Circulation Journal
Official Journal of the Japanese Circulation Society
http://www.j-circ.or.jp

ORIGINAL ARTICLE
Imaging

Normal Values of Real-Time 3-Dimensional Echocardiographic Parameters in a Healthy Japanese Population

– The JAMP-3D Study –

Shota Fukuda, MD; Hiroyuki Watanabe, MD; Masao Daimon, MD; Yukio Abe, MD; Akihiro Hirashiki, MD; Kumiko Hirata, MD; Hiroshi Ito, MD; Masumi Iwai-Takano, MD; Katsuomi Iwakura, MD; Chisato Izumi, MD; Takayuki Hidaka, MD; Toshinori Yuasa, MD; Kazuya Murata, MD; Satoshi Nakatani, MD; Kazuaki Negishi, MD; Kazuhiro Nishigami, MD; Tomoko Nishikage, BSc; Takahiro Ota, MD; Akihiro Hayashida, MD; Konomi Sakata, MD; Nobuhiro Tanaka, MD; Satoshi Yamada, MD; Kazuhiro Yamamoto, MD; Junichi Yoshikawa, MD

Background: The recently developed real-time 3-dimensional echocardiography (RT3DE) is a promising imaging method to quantify cardiac chamber volumes and their functions in clinical practice. However, normal reference values of RT3DE parameters have not been fully investigated in a large, healthy Japanese population.

Methods and Results: This study consisted of 410 healthy subjects aged from 20 to 69 years who had a RT3DE at one of the 23 collaborating institutions. All subjects had no history of cardiac disease and no risk factors. The mean values in men and women were as follows: 50±12 ml/m^2 and 46±9 ml/m^2 for left ventricular (LV) end-diastolic volume index, 19±5 ml/m^2 and 17±4 ml/m^2 for end-systolic volume index, 61±4% and 63±4% for ejection fraction, 64±12 g/m^2 and 56±11 g/m^2 for mass index, 23±6 ml/m^2 and 24±6 ml/m^2 for left atrial (LA) maximum volume index, 10±3 ml/m^2 and 10±3 ml/m^2 for minimum volume index, and 58±6% and 58±6% for percent volume change. LV sizes decreased with age, whereas LV mass index did not change. LA sizes slightly increased with age.

Conclusions: This multicenter investigation determined normal reference values for LV and LA sizes, and their functional parameters on RT3DE in a large, healthy Japanese population. The results of the present study support the use of RT3DE for the diagnosis and management of cardiovascular disease. (*Circ J* 2012; **76:** 1177–1181)

Key Words: Echocardiography; Japanese; Population

Transthoracic echocardiography is the standard imaging modality for the assessment of cardiovascular anatomy, function and physiology in clinical practice.[1] The available normal reference values for echocardiographic measurements have been provided by the American Society of Echocardiography and European Association of Echocardiog-

Received November 1, 2011; revised manuscript received January 16, 2012; accepted January 17, 2012; released online February 24, 2012
Time for primary review: 14 days

Department of Medicine, Osaka Ekisaikai Hospital, Osaka (S.F.); Department of Cardiology, Sakakibara Heart Institute, Japan Research Promotion Society of Cardiovascular Disease, Tokyo (H.W.); Department of Cardiology, Juntendo University School of Medicine, Tokyo (M.D.); Department of Cardiology, Osaka City General Hospital, Osaka (Y.A.); Department of Cardiology, Nagoya University Hospital, Nagoya (A. Hirashiki); Department of Cardiology, Wakayama Medical University, Wakayama (K.H.); Department of Cardiovascular Medicine, Okayama University Graduate School of Medicine, Okayama (H.I.); Department of Infection Control and Laboratory Medicine, Fukushima Medical University, Fukushima (M.I.-T.); Division of Cardiology, Sakurabashi Watanabe Hospital, Osaka (K.I.); Department of Cardiology, Tenri Hospital, Tenri (C.I.); Department of Cardiovascular Medicine, Hiroshima University Hospital, Hiroshima (T.H.); Department of Cardiovascular, Respiratory and Metabolic Medicine, Graduate School of Medicine, Kagoshima University, Kagoshima (T.Y.); Division of Laboratory, Yamaguchi University Hospital, Ube (K.M.); Department of Health Sciences, Osaka University Graduate School of Medicine, Suita (S.N.); Department of Medicine and Biological Science, Gunma University Graduate School of Medicine, Maebashi (K. Negishi); Department of Critical Care and Cardiology, Saiseikai Kumamoto Hospital, Kumamoto (K. Nishigami); Department of Physiological Laboratory, Osaka Seamen's Insurance Hospital, Osaka (T.N.); Division of Cardiology, Fuchu Hospital, Izumi (T.O.); Division of Cardiology, Kawasaki Medical School, Kurashiki (A. Hayashida); Second Department of Internal Medicine, Kyorin University School of Medicine, Mitaka (K.S.); Department of Cardiology, Tokyo Medical University, Tokyo (N.T.); Department of Cardiovascular Medicine, Hokkaido University Graduate School of Medicine, Sapporo (S.Y.); Department of Cardiovascular Medicine, Osaka University Graduate School of Medicine, Suita (K.Y.); and Nishinomiya Watanabe Cardiovascular Center, Nishinomiya (J.Y.), Japan
Mailing address: Shota Fukuda, MD, PhD, Department of Medicine, Osaka Ekisaikai Hospital, 2-1-10 Honden, Nishi-ku, Osaka 550-0022, Japan. E-mail: h-syouta@mve.biglobe.ne.jp

ISSN-1346-9843 doi:10.1253/circj.CJ-11-1256

Table 1. Clinical Characteristics of the Enrolled Subjects

Age (years)	Men						Women					
	Overall	20–29	30–39	40–49	50–59	60–69	Overall	20–29	30–39	40–49	50–59	60–69
n	253	55	67	51	41	39	157	41	34	30	28	24
Weight, kg	66±9	65±8	67±8	67±9	69±10	62±11	50±6*	50±5*	50±5*	52±5*	49±6*	50±7*
Height, cm	170±6	171±6	171±5	171±7	170±7	165±6	156±5*	157±5*	157±5*	158±6*	153±4*	153±6*
BSA, kg/m²	1.8±0.1	1.8±0.1	1.8±0.1	1.8±0.1	1.8±0.2	1.7±0.1	1.5±0.1*	1.5±0.1*	1.5±0.1*	1.5±0.1*	1.4±0.1*	1.5±0.1*
HR, beats/min	66±10	65±10	65±9	67±10	65±10	65±9	67±9	66±10	69±8	67±9	66±8	67±10
SBP, mmHg	121±10	117±10	121±10	123±10	122±10	125±10	115±12*	111±8*	113±11*	113±12*	121±14	123±13
DBP, mmHg	73±9	70±8	73±10	76±7	74±10	73±8	69±9	65±7*	68±8*	68±10*	73±11	72±9

Data are presented as mean±SD. *P<0.05 vs. the corresponding parameter in men.
BSA, body surface area; HR, heart rate; SBP, systolic blood pressure; DBP, diastolic blood pressure.

Table 2. Normal Values of LV Parameters

Age (years)	Men						Women					
	Overall	20–29	30–39	40–49	50–59	60–69	Overall	20–29	30–39	40–49	50–59	60–69
n	222	48	58	46	36	34	134	37	27	25	23	22
EDV, ml	86±22	98±22	93±19	90±19	82±22	73±18	67±14*	68±15*	67±9*	76±14*	63±11*	59±12*
ESV, ml	34±10	39±10	36±8	36±9	31±9	28±8	25±6*	25±6*	25±4*	29±6*	23±5*	22±6*
EDV/BSA, ml/m²	50±12	56±12	52±10	51±11	45±12	44±12	46±9*	46±9*	46±7*	50±9	44±8	41±8
ESV/BSA, ml/m²	19±5	22±6	20±4	20±5	17±5	17±5	17±4*	17±4*	17±3*	19±4	16±4	15±4
EF, %	61±4	61±3	62±3	61±4	63±3	61±5	63±4*	63±4*	62±4	63±3*	64±3	63±5
Mass, g	113±22	115±23	112±21	115±23	113±23	107±17	83±17*	81±16*	80±16*	90±20*	84±15*	80±16*
Mass/BSA, g/m²	64±12	66±12	63±12	64±12	64±13	64±10	56±11*	55±10*	55±11*	58±12	58±9	55±9*
MV ratio	1.3±0.3	1.2±0.3	1.2±0.3	1.3±0.2	1.5±0.3	1.5±0.3	1.3±0.2*	1.2±0.3	1.2±0.2	1.2±0.2	1.4±0.2	1.3±0.2*

Data are presented as mean±SD. *P<0.05 vs. the corresponding parameter in men.
LV, left ventricle; EDV, end-diastolic volume; ESV, end-systolic volume; BSA, body surface area; EF, ejection fraction; MV ratio, mass to volume ratio.

