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Changes in the Baseline Clinical Characteristics of Hospitalized Patients with Congestive Heart Failure

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Abstract：Background： The epidemiology of heart failure（HF）has changed over time because of an increasingly aging population and lifestyle-related disorders. We studied the changes in the clinical characteristics of hospitalized patients with CHF. Methods and Results： We conducted a retrospective study of 121 patients who were hospitalized due to HF between 2000-2002（Group 2000）and 131 patients who were hospitalized between 2007-2009（Group 2008）in the Department of Cardiology, Fukuoka University Hospital. We analyzed the differences in the characteristics at admission, including medication and laboratory and echocardiographic parameters, between the groups. The major causes of HF were ischemic and hypertensive heart disease in both groups. Although higher levels of B-type natriuretic peptide were seen in Group 2008, there were no differences in the left ventricular ejection fraction（LVEF）, left ventricular end-diastolic diameter（LVEDd）or left atrial dimension（LAd）between the groups. In addition, the EF was negatively correlated with the LVEDd in both groups. Interestingly, the LVEDd was positively correlated with the LAd in Group 2008, but not in Group 2000, whereas the EF was positively correlated with the LAd in Group 2000, but not in Group 2008. In addition, 68% of the patients in Group 2008 initially started treatment with carperitide compared to 22% in Group 2000. Conclusions： The differences in the clinical characteristics of hospitalized patients with CHF may have important therapeutic implications.

Key words：**Heart failure, Clinical characteristics, B-type natriuretic peptide, Left ventricular end-diastolic diameter**

Introduction

Heart failure（HF）is a possible end-stage of all types of heart disease. HF is epidemic in the developed world. In the United States, HF is a major and growing public health problem. This syndrome is now the most common hospital discharge diagnosis in the population over age 65; it accounts for more than 1, 000, 000 of the patients discharged in 2003, and the estimated cost of caring for these patients in 2006 was ~$30 billion [1]. In addition, HF can be diagnosed in ~5% of individuals between the ages 65 and 74, and in ~10% of the population over age 75.

However, these results are almost entirely based on studies in the United States and Europe. Although little epidemiological data are available regarding the mortality rate and prevalence of HF in Japan, the morbidity and mortality rates are also continuing to increase in Japan. The morbidity of HF is forecast to be 3-20 people per 1000 people per year [2]. With a Japanese population of about 120 million, the morbidity of HF is forecast to be 360, 000-2.4 million people per year. Tsuchihashi *et al*. reported that the 1-year mortality rate was 8.3%, and this value was lower than that reported in the United States and Europe [3].

Forty years ago, the standard therapy for HF was rest and diuretics. Studies with positive inotropic drugs that became available in the late 1970s initially focused on β-adrenergic agonists and later on phosphodiesterase inhibitors. Further studies showed that the effects of afterload reduction on the long-term prognosis are due,

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in part, to the inhibition of maladaptive neurohumoral signaling. This shift continued during the late 1990s, when it became clear that β-blockers, despite their short-term negative inotropic action, prolonged the long-term survival of patients. The amount of focus devoted to cardiac glycosides decreased in 2005, and the use of devices, such as implantable defibrillators and cardiac resynchronization therapy, increased. We herein examined the changes in the baseline clinical characteristics of hospitalized patients with CHF to evaluate how the etiology of CHF is changing over time.

Methods

Study Population

We retrospectively examined the records of patients who had been hospitalized with their main disease as HF between April 2000-March 2002 (Group 2000) and between April 2007-March 2009 (Group 2008) in the Department of Cardiology, Fukuoka University Hospital. The cause of HF was classified as ischemic heart disease (IHD), hypertensive heart disease (HHD), dilated cardiomyopathy (DCM), hypertrophic cardiomyopathy, valvular disease, arrhythmia, or other. When the causes of HF overlapped, the main cause of HF was assumed based on the patient's medical history.

Clinical Parameters

The blood pressure and heart rate were determined, and echocardiography was performed just prior to admission. The echocardiographic parameters examined were the left atrial dimension (LAd), left ventricular end diastolic dimension (LVEDd), interventricular septal thickness (IVS), posterior wall thickness (PW) and ejection fraction (EF). Blood samples were drawn in the morning after the patients had fasted overnight. We analyzed the white blood cells (WBC), red blood cells (RBC), hemoglobin (Hb), platelets (PLT), C-reactive protein (CRP), uric acid (UA), natremia, total cholesterol (TC), triglycerides (TG), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), creatine, brain natriuretic peptide (BNP), and the estimated glomerular filtration rate (eGFR).

