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

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

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

Values are expressed as mean±SD.

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

Serial Changes of Echocardiographic Parameters Before and After DFT Testing

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

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

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

Changes of Central Arterial Pressure Before and After DFT Testing

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

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

Discussion

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

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

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

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

Values are expressed as mean±SD.

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

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

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

Effect of ICD Shock on Cardiac Function

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

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

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

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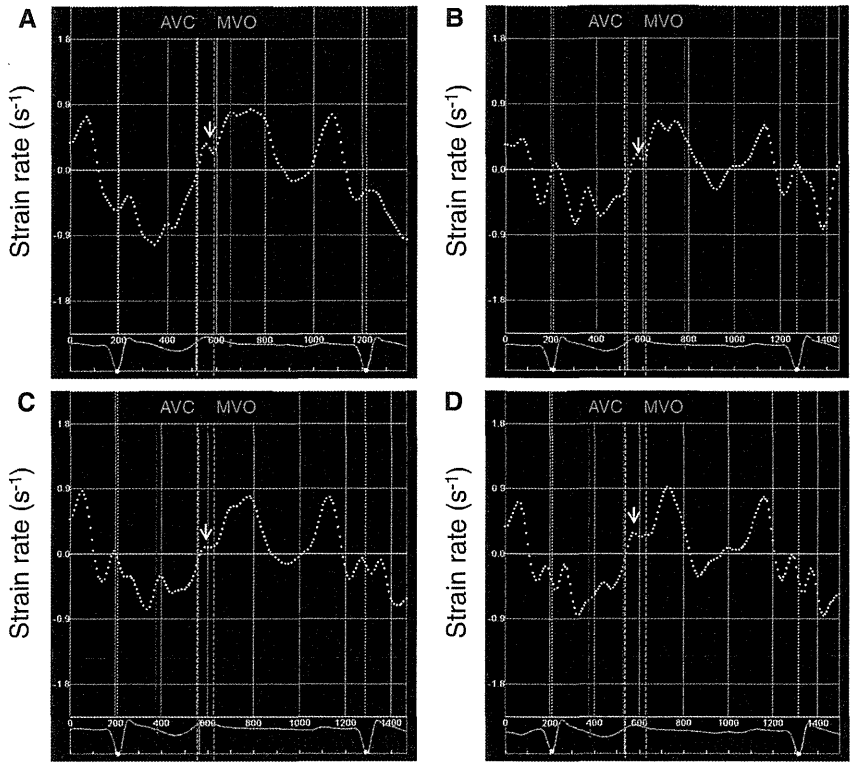

Figure 2. Serial changes of global strain rate during the isovolumetric relaxation period (SRIVR) before and after defibrillation threshold (DFT) testing in patients with preserved left ventricular ejection fraction (LVEF). A representative case of preserved LVEF. **A**, Before DFT testing, global SRIVR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

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

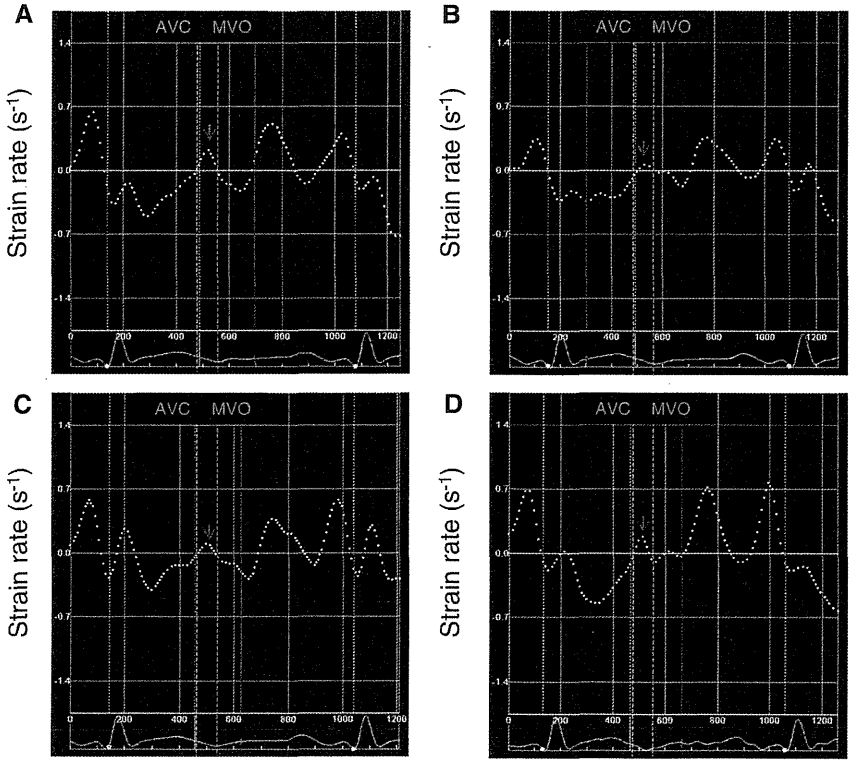

Figure 3. Serial changes of global strain rate during the isovolumetric relaxation period (SRIVR) before and after defibrillation threshold (DFT) testing in patients with reduced left ventricular ejection fraction (LVEF). A representative case of reduced LVEF. **A**, Before DFT testing, global SRIVR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

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

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

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

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

Implications of Echocardiographic Parameters

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

Study Limitations

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

Conclusions

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

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Disclosures

None.

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CLINICAL PERSPECTIVE

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

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Elevated serum adipocyte fatty acid-binding protein concentrations are independently associated with renal dysfunction in patients with stable angina pectoris

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Abstract

Background: Chronic kidney disease (CKD) is associated with cardiovascular events. Adipocyte fatty acid-binding protein (A-FABP) plays an important role in atherosclerosis. We investigated whether plasma A-FABP is involved in renal function in patients with stable angina pectoris.

Methods: A total of 221 patients with significant coronary artery stenosis were enrolled after coronary angiography. CKD was defined as an estimated glomerular filtration rate (eGFR) < 60 ml/min/1.73 m^2. The severity of coronary stenosis was assessed using a modified Gensini score and coronary angiography. Serum A-FABP levels were determined by enzyme-linked immunosorbent assay.

Results: Serum A-FABP levels were significantly correlated with both eGFR ($r = -0.41$, $p < 0.01$) and the severity of coronary artery stenosis ($r = 0.16$, $p = 0.02$), and these relationships remained significant after adjusting for confounding factors. The prevalence of CKD and multi-vessel disease was significantly higher among patients with serum A-FABP levels above the median value of 20.3 ng/ml than among patients with serum A-FABP levels below the median value (57% vs. 27%, $p < 0.01$ and 64% vs. 48%, $p = 0.02$, respectively). Multivariate analysis revealed that the presence of three-vessel disease in comparison with single-vessel disease was independently associated with the higher A-FABP (per doubling) (odds ratio; 2.26, 95% confidential interval; 1.28-3.98, $p < 0.01$) and tended to be associated with the lower eGFR ($p = 0.06$).

Conclusion: Serum A-FABP may have a significant role in the interplay between renal dysfunction and coronary atherosclerosis.

