Comparative Analysis of Systolic and Isolated Diastolic Dysfunction

Sado Heart Failure Study

Mahmoud M. RAMADAN,¹ MD, Yuji OKURA,¹ MD, Yukiko OHNO,¹ MD,
Keisuke SUZUKI,² MD, Koji TANEDA,² MD, Makoto HOYANO,¹ MD,
Kazuhisa HAO,¹ MD, Shinpei KIMURA,¹ MD, Makoto KODAMA,¹ MD,
and Yoshifusa AIZAWA,¹ MD

SUMMARY

Determining the type of cardiac dysfunction is important for implementing therapeutic strategies and for prognostic insights. We characterized systolic dysfunction (SD) and isolated diastolic dysfunction (IDD) in adults referred for echocardiographic evaluation, and compared their clinical and other characteristics. In the present work, we studied 218 patients (137 males) with cardiac dysfunction (mean age, 66.3 ± 8.3 years). SD was defined as a left ventricular ejection fraction (LVEF) of $< 45\%$, whereas IDD was defined as a LVEF $\geq 45\%$ in addition to the standard Doppler-echocardiography diagnostic criteria for IDD. Approximately 68% of subjects had SD (70% males). The proportions of hypertension, diabetes, and dyslipidemia were 44%, 26%, and 22%, respectively, without significant association with the type of dysfunction. Myocardial infarction (MI) was found in 31% of patients, and was significantly ($P < 0.001$) more prevalent among SD compared with IDD cases. Cerebral stroke (18%) and malignancy (16%) were significantly associated with IDD (29% versus 13% for SD in the case of stroke, and 26% versus 11% for SD in the case of malignancy; $P = 0.008$ for each). In multivariately-adjusted logistic regression analysis, the following variables were found to be significantly ($P < 0.05$) and independently associated with IDD: female gender (odds ratio [OR] = 2.207 [95% CI = 1.302-4.608]), stroke (OR = 2.009 [1.119-3.980]), and malignancy (OR = 2.016 [1.230-4.010]). On the other hand, previous MI (OR = 2.075 [1.769-4.808]) was independently associated with SD. In conclusion, some factors/comorbidities were more likely to associate with IDD (female gender, stroke, and malignancy) or SD (previous MI) when IDD and SD were compared with each other. (Int Heart J 2008; 49: 459-469)

Key words: Cardiac dysfunction, Heart failure, Echocardiography, Doppler

From the ¹ Division of Cardiology, Niigata University Graduate School of Medical and Dental Sciences, and ² Sado General Hospital, Niigata, Japan.

Address for correspondence: Yuji Okura, MD, Division of Cardiology, Niigata University Graduate School of Medical and Dental Sciences, 1-754 Asahi Machi Dori, Niigata City, Niigata 951-8510, Japan.

This study was supported by a Grant-in-Aid for Basic Research on Science and Technology (C): "Comprehensive comparative evaluation of risk factors for hospitalization and death of patients with chronic heart failure in urban and rural regions" (17606003).

Received for publication January 11, 2008.

Revised and accepted June 2, 2008.

CHRONIC heart failure (HF) represents a major and growing public health concern in terms of incidence, prevalence, morbidity, mortality, and economic burden.¹⁾ Despite significant progress in the prevention and treatment of cardiovascular diseases over the last 2 decades, the incidence and prevalence of HF have steadily increased in recent years,¹⁾ reaching 1%-3% of the adult population worldwide with a steep increase to approximately 10% in the elderly.²⁾

Cardiac dysfunction is a broad term used to describe the mechanical derangement of the systolic and diastolic functions of the heart--hence the terms systolic dysfunction (SD) and diastolic dysfunction (DD)--and encompasses asymptomatic as well as symptomatic patients presenting clinically with congestive HF.³⁾ Nearly all patients with SD have some degree of concomitant DD,⁴⁾ and even patients with a normal left ventricular ejection fraction (LVEF) can display impaired diastolic function (isolated DD [IDD]).⁵⁾

In fact, most studies have focused on the comparison of patients with systolic and diastolic HF, so that limited data are available that compare SD and IDD patients without validated congestive HF. Thus, our objective was to characterize SD and IDD using standardized Doppler-echocardiography criteria in Japanese adults without previous congestive HF that had been referred for echocardiographic evaluation. Also, we sought to compare demographic, clinical, and echocardiographic data, along with other features of individuals with IDD to those with SD, in order to identify the factors associated with these 2 conditions.