Table 3. Normal Values of LA Parameters

Age (years)	Men						Women					
	Overall	20–29	30–39	40–49	50–59	60–69	Overall	20–29	30–39	40–49	50–59	60–69
n	222	45	63	43	37	34	139	38	30	27	26	18
Maximum volume, ml	41±11	39±8	40±10	42±12	43±12	43±10	36±9*	34±7*	34±6*	39±9	37±11*	38±10
Minimum volume, ml	17±5	16±4	16±5	18±6	18±6	18±5	15±4*	14±3*	14±3*	16±5	16±6	16±5
Maximum volume/BSA, ml/m²	23±6	22±4	23±5	23±6	24±7	26±6	24±6	23±5	23±5	25±6	25±8	26±6
Minimum volume/BSA, ml/m²	10±3	9±2	9±3	10±3	10±3	11±3	10±3	9±2	9±2	10±3	11±3	11±3
Percent volume change, %	58±6	58±6	60±5	68±5	57±5	57±6	58±6	59±7	59±5	59±6	56±7	60±6

Data are presented as mean±SD. *P<0.05 vs. the corresponding parameter in men.
BSA, body surface area; LA, left atrium.

raphy.[2] Considering the physical and racial differences between Western and Asian populations,[3–5] it is important to establish reference values of echocardiographic parameters for the Japanese population. We have already published details from the Japanese Normal Values for Echocardiographic Measurements Project (JAMP) study to determine the normal values of 2-dimensional echocardiography (2DE).[6,7]

The recently developed real-time 3-dimensional (3D) echocardiography (RT3DE) provides fast and non-invasive 3D estimates with high image resolution that are more accurate and physiologic than those measured by conventional imaging techniques.[8,9] A number of previous studies have revealed the advantages of RT3DE for the assessment of left ventricular (LV) volume, mass and output,[10–12] as well as for the 3D geometry of the heart structure.[13–15] However, the normal values of RT3DE parameters have not been fully investigated, especially for a healthy Japanese population. Therefore, as an extension to the JAMP study with 2DE, this study was designed to determine the normal reference values of RT3DE parameters in a large, healthy Japanese population.

Methods

Study Population

The study population was consisted of 410 healthy volunteers aged from 20 to 69 years (253 males, mean age 42±14 years) at 23 collaborating institutions. None of the subjects had a history of cardiac disease or risk factors. Furthermore, none of the subjects had fever, anemia, or high blood pressure (systolic >135 mmHg or diastolic >85 mmHg) that could have affected the results of echocardiography. All electrocardiographic and 2DE recordings in the recruited subjects were normal. The dataset of RT3DE was obtained from each institution and sent to the Osaka Ekisaikai Hospital for analysis. A single expert

sonographer (T.N.), who had 10 years of experience in echocardiography with approximately 6000 2DE and 200 RT3DE examinations, analyzed the RT3DE dataset. This study was approved by the Ethics Committee of each institution.

Transthoracic 3D Echocardiography

The transthoracic RT3DE was examined by SONOS 7500 and iE-33 (Philips Medical Systems, Andover, MA, USA) in 191 subjects (47%), Vivid 7 and Vivid E9 (GE Medical Systems, Milwaukee, WI, USA) in 150 subjects (37%), SC2000 (Siemens Mountainview, CA, USA) in 41 subjects (10%), and Artida (Toshiba Medical Systems, Tokyo, Japan) in 28 subjects (7%). RT3DE images from the apical view were acquired during a breath hold with electrocardiogram gating. Gain and compression controls as well as the time gain compensation settings were optimized for the quality of the echocardiographic images. All RT3DE data-sets were digitally stored and analyzed off-line.

RT3DE was analyzed using commercially available software for each RT3DE system; QLAB for SONOS 7500 and iE-33, EchoPac (TomTec LV volume) for Vivid 7 and Vivid E9, SC2000 Workplace (eSie LVA) for SC2000, and Advanced Cardiology Package for Artida. The off-line software automatically identified the cavity wall interface in the 3D space throughout the cardiac cycle. Manual adjustments were performed, when necessary, to include the papillary muscles and trabeculae in the LV cavity, and to exclude the left atrial (LA) appendage and pulmonary vein in the LA cavity, respectively. The following parameters were then obtained: (1) LV end-diastolic (EDV), end-systolic volumes (ESV), and ejection fraction (EF); (2) maximal and minimal LA volumes, and percent change; calculated as (diastolic volume−systolic volume)/diastolic volume× 100; and (3) LV mass, and the ratio of LV mass to EDV (MV ratio). LV epicardial borders at the end-diastole were traced for the measurement of LV mass by using the following formula: (end-diastolic epicardial volume−EDV)×1.05. The LV mass was determined by multiplying the volumetric parameter by the specific density of the myocardium (1.05 g/ml).

Each parameter was indexed for body surface area (BSA) when appropriate.

Statistical Analysis

Values were expressed as mean±SD. The parametric data of men and women, and those of multi-beat and single-beat RT3DE systems were compared by using the unpaired t-test. Linear regression was used for the correlation of variables of interest. Differences were considered significant at $P<0.05$. Inter-observer variability for echocardiographic measurements was analyzed in 15 random subjects by 2 independent blinded observers (T.N. and K.M.). Intra-observer variability was analyzed in another group of 15 subjects by the same observer at 2 different time-points. The results were analyzed by using the Bland-Altman method.

Table 4. Relationship Between Age and Various Echocardiographic Parameters

	Men		Women	
	r	P value	r	P value
LV				
EDV	−0.40	<0.001	−0.21	0.01
ESV	−0.37	<0.001	−0.21	0.01
EDV/BSA	−0.36	<0.001	−0.20	0.02
ESV/BSA	−0.34	<0.001	−0.20	0.02
EF	0.08	0.2	0.09	0.3
Mass	−0.13	0.05	0.06	0.5
Mass/BSA	−0.04	0.5	0.11	0.2
MV ratio	0.36	<0.001	0.22	0.009
LA				
Maximum volume	0.14	0.04	0.17	0.04
Minimum volume	0.18	0.009	0.24	0.004
Maximum volume/BSA	0.19	0.004	0.21	0.01
Minimum volume/BSA	0.22	<0.001	0.27	0.001
Percent volume change	−0.12	0.07	−0.16	0.07

Abbreviations see in Tables 2,3.

Results

Feasibility of RT3DE

Among the total of 410 subjects, 54 and 43 subjects were excluded due to inadequate delineation of the chamber wall in images of the LV and LA, respectively. Thus, the feasibility of RT3DE measurement was 87% for LV and 90% for LA.

Values of RT3DE Parameters and Their Relationship to Gender and Age

Table 1 shows the characteristics of 410 healthy subjects by overall, age- and gender-groups. Men were heavier, taller and had larger BSA than women. There were not differences in heart rate between men and women, although blood pressure in men was slightly higher than that in women.

The mean values of LV and LA parameters in overall, age- and gender-groups are shown in Tables 2 and 3, respectively. LV volumes, mass, and LA volumes were larger in men than in women, even after normalization by BSA. There were no significant differences in LVEF and LA percent volume change between men and women. Table 4 summarizes the relationship between age and the RT3DE parameters. LV volumes decreased with age. This relationship was still evident after adjustment for BSA. Age did not correlate with LV mass, and thus the MV ratio increased with age. LA volumes increased with age, whereas its percentage change did not correlate with age. The increases in the maximum and minimum volumes were 0.83 ml/BSA/10 year (y=0.083x+19.7) and 0.46 ml/BSA/10 year (y=0.046x+7.8) for men and 0.87 ml/BSA/10 year (y=0.087x+20.6) and 0.58 ml/BSA/10 year (y=0.058x+7.8) for women, respectively. Table 5 summarized the results of the

Table 5. Intra- and Inter-Observer Variabilities in RT3DE Measurements

	LV				LA		
	EDV	ESV	EF	Mass	Maximum volume	Minimum volume	Percent volume change
Intra-observer variability	2.4 ml	1.2 ml	1.4%	7.9 g	3.3 ml	1.2 ml	3.6%
Inter-observer variability	4.9 ml	4.0 ml	1.7%	8.1 g	2.9 ml	1.7 ml	2.1%

RT3DE, real-time 3-dimensional echocardiography. Other abbreviations see in Tables 2,3.

Bland-Altman analysis.

Discussion

This study evaluated the normal reference values for LV and LA volumes, and their functional parameters, measured on RT3DE in a healthy Japanese population, and analyzed the effects of age and gender on these parameters.

Advantages of RT3DE

In clinical practice, 2DE is generally used as the initial diagnostic imaging modality for evaluation of the structure and function of the cardiovascular system and establishment of clinical diagnosis. However, it is clear that geometric assumption in quantification of chamber volume precludes a precise measurement using 2DE. Recently, 3D imaging techniques, including RT3DE, magnetic resonance imaging (MRI) and computed tomography (CT), have provided unique anatomic views of different cardiac structures as well as accurate quantification of LV volume, mass and output. However, the utility of cardiac MRI and CT might be restricted, especially in sequential or follow-up studies, by their inherent limitations, such as expense, being time-consuming, the use of a contrast agent, and radiation exposure (CT only). The developed RT3DE offers an opportunity for rapid, non-invasive, physiologic image acquisition with high image quality and good reproducibility, which would be more feasible than other 3D imaging techniques.[16] However, the lack of the reference values might have so far, at least in part, limited the use of RT3DE in the clinical and research mainstream in the field of cardiovascular disease.

Comparison With Previous 2DE Observations

In a comparison with our previous 2DE observations,[6] LV and LA volumes were similar between RT3DE and 2DE. For example, LV EDV/BSA of RT3DE and 2DE was 50±12 ml/m^2 and 53±11 ml/m^2 for men and 46±9 ml/m^2 and 49±11 ml/m^2 for women, respectively. It is recognized that volume quantification of 2DE using the biplane Simpson disk method has limitations of image plane positioning errors and geometric assumptions, which results in low reproducibility and tendency to underestimate absolute volume, especially in the remodeling heart.[2] However, our results indicated that in the experienced laboratories that are aware of the above-mentioned limitations of 2DE, volumetric quantification using the biplane Simpson disk method is acceptable at least for normal-shaped hearts, and the same normal reference values of LV and LA volumes can be used between RT3DE and 2DE.