Keywords: Adipocyte, Fatty acid-binding protein, Renal dysfunction, Coronary artery disease

Background

Obesity and obesity-associated disorders, including insulin resistance, type 2 diabetes, dyslipidemia, and hypertension, are rapidly increasing in developed countries. In association with weight gain, the hyperplasia and hypertrophy of adipocytes influence the secretion pattern of adipocyte-derived proteins, adipokines, by adipose tissue. Recent evidence shows that adipokines contribute to the increased metabolic and cardiovascular risk among obese patients [1]. Among those adipokines, adipocyte fatty acid-binding protein (A-FABP), also known as aP2 or FABP4, is small intracellular lipid-binding protein which is expressed abundantly in adipocytes and activated macrophages [2]. Now, there are nine types of FABPs, showing tissue-specific expression patterns, and several members of the FABP family have been shown to have important roles in regulating metabolism and have links to the development of insulin resistance and

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the metabolic syndrome [3]. A-FABP was reported to play an essential regulatory role in energy metabolism and inflammation [4], and found not only in tissue, but also in blood stream [5].

The pathophysiological role of A-FABP has been investigated in murine experimental models and clinical studies. In mice, A-FABP deficiency ameliorates the development of insulin resistance in diet-induced obesity [2], type 2 diabetes [6], and atherosclerosis in models of hypercholesterolemia [7]. Clinically, A-FABP is detected in human serum [5]. Higher serum A-FABP levels are used to predict and diagnose obesity-related metabolic syndrome and type 2 diabetes [8,9]. Previous studies also showed that serum A-FABP levels are associated with carotid intima-media thickness [10], coronary artery disease [11], the number of stenotic coronary arteries [12], and coronary plaque volume, as determined by intravascular ultrasound [13]. Furthermore, the involvement of A-FABP in atherosclerosis is supported by a genetic study in humans. Carriers of the T87C polymorphism have lower serum triglyceride levels, demonstrating a reduced cardiovascular risk [14]. These findings demonstrate that A-FABP may play a critical role in the development of metabolic syndrome, type 2 diabetes, and cardiovascular disease.

Although the association between A-FABP and several metabolic parameters has been studied in detail, little is known about the relationship between this adipokine and renal function. One study showed that serum A-FABP concentrations in patients with chronic hemodialysis are higher than those in control patients without hemodialysis [15], although serum A-FABP levels in patients with a mild to moderate decrease in glomerular filtration rate (GFR) remain untested. Furthermore, the association between serum A-FABP, eGFR, and severity of coronary artery disease has not been evaluated. Therefore, we determined serum A-FABP levels in 221 patients with stable angina pectoris and assessed the correlation between serum A-FABP levels and biochemical measures of renal function, as well as the severity of coronary artery disease.

Methods

Study group

This study included 221 patients with stable angina pectoris who underwent coronary angiography between April 2008 and September 2009 at Kagawa Prefectural Central Hospital, Japan. Patients who had 75% or greater organic stenosis of at least one major coronary artery or who had previously undergone percutaneous transluminal coronary angioplasty were included. Patients with chronic hemodialysis, acute coronary syndrome, recent (within 4 weeks) myocardial infarction, or malignancies were excluded. The study protocol complied with the Declaration of Helsinki and was approved by the Ethics Committees of the institute. Written informed consent was obtained from all patients before study enrollment.

Clinical and biochemical assessments

Blood samples were taken after overnight fasting. The serum was separated and stored at -80°C, and serum levels of A-FABP (Biovendor Laboratory Medicine, Modrice, Czech Republic) and high-sensitivity C-reactive protein (hs-CRP; R&D Systems, Minneapolis, MN, USA) were measured by enzyme-linked immunosorbent assay [13]. The performance characteristics of these assays were < 7% and < 8% intra-assay coefficient of variation (CV), and < 5% and < 7% inter-assay CV for A-FABP and hs-CRP, respectively.

Risk factors were defined as follows. Diabetes was confirmed using the criteria of the American Diabetes Association [16] or by a history of treatment for diabetes mellitus. Dyslipidemia was defined as one or more of the following criteria: (1) serum triglyceride ≥ 150 mg/dl; (2) high-density lipoprotein (HDL)-cholesterol < 40 mg/dl; (3) low-density lipoprotein (LDL)-cholesterol ≥ 140 mg/dl; and (4) current use of lipid-lowering medication. Hypertension was defined as a sitting blood pressure ≥ 140/90 mmHg or current use of antihypertensive medication. Smoking status was determined and classified as current smoker or not. The estimated GFR (eGFR) was calculated using the equation put forth by the Modification of Diet in Renal Disease (MDRD) Study Group [17], with coefficients modified for Japanese patients [18]: eGFR (ml/min/1.73 m^2) = 194 × (serum creatinine)$^{-1.094}$ × (age)$^{-0.287}$ (x0.739 if female). The distribution of the eGFR was divided into three categories: less than 60 (moderately decreased eGFR, n = 93), 60-89 (mildly decreased eGFR, n = 106) and at least 90 ml/min/1.73 m^2 (normal eGFR, n = 22). Patients with end stage renal disease were not included. Chronic kidney disease (CKD) was defined as eGFR < 60 ml/min/1.73 m^2.

Coronary angiography

Coronary angiography was performed according to standard methods. After intracoronary injection of isosorbide dinitrate, angiograms were obtained in two or more views. The coronary angiogram was scored by two independent investigators. The stenosis score is a modified Gensini score [19]. Briefly, the most severe stenosis in each of eight segments was graded according to severity, from 1 to 4. The scores in each of the eight segments were added to provide a total stenosis score out of a maximum of 32.

Statistical analysis

Continuous variables are presented as mean ± standard deviation (SD) or median (interquartile range [(IQR]) values, and differences between groups were analyzed using an unpaired Student's *t* test. Data that were not normally distributed, as determined using the Kolmogorov-Smirnov test, were logarithmically transformed before linear regression analysis. Categorical variables are presented as frequency counts and corresponding percentages, and intergroup comparisons were analyzed using the chi-square test. Associations between serum A-FABP and other parameters were first analyzed by simple linear regression analysis and then by multivariate logistic regression analysis. To assess the association between serum A-FABP level and the presence of CKD or three-vessel coronary artery disease, logistic regression analyses were performed. In those analyses, factors that were associated with the dependent variable at $p < 0.05$ in the univariate analysis were entered into the multivariate model. In multivariate model, diabetes was selected as a covariate because fasting glucose levels, hemoglobinA1c, the homeostasis model assessment ratio are confounding factors of diabetes. Statistical significance was defined as $p < 0.05$. Statistical analyses were performed using SPSS 16.0 for Windows (SPSS Inc., Chicago, IL, USA).

Results

Patient characteristics

The clinical characteristics of the study population are shown in Table 1. Patients with eGFR levels < 60, 60-89, or > 90 ml/min/1.73 m^2 differed in age, the presence of hypertension, smoking status, serum triglycerides levels, uric acid levels, fasting glucose levels, hemoglobinA1c, the homeostasis model assessment ratio (HOMA-R), and serum A-FABP levels but not in the number of diseased vessels or the stenosis score. The eGFR value was significantly lower among patients with hypertension than among patients without hypertension (mean ± SD, 66.3 ± 18.1 ml/min/1.73 m^2 vs. 73.1 ± 18.6 ml/min/1.73 m^2, $p < 0.01$ by Student's *t* test). The eGFR value was significantly higher among smokers than among non-smokers (76.1 ± 17.3 ml/min/1.73 m^2 vs. 63.9 ± 18.5 ml/min/1.73 m^2, $p < 0.01$). The eGFR value did not vary by the presence or absence of diabetes mellitus or dyslipidemia, gender, or the use of specific medications (data not shown). The stenosis score was significantly higher among patients with diabetes mellitus than among patients without diabetes mellitus (1.9 ± 0.8 vs. 1.6 ± 0.7, $p < 0.01$). The stenosis score did not vary by the presence or absence of hypertension or dyslipidemia, smoking status, gender, or the use of specific medications (data not shown). The prevalence of CKD and multi-vessel disease based on the median value of serum A-FABP (20.7 ng/ml) were shown in Figures 1A and 1B. The prevalence of CKD and multi-coronary vessel disease was significantly higher among patients with serum A-FABP levels over the median value than among patients with serum A-FABP levels less than the median value (57% vs. 27%, $p < 0.01$ and 64% vs. 48%, $p = 0.02$, respectively).

