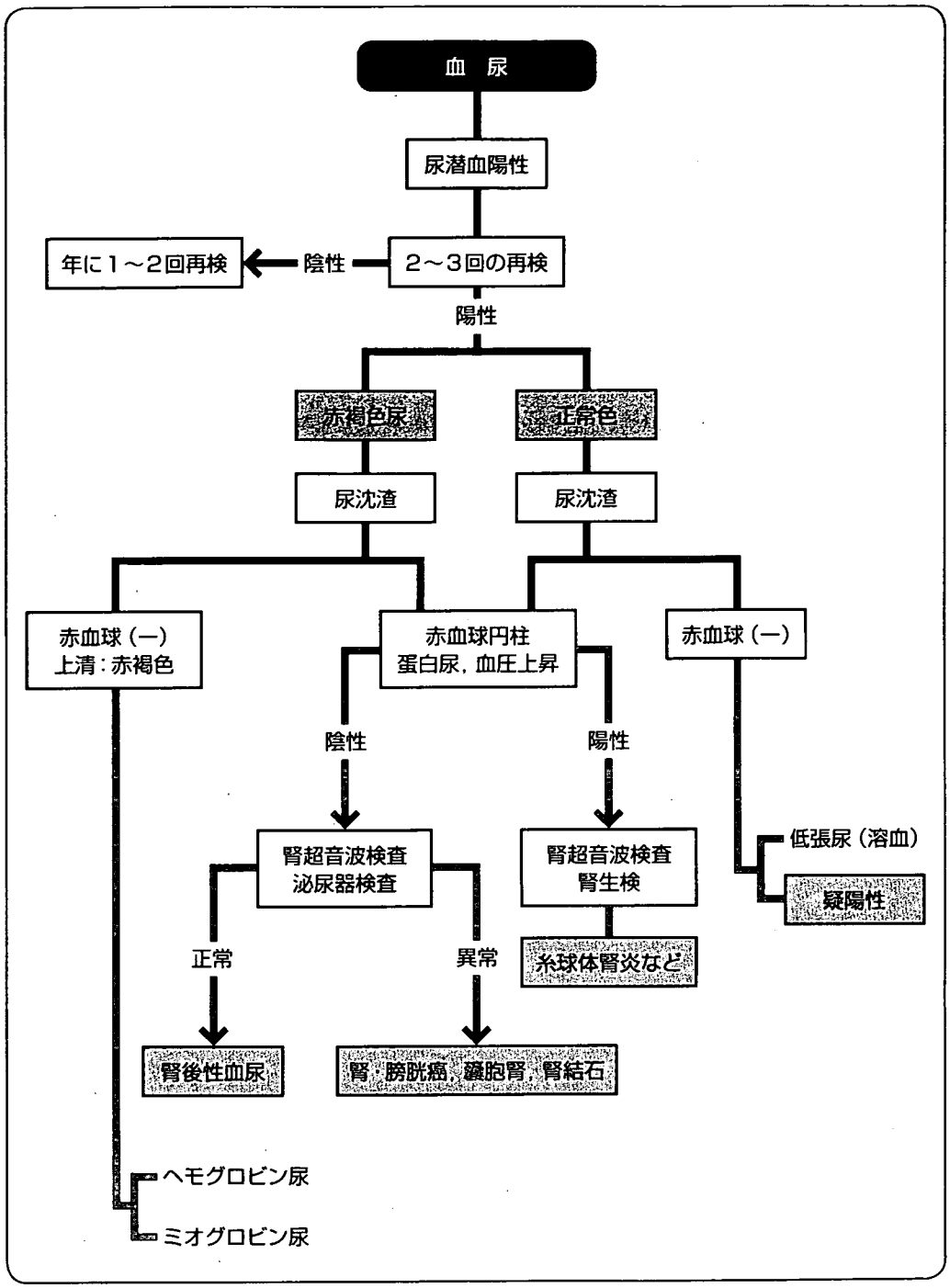

鑑別診断のフローチャート（尿潜血陽性時のフロー）

ANCA 関連腎炎に伴う血管病変*

武曾惠理** 猪原登志子** 古宮俊幸**

はじめに

1982 年に Davies らによって見出された抗好中球細胞質抗体（anti-neutrophil-cytoplasmic antigen：ANCA）[1]陽性の腎症は急速進行性糸球体腎炎を呈することが多く，さらに老年者に多発し，その血管病変は腎のみならず肺など全身臓器に及び，生命予後も必ずしも良好とはいえず，難治性血管炎を呈する。好中球細胞質内酵素のなかでもペロキシダーゼ 3（PR3）に対する抗体（PR3-ANCA），ミエロペロキシダーゼ（MPO）に対する抗体（MPO-ANCA）は，好中球の蛍光抗体法染色所見がそれぞれ細胞質全体に染まる型 C（cytoplasmic）パターンと，細胞核周囲に染色される型 P（perinuclear）パターンに分かれ，しばしば C-ANCA，P-ANCA と呼称された。これらの ANCA が血中で陽性となる腎炎に伴う全身性血管炎を呈する代表的な疾患は，Wegener 肉芽腫症（Wegener's granulomatosis：WG），顕微鏡的多発血管炎（microscopic polyangiitis：MPA），アレルギー性肉芽腫性血管炎（Churg-Strauss 症候群：CSS）などで，これらは 1994 年，Chapell Hill Consensus Conference on the Nomenclature of Systemic Vasculitis（Chapell Hill Conference）[2]において，侵される血管の大きさにより分類された全身血管炎の小動脈炎に属する。これらのうち，特に WG には PR3-ANCA，MPA，CSS には MPO-ANCA がかかわる傾向がある。近年このうち特にわが国では MPO-ANCA 関連 MPA に急速な進行性腎炎をきたす症例の報告が増えた。これらの疾患の血管病変は病理学的に類似性もあるが，ある程度特異性もあり，臓器特異性も強い。本稿では，ANCA に伴う糸球体毛細血管を巻き込む血管炎の推測される発症機序とその特異的病理所見について述べる。

Ⅰ．ANCA 関連腎炎における血管炎の発症機序[3]

ANCA 関連腎炎における血管病変は**図 1** のような機序で発症すると考えられている。すなわち，何らかの細菌や化学物質の侵入によって活性化されたマクロファージや好中球から産生された TNFα はさらに好中球を活性化準備状態（primed）とする。この状態の好中球からは，静止状態では細胞質内にある PR3 や MPO が細胞表面に移動し（translocate），さらに血中に分泌される。この放出された酵素が抗原となって，T 細胞を活性化，さらに B 細胞も活性化され抗原特異的な抗体群すなわち ANCA が産生される。この状態で二次的に感染やさらなる化学物質などの刺激が入ると，ここでさらに活性化準備状態になっている好中球から MPO，PR3 が表面に露出し分泌される。細胞表面に露出したこれらの酵素には ANCA が結合し，

* Vascular lesion in ANCA positive glomerulonephritis

key words：ANCA 関連腎炎，Wegener 肉芽腫症，顕微鏡的多発血管炎

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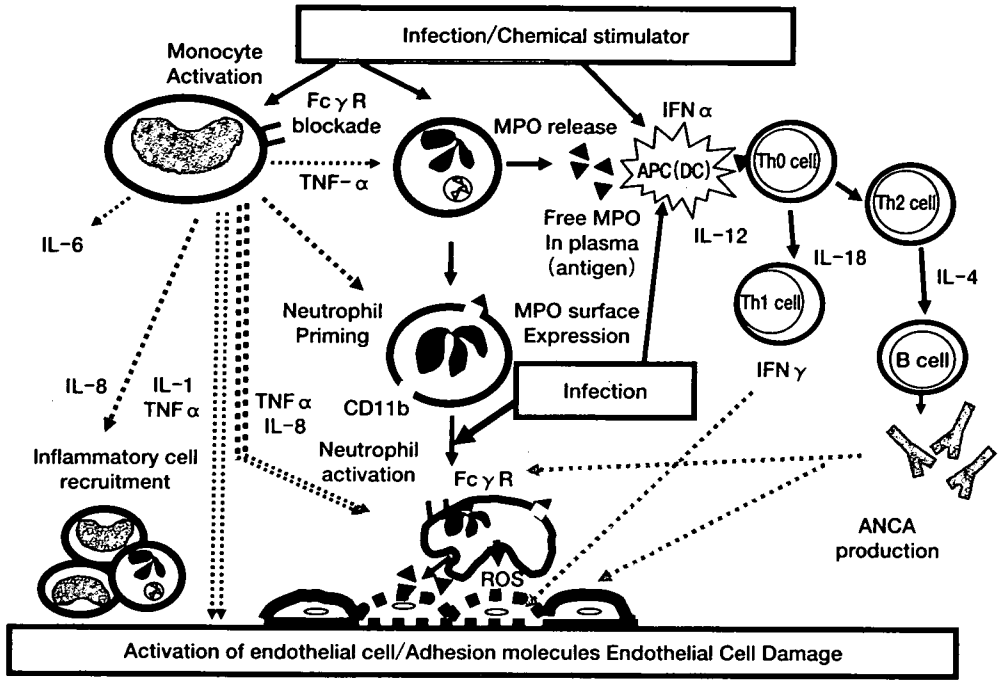

図1 Mechanism of active vasculitis development in MPO-ANCA related RPGN

一方ではその抗体 Fc 部分が好中球やマクロファージの Fcγ レセプターに結合して架橋をつくり，さらにこれらの細胞を活性化する。活性化したマクロファージや好中球からは，多彩な炎症性サイトカインが発生し，血中に放出されてサイトカイン血症を引き起こし，さらに T，B 細胞の活性化を引き起こすが，一方，これらサイトカインは血管内皮細胞の接着因子 ICAM-1 や E-セレクチンなどを発現させ，好中球の接着を促す。接着し活性化した好中球からは，過酸化水素を介した活性酸素の発生が起こり，局所で細胞融解が発生する。また，特に MPO は陽性に荷電しており，陰性荷電している血管内皮細胞とは結合しやすく，この MPO と ANCA が抗原抗体反応を内皮細胞上で起こし，補体の活性化も関与して，内皮細胞障害が進行する[4]。これらの血管障害はどのようなサイズの血管でも発症し得るが，ANCA 関連血管炎の発症する血管は，毛細血管，糸球体内血管や，小細動脈，小動脈レベルの血管に比較的限定して起こるのが特徴的である。