In contrast, LV mass/BSA of RT3DE (64±12 g/m^2 for men and 56±11 g/m^2 for women) tended to be smaller than those of 2DE based on the area-length formula (76±16 g/m^2 for men and 70±14 g/m^2 for women). This observation was supported by a previous study that showed that LV mass was underestimated by RT3DE and overestimated by 2DE, as compared with MRI findings.[8] Furthermore, low reproducibility of 2DE for LV mass measurement has been reported.[8,17,18] Therefore, the difference in the normal reference value between RT3DE and 2DE should be taken into the consideration when determining the presence or absence of LV hypertrophy in clinical practice.

Relationship to Age, Gender and Race

It is generally accepted that age-related changes in cardiac structure and function occur in healthy subjects. Our results of age-related changes of the heart are consistent with the findings of previous studies in normal subjects using 2DE,[6] MRI,[19–21] and CT.[22] LV size decreases with age, whereas LV mass remains unchanged. This LV remodeling indicates age-related LV "concentric hypertrophy" as a response to increased arterial pressure and afterload with age. LV volume declines are likely offset by elevated or maintained LVEF. In contrast, LA volumes slightly increase with age, which might reflect age-related LV diastolic dysfunction.[23,24] Such LA remodeling due to age-related LV diastolic dysfunction might be subtle enough to be determined by 2DE. In fact, our previous 2DE study found a discrepancy in the result, that LA length in antero-posterior direction increased with age, although the estimated LA volume, calculated from 2 orthogonal 2D planes, was unchanged.[6]

In the present study, LV size was larger in men than in women. This gender difference became smaller after correction for BSA, which is similar to the results of previous reports.[19,25]

Two studies have previously examined the reference values of RT3DE parameters in healthy subjects. In the study by Aune et al from Norway, the mean value of EDV was 136 ml in men and 104 ml in women.[26] Even after correction for BSA (2.05 m^2 for men and 1.78 m^2 for women), these values are still lager than our results (66 ml/m^2 vs. 50 ml/m^2 in men, and 5 ml/m^2 vs. 46 ml/m^2, respectively). A previous JAMP study of 2DE confirmed that Japanese hearts were smaller than those of the Western population.[6] These observations strongly indicate the existence of race-related differences in echocardiographic measurements. Kaku et al recently investigated the growing process of LV geometry in 280 healthy subjects, between the age of 1 to 88 years.[27] These subjects were enrolled in Japan and the USA. Because of the race differences in the heart,[3–6,26] the use of their results as the Japanese reference values might be limited. Our study is the first that provides age- and gender-specific reference values of RT3DE parameters in a large, healthy Japanese population. These results should be helpful for disease classification, stratification of risk, and guidance of therapy using RT3DE.

Study Limitations

This study has several limitations. Although all subjects were interviewed by physicians in participating institutions, one cannot rule out the presence of an unrecognized cardiovascular disease. Furthermore, the differences among the RT3DE systems might affect the results of this study. Although no significant differences were observed in RT3DE results between multi-beat and single-beat RT3DE systems among all 10 age- and gender-subgroups (multi-beat: SONOS 7500, iE-33, Vivid 7, and Artida; single-beat: Vivid E9 and SC2000), the impact of the differences among 7 different echo systems on the results remained unknown because of a relatively small number of subjects in each age- and gender-subgroup ranged approximately from 20 to 60. The number of examinations with Artida (n=28), Vivid E9 (n=15) and SC2000 (n=41), which were introduced within several recent years, were low. Therefore, future investigations might be necessary to answer this question. Also, RT3DE was performed at each institution, and analysis was completed by experienced sonographers in the center, who were blinded to clinical information. These processes might be different to real, clinical situations, which might influence the reproducibility of RT3DE results. Finally, although there were significant correlations between age and LA volumes, these age-related changes in LA volume were relatively small, and therefore, further investigations are necessary to evaluate the importance of age-related LA volume

changes in clinical practice.

Conclusions

Our multicenter investigation provided normal reference values for LV and LA volumes, and their functional correlates from RT3DE in a large, healthy Japanese population. The results of analysis showed age- and gender-differences in these parameters. The results of present study should be considered in the clinical and research studies that use RT3DE for the management of cardiovascular disease.

Acknowledgments

This work was supported, in part, by a research grant from the Fukuda Foundation for Medical Technology, Japan.

Disclosures

The authors declare no conflict of interest.

References

1. Okura H, Takada Y, Yamabe A, Ozaki T, Yamagishi H, Toda I, et al. Prevalence and correlates of physiological valvular regurgitation in healthy subjects. *Circ J* 2011; **75:** 2699–2704.
2. Lang RM, Bierig M, Devereux RB, Flachskampf FA, Foster E, Pellikka PA, et al. Recommendations for chamber quantification: A report from the American Society of Echocardiography's Guidelines and Standards Committee and the Chamber Quantification Writing Group, developed in conjunction with the European Association of Echocardiography, a branch of the European Society of Cardiology. *J Am Soc Echocardiogr* 2005; **18:** 1440–1463.
3. Hinderliter AL, Light KC, Willis PW 4th. Racial differences in left ventricular structure in healthy young adults. *Am J Cardiol* 1992; **69:** 1196–1199.
4. Harshfield GA, Koelsch DW, Pulliam DA, Alpert BS, Richey PA, Becker JA. Racial differences in the age-related increase in left ventricular mass in youths. *Hypertension* 1994; **24:** 747–751.
5. Schieken RM, Schwartz PF, Goble MM. Tracking of left ventricular mass in children: Race and sex comparisons: The MCV Twin Study: Medical College of Virginia. *Circulation* 1998; **97:** 1901–1906.
6. Daimon M, Watanabe H, Abe Y, Hirata K, Hozumi T, Ishii K, et al. Normal values of echocardiographic parameters in relation to age in a healthy Japanese population: The JAMP study. *Circ J* 2008; **72:** 1859–1866.
7. Daimon M, Watanabe H, Abe Y, Hirata K, Hozumi T, Ishii K, et al. Gender differences in age-related changes in left and right ventricular geometries and functions. *Circ J* 2011; **75:** 2840–2846.
8. Jenkins C, Bricknell K, Hanekom L, Marwick TH. Reproducibility and accuracy of echocardiographic measurements of left ventricular parameters using real-time three-dimensional echocardiography. *J Am Coll Cardiol* 2004; **44:** 878–886.
9. Shiota T. Clinical application of 3-dimensional echocardiography. *J Echocardiogr* 2005; **3:** 93–103.
10. Mor-Avi V, Sugeng L, Weinert L, MacEneaney P, Caiani EG, Koch R, et al. Fast measurement of left ventricular mass with real-time three-dimensional echocardiography: Comparison with magnetic resonance imaging. *Circulation* 2004; **110:** 1814–1818.
11. Pemberton J, Li X, Karamlou T, Sandquist CA, Thiele K, Shen I, et al. The use of live three-dimensional Doppler echocardiography in the measurement of cardiac output: An in vivo animal study. *J Am Coll Cardiol* 2005; **45:** 433–438.
12. Takeuchi M, Nishikage T, Mor-Avi V, Sugeng L, Weinert L, Nakai H, et al. Measurement of left ventricular mass by real-time three-dimensional echocardiography: Validation against magnetic resonance and comparison with two-dimensional and M-mode measurements. *J Am Soc Echocardiogr* 2008; **21:** 1001–1005.
13. Watanabe N, Ogasawara Y, Yamaura Y, Kawamoto T, Toyota E, Akasaka T, et al. Quantitation of mitral valve tenting in ischemic mitral regurgitation by transthoracic real-time three-dimensional echocardiography. *J Am Coll Cardiol* 2005; **45:** 763–769.
14. Daimon M, Shiota T, Gillinov AM, Hayase M, Ruel M, Cohn WE, et al. Percutaneous mitral valve repair for chronic ischemic mitral regurgitation: A real-time three-dimensional echocardiographic study in an ovine model. *Circulation* 2005; **111:** 2183–2189.
15. Fukuda S, Saracino G, Matsumura Y, Daimon M, Tran H, Greenberg NL, et al. Three-dimensional geometry of the tricuspid annulus in healthy subjects and in patients with functional tricuspid regurgitation: A real-time, 3-dimensional echocardiographic study. *Circulation* 2006; **114:** I492–I498.
16. Hare JL, Jenkins C, Nakatani S, Ogawa A, Yu CM, Marwick TH. Feasibility and clinical decision-making with 3D echocardiography in routine practice. *Heart* 2008; **94:** 440–445.
17. Qin JX, Jones M, Travaglini A, Song JM, Li J, White RD, et al. The accuracy of left ventricular mass determined by real-time three-dimensional echocardiography in chronic animal and clinical studies: A comparison with postmortem examination and magnetic resonance imaging. *J Am Soc Echocardiogr* 2005; **18:** 1037–1043.
18. Oe H, Hozumi T, Arai K, Matsumura Y, Negishi K, Sugioka K, et al. Comparison of accurate measurement of left ventricular mass in patients with hypertrophied hearts by real-time three-dimensional echocardiography versus magnetic resonance imaging. *Am J Cardiol* 2005; **95:** 1263–1267.
19. Sandstede J, Lipke C, Beer M, Hofmann S, Pabst T, Kenn W, et al. Age- and gender-specific differences in left and right ventricular cardiac function and mass determined by cine magnetic resonance imaging. *Eur Radiol* 2000; **10:** 438–442.
20. Nikitin NP, Loh PH, de Silva R, Witte KK, Lukaschuk EI, Parker A, et al. Left ventricular morphology, global and longitudinal function in normal older individuals: A cardiac magnetic resonance study. *Int J Cardiol* 2006; **108:** 76–83.
21. Cheng S, Fernandes VR, Bluemke DA, McClelland RL, Kronmal RA, Lima JA. Age-related left ventricular remodeling and associated risk for cardiovascular outcomes: The Multi-Ethnic Study of Atherosclerosis. *Circ Cardiovasc Imaging* 2009; **2:** 191–198.
22. Lin FY, Devereux RB, Roman MJ, Meng J, Jow VM, Jacobs A, et al. Cardiac chamber volumes, function, and mass as determined by 64-multidetector row computed tomography: Mean values among healthy adults free of hypertension and obesity. *JACC Cardiovasc Imaging* 2008; **1:** 782–786.
23. Sohn DW, Chai IH, Lee DJ, Kim HC, Kim HS, Oh BH, et al. Assessment of mitral annulus velocity by Doppler tissue imaging in the evaluation of left ventricular diastolic function. *J Am Coll Cardiol* 1997; **30:** 474–480.
24. Abhayaratna WP, Seward JB, Appleton CP, Douglas PS, Oh JK, Tajik AJ, et al. Left atrial size: Physiologic determinants and clinical applications. *J Am Coll Cardiol* 2006; **47:** 2357–2363.
25. Byrd BF 3rd, Wahr D, Wang YS, Bouchard A, Schiller NB. Left ventricular mass and volume/mass ratio determined by two-dimensional echocardiography in normal adults. *J Am Coll Cardiol* 1985; **6:** 1021–1025.
26. Aune E, Baekkevar M, Rodevand O, Otterstad JE. Reference values for left ventricular volumes with real-time 3-dimensional echocardiography. *Scand Cardiovasc J* 2010; **44:** 24–30.
27. Kaku K, Takeuchi M, Otani K, Sugeng L, Nakai H, Haruki N, et al. Age- and gender-dependency of left ventricular geometry assessed with real-time three-dimensional transthoracic echocardiography. *J Am Soc Echocardiogr* 2011; **24:** 541–547.