Table 1 Patient characteristics in this study

		eGFR (ml/min/1.73 m^2)			
	ALL (n = 221)	< 60 (n = 93)	60-89 (n = 106)	≥ 90 (n = 22)	p
Age (years)	71 ± 10	76 ± 8	68 ± 10	62 ± 11	< 0.01
Male, n (%)	185(84)	74(80)	92(87)	19(86)	0.36
Body mass index (kg/m^2)	24.7 ± 3.6	24.5 ± 3.7	25.0 ± 3.4	24.0 ± 4.5	0.29
Hypertension, n (%)	157(71)	77(83)	77(73)	12(55)	0.02
Dyslipidemia, n (%)	183(83)	75(81)	89(84)	19(86)	0.72
Diabetes Mellitus, n (%)	96(43)	31(33)	53(50)	12(54)	0.03
Smoking (Yes)	28(13)	5(5)	18(16)	5(23)	0.02
LDL-Cholesterol (mg/dl)	102 ± 28	100 ± 28	103 ± 29	10.4 ± 26	0.77
HDL-Cholesterol (mg/dl)	43 ± 12	42 ± 11	44 ± 12	44 ± 11	0.59
Triglycerides (mg/dl)	163(79)	155 (107)	169(61)	167(68)	< 0.01
Uric acid (mg/dl)	5.8 ± 1.6	6.4 ± 1.6	5.5 ± 1.4	4.9 ± 1.6	< 0.01
Fasting blood glucose (mg/dl)	100(25)	96(18)	102(34)	104(28)	< 0.01
HOMA-R	1.7(1.5)	1.7(1.3)	1.8(1.7)	1.3(1.1)	< 0.01
HemoglobinA1c (%)	5.6(1.2)	5.4(0.8)	5.7(1.2)	5.9(1.0)	0.04
hs-CRP(mg/l)	0.97 (2.35)	1.25 (3.27)	0.82 (1.79)	1.59 (2.72)	0.10
Serum A-FABP (ng/ml)	20.3 (13.6)	26.9 (19.5)	19.6 (11.1)	16.1(4.7)	< 0.01
Number of diseased vessels	1.8 ± 0.8	1.9 ± 0.8	1.7 ± 0.8	1.5 ± 0.7	0.12
Stenosis score	9.9 ± 4.9	9.3 ± 4.5	9.5 ± 5.8	10.2 ± 5.1	0.71
Medications	28(13)	5(5)	18(16)	5(23)	0.02
ACEI/ARB, n (%)	119(54)	39(43)	66(62)	14(64)	0.18
CCBs, n (%)	120(54)	48(52)	57(38)	15(68)	0.39
β-blockers, n (%)	73(33)	27(29)	40(38)	6(27)	0.36
Statins, n (%)	126(57)	49(52)	63(59)	14(63)	0.50

Data are presented as the mean ± SD, median (IQR), or frequency counts (percentages), as appropriate. LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; FBS, fasting blood glucose; HOMA-R, homeostasis model assessment ratio; hs-CRP, high-sensitivity C-reactive protein; eGFR, estimated glomerular filtration rate; A-FABP, adipocyte fatty acid-binding protein: ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; CCBs, calcium channel blockers

Serum A-FABP levels and other biochemical parameters

Serum A-FABP levels were significantly higher among females than among males (median (IQR), 30.9 (26.7)

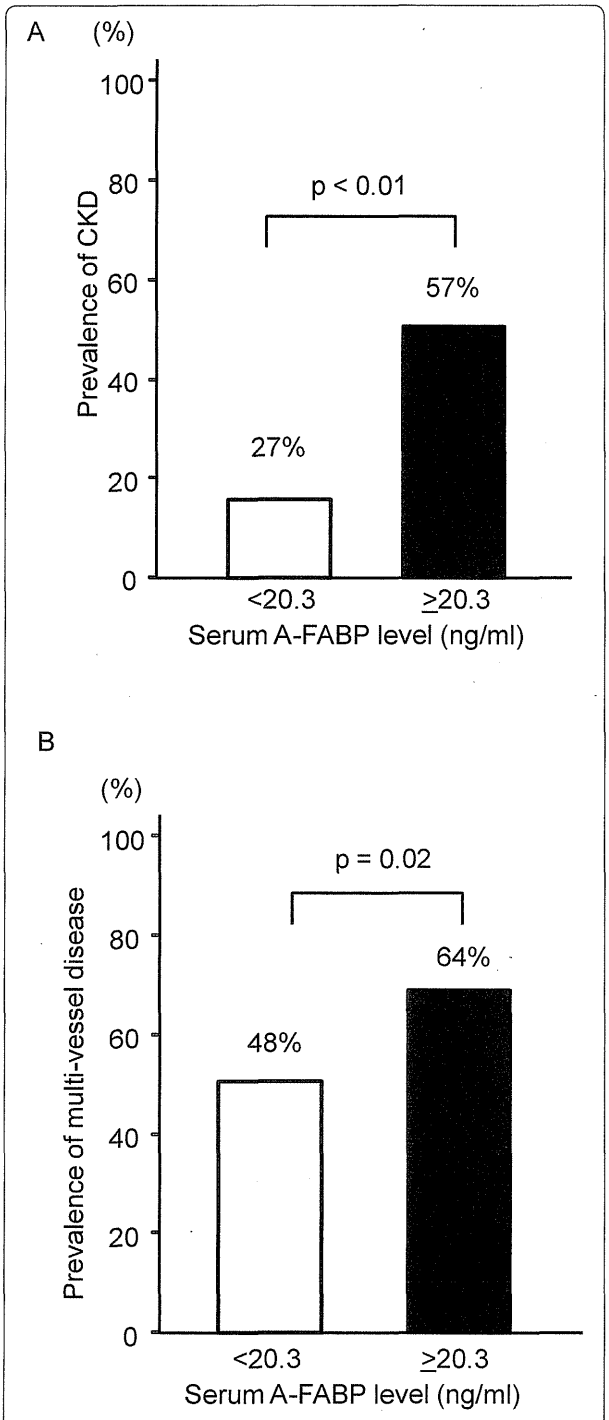

Figure 1 Prevalence of CKD (A) and multi-vessel disease (B) among patients grouped according to the median value of serum A-FABP (20.3 ng/ml).

ng/ml vs. 19.79(11.5) ng/ml, p < 0.01). Serum A-FABP levels were also significantly higher in patients with hypertension than those without hypertension (21.4 (14.9) ng/ml vs. 18.5(13.3) ng/ml, p = 0.02). Serum A-FABP levels did not vary by the presence or absence of diabetes mellitus, dyslipidemia, smoking status, or the use of specific medications (data not shown). As shown in Table 2 and Figure 2, serum A-FABP levels correlated significantly with gender, eGFR levels (Figure 2A), body mass index, hs-CRP levels, and stenosis scores (Figure 2B). Multiple linear regression analysis revealed that the serum A-FABP level was independently associated with the eGFR value and the stenosis score along with gender or body mass index. Next, the associations between CKD and other biochemical parameters were assessed (Table 3). Multiple logistic regression analysis revealed that the serum-A-FABP level (per doubling) was independently associated with CKD, with an odds ratio of 3.7 (95% confidential interval; 2.14-6.461, p < 0.01). Finally, the associations of the severity coronary artery disease with the levels of eGFR and serum A-FABP were analyzed by logistic regression analysis (Table 4). Multivariate analysis revealed that the presence of three-vessel disease in comparison with single-vessel disease was independently associated with the higher A-FABP level(per doubling) (odds ratio; 2.26, 95% confidential interval; 1.28-3.98, p < 0.01) and tended to be involved in the lower eGFR value (per ml/min/1.73 m^2)(odds ratio; 0.98, 95% confidential interval; 0.96-1.00, p < 0.06).

