(UBCR) is an independent predictor for deterioration of renal function.[4,11] However, the impact of RTD on cardiac prognosis in patients with CHF has not yet been fully elucidated. The aim of the present study was to determine whether the comorbidity of RTD, as assessed by UBCR, predicts cardiac prognosis in patients with CHF.

Methods

Study Subjects

This was a prospective study of 315 consecutive patients who were admitted to our hospital for the diagnosis or treatment of CHF. Patients were stable for a median 713 days before their admission. The diagnosis of CHF was made by 2 cardiologists who used the generally accepted Framingham criteria, including a history of dyspnea and symptomatic exercise intolerance, with signs of pulmonary congestion or peripheral edema and radiological or echocardiographic evidence of left ventricular enlargement or dysfunction.[12]

Transthoracic echocardiography was performed by physicians who were blinded to the biochemical data. The diagnoses of hypertension, diabetes mellitus, and hyperlipidemia were established on the basis of the patient's medical records or history of current or previous medical therapy. Twenty-two patients were excluded from the present study because of acute coronary syndrome within 3 months preceding admission, dialysis, active hepatic disease, pulmonary disease, or malignant disease.

Demographic and clinical data, including age, sex, and New York Heart Association (NYHA) functional class, were collected from hospital medical records and patient interviews. Medications at discharge were also collected from hospital medical records.

Biochemical Markers

Urine and venous blood samples were obtained in the early morning within 24 hours after admission. Urinary β_2–microglobulin

Table 1. Comparison of Clinical Characteristics Between CHF Patients With RTD and Those Without RTD

Variables	All Patients (N=315)	RTD (–) (n=195)	RTD (+) (n=120)	*P* Value
Age, y	72±11	69±12	76±10	<0.0001
Men/women	181/134	117/78	64/56	0.2452
NYHA functional class (I/II/III/IV)	80/115/82/38	68/71/39/17	12/44/43/21	0.0001
Hypertension, n (%)	194 (62)	114 (58)	80 (67)	0.1460
Diabetes mellitus, n (%)	94 (30)	50 (26)	44 (37)	0.0378
Hyperlipidemia, n (%)	95 (30)	56 (29)	39 (33)	0.4775
Pathogenesis, n (%)				0.1979
Dilated cardiomyopathy	61 (19)	43 (22)	18 (15)	
Ischemic heart disease	72 (23)	38 (19)	34 (28)	
Valvular heart disease	100 (32)	64 (26)	36 (30)	
Others	82 (26)	50 (33)	32 (27)	
Blood examination				
eGFR, mL/min per 1.73 m^2	64±26	68±22	57±31	0.0003
BNP, pg/mL	362 (129–875)	252 (101–529)	619 (294–1260)	<0.0001
Hb, g/dL	12.3±2.3	13.1±2.1	11.1±2.1	<0.0001
Urinalysis				
Log_{10} UBCR, μg/g	2.25±0.95	1.69±0.57	3.21±0.62	<0.0001
Log_{10} UACR, mg/g	1.50±0.65	1.27±0.53	1.88±0.66	<0.0001
Proteinuria, n (%)	58 (18)	18 (9)	40 (33)	<0.0001
Log_{10} NAG, U/g	1.05±0.32	0.95±0.27	1.23±0.33	<0.0001
CKD, n (%)	166 (53)	85 (44)	81 (68)	<0.0001
Echocardiography				
LVEDD, mm	54±10	54±10	55±10	0.5627
LVEF, %	51±17	52±18	49±15	0.1433
Medicine				
ACEIs or ARBs, n (%)	239 (76)	141 (72)	98 (82)	0.0594
β-Blockers, n (%)	212 (67)	124 (64)	88 (73)	0.0734
Aldosterone blockers, n (%)	99 (31)	62 (32)	37 (31)	0.8583
Loop diuretics, n (%)	207 (66)	118 (61)	89 (74)	0.0132
Doses of furosemide	20 (0–20)	10 (0–20)	20 (0–30)	0.0103
Statins, n (%)	109 (35)	67 (34)	42 (35)	0.9075

Data are expressed as mean±SD, number (percentage), or median (interquartile range). ACEIs indicates angiotensin-converting enzyme inhibitors; ARBs, angiotensin II receptor blockers; BNP, brain natriuretic peptide; CHF, chronic heart failure; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; Hb, hemoglobin; LVEDD, Left ventricular end-diastolic dimension; LVEF, Left ventricular ejection fraction; NAG, N-acetyl-β-D-glucosamidase; NYHA, New York Heart Association; RTD, renal tubular damage; UACR, urinary microalbumin–creatinine ratio; and UBCR, urinary β_2–microglobulin–creatinine ratio.

concentrations were determined by the latex agglutination method (BML, Inc, Tokyo, Japan). β_2-microglobulin levels were corrected for urinary creatinine (UBCR). Because UBCR was not normally distributed, we used $\log_{10}$ UBCR for all analyses. RTD was defined as a UBCR≥300 μg/g ($\log_{10}$ UBCR≥2.47 μg/g), as previously reported.[4] We quantitatively measured urinary albumin by immunoturbidimetry in a single spot urine specimen collected in the early morning. Urinary albumin levels were corrected for urinary creatinine in a single manner to urinary microalbumin–creatinine rate (UACR). N-acetyl-β-D-glucosamidase (NAG) level, a marker of early RTD, was measured in single spot urine specimens. UACR and NAG were also not normally distributed, and we used $\log_{10}$ UACR and $\log_{10}$ NAG for all analyses. We detected urinary protein with albumin-specific dipsticks at the same time. We defined proteinuria as positive dipstick test (≥1+). The glomerular filtration rate (GFR) was estimated using the modification of diet in the equation of the renal disease with the Japanese coefficient, as previously reported.[13] Chronic kidney disease (CKD) was defined as a reduced estimated GFR (eGFR; <60 mL/min per 1.73 m^2) or presence of proteinuria according to K/DOQI (Kidney Disease Outcomes Quality Initiative) clinical guideline.[14,15]

End Points and Follow-up

Patients were prospectively followed up for a median period of 1097 days (range, 794–1244). Patients were followed by telephone interview or review of the medical record twice a year until 1250 days. There were 14 patients who were not followed up because of noncardiac death. The end points were cardiac death, defined as death attributable to progressive heart failure, sudden cardiac death, acute myocardial infarction, and progressive heart failure requiring rehospitalization. Sudden cardiac death was defined as death without definite premonitory symptoms or signs, and was confirmed by the attending physician. The study was approved by the Institutional Ethics Committee, and all patients gave written informed consent.

Statistical Analysis

All values are expressed as mean±SD or medians. The *t* test and χ^2 test or linear regression analysis was used for comparison of continuous and categorical variables, respectively. The receiver-operating characteristics curves for cardiac event were constructed to determine optimal sensitivity and specificity. The area under the receiver-operating characteristics curve (AUC) was calculated by using the trapezoidal rule.[16] The Cox proportional hazard analysis was performed to identify the independent predictors for cardiac events. Predictors that were significant by univariate analysis were entered into the multivariate analysis. Proportionality assumption in Cox model was evaluated by log-minus-log survival plot. Cardiac event-free curves were constructed according to the Kaplan–Meier method and were compared using the log-rank test. Differences among groups were analyzed by ANOVA with Scheffe post hoc test. A *P* value <0.05 was considered statistically significant. Statistical analyses were performed using a standard software package (JMP version 8; SAS Institute, Inc, Cary, NC).

Results

Baseline Characteristics of the Study Population

The baseline characteristics of the patients are presented in Table 1. There were 80 patients in NYHA functional class I, 115 in NYHA class II, 82 in NYHA class III, and 38 in NYHA class IV. Hypertension, diabetes mellitus, and hyperlipidemia were identified in 194 (62%), 94 (30%), and 95 (30%) patients, respectively. The pathogenesis of heart failure was dilated cardiomyopathy in 61 (19%) patients, ischemic heart disease in 72 (23%) patients, valvular heart disease in 100 (32%) patients, and other conditions in the remaining 82 (26%) patients. The median $\log_{10}$ UBCR was 2.25 μg/g. The relationships between UBCR and eGFR and UBCR and UACR was weak and moderate, respectively (eGFR: r=−0.232, P<0.0001; UACR: r=0.412, P<0.0001, respectively). RTD was identified in 120 (38%) patients. All CHF patients were divided into 2 groups according to the presence of RTD. Patients with RTD were older and were in more severe NYHA functional classes than those without RTD. The prevalence of diabetes mellitus and proteinuria was higher in patients with compared with those without RTD. Furthermore, patients with RTD had a lower eGFR and hemoglobin (Hb) level and higher brain natriuretic peptide (BNP), UACR, and NAG levels. Patients with RTD took more loop diuretics and higher dose of furosemide than those without RTD. There were no significant differences in other variables, including sex, prevalence of hypertension and hyperlipidemia, pathogenesis of CHF, and medication, excluding loop diuretics and echocardiographic parameters between patients with and without RTD.

UBCR and Clinical Outcomes

Log_{10} UBCR was increased with advancing NYHA functional class (Figure 1). During the follow-up period, there were 91 cardiac events (29%), including 16 cardiovascular deaths and 75 rehospitalizations for worsening heart failure. The causes of cardiac death were worsening CHF in 14 patients, sudden cardiac death in 1 patient, and acute myocardial infarction in 1 patient.