Appendix

We appreciate the assistance of many colleagues in the echocardiographic recordings and management: Kumiko Maeda, RMS, Reiko Miyahana, RMS (Osaka Ekisaikai Hospital); Kiyomi Saito, RMS (Sakakibara Heart Institute); Sakiko Miyazaki, MD, Yoko Koiso, MD (Juntendo University School of Medicine); Noriyo Fujii, RMS, Rieko Nakamura, RMS (Osaka City General Hospital); Hiroki Matsubara, RMS, Kaori Kato, RMS (Nagoya University Hospital); Yuko Wakinishi, RMS, Nozomi Wada, MD (Wakayama Medical University); Hiroki Oe, MD (Okayama University Graduate School of Medicine); Shuichi Takahashi, JRDCS (Tenri Hospital); Hiroto Utsunomiya, MD, Yasuki Kihara, MD (Hiroshima University Hospital); Akira Kisanuki, MD, Kunitsugu Takasaki, MD (Kagoshima University); Yasuaki Wada, MD, Kosuke Uchida, MD (Yamaguchi University Hospital); Rieko Takahashi, MD (Gunma University Graduate School of Medicine); Tomoko Takada, RMS (Gunma University Hospital); Ayako Tomita, RMS (Saiseikai Kumamoto Hospital), Shinichi Iwata, MD, Nobuhiro Nonaka, RMS (Fuchu Hospital); Hiroyuki Okura, MD, Kiyoshi Yoshida, MD (Kawasaki Medical School); Hideaki Yoshino, MD, Kazuki Satou, MD (Kyorin University School of Medicine); Yasuyoshi Takei, MD, Nori Takahashi, RMS (Tokyo Medical University); Hiroyuki Iwano, MD (Hokkaido University Graduate School of Medicine); Sanae Kaga, RMS (Hokkaido University Hospital); Yasushi Sakata, MD, Yasuharu Takeda, MD (Osaka University Graduate School of Medicine).

Circulation Journal
Official Journal of the Japanese Circulation Society
http://www.j-circ.or.jp

ORIGINAL ARTICLE
Imaging

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

Kazuhiro Osawa, MD; Toru Miyoshi, MD; Shuhei Sato, MD; Noriaki Akagi; Yusuke Morimitsu; Kazufumi Nakamura, MD; Kunihisa Kohno, MD; Kengo Kusano, MD; Susumu Kanazawa, MD; Hiroshi Ito, MD

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-

Received May 17, 2012; revised manuscript received August 3, 2012; accepted September 3, 2012; released online October 3, 2012 Time for primary review: 20 days

Department of Cardiovascular Medicine (K.O., K.N., K. Kohno, K. Kusano, H.I.), Department of Cardiovascular Therapeutics (T.M.), and Department of Radiology (S.S., N.A., Y.M., S.K.), Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences, Okayama, Japan

Mailing address: Toru Miyoshi, MD, Department of Cardiovascular Therapeutics, Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences, 2-5-1 Shikata-cho, Okayama 700-8558, Japan. E-mail: miyoshit@cc.okayama-u.ac.jp

ISSN-1346-9843 doi:10.1253/circj.CJ-12-0663

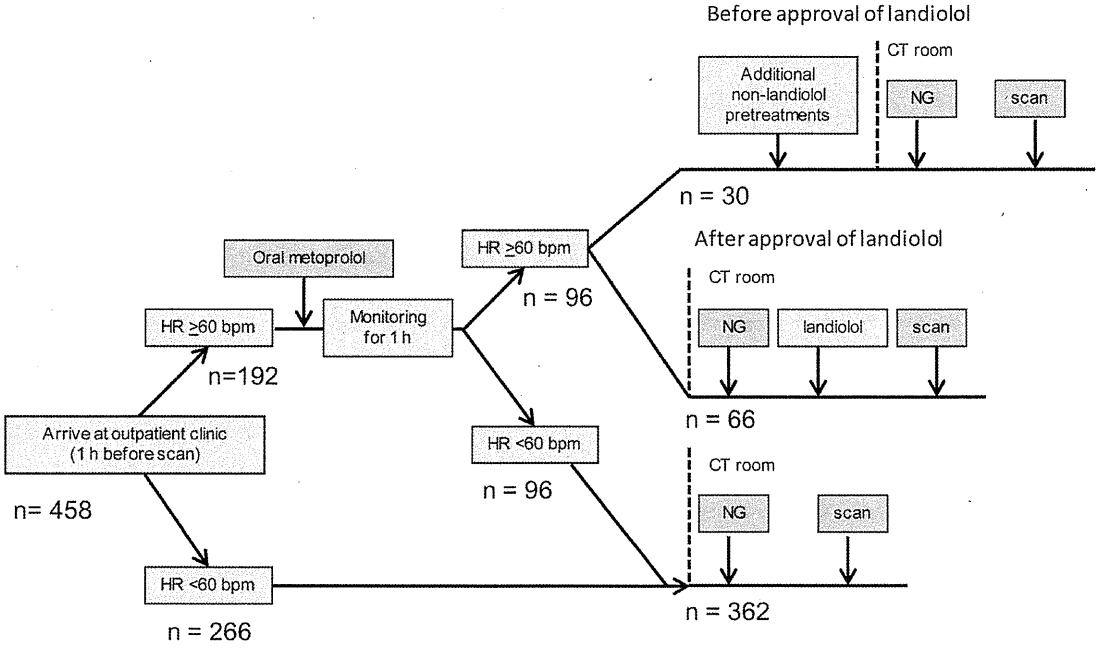

Figure 1. Diagram of steps involved in MDCT coronary angiography. All patients arrived at the hospital 1 h before the scheduled scanning time. All patients whose heart rate was ≥60 beats/min received oral metoprolol (20–40 mg). Before the approval of landiolol, if heart rate was still ≥60 beats/min, 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/m²)	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