血管炎発症に影響を与える要因として，ANCA の種類による発生頻度の民族差がある。すなわち MPO-ANCA 陽性の MPA と PR3-ANCA 陽性の WG の発生頻度は，わが国では MPA の発生が圧倒的に多く 8：1 程度であるが，欧米ではほぼ 1：1 の比率である[5]。これらの遺伝的背景で HLA-DR9 陽性者が多いことも事実で，わが国で MPA の頻度が高いことと HLA-DR9 陽性者の頻度が高いことなどが着目されているが，明らかな遺伝的傾向は現在まで知られていない。一方，好中球を priming する最初の誘因として，各種の細菌やウイルス以外に，化学物質としてシリカや一部の薬剤，特に甲状腺障害に対する薬剤であるプロピルチオウラシルなどが注目されている。建造物崩壊後の大気汚染や家屋からでる大量のホコリの吸引による肺胞障害が誘因となって本疾患が発生することも経験されているが，その機序の直接の証明系はまだ十分とはいえない[6]。

II. 各種 ANCA 陽性血管炎の病変の特徴

代表的な ANCA 関連腎炎 MPA, WG, CSS に起こる血管炎の病理像の特徴を記す。上述したように，これらの血管炎は小・細動脈から毛細血管およびその下流の小静脈に発症し，さらに免疫複合体によらない pauci-immune 型の半月体形成性糸球体腎炎をきたすことなどの共通点が多いが，また三者それぞれに特徴的な傾向も認める。

1．顕微鏡的多発血管炎（microscopic polyangiitis：MPA）

P-ANCA 陽性の肉芽腫を作ることがまれな壊死性血管炎を呈し（図 2），好中球の浸潤を伴った毛細管炎がしばしば腎糸球体の壊死性細胞性半月体形成（図 3）を起こして，臨床的に血尿，蛋白尿，急速進行性腎機能低下をきたす。日本人の急速進行性糸球体腎炎の 70%近くがこの疾患によるもので[7]，これらの病変が肺に及べば，びまん性肺胞

図 2　MPA 症例の壊死性血管炎（Masson Trichrome 染色，×100）

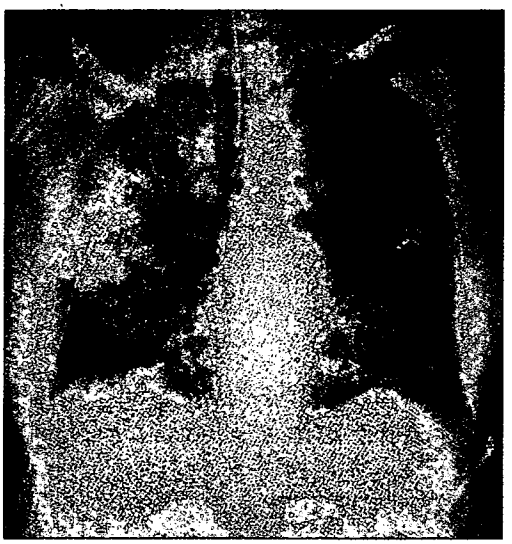

図 4　MPA 症例に発症したびまん性肺出血の胸部 X 線写真像

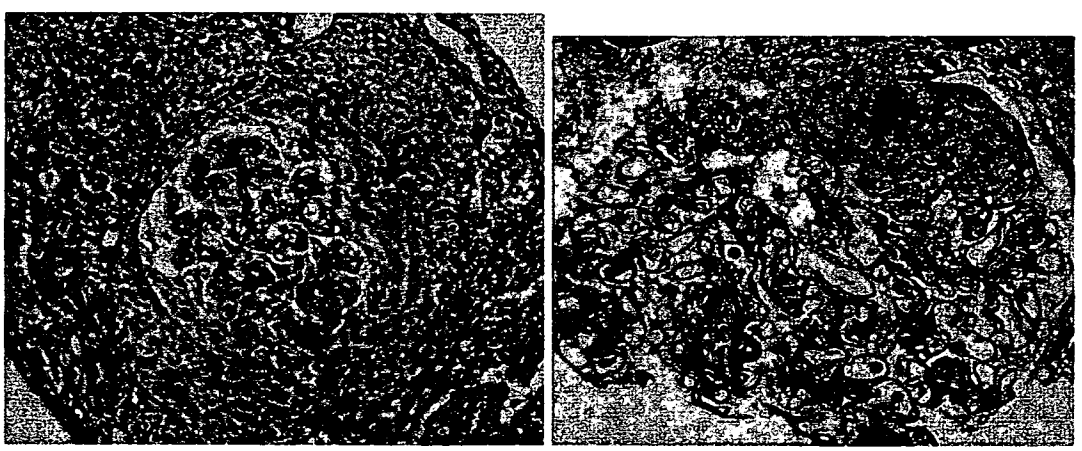

図 3　MPA 症例に認められた細胞性半月体形成（左：PAM 染色，×200）と壊死性糸球体毛細管炎（右：PAM 染色，×400）

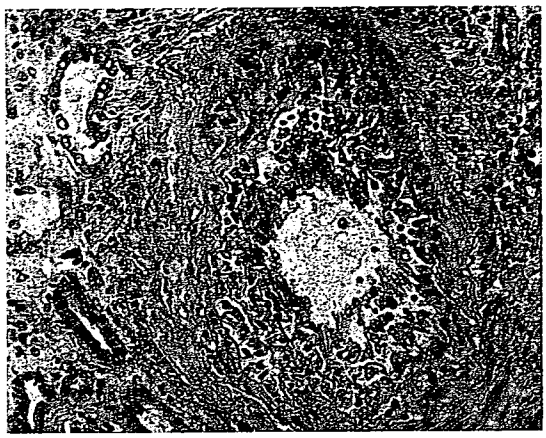

図5 WG 症例の腎内壊死性小動脈炎(HE 染色，×200)

出血となる（図4)。

2．Wegener 肉芽腫症（Wegener's granulomatosis：WG)

C-ANCA 陽性の血管炎で，腎に発症することもある（図5）が，しばしば鼻腔粘膜や副鼻腔などを巻き込む耳鼻科領域の血管炎を呈する。その病理像では，肉芽腫性病変を呈することが比較的多く，この疾患名がついたが，必ずしも常に肉芽があるとは限らない。

3．アレルギー性肉芽腫性血管炎，Churg-Straus 血管炎（CSS)

P-ANCA が陽性のことが多く，しばしば好酸球増多症と喘息を伴っており，病理学的には壊死性肉芽腫を腎や肺を含む全身の小動脈にきたすが，特に好酸球の浸潤を伴うことが特徴である。急速進行性糸球体腎炎をとることは MPA に比べて低率である。

以上の各所見に加え，間質の傍尿細管毛細血管腔には急性期に好中球が多数接着してとどまっている peritubular capillaritis の所見（図6）をしばしば認め，ステロイド剤投与などの治療で，比較的速やかにこれらは消失する。

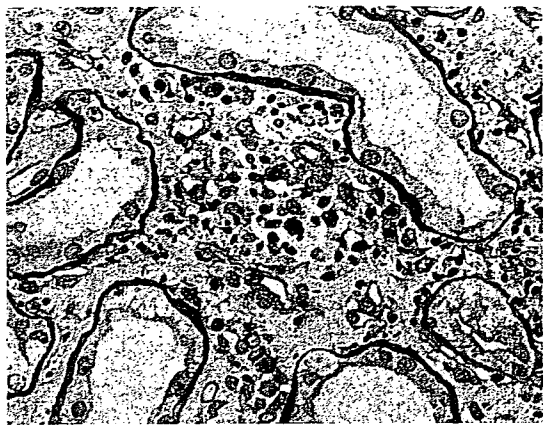

図6 CSS 症例に認められた傍尿細管毛細管炎

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Circ J 2007; **71:** 1004 – 1012

Characterization of Outpatients With Systolic Dysfunction in a Japanese Community by Total Enumeration

— Sado Heart Failure Study —

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Background The prevalence of congestive heart failure (CHF) is increasing with the aging of the community. Management of patients with systolic dysfunction (SD) is important for prevention of CHF, but there is little information regarding the burden of SD on Japanese communities.

Methods and Results In order to delineate the epidemiological and clinical characteristics of SD patients, the medical records of patients from Sado Island were collected and summarized in 2003. From the 5 years prior to 2003, data for 497 patients were extracted. The mortality rate was significantly higher compared with the general population; and the total number of survivors had decreased to 410 by 2003. The proportion of SD patients in the general population increased sharply after the age of 65 years in males and 70 years in females, reaching 3.3% and 1.7% for men and women, respectively, in their 80s. In 49% of the patients, the Charlson comorbidity index was ≥2, whereas 24% of females led a solitary life.

Conclusions The total count of outpatients with SD is progressively increasing with age. These patients have multiple comorbidities, making the outcome of SD a poor one. The gender difference in disease characteristics and living conditions should be taken into consideration when establishing preventive strategies for CHF in Japanese communities. (*Circ J* 2007; **71:** 1004 – 1012)

Key Words: Charlson comorbidity index; Heart failure; Systolic dysfunction

In developed countries, the number of patients with heart failure (HF) is increasing progressively with the aging of the population, and the "New Epidemic" which Braunwald predicted at the end of the 20th century has now come true! Population-based studies in the United States and Europe have indicated that a large number of individuals with left ventricular (LV) systolic dysfunction (SD) are "hidden" behind those with symptomatic chronic HF[2–4] Therefore, guidelines for the management of HF emphasize the early detection and treatment of patients with SD as an important step in the strategy to reduce this burden in the future[5,6] Management of SD may also be important for reducing the future burden in Asian communities, where aging of the populating is rapidly advancing[7]

Japan has a universal health insurance system for treatment of diseases and local governments provide financial support for medical check-ups aimed at early detection of diseases. Because of good accessibility to medical services, a considerable percentage of residents have been screened for heart disease, so much information has accumulated in the local medical centers. Not a few patients are presumed to be under treatment for SD; however, scarce information is available. Therefore, in order to delineate the epidemiological and clinical characteristics of patients with SD in January 2003, we carried out a complete enumeration of the patients in Sado City (an island city in Japan) via cooperation with the local core hospitals and medical societies.

(Received December 25, 2006; revised manuscript received March 22, 2007; accepted April 11, 2007)

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Methods

Study Design and Participants

The Niigata-Sado Heart Failure Study was a complete enumeration survey for outpatients with SD at hospitals and clinics in 2 cities in Japan: Niigata and Sado (Fig 1). Sado City is an island with a surface area of 855 km^2 (about 1.4-fold the size of Tokyo metropolis), having a total population of 70,000 (almost all Japanese). This study was carried out at 4 core hospitals with hospitalization capacity, in collaboration with the local medical society. SD was defined as LV ejection fraction (LVEF) ≤50%. Within a total period of 6 years (extending from January 1st 1997 to December 31st 2002), data for patients with SD were extracted from the records of approximately 7,982 consecutive individuals who had their echocardiographic (Echo) examinations performed at 3 of the core hospitals in Sado City.