Discussion

We demonstrated that the serum A-FABP level was independently correlated with the eGFR value in patients with stable angina pectoris without hemodialysis. Serum A-FABP may be a novel marker of renal function as well as the severity of coronary artery

Table 2 Relationship between serum A-FABP and other parameters

	Univariate		Multivariate	
	r	p	β	p
Age	0.09	0.14		
Gender (male = 1)	-0.33	< 0.01	-0.31	< 0.01
Body mass index	0.35	< 0.01	0.35	< 0.01
Uric acid	0.12	0.08		
LDL-cholesterol	0.06	0.37		
HDL-cholesterol	-0.12	0.09		
Triglycerides*	-0.05	0.50		
HbA1c*	0.06	0.46		
HOMA-R*	0.11	0.10		
hs-CRP*	0.15	0.03	0.05	0.32
eGFR	-0.41	< 0.01	-0.40	< 0.01
Stenosis score	0.16	0.02	0.15	< 0.01

Values indicated with * were included in the model after log-transformation.
In the model, $R^2 = 0.42$

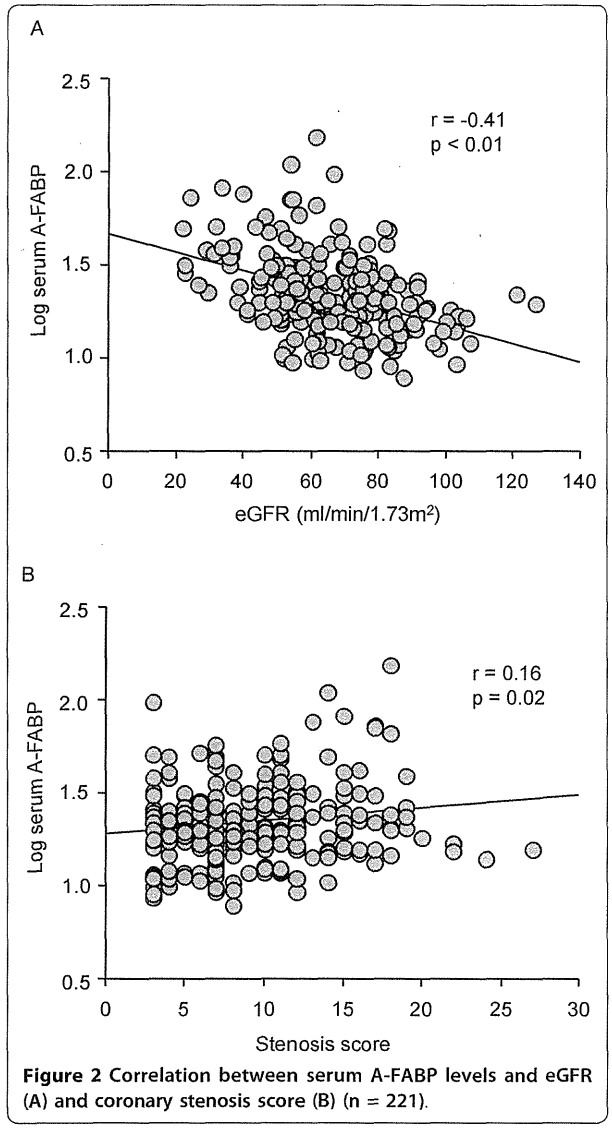

Figure 2 Correlation between serum A-FABP levels and eGFR (A) and coronary stenosis score (B) (n = 221).

disease in patients with a mild to moderate decrease in eGFR. Our findings suggest that circulating A-FABP may have an important role in the interplay between renal dysfunction and the development of coronary atherosclerosis.

The mechanism underlying the relationship between A-FABP and eGFR has not been fully clarified. Sommer et al. reported that serum A-FABP levels are more than 10-fold higher among patients with chronic hemodialysis than among controls [15]. In addition to A-FABP, circulating levels of adiponectin, leptin, and retinol-binding protein 4 have been reported to be higher among patients with chronic hemodialysis than among controls [20-22]. These results suggest that renal elimination plays an important role in determining the serum concentration of various adipocyte-derived proteins, including adiponectin, leptin, retinol-binding protein 4, and A-FABP, although the causal relationship between the elevated circulating A-FABP and renal dysfunction remains unclear. More mechanistic studies involving animal experiments are necessary to prove the concept that A-FABP is not only secreted from adipose tissue but also is cleared by the kidneys. Furthermore, markers of renal function should be included in future studies as potential confounders when examining the physiology and regulation of A-FABP in humans.

The finding that serum A-FABP was independently associated with the severity of coronary atherosclerosis is in agreement with our previous findings [11]. In human, recent study showed that circulating A-FABP levels were shown to be associated with vascular inflammation, as measured using (18)F-fluorodeoxyglucose positron emission tomography [23]. Peeters et al. reported that serum A-FABP levels and A-FABP concentrations in human carotid tissue were associated with the vulnerability of carotid plaques [24]. On the other hand, experimental studies showed that A-FABP plays a critical role in the development of atherosclerosis by coordinating the cholesterol-trafficking and inflammatory activity of macrophages [25]. A-FABP deficiency reduces foam cell formation in response to oxidized LDL and increases the cholesterol efflux pathway [25]. A-FABP-deficient mice also show a significant decrease in vascular atherosclerosis in the absence of differences in serum lipid levels or insulin sensitivity in a model of hyperlipidemia, and this effect is due OR has been attributed to the effects of A-FABP on macrophages [7]. In addition, A-FABP can activate several key inflammatory pathways. In A-FABP-deficient macrophages, the activity of the peroxisome proliferator-activated receptor γ and the liver X receptor α is enhanced, leading to suppressed transcription of several inflammatory genes [26,27]. In addition, the NF-κB pathway is impaired, resulting in suppression of inflammatory function [25].

The physiological significance of increased serum A-FABP in renal failure remains to be elucidated. CKD is strongly associated with the development of atherosclerotic lesions and mortality from cardiovascular disease [28]. Because A-FABP has been reported to induce dyslipidemia and atherosclerosis in animal models [7], A-FABP may contribute to the significantly increased cardiovascular mortality among patients with CKD. Recently, Furuhashi et al. reported that the circulating A-FABP level is a predictor of cardiovascular events in end-stage renal disease [29]. Peeters et al. also reported that the serum A-FABP levels in human carotid athermanous plaques were associated with adverse cardiovascular events [30]. Regarding a circulating FABP, recent studies showed heart -FABP may represent a marker for