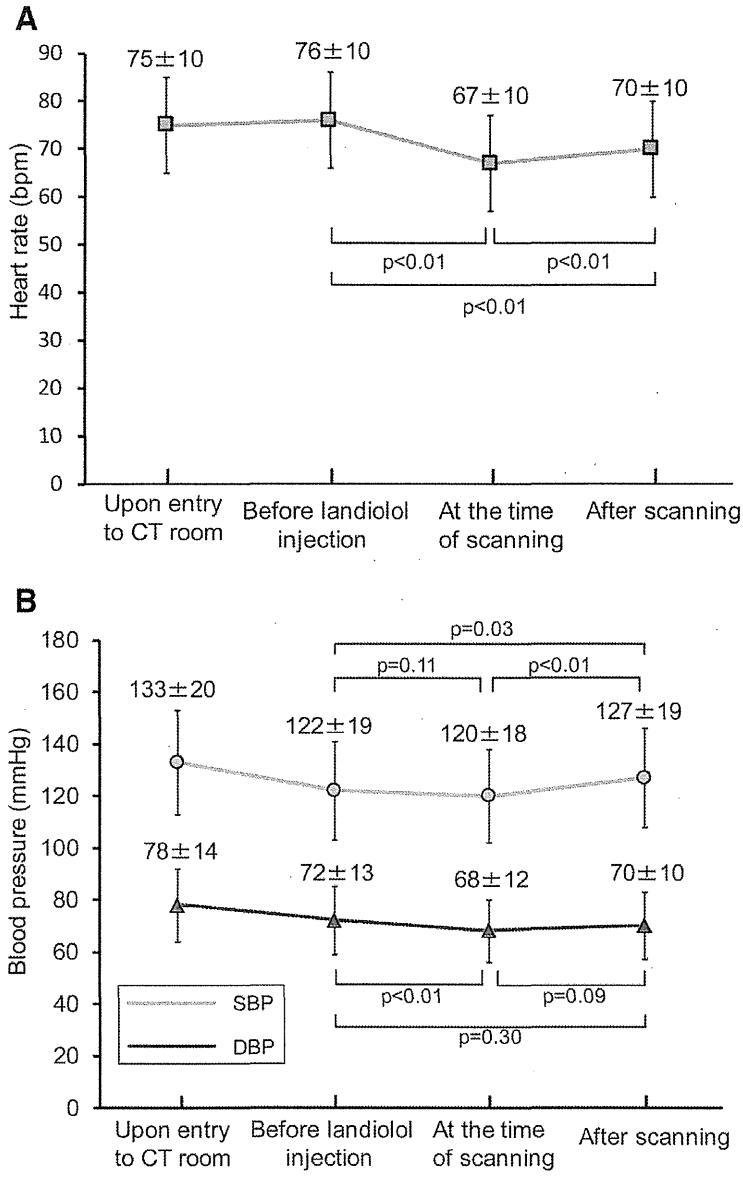

Figure 2. Graph showing the sequential changes in heart rate (A) and blood pressure (B) immediately after scanning of 66 patients given landiolol upon entry to the CT room. Data are expressed as mean±SD. SBP, systolic blood pressure; DBP, diastolic blood pressure; HR, heart rate.

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.

Acknowledgments

The authors thank Y. Koyama, T. Oka, M. Yoshikawa, J. Iwasaki, S. Sakuragi and Y. Katayama for participating in study design, and M. Yamagami, S. Kusai, S. Koumoto, M. Taira and J. Suetoshi for their excellent technical support.

Disclosures

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

References

1. Achenbach S, Giesler T, Ropers D, Ulzheimer S, Derlien H, Schulte C, et al. Detection of coronary artery stenoses by contrast-enhanced, retrospectively electrocardiographically-gated, multislice spiral computed tomography. *Circulation* 2001; **103:** 2535–2538.
2. Matsumoto N, Nagao K, Hirayama A, Sato Y. Non-invasive assessment and clinical strategy of stable coronary artery disease by magnetic resonance imaging, multislice computed tomography and myocardial perfusion SPECT. *Circ J* 2010; **74:** 34–40.
3. Motoyama S, Kondo T, Anno H, Sugiura A, Ito Y, Mori K, et al. Atherosclerotic plaque characterization by 0.5-mm-slice multislice computed tomographic imaging. *Circ J* 2007; **71:** 363–366.
4. Nieman K, Cademartiri F, Lemos PA, Raaijmakers R, Pattynama PM, de Feyter PJ. Reliable noninvasive coronary angiography with fast

submillimeter multislice spiral computed tomography. *Circulation* 2002; **106:** 2051–2054.
5. Shim SS, Kim Y, Lim SM. Improvement of image quality with beta-blocker premedication on ECG-gated 16-MDCT coronary angiography. *Am J Roentgenol* 2005; **184:** 649–654.
6. Sugiyama A, Takahara A, Hashimoto K. Electrophysiologic, cardiohemodynamic and beta-blocking actions of a new ultra-short-acting beta-blocker, ONO-1101, assessed by the in vivo canine model in comparison with esmolol. *J Cardiovasc Pharmacol* 1999; **34:** 70–77.
7. Ikeshita K, Nishikawa K, Toriyama S, Yamashita T, Tani Y, Yamada T, et al. Landiolol has a less potent negative inotropic effect than esmolol in isolated rabbit hearts. *J Anesth* 2008; **22:** 361–366.
8. Sakamoto A, Kitakaze M, Takamoto S, Namiki A, Kasanuki H, Hosoda S. Landiolol, an ultra-short-acting β_1-blocker, more effectively terminates atrial fibrillation than diltiazem after open heart surgery. *Circ J* 2012; **76:** 1097–1101.
9. Nakano T, Shimizu K, Kawashima O, Kamiyoshihara M, Nagashima T, Ibe T, et al. Effect of landiolol hydrochloride, an ultra-short-acting beta 1-selective blocker, on supraventricular tachycardia, atrial fibrillation and flutter after pulmonary resection. *J Clin Pharm Ther* 2012; **37:** 431–435.
10. Miwa Y, Ikeda T, Mera H, Miyakoshi M, Hoshida K, Yanagisawa R, et al. Effects of landiolol, an ultra-short-acting β_1-selective blocker, on electrical storm refractory to class III antiarrhythmic drugs. *Circ J* 2010; **74:** 856–863.
11. Kobayashi S, Susa T, Tanaka T, Murakami W, Fukuta S, Okuda S, et al. Low-dose β-blocker in combination with milrinone safely improves cardiac function and eliminates pulsus alternans in patients with acute decompensated heart failure. *Circ J* 2012; **76:** 1646–1653.
12. Hanada K, Higuma T, Nishizaki F, Sukekawa T, Yokota T, Yamada M, et al. Randomized study on the efficacy and safety of landiolol, an ultra-short-acting β1-adrenergic blocker, in patients with acute myocardial infarction undergoing primary percutaneous coronary intervention. *Circ J* 2012; **76:** 439–445.
13. Fujii M, Bessho R, Ochi M, Shimizu K, Terajima K, Takeda S. Effect of postoperative landiolol administration for atrial fibrillation after off pump coronary artery bypass surgery. *J Cardiovasc Surg (Torino)* 2012; **53:** 369–374.
14. Isobe S, Sato K, Sugiura K, Mimura T, Kobayashi M, Meno C, et al. Feasibility of intravenous administration of landiolol hydrochloride for multislice computed tomography coronary angiography: Initial experience. *Circ J* 2008; **72:** 1814–1820.
15. Sato Y, Matsumoto N, Kato M, Inoue F, Horie T, Kusama J, et al. Noninvasive assessment of coronary artery disease by multislice spiral computed tomography using a new retrospectively ECG-gated image reconstruction technique. *Circ J* 2003; **67:** 401–405.
16. Austen WG, Edwards JE, Frye RL, Gensini GG, Gott VL, Griffith LS, et al. A reporting system on patients evaluated for coronary artery disease: Report of the Ad Hoc Committee for Grading of Coronary Artery Disease, Council on Cardiovascular Surgery, American Heart Association. *Circulation* 1975; **51:** 5–40.
17. Hoffmann MH, Shi H, Manzke R, Schmid FT, De Vries L, Grass M, et al. Noninvasive coronary angiography with 16-detector row CT: Effect of heart rate. *Radiology* 2005; **234:** 86–97.
18. Leber AW, Knez A, Becker C, Becker A, White C, Thilo C, et al. Non-invasive intravenous coronary angiography using electron beam tomography and multislice computed tomography. *Heart* 2003; **89:** 633–639.
19. Shuman WP, Branch KR, May JM, Mitsumori LM, Lockhart DW, Dubinsky TJ, et al. Prospective versus retrospective ECG gating for 64-detector CT of the coronary arteries: Comparison of image quality and patient radiation dose. *Radiology* 2008; **248:** 431–437.
20. Cademartiri F, Mollet NR, Runza G, Belgrano M, Malagutti P, Meijboom BW, et al. Diagnostic accuracy of multislice computed tomography coronary angiography is improved at low heart rates. *Int J Cardiovasc Imaging* 2006; **22:** 101–105; Discussion 107–109.
21. Hoffmann MH, Shi H, Schmitz BL, Schmid FT, Lieberknecht M, Schulze R, et al. Noninvasive coronary angiography with multislice computed tomography. *JAMA* 2005; **293:** 2471–2478.
22. Mark DB, Berman DS, Budoff MJ, Carr JJ, Gerber TC, Hecht HS, et al. ACCF/ACR/AHA/NASCI/SAIP/SCAI/SCCT 2010 expert consensus document on coronary computed tomographic angiography: A report of the American College of Cardiology Foundation Task Force on Expert Consensus Documents. *Circulation* 2010; **121:** 2509–2543.
23. Shibata S, Okamoto Y, Endo S, Ono K. Direct effects of esmolol and landiolol on cardiac function, coronary vasoactivity, and ventricular electrophysiology in guinea-pig hearts. *J Pharmacol Sci* 2012; **118:** 255–265.
24. Mollet NR, Cademartiri F, Nieman K, Saia F, Lemos PA, McFadden EP, et al. Multislice spiral computed tomography coronary angiography in patients with stable angina pectoris. *J Am Coll Cardiol* 2004; **43:** 2265–2270.
25. Leschka S, Wildermuth S, Boehm T, Desbiolles L, Husmann L, Plass A, et al. Noninvasive coronary angiography with 64-section CT: Effect of average heart rate and heart rate variability on image quality. *Radiology* 2006; **241:** 378–385.