METHODS

Study design and selection of participants: This was a cross-sectional retrospective study designed to characterize outpatients with cardiac dysfunction in a local Japanese community, via the cooperation and integration of echocardiography-equipped centers in Sado City (Japan). We retrospectively reviewed echocardiograms performed on adults referred for assessment of cardiac function in the echocardiography laboratories of 2 core hospitals located in Sado City (area, 855 km², population, 70,000). The main indications for performing echocardiography in the study population included 1) the presence of symptoms suggestive of cardiac disease; 2) following cerebrovascular and peripheral vascular emboli; 3) to confirm physical signs on examination (murmurs, etc.); 4) to confirm electrocardiographic abnormalities (LV hypertrophy criteria, ST-T wave changes, abnormal Q-waves, bundle branch blocks, dysrhythmias, etc.); 5) presence of cardiomegaly on chest X-ray; and 6) the presence of any past or therapeutic history suggestive of cardiac dysfunction.

Within a total period of 3 years (from January 1, 2000 until December 31, 2002), subjects with SD and IDD were extracted from the records of about 4,500

Sado patients who underwent echocardiographic evaluation in the island's 2 core hospitals. All available medical records of the extracted SD and IDD patients were reviewed by 2 cardiologists regarding demography, medical history, associated co-morbidities, medications, laboratory data, electrocardiographic data, and echocardiographic data. The study was limited to those aged 45-75 years and patients with chronic atrial fibrillation or validated diagnosis of congestive HF (according to Framingham criteria)⁶⁾ were also excluded. Patients with atrial fibrillation were excluded due to the difficult identification of the Doppler-echocardiographic diagnostic criteria of IDD. We excluded patients with congestive HF to focus only on the issue of cardiac dysfunction, which is usually overlooked by medical practitioners who pay much attention to the overt HF syndrome. In addition to the above-mentioned criteria, we excluded some patients since they resided outside Sado City, medical records were incomplete, echocardiography was technically difficult, or they died in the hospital. Thus, 148 outpatients with SD and 70 outpatients with IDD were eligible for inclusion in this study.

Sado City, being an island, is relatively isolated from other urban centers and patient care is available from 2 core hospitals, which also maintain a unified medical record system that includes all diagnoses and consultations made during outpatient and emergency department visits, hospital admissions, and death certification. It is likely that all patients on the island with clinically significant cardiac issues were referred to these 2 hospitals.

Definition of cardiac dysfunction: SD was defined as an LVEF < 45% by 2-dimensionally guided M-mode measurements. IDD was defined as an LVEF $\geq$ 45%, in addition to at least 2 of the following Doppler-echocardiography diagnostic criteria of moderate-severe DD⁷⁾ (after excluding moderate or severe mitral or aortic insufficiency)^{3,5,8-10)}:

- (1) Deceleration time of the mitral E-wave < 140 msec.
- (2) The ratio between systolic and early-diastolic waves of the antegrade flow of the pulmonary venous flow velocity (S/D ratio) < 1.
- (3) The difference between the duration of pulmonary venous atrial reversal flow (AR) and trans-mitral flow (A) at the atrial contraction phase, that is AR-A > 30 msec.

Statistical analysis: Data analyses were performed with SPSS for Windows version 13 (SPSS Inc., Chicago, IL). Results are expressed as the mean $\pm$ standard deviation for continuous data. Comparison of means of continuous variables across a grouping variable with 2 levels was performed using Student's *t*-test. Proportions were compared by the χ^2 test or Fisher's exact test when appropriate. A 2-sided significance level of 0.05 was used for all analyses.