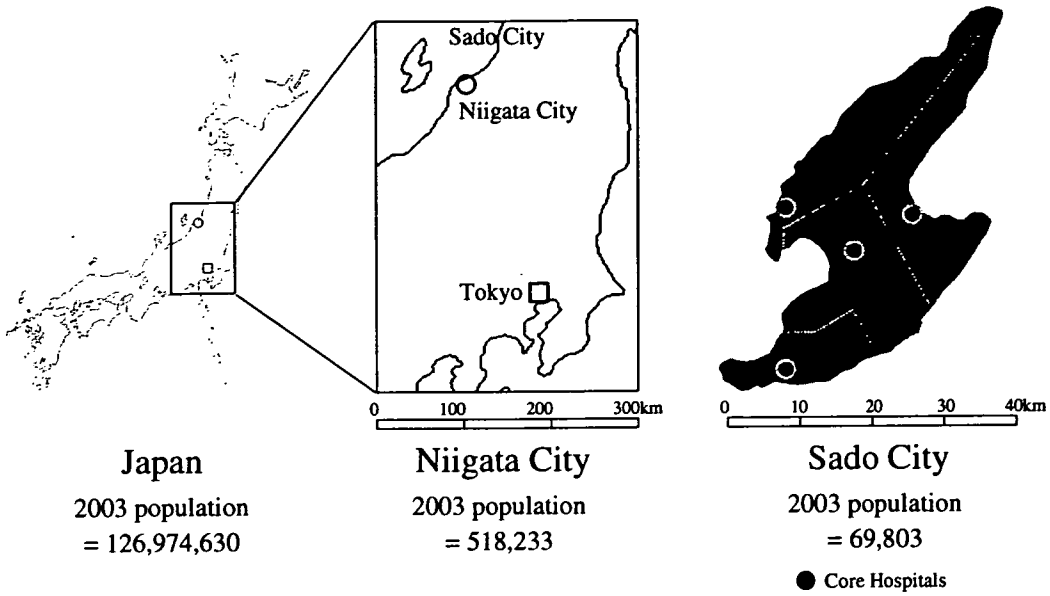

Fig 1. Map of the location and population of Niigata City and Sado Island in Japan on January 1st 2003: with details of the study area and its administrative divisions.

Niigata City is the nearest port to Sado City and has a population of 518,233 persons (Fig 1). Similarly, we examined all records of patients who underwent Echo examination in 14 hospitals in Niigata City to extract the total number of SD patients there.

Determination of Recruitment Period

The extraction of SD patients was begun on January 1st for 6 consecutive years (such as 2002, 2001, 2000, 1999, 1998, and 1997), and continued until December 31st 2002. Thus, SD patients were extracted from the Echo logs by tentatively setting the recruitment periods at 1, 2, 3, 4, 5, and 6 years. We noticed that the number of extracted patients increased with the extension of the recruitment period. However, the earlier the patients were identified, the more information was lost before 2003 because of death or missing data. Therefore, we compared the total counts of recruited patients in these 6 intervals to find the optimal period for identifying the proportion of SD patients in the general population in 2003. In case the same patient was extracted twice or more during the recruitment period, only data from the first extraction was considered.

Review of Cases

All medical records of the extracted patients were reviewed, and their clinical data were collected and summarized according to a predetermined protocol. If a patient consulted 2 or more institutions during the recruitment period, all the records at these institutions were reviewed.

Extraction of Patients' Data

The available clinical records were reviewed with regard to demography, medical history, SD etiology, associated comorbidities or complications, medical therapies, laboratory investigations, ECG and Echo examinations. For the patients who survived until 2003, the information was collected up to January 1st 2003. Present or past history of congestive HF (CHF) was confirmed using the Framingham criteria[8]

Determination of SD Etiology

Three cardiologists (Y Okura, K Suzuki, K Taneda) collaboratively consulted and diagnosed the etiology of SD. Ischemic heart disease (IHD) was considered as an etiology if the patient had 1 of the following: (1) documented history of myocardial infarction (MI), angina or prior coronary revascularization; (2) pathologic Q waves on ECG; or (3) >75% stenosis in 1 or more coronary arteries on coronary angiograms. Dilated cardiomyopathy (DCM) was diagnosed by the presence of global LV dilatation with impaired systolic function occurring in the absence of known cardiac or systemic causes. Valvular heart disease (VHD) was considered as an etiology of SD if mitral or aortic valve involvement was documented by Echo in the absence of IHD or DCM. Hypertensive heart disease was considered present if there was a history of hypertension and LV hypertrophy confirmed by Echo.

Confirmation of Survival

The survival of SD patients up to or beyond January 1st 2003 was confirmed by medical records. For those lacking records up to that date, direct phone calls to the family or attending physician were undertaken.

Determination of the Proportion of SD Patients in the General Population

This was done using the following equation:

$$\frac{\text{No. of SD survivors up to January 1st 2003}}{\text{Estimated population of Sado City on January 1st 2003}} \times 100$$

The numerator represents the Echo-documented SD patients extracted within the 5-year period after excluding those for whom survival status was impossible to determine. The denominator estimate was obtained from the Niigata Prefectural Department of Policy and Planning, Niigata,

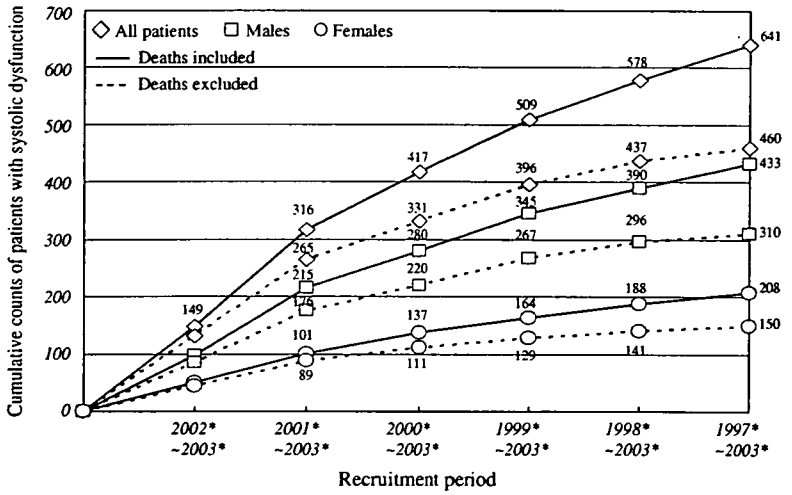

Fig 2. Cumulative frequency plot showing the yearly-partitioned recruitment period and the corresponding numbers of patients with systolic dysfunction extracted from the echocardiography files up to January 1st 2003. The increase in the number of patients was negligible when the recruitment period exceeded 5 years (dotted line). The number of patients missed because of a lack of medical records also increased with prolongation of the recruitment period (not shown). *January 1st of each year.

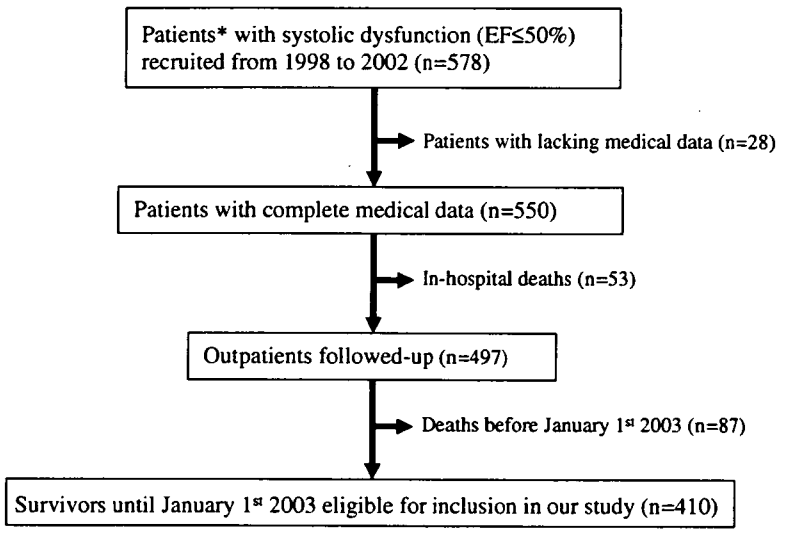

Fig 3. Flow chart of Sado Heart Failure study, showing the process of extraction and follow-up of patients with systolic dysfunction. When the starting date of the recruitment period was set at 5 years (from January 1st 1998 until December 31st 2002), 578 patients were extracted. Of them, 168 patients were excluded because of a lack of medical records, in-hospital (pre-discharge) mortality, or death during follow-up. Thus, 410 patients finally survived until January 1st 2003 and were included in the analysis. *Residents of Sado City with expected age range 45–84 years at January 1st 2003.

Japan? The obtained proportion was compared after stratification by gender and 5-year age intervals.

Survival Analysis

Survival curves of the general population of Sado City were prepared for both genders on the basis of the Niigata Prefecture Life Table (2000) using actuarial analysis[10,11] The latter table was made according to the National Life Table, which is based on the results of the Japan Population Census (2000). Similarly; survival curves of patients with LVEF ≤40% and those with LVEF 41–50% at the time of diagnosis were prepared, stratified by gender, and compared with the general population curves by log-rank test. Each of these curves was drawn by linking the points representing the average survival rate of each 5-year age group.

In addition, we evaluated the effects of associated comorbidities (included or not in the Charlson comorbidity index (CCI))[12,13] on patient's survival. Although CCI is a survival index, it has also been validated to correlate with physical disabilities and the re-admission rate in patients with chronic HF[13,14]

Statistical Analysis

Data analyses were performed using SPSS for Windows Version 13 (SPSS Inc, Chicago, IL, USA). Results for continuous normal data were expressed as mean±standard deviation. Comparison of means of continuous normal variables across a grouping variable with 2 was undertaken using Student's t-test. Comparison of proportions was made by χ^2 test with Yates's correction. 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 medical institution participating in this study, including the Niigata University Graduate School of Medical and Dental Sciences, and written consent was given by all patients.