Circulation Journal
Official Journal of the Japanese Circulation Society
http://www.j-circ.or.jp

ORIGINAL ARTICLE
Renal Disease

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

Kazuhiro Dan, MD; Toru Miyoshi, MD; Masayuki Ueeda, MD; Hiroaki Ohtsuka, MD; Satoko Ugawa, MD; Nobuhiko Ohnishi, MD; Atsushi Takaishi, MD; Kazufumi Nakamura, MD; Kengo Kusano, MD; Hiroshi Ito, MD

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

Received December 13, 2011; revised manuscript received April 22, 2012; accepted May 1, 2012; released online June 9, 2012
Time for primary review: 23 days

Department of Cardiovascular Medicine (K.D., T.M., K.N., K.K., H.I.), Department of Cardiovascular Therapeutics (T.M.), Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences, Okayama; and Department of Cardiovascular Medicine, Mitoyo General Hospital, Kagawa (M.U., H.O., S.U., N.O., A.T.), Japan

Mailing address: Toru Miyoshi, MD, Department of Cardiovascular Therapeutics, Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences, 2-5-1 Shikata-cho, Okayama 700-8558, Japan. E-mail: miyoshit@cc.okayama-u.ac.jp

ISSN-1346-9843 doi:10.1253/circj.CJ-11-1455

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 ($ml \cdot min^{-1} \cdot 1.73 m^{-2}$)	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

Table 2. Impact of CKD on Prevalence of LMCAD

	Univariate analysis			Multivariate analysis		
	OR	95%CI	P value	OR	95%CI	P value
CKD	1.67	1.07–2.60	0.02	1.74	1.09–2.76	0.01
Age	1.01	0.99–1.04	0.12			
Male gender	1.24	0.76–2.02	0.37			
Diabetes mellitus	0.87	0.51–1.48	0.61			
Hypertension	1.44	0.87–2.38	0.14			
Dyslipidemia	1.47	0.92–2.34	0.10	1.48	0.92–2.37	0.09
Smoking	0.79	0.51–1.24	0.31			

OR, odds ratio; CI, confidence interval. Other abbreviations as in Table 1.

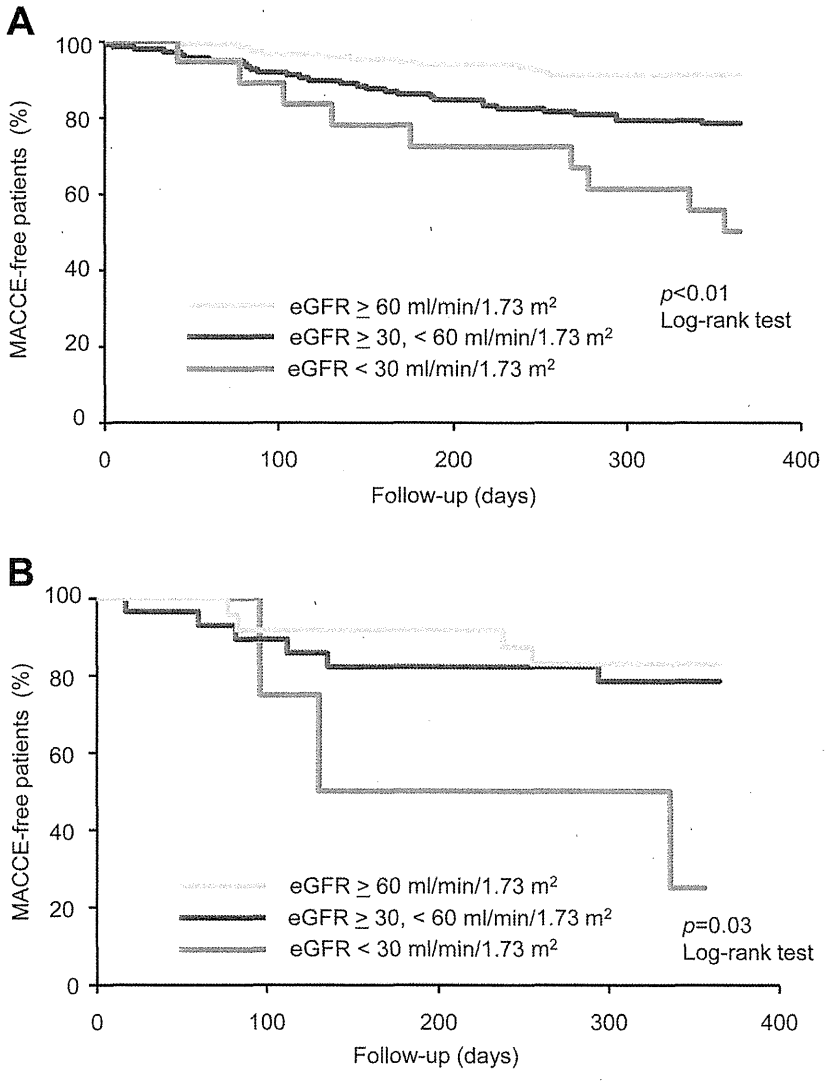

Figure. Kaplan-Meier analysis in patients with (A) stable angina pectoris or (B) left main coronary artery disease. Major adverse cardiovascular and cerebrovascular events (MACCE) were defined as one of the following conditions: revascularization due to new or recurrent fatal and non-fatal acute myocardial 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. eGFR, estimated glomerular filtration rate.

(10%), and 68 were treated with medication only (27%). Patients with eGFR <30 ml·min^{-1}·1.73 m^{-2} more frequently experienced MACCE. This held true for both patients with stable angina pectoris and patients with LMCAD.

Patients subsequently were reassigned to 6 groups on the basis of their LMCAD status and eGFR. The MACCE for those groups are listed in Table 3. Clinical characteristics such as age, gender, hypertension, diabetes mellitus, dyslipidemia, and medications did not differ between the groups, but treatments such as PCI and CABG did differ (Table S1). As shown in Table 4, multivariate logistic analysis indicated that the risk of MACCE in non-LMCAD patients with eGFR <30 ml·

Table 3. MACCE vs. Presence of LMCAD

	eGFR (ml·min^{-1}·1.73 m^{-2})			P value
	<30	≥30, <60	≥60	
Non-LMCAD				
n	15	111	123	
MACCE (total)	6	23	8	<0.01
Revascularization	2	10	8	NS
Hospitalization for HF	2	8	0	0.01
Cardiac death	1	3	0	NS
Cerebrovascular events	1	2	0	NS
LMCAD				
n	4	28	24	
MACCE (total)	3	6	5	0.05
Revascularization	2	2	2	0.03
Hospitalization for HF	1	4	2	NS
Cardiac death	0	0	1	NS
Cerebrovascular events	0	0	0	NS

MACCE, major adverse cardiovascular and cerebrovascular events; HF, heart failure. Other abbreviations as in Table 1.

Table 4. Effect of Renal Dysfunction on MACCE vs. Presence of LMCAD

eGFR (ml·min^{-1}·1.73 m^{-2})	No. patients	MACCE (%)	HR (95%CI)	P value
Non-LMCAD				
≥60	123	7	1.00	
≥30, <60	111	21	2.39 (1.35–4.26)	<0.01
<30	15	40	6.82 (3.21–14.52)	<0.01
LMCAD				
≥60	24	17	2.25 (0.86–5.88)	NS
≥30, <60	28	21	1.86 (0.70–4.93)	NS
<30	4	75	9.54 (3.15–28.89)	<0.01

This multivariate logistic analysis was adjusted for PCI and CABG.
HR, hazard ratio. Other abbreviations as in Tables 1–3.

min^{-1}·1.73 m^{-2} was approximately 7-fold higher than for non-LMCAD patients with eGFR ≥60 ml·min^{-1}·1.73 m^{-2}. Furthermore, the risk of MACCE in LMCAD patients with eGFR <30 ml·min^{-1}·1.73 m^{-2} was approximately 9-fold higher than for non-LMCAD patients with eGFR ≥60 ml·min^{-1}·1.73 m^{-2}. Thus, the risks of MACCE in both groups for patients with eGFR <30 ml·min^{-1}·1.73 m^{-2} were similarly high in spite of the presence or absence of LMCAD.

Discussion

In this study, we demonstrated that (1) CKD was independently associated with the presence of LMCAD in patients with stable angina pectoris, even though the frequency of traditional risk factors such as advanced age, male gender, hypertension, dyslipidemia, diabetes mellitus, and smoking did not differ between patients with and without LMCAD; and (2) the risk ratio of MACCE in patients with eGFR <30 ml·min^{-1}·1.73 m^{-2} was similar between patients with stable angina pectoris with and without LMCAD. These results suggest that CKD is an independent risk factor of LMCAD and that the impact of CKD adversely affects the outcomes of patients both with and without LMCAD treated with optimal initial treatment.