Ethical considerations: The study protocol was reviewed and accepted by the local Ethical Review Board of each institution participating in this study, including Niigata University Graduate School of Medical and Dental Sciences. All subjects gave written informed consent to participate in the study.

RESULTS

Table I. Characteristics and Comparisons of Patients With SD and IDD

Variable	All patients (<i>n</i> = 218)	SD (<i>n</i> = 148)	IDD (<i>n</i> = 70)	<i>P</i>
Demographic data				
Age (year)	66.3 ± 8.3	65.7 ± 7.3	67.5 ± 10.2	0.191
Age ≥ 65 years	140 (62.2%)	93 (62.8%)	47 (67.1%)	0.640
Age ≥ 70 years	89 (40.8%)	55 (37.2%)	34 (48.6%)	0.146
Gender				
Male	137 (62.8%)	103 (69.6%)	34 (48.6%)	0.004*
Female	81 (37.2%)	45 (30.4%)	36 (51.4%)	
Level of daily activities				
Independently ambulant	210 (96.3%)	144 (97.3%)	66 (94.3%)	0.282
Wheel chair dependent	1 (0.5%)	1 (0.7%)	0 (0.0%)	
Bed-ridden	7 (3.2%)	3 (2.0%)	4 (5.7%)	
Anthropometric / medical measurements				
Body weight (kg)	58.5 ± 10.8	59.7 ± 10.5	55.8 ± 11.4	0.013*
Height (cm)	159.6 ± 7.8	159.7 ± 7.9	159.5 ± 7.4	0.884
Body mass index (kg/m ²)	22.9 ± 3.4	23.3 ± 3.2	21.8 ± 3.7	0.002*
Systolic blood pressure (mmHg)	132.7 ± 15.6	132.4 ± 14.4	133.2 ± 17.9	0.174
Diastolic blood pressure (mmHg)	76.7 ± 8.9	76.3 ± 8.7	77.3 ± 9.2	0.996
Associated comorbidities and their management				
Cardiovascular risk factors/chronic medical illnesses				
Hypertension	96 (44.0%)	63 (42.6%)	33 (47.1%)	0.625
Diabetes	56 (25.7%)	39 (26.4%)	17 (24.3%)	0.873
Dyslipidemia	47 (21.6%)	32 (21.6%)	15 (21.4%)	0.974
Cardiac disorders				
Angina pectoris	24 (11.0%)	20 (13.5%)	4 (5.7%)	0.137
Myocardial infarction	67 (30.7%)	60 (40.5%)	7 (10.0%)	< 0.001*
Arrhythmias/antiarrhythmic devices				
Nonsustained ventricular tachycardia	3 (1.4%)	2 (1.4%)	1 (1.4%)	0.999
Permanent pacemaker	2 (0.9%)	0 (0.0%)	2 (2.9%)	0.112
Intraventricular cardioverter defibrillator	1 (0.5%)	1 (0.7%)	0 (0.0%)	0.999
Cardiac surgery/intervention				
Valve replacement	3 (1.4%)	3 (2.0%)	0 (0.0%)	0.564
Diagnostic coronary angiography	90 (41.3%)	75 (50.7%)	15 (21.4%)	< 0.001*
Percutaneous coronary intervention	33 (15.1%)	25 (16.9%)	8 (11.4%)	0.396
Coronary artery bypass grafting	15 (6.9%)	13 (8.8%)	2 (2.9%)	0.184
Pulmonary disorders				
Chronic obstructive pulmonary disease	4 (1.8%)	3 (2.0%)	1 (1.4%)	0.999
Renal disorders				
Chronic kidney disease §	19 (8.7%)	13 (8.8%)	6 (8.6%)	0.959

