardiac markers were unaffected or did not exceed normal values at any time point in either group, suggesting that transient ventricular dysfunction was not a result of myocardial injury. Furthermore, time to recovery of central arterial pressure to the baseline level was significantly longer in patients with reduced LVEF than in patients with preserved LVEF. Therefore, even though the effects of ICD shocks on cardiac function and hemodynamics are transient, clinicians should select optimal medical therapy for avoiding ICD shocks. In addition, the necessity for defibrillation threshold testing should be reconsidered, especially in patients with reduced LVEF.

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ORIGINAL ARTICLE
Renal Disease

Impact of Chronic Kidney Disease on Left Main Coronary Artery Disease and Prognosis in Japanese Patients

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Background: Renal insufficiency plays a critical role in the pathogenesis of ischemic heart disease. The aim of the present study was to investigate the prevalence of renal dysfunction and its impact on prognosis in patients with left main coronary artery disease (LMCAD) and stable angina pectoris.

Methods and Results: A total of 626 consecutive patients with significant coronary artery stenosis were enrolled. Renal insufficiency was graded using estimated glomerular filtration rate (eGFR) before coronary angiography. Chronic kidney disease (CKD) was defined as eGFR <60 ml·min^{-1}·1.73 m^{-2} and/or proteinuria. Patients with LMCAD (n=95) had a significantly higher prevalence of CKD than those without LMCAD (P=0.02). Multiple logistic regression analysis showed that CKD was independently associated with LMCAD (adjusted odds ratio, 1.74; 95% confidence interval [CI]: 1.09–2.76, P=0.01). A 1-year follow-up of patients with LMCAD showed that the cumulative incidence of major adverse cardiovascular events among patients with eGFR <30 ml·min^{-1}·1.73 m^{-2} was higher than that among patients with eGFR ≥60 ml·min^{-1}·1.73 m^{-2} (P=0.03). The hazard ratio for a cardiovascular event was 9.54 (95% CI: 3.15–28.89, P<0.01) when comparing patients with LMCAD and eGFR <30 ml·min^{-1}·1.73 m^{-2} vs. patients without LMCAD and eGFR ≥60 ml·min^{-1}·1.73 m^{-2}.

Conclusions: Renal insufficiency is a risk factor for LMCAD and predicts poor prognosis in Japanese patients. (*Circ J* 2012; **76:** 2266–2272)

Key Words: Chronic kidney disease; Coronary artery disease; Left main coronary artery; Risk factor

Obstructive disease of the left main coronary artery (LMCAD) is associated with poor prognosis.[1] Previous studies have sought to identify clinical characteristics linked to LMCAD, but those studies demonstrated only that patients with LMCAD have clinical features associated with diffuse, multi-vessel, coronary artery disease, and clinical features specific to LMCAD were not identified.[2–4]

In addition to the major traditional risk factors for cardiovascular disease (ie, advanced age, hypertension, diabetes mellitus, dyslipidemia, and smoking), recent studies suggest that chronic kidney disease (CKD) is an independent risk factor.[5] Several groups have reported that coronary artery disease severity and lesion complexity are associated with a decrease in the estimated glomerular filtration rate (eGFR).[6,7] Recent epidemiological studies and clinical trials have demonstrated that CKD is associated with increased mortality rate in patients with cardiovascular disease.[8,9] Extremely poor outcomes have been reported for patients with cardiovascular disease and CKD who were treated with percutaneous coronary intervention (PCI).[10–12] Although coronary artery bypass grafting (CABG) was an established therapy for patients with LMCAD, recent studies showed that the use of a coronary stent has made it feasible to treat LMCAD using PCI.[13] The decreased risk of periprocedural mortality after cardiac catheterization may improve outcomes for patients with LMCAD. The impact of CKD on the prognosis of patients with LMCAD has not been fully elucidated, however.

In the present study, we investigated whether CKD is an important risk factor for LMCAD, as detected on coronary angiography. In addition, we investigated whether the severity of renal dysfunction affects the prognosis of patients with LMCAD after optimal initial treatment.

Methods

Subjects

Between February 2006 and March 2009, we registered 1,601

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consecutive patients who underwent coronary angiography at Mitoyo General Hospital, Kagawa, Japan. Patients with significant stenosis of at least 1 epicardial coronary artery were enrolled in the study. Patients with acute coronary syndrome, cardiogenic shock, valvular heart disease, or cardiomyopathy were excluded. The final analysis involved 626 patients with stable angina pectoris who had significant stenosis of at least 1 epicardial coronary artery. Twenty subjects who had stenosis <25% luminal reduction in all coronary arteries were defined as the control group after angiography due to suspected CAD. Written, informed consent for study participation was obtained from each patient, in accordance with the Helsinki declaration, and the study was approved by the Institutional Ethics Committee.