In this study, LMCAD occurred in 15% of patients with stable angina pectoris. Previous studies have reported LMCAD in approximately 3–8% of stable angina pectoris patients.[2,20,21] The high level of LMCAD in the present study may reflect the criteria for patient selection. The present subjects had significant stenosis (>50% coronary artery narrowing in at least 1 vessel, as determined on coronary angiography). As a consequence, subjects with stable angina pectoris and coronary narrowing <50% were excluded from the study. Among the 1,601 consecutive patients who underwent coronary angiography during the study period, the percentage of patients with LMCAD was 5.9%. Further, almost all of the present patients with LMCAD had significant stenosis in an additional major coronary artery. These findings support the hypothesis that LMCAD represents the most advanced stage of coronary atherosclerosis. These results also are consistent with earlier studies, which demonstrated that >90% of patients with LMCAD have significant disease in an additional coronary artery.[20,22–24]

The present results show for the first time that CKD is an independent factor associated with LMCAD. Efforts have been made in the past to identify clinical risk profiles that predict LMCAD, but those efforts have had limited success.[2,4,25] The LMCAD risk factor profile established to date is similar to that associated with diffuse and multi-vessel coronary artery disease. In agreement with previous studies, the present findings identified comparable clinical characteristics between patients with stable angina pectoris and multi-vessel disease and patients with LMCAD. The eGFR, however, was the only factor that differed between the non-LMCAD and LMCAD groups. Intriguingly, eGFR levels gradually decreased as the severity of coronary artery disease worsened. Specifically, patient

groups could be ranked on the basis of eGFR level (high to low): (1) control; (2) single-vessel disease without LMCAD; (3) multi-vessel disease without LMCAD; and (4) LMCAD. Many patients with LMCAD had the most advanced stage of coronary atherosclerosis, and the severity of renal insufficiency has been shown to correlate closely with the severity of coronary artery disease.[26] In the present study, the prevalence of dyslipidemia in the LMCAD group was shown to be higher than that in the control group and the non-LMCAD group, but logistic analysis failed to confirm dyslipidemia as an independent risk factor for LMCAD. One possible reason is that the statistical power was not sufficient due to the relatively small number of subjects. We also evaluated the relationship between LMCAD and AA/EPA ratio, which is a promising risk factor for cardiovascular events.[27] We found that the AA/EPA ratio did not correlate with the prevalence of LMCAD or with the severity of coronary artery disease. In addition, the risk factors for CKD such as advanced age, hypertension, dyslipidemia, diabetes mellitus, and smoking are, however, also risk factors of severe coronary artery disease. Therefore, it is possible that the association between CKD and the prevalence of LMCAD was simply due to residual confounding factors. In this study, CKD was found to be an increased risk for the presence of LMCAD, while the number of patients enrolled in this study was limited. A larger study is needed to clarify other potential risk factors of LMCAD.

The mechanisms that underlie the association between renal dysfunction and coronary artery disease have not been elucidated fully. Previous studies have shown that renal dysfunction is associated with low-grade inflammation and activation of the sympathetic nervous system or the rennin-angiotensin-aldosterone system.[28–30] Other factors such as calcium-phosphate production, oxidative stress, and abnormal apolipoprotein levels also were shown to promote renal dysfunction.[31,32] As such, these factors could also contribute to the pathogenesis of atherosclerosis. To evaluate the relationship between oxidative stress and LMCAD, we measured plasma levels of malondialdehyde-modified low-density lipoprotein (MDA-LDL) in approximately half of the subjects enrolled in this study (data not shown). No association was found, however, between the presence of LMCAD and MDA-LDL levels. Further investigation is needed to identify the specific factors that link CKD and LMCAD.

The present study evaluated the impact of renal dysfunction on MACCE in patients with or without LMCAD, who were treated with only medication or PCI or CABG. In patients with severe renal dysfunction, the risk of MACCE was 7–9-fold higher than for patients with mild renal dysfunction (regardless of their LMCAD status). In contrast, as shown in Table 3, patients with eGFR $<30\,ml \cdot min^{-1} \cdot 1.73\,m^{-2}$ and LMCAD had a 2-fold greater chance of suffering MACCE than patients with eGFR $<30\,ml \cdot min^{-1} \cdot 1.73\,m^{-2}$ and non-LMCAD. These results imply that the influence of renal dysfunction on cardiovascular events after revascularization is greater than the influence of LMCAD. Recent improvements in PCI or CABG have provided a safer and more feasible treatment for LMCAD.[13] Even if PCI and CABG effectively resolve the stenosis associated with left main coronary artery, the incidence of new lesions and other complications remains high in patients with severe renal dysfunction. Medications do not adequately protect against the development of new coronary lesions in patients with severe renal dysfunction. This may explain the comparable impact of renal dysfunction on MACCE regardless of LMCAD, but the follow-up in the present study was limited to 1 year. Longer follow-up is required to evaluate cardiovascular death. There are many theories to explain the association between renal dysfunction and increased risk of MACCE. For example, patients with chronic renal failure may not have symptoms typically associated with restenosis, which could result in severe silent ischemia. Suboptimal medical therapies (eg, under-use of beta-blockers, angiotensin-converting enzyme inhibitors, and statins) also worsen health outcomes for these patients. We also found that the proportion of patients under statins was smaller in the LMCAD group than in the non-LMCAD group. In addition, recent studies showed that lower eGFR is associated with lipid-rich composition in coronary plaque, using integrated backscatter intravascular ultrasound,[33] and with PCI-related myocardial injury. Thus, plaque vulnerability associated with lower eGFR explains the relationship between renal dysfunction and increased risk of MACCE.

Study Limitations

First, only approximately half of the enrolled patients were followed up. In addition, the follow-up period was short. Therefore, we cannot deny that those lost subjects and the short-follow up period may have affected the impact of renal function on outcomes and the comparison of outcomes between patients with and without LMCAD. Second, some patients with CKD were categorized on the basis of a single eGFR measurement. This eGFR value was derived from a single serum creatinine determination done on the day of the coronary angiogram. This creatinine value may have been influenced by medication or an acute clinical status. Third, we did not have data concerning the course of renal function in these patients, either before or after the angiogram. There is a common tendency to refrain from coronary angiography, which can decrease the eGFR. As such, we could not address the influence of these factors on outcomes. Fourth, we included a few patients with end-stage renal disease who required dialysis. The data for these patients may have affected the relationships between risk factors and health outcomes. Fifth, patients underwent PCI or medication only, instead of CABG, because of either the patient's or physician's preference or the high risk associated with CABG. We cannot deny the possibility that the selection of treatment could have affected the results.

Conclusions

CKD is independently associated with LMCAD in patients with stable angina pectoris. Furthermore, severe renal dysfunction significantly affected the incidence of MACCE after optimal initial treatment of patients with and without LMCAD. Therefore, meticulous attention is required with regard to renal dysfunction when treating patients with stable angina pectoris.

Acknowledgment

There is no conflict of interest.

References

1. Yusuf S, Zucker D, Peduzzi P, Fisher LD, Takaro T, Kennedy JW, et al. Effect of coronary artery bypass graft surgery on survival: Overview of 10-year results from randomised trials by the coronary artery bypass graft surgery trialists collaboration. *Lancet* 1994; **344:** 563–570.
2. Giannoglou GD, Antoniadis AP, Chatzizisis YS, Damvopoulou E, Parcharidis GE, Louridas GE. Prevalence of narrowing > or =50% of the left main coronary artery among 17,300 patients having coronary angiography. *Am J Cardiol* 2006; **98:** 1202–1205.
3. Pryor DB, Shaw L, Harrell FE Jr, Lee KL, Hlatky MA, Mark DB, et al. Estimating the likelihood of severe coronary artery disease. *Am J*