Neuro-psychiatric disorders				
Cerebral stroke	39 (17.9%)	19 (12.8%)	20 (28.6%)	0.008*
Psychiatric diagnosis	28 (12.8%)	19 (12.8%)	9 (12.9%)	0.997
Neoplastic disorders				
Malignancy	34 (15.6%)	16 (10.8%)	18 (25.7%)	0.008*
Electrocardiographic data				
Pathologic Q-wave	39 (17.9%)	33 (22.3%)	6 (8.6%)	0.023*
Left ventricular hypertrophy in ECG	42 (19.3%)	26 (17.6%)	16 (22.9%)	0.429
Right bundle branch block	12 (5.5%)	7 (4.7%)	5 (7.1%)	0.681
Left bundle branch block	7 (3.2%)	7 (4.7%)	0 (0.0%)	0.124
Echocardiographic data				
Ejection fraction (%)	49.2 ± 9.5	41.3 ± 5.6	65.8 ± 8.2	< 0.001*
Fractional shortening (%)	26.2 ± 8.3	21.2 ± 5.4	36.9 ± 6.3	< 0.001*
Left ventricular diastolic dimension (mm)	53.9 ± 8.1	56.4 ± 7.7	48.8 ± 6.3	< 0.001*
Left ventricular systolic dimension (mm)	40.4 ± 6.3	44.6 ± 4.6	31.5 ± 5.8	< 0.001*
Septal wall thickness (mm)	10.2 ± 3.1	10.4 ± 3.2	10.2 ± 3.0	0.771
Posterior wall thickness (mm)	9.7 ± 1.9	9.8 ± 1.8	9.8 ± 1.7	0.809
Left ventricular mass index (g/m ²) #	92.8 ± 30.6	99.4 ± 30.5	78.8 ± 26.1	< 0.001*
Left atrial diameter (mm)	40.5 ± 6.9	40.1 ± 7.1	41.2 ± 6.4	0.259
Deceleration time (msec)	148.9 ± 47.5	158.7 ± 49.7	128.4 ± 34.7	< 0.001*
AR-A estimate (msec)	49.2 ± 14.9	40.5 ± 13.6	67.7 ± 17.8	< 0.001*
S/D ratio	2.0 ± 0.56	2.6 ± 0.33	0.8 ± 0.29	< 0.001*
E/A ratio	0.67 ± 0.32	0.64 ± 0.29	0.74 ± 0.35	0.020*
Laboratory data				
Hemoglobin (g/dL)	13.1 ± 2.1	13.2 ± 2.0	12.9 ± 2.2	0.359
Total cholesterol (mg/dL)	187.0 ± 36.2	189.1 ± 37.9	182.6 ± 32.1	0.402
HDL-cholesterol (mg/dL)	49.3 ± 12.9	48.1 ± 11.8	51.5 ± 14.7	0.190
LDL-cholesterol (mg/dL)	110.4 ± 29.6	112.2 ± 31.4	106.5 ± 25.3	0.410
Medications				
Angiotensin-converting enzyme inhibitors	70 (32.1%)	52 (35.1%)	18 (25.7%)	0.217
Angiotensin receptor blockers	20 (9.2%)	13 (8.8%)	7 (10.0%)	0.969
Beta-blockers	45 (20.6%)	30 (20.3%)	15 (21.4%)	0.986
Calcium channel blockers	84 (38.5%)	59 (39.9%)	25 (35.7%)	0.661
Digoxin	32 (14.7%)	25 (16.9%)	7 (10.0%)	0.255
Loop diuretics	56 (25.7%)	44 (29.7%)	12 (17.1%)	0.047*
Spironolactone	8 (3.7%)	6 (4.1%)	2 (2.9%)	0.958
Aspirin	59 (27.1%)	43 (29.1%)	16 (22.9%)	0.425
Ticlopidine	16 (7.3%)	12 (8.1%)	4 (5.7%)	0.723
Warfarin	40 (18.3%)	29 (19.6%)	11 (15.7%)	0.614
Nitroglycerin	36 (16.5%)	28 (18.9%)	8 (11.4%)	0.232
Statins	46 (21.1%)	34 (23.0%)	12 (17.1%)	0.420

Values are expressed as the mean ± standard deviation, or number of subjects (%).