Table 3 Relationship between CKD and other parameters

	Crude		Adjusted	
Factors	OR (95%CI)	p	OR (95%CI)	p
Age (per year)	1.11(1.08-1.16)	< 0.01	1.11(1.07-1.17)	< 0.01
Male	0.59(0.29-1.22)	0.16		
Smoking (yes)	0.28(0.10-0.76)	0.01	0.44(0.13-1.49)	0.18
Hypertension (yes)	2.19(1.13-4.29)	0.03	1.25(0.54-2.914)	0.56
Diabetes (yes)	0.53(0.31-0.93)	0.03	0.62(0.29-1.33)	0.22
Fasting blood glucose (per doubling)	0.16 (0.05-0.46)	< 0.01		
HOMA-R* (per doubling)	0.99(0.78-1.27)	0.97		
HbA1c (per doubling)	0.192(0.05-0.74)	0.02		
Dyslipidemia	0.77(0.38-1.56)	0.47		
HDL (per mg/dl)	0.99(0.97-1.01)	0.31		
LDL (per mg/dl)	0.99(0.98-1.00)	0.49		
Triglycerides (per doubling)	0.44(0.27-0..71)	< 0.01	0.49(0.26-0.93)	0.03
Uric acid (per mg/dl)	1.59(1.29-1.94)	< 0.01	1.70 (1.02-2.22)	< 0.01
A-FABP (per doubling)	3.03(1.94-4.72)	< 0.01	3.14(1.89-5.31)	0.01

In the model, $R^2 = 0.34$

early atherosclerosis [31]. Thus, the roles of FABPs as a predictor of cardiovascular events are promising. Taken together with our findings, the elevated serum A-FABP in patients with CKD may be involved in plaque vulnerability in atherosclerotic lesions and may predict a future cardiovascular event.

The role of circulating A-FABP as an atherogenic factor remains unknown. A recent study reported that A-FABP directly and acutely depresses the contraction of cardiomyocytes by decreasing intracellular Ca^{2+} levels [32], suggesting that a direct bioactive role for A-FABP may exist in cells. It is well established that A-FABP is expressed by adipocytes, which may be major contributors to circulating A-FABP levels. Therefore, A-FABP secreted from adipose tissue may contribute to the development of atherosclerosis. Future studies should address whether circulating A-FABP induces atherosclerosis by activating macrophages and vascular cells.

Table 4 Relationship between severe coronary artery disease and other parameters

	Crude		Adjusted	
Factors	OR (95%CI)	p	OR (95%CI)	p
Age (per year)	1.01(0.98-1.04)	0.55		
Male	1.39(0.51-3.79)	0.51		
Smoking (yes)	1.16(0.39-3.40)	0.79		
Hypertension (yes)	1.63(0.69-3.84)	0.26		
Diabetes (yes)	2.63(1.29-5.36)	< 0.01	3.20(1.43-7.17)	< 0.01
FBS (per doubling)	3.6(1.26-10.53)	0.02		
HOMA-R (per doubling)	1.31(0.95-1.80)	0.10		
HbA1c (per doubling)	5.95(1.21-29.14)	0.03		
Dyslipidemia	1.72(0.64-4.66)	0.28		
Triglycerides (per doubling)	1.11(0.63-1.95)	0.72		
HDL (per mg/dl)	0.97(0.94-1.00)	0.05		
LDL (per mg/dl)	0.99(0.98-1.00)	0.16		
Uric acid (per mg/dl)	1.02(0.82-1.27)	0.87		
eGFR (per ml/min/1.73m2)	0.97(0.95-0.99)	< 0.01	0.98(0.95-1.00)	0.06
A-FABP (per doubling)	2.97(1.77-4.98)	< 0.01	2.26(1.28-3.98)	0.01

In the model, $R^2 = 0.16$

Limitations

This study has several limitations that should be considered when interpreting the results. First, the sample size was not large. Second, our study was cross-sectional, which does not allow us to determine if a causal relationship exists between A-FABP and renal dysfunction or between A-FABP and the development of coronary artery disease. Prospective population-based studies are needed to address whether serum A-FABP is a risk factor for CKD or coronary artery disease. Finally, we enrolled patients who were admitted to the hospital for coronary angiography in order to obtain more accurate data on coronary stenosis. Most of our patients had established risk factors for coronary artery disease, and so, the generalizability of our findings to other patient populations is unclear.

Conclusions

We demonstrated that the serum A-FABP level was independently associated with CKD. Serum A-FABP may be a marker of renal dysfunction and may be associated with the severity of coronary artery disease in patients with a mild to moderate decrease in eGFR.

Thus, circulating A-FABP may have an important role in the interplay between renal dysfunction and the development of coronary atherosclerosis. Further studies with larger cohorts derived from the general population are necessary to evaluate whether circulating A-FABP levels can be used to predict the risk of renal dysfunction and the development of coronary artery disease.

Abbreviations

A-FABP: Adipocyte fatty acid-binding protein; ACEI: Angiotensin-converting enzyme inhibitor; ARB: Angiotensin II receptor blocker; CCBs: Calcium channel blockers.; CKD: Chronic kidney disease; CV: intra-assay coefficient of variation; eGFR: estimated glomerular filtration rate; FBS: fasting blood glucose; HDL-C: high-density lipoprotein cholesterol; HOMA-R: homeostasis model assessment ratio; hs-CRP: high-sensitivity C-reactive protein; IQR: interquartile range; LDL-C: low-density lipoprotein cholesterol.

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Authors' contributions

MI, TM, MD, KT, MK, KN, SK and RN conceived the study, participated in study design and coordination, and assisted with the preparation of this manuscript. SU conducted the immunoassays. SH, SK, KN, and HI assisted with the preparation or critical review of this manuscript. All authors read and approved the submitted manuscript.

Competing interests

The authors declare that they have no competing interests.

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Transcatheter Closure of Atrial Septal Defect in a Geriatric Population

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Objectives: To evaluate the efficacy and safety of transcatheter closure of atrial septal defects (ASD) in patients over 70 years of age. **Background:** Transcatheter closure of ASD is an established procedure in children and young adults, but the benefits of this procedure in geriatric patients are still unclear. **Methods:** Between 2005 and 2010, 430 patients with ASD underwent transcatheter closure in our hospital. Among those patients, 30 consecutive patients older than 70 years of age were prospectively evaluated. **Results:** Mean age at procedure was 75.8 ± 3.8 years (range: 70–85 years). Mean Qp/Qs was 2.4 ± 0.7 and mean ASD diameter was 20.3 ± 6.4 mm. Nine patients (30%) had a history of hospitalization due to heart failure. ASD closure was successfully performed in 28 patients (93%) without significant complications. During the follow-up period (mean period of 19.1 ± 11.3 months), New York Heart Association (NYHA) functional class was significantly improved in 20 patients (74%). Significant improvements of plasma BNP level, resting heart rate, and systolic pulmonary artery pressure were also observed. Improvement of tricuspid regurgitation was observed in 11 of 17 patients with moderate or severe regurgitation during the follow-up period. Conversely, worsening of mitral regurgitation was observed in 10 of the 27 patients. **Conclusion:** Transcatheter closure of ASD in geriatric patients can be performed safely. This procedure contributes to significant improvement of symptoms and positive cardiac remodeling. Long-term follow-up is mandatory, especially for patients with mitral regurgitation. © 2012 Wiley Periodicals, Inc.

Key words: atrial septal defect; transcatheter closure; elderly

INTRODUCTION

The clinical features of atrial septal defect (ASD) in the elderly are significantly different from those in children and young adults. Elderly patients with ASD frequently present with hemodynamic abnormalities such as pulmonary hypertension, atrial arrhythmias, and valvular regurgitation, which cause congestive heart failure. Moreover, various comorbidities, such as hypertension, chronic obstructive pulmonary disease, coronary artery disease and left ventricular diastolic dysfunction often complicate the clinical features in this population. Left ventricular diastolic dysfunction, which is also seen as part of normal aging and frequently occurs in elderly individuals with hypertension or increased arterial stiffness [1,2], may cause acute

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Conflict of interest: Nothing to report.