Information regarding medical treatment was collected at 3 timepoints (upon admission, in the hospital and at discharge). The body mass index (BMI), systolic blood pressure (SBP), diastolic blood pressure (DBP), serum levels of TG, TC, HDL-C, and LDL-C, fasting plasma glucose, hemoglobin, smoking status and medication use were recorded as cardiovascular risk factors.

Results

Major Causes of HF

The potentially remediable causes include coronary occlusive disease, hypertension, valvular heart disease, congenital heart disease, pericardial disease, toxins (including alcohol and cocaine), infections, collagen vascular and vasculitic diseases, infiltrative processes, endocrine and metabolic disorders, and obstructive sleep apnea. The major causes of HF in our study were ischemic or hypertensive HHD and DCM in both groups. In an analysis of the two groups, the % valvular disease decreased from 16% in Group 2000 to 10% in Group 2008, and the % arrhythmia was increased in Group 2008.

Clinical Characteristics

Table 1 shows the clinical characteristics of the two groups. The average number of hospitalizations in Group 2000 and Group 2008 was 2.4 ± 1.4 and 2.4 ± 2.2, respectively, and the average number of days hospitalized was 29 ± 9 and 24 ± 2 days. There were no differences in age, sex, NYHA classification or other risk factors. Group 2008 showed a higher % device use (pacemaker, implantable cardioverter defibrillation or cardiac resynchronization therapy) for arrhythmia. There was a significant difference in the BNP between

Table 1. Clinical characteristics (1)

	Group 2000	Group 2008
n	121	131
Male (%)	72 (60)	78 (60)
Age	70 ± 12	72 ± 12
Times	2.4 ± 1.4	2.4 ± 2.2*
NYHA	2.7 ± 0.8	2.6 ± 0.7
Days	29 ± 9	24 ± 2*
Risk factor : n (%)	HT : 81 (67)	HT : 86 (66)
	DM : 30 (25)	DM : 45 (34)
	DL : 40 (33)	DL : 45 (34)
	Smoking : 48 (40)	Smoking : 51 (39)
Device : n	PM : 7	PM : 22
	ICD : 2	ICD : 13
	CRT : 0	CRT : 2

HT, hypertension; DM, diaetes; DL, dyslipidemia; PM, pacemaker; ICD, implantable cardioverter defibrillator; CRT; cardiac resynchronization therapy; *P<0.05 vs. Group 2000.

Table 2. Clinical characteristics (2)

	Group 2000	Group 2008
BNP (pg/ml)	487 ± 598	853 ± 788*
Cr (mg/dl)	1.5 ± 1.4	1.5 ± 1.0
eGFR (ml/min/1.73m^2)	43 ± 23	45 ± 21
UA (mg/dl)	7.2 ± 2.4	7.4 ± 2.3
Na (mEq/l)	140 ± 4	138 ± 10
Hb (g/dl)	11.9 ± 2.2	11.9 ± 2.8
CRP (mg/dl)	1.8 ± 3.3	2.2 ± 5.4
TC (mg/dl)	177 ± 48	164 ± 42
TG (mg/dl)	101 ± 59	94 ± 46
HDL-C (mg/dl)	48 ± 25	43 ± 12
LDL-C (mg/dl)	109 ± 36	103 ± 35
SBP (mmHg)	136 ± 30	130 ± 28
DBP (mmHg)	80 ± 19	76 ± 20
HR (/min)	88 ± 24	90 ± 27
LAd (mm)	44 ± 11	45 ± 11
LVEDd (mm)	56 ± 12	56 ± 12
EF (%)	46 ± 18	45 ± 18

BNP, brain natriuretic peptide; UA, uric acid; eGFR, estimated glomerular filttration rate;CRP, C-reactive protein; TC, total cholesterol; TG, triglyceride; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol SBP, systolic blood pressure; DBP, diastolic blood pressure; HR, heart rate; LAd, left atrial dimension; LVEDd, left venticlar end diastolic dimension, EF, ejection fraction *P<0.001 vs. Group 2000.

the groups (853 ± 788 and 487 ± 598 pg/ml in Group 2000 and Group 2008, respectively) (Table 2).