SD indicates systolic dysfunction; IDD, isolated diastolic dysfunction; ECG, electrocardiogram; AR-A, the difference between the duration of pulmonary venous atrial reversal flow (AR) and trans-mitral flow (A) at the atrial contraction phase; S/D, the ratio between peak velocity of pulmonary venous forward flow during systole (S) and peak velocity of pulmonary venous forward flow during diastole; E/A, the ratio between peak early mitral inflow filling velocity (E) and peak mitral filling velocity (A) at atrial contraction; HDL, high-density lipoprotein; and LDL, low-density lipoprotein.

§ : serum creatinine ≥ 2 mg/dL or the need for hemodialysis.

: Left ventricular mass (g) was calculated according to the method recommended by the American Society of Echocardiography [LV mass = 0.8 × (1.04 [LVDd + IVST + PWT]³ - LVDd³) + 0.6] and then was indexed to body surface area (m²); where LVDd = left ventricular diastolic dimension (mm), IVST = interventricular septum thickness (mm), and PWT = posterior wall thickness (mm).

* : statistical significance.

A total of 218 subjects were included in the study, 137 men and 81 women, aged 66.3 ± 8.3 years (range, 45-75 years). SD was diagnosed in 68% of participants, the remainder was diagnosed with IDD. Characteristics and comparisons of the SD and IDD cases are shown in Table I.

The study cohort exhibited many classic cardiovascular risk factors such as hypertension (44%), diabetes (26%), and dyslipidemia (22%). The prevalence of these risk factors did not show significant association with the type of cardiac dysfunction. The most prevalent comorbidity in the subjects studied was myocardial infarction (MI), which was documented in 31% of subjects, and significantly ($P < 0.001$) prevailed among SD (41%) compared with IDD (10%) cases. Eighteen percent of cases had cerebral stroke (documented by imaging techniques), particularly those with IDD (29% versus 13% for SD cases; $P = 0.008$); whereas 28 patients (13%) suffered psychiatric illnesses (especially depression and dementia). A history of malignancy (up to TNM grade II) was found for 16% of patients, and was significantly ($P = 0.008$) more prevalent in cases with IDD (26% compared with 11% for SD). Most of the echocardiographic parameters studied were significantly different between SD and IDD patients, whereas electrocardiographic findings and medications were generally similar (Table I).

We performed simple univariate logistic regression analysis for each of the independent variables against a binary outcome representing the type of cardiac dysfunction (SD and IDD); and the variables associated with this outcome at $P \leq 0.1$ (other than those used as classifiers for each condition) were then included in a final forward stepwise logistic regression model. In addition to adjustment for age, these variables included gender, body mass index, diastolic blood pressure, history of MI, history of cerebrovascular accident, past or present history of malignancy, pathologic Q-wave, and echocardiographic data (LV diastolic

Table II. Results of the Final Multivariate Logistic Regression Model Used to Test the Independent Association of Different Variables With the Type of Cardiac Dysfunction

Variable	Association with SD			Association with IDD			<i>P</i>
	β	OR	95% CI for OR	β	OR	95% CI for OR	
Female gender	-0.792	0.453	0.217-0.768	0.792	2.207	1.302-4.608	0.006
Myocardial infarction	0.730	2.075	1.769-4.808	-0.730	0.482	0.208-0.565	0.002
Stroke	-0.698	0.498	0.251-0.894	0.698	2.009	1.119-3.980	0.031
Malignancy	-0.701	0.496	0.249-0.813	0.701	2.016	1.230-4.010	0.013
LVDd $\times$ LVDs interaction	0.311	1.364	1.237-1.506	-0.311	0.733	0.664-0.808	< 0.001
E/A ratio	-1.002	0.367	0.199-0.717	1.002	2.724	1.395-5.021	0.004

OR indicates odds ratio; CI, confidence interval; LVDd, left ventricular diastolic dimension; and LVDs, left ventricular systolic dimension, other abbreviations as in Table I.