Results

Evaluating the Cumulative Counts of SD Patients

The cumulative counts of SD patients recruited during the periods of varying length (ie, from 1 to 6 years) are shown in Fig 2. In order to determine the appropriate re-

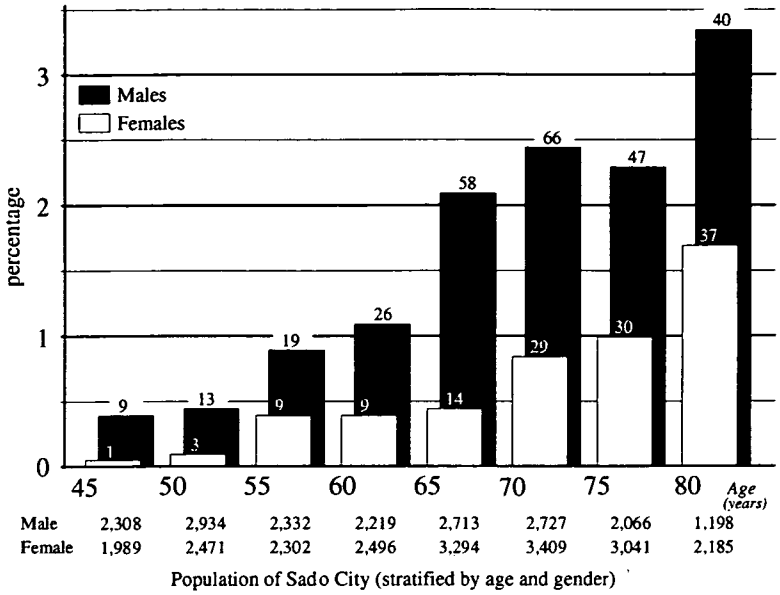

Fig 4. Bar graphs showing the proportion of patients with systolic dysfunction (SD) in the general population on January 1st 2003. The number shown at the upper end of each bar represents the SD patients' count, while the numbers below each age range along the horizontal axis represent the male and female populations for that range.

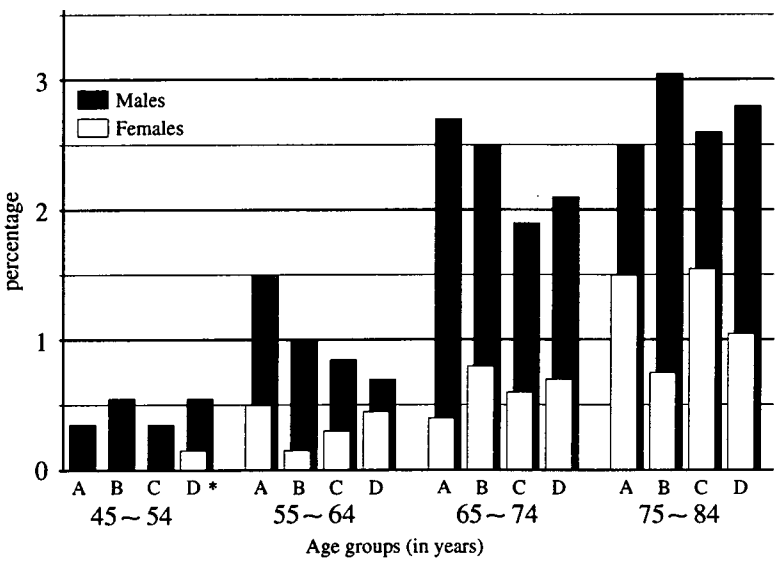

Fig 5. Bar graphs showing the regional proportions of patients with systolic dysfunction (SD) in the general population in Sado City on January 1st 2003. there is no significant difference regarding these proportions among the 4 regions. *The letters A to D represent the 4 divisions of Sado City (Island).

cruitment period for counting surviving patients in 2003, we evaluated the relationship between recruitment period and the cumulative counts of SD patients. Because some of the recruited patients died before 2003, the number of SD patients who were alive was somewhat fewer than those who were recruited. As shown in Fig 2, solid lines connect the total counts of recruited patients, including those who died before 2003 (Deaths included) and the dotted lines connect the counts of recruited patients who survived until 2003 (Deaths excluded). Considering the yearly intervals as a continuum, a significant positive trend was found for the cumulative counts of SD patients in all patients and in both genders (Deaths included). Nevertheless, such an estimate showed a weak trend relative to the increment of the recruitment period when considering only the cumulative numbers of survivors; that is, the patients' cumulative count curve became nearly flat on moving from 2002–2003 to 1997–2003 (Deaths excluded).

Follow-up of Extracted Patients

A total of 578 patients were extracted within the 5-year recruitment period (from January 1st 1998 till December 31st 2002) (Fig 2) and of them 28 (5%) were excluded because of either the absence of medical records or inability to confirm survival (Fig 3). Moreover, 53 in-hospital deaths (before discharge) were excluded, as well as 87 deaths that were ascertained to have taken place before January 1st 2003 on careful follow-up. Thus, 410 patients were confirmed to have survived up to that date and were eventually included in our study. We found 18 Sado residents with SD in the Echo logs of the Niigata hospitals, but they had already been diagnosed as SD in Sado.

Proportion of SD Patients in the General Population in Relation to Age, Gender, and Region

The proportion of SD patients in the general population sector aged 45–84 years was 1.5% for males and 0.6% for

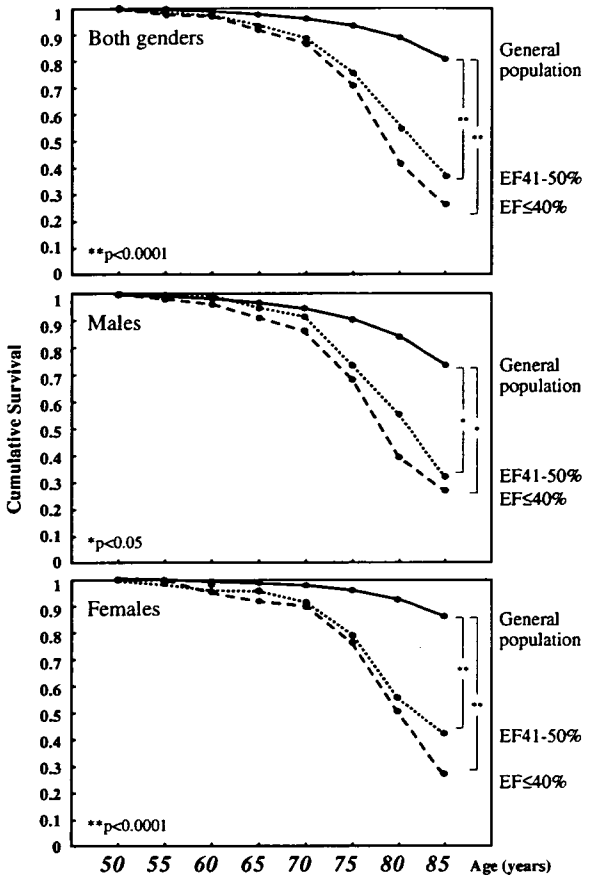

Fig 6. Comparative analysis of survival between patients with systolic dysfunction (SD) and the general population. Survival curves of the general population (on the basis of the Niigata Prefecture Life Table [2000]), and those of patients with mild (left ventricular ejection fraction (LVEF) 41–50%) and severe (LVEF ≤40%) SD were prepared using actuarial methods; and comparisons were made by log-rank test. Compared with the general population, the survival rate was significantly lower in both the mild and severe SD patient groups. On the other hand, this rate did not significantly differ between the 2 groups.

females (Fig 4). This proportion increased sharply after the age of 65 years in males and 70 years in females; reaching 3.3% in males and 1.7% in females in their 80 s. The proportion in the 4 zones of Sado Island (labeled A–D in Fig 1) was compared after stratification by gender and age decades (Fig 5) and no significant difference in that proportion was found in either gender within any age group among the 4 areas.

Comparison of Patients' Survival Rates Relative to the General Population

We followed 497 outpatients with SD from diagnosis. The duration of follow-up was 4.5±2.3 years. Fig 6 shows survival curves of the general population (based on the life table), compared with those of SD patients, before and after stratification by gender. In comparison with the general population, the cumulative survival was significantly lower in patients with mild SD (LVEF 41–50%) as well as in those with severe SD (LVEF ≤40%). However, this rate was not significantly different between the 2 groups.

Characteristics of SD Patients

Demographic Characteristics We included 410 patients with SD whose survivalp until January 1st 2003 was correctly confirmed. Approximately two-thirds of them (68%) were males, who were significantly younger than the females (70.2±8.2 vs 73.9±8.6 years; p<0.01).

Primary Etiologies of SD Two hundred and three patients (50%) underwent diagnostic coronary angiography. As shown in Table 1, IHD was the most frequent etiology of SD in all cases (34%) and in males (41%), whereas VHD was the most prevalent in females (24%). Hypertensive heart disease was the second important cause of in all cases (21%). The primary disease could not be determined in 10% of cases, particularlyin those with mild SD.

Associated Comorbidities Adequately documented present or past histories of comorbidities are shown for both genders in Table 2. Hypertension was the most prevalent comorbidity found in all cases (≈41%) and males (42%). CHF was significantly associated with SD and was the second most prevalent comorbidity in all cases (29%) and the first one in females (42%). MI occurred more often in males (32%) than did CHF (23%) which came next in importance. Notably; cerebral stroke was markedly prevalent in SD patients (20% of all cases), especially males (23% compared with 14% in females); as well as psychiatric disorders, such as depression and dementia, which were found in 13% of patients.

Level of Daily Activities and Lifestyle As can be ascertained from Table 2, the majority of patients (92%) were independently mobile and wheel-chair-dependents constituted the minority (3%). Notably, women tended to lead a more solitary life than men who tended to live in families.

CCI In this index, a score of 1 point is given for each of the following conditions: CHF, MI, and diabetes. Thus, nearly one-quarter (24%) of patients were free of comorbidities (a score of 0), and similar proportions (27% and 25%) had scores of 1 and 2, respectively. Half of the patients had a CCI score ≥2, which was considered to indicate a poor prognosis. Approximately 12% of patients had a score ≥4, indicating a low possibility of survival![4]

Table 1 Primary Etiologies of SD in the Study Patients

Primary etiology of SD	*Male (n=278)*	*Female (n=132)*	*p value*
Ischemic heart disease	*113 (40.6%)*	*26 (19.7%)*	*<0.01*
Hypertensive heart disease	*60 (21.6%)*	*27 (20.5%)*	*NS*
Valvular heart disease	*26 (9.4%)*	*32 (24.2%)*	*<0.01*
Dilated cardiomyopathy	*39 (14%)*	*14 (10.6%)*	*NS*
Chronic renal failure	*8 (2.9%)*	*4 (3.0%)*	*NS*
Tachyarrhythmias	*6 (2.2%)*	*8 (6.1%)*	*<0.01*
Congenital cardiac malformations	*5 (1.8%)*	*0 (0%)*	*NS*

SD, systolic dysfunction.