Changes in Medications

During the acute phase, there was a three-fold higher use of carperitide in Group 2008 than in Group 2000 (Figure 1a). At admission, Group 2008 showed higher rates of administration of aldosterone antagonists, angiotensin II receptor blockers (ARBs), β-blockers and calcium channel blockers (CCBs) than Group 2000. At discharge, Group 2008 showed a higher rate of β-blocker, and a lower rate of angiotensin converting enzyme inhibitor (ACE-I) and digoxin use (Figures 1b and c).

Associations Among Echocardiographic Parameters

With regard to echocardiography, the EF was negatively correlated with the LVEDd in both groups. Interestingly, the LVEDd was positively correlated with the LAd in Group 2008 but not in Group 2000, whereas the EF was positively correlated with the LAd in Group 2000 but not in Group 2008 (Figure 2).

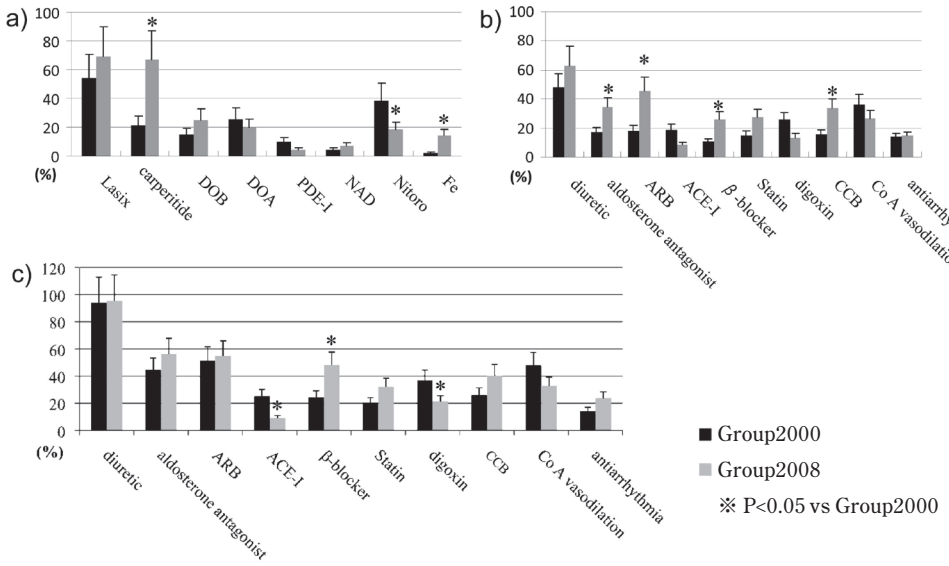

Fig. 1. Changes in medications

a) In the acute phase of heart failure, Group 2008 more often received carperitide and Fe than Group 2000, and received less Nitro than Group 2000.

b) At admission, Group 2008 patients were receiving more aldosterone antagonists, ARBs, β-blockers and CCBs than Group 2000.

c) At discharge, Group 2008 received more β-blockers than Group 2000, and received ACE-I and digoxin than frequently than Group 2000.

DOB, dobutamine; DOA, dopamine; PDE-I, phosphodiesterase inhibitor; NAD, noradrenaline; Fe, iron or blood transfusion; ARB, angiotensin II receptor blocker; CCB, calcium channel blocker ACE-I; angiotensin converting enzyme inhibitor.