Figure. Point estimates representing odds ratio and corresponding 95% confidence interval for the variables independently associated with each type of cardiac dysfunction.

MI indicates myocardial infarction; LVDd, left ventricular diastolic dimension; LVDs, left ventricular systolic dimension; E/A, the ratio between peak early mitral inflow filling velocity (E) and peak mitral filling velocity (A) at atrial contraction; SD, systolic dysfunction; and IDD, isolated diastolic dysfunction.

dimension [LVDd], LV systolic dimension [LVDs], LV mass index, and E/A ratio, which is the ratio between peak early mitral inflow filling velocity (E) and peak mitral filling velocity (A) at atrial contraction). Owing to the high correlation between LVDs and LVDd, they were entered in the model as interaction terms (LVDs × LVDd in cm²) to avoid colinearity. The final logistic model showed a good fitting of data (Hosmer-Lemeshow $\chi^2 = 6.335$, $P = 0.610$) with high discriminative power (C-statistic = 0.860 [0.829-0.891]; $P < 0.001$) and R^2 value (Nagelkerke $R^2 = 0.65$). The following variables were found to be significantly ($P < 0.05$) and independently associated with IDD (Table II, Figure): female gender, stroke, malignancy, and E/A ratio. On the other hand, MI and the LVD interaction were independently associated with SD.

DISCUSSION

In the past 2 decades, IDD has been extensively studied by cardiac catheterization, so that its pathophysiological features have been well identified in comparison to SD and normal subjects.¹¹⁾ However, the identification of IDD on a

large scale or community basis by invasive methods has ethical and economic impediments. Therefore, the clinical characteristics of pure IDD (ie, without clinical HF) are not fully understood, especially in Japan, when compared with patients with SD or IDD with clinical HF.

Doppler-echocardiography is commonly used as a noninvasive diagnostic tool to distinguish between SD and IDD.¹²⁾ It can reliably detect and grade the severity of IDD, estimate filling pressure, and provide prognostic insights for diastolic and systolic HF.^{4,13)} Just as 2-dimensional echocardiography is an excellent tool for diagnosing SD, so Doppler-echocardiography has become accepted as a reliable, reproducible, and practical noninvasive method for diagnosis and follow-up of IDD and diastolic HF.⁴⁾

With regard to our choice of LVEF cutoff to define SD, there is no consensus in the published literature to support a single most appropriate definition of normal systolic function.¹⁴⁾ However, it has been reported that an LVEF range of 40-50% would include the cutoff value presumed to define normal systolic function.⁸⁾ As employed in this and some previous studies,¹⁵⁻¹⁷⁾ normal systolic function was defined as $LVEF \geq 45\%$. In fact, the guidelines of the European Society of Cardiology specified this cutoff ($LVEF \geq 45\%$) as part of the diagnostic triad of diastolic HF.¹⁸⁾

The present work is the first to compare pure SD and IDD, making comparisons with other studies impossible. However, some epidemiological (population and hospital-based) studies have compared clinical characteristics and risk factors in patients with systolic HF versus those with diastolic HF.^{2,14,19-21)} In general, these studies suggest that patients with diastolic HF are older and more likely to be female than patients with systolic HF. Our results showed an independent association of female gender with IDD, in agreement with previous studies conducted on HF patients, but, in contrast, found different results regarding age, which in our study was similar for patients with SD and IDD. The discrepancy in the association with age may be due to the inclusion of only those aged 45-75 years in this study. The aforementioned studies^{2,17,19-21)} reported also that the prevalences of diabetes and hyperlipidemia were similar in patients with diastolic HF and systolic HF, whereas body mass index was higher in those with diastolic HF than in those with systolic HF. Similar results were found in our study, in that the prevalences of diabetes and hyperlipidemia did not differ significantly between types of cardiac dysfunction. However, body mass index was significantly associated with SD (in comparison with IDD) in univariate analysis, but this association was lost after multivariate adjustment. In most of these studies, the prevalence of recognized coronary artery disease or previous MI was lower in patients with diastolic HF than in those with systolic HF, supporting our finding of association between ischemic heart disease and SD in univariate analysis and

independent association of MI with SD in the multivariate model. This observation is consistent with the well recognized adverse impact of myocardial damage on LV contractility.²⁾