To determine the risk factors for cardiac events, univariate and multivariate Cox proportional hazard regression analyses were performed (Table 2). Univariate analysis showed that $\log_{10}$ UBCR and RTD were significantly associated with cardiac events. Furthermore, age, NYHA functional class, eGFR, BNP, Hb, UACR, proteinuria, left ventricular ejection fraction (EF), NAG, CKD, and dosages of furosemide were associated with cardiac events. Multivariate Cox proportional hazard analysis revealed that RTD was an independent predictor for cardiac events after adjustment of age, NYHA functional class, BNP, Hb, proteinuria, dosages of furosemide, and CKD (hazard ratio, 3.18; 95% confidence interval, 1.92–5.30; P<0.0001; Table 2). Furthermore, when NAG was substituted for RTD, NAG was also an independent predictor for cardiac events after adjustment for other confounding factors (data not shown).

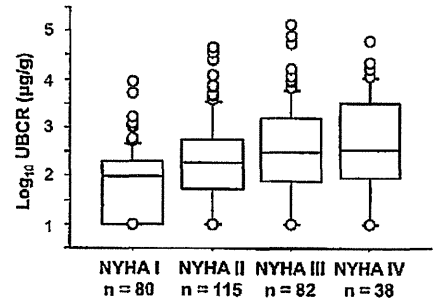

Figure 1. The association between urinary β_2-microglobulin–creatinine ratio (UBCR) and New York Heart Association (NYHA) functional class. Log_{10} UBCR was increased with worsening NYHA functional class (Kruskal–Wallis test, P<0.0001).

Table 2. Univariate and Multivariate Cox Proportional Hazard Analyses of Predicting Cardiac Events in Patients With Chronic Heart Failure

Variables	Hazard Ratio	95% Confidence Interval	*P* Value
Univariate analysis			
Age (per 1-year increase)	1.04	1.02–1.07	0.0002
Sex (women vs men)	0.98	0.65–1.50	0.9597
NYHA (II vs I)	1.95	0.99–3.82	0.0524
NYHA (III vs I)	3.44	1.77–6.71	0.0003
NYHA (IV vs I)	4.55	2.19–9.50	<0.0001
Hypertension	1.18	0.78–1.78	0.4475
Diabetes mellitus	0.79	0.51–1.23	0.2970
Hyperlipidemia	0.82	0.53–1.27	0.3790
Estimated GFR (per 1-SD increase)	0.50	0.39–0.64	<0.0001
BNP (per 1-SD increase)	1.30	1.10–1.48	<0.0001
Hb (per 1-SD increase)	0.55	0.44–0.67	<0.0001
Log_{10} UBCR (per 1-SD increase)	2.01	1.65–2.44	<0.0001
Log_{10} UACR (per 1-SD increase)	1.87	1.50–2.41	<0.0001
Proteinuria	2.44	1.56–3.82	0.0003
Log_{10} NAG (per 1-SD increase)	1.63	1.34–1.98	<0.0001
LVEDD (per 1-SD increase)	1.19	0.97–1.47	0.1016
LVEF (per 1-SD increase)	0.74	0.60–0.90	0.0026
Furosemide (per 1-mg increase)	1.02	1.01–1.03	<0.0001
CKD	3.43	2.12–5.55	<0.0001
RTD	5.08	3.24–8.00	<0.0001
Multivariate analysis			
Age (per 1-year increase)	1.02	0.99–1.04	0.1819
NYHA (II vs I)	1.13	0.57–2.27	0.7245
NYHA (III vs I)	1.89	0.92–3.89	0.0829
NYHA (IV vs I)	2.33	1.08–5.05	0.0309
BNP (per 1-SD increase)	0.96	0.82–1.10	0.6202
Hb (per 1-SD increase)	0.81	0.63–1.07	0.1563
Proteinuria	1.12	0.67–1.85	0.6668
Furosemide (per 1-mg increase)	1.01	0.99–1.02	0.0995
CKD	2.05	1.18–3.55	0.0110
RTD	3.18	1.92–5.30	<0.0001

BNP indicates brain natriuretic peptide; CKD, chronic kidney disease; GFR, glomerular filtration rate; Hb, hemoglobin; LVEDD, left ventricular end-diastolic dimension; LVEF, left ventricular ejection fraction; NAG, N-acetyl-β-D-glucosamidase; NYHA, New York Heart Association; RTD, renal tubular damage; UACR, urinary microalbumin–creatinine ratio; and UBCR, urinary β_2–microglobulin–creatinine ratio.

Kaplan–Meier analysis demonstrated that patients with RTD had a significantly higher rate of cardiac events compared with those without RTD (Figure 2A). Furthermore, cardiac mortality was higher in patients with compared with those without RTD (Figure 2B).

Comorbidity of RTD and CKD in Patients With CHF

All patients with CHF were divided into 4 groups according to the presence of CKD and RTD: (1) normal group (n=110): CKD (−) and RTD (−); (2) CKD group (n=85): CKD (+) and RTD (−); (3) RTD group (n=39): CKD (−) and RTD (+); (4) CKD+RTD group (n=81): CKD (+) and RTD (+). As shown in Table 3, levels of Hb were lower in RTD group than in normal group and CKD group. CKD+RTD group were older and had higher BNP, log_{10} UBCR, and log_{10} NAG than normal group and CKD group. CKD+RTD group also had lower Hb compared with normal group and CKD group. CKD+RTD group showed higher prevalence of proteinuria, higher log_{10} UACR, and lower eGFR compared with other groups. The Cox proportional hazards regression analysis revealed that the CKD+RTD group had the highest risk for cardiac events among 4 groups after adjustment of age, NYHA functional class, BNP, Hb, proteinuria, and dosages of furosemide (Figure 3A). Because RTD is a risk factor for deterioration of CKD, new development of CKD is likely to occur in RTD group during follow-up periods. We divided the study patients into the following 3 groups: normal group, CKD or RTD group, and CKD+RTD group. Log-minus-log survival plot showed that hazard ratios of variables were constant overtime. Kaplan–Meier analysis

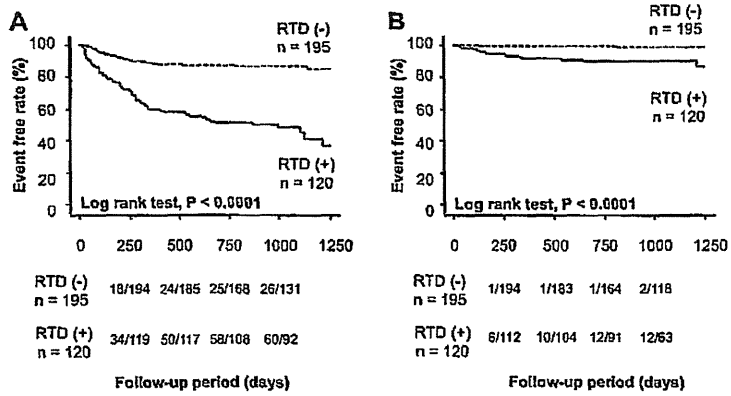

Figure 2. A, Kaplan–Meier analysis of all cardiac events in patients with and without renal tubular damage (RTD). B, Kaplan–Meier analysis of cardiac deaths in patients with and without renal tubular damage.

demonstrated that CKD+RTD group had the highest rate of cardiac events in patients with CHF (Figure 3B). Furthermore, we performed subgroup analysis. Kaplan–Meier analysis showed that the rate of cardiac events was higher in patients with RTD than in those without it, irrespective of having CKD (Figure 2 in the online-only Data Supplement).

Comparison of Prognostic Value Between UBCR and Traditional Markers

We performed the receiver-operating characteristics analyses to evaluate whether $\log_{10}$ UBCR could add clinical information to traditional markers, such as left ventricular EF, left ventricular end-diastolic dimension, and BNP. As shown in Figure 4, the AUC, sensitivity, and specificity of $\log_{10}$ UBCR was 0.74, 68%, and 77%, respectively. The AUC of UBCR was higher than that of traditional markers of heart failure.

Discussion

The new and important findings from this study were (1) RTD was increased with advancing NYHA functional class; (2) multivariate Cox proportional hazard analysis demonstrated that RTD was an independent predictor of cardiac events; (3) Kaplan–Meier analysis demonstrated that the rate of cardiac events was higher in patients with RTD compared with those without RTD; (4) the Cox proportional hazard regression analysis revealed that comorbidity of RTD and CKD was associated with the highest risk in patients with CHF.

Association Between CHF and RTD

A cardiorenal interaction was noted in patients with CHF.[17–19] Accumulating evidence indicates that renal dysfunction has a close association with cardiac function in patients with CHF through activation of the renin–angiotensin system, volume expansion, cytokine secretion, sympathetic nerve activation, and anemia.[1,2,17,19] Cardiac dysfunction with low cardiac output decreases renal perfusion and leads to renal parenchymal hypoxia.[17] Renal parenchymal hypoxia plays a pivotal role in the development of RTD.[20] We previously reported that the prevalence of RTD is ≈13% in the Japanese general population.[4] In the present study, 38% of patients with CHF were found to have RTD. The prevalence of RTD was higher in patients with CHF than in the general population, suggesting an association between cardiac function and RTD.