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congestive heart failure after ASD closure [3]. Therefore, ASD closure alone is sometimes insufficient for improvement of symptoms and heart failure in elderly ASD patients. Transcatheter ASD closure is a well-established alternative to surgical closure in children and young adults [4], and it has been shown to improve symptoms and hemodynamic abnormalities [5–11]. Recently, several studies have demonstrated that symptomatic reduction and cardiac remodeling can occur even in patients older than 60 years of age [12–15]. However, the benefits of transcatheter ASD closure in geriatric patients are still uncertain. In the present study, we focused on patients older than 70 years of age and assessed the clinical background of ASD and the feasibility of transcatheter ASD closure in this geriatric population.

METHODS

Study Population

From 2005 to 2010, transcatheter closure of ASD was attempted in 420 patients in our hospital. Of those patients, 30 patients who were older than 70 years were retrospectively assessed.

Indications for ASD closure were a significant left-to-right shunt, pulmonary and systemic blood flow ratio >1.5, volume overload of the right ventricle, and/or clinical symptoms of dyspnea, decompensation, or paradoxical embolism. Exclusion criteria included maximum defect diameter >38 mm evaluated by transesophageal echocardiography (TEE), other concomitant congenital heart disease, and pulmonary hypertension with pulmonary vascular resistance >8 Wood units.

Transcatheter ASD Closure

Transcatheter ASD closure was conducted under general anesthesia with the guidance of fluoroscopy and TEE. Amplatzer® Septal Occluder (St. Jude Medical; St. Paul, MN) was used for all closures, and the procedure was performed as previously described [16]. Because the largest device size available in Japan was 38 mm, the defect diameter >38 mm was included in exclusion criteria. For patients who had a history of heart failure and were considered to be hemodynamically highrisk, we placed a Swan-Ganz catheter into pulmonary artery from the other femoral vein and monitored pulmonary artery wedge pressure (PCWP) during subsequent procedure. And if mean PCWP increased >5 mm Hg from the baseline value during balloon occlusion of the defect (test balloon occlusion), the procedure was abandoned. All patients received 100 mg/day aspirin at least 48 hr before the procedure. After the procedure, the same dose of aspirin was continued for 6 months and clopidogrel was also given at 50 mg/day for 1 month in addition to aspirin. Other medications such as diuretics, warfarin, and antihypertension and antiarrhythmia drugs were continued at the same doses after the procedure. The procedure was explained and written informed consent was obtained from all patients.

Clinical Assessment and Follow-Up

All patients were assessed for medical history and comorbidity before ASD closure. Diagnostic cardiac catheter examinations including coronary angiography were performed before ASD closure. Pulmonary to systemic flow ratio (Qp/Qs) and pulmonary artery pressure were evaluated with cardiac catheterization. Mean pulmonary artery pressure =25 mm Hg at heart catheterization was considered as pulmonary artery hypertension. New York Heart Association (NYHA) functional class was assessed before and after ASD closure. Measurement of plasma B-type natriuretic peptide (BNP) and transthoracic echocardiographic evaluation were performed before ASD closure, 1 day and 6 to 12 months after the procedure, and annually thereafter. Both right ventricular end-diastolic dimension (RVEDD) and left ventricular end-diastolic dimension (LVEDD) were measured from two-dimensional parasternal long-axis views. Systolic pulmonary artery pressure was estimated by tricuspid regurgitation (TR) velocity and dimensions of the inferior vena cava [17]. The degrees of TR and mitral regurgitation (MR) were quantified by color Doppler imaging [18]. Early diastolic mitral valve flow velocity (E) and early diastolic septal mitral annular velocity (e') were obtained by pulse wave Doppler and Tissue Doppler imaging, respectively. The value of e' is an index of left ventricular diastolic function [19], and the ratio of E derived by e' (E/e') correlates closely with left ventricular filling pressure [20]. Residual shunt was evaluated by color Doppler signal width: <2 mm was considered as small, 2–4 mm as moderate and >4 mm as severe [21]. In patients with atrial fibrillation, echocardiographic data were derived from corresponding mean values of 10 continuous cardiac cycles.

Statistical Analysis

Statistical analysis was performed using SPSS (SPSS, Chicago, IL). Data are expressed as mean values ± SD. As appropriate, Student's t-test or Wilcoxon signed-rank test was performed to test for statistical differences between variables. Pearson's correlation coefficient was used to analyze relations between variables and NYHA functional class at the latest follow-up. The significant data obtained from univariate analysis were applied to multivariate linear regression analysis to

TABLE I. Patients Characteristics

Total patients	30
Gender, F/M	20/10
Age, (range), years	75.8 ± 3.8 (70–85)
BSA, m^2	1.5 ± 0.2
Hypertension	12 (40%)
Stroke	4 (13%)
CAD	2 (7%)
COPD	5 (17%)
Atrial fibrillation	16 (53%)
Paroxysmal	3 (10%)
Permanent	13 (43%)
RBBB	22 (74%)
Systolic PAP*, mm Hg	35.6 ± 11.8
PAH	16 (53%)
E′, cm/s	7.1 ± 1.9
E/E′	11.0 ± 3.9
Diuretic use	17 (57%)
Hospitalization for HF	9 (30%)
NYHA functional class, I/II/III	5/17/8
Qp/Qs*	2.4 ± 0.7
ASD diameter, mm	20.3 ± 6.4
Rim type	
Sufficient rim, *n* (%)	8 (27%)
Aortic rim deficient, *n* (%)	19 (63%)
Aortic and anterosuperior rim deficient, *n* (%)	1 (3%)
IVC rim deficient, *n* (%)	2 (7%)

BSA, body surface area; CAD, coronary artery disease; COPD, chronic obstructive pulmonary disease; RBBB, right bundle branch block; PAP, pulmonary artery pressure; PAH, pulmonary artery hypertension; E, early diastolic mitral valve flow velocity; *E′*, early diastolic mitral annular velocity; HF, heart failure; NYHA, New York Heart Association; Qp, pulmonary flow; Qs, systemic flow; IVC, inferior vena cava.

assess factors independently associated with NYHA functional class at the latest follow-up. A value of $P < 0.05$ was considered to be statistically significant.

RESULTS

Baseline Characteristics

Patient characteristics, clinical, hemodynamic and echocardiographic data, and ASD morphology are shown in Table I. The patients in this study included 10 males and 20 females with a mean age of 75.8 ± 3.8 years and age range of 70–85 years. Eighteen of the 30 patients had been diagnosed with ASD within 2 years before transcatheter closure was attempted but the others well before that. Most of the patients had at least one major comorbidity, including systemic hypertension, stroke, coronary artery disease, and atrial fibrillation. Mean systolic pulmonary artery pressure at the time of diagnostic catheterization was 35.6 ± 11.8 mm Hg. Mean early diastolic mitral annular velocity (*e'*) and the ratio of early diastolic mitral valve flow velocity (*E*) to *e'* (*E/e'*) were 7.1 ± 1.9 cm/s and 11.0 ± 3.9, respectively, suggesting that our cohort generally had impaired myocardial relaxation [19]. More than half of the patients were being treated with a diuretic for congestive heart failure, and 30% of the patients had a history of hospitalization due to heart failure. Seventeen patients were classified as NYHA functional class II and eight patients were classified as class III. Only five patients had no symptoms despite significant shunt flow and were classified as NYHA functional class I. One patient had two defects. Mean defect diameter was 20.3 ± 6.4 mm, and a circumferentially sufficient rim (>5 mm rim around the defect) was observed in only eight patients. Mean pulmonary-systemic flow ratio (Qp/Qs) calculated by using the Fick principle was 2.4 ± 0.7.