Table 2 Clinical and Other Characteristics of Surviving Patients With SD*

	Male (n=278)	Female (n=132)	p value
Associated comorbidities and their management			
Cardiovascular risk factors/chronic medical illnesses			
Age (years)	70.2±8.9	73.9±8.6	<0.01
Hypertension	117 (42.1%)	49 (37.1%)	NS
Diabetes mellitus	82 (29.5%)	18 (13.6%)	<0.01
Dyslipidemia	54 (19.4%)	25 (18.9%)	NS
Body mass index			
≥25 to <30 kg/m² (overweight)	47 (16.9%)	13 (9.6%)	<0.05
≥30 kg/m² (obesity)	5 (1.7%)	4 (2.7%)	NS
Cardiac disorders			
CHF hospital admission	65 (23.4%)	55 (41.7%)	<0.01
Angina pectoris	34 (12.2%)	4 (3%)	<0.01
Myocardial infarction	89 (32.0%)	24 (18.2%)	<0.01
Arrhythmias			
Atrial fibrillation			
Paroxysmal	31 (11.2%)	9 (6.8%)	NS
Chronic	55 (19.8%)	33 (25.0%)	NS
Sustained ventricular tachyarrhythmia	5 (1.8%)	2 (1.5%)	NS
Permanent cardiac pacemaker	8 (2.9%)	0 (0%)	<0.05
Intraventricular cardioverter defibrillator	0 (0%)	1 (0.8%)	NS
Cardiac surgery/intervention			
Cardiac valve replacement	12 (4.3%)	10 (7.6%)	NS
Diagnostic coronary angiography	151 (54.3%)	52 (39.4%)	NS
Percutaneous coronary intervention	45 (16.2%)	12 (9.1%)	NS
Coronary artery bypass graft operation	23 (8.3%)	3 (2.3%)	<0.05
Neuropsychiatric disorders			
Stroke	63 (22.7%)	18 (13.6%)	<0.05
Psychiatric illness	31 (11.2%)	22 (16.7%)	NS
Chronic kidney disease			
CRI (serum creatinine ≥2 mg/dl)	10 (3.6%)	6 (4.5%)	NS
CRF (on regular hemodialysis)	16 (5.8%)	4 (3.0%)	NS
Pulmonary disorders			
Bronchial asthma	16 (5.8%)	1 (0.8%)	<0.05
Chronic obstructive pulmonary disease	18 (6.5%)	2 (1.5%)	<0.05
Home oxygen therapy	6 (2.2%)	1 (0.8%)	NS
Malignancy			
Nonmetastatic	23 (8.3%)	14 (10.6%)	
Advanced	10 (3.5%)	3 (2.3%)	NS
Level of daily activities and lifestyle			
Independently mobile	263 (94.6%)	115 (87.2%)	
Wheel chair-dependent	6 (2.0%)	6 (4.3%)	<0.05
Bedridden	9 (3.4%)	11 (8.5%)	
Solitary life	35 (12.7%)	31 (23.6%)	<0.01
Educational background			
≤12 years	241 (86.7%)	119 (90.3%)	
>12 years	37 (13.3%)	13 (9.7%)	NS
Medications			
ACEIs	98 (35.3%)	42 (31.8%)	NS
Angiotensin-II receptor blockers	32 (11.5%)	6 (4.5%)	<0.05
β-adrenergic receptor blockers	51 (18.3%)	12 (9.1%)	<0.05
Calcium-channel blockers	92 (33.1%)	46 (34.8%)	NS
Loop diuretics	120 (43.2%)	74 (56.1%)	<0.05
K⁺-sparing diuretics	42 (15.1%)	23 (17.4%)	NS
Digitalis glycosides	49 (17.6%)	38 (28.8%)	<0.01
Aspirin	87 (31.3%)	32 (24.2%)	NS
Ticlopidine	30 (10.8%)	8 (6.1%)	NS
Oral anticoagulants	98 (35.3%)	32 (24.2%)	<0.05
Nitrates	59 (21.2%)	26 (19.7%)	NS
Statins	55 (19.8%)	20 (15.2%)	NS
Electrocardiographic data			
LV hypertrophy	50 (18.0%)	27 (20.5%)	NS
Left bundle branch block	17 (6.1%)	6 (4.5%)	NS
Right bundle branch block	18 (6.5%)	7 (5.3%)	NS
Pathologic Q-wave	60 (21.6%)	11 (8.3%)	<0.01
Echocardiographic data			
Ejection fraction (%)	39.4±8.8	41.2±8.1	<0.05
Fractional shortening (%)	19.8±5.1	20.5±4.3	NS
LVDd (mm)	56.4±9	54.3±8.2	<0.05
LVDs (mm)	45.7±7.6	43.3±7.6	<0.01
IVST (mm)	10.5±3.0	9.6±2.7	<0.01
PWT (mm)	10.4±2.4	9.8±2.1	<0.05
LV mass index (g/m²)	149.5±52.0	145.9±46.9	NS

Left atrial diameter (mm)	*41.9±8.8*	*43.3±9.7*	*NS*
Tricuspid valve regurgitation	*45 (16.2%)*	*27 (20.5%)*	*NS*
Mitral valve regurgitation	*28 (10.1%)*	*20 (15.2%)*	*NS*
Aortic valve regurgitation	*12 (4.3%)*	*7 (5.3%)*	*NS*
Functional and prognostic indices			
New York Hear Association functional class			
Class I	*74 (26.5%)*	*25 (19.0%)*	
Class II-III	*193 (69.5%)*	*107 (81.0%)*	*<0.05*
Class IV	*11 (4.0%)*	*0 (0%)*	
Charlson comorbidity index			
0 point	*57 (20.5%)*	*41 (31.1%)*	
1 point	*76 (27.3%)*	*34 (25.8%)*	
2 points	*69 (24.8%)*	*32 (24.2%)*	*NS*
3 points	*43 (15.5%)*	*11 (8.3%)*	
≥4 points	*33 (11.9%)*	*14 (10.6%)*	

**Survived until January 1st 2003.*
Echocardiography data shown are those obtained on the initial diagnosis of SD. LV 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] then was indexed to body surface area (m²).
CHF, congestive heart failure; CRI, chronic renal impairment; CRF, chronic renal failure; ACEIs, angiotensin-converting enzyme inhibitors; LV, left ventricular; LVDd, left ventricular diastolic dimension; LVDs, left ventricular systolic dimension; IVST, interventricular septal thickness; PWT, posterior wall thickness.
Values are mean±SD or number of subjects (%).

Table 3 Variables Independently Associated With Mortality*

	β-coefficient	*OR*	*95%CI of OR*	*p value*
Body mass index (kg/m²)	*−0.168*	*0.845*	*0.796–0.898*	*<0.001*
Age at diagnosis	*0.033*	*1.034*	*1.012–1.055*	*0.002*
LVDd×LVDs interaction (cm²)	*0.039*	*1.040*	*1.020–1.060*	*<0.001*
CHF history	*0.525*	*1.690*	*1.218–2.346*	*0.002*
Malignancy	*0.788*	*2.199*	*1.492–3.242*	*<0.001*
Stroke	*0.798*	*2.221*	*1.591–3.101*	*<0.001*
Chronic kidney disease	*0.921*	*2.511*	*1.655–3.808*	*<0.001*

**Using stepwise Cox proportionate hazard regression model, with the corresponding ORs.*
OR, odds ratio; CI, confidence interval. Other abbreviations see in Table 2.

Predictors of Mortality

A Cox proportionate hazard regression model was constructed for identifying the prognostic predictors of death. Simple univariate analysis was done first for each of the input variables against positive death outcome, and all the variables (except for gender) associated with it at p≤0.1 were finally entered in a multivariate backward stepwise Cox regression model. Owing to the high correlation between LV systolic dimension (LVDs) and LV diastolic dimension (LVDd), as well as LVEF and fraction shortening (FS), these 2 pairs of variables were entered into the model as interaction terms (ie, LVDd×LVDs in cm^2 and LVEF×FS) to avoid collinearity. Thus, the following variables were included in the final model: age at diagnosis, gender, body mass index (BMI), presence of dyslipidemia, history of CHF, chronic kidney disease (CKD) (serum creatinine ≥2 mg/dl or regular hemodialysis), stroke, malignancy, treatment with angiotensin-converting enzyme inhibitors or diuretics, and the interactions of LVDd/LVDs and EF/FS. The model was proven to be highly significant (p-value for the omnibus tests of model coefficients <0.001). Eventually, age at primary diagnosis, LVDd×LVDs interaction, history of CHF, presence of stroke, CKD, and malignancy were found to be significantly and independently associated with death, and BMI was an independent inverse correlate of that event (Table 3).

Discussion

Evaluating the burden of cardiovascular disease on society has become an urgent requirement because disease profiles have changed rapidly in accordance with aging of the general population. The Niigata-Sado Heart Failure Study was conducted to provide such information. The demo-geographic characteristics of the study area (ie, an island) facilitated follow-up of the study cohort and improved subject inclusiveness and the sequentiality of enrollment, giving the advantage of reducing bias in patient selection. From this study, we have the following new observations: (1) the number of outpatients with SD amount to 2–3% of the population; (2) there is a gender difference in the characteristics of patients with SD; (3) patients with SD have several comorbidities that affect prognosis; and (4) the prognosis of patients with SD, even with favorable LVEF (41–50%), is worse than that of the general population.

The aim of this study was to count the number of outpatients with SD in 2003 and clarify their characteristics. Before doing so, we verified whether recruitment period was appropriate (Fig 2), and SD patients were collected without regional difference on the island (Fig 5). The dates when the patients were diagnosed to have SD varied; for example, when considering 2 patients who were diagnosed in 2002 and in 1999, the recruitment from 2002 to 2003 could identify the former but not the latter, whereas recruitment from 1999 to 2003 could identify both. Because there

was a directly proportional relationship between the number of identified patients and the length of the recruitment period; high inclusiveness was expected by setting the starting point of the period as early as possible (even more than 5 years) as shown in Fig 2. However, some SD patients died before 2003, and there was also an incremental relationship between the number of SD patients who died before 2003 and the length of the recruitment period. Therefore, the net increase in SD survivors by 2003 was suppressed by extending the recruitment period (Fig 2). Thus, we believe that the 5-year recruitment period (from 1998 to 2002) was efficient and appropriate for counting SD survivors in 2003.