Protocols

Protocol 1 The patients were separated according to an angiographic assessment as having LMCAD (LMCAD group) or not having LMCAD (non-LMCAD group). This study examined the relationship between the presence of LMCAD and the eGFR values and traditional coronary risk factors.

Protocol 2 The patients who were able to be followed up after discharge were reassigned according to eGFR and the presence or absence of LMCAD. Outcome of primary interest in protocol 2 was the incidence of subsequent major adverse cardiovascular and cerebrovascular events (MACCE).

Cardiac Catheterization

Significant stenosis was defined as >50% luminal reduction in the left main trunk and >75% luminal reduction in the left anterior descending, left circumflex, or right coronary artery. Control subjects were defined as having stenosis <25% luminal reduction in all coronary arteries. The subjects with significant stenosis were categorized into 2 groups on the basis of the presence of significant stenosis in left main trunk; LMCAD group; and non-LMCAD group. Each coronary angiogram was analyzed using the automated edge-detection system or by careful visual inspection by at least 2 cardiologists with expertise in coronary catheter intervention.

Blood Sampling

Blood samples were collected from fasting patients early in the morning on the day of coronary angiography. Concentration of serum lipids was measured using automated enzymatic methods.[14] Concentration of low-density lipoprotein cholesterol (LDL-C) was calculated using the Friedewald equation.[15] Hemoglobin A_{1c} was expressed in units as defined by the Japan Diabetic Society (JDS).[16] Serum creatinine was measured automatically using an enzyme assay. Plasma concentration of polyunsaturated fatty acids (ie, arachidonic acid [AA] and eicosapentaenoic acid [EPA]) was measured using capillary gas chromatography as described previously.[17]

Definition of Risk Factors

Diabetes mellitus was defined as the presence of any of the following: fasting plasma glucose levels ≥126 mg/dl; casual plasma glucose levels ≥200 mg/dl; or a history of treatment for diabetes mellitus. Hypertension was confirmed if any of the following criteria were met: systolic blood pressure ≥140 mmHg; diastolic blood pressure ≥90 mmHg; or the current use of antihypertensive agents. Dyslipidemia was defined as the use of lipid-lowering agents or if one or more of the following criteria from the first fasting blood sample were met: LDL-C ≥140 mg/dl; triglyceride ≥150 mg/dl; or high-density lipoprotein cholesterol (HDL-C) <40 mg/dl. eGFR was calculated using the equation from the Modification of Diet in Renal Disease Study Group,[18] with coefficients modified for Japanese patients:[19] eGFR ($ml \cdot min^{-1} \cdot 1.73\,m^{-2}$) = 194 × serum creatinine$^{-1.094}$ × age$^{-0.287}$ × [0.739 if female]. CKD was defined as eGFR <60 $ml \cdot min^{-1} \cdot 1.73\,m^{-2}$ and/or proteinuria.

Definition of MACCE

The treatment that was finally performed on de novo lesions in all patients was considered to be the initial treatment. The initial treatment was defined as medical therapy alone, initial successful PCI, or initial CABG. MACCE was defined as one of the following conditions: revascularization due to new or recurrent fatal and non-fatal acute myocardial infarction; new or recurrent unstable angina pectoris; and de novo stable lesion and target lesion restenosis; heart failure admission; stroke and transient ischemic attack; cardiac death.

Statistical Analysis

Statistical analysis was performed using SPSS 11.0 for Windows (SPSS, Chicago, IL, USA). Data that were not distributed normally, as determined using the Kolmogorov-Smirnov test, were logarithmically transformed before analysis. Continuous variables were compared using unpaired Student's t-test or 1-way analysis of variance. These data are presented as mean±SD. Categorical variables were compared using either chi-square test or Fisher's exact test and are expressed as frequencies with percentages. Multivariate multiple logistic regression was used to detect associations between LMCAD and various risk factors including CKD, age, male gender, diabetes mellitus, hypertension, dyslipidemia, and smoking. MACCE event time was defined as the time between discharge from hospital after the procedure and the occurrence of the first MACCE. Cumulative MACCE-free survival rates were estimated using the Kaplan-Meier method and represented patients who did not experience MACCE over the 1-year follow-up period. Survival rates were compared among groups using the log-rank test. The association with MACCE was assessed using a multivariate Cox proportional hazards model. Group differences associated with $P<0.05$ were considered statistically significant.