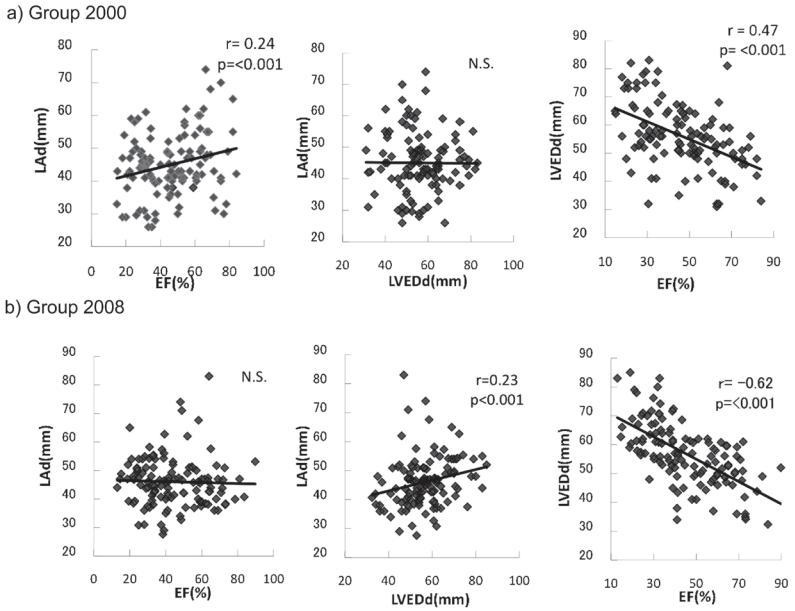

Fig. 2. Associations among echocardiographic parameters in Group 2000 (a) and Group 2008 (b). In both groups, the LVEDd was negatively correlated with the EF. The LAd was positively correlated with the EF in Group 2000, but not in Group 2008. In addition, the LAd was positively correlated with the LVEDd in Group 2008, but not Group 2000.
LAd, left atrial dimension; LVEDd, left ventricular end-diastolic dimension; EF, ejection fraction.

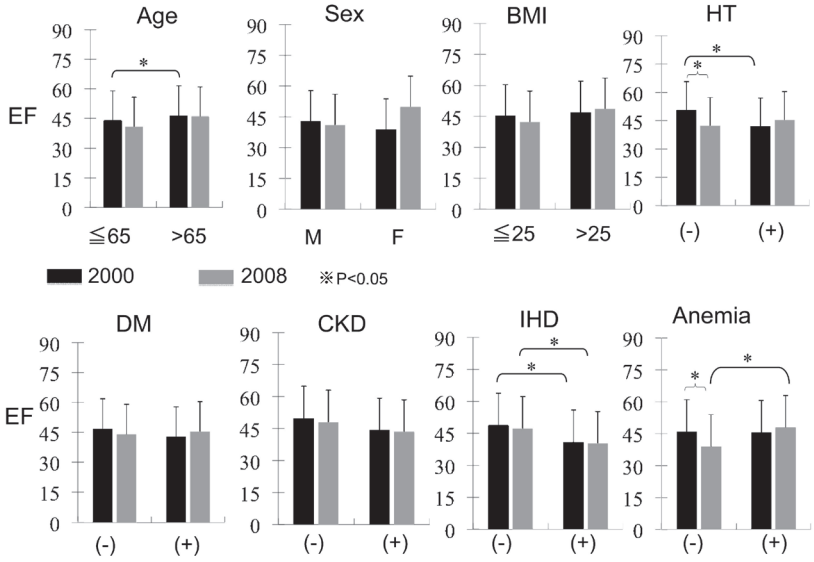

Fig. 3. Associations among the EF and risk factors for HF (age, sex, BMI, HT, DM, CKD, IHD and anemia). In Group 2000, older patients (>65) had a significantly higher EF than those of a younger age (<65). In addition, patients without HT or IHD had a higher EF than those with HT or IHD in Group 2000. In Group 2008, patients with anemia had a higher EF than those without anemia.
EF, ejection fraction; HF, heart failure; BMI, body mass index; HT, hypertension; DM, diabetes mellitus; CKD, chronic kidney disease; IHD, ischemic heart disease.

Associations Among the EF and Risk Factors for HF

We examined the relationship between the EF and coronary risk factors. In both groups, the subjects who had a past history of IHD had a low EF. In Group 2008, female subjects and those with HT or anemia had a higher EF (Figure 3).

Association Between the Ejection Fraction and Risk Factors for CHF

Finally, a stepwise logistic regression analysis was performed to identify factors that contributed to the

Table 3. Association between Ejection franction and risk factors of CHF as assessed by multiple regression analysis

Group2000

Factors	Standardized Regression Coefficient	p value
Age, yrs	0.11	0.283
Male, %	-0.13	0.245
BMI>25, %	-0.08	0.468
HT, %	-0.23	0.015
DM, %	-0.02	0.859
IHD, %	-0.25	0.009
CKD, %	-0.17	0.109
Anemia, %	-0.01	0.918

Group2008

Factors	Standardized Regression Coefficient	p value
Age, yrs	0.27	0.005
Male, %	-0.36	<0.0001
BMI>25, %	0.17	0.048
HT, %	0.03	0.691
DM, %	0.14	0.117
IHD, %	-0.26	0.004
CKD, %	-0.25	0.007
Anemia, %	-0.08	0.376

BMI, body mass index; HT, hypertension; DM, diabetes mellitus; IHD, ischemic heart disease; CKD, chonic kidney disease.