One important finding of this study was the independent association between IDD and malignancy, which might be explained by the preferential impact of malignancy - either by itself or due to the effects of associated chemotherapeutic medications - on LV diastolic rather than systolic function. Another finding was the strong link between stroke and IDD, for which we do not have a clear explanation (but may be the result of more frequent atrial fibrillation paroxysms in IDD than SD patients). However, these last 2 results require validation in large prospective studies, because the cross-sectional nature of our study makes it difficult to infer causality between IDD and either malignancies or cerebral stroke, but only permits us to make (not test) hypotheses about the possible etiological relationships.

We acknowledge some limitations to this study. It is difficult to compare our results with previous studies because of the differences in study design, criteria to diagnose IDD, LVEF cutoff value, and variations pertaining to the population studied (ethnicity, age, gender, prevalence of associated comorbidities, etc). Unfortunately, the diagnosis of IDD by tissue Doppler was not available. Also, we did not measure brain natriuretic peptide, the level of which has been recently shown to be indicative of the severity of IDD.²²⁾ Besides being cross-sectional, this study was not a prospective population-based randomized investigation, but rather a retrospective observational study of individuals presenting to outpatient clinics; therefore, the potential for selection bias cannot be excluded. However, besides the aforementioned unique geo-demographic characteristic of the study area, this work was performed at 2 large community-based hospitals, thus this sample may largely represent the typical population with cardiac dysfunction seen by a general practitioner. The use of medications could be thought to improve LVEF in some patients with SD, resulting in classification bias. However, we have checked the medical records of the patients from 2002 back until 1996 and have not found any history of SD in IDD patients.

Conclusions Differences in clinical and echocardiographic features do exist between SD and IDD patients: these include association of female gender, stroke, and malignancy with IDD and association of MI with SD in a comparison of the two types of cardiac dysfunction. Though not inferring causality, these findings may serve to extend our understanding of preclinical IDD.

ACKNOWLEDGMENTS

This study was performed in collaboration with Dr. Akira Hattori, ex-director, and Dr. Takeshi Momotsu, Director of Sado General Hospital; Drs. Kenjiro Kikuchi, Takashi Ishikawa, Yoshio Kitami, and Keiko Saito of the Physiologic Laboratory; and the physicians of Sado Medical Society.