Med 1991; **90:** 553–562.
4. Taylor HA, Deumite NJ, Chaitman BR, Davis KB, Killip T, Rogers WJ. Asymptomatic left main coronary artery disease in the coronary artery surgery study (CASS) registry. *Circulation* 1989; **79:** 1171–1179.
5. Culleton BF, Larson MG, Wilson PW, Evans JC, Parfrey PS, Levy D. Cardiovascular disease and mortality in a community-based cohort with mild renal insufficiency. *Kidney Int* 1999; **56:** 2214–2219.
6. Kilickesmez KO, Abaci O, Okcun B, Kocas C, Baskurt M, Arat A, et al. Chronic kidney disease as a predictor of coronary lesion morphology. *Angiology* 2010; **61:** 344–349.
7. Yagi H, Kawai M, Komukai K, Ogawa T, Minai K, Nagoshi T, et al. Impact of chronic kidney disease on the severity of initially diagnosed coronary artery disease and the patient prognosis in the Japanese population. *Heart Vessels* 2011; **26:** 370–378.
8. Go AS, Chertow GM, Fan D, McCulloch CE, Hsu CY. Chronic kidney disease and the risks of death, cardiovascular events, and hospitalization. *N Engl J Med* 2004; **351:** 1296–1305.
9. Kinoshita T, Asai T, Murakami Y, Suzuki T, Kambara A, Matsubayashi K. Preoperative renal dysfunction and mortality after off-pump coronary artery bypass grafting in Japanese. *Circ J* 2010; **74:** 1866–1872.
10. Best PJ, Lennon R, Ting HH, Bell MR, Rihal CS, Holmes DR, et al. The impact of renal insufficiency on clinical outcomes in patients undergoing percutaneous coronary interventions. *J Am Coll Cardiol* 2002; **39:** 1113–1119.
11. Blackman DJ, Pinto R, Ross JR, Seidelin PH, Ing D, Jackevicius C, et al. Impact of renal insufficiency on outcome after contemporary percutaneous coronary intervention. *Am Heart J* 2006; **151:** 146–152.
12. Cooper WA, O'Brien SM, Thourani VH, Guyton RA, Bridges CR, Szczech LA, et al. Impact of renal dysfunction on outcomes of coronary artery bypass surgery: Results from the society of thoracic surgeons national adult cardiac database. *Circulation* 2006; **113:** 1063–1070.
13. Park SJ, Kim YH, Park DW, Yun SC, Ahn JM, Song HG, et al. Randomized trial of stents versus bypass surgery for left main coronary artery disease. *N Engl J Med* 2011; **364:** 1718–1727.
14. Pitt B, Mancini GB, Ellis SG, Rosman HS, Park JS, McGovern ME. Pravastatin limitation of atherosclerosis in the coronary arteries (PLAC I): Reduction in atherosclerosis progression and clinical events: PLAC I investigation. *J Am Coll Cardiol* 1995; **26:** 1133–1139.
15. Friedewald WT, Levy RI, Fredrickson DS. Estimation of the concentration of low-density lipoprotein cholesterol in plasma, without use of the preparative ultracentrifuge. *Clin Chem* 1972; **18:** 499–502.
16. Geistanger A, Arends S, Berding C, Hoshino T, Jeppsson JO, Little R, et al. Statistical methods for monitoring the relationship between the IFCC reference measurement procedure for hemoglobin A1c and the designated comparison methods in the United States, Japan, and Sweden. *Clin Chem* 2008; **54:** 1379–1385.
17. Ueeda M, Doumei T, Takaya Y, Shinohata R, Katayama Y, Ohnishi N, et al. Serum N-3 polyunsaturated fatty acid levels correlate with the extent of coronary plaques and calcifications in patients with acute myocardial infarction. *Circ J* 2008; **72:** 1836–1843.
18. Levey AS, Bosch JP, Lewis JB, Greene T, Rogers N, Roth D. A more accurate method to estimate glomerular filtration rate from serum creatinine: A new prediction equation: Modification of diet in renal disease study group. *Ann Intern Med* 1999; **130:** 461–470.
19. Matsuo S, Imai E, Horio M, Yasuda Y, Tomita K, Nitta K, et al. Revised equations for estimated gfr from serum creatinine in Japan. *Am J Kidney Dis* 2009; **53:** 982–992.
20. Atie J, Brugada P, Brugada J, Smeets JL, Cruz FE, Roukens MP, et al. Clinical presentation and prognosis of left main coronary artery disease in the 1980s. *Eur Heart J* 1991; **12:** 495–502.
21. Cohen MV, Gorlin R. Main left coronary artery disease: Clinical experience from 1964-1974. *Circulation* 1975; **52:** 275–285.
22. Bulkley BH, Roberts WC. Atherosclerotic narrowing of the left main coronary artery: A necropsy analysis of 152 patients with fatal coronary heart disease and varying degrees of left main narrowing. *Circulation* 1976; **53:** 823–828.
23. DeMots H, Bonchek LI, Rosch J, Anderson RP, Starr A, Rahimtoola SH. Left main coronary artery disease: Risks of angiography, importance of coexisting disease of other coronary arteries and effects of revascularization. *Am J Cardiol* 1975; **36:** 136–141.
24. Khaja F, Sharma SD, Easley RM Jr, Heinle RA, Goldstein S. Left main coronary artery lesions: Risks of catheterization; exercise testing and surgery. *Circulation* 1974; **50:** II136–II140.
25. Nemetz PN, Roger VL, Ransom JE, Bailey KR, Edwards WD, Leibson CL. Recent trends in the prevalence of coronary disease: A population-based autopsy study of nonnatural deaths. *Arch Intern Med* 2008; **168:** 264–270.
26. Kiyosue A, Hirata Y, Ando J, Fujita H, Morita T, Takahashi M, et al. Relationship between renal dysfunction and severity of coronary artery disease in Japanese patients. *Circ J* 2010; **74:** 786–791.
27. Yokoyama M, Origasa H, Matsuzaki M, Matsuzawa Y, Saito Y, Ishikawa Y, et al; Japan EPA lipid intervention study (JELIS) Investigators. Effects of eicosapentaenoic acid on major coronary events in hypercholesterolaemic patients (JELIS): A randomised open-label, blinded endpoint analysis. *Lancet* 2007; **369:** 1090–1098.
28. Schiffrin EL, Lipman ML, Mann JF. Chronic kidney disease: Effects on the cardiovascular system. *Circulation* 2007; **116:** 85–97.
29. Manabe I. Chronic inflammation links cardiovascular, metabolic and renal diseases. *Circ J* 2011; **75:** 2739–2748.
30. Iwanaga Y, Miyazaki S. Heart failure, chronic kidney disease, and biomarkers: An integrated viewpoint. *Circ J* 2010; **74:** 1274–1282.
31. Foley RN, Collins AJ, Ishani A, Kalra PA. Calcium-phosphate levels and cardiovascular disease in community-dwelling adults: The atherosclerosis risk in communities (ARIC) study. *Am Heart J* 2008; **156:** 556–563.
32. Muntner P, Hamm LL, Kusek JW, Chen J, Whelton PK, He J. The prevalence of nontraditional risk factors for coronary heart disease in patients with chronic kidney disease. *Ann Intern Med* 2004; **140:** 9–17.
33. Miyagi M, Ishii H, Murakami R, Isobe S, Hayashi M, Amano T, et al. Impact of renal function on coronary plaque composition. *Nephrol Dial Transplant* 2010; **25:** 175–181.

Supplementary Files

Supplementary File 1

Table S1. Patient Characteristics vs. Presence of LMCAD and Renal Function

Please find supplementary file(s);
http://dx.doi.org/10.1253/circj.CJ-11-1455

Outcomes of One-Lung Fontan Operation: A Retrospective Multicenter Study in Japan

Yasuhiro Fujii, MD, Shunji Sano, MD, Toshihide Asou, MD, Yutaka Imoto, MD, Yoshihiro Oshima, MD, Shiori Kawasaki, MD, Hidefumi Kishimoto, MD, Kisaburo Sakamoto, MD, Masanobu Maeda, MD, Masaaki Yamagishi, MD, and Kozo Matsuo, MD

Department of Cardiovascular Surgery, Okayama University Hospital, Okayama; Department of Cardiovascular Surgery, Kanagawa Children's Medical Center, Kanagawa; Department of Cardiovascular Surgery, Kyushu Kouseinenkin Hospital, Fukuoka; Department of Cardiovascular Surgery, Kobe Children's Hospital, Hyogo; Department of Cardiovascular Surgery, Juntendo University School of Medicine, Tokyo; Department of Cardiovascular Surgery, Osaka Medical Center and Research Institute for Maternal and Child Health, Osaka; Department of Cardiovascular Surgery, Mt. Fuji Shizuoka Children's Hospital, Shizuoka; Department of Cardiovascular Surgery, Aichi Children's Health and Medical Center, Aichi; Department of Pediatric Cardiovascular Surgery, Kyoto Prefectual University of Medicine, Kyoto; and Department of Cardiovascular Surgery, Chiba Cardiovascular Center, Chiba, Japan

Background. The Fontan operation for patients with one available lung is an extremely challenging situation. However, few reports are available on this procedure. The purpose of this study was to describe outcomes of one-lung Fontan operation.

Methods. A retrospective multicenter study was performed. Twelve of 1,142 patients whose data were recorded here underwent one-lung Fontan operation between September 1989 and October 2009. Preoperative, operative, and postoperative data were reviewed.

Results. Median age at operation was 3.5 years (range, 1.0 to 22.8), the preoperative mean pulmonary pressure was 11.5 ± 3.3 mm Hg (range, 7.0 to 18.0), the ventricular ejection fraction was 58% ± 13% (range, 39 to 76), and end-diastolic ventricular pressure was 7.5 ± 3.5 mm Hg (range, 1.0 to 12.0). The available lung was right in 9 patients and left in 3 patients. Eleven patients underwent a two-staged Fontan completion. Extracardiac conduit total cavopulmonary connection, intraatrial extracardiac conduit total cavopulmonary connection, and atriopulmonary connection were performed in 10 patients, 1 patient, and 1 patient, respectively. The estimated actuarial survival was 83% at 1year, 73% at 5 years, and 73% at 10 years. Impaired ventricular function was found to be a significant risk factor for mortality by univariate analysis (43.0% ± 9.5% versus 64.0% ± 9.5%, $p < 0.01$), but not by multivariate analysis.

Conclusions. One-lung Fontan operation can be performed with an acceptable midterm to long-term mortality rate in patients without impaired ventricular function. Thus, absence of one lung itself is not a contraindication to the Fontan operation.

(Ann Thorac Surg 2012;94:1275–80)

Since Fontan and Baudet first described their procedure for the correction of tricuspid atresia in 1971, its principles have been applied to all forms of functional single ventricle [1]. Having made several modifications, the total cavopulmonary connection (TCPC) that was first reported by de Leval and coworkers [2] became a standard method for the Fontan operation because of its better venous hemodynamics [3] and because it is less arrhythmogenic [4] than the others. In addition, several management strategies have been incorporated to achieve a low mortality rate: the adoption of universal risk factors that have resulted in better patient selection [5], a "staged" approach [6], fenestration [7], and modified ultrafiltration [8]. With these modifications, the indications for the Fontan operation have gradually extended. One of the most challenging situations is a patient with a single ventricle who has only one available lung. A one-lung Fontan operation seems possible if the patient's pulmonary arterial resistance is low. However, very few reports are available on this procedure because it is an extremely rare situation. Therefore, we conducted a retrospective multicenter study to describe the early to late outcomes for one-lung Fontan operation.

Patients and Methods

Study Subjects

The data were collected retrospectively by filling out questionnaires by doctors of each institute. Ten institutes in Japan participated in this study and reported a total of 1,142 Fontan operations performed from September 1989 to October 2009. Four institutions supplied 12 one-lung Fontan operations (1.1%) and six did not. Ethical Committee approval was obtained for each institution. The

Accepted for publication April 23, 2012.

Presented at the Forty-eighth Annual Meeting of The Society of Thoracic Surgeons, Fort Lauderdale, FL, Jan 28–Feb 1, 2012.

Address correspondence to Dr Fujii, Department of Cardiovascular Surgery, Okayama University Hospital, 2-5-1 Shikata-cho, Kita-ku, Okayama City, Okayama 700-8558, Japan; e-mail: yasuhiro-f@live.jp.

0003-4975/$36.00
http://dx.doi.org/10.1016/j.athoracsur.2012.04.080