EF. HT and IHD were contributing factors to the EF in Group 2000, while age, sex, obesity, IHD and chronic kidney disease (CKD) predominantly contributed to the EF in Group 2008 (Table 3).

Discussion

The main finding in this study was that the major causes of HF in both groups were IHD and HHD. Although higher levels of BNP were seen in Group 2008, there were no differences in the LVEF, LVEDd or LAd between the groups. In addition, the EF was negatively correlated with the LVEDd. In addition, 68% of the patients in Group 2008 but only 22% of those in Group 2000, initially started carperitide treatment.

In the 1970s, hypertension and coronary disease, particularly myocardial infarction, were the primary causes of HF in the United States and Europe [4, 5]. However, coronary artery disease (CAD) and diabetes mellitus have become increasingly responsible for HF, while hypertension and valvular disease have become less common because of improvements in their detection and treatment [6-8]. Over four decades of observation in the Framingham Study, the prevalence of CAD as a cause of HF increased 41% per calendar decade in males and 25% in females; the prevalence of diabetes as a contributing cause increased by more than 20% per decade [6]. Our study found that the incidence of valvular disease decreased and that of arrhythmia increased in Group 2008, but that there was no difference in the % IHD between the groups. In Japan, diabetes mellitus (DM) is not a common cause of HF [7, 9]. When DM is a complication of IHD, it is difficult to classify.

Beginning in the mid-1990s, large-scale controlled trials revealed an improvement in the clinical outcome among patients with HF and a reduced LVEF (dilated LV), of both ischemic and nonischemic causes, who randomly received a β-blocker [10]. This finding created a paradigm shift in our thinking about the treatment of HF. Since that time, β-blockers have become a mainstay of therapy in patients with HF and a reduced LVEF, with a recommendation for cautious administration even in patients with advanced HF. The characteristics of HF may become clearer by comparing the baseline clinical characteristics of hospitalized patients over time. With regard to the treatment of HF, the use of an ARB, β-blocker, and cardiac resynchronization therapy has increased. In our study, the frequencies of β-blocker therapy and ARB/ACE-I therapy in Group 2008 were higher than those in Group 2000. This result shows that these therapies have become common treatments for CHF.

Suchihashi *et al.* reported that 70% of HF patients are 65 years old or older [7]. In this study, the mean age of the patients was more than 70 years in both groups, and there was no significant difference between the two groups with regard to age (70 ± 12 vs. 72 ± 12 y; Group 2000 vs. Group 2008). However, both age and sex predicted the EF in Group 2008. Lower EF values were seen in younger patients and higher values were seen in females. Thus, older and female patients were associated with HF with a preserved ejection fraction (HFPEF).

HF is a complex clinical syndrome that can result from any structural or functional cardiac disorder. While advances are being made in the management of HF, there is still an increasing trend for the development

of HF in Japan due to an increasingly older society and an increase in lifestyle-related diseases (HT, IHD, DM, CKD) associated with the adoption of a western lifestyle. The risk factors for HF include age, sex, alcohol, smoking, DM, high blood pressure, kidney disease, CAD, anemia, obesity, sleep apnea and depression [9, 11]. The relationships between these factors and cardiac function were investigated in this study. Low EF HF was associated with HT and IHD in Group 2000, and with IHD and CKD in Group 2008. It has been reported that renal dysfunction is an independent risk factor in patients with CHF. We found that CKD significantly contributed to the EF in Group 2008. Sliverberg *et al*. recently reported [8] that not only renal failure, but also anemia, are closely associated with HF. However, we found that anemia was associated with a high EF. One possible explanation for this finding is that, under conditions of anemia, the EF may increase in a compensatory manner.

HF is a complex disease that can occur as a result of any type of cardiac failure. The present results showed that there has been a change in the background etiologies of HF, and a better understanding of this change may help to improve the prognosis for HF patients.

Conclusions

We demonstrated that there have been changes in the baseline clinical characteristics of hospitalized patients with HF between 2000-2002 and 2007-2009. Recently, CKD and atherosclerosis have emerged as major risk factors that may predict HF.

Conflict of interest

The authors declare no conflict of interest.

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