Results

Protocol 1

Renal Dysfunction and LMCAD Patient characteristics and laboratory values are summarized in Table 1. Among 625 patients with stable angina pectoris, 95 (15%) were found to have LMCAD. Conventional risk factors for coronary artery disease were examined among 3 groups: control; non-LMCAD; and LMCAD. The percentage of elderly subjects, male subjects, subjects with dyslipidemia, and smokers was higher in the LMCAD group than in the control group. Except for dyslipidemia, the frequency of these factors did not differ between the LMCAD and non-LMCAD groups. With regard to biochemistry parameters (ie, lipid profiles and glucose metabolism), patients with LMCAD had significantly lower levels of HDL-C than the control subjects. HDL-C level did not differ, however, between patients with and without LMCAD. AA/EPA and B-type natriuretic peptide level also did not differ between patients with and without LMCAD. eGFR was highest in the control group and was decreased significantly in non-LMCAD patients. Patients with LMCAD, however, had the greatest reduction in kidney function. As such, both eGFR and the prevalence of dyslipidemia differed between patients with and without LMCAD (both the control and non-LMCAD groups). In addition, when patients with stable angina were classified into

Table 1. Patient Characteristics

	Controls (n=20)	Non-LMCAD			LMCAD (n=95)
		Total (n=531)	Single-vessel (n=314)	Multi-vessel (n=217)	
Age (years)	65±11	69±10	69±11	69±10	71±9*
Male (%)	45	75*	75	74	71*
Hypertension (%)	55	67	62	73	74
Diabetes mellitus (%)	15	24	21	27	22
Dyslipidemia (%)	26	31	27	36	51*,†
Smoking (%)	20	55*	56	54	50*
eGFR ($ml \cdot min^{-1} \cdot 1.73m^{-2}$)	79±25	63±22*	65±20	60±24	54±25*,#
eGFR ≥60 (%)	75	55	58	52	43
30≤eGFR<60 (%)	20	38	38	38	41
eGFR <30 (%)	5	7	4	10	16
Proteinuria (%)	0	8	5	12	17*,†
CKD (%)	25	45*	42	49	58*,†
Hemodialysis (%)	0	3	1	5	9†
LDL-C (mg/dl)	107±32	109±31	106±29	113±32	111±32
HDL-C (mg/dl)	64±15	51±13	52±13	50±13	50±13*
HbA_{1c} (%)	5.9±1.2	6.1±1.2	5.9±1.1	6.2±1.3	6.1±1.1
AA/EPA	1.9±0.7	2.5±1.5	2.5±1.3	2.6±1.7	2.3±1.4
BNP (pg/dl)	28±35	206±680	170±376	264±605	252±452
CRP (mg/dl)	0.26±0.45	0.49±1.49	0.37±1.12	0.67±1.9	0.74±1.9
Angiographic findings (%)					
LAD	–	61	49	77	65
LCX	–	45	24	75	53
RCA	–	43	27	67	50
Medications (%)					
ACEI/ARB	47	64	71	58	50
CCB	47	44	47	40	50
Statin	37	46	50	42	44
β-blocker	16	23	20	27	19
Aspirin	42	58	63	52	69
Nitrate	21	10	13	6	31
Treatment (%)					
Medication only	–	27	33	23	20
PCI	–	63	63	63	23†
BMS	–	55	60	47	15†
DES	–	45	40	53	85†
CABG	–	10	4	14	57†

Data given as mean±SD or (%).
*P<0.05 vs. normal; †P<0.05 vs. all non-LMCAD. HbA_{1c} was determined according to the definition of Japan Diabetes Society.
LMCAD, left main coronary artery disease; eGFR, estimated glomerular filtration rate; CKD, chronic kidney disease; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; HbA_{1c}, hemoglobin A_{1c}; AA, arachidonic acid; EPA, eicosapentaenoic acid; BNP, brain natriuretic peptide; CRP, C-reactive protein; LAD, left anterior descending artery; LCX, left circumflex coronary artery; RCA, Right coronary artery; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; CCB, calcium channel blocker; PCI, percutaneous coronary intervention; BMS, bare metal stent; DES, drug-eluting stent; CABG, coronary artery bypass grafting.

3 groups (single-vessel disease without LMCAD, n=314; multi-vessel disease without LMCAD, n=271; and LMCAD, n=95), eGFR clearly decreased as coronary artery disease became more severe, and patients with LMCAD had the lowest mean eGFR among the 3 groups. CKD was more prevalent among patients with LMCAD than among non-LMCAD patients (58% vs. 45%, P=0.02).

The risk factors associated with LMCAD were analyzed on multivariate logistic regression. As shown in Table 2, CKD was independently associated with LMCAD (adjusted odds ratio, 1.74, 95% confidence interval: 1.09–2.76, P=0.01).

Protocol 2

Clinical Outcomes Kaplan-Meier curves that illustrate the percentage of MACCE-free patients over time during the first year after treatment are shown in Figure. Data for all patients (Figure A) and for patients with LMCAD (Figure B) are shown. During this time interval, we were able to track 56 patients with LMCAD. Of these 56 individuals, 13 received PCI (23%), 32 had CABG (57%), and 11 were treated with medication only (20%) as initial therapies. With regard to the non-LMCAD patients, we were able to track 249 patients. Of these 249 individuals, 157 received PCI (63%), 24 had CABG