The proportion of SD patients in the general population sector aged 45–84 years was 1.5% for males and 0.6% for females (Fig 4). This proportion increased after the age of 65 years in males and 70 years in females, reaching 3.3% in males and 1.7% in females in their 80s. These estimates were only based on the number of patients who were confirmed to have SD, and those in the general population with latent cardiac dysfunction who did not undergo Echo examinations were not included. Therefore, the estimates presented here are virtually lower than the true counts, and more residents may have untreated SD. These estimates differ considerably from the prevalence rates reported by population-based studies in the United States and Europe (6.9–10.2% for males and 3.4–3.8% for females; 11.2% for males and 8.3% for females in their 80s)[2,3] In fact, detailed comparison would be impossible for many reasons (eg, geo-demographic, ethnic and methodological differences); however, the lower incidence of MI in the Japanese population compared with those of Western countries may be the reason for the lower prevalence of SD in Japan![5,16]

Our results highlighted the average characteristics of patients who were often clinically observed with the least possible selection bias, unlike the data derived from large-scale clinical studies conducted on subjects who have passed multiple exclusion criteria. Tsutsui et al[17] and Shiba et al[18] reported the clinical characteristics of Japanese patients with CHF in Fukuoka and Tohoku, respectively. The prevalence of hypertension, IHD, and atrial fibrillation (AF) was 39–41%, 25–44%, and 31–41%, respectively. Compared with their cohorts in which most patients had a history of hospital admission for CHF, the majority (71%) of our SD cohort did not have such a history. However, the prevalences of hypertension (40%), IHD (34%), and AF (31%) were consistent with these previous reports. Senni et al[19] reported the clinical characteristics of white patients who were admitted with new-onset CHF in Olmsted County. They categorized 137 patients into CHF with reduced LVEF (<50%) group and that with preserved LVEF (≥50%). Seventy-eight patients (57%) showed reduced LVEF, males were dominant (59%), and the average age was 74.2 years. The prevalences of hypertension, IHD, AF and DCM were 50%, 53%, 24%, and 3% respectively. Hypertension and IHD prevailed more in the white cohorts than in ours, whereas AF and DCM were more prevalent in our cohort.

Comorbidity was a significant health problem for the patients with SD in this study. Half of them had a CCI score ≥2 (Table 2), and were thus considered as a poor prognosis group[20,21] Compared with the reports from North America[20,21] our cohort had a higher CCI score; for example, the proportion of patients (or residents) with CCI score ≥2 in the Duke databank of IHD (1,471 patients, 61 years old on average)[20] the population-based cohort of Olmsted county (2,037 people, average age of 61 years)[22] and in the HF registry of Ontario (38,702 patients, 85% of the patients were over 65 years old)[21] was only 19%, 32%, and 29%, respectively. The reasons for the higher CCI score in our cohort are not clear, but we hypothesize higher age, the hospital-based study design, and the meticulous archiving of patients data, which maximized the diagnosis of associated comorbidities.

Additionally, some of the comorbidities (CHF, stroke, CKD, and malignancy), which were also scored by CCI, were shown to be independently and significantly associated with death in our cohort. In general, the high prevalence of poor prognostic comorbidities worsens the survival of the cohort. Therefore, the survival of these patients was poorer than that of the general population, in either those with relatively favorable systolic function (LVEF 41–50%) or those with significantly impaired LVEF (≤40%) (Fig 6).

Study Limitations

First, because this study was hospital-based and not population-based, it might have missed the latent SD patients in the community. In Sado City, 43% of residents over 45 years annually undergo medical check-up for early detection of disease, which is supported by the local government. However, we cannot exactly define the proportion of residents who proceeded to Echo examinations out of the total number examined clinically. Accordingly, estimation of the precise prevalence of SD in the general population was not possible, so instead we have shown the proportion of Echo-documented SD. Also, the literature has indicated a gender difference regarding consultation, examination, and treatment of cardiac patients[23] which our study could not avoid. Moreover, the limitation of the study area to Sado Island may restrict the generalization of our results to other areas in Japan. In addition, half of the patients, especially asymptomatic ones with mild SD, did not undergo diagnostic coronary angiography. In this respect, it is known whether noninvasive diagnostic processes have limitations in classifying disease etiology precisely.

Conclusions

We carried out the first complete enumeration survey of SD in a Japanese community. The Sado Heart Failure Study is a highly inclusive hospital-based study that may be able to characterize patients with SD in the community. The proportion of patients with SD in the general population increases progressively with age. These patients often have multiple comorbidities, making the outcome of even mild SD a poor one. The gender difference in disease characteristics and living conditions of patients should be taken into consideration when establishing preventive strategies for HF in Japanese communities.

Acknowledgments

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

It 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).

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Circ J 2007; **71**: 1013–1021

Characterization of Outpatients With Isolated Diastolic Dysfunction and Evaluation of the Burden in a Japanese Community

—— Sado Heart Failure Study ——

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Background The incidence of diastolic heart failure (DHF) is increasing with the aging of the community and identifying patients with isolated diastolic dysfunction (IDD) is important for preventing DHF. However, very little information is available about such patients in the Japanese community.

Methods and Results The medical information of all outpatients with moderate to severe IDD was extracted from the records of approximately 6,948 individuals who underwent echocardiographic (Echo) examinations during the past 5 years in Sado Island. Of the 284 patients extracted, 272 survived until 2003. In January 2003 the proportion of patients with moderate to severe IDD in the general population sector aged 45–84 years was 0.9% for males and 0.5% for females, and this proportion increased sharply after the age of 65 in both genders, reaching 1.6% for men in their 70s and 0.8% for women in their 80s. On Echo, 165 patients (61%) showed hypertrophic left ventricular geometry. The Charlson comorbidity index score was ≤1 in 63% of patients. The cumulative survival of IDD patients, irrespective of a history of congestive heart failure (HF), was significantly lower than in the general population.

Conclusions Moderate to severe IDD is not uncommon in the elderly and has a poor prognosis. Characteristics of outpatients with IDD should be taken into consideration when establishing a preventive strategy for HF in the Japanese community. (*Circ J* 2007; **71**: 1013–1021)

Key Words: Diastolic dysfunction; Disease burden; Charlson comorbidity index; Heart failure

The prevalence of heart failure (HF) is increasing progressively in developed countries with the aging of the population! Recently, some studies have reported a large number of individuals with isolated diastolic dysfunction (IDD) in the general population[2,3] The clinical presentation of IDD is very diverse, ranging from no symptoms to so-called diastolic HF (DHF), which manifests clinically as congestive HF (CHF). IDD is a new target of therapy for the prevention of HF. Compared with the diagnosis of left ventricular (LV) systolic dysfunction (SD), the diagnosis of IDD is rather more complicated and easily overlooked.

Management of IDD may be important for reducing the future burden of HF in Asian communities, where aging of the populating is rapidly advancing[4] Not a few patients are presumed to be under treatment for IDD, but information is scarse. Therefore, to delineate the epidemiological and clinical features of patients with IDD, we carried out complete enumeration of them in Sado City, via co-operation with the core hospitals and medical societies.

(Received January 23, 2007; revised manuscript received April 12, 2007; accepted April 17, 2007)

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Methods

Selection of Cases

The Sado Heart Failure Study was designed to characterize outpatients with cardiac dysfunction at the hospitals and clinics of Sado City, an island city in Japan. Within a total period of 5 years (extending from January 1st 1998 till December 31st 2002), patients with IDD were extracted from the records of 6,948 consecutive individuals who had their echocardiographic (Echo) examinations performed at 2 core hospitals in Sado City. In case the same patient was extracted twice or more during the recruitment period, only the data for the first extraction was considered.

Definition of IDD

IDD was defined as LV ejection fraction (LVEF) ≥40%, plus at least 1 of the following criteria (after excluding moderate or severe mitral and aortic insufficiency): (1) deceleration time (DCT) <140 ms; (2) ratio between systolic (S) and early diastolic (D) waves of the antegrade flow of the pul-

Table 1 Charlson Comorbidity Index[7,8]

Disease	*Assigned weight*
Myocardial infarction	
Congestive heart failurex	
Peripheral vascular disease (arteriosclerosis obliterans, acute arterial occlusion)	
Dementia	*1*
Chronic pulmonary disease	
Connective tissue disease	
Mild liver disease (chronic viral hepatitis)	
Diabetes mellitus	
Hemiplegia	
Moderate or severe renal disease (serum creatinine ≥2 mg/dl or hemodialysis)	
Any tumor	*2*
Leukemia	
Lymphoma	
Moderate or severe liver disease (fulminant hepatitis, esophageal varices, liver cirrhosis)	*3*
Metastatic solid tumor	*6*

monary venous flow velocity tracing (S/D ratio) <1; and (3) difference between the duration of pulmonary venous atrial reversal flow and transmitral flow at atrial contraction tracing (literally AR-A) >30 ms.

These criteria have been used to identify moderate (pseudonormal) or severe (restrictive) diastolic dysfunction (DD) in other studies[2,3] In order to reduce oversight and include suspected cases, we included any patient who fulfilled at least 1 of the criteria. The possession of the first criterion was necessary to include patients with chronic atrial fibrillation (AF). Patients with LVEF <40% were counted and grouped under the SD category, whereas those with LVEF <50% (with none of the abovementioned criteria) were considered as the control group for IDD patients for comparative purposes.

Review of Cases

All medical records of the extracted patients were reviewed, and their clinical data were collected and summarized according to a predetermined protocol. If a patient consulted 2 or more medical institutions during the recruitment period, as far as possible all the records at those institutions were reviewed.

Extraction of Patients' Data

The available clinical records were reviewed with regard to demography, medical history, comorbidities, medical therapies, laboratory investigations, electrocardiographic (ECG) and Echo examinations. LV hypertrophy (LVH) was defined as high voltage [Sokolow-Lyon voltage (SV1+RV5/6) >38 mm] associated with left atrial enlargement and/or ST-T change in the left precordial leads of the ECG. Echocardiographic LV 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−LVDd^3)+0.6] and then indexed to body surface area (m^2) (LVDd, LV diastolic dimension; IVST, interventricular septal thickness; PWT, posterior wall thickness).[5] In the patients who survived, the information was collected up to January 1st 2003. Present or past history of CHF was confirmed using the Framingham criteria.[6] In addition, we evaluated the effects of comorbidities (included or not in the Charlson comorbidity index (CCI)) on patients' survival[7,8] (Table 1). Although the CCI is a survival index, it has also been validated to correlate with physical disabilities and re-admission rates in patients with chronic HF.[8,9]

Confirmation of Survival

Confirming the survival of patients with available hospital records up to or beyond January 1st 2003 was quite easy; but for those without such records, direct phone calls to their families or attending physicians were made. Based on the available clinical information, professional cardiologists classified the causes of death as cardiac or noncardiac, according to previous epidemiological studies conducted in Japan.[10,11] Cardiac death was defined as death from cardiac events: fatal myocardial infarction (MI), HF, or sudden cardiac death. Noncardiac death was defined as death from noncardiac causes (such as cancer).

Determination of the Proportion of IDD Patients in the General Population

This was done using the following equation:

$$\frac{\text{No. of DD survivors up to January 1st 2003}}{\text{Estimated population of Sado City on January 1st 2003}} \times 100$$

The numerator estimate represents the Echo-documented IDD patients extracted for the whole period of this study (5 years) after excluding those in whom survival status was impossible to be determined. The denominator estimate was obtained from the Niigata Prefectural Department of Policy and Planning, Niigata, Japan.[12] The obtained proportion was compared after stratification by gender and 5-year age intervals.