Table 3. Clinical Characteristics of the 4 Subgroups of CHF

Variables	Normal (n=110)	CKD (n=85)	RTD (n=39)	CKD+RTD (n=81)
Age, y	67±11	72±10	73±12	77±10*†
Blood examination				
eGFR, mL/min per 1.73 m²	81±16	51±15*	87±29†	42±20*†‡
BNP, pg/mL	186 (67–397)	414 (167–1106)	395 (161–1238)	694 (409–1270)*†
Hb, g/dL	13.3±2.0	12.8±2.3	11.7±2.3*†	10.8±1.9*†
Urinalysis				
$\log_{10}$ UBCR, μg/g	1.8±0.5	1.5±0.6	3.0±0.5*†	3.3±0.7*†
$\log_{10}$ UACR, mg/g	1.18±0.49	1.39±0.57	1.47±0.43	2.09±0.65*†‡
Proteinuria	0 (0%)	18 (31%)	0 (0%)	40 (69%)§
$\log_{10}$ NAG, U/g	0.94±0.29	0.94±0.25	1.20±0.34*†	1.22±0.29*†

Data are expressed as mean±SD, number (percentage), or median (interquartile range). BNP indicates brain natriuretic peptide; CHF, chronic heart failure; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; Hb, hemoglobin; NAG, N-acetyl-β-D-glucosamidase; RTD, renal tubular damage; UACR, urinary microalbumin-creatinine ratio; and UBCR, urinary β_2–microglobulin–creatinine ratio.

*P<0.05 vs normal group.

†P<0.05 vs CKD group.

‡P<0.05 vs RTD group.

§P<0.05 by χ^2 test.

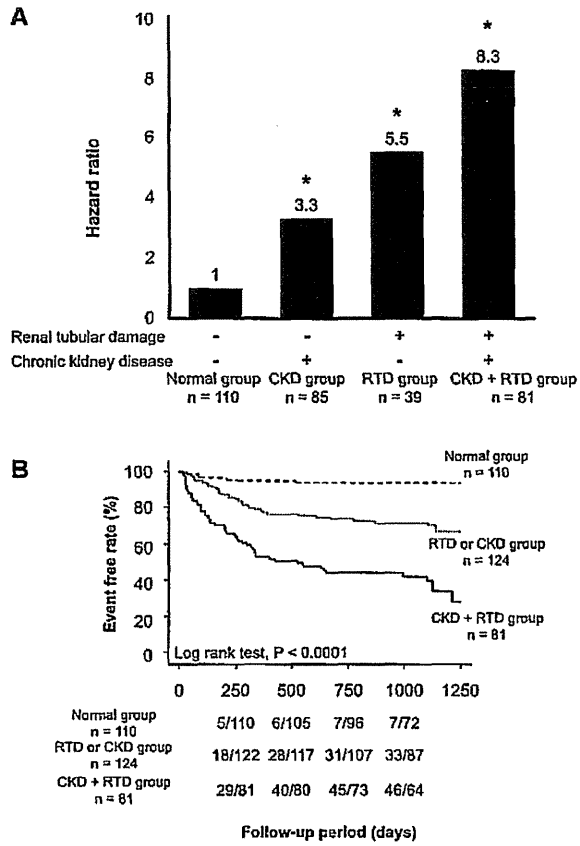

Figure 3. A, The Cox proportional hazard regression analysis of 4 groups. Hazard ratio relative to normal group. *$P<0.05$ vs normal group. **B**, Kaplan–Meier analysis of all cardiac events among 3 groups. CKD indicates chronic kidney disease; and RTD, renal tubular damage.

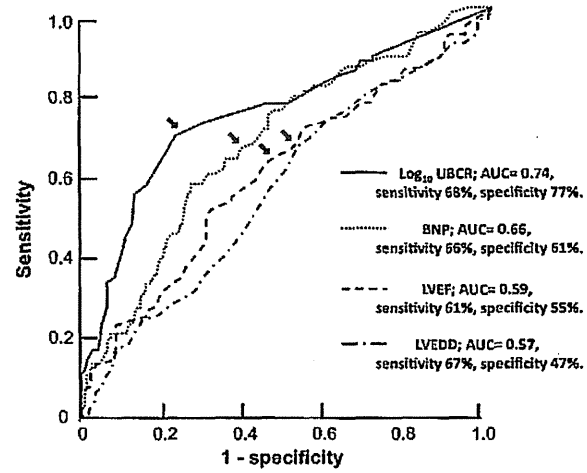

Figure 4. The receiver-operating characteristics curves of $\log_{10}$ urinary β_2-microglobulin–creatinine ratio (UBCR), brain natriuretic peptide (BNP), left ventricular ejection fraction (LVEF), and left ventricular end-diastolic dimension (LVEDD) for cardiac events. AUC indicates area under the receiver-operating characteristics curve.

Renal parenchymal hypoxia and, in particular, chronic tubulointerstitial hypoxia is recognized as a final common pathway for end-stage renal dysfunction, that eventually leads to a decreased GFR.[21,22] Therefore, CHF patients with RTD may have a poor prognosis because of their renal dysfunction. However, left ventricular EF was not lower in patients with RTD compared with those without RTD. This may be attributed to the fact that chronic tubulointerstitial hypoxia is induced by several factors, including age, hypertension, diabetes mellitus, and CKD itself.[23]

Because peritubular interstitial cells produce erythropoietin,[24] RTD is likely to cause renal anemia. As shown in Table 3, decreased Hb levels were more closely associated with RTD than CKD. Anemia promoted by RTD may deteriorate cardiac prognosis in patients with CHF.

Differences Between NAG and UBCR in Patients With CHF

Both urinary NAG and UBCR are considered to be reliable markers for RTD. NAG is an enzyme, which localizes in the lysosomes of proximal tubular cells. Urinary NAG levels often increase through the exocytosis–endocytosis pathway, which is a different pathway from that of RTD.[25,26] A previous report suggested that UBCR is superior to NAG for predicting renal dysfunction.[27] UBCR was considered as a more specific marker than NAG. Damman et al[28] showed that a high NAG level was a risk factor for future cardiac events in patients with CHF. Similarly, NAG was also an independent predictor for cardiac events in the present study. These findings supported our hypothesis that the comorbidity of RTD is associated with a poor prognosis in patients with CHF.

The limitation of this study was relatively high EF in the study population. The relatively high EF (51±17%) observed in this study may primarily be the result of a lower prevalence of ischemic heart diseases in Japan (23%). The prevalence of ischemic heart disease is reportedly relatively lower in Japan compared with the United States and European countries.[29,30] The mean EF in this study is thought to be equivalent to that seen in Japanese heart failure study and the Japanese heart failure registry.[31,32] Another limitation of the present study was the relatively small number of study subjects.

In conclusion, RTD, as assessed by UBCR, was related to the severity of heart failure and was associated with a high risk of cardiac events in patients with CHF. The comorbidity of RTD could add clinical information to CKD and may be a crucial risk factor for cardiac events in patients with CHF.

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Disclosures

None.

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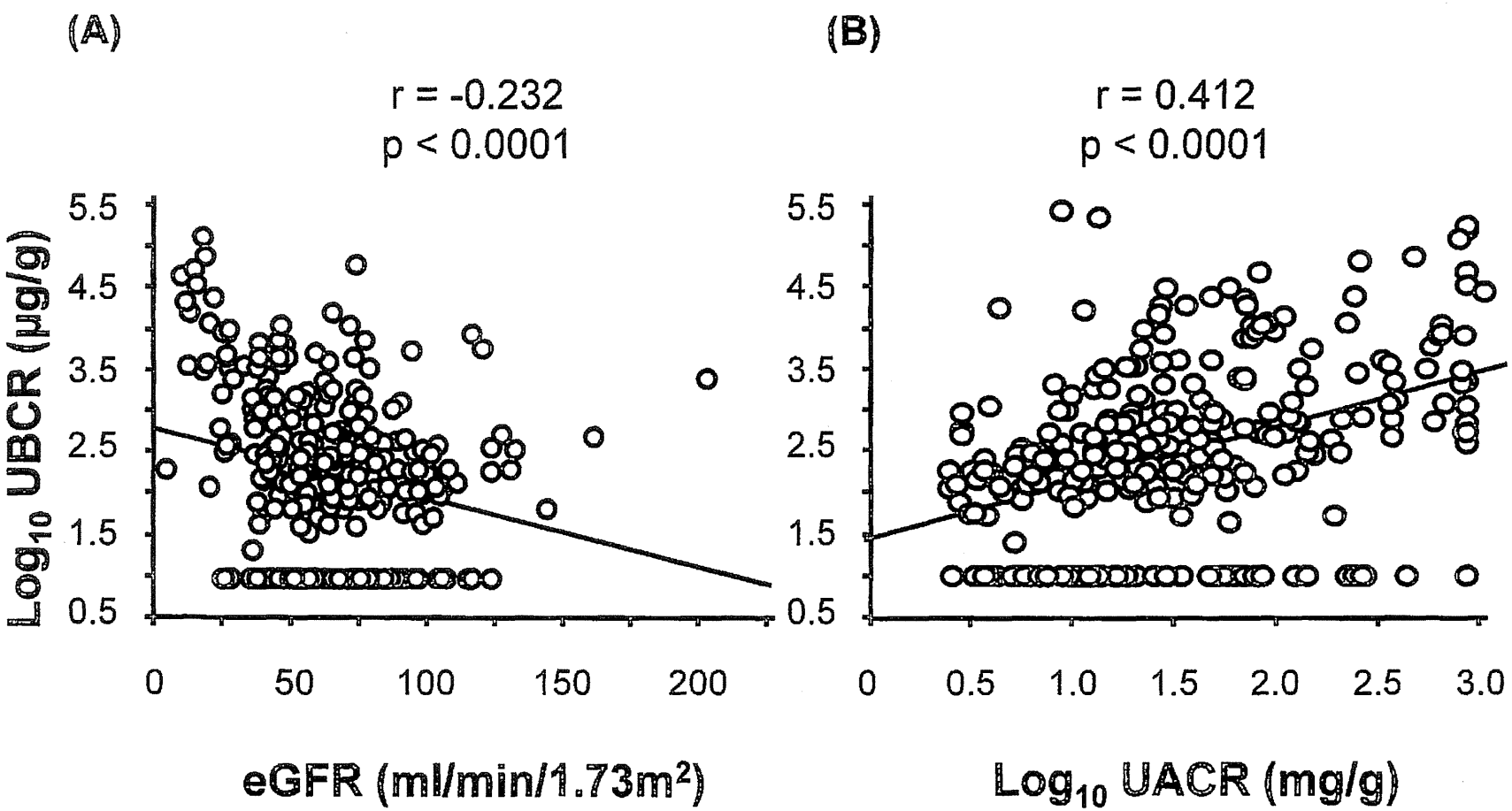
CLINICAL PERSPECTIVE