TABLE II. Procedural and Mid-Term Results

Procedural results (*n* = 30)	
Success deployment, *n* (%)	28 (93%)
Device size, mm	23.3 ± 6.0
Acute complication, *n* (%)	0 (0%)
Mid-term results (*n* = 28)	
Mean follow-up period, *m*	19.1 ± 11.3
Residual shunt, *n* (%)	2 (8%)
Small, *n* (%)	2 (8%)
Major events	
Death, *n* (%)	2 (8%)
Unknown cause, *n* (%)	1 (4%)*
Prostate cancer, *n* (%)	1 (4%)
Pacemaker implantation, *n* (%)	1 (4%)
TIA, *n* (%)	1 (4%)*
Persistent AF, *n* (%)	1 (4%)

*The same case.
TIA, transient ischemic attack; AF, atrial fibrillation.

Procedural and Mid-Term Results

Table II shows the procedural and mid-term results. The first procedure was successful in 27 of 30 cases in which transcatheter ASD closure was attempted. On the other hand, the procedure was abandoned in three cases.

Before to ASD closure, test balloon occlusion were performed in 7 of 30 cases. As a result, the procedure was abandoned in one case due to a significant elevation of PCWP during test occlusion of the ASD. This patient was an 84-year-old thin woman who had permanent atrial fibrillation, hypertension, chronic kidney disease, chronic anemia, and severe TR. She had been repeatedly hospitalized with congestive heart failure in past years. Her ASD diameter was 24 mm and Qp/Qs was 2.6. During test balloon occlusion, her PCWP immediately increased from 8 mm Hg to 22 mm Hg and remained at 16 mm Hg after 20 min. At that point, we decided to abandon the procedure. In the other two cases, the device was difficult to deploy because of large size defect. One of those cases proceeded to surgical closure, and the other case was successfully closed in the second attempt of catheter intervention

TABLE III. Changes in Clinical Echocardiographic Parameters

	Pre-procedure ($n = 27$)	Follow-up ($n = 27$)	P value
NYHA functional class, *n* (%)			
I	3 (11%)	21 (78%)	<0.001
II	17 (63%)	5 (18%)	
III	7 (26%)	1 (4%)	
Plasma BNP level, pg/mL	175.9 ± 249.7	99.2 ± 83.2	0.013
HR at rest, bpm	74.4 ± 14.5	66.7 ± 8.7	0.005
Estimated systolic PAP, mm Hg	38.5 ± 12.7	27.2 ± 7.3	<0.001
RVEDD, mm	40.8 ± 6.0	31.6 ± 4.5	<0.001
LVEDD mm	39.7 ± 4.8	45.3 ± 4.6	<0.001
RVEDD/LVEDD ratio	1.05 ± 0.24	0.70 ± 0.12	<0.001
LAD, mm	46.1 ± 9.9	44.3 ± 9.3	0.128
LVEF, %	70.5 ± 6.1	70.5 ± 5.7	0.611
TR, *n* (%)			
≤Mild	10 (37%)	20 (74%)	0.002
Moderate	13 (48%)	7 (26%)	
Severe	4 (15%)	0 (0%)	
MR, *n* (%)			
None or trivial	18 (67%)	8 (30%)	0.004
Mild	6 (22%)	16 (59%)	
>Moderate	3 (11%)	3 (11%)	

BNP, brain natriuretic peptide; PAP, pulmonary artery pressure; RVEDD, right ventricular end-diastolic dimension; LVEDD, left ventricular end-diastolic dimension; LAD, left ventricular dimension; LVEF, left ventricular ejection fraction; TR, tricuspid regurgitation; MR, mitral regurgitation.

on a later day. Finally, 28 (93%) of the 30 patients were treated successfully by catheter closure. A single device was placed in 27 patients. In the remaining patient with multiple defects, two devices were deployed at the time of the same procedure. Mean device diameter was 23.3 ± 6.0 mm. Mean follow-up period was 19.1 ± 11.3 months.

Two patients died during the follow-up period. One died of prostatic cancer 20 months after ASD closure. The other patient died 2 months after the procedure. This patient was a 70-year-old woman who had permanent atrial fibrillation, severe chronic obstructive pulmonary disease, mild left ventricular dysfunction, history of pacemaker implantation for sick sinus syndrome, and mitral valve replacement and was in NYHA functional class III. Her ASD was 22 mm with a sufficient atrial rim, and a 26 mm device was used for closure. She died from unknown cause at home; however, a history of transient cerebral ischemic attack was reported one week before her death. Autopsy was not performed. Two patients were complicated with new arrhythmia. One patient who had permanent atrial fibrillation underwent pacemaker implantation for slow ventricular response 6 months after ASD closure. The other patient with paroxysmal atrial fibrillation before ASD closure developed persistent atrial fibrillation during the follow-up period. The remaining 24 patients had no late complication during the follow-up period. No patient had hemodynamically significant residual shunt.

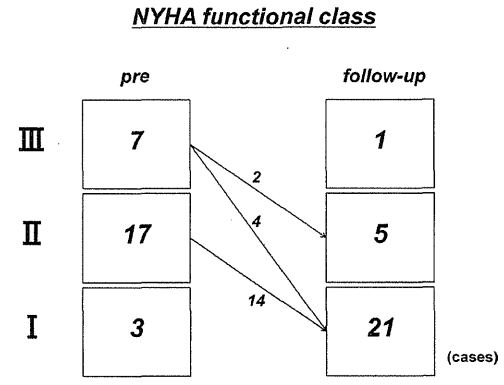

Fig. 1. NYHA functional class before the procedure and at follow-up.

Table III shows time course changes in clinical and echocardiographic parameters. Follow-up data (at more than 6 months after the procedure) were available in all of the 28 patients with exception of one patient who died 2 months after the procedure. NYHA functional class was significantly improved in 20 (74%) of the 27 patients at the latest follow-up (Fig. 1). One patient who remained in NYHA class III was complicated with severe chronic obstructive pulmonary disease. There was also a significant improvement in plasma BNP level (175.9 ± 64.7 vs. 99.2 ± 83.2 pg/ml, $P = 0.013$). Resting heart rate also decreased significantly (74.4 ± 14.5 vs. 66.7 ± 8.7 beats/min, $P = 0.005$), although no cardiac chronotropic drug was administered to any of the patients.

Cardiac Remodeling

RVEDD and estimated systolic pulmonary artery pressure decreased significantly (40.8 ± 6.0 vs. 31.6 ± 4.5 mm, $P < 0.001$, 38.5 ± 12.7 vs. 27.2 ± 7.3 mm Hg, $P < 0.001$, respectively). At the same time, LVEDD increased significantly (39.7 ± 4.8 vs. 45.3 ± 4.6 mm, $P < 0.001$). Therefore, the RVEDD/LVEDD ratio significantly decreased (1.05 ± 0.24 vs. 0.70 ± 0.12 mm, reduction of 67%, $P < 0.001$), indicating ventricular reverse remodeling. Left atrial dimension, above the normal level at baseline, did not change significantly during the follow-up period. Left ventricular ejection fraction also did not change.

AV Valve Regurgitation

Improvement of TR was observed in 11 of 17 patients (65%) with moderate or severe degree of regurgitation during the follow-up period (Fig. 2). On the other hand, MR was increased in 10 (37%) of the 27 patients and

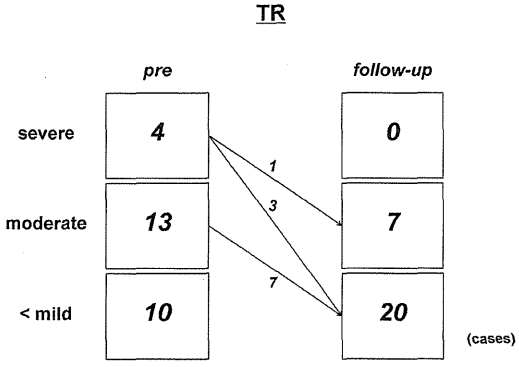

Fig. 2. Degrees of TR before the procedure and at follow-up.