Survival Analysis

Survival curves of the general population of Sado City were prepared for both genders on the basis of the Niigata Prefecture Life Table (2000) using actuarial analysis.[13,14] The latter table was made according to the National Life Table, which is based on the results of the Japan Population Census (2000). Similarly, survival curves of patients with IDD were prepared, stratified by gender, and compared with the general population curves by log-rank test. Each of these curves was drawn by linking the points representing the average survival rate of each 5-year age group. We excluded patients with malignant conditions (n=34), because they may have an impact on the effect of IDD on survival.

Statistical Analysis

Data analyses were performed with SPSS for Windows Version 13 (SPSS Inc, Chicago, IL, USA). Results for con-

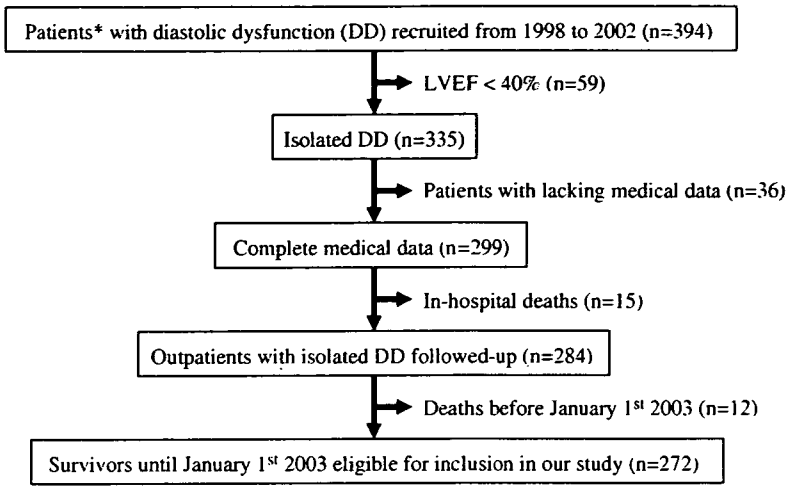
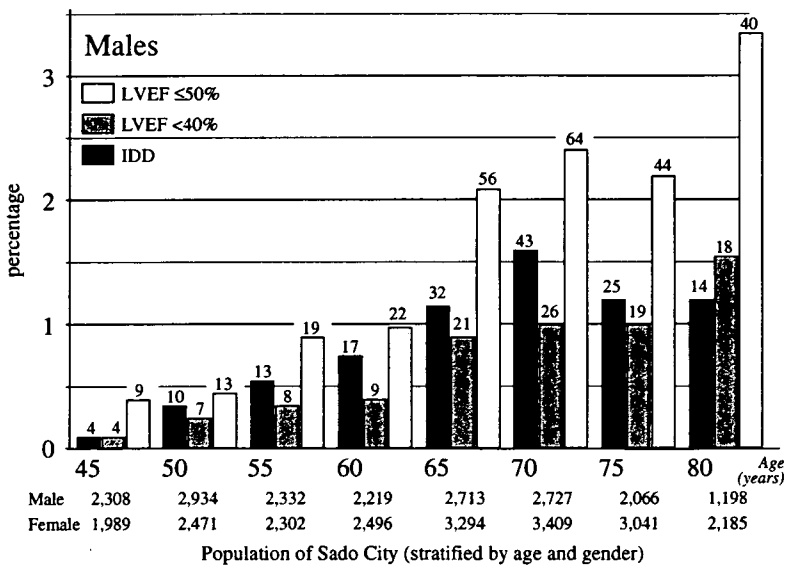


Fig 1. Flow chart of Sado Heart Failure study, showing the process of extraction and follow-up of patients with isolated diastolic dysfunction (IDD). The starting date of the recruitment period was set at 5 years (from January 1st 1998 until December 31st 2002), and 335 patients were extracted. Out of this number, 63 patients were excluded due to a lack of medical records, unavailable diagnosis, in-hospital (pre-discharge) mortality, or death on follow-up. Thus, 272 patients finally survived until January 1st 2003 and were included in the calculation of the prevalence of IDD. *Residents of Sado City with expected age range 45–48 years on January 1st 2003.



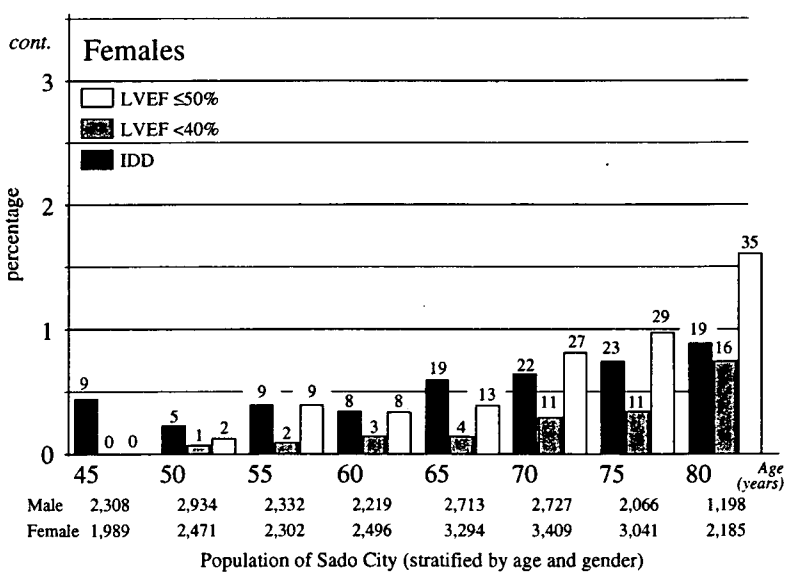


Fig 2. Bar graphs showing the proportion of isolated diastolic dysfunction (IDD) and systolic dysfunction (SD) patients in the general population for males and females on January 1st 2003. The number shown at the upper end of each bar represents patients' count, while the numbers below each age range along the horizontal axis represent the male and female populations for that range. LVEF, left ventricular ejection fraction.

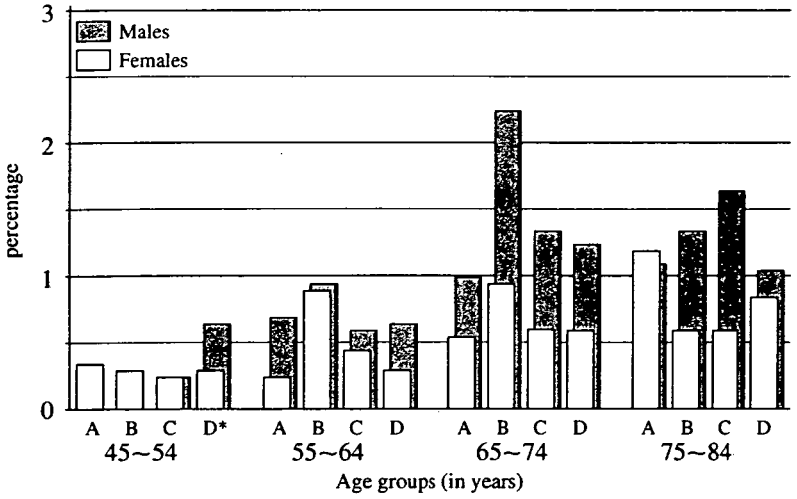


Fig 3. Bar graphs showing the regional proportion of isolated diastolic dysfunction (IDD) patients in the general population of Sado City on January 1st 2003 (classified by gender and age groups). No significant difference regarding the proportion of IDD was observed among the 4 regions in any age group for either gender. *The letters A to D represent the 4 divisions of Sado Island.

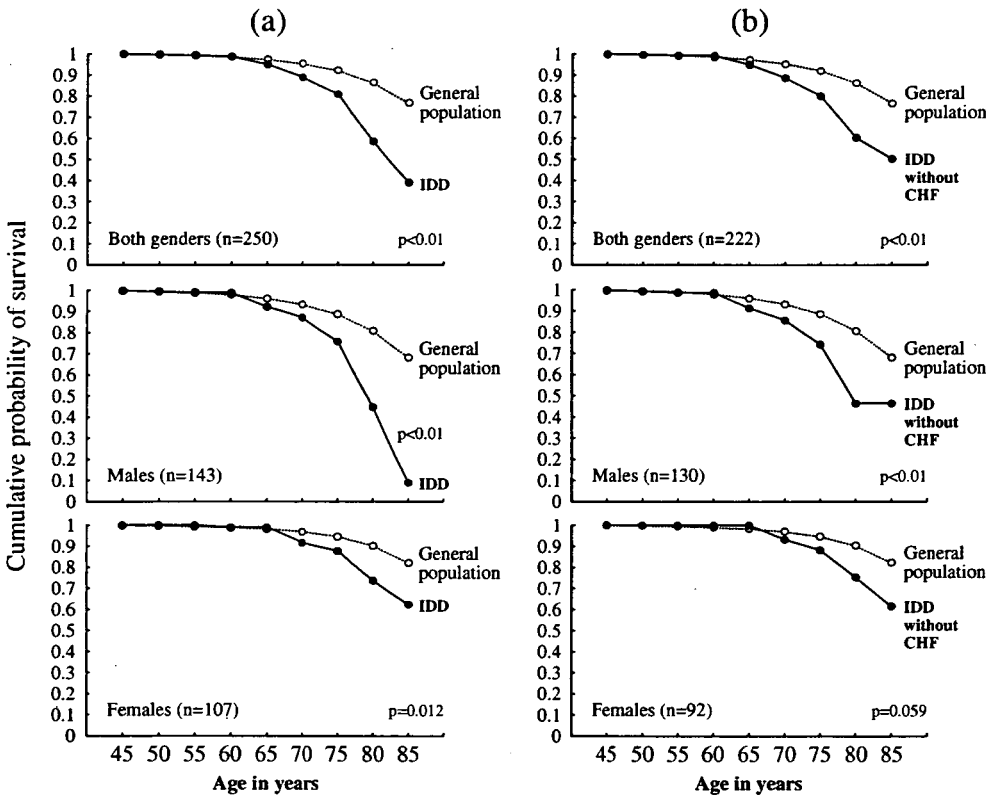


Fig 4. Comparative analysis of survival between patients with isolated diastolic dysfunction (IDD) and the general population. Survival curves of the general population (on the basis of Niigata Prefecture Life Table [2000]), and those of patients with IDD (a) as well as those of IDD without history of congestive heart failure (CHF) (b) were prepared by using actuarial methods: and comparisons were made by log rank test. Compared to the general population, the survival rate was significantly lower in patients with IDD and IDD without history of CHF. IDD without CHF, IDD without history of CHF.

tinuous normal data are expressed as mean ± standard deviation. Comparison of means of continuous variables across a grouping variable with 2 levels was done by Student's t-test. Comparison of proportions was made by χ^2 test with Yates's correction. 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 medical institution participating in this study, including the Niigata University Graduate School of Medical and Dental Sciences, and written consent was given by all patients.