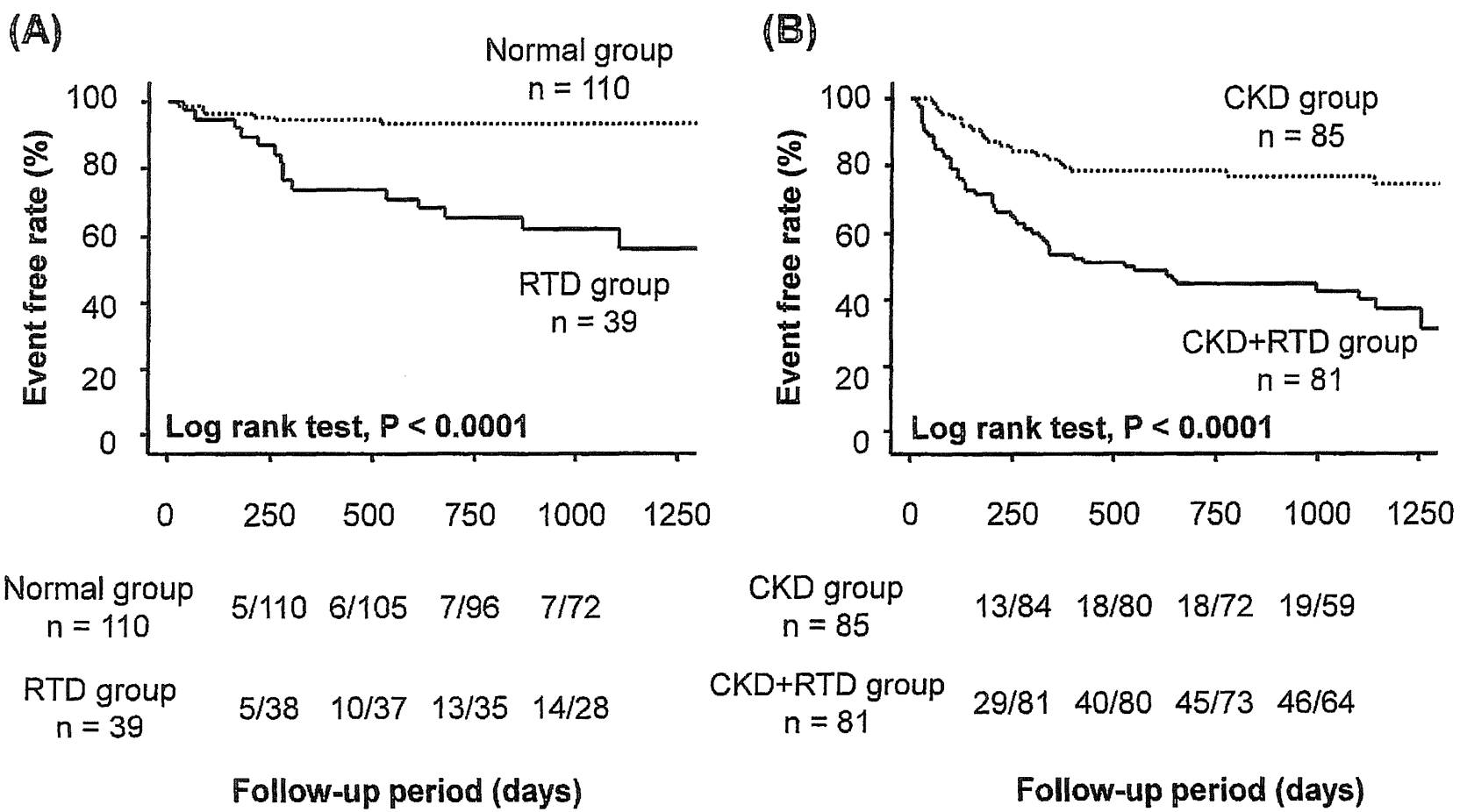
Kidney dysfunction is common and associated with a poor cardiac prognosis in patients with chronic heart failure (CHF). Many previous studies have focused on the role that glomerular damage plays as a contributor to the renal comorbidity of CHF. Although renal tubular damage is recognized as a final common pathway to end-stage renal dysfunction, the impact of renal tubular damage in CHF remains to be determined. For the first time, we have demonstrated that renal tubular damage, as assessed by urinary β_2–microglobulin–creatinine ratio, is also a common comorbidity and a novel risk factor for cardiac events, similar to that of glomerular damage in patients with CHF. Taking renal tubular damage into consideration may help clinicians to assess the underlying pathophysiology of kidney dysfunction more precisely in patients with CHF.

SUPPLEMENTAL MATERIAL

Supplemental Figure 1



Supplemental Figure 2



Supplemental figure legend

Supplemental figure 1.
(A) The relationship between $\log_{10}$ UBCR and eGFR.
(B) The relationship between $\log_{10}$ UBCR and $\log_{10}$ UACR.

Supplemental figure 2.
(A) Kaplan-Meier analysis of all cardiac events between normal group and RTD group.
(B) Kaplan-Meier analysis of all cardiac events between CKD group and CKD + RTD group.

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Gender Differences in Clinical Characteristics, Treatment and Long-Term Outcome in Patients With Stage C/D Heart Failure in Japan

– Report From The CHART-2 Study –

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Background: The gender differences in patients with chronic heart failure (CHF) remain to be fully elucidated in the Japanese population.

Methods and Results: We examined gender differences in clinical characteristics, treatment and long-term outcome in 4,736 consecutive CHF patients in stage C/D (mean age, 69 years) out of 10,219 patients registered in the CHF Registry, named CHART-2 Study (NCT 00418041). Compared with male patients (68%, n=3,234), female patients (32%, n=1,502) were 3.8 years older and had lower prevalence of ischemic heart disease, diabetes, smoking, myocardial infarction and cancer. At baseline, women had higher prevalence of preserved left ventricular function but had higher NYHA functional class and increased brain natriuretic peptide level. In women, aspirin, β-blockers and statins were less frequently used and diuretics were more frequently used. Crude mortality rate was similar between the genders during the median 3.1-year follow-up (52.4/1,000 and 47.3/1,000 person-years for women and men, respectively, P=0.225). On multivariate Cox regression analysis, women had a reduced risk of mortality (adjusted HR, 0.791; 95% CI: 0.640–0.979, P=0.031).

Conclusions: Substantial gender differences exist in stage C/D CHF patients in real-world practice in Japan. Although female CHF patients had better survival than male patients after adjustment for baseline differences, crude mortality rate was similar between the genders, possibly reflecting relatively severer clinical manifestations in women.

Key Words: Gender difference; Heart failure; Observational study; Prognosis

It has been reported that women with chronic heart failure (CHF) have better survival than men in general.[1–11] The Framingham Study reported that among the 5,192 subjects without CHF aged 30–62 at the time of entry in 1949,[1] overt heart failure (HF) developed in 142 during the 16-year follow-up, that the incidence rate was greater in men than in women and that the probability of death within 5 years after onset of HF was 62% in men and 42% in women.[1] After this report, a number of studies have been conducted that also found better survival in female patients compared with male patients,[2–11] in the broad spectrum of HF, including advanced CHF[7] and HF with preserved left ventricular (LV) ejection fraction (HFpEF).[10,11]

Editorial p????