REFERENCES

1. Pedersen F, Raymond I, Madsen LH, Mehlsen J, Atar D, Hildebrandt P. Echocardiographic indices of left ventricular diastolic dysfunction in 647 individuals with preserved left ventricular systolic function. *Eur J Heart Fail* 2004; 6: 439-47.
2. Vasan RS, Larson MG, Benjamin EJ, Evans JC, Reiss CK, Levy D. Congestive heart failure in subjects with normal versus reduced left ventricular ejection fraction: prevalence and mortality in a population-based cohort. *J Am Coll Cardiol* 1999; 33: 1948-55.
3. Zile MR, Brutsaert DL. New concepts in diastolic dysfunction and diastolic heart failure: Part I: diagnosis, prognosis, and measurements of diastolic function. *Circulation* 2002; 105: 1387-93.
4. Nishimura RA, Tajik AJ. Evaluation of diastolic filling of left ventricle in health and disease: Doppler echocardiography is the clinician's Rosetta Stone. *J Am Coll Cardiol* 1997; 30: 8-18. (Review)
5. Zile MR, Gaasch WH, Carroll JD, *et al.* Heart failure with a normal ejection fraction: is measurement of diastolic function necessary to make the diagnosis of diastolic heart failure? *Circulation* 2001; 104: 779-82.
6. McKee PA, Castelli WP, McNamara PM, Kannel WB. The natural history of congestive heart failure: the Framingham Study. *N Engl J Med* 1971; 285: 1441-6.
7. Redfield MM, Jacobsen SJ, Burnett JC Jr, Mahoney DW, Bailey KR, Rodeheffer RJ. Burden of systolic and diastolic ventricular dysfunction in the community: appreciating the scope of the heart failure epidemic. *JAMA* 2003; 289: 194-202.
8. Yu CM, Lin H, Yang H, Kong SL, Zhang Q, Lee SW. Progression of systolic abnormalities in patients with "isolated" diastolic heart failure and diastolic dysfunction. *Circulation* 2002; 105: 1195-201.
9. Gaasch WH, Zile MR. Left ventricular diastolic dysfunction and diastolic heart failure. *Annu Rev Med* 2004; 55: 373-94. (Review)
10. Zile MR, Baicu CF, Gaasch WH. Diastolic heart failure--abnormalities in active relaxation and passive stiffness of the left ventricle. *N Engl J Med* 2004; 350: 1953-9.
11. Redfield MM. Heart failure with normal ejection fraction. In: *Braunwald's Heart Disease*. 8th ed. Philadelphia, PA: Saunders; 2007: 641-56.
12. Thomas JD, Weyman AE. Echocardiographic Doppler evaluation of left ventricular diastolic function. Physics and physiology. *Circulation* 1991; 84: 977-90. (Review)
13. Oh JK, Hatle L, Tajik AJ, Little WC. Diastolic heart failure can be diagnosed by comprehensive two-dimensional and Doppler echocardiography. *J Am Coll Cardiol* 2006; 47: 500-6. (Review)
14. Franklin KM, Aurigemma GP. Prognosis in diastolic heart failure. *Prog Cardiovasc Dis* 2005; 47: 333-9. (Review)
15. van Heerebeek L, Borbély A, Niessen HW, *et al.* Myocardial structure and function differ in systolic and diastolic heart failure. *Circulation* 2006; 113: 1966-73.
16. Ceia F, Fonseca C, Mota T, *et al.* Prevalence of chronic heart failure in Southwestern Europe: the EPICA study. *Eur J Heart Fail* 2002; 4: 531-9.
17. Yip GW, Ho PP, Woo KS, Sanderson JE. Comparison of frequencies of left ventricular systolic and diastolic heart failure in Chinese living in Hong Kong. *Am J Cardiol* 1999; 84: 563-7.
18. Swedberg K, Cleland J, Dargie H, *et al.* Guidelines for the diagnosis and treatment of chronic heart failure: executive summary (update 2005): The Task Force for the Diagnosis and Treatment of Chronic Heart Failure of the European Society of Cardiology. *Eur Heart J* 2005; 26: 1115-40.
19. Gottdiener JS, McClelland RL, Marshall R, *et al.* Outcome of congestive heart failure in elderly persons: influence of left ventricular systolic function. The Cardiovascular Health Study. *Ann Intern Med* 2002; 137: 631-9.

20. Devereux RB, Roman MJ, Liu JE, *et al.* Congestive heart failure despite normal left ventricular systolic function in a population-based sample: the Strong Heart Study. *Am J Cardiol* 2000; 86: 1090-6.
21. Senni M, Tribouilloy CM, Rodeheffer RJ, *et al.* Congestive heart failure in the community: a study of all incident cases in Olmsted County, Minnesota, in 1991. *Circulation* 1998; 98: 2282-9.
22. Eroglu S, Yildirim A, Bozbas H, *et al.* Brain natriuretic peptide levels and cardiac functional capacity in patients with dyspnoea and isolated diastolic dysfunction. *Int Heart J* 2007; 48: 97-106.