Results

Follow-up of Extracted Patients (Fig 1)

A total of 394 patients with DD were extracted within the 5-year recruitment period (from January 1st 1998 till December 31st 2002). We excluded 85 patients: 59 with LVEF <40%, and 36 who either lacked medical records or we were unable to confirm their survival. Moreover, 15 in-hospital deaths (before discharge) were excluded, as well as 12 deaths that, on careful follow-up, were ascertained to take place before January 1st 2003. Thus, 272 patients (58% males) were confirmed to have survived up to that date and were eventually included in the study.

Proportion of IDD Patients in the General Population in Relation to Age, Gender, and Region

The proportion of IDD patients in the general population sector aged 45–84 years was 0.85% for males and 0.54% for females (Fig 2). This proportion increased sharply after the age of 65 in both genders, reaching 1.6% for men in their 70 s and 0.8% for women in their 80 s.

The proportion of IDD in the 4 zones of Sado Island was compared after stratification by gender and age decades (Fig 3). No significant difference in the proportion of IDD was found in either gender within any age group among the 4 areas.

Comparison of Patients' Survival Rates Relative to the General Population

We followed 284 outpatients with IDD from diagnosis (mean follow-up 4.4±1.7 years). Fig 4 shows the survival curves of the general population (based on the life table) compared with those of the IDD patients without a history of malignancies (n=250), before and after stratification by gender. In comparison with the general population, the IDD patients cumulative survival rate was significantly lower for both males and females. On the other hand, in patients with IDD without CHF history, the survival of males was significantly lower than that of the general population; females did not exhibit such a significant difference.

Characteristics of IDD Patients

Associated Comorbidities Adequately documented present or past histories of comorbidities are shown for both genders in Table 2. Hypertension was the most prevalent comorbidity (46%) for both genders. Traditional cardiovascular risk factors were also prevalent among these patients; nearly one-quarter (24%) were diabetic, and dyslipidemia and abnormal body weight were found in 22% and 19% of cases, respectively. Twenty-eight percent of all patients underwent cardiac catheterization, and ischemic heart disease was frequently observed in males (19%) and females (15%). AF was the second most prevalent comorbidity associated with IDD in all cases (33%) and in either gender. Of 206 patients with normal sinus rhythm in 2003, 25 (12%) of them had a history of AF (ie, paroxysmal AF). Notably, a considerable percentage (21%) of patients had had a cerebral stroke, and psychiatric disorders, such as depression and dementia, were found in 11% of all cases (significantly more prevalent in females).

Level of Daily Activities and Lifestyle The majority of patients (93%) were independently mobile (Table 2) and wheel chair-dependents actually constituted a minority (3%). Notably, women tended to lead a solitary life more often than men who tended to live in families.

Medications Approximately 41% of patients were on calcium-channel blocker blockers (CCBs), and 39% were taking angiotensin-converting enzyme inhibitors or angiotensin-II receptor blockers (Table 2). Diuretics were given to 28% of patients, and a considerable percentage of cases were being maintained on anticoagulant (28%) and antiplatelet (23%) therapy.

ECG Findings As shown in Table 2, the most frequent abnormality found in patients with IDD was AF (24%) followed by LVH (17%); none of them had left bundle branch block.

Echo Findings Left atrial enlargement was observed in males and females with IDD, and LVEF was in the normal range. Various LV geometric patterns[5] were carefully evaluated in these patients. Hypertrophic geometry, such as eccentric or concentric hypertrophy, was the most frequent pattern (54% of males, 69% of females), followed by normal LV geometry (34% of males, 28% of females). Concentric remodeling was rarely found in either gender (only 8% of all cases). Regarding the Doppler Echo findings, DCT <140 ms, S/D ratio <1, and AR-A duration >30 ms were observed in 45%, 51% and 29% of patients, respectively. The isovolumetric relaxation time (IRT) was shortened in both genders compared with the normal average. Apart from the S/D ratio, none of the Doppler-Echo parameters exhibited a significant association with gender.

Functional and Prognostic Indices Cardiac function was controlled at New York Heart Association class II or III in 58% of patients, but a minority (1%, all were males) progressed to the gravest class IV (Table 2). For the CCI, a score of 1 point is given for each of the following conditions: CHF, MI, and diabetes (Table 1). Thus, approximately 36% of IDD patients were free of comorbidities (a score of 0), and nearly equal proportions (28% and 25%) had scores of 1 and 2–3, respectively. Only 11% of patients had a score ≥4, indicating a low possibility of survival?

Predictors of Mortality Mortality was reported in 50 patients (6.3%) on follow-up: 12 (24%) from cardiac causes and 30 (60%) from noncardiac reasons (11 strokes, 11 deaths from cancer, 8 for other reasons). The cause of death was unknown in 8 cases (16%). A Cox proportionate hazard regression model was constructed for identifying the independent predictors of death for each gender. Simple univariate analysis was done first for each of the input variables against positive death outcome, and all the variables associated with it at $p \leq 0.15$ were finally entered in a multivariate forward stepwise Cox regression model. The correlation matrix was carefully checked to avoid collinearity. Thus, the following variables were included in the final model (for both genders): age at diagnosis, body mass index, presence of history of CHF, MI, stroke, chronic kidney disease (CKD: serum creatinine ≥2 mg/dl or regular hemodialysis), as well as treatment with CCBs. In addition to these previously-mentioned variables, the variables that were included in the final model for males were diabetes, malignancy, β-blockers and statins, and for females, hypertension, and LVEF. The model was proven to be highly significant (p-value of the omnibus test for model coefficients <0.001). Eventually, age at diagnosis and the presence of CKD were significantly and independently associated with death, and CCB therapy was an independent inverse correlate of that event in both genders (Table 3). Additionally, the presence of diabetes (in males) and history of CHF (in females) were independently associated with higher mortality.

Table 2 Clinical and Other Characteristics of Patients With IDD Who Survived Until January 1st 2003

Variable	Male (n=158)	Female (n=114)	p value
Associated co-morbidities and their management			
Cardiovascular risk factors/chronic medical illnesses			
Age (years)	68.5±8.7	69.3±10.6	NS
Hypertension	70 (44.3%)	55 (48.2%)	NS
Diabetes mellitus	46 (29.1%)	18 (15.8%)	0.016
Dyslipidemia	25 (15.8%)	27 (23.7%)	NS
Body mass index			
≥25 to <30 kg/m² (overweight)	35 (22.2%)	16 (14.0%)	NS
≥30 kg/m² (obesity)	7 (4.4%)	2 (1.8%)	NS
Cardiac disorders			
CHF hospitalization	14 (8.9%)	13 (11.4%)	NS
Angina pectoris	10 (6.3%)	4 (3.5%)	NS
Myocardial infarction	20 (12.7%)	12 (10.5%)	NS
Arrhythmias			
Atrial fibrillation	61 (38.6%)	30 (26.3%)	0.046
Paroxysmal	15 (9.5%)	10 (8.8%)	NS
Chronic	46 (29.1%)	20 (17.5%)	0.031
Sustained ventricular tachyarrhythmia	2 (1.3%)	0 (0.0%)	NS
Permanent cardiac pace maker	9 (5.7%)	3 (2.6%)	NS
Cardiac surgery/intervention			
Diagnostic coronary angiography	50 (31.7%)	27 (23.7%)	NS
Percutaneous coronary intervention	11 (7.0%)	11 (9.6%)	NS
Coronary artery bypass graft	6 (3.8%)	3 (2.4%)	NS
Cardiac valve replacement	4 (2.5%)	0 (0.0%)	NS
Neuropsychiatric disorders			
Cerebral stroke	37 (23.4%)	19 (16.7%)	NS
Psychic illness	9 (5.7%)	20 (17.5%)	0.004
Renal disorders			
CKD (serum creatinine ≥2 mg/dl or regular hemodialysis)	15 (9.5%)	8 (7.0%)	NS
Pulmonary disorders			
Bronchial asthma	4 (2.5%)	2 (1.8%)	NS
Chronic obstructive pulmonary disease	6 (3.8%)	0 (0.0%)	NS
Level of daily activities and life style			
Independently mobile	151 (95.6%)	102 (89.8%)	
Wheel chair-dependent	4 (2.5%)	4 (3.5%)	NS
Bed-ridden	3 (1.9%)	7 (6.1%)	
Solitary life	12 (7.6%)	17 (14.9%)	NS
Educational background			
≤12 years	141 (89.2%)	101 (88.6%)	NS
>12 years	17 (10.8%)	13 (11.4%)	
Medications			
Calcium-channel blockers	69 (43.7%)	42 (36.8%)	NS
ACEIs or ARBs	68 (43.0%)	38 (33.3%)	NS
Diuretics	50 (31.6%)	26 (22.8%)	NS
Oral anticoagulants (warfarin)	45 (28.5%)	30 (26.3%)	NS
Acetyl salicylic acid (aspirin)	39 (24.7%)	23 (20.2%)	NS
β-adrenergic receptor blockers	32 (20.3%)	17 (14.9%)	NS
Statins	25 (15.8%)	17 (14.9%)	NS
Nitrates	20 (12.7%)	15 (13.2%)	NS
Electrocardiographic data			
Atrial fibrillation	46 (29.1%)	20 (17.5%)	0.031
Left ventricular hypertrophy	27 (17.1%)	18 (15.8%)	NS
Right bundle branch block	16 (10.1%)	7 (6.1%)	NS
Pathologic Q-wave	17 (10.8%)	8 (7.0%)	NS
Echo data			
Cardiac measurements			
Ejection fraction (%)	63.9±10.0	68.5±8.4	<0.001
Left ventricular diastolic dimension (mm)	50.6±6.1	48.2±5.7	0.001
Interventricular septum thickness (mm)	11.1±2.9	10.3±3.3	0.035
Posterior wall thickness (mm)	10.5±2.2	9.7±2.1	0.003
RWT	0.42±0.10	0.41±0.10	NS
LVMI (g/m²)	128.0±41.8	123.7±51.0	NS
Left atrial diameter (mm)	42.9±7.5	40.8±8.0	0.028
Left ventricular geometry			
Normal	53 (33.5%)	32 (28.1%)	
Eccentric hypertrophy	37 (23.4%)	47 (41.2%)	0.002
Concentric hypertrophy	49 (31.0%)	32 (28.1%)	
Concentric remodeling	19 (12.0%)	3 (2.6%)	
Doppler data			
E/A ratio	1.3±0.5	1.2±0.4	NS
Deceleration time (ms)	161.3±63.6	150.1±48.6	NS
Deceleration time <140 ms	66 (41.8%)	56 (49.1%)	NS