In Japan, the number of CHF patients has been rapidly increasing along with the advancement of the aging society, particularly in women.[12,13] It remains to be fully elucidated, however, whether gender differences exist among Japanese CHF patients. Thus, in the present study, we addressed this important issue using a CHF registry database, named Chronic Heart Failure Analysis and Registry in the Tohoku District-2 (CHART-2), a prospective multicenter observational study, in

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Table 1. **Baseline Characteristics**

	Male (n=3,234)	Female (n=1,502)	P-value
Age (years)	67.7±12.1	71.5±12.3	<0.001
Body weight (kg)	64.5±11.3	52.1±11.2	<0.001
Height (cm)	163.7±7.1	149.4±6.8	<0.001
Body mass index (kg/m²)	24±3.5	23.3±4.5	<0.001
NYHA functional class			<0.001
I	841 (26.1)	251 (16.8)	
II	2,080 (64.6)	1,011 (67.6)	
III	277 (8.6)	217 (14.5)	
IV	23 (0.7)	16 (1.1)	
Baseline cardiovascular disease			
Ischemic heart disease	1,749 (54.1)	483 (32.2)	<0.001
Cardiomyopathy	638 (19.7)	284 (18.9)	0.533
Valvular heart disease	263 (8.1)	235 (15.6)	<0.001
Hypertensive heart disease	193 (6.0)	90 (6.0)	<1.000
Risk factors			
Hypertension	2,518 (77.9)	1,154 (76.8)	0.441
Diabetes mellitus	1,176 (36.4)	476 (31.7)	0.002
Dyslipidemia	2,371 (73.3)	1,062 (70.7)	0.066
Smoking	713 (23.4)	92 (6.6)	<0.001
Previous history			
Myocardial infarction	1,304 (40.3)	299 (19.9)	<0.001
Cerebral infarction	114 (3.5)	55 (3.7)	0.879
Atrial fibrillation	1,055 (32.9)	516 (34.7)	0.231
Malignant diseases	399 (12.3)	155 (10.3)	0.049
Hemodynamics and LV function			
SBP (mmHg)	126.1±18.9	126.7±19.8	0.32
DBP (mmHg)	72.7±11.8	71.2±12.2	<0.001
Heart rate (beats/min)	71.7±14.6	74.1±15.5	<0.001
LVDd (mm)	53.6±9	48.8±8.9	<0.001
LVEF (%)	55.5±15.2	60±15.4	<0.001
LVEF≥50%	2,041 (65.8)	1,083 (75.1)	<0.001
Laboratory findings			
Hemoglobin (g/dl)	13.6±2	12.3±2.2	<0.001
BUN (mg/dl)	20±10.4	20.3±10.8	0.337
Creatinine (mg/dl)	1.1±0.9	0.9±0.7	<0.001
Albumin (mg/dl)	4.1±0.5	4±0.5	<0.001
LDL-C (mg/dl)	103.5±30.6	108.3±31	<0.001
eGFR ($ml \cdot min^{-1} \cdot 1.73 m^{-2}$)	61.6±24.5	58.3±22.8	<0.001
BNP (pg/ml)	184.7±275.6	219.6±323.8	<0.001

Data given as mean±SD or n (%).
BNP, brain natriuretic peptide; BUN, blood urea nitrogen; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; LDL-C, low-density lipoprotein cholesterol; LV, left ventricular; LVDd, left ventricular diastolic dimension; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; SBP, systolic blood pressure.

which 10,219 patients have been enrolled in the Tohoku district, Japan (NCT 00418041).[13–16]

Methods

CHART-2 Study

Details of the CHART-2 study have been described previously.[13–16] Briefly, the CHART-2 study is a multicenter, prospective observational study, in which 10,219 patients >20 years of age with significant coronary artery disease (stage A) and those in stages B–D HF were enrolled between October 2006 and March 2010.[13–16] All information, including medical history, laboratory data, and echocardiography data, were recorded at the time of enrollment, and thereafter annually by trained clinical research coordinators. Baseline cardiovascular disease, risk factors, and previous history were determined according to the data obtained from the case records at the time of enrollment. Valvular heart disease was defined as moderate to severe aortic and/or mitral valve disease without a previous history of valvular surgery, while hypertensive heart disease was defined as the presence of concentric hypertrophy (mean thickness of the ventricular septum and LV posterior wall ≥12mm) in patients with a history of hypertension but without a diagnosis of hypertrophic cardiomyopathy. The CHART-2 study was approved by the local ethics committee in each participating hospital and informed consent was obtained from all patients.

Table 2. Past History and Medication

	Male (n=3,234)	Female (n=1,502)	P-value
Past history			
PCI	1,231 (38.1)	304 (20.2)	<0.001
CABG	344 (10.6)	86 (5.7)	<0.001
ICD/CRT implantation	111 (3.4)	37 (2.5)	0.009
Other pacemaker implantation	209 (6.5)	165 (11)	<0.001
Medications			
Aspirin	2,016 (62.3)	706 (47)	<0.001
β-blocker	1,659 (51.3)	660 (43.9)	<0.001
RAS inhibitor	2,542 (78.6)	1,148 (76.4)	0.101
Diuretics	1,609 (49.8)	897 (59.7)	0.001
Calcium channel blocker	1,243 (38.4)	588 (39.1)	0.662
Statin	1,271 (39.3)	532 (35.4)	0.011

Data given as n (%).
CABG, coronary artery bypass grafting; CRT, cardiac resynchronization therapy; ICD, implantable cardioverter defibrillator; PCI, percutaneous coronary intervention; RAS, renin-angiotensin system.

Study Design

Among the 10,219 patients enrolled, 4,736 had HF in stage C/D. Stages A–D were defined at the time of registration in the CHART-2 study, according to the ACC/AHA guidelines classification:[17] stage A, at high risk for HF but without structural heart disease or symptoms of HF; stage B, structural heart disease but without signs or symptoms of HF; stage C, structural heart disease with prior or current symptoms of HF; and stage D, refractory HF requiring specialized interventions. The diagnosis of HF was made based on the criteria of the Framingham study.[1] Among the 4,736 stage C/D patients, 3,234 (68%) were male and 1,502 (32%) were female. Using the registry data of these patients, we examined gender differences in terms of clinical characteristics, management and long-term outcome in patients with stage C/D HF.

Statistical Analysis

All continuous variables are shown as mean±SD. Clinical characteristics of female and male patients were compared using Welch's t-test and Fisher's exact test with 2-sided P-values. Primary outcome measures of survival and HF-free survival were estimated by the Kaplan-Meier curve, and tested by the log-rank test in both genders. Incidence rates per 1,000 person-years for all-cause death, modes of death, HF requiring admission, acute myocardial infarction (AMI) and stroke were compared with the exact binominal test. Determinants of all-cause death were examined by the multivariate Cox proportional hazard model. Potential confounding factors with regard to baseline characteristics and treatments were included in multivariate analysis. The covariates for the multivariate analysis included gender, age, body mass index (BMI), history of hypertension, diabetes mellitus, dyslipidemia, and smoking, LVEF, systolic blood pressure (SBP), heart rate, hemoglobin, serum creatinine and brain natriuretic peptide (BNP) and treatment with β-blocker, renin-angiotensin system inhibitor (RASI) and statin. Interactions of gender and subgroups were estimated by the Cox proportional hazard model including interaction terms using the same variables listed here. Continuous variables were transformed into binary variables for estimation of interactions in the Cox model. P<0.05 and P-value for interaction <0.1 were considered as statistically significant in the present study. Statistical analysis was performed using IBM SPSS Statistics version 19 (IBM, Armonk, NY, USA) and R version 3.0.2.

Results

Baseline Characteristics

Baseline characteristics are listed in **Table 1**. Among the 4,736 Stage C/D patients, 1,502 (32%) were female and were 3.8 years older than men. Compared with men, women were more likely to be less obese, and were characterized by lower prevalence of ischemic heart disease, and had higher prevalence of valvular heart disease. In contrast, the prevalences of diabetes, smoking, MI and malignant disease were lower in women than in men. Although women had a higher prevalence of preserved LV function, they had relatively severe manifestation of CHF compared with men, including higher heart rate, higher NYHA class and increased BNP level. Baseline information regarding CHF treatment at the time of registration is given in **Table 2**. Women were less frequently treated with aspirin, β-blocker and statin, but more frequently with diuretics. In accordance with the lower prevalence of ischemic heart disease, women were less likely to undergo percutaneous coronary intervention or coronary artery bypass grafting. Furthermore, women were less frequently treated with implantable cardioverter defibrillator and/or cardiac resynchronization therapy, while more frequently treated with other cardiac pacemaker.