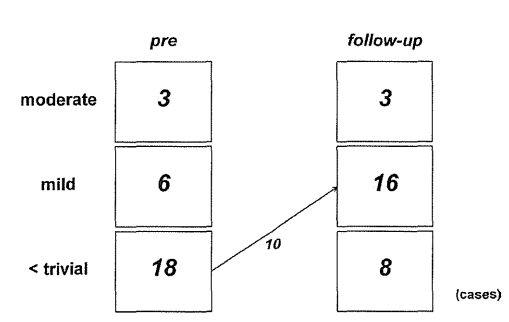

Fig. 3. Degrees of MR before the procedure and at follow-up.

was unchanged in the others (63%) during the follow-up period (Fig. 3). In our cohort, there was no patient with mitral valve prolapse as a cause for MR.

Associations Between NYHA Functional Class and Echocardiographic Parameters in the Follow-Up Period

Table IV shows associations of clinical and echocardiographic parameters with NYHA functional class. In the follow-up period, RVEDD/LVEDD ratio was identified as a factor associated with NYHA functional class. On the other hand, *E/e'*, *e'*, degree of TR or MR and increase in MR were not associated with NYHA functional class.

DISCUSSION

In this study, we demonstrated that transcatheter ASD closure can be performed safely and contributes to symptom reduction and cardiac remodeling even in patients older than 70 years of age.

Twelve of the 30 patients had been diagnosed with ASD well before trascatheter closure was attempted

TABLE IV. Associations of Clinical and Echocardiographic Parameters with NYHA Functional Class in the Follow-Up Period

Variable	*r*	Univariate *P* value	Multivariate *P* value
Age		0.349	
Qp/Qs		0.807	
HR at rest		0.260	
plasma BNP level		0.146	
Estimate systolic PAP		0.382	
RVEDD/LVEDD ratio	0.491	0.009	0.009
LVEF, %		0.971	
E'		0.962	
E/E'		0.688	
Degree of TR		0.282	
Degree of MR		0.682	
Increase in MR		0.764	

but they had refused or hesitated to receive ASD closure. We think that this was partially because they had no recognizable symptom, but mainly because surgical closure was the only treatment at the time when they had been first diagnosed with ASD.

Device closure was successfully performed in 28 (93%) of the 30 patients without acute complications. In the other two patients, the procedures were abandoned because of technical issues. While only eight (27%) of the 30 patients had sufficient rim type ASD, 19 (63%) had aortic rim deficient type. However, there was not much difference in our device selection between sufficient rim and aortic rim deficient type. Therefore, we think that the small percentage of patients with sufficient rim did not have a great impact on device size selection in the present study. Although the majority of our patients were complicated with various comorbidities, such as pulmonary artery hypertension, systemic hypertension and atrial fibrillation, high procedural success rate can be expected even in this aged group. Also, significant improvement of NYHA functional class was observed after closure even though about 30% of the patients in this study had a history of hospitalization for congestive heart failure. No patient required additional hospitalization for congestive heart failure during the follow-up period.

Several studies have suggested that development of acute congestive heart failure is due to abrupt elevation in left ventricular preload following transcatheter ASD closure, especially in elderly patients with impaired left ventricular systolic or diastolic function [3,22,23]. In our study, despite the fact that our patients had impaired left ventricular diastolic function estimated by decreased *e'* and increased *E/e'* [19,20] as well as various comorbidities such as systemic hypertension, pulmonary artery hypertension and atrial fibrillation, acute congestive heart failure after the ASD closure did not

develop in any of the patients except in one patient in whom the procedure was abandoned due to PCWP elevation during test balloon occlusion. Schubert et al. reported that periprocedural anticongestive medication was effective in preventing congestive heart failure after ASD closure in elderly patients [24]. In our study, 57% of the 30 patients previously used oral diuretics, and this high rate of diuretic usage might have contributed to prevention of acute congestive heart failure after closure.

During the follow-up period, NYHA functional class significantly improved in 20 (74%) of the 27 patients. Our data also demonstrated significant decreases of heart rate, pulmonary artery pressure and plasma BNP level, and these changes contributed to the improvement of NYHA functional class. Decrement of heart rate is presumably evidence of increment of left ventricular stroke volume following increased left ventricular preload after abolishment of left-to-right shunt. Significant decrease in RVEDD/LVEDD ratio was observed even in our geriatric patients, although RVEDD did not reach the normal level. Interestingly, percentage change in RVEDD/LVEDD ratio in our cohort was equivalent to results of other studies in younger populations [6,23]. Furthermore, it was revealed that RVEDD/LVEDD ratio was independently correlated with NYHA functional class in the follow-up period.

In this study, the degree of TR was decreased in 11 patients (41%) and exacerbation of TR was not observed during the follow-up period. Interestingly, in the case of moderate or severe TR before ASD closure, the degree of TR was improved in 11 (65%) of the 17 patients. TR can be improved functionally following decrement of right ventricular preload after ASD closure. Improvement of TR also can be expected following improvement of right ventricular geometric abnormality [25]. Our results suggest that TR can be improved even in geriatric patients and that the severity of TR does not become a factor to exclude them as candidates for transcatheter ASD closure. On the other hand, the degree of MR was slightly increased in 10 patients (37%) and unchanged in the others (63%) during the follow-up period. Wilson et al. reported that the degree of MR was unchanged in 83% and increased in 10% of their 194 patients, including 78 patients aged younger than 15 years, after transcatheter ASD closure [26]. In elderly ASD patients, the severity of MR might be masked by the presence of ASD effectively reducing left ventricular preload. Additionally, degenerated change of the mitral valve leaflet also influenced the increase in MR. Although the degree of MR and the increase in MR were not associated with NYHA functional class in the follow-up period in our study, further long-term follow-up is mandatory.

During the follow-up period, three complications occurred. One patient who was complicated with several cardiac comorbidities died 2 months after the procedure. An autopsy was not performed and it was therefore not known whether the cause of sudden death was ASD device-associated. Pacemaker implantation was required in one patient 6 months after the procedure, even though bradycardia was not observed before or just after ASD closure. In one patient, paroxysmal atrial fibrillation progressed into persistent atrial fibrillation 2 years after ASD closure. In previous studies, the incidence of atrial fibrillation in patients after transcatheter ASD closure was estimated to be 5% to 18% [27–29]; however, especially in elderly patients, atrial fibrillation is one of the expected findings for their natural course after ASD closure.

Limitations

This study has several limitations. The main limitation of our study is the small number of patients and lack of a control group. In addition, the follow-up period was relatively short. Long-term, randomized comparisons with large numbers of subjects are required to establish the survival benefit of transcatheter ASD closure in elderly patients. Another limitation is that our conclusion about improvement in exercise capacity was made on the basis of the patients' subjective impressions and not on the basis of oxygen uptake or other functional measurement. However, especially in elderly patients, performance in cardiopulmonary exercise testing is affected by lower-extremity muscle weakness. Thus, improvement of NYHA functional class can be considered as improvement of exercise tolerance in this patient population.

CONCLUSION

Even in elderly patients older than 70 years, transcatheter closure of ASD can be performed safely and contributes to significant improvement of NYHA functional class and positive cardiac remodeling. Further investigation is required especially for the outcome of MR.

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