Gender Differences in Long-Term Outcome

There were 674 deaths during a median follow-up of 3.8 years, of which 338 (50.1%), 285 (42.3%), and 51 (7.7%) were due to cardiovascular, non-cardiovascular and unknown causes, respectively. Incidence of all-cause death was similar between the genders (52.4/1,000 vs. 47.3/1,000 person-years for women and men, respectively, P=0.225; **Figures 1,2**). Incidences of CHF requiring admission, AMI and stroke were also similar between the genders (**Figure 2**). As shown in **Figure 3**, women had higher cardiovascular mortality than men, particularly that due to HF, while men died more frequently of cancer. Although incidence of all-cause death was similar between the genders, multivariate Cox regression analysis revealed that women had a reduced risk of all-cause events than men after adjustment for clinical variables (hazard ratio [HR], 0.791; 95% confidence interval (95% CI): 0.640–0.9798, P=0.031), while it was not evident for cardiovascular death (HR, 1.027; 95% CI: 0.767–1.374, P=0.859) or HF requiring hospitalization (HR 0.858; 95% CI: 0.701–1.051, P=0.139; **Table 3**). Subgroup anal-

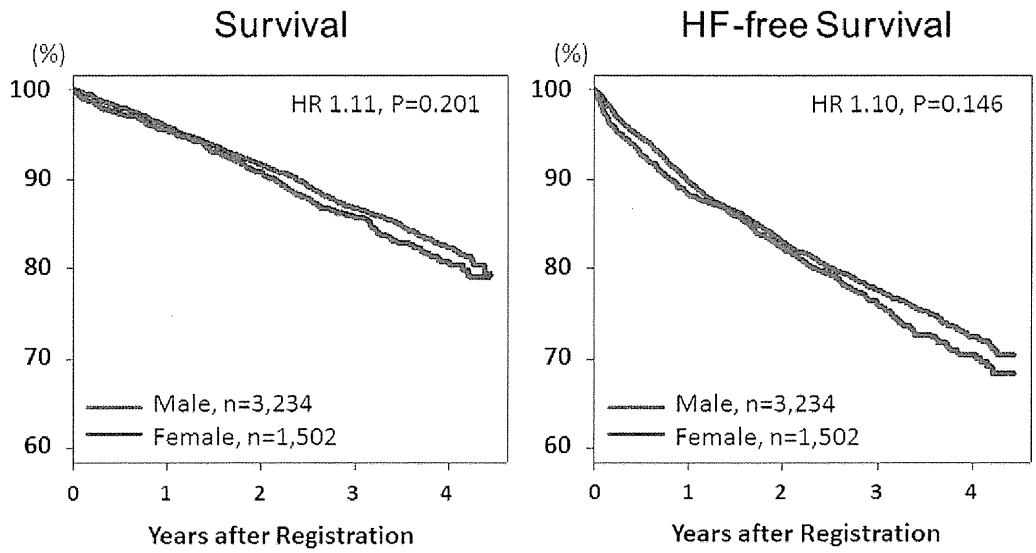

Figure 1. Kaplan-Meier estimates for survival. There were no differences in survival and heart failure (HF)-free survival between female and male patients. HR, hazard ratio.

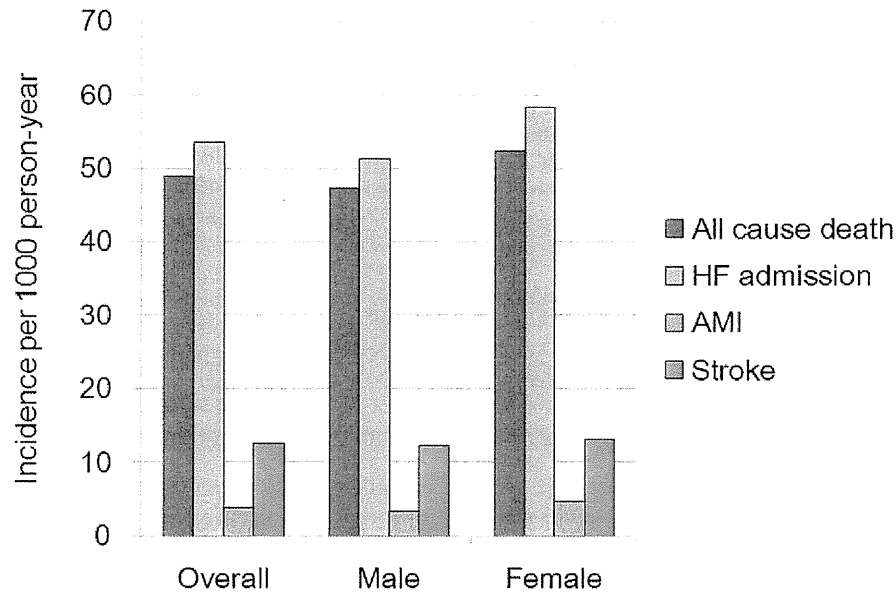

Figure 2. Incidence of all-cause death and cardiovascular event rates. Among the adverse events, death and heart failure (HF) requiring admission were most frequent. Rates of each event were similar between the genders during the median follow-up of 3.1 years (P=0.225, 0.113, 0.293, and 0.678 for all-cause death, HF admission, acute myocardial infarction [AMI], and stroke, respectively).

ysis showed that the prognostic impact of clinical variables on all-cause mortality was similar between the genders (**Figure 4**).

Discussion

The major findings of the present study are that substantial gender differences exist among Japanese HF patients, and that female CHF patients have better long-term survival compared with male CHF patients after adjustment for clinical parameters, although crude mortality rate was similar between the genders, possibly reflecting the relatively severer clinical manifestation in women. To the best of our knowledge, this is

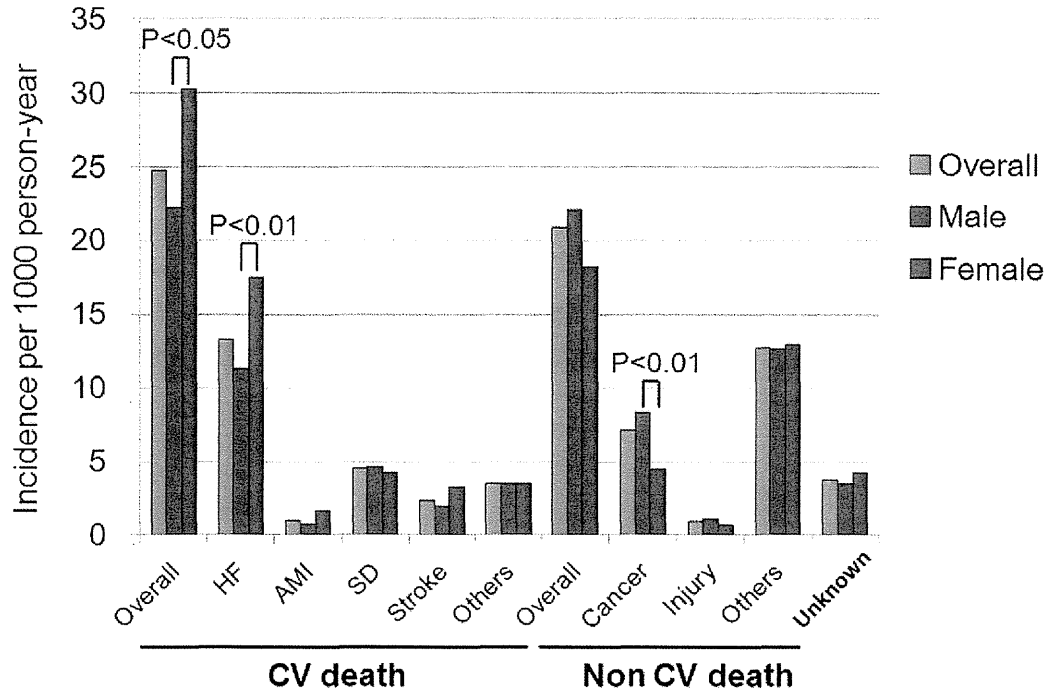

Figure 3. Gender and mode of death. Prevalence of modes of death was different between the genders. Particularly, incidence of death due to heart failure (HF) was more frequent in women, whereas that of malignant disease was more frequent in men. AMI, acute myocardial infarction; CV death, cardiovascular death; non-CV death, non-cardiovascular death; SD, sudden death.

Table 3. Predictors of All-Cause Death, CV Death and HF Admission

	All-cause death			CV death			HF admission		
	HR	95% CI	P-value	HR	95% CI	P-value	HR	95% CI	P-value
Female gender	0.791	0.640–0.979	0.031	1.027	0.767–1.374	0.859	0.858	0.701–1.051	0.139
Age per 10 years	1.568	1.413–1.741	<0.001	1.541	1.333–1.782	<0.001	1.084	0.995–1.181	0.066
BMI	0.955	0.929–0.981	0.001	0.985	0.949–1.022	0.410	1.015	0.991–1.038	0.219
Hypertension	0.894	0.719–1.113	0.316	0.877	0.648–1.188	0.396	1.061	0.857–1.314	0.585
Diabetes mellitus	1.127	0.936–1.358	0.208	0.986	0.756–1.286	0.916	1.249	1.047–1.489	0.013
Dyslipidemia	0.961	0.782–1.181	0.708	1.062	0.790–1.428	0.691	0.794	0.649–0.972	0.025
Smoking	1.168	0.963–1.417	0.114	1.124	0.855–1.478	0.403	0.903	0.749–1.090	0.289
LVEF per 10%	0.988	0.929–1.051	0.704	0.920	0.844–1.003	0.057	0.855	0.806–0.907	<0.001
SBP per 10mmHg	0.954	0.909–1.000	0.052	0.925	0.864–0.989	0.023	0.981	0.937–1.027	0.420
Heart rate per 10beats/min	1.096	1.038–1.157	0.001	1.074	0.994–1.160	0.072	1.040	0.987–1.096	0.146
Hemoglobin	0.882	0.838–0.928	<0.001	0.910	0.848–0.977	0.009	0.866	0.826–0.908	<0.001
Creatinine	1.154	1.082–1.231	<0.001	1.166	1.065–1.277	0.001	0.987	0.906–1.075	0.762
BNP per 100pg/ml	1.494	1.362–1.639	<0.001	1.696	1.484–1.938	<0.001	1.659	1.518–1.813	<0.001
β-blocker	0.826	0.683–0.998	0.048	0.767	0.588–1.000	0.050	0.870	0.726–1.043	0.131
RAS inhibitor	1.054	0.833–1.335	0.661	1.161	0.813–1.660	0.412	1.138	0.887–1.460	0.310
CCB	0.979	0.808–1.186	0.831	1.122	0.857–1.469	0.404	1.019	0.844–1.231	0.843
Statin	0.850	0.682–1.060	0.149	0.975	0.724–1.314	0.869	0.909	0.739–1.118	0.366
Diuretics	1.388	1.133–1.700	0.002	1.874	1.374–2.556	<0.001	2.337	1.878–2.909	<0.001

BMI, body mass index; CCB, calcium channel blocker; CV, cardiovascular; HF, heart failure. Other abbreviations as in Tables 1,2.

the first study to identify gender differences in clinical characteristics, management and long-term outcome in a large CHF cohort in Japan.

Gender Difference in Clinical Characteristics in Japanese CHF Patients

The present study identified gender differences in clinical characteristics, management and long-term outcome in patients

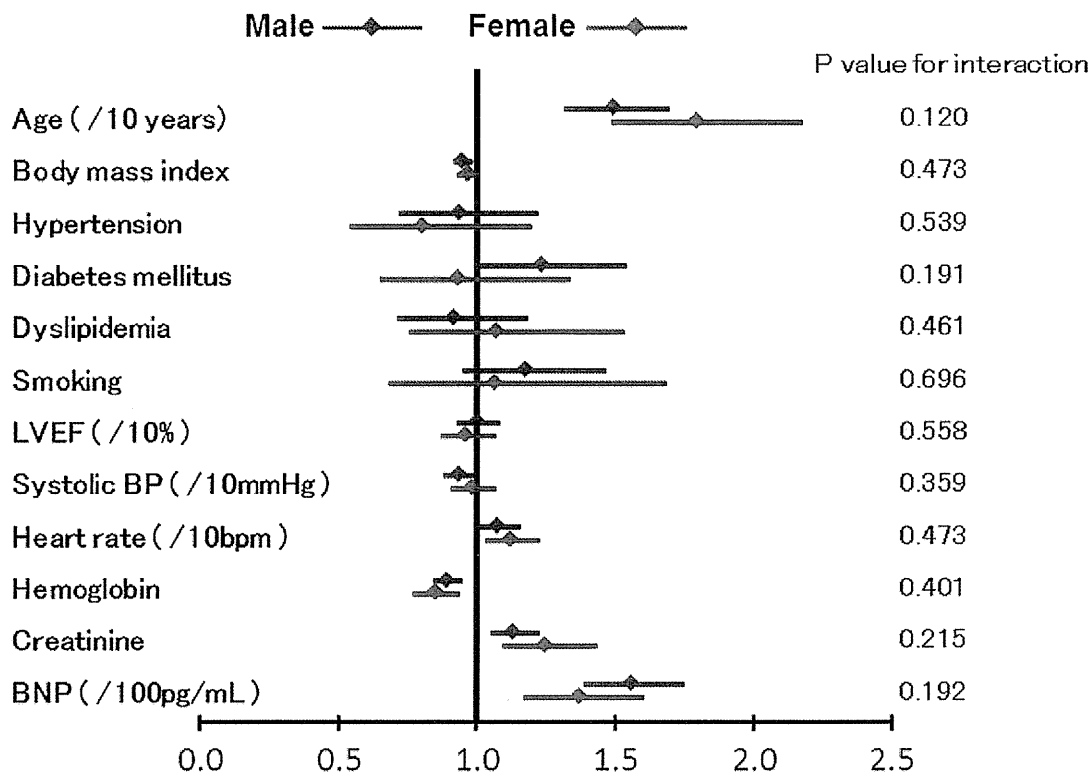

Figure 4. Predictors for all-cause mortality in both genders. Predictors for all-cause mortality were compared between the genders on multivariate Cox proportional hazard modeling. P-value for interaction was significant (P<0.1) for diabetes mellitus. BNP, brain natriuretic peptide; BP, blood pressure; LVEF, left ventricular ejection fractio

with stage C/D HF registered in the CHART-2 study, the largest prospective observational study for HF in Japan. The present results are of great importance given that no studies have comprehensively reported gender differences in HF patients in a large cohort in Japan. We initially found that clinical characteristics were different between the genders in stage C/D HF patients. Particularly, female patients were characterized by higher age, higher prevalence of preserved LVEF, lower prevalence of ischemic heart disease and higher prevalence of valvular heart disease in the present study (Table 1), consistent with previous reports.[9-11] The clinical manifestations of HF appeared to be more severe in women compared with men, in that female patients had a higher NYHA functional class and elevated serum BNP despite the higher prevalence of preserved LVEF (Table 1). Treatment with evidence-based medication (EBM), however, was equally (RASI) or even less frequently (β-blockers and statins) given to women compared with men (Table 2). Thus, it is highly possible that female patients with stage C/D HF are less adequately treated and consequently manifest severer HF conditions compared with male patients. But it is also possible that EBM itself has not been fully established for female patients, who have a higher prevalence of preserved LVEF.[18-26]

Gender Difference in Long-Term Prognosis in Japanese HF Patients

One of the strengths of the present study is that we calculated the incidence of all-cause death and other events by the person-year method. The analysis found that female and male patients with stage C/D HF experienced 52.4 and 47.3 deaths per 1,000 person-years (P=0.225) and 58.3 and 51.3 cases of HF requiring admission per 1,000 person-years (P=0.189), respectively. Thus, there are no gender differences in all-cause death and HF requiring admission, although the incidences of both events are much higher than those of AMI or stroke (Figure 2). Regarding the modes of death in HF patients, the incidence of cardiovascular death, particularly that due to HF, was significantly higher in female patients, whereas that of cancer death was more frequent in male patients (Figure 3). It is thus conceivable that more severe clinical manifestations in female patients resulted in the increased cardiovascular mortality in the present study.

It has been generally accepted that female gender is associated with better survival (either crude and/or age-adjusted) compared with male gender in the broad spectrum of HF.[1-11] Several studies suggested that the gender difference in long-term prognosis of HF could be explained by the higher prevalence of preserved LVEF in women.[4-6] This, however, should be viewed with caution,[9] because gender differences in LVEF in HF patients are due to underlying disease, age and other factors. In the present study, the female CHF patients had better long-term survival than men after adjustment for clinical parameters including LVEF. Thus, unmeasured confounding factors other than LVEF could have affected the better mortality in female CHF patients in the present study.

It is noteworthy that the crude mortality rate did not differ

between the genders in the present study, whereas most of the previous studies reported better crude or unadjusted survival for female CHF patients.[1–3,7–10] One possible explanation for this discrepancy is the higher prevalence of HFpEF in the present study (65.8% for men and 75.1% for women, Table 1), given that similar crude mortality between the genders was also reported in patients with HFpEF enrolled in the ancillary arm of the Digitalis Investigation Group trial.[11] Another explanation would be that female CHF patients might have visited the hospital with a more advanced stage of HF than male CHF patients in the present study, a possible problem in daily practice in Japan.

Life Expectancy in Female CHF Patients

In Japan, the average life expectancy has been increasing in both genders. In 2010, the expectancy at birth was 79.55 years for men and 86.30 years for women,[28] with a 6.35-year difference between the genders that is greater than the 3.8-year difference between the genders in the present study (67.7 vs. 71.5 years, P<0.001). Given that the average life expectancy for a 67.7-year-old Japanese man and 71.5-year-old Japanese women is between 16.44 and 17.20 years, and between 17.73 and 18.58 years in 2010, respectively,[27] women could live an average of approximately 1.5 years longer than men in the general population if their age distribution is similar to that in the present study. The present study, however, found that female CHF patients did not have better survival than men in real-world practice. These lines of evidence suggest that life expectancy was shortened in female HF patients compared with male HF patients in the present study. Further studies are warranted to achieve better HF management based on gender differences, especially for women.

Study Limitations

Several limitations should be mentioned. First, the number of death events was relatively small, which might have limited the power to find significant observations. Second, because all subjects were recruited in the Tohoku district in Japan, caution may be needed when generalizing the present results to other cohorts.

Conclusions

Substantial gender differences were found in clinical characteristics, management and long-term outcome in the present CHART-2 Study. Although women had better survival than men after adjustment for baseline differences, crude mortality rate was similar between the genders, possibly reflecting the relatively severer clinical manifestations in female patients with HF in real-world practice.

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Appendix

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Angiogenesis and Cardiac Hypertrophy: Maintenance of Cardiac Function and Causative Roles in Heart Failure

Toru Oka, Hiroshi Akazawa, Atsuhiko T. Naito and Issei Komuro

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Angiogenesis and Cardiac Hypertrophy

Maintenance of Cardiac Function and Causative Roles in Heart Failure

Toru Oka, Hiroshi Akazawa, Atsuhiko T. Naito, Issei Komuro

Abstract: **Cardiac hypertrophy is an adaptive response to physiological and pathological overload. In response to the overload, individual cardiac myocytes become mechanically stretched and activate intracellular hypertrophic signaling pathways to re-use embryonic transcription factors and to increase the synthesis of various proteins, such as structural and contractile proteins. These hypertrophic responses increase oxygen demand and promote myocardial angiogenesis to dissolve the hypoxic situation and to maintain cardiac contractile function; thus, these responses suggest crosstalk between cardiac myocytes and microvasculature. However, sustained pathological overload induces maladaptation and cardiac remodeling, resulting in heart failure. In recent years, specific understanding has increased with regard to the molecular processes and cell–cell interactions that coordinate myocardial growth and angiogenesis. In this review, we summarize recent advances in understanding the regulatory mechanisms of coordinated myocardial growth and angiogenesis in the pathophysiology of cardiac hypertrophy and heart failure. (*Circ Res.* 2014;114:565-571.)**

Key Words: anoxia ■ angiogenesis factor ■ heart failure ■ hypertrophy ■ ischemia

The heart is one of the first organs to develop in the embryo. During embryonic development, the heart grows via proliferation and hypertrophy of cardiac myocytes.[1] Heart tube formation is initiated around embryonic day 8 in the mouse, and this primitive avascular structure consists of a few layers of cardiac myocytes, which are located adjacent to endocardial cells and receive nutrients and oxygen through diffusion.[2] Because the myocardial wall increases in thickness by myocyte proliferation, the endocardial surface area also increases by progressive trabeculation, allowing maximal diffusion. However, as the myocardium grows further, nutrients and oxygen delivered by diffusion become insufficient, a primitive vascular plexus starts to develop shortly after initiation of heart contraction.[3] Angiogenic precursor cells, including angioblasts from the proepicardial organ and from the sinus venosus, differentiate into endothelial cells and assemble into a primitive capillary network in a process known as coronary vasculogenesis. Subsequently, this primitive capillary plexus expands by endothelial sprouting from preexisting capillaries in a process referred to as coronary angiogenesis.[2,3]

Because cardiac myocytes discontinue the cell cycle soon after birth, subsequent growth of the heart is achieved predominantly by hypertrophy of individual cardiac myocytes during postnatal development. Individual cardiomyocytes increase in size ≥3- to 4-fold after birth.[2] The increased oxygen and metabolic demands of growing cardiac myocytes are accommodated by a significant expansion of the myocardial vasculature. These vessels further differentiate and acquire specific properties of coronary arteries or veins. After birth, the myocardial vascular plexus expands through not only angiogenesis but also physiological neovascularization, in which endothelial progenitor cells are involved.[2,3]

Cardiac hypertrophy in normal growth or in trained athletes is referred to as physiological hypertrophy and is characterized by normal or enhanced contractile function and normal architecture and organization of cardiac structure.[4] In contrast, cardiac hypertrophy in patients with hypertension, myocardial infarction (MI), cardiomyopathy, or structural heart diseases is referred to as pathological hypertrophy and is often associated with contractile dysfunction, interstitial fibrosis, and re-expression of fetal cardiac genes, such as genes coding natriuretic peptides and the β-myosin heavy chain.[4,5] Pathological hypertrophy is also associated with cardiac structural remodeling and myocardial fibrosis, and sustained pathological hypertrophy leads to congestive heart failure, arrhythmia, and sudden death.[6] During the development of hypertrophy, interstitial cells, such as capillary endothelial cells and cardiac fibroblasts, also dynamically undergo a phenotypic change to support contractile function of the myocardium.[5,6] According to morphometry of hypertrophied hearts in animal models, capillary microvasculature and myocytes grow in proportion to the increase of heart mass,[7,8] suggesting that disproportional

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Nonstandard Abbreviations and Acronyms	
CHIP	carboxyl terminus of Hsc70-interacting protein
Hif-1	hypoxia inducible factor-1
NO	nitric oxide
p53	transformation-related protein 53
PlGF	placental growth factor
VEGF	vascular endothelial growth factor
VEGFR	VEGF receptor

growth of capillaries and myocytes could cause myocardial ischemia in pathologically hypertrophied hearts.[9,10] In this review, we summarize recent advances in our understanding of cardiac hypertrophy and myocardial angiogenesis and discuss molecular mechanisms regulating capillary angiogenesis and cardiomyocyte hypertrophy in pathophysiological conditions.

Myocardial Angiogenesis Induces Cardiac Hypertrophy

Under a spectrum of conditions that trigger both physiological and pathological myocardial hypertrophy, the myocardium secretes angiogenic growth factors, which stimulate coordinated vascular growth to meet demands for blood supply that is sufficient to sustain the increase in myocardial mass and performance. Interestingly, enhanced vascular growth promotes myocardial hypertrophy even in the absence of hypertrophic stimulations. Although transgenic overexpression of vascular endothelial growth factors (VEGFs) in the myocardium induced the formation of vasculature with abnormal structure and connectivity without promoting cardiac hypertrophy,[11] transgenic overexpression of proline-arginine–rich with a size of 39 residues or placental growth factor (PlGF) induced cardiac angiogenesis and cardiac hypertrophy.[12,13] Importantly, proline-arginine–rich with a size of 39 residues and PlGF had no direct hypertrophic effect on cultured cardiomyocytes,[13,14] suggesting that enhanced formation of coronary vasculature itself leads to myocardial hypertrophy in mice.

The precise mechanisms underlying angiogenesis-induced myocardial hypertrophy remain to be fully elucidated. One possible explanation is that superfluous delivery of nutrients and oxygen, transported because of an increase in capillary mass, might simply promote the hypertrophic growth of cardiomyocytes (Figure 1). Alternatively, an increase in capillary mass might boost the production of endothelium-derived secreted factors, which promote myocardial hypertrophy. Endothelium-derived nitric oxide (NO) is one of the critical factors that mediate angiogenesis-induced myocardial hypertrophy (Figure 1). This mediation is evidenced because an NO synthase inhibitor, NG-nitro-L-arginine methylester, or genetic disruption of endothelial NOS were both able to prevent cardiac hypertrophy induced by proline-arginine–rich with a size of 39 residues or PlGF partially, respectively.[12,13] Mechanistically, NO promoted proteasomal degradation of regulators of G-protein signaling,[12] and thereby potentiated G-protein–mediated hypertrophic signaling involving the phosphatidylinositol 3-kinase γ/thymoma viral proto-oncogene (Akt)/mammalian target of rapamycin C1 pathway (Figure 1).[15] Either NG-nitro-L-arginine methylester treatment or transgenic rescue of regulators of G-protein signaling 4 were able to attenuate the activation of the Akt/mammalian target of rapamycin C1 pathway and cardiac hypertrophy in PlGF transgenic mice. It will be of particular interest to elucidate the mechanisms further underlying angiogenesis-induced myocardial hypertrophy.

Hypertrophic Responses Induce Angiogenesis

A significant increase in the number of myocardial capillaries was observed in physiological cardiac hypertrophy, whereas capillary density was reduced in pathological hypertrophy,[7–10,16] suggesting that myocardial capillary number is controlled by the myocardium, and that rarefaction of capillary density may cause myocardial hypoxia and contractile dysfunction (Figure 2). Myocardial angiogenesis is regulated by secreted angiogenic growth factors, including VEGFs, angiopoietin-1 and -2,[17] fibroblast growth factors,[18] transforming growth factors,[19] and platelet-derived growth factors.[20] Among them, VEGFs and angiopoietins are the prime regulators of myocardial angiogenesis, and their functions and roles have been investigated thoroughly. Akt is a serine-threonine protein kinase that mediates hypertrophic growth of cardiac myocytes. Short-term Akt1 activation induced physiological hypertrophy via coordinated upregulation of VEGF expression,[21] whereas long-term Akt1 activation promoted pathological hypertrophy.[22,23] Shiojima et al[24] have reported, using cardiac-specific inducible Akt1 transgenic mice, that short-term Akt activation in the myocardium increased production of angiogenic growth factors, such as VEGF-A and angiopoietin-2, and maintained myocardial capillary density in the adaptive phase. Conversely, inhibition of VEGF signaling resulted in capillary rarefaction and an early transition to heart failure.[24] This study suggested that cardiomyocytes themselves produce angiogenic factors to maintain capillary density, oxygen supply, and their function. Furthermore, in endothelial cells, brief activation of Akt attenuated damage caused by ischemia, whereas prolonged Akt activation results in unorganized blood vessel formation, similar to tumor vasculature.[25] In the heart failure model of Dahl salt-sensitive rats, exercise training attenuated heart failure through further activation of the phosphatidylinositol 3-kinase/Akt/mammalian target of rapamycin pathway,[26] suggesting that effects of Akt signaling on heart failure depend on the timing and length of Akt activation.

Transverse aortic constriction, a model of pathological cardiac hypertrophy caused by pressure overload, induced an increase in myocardial oxygen demand, because of a high workload against an increased afterload. In addition, transverse aortic constriction decreased coronary perfusion pressure and increased extrinsic compressive forces on microvasculature. In transverse aortic constriction-operated hearts, coronary resistance also increased, and the imbalance between myocardial demand and oxygen supply led to relative ischemia/hypoxia in hypertrophied hearts.[27] In VEGF-deficient mice, transverse aortic constriction induced cardiac hypertrophy, which was associated with a rarefaction of myocardial capillary density, and accelerated the transition to decompensated heart failure.[28] In contrast, supplementation of VEGF for a failing heart preserved systolic function of the heart.[27,29] These results suggest that