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Letters to the Editor

Sex differences with respect to clinical characteristics, treatment, and long-term outcomes in patients with heart failure

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The effect of sex on the etiology, risk factors, comorbidities, treatment and prognosis in patients with heart failure (HF) encountered in routine clinical practice in Asian populations has not been well described. The objective of the present study was to elucidate sex differences with respect to the clinical characteristics, treatment, and prognosis of HF patients treated in routine clinical practice settings using the Japanese Cardiac Registry of Heart Failure in Cardiology (JCARE-CARD) database, which is a nationwide registry for hospitalized patients with HF in Japan.

JCARE-CARD enrolled 2675 patients hospitalized for HF at 164 participating hospitals from January 2005 to June 2006. HF was diagnosed by the simultaneous presence of at least two major criteria or one major criterion in conjunction with two minor criteria by use of the criteria from the Framingham Heart Study [1]. For each patient, baseline data recorded on the form were: demography; HF causes; comorbidities; complications; clinical status; echocardiographic findings; plasma B-type natriuretic peptide (BNP); and treatments. Long-term follow-up data could be obtained from 2305 patients after hospital discharged. Mean post-discharge follow-up was 2.3 ± 0.7 years.

To evaluate the effects of sex on the outcomes, the propensity score which is one of the most widely employed covariate adjustment methods was used to adjust the confounding factors between sex and the outcomes. Multiple covariate Cox regression analyses were used to assess the association of sex with long-term outcomes using all variables and individual propensity scores.

JCARE-CARD collected data from 2675 patients hospitalized with HF, of which 1598 (60%) were male and 1077 (40%) were female. Table 1 provides a comparison of demographic and clinical characteristics for the entire cohort according to sex. Female patients were a mean of 5.7 years older than male patients. Ischemic etiology was more common in males than in females (36% vs 26%). Hypertensive etiology was more common in females than in males (27% vs 23%). Females were more likely to have hypertension, hyperlipidemia, and anemia than males. However, renal failure, hyperuricemia, COPD, and smoking were more frequent in males. These findings of the different clinical characteristics between male and female are similar to the results of other registries in US [2,3]. Mean LVEF was significantly higher in females. Females had a significantly higher level of BNP in serum upon hospital admission, although there was no significant difference in New York Heart Association (NYHA) class. A lower proportion of female patients received ACE inhibitors (32.1% vs 40.9%), β-blockers (44.5% vs 51.6%), antiarrhythmics (13.6% vs 18.6%), aspirin (44.5% vs 49.0%), and warfarin (36.0% vs 43.9%), but a higher proportion received a calcium channel blocker (28.3% vs 23.1%).

There were 282 deaths from any cause (20.5%) in males and 192 (20.7%) in females ($P=0.836$) The prevalence of cardiac mortality (12.5% vs 12.9%; $P=0.729$), sudden cardiac deaths (3.3% vs 3.3%; $P=0.729$), and hospitalization due to the worsening of HF (36.2% vs 36.4%; $P=0.985$) were also comparable between males and females (12.5% vs 12.9%; $P=0.729$). After adjustment for multiple variables predictive of mortality after hospital discharge, there was no significant difference in all-cause mortality between males and females (adjusted hazard ratio [HR] 0.97, 95% confidence interval (CI) 0.80–1.19, $P=0.774$). Risk of cardiac mortality (adjusted HR 1.06; 95% CI 0.82–1.36; $P=0.665$), sudden cardiac mortality (adjusted HR 1.04; 95% CI 0.64–1.69; $P=0.870$), and hospitalization due to the worsening of HF (adjusted HR 1.05; 95% CI 0.90–1.22; $P=0.529$) were also similar between males and females.

Despite the low rate of prescription of drugs to females, their prognosis was equal to that of males. Possible explanations of this finding might be the sex-related differences of the pathophysiology of HF [4], psychosocial factors [5], and life circumstances (e.g., support from the family and partner as well as social services). Consequently, to explain sex differences in the prognoses for HF, a multidimensional

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[2] Dr. Akira Takeshita died on 15 March 2009.

Table 1
Baseline demographic and clinical characteristics.

Characteristics	All ($n=2675$)	Male ($n=1598$)	Female ($n=1077$)	P
Age, years	71.0 ± 13.4	68.7 ± 13.3	74.4 ± 12.7	<0.001
Older than 65 years, %	72.5	66.0	82.2	<0.001
Body mass index, kg/m^2	22.3 ± 4.1	22.7 ± 4.0	21.7 ± 4.3	<0.001
Causes of HF, %				
Ischemic	32.0	36.3	25.6	<0.001
Hypertensive	24.6	22.8	27.3	0.008
Cardiomyopathic	21.9	26.2	15.5	<0.001
Valvular	27.7	21.8	36.6	<0.001
Undetermined	15.7	14.2	17.9	0.010
History, %				
Previous myocardial infarction	26.9	31.7	19.9	<0.001
Hypertension	52.9	51.2	55.4	0.036
Diabetes mellitus	29.9	31.1	28.2	0.116
Hyperlipidemia	24.8	22.9	27.6	0.006
Renal failure	11.7	13.0	9.9	0.014
Serum creatinine, mg/dL	1.4 ± 1.2	1.5 ± 1.3	1.2 ± 1.0	<0.001
Hyperuricemia	46.8	51.9	39.3	<0.001
Stroke	15.0	15.3	14.5	0.594
Anemia	20.8	17.5	25.6	<0.001
Hemoglobin, g/dL	12.0 ± 3.2	12.6 ± 3.7	11.2 ± 2.3	<0.001
COPD	6.7	8.5	4.1	<0.001
Smoking	37.7	57.4	9.2	<0.001
Atrial fibrillation	35.2	36.5	33.4	0.103
Sustained VT/Vf	6.2	7.2	4.8	0.013
Prior hospitalization due to HF	48.3	50.0	45.9	0.044
PCI	17.7	21.0	12.8	<0.001
CABG	9.2	11.7	5.6	<0.001
Valve surgery	6.7	5.9	7.9	0.053
NYHA class on hospital admission				
I	1.2	1.4	0.8	
II	11.4	12.5	9.8	0.523
III	44.6	43.7	45.8	0.173
IV	42.9	42.4	43.5	0.189
Echocardiographic data on hospital admission				
LV EDD, mm	56.1 ± 10.5	58.7 ± 10.0	52.2 ± 10.1	<0.001
LV ESD, mm	44.1 ± 12.5	46.9 ± 12.1	39.8 ± 11.7	<0.001
LVEF, %	42.2 ± 17.6	39.4 ± 17.1	46.5 ± 17.6	<0.001
<40%	49.7	56.5	39.2	
40–50%	16.0	15.8	16.4	0.001
>50%	34.2	27.6	44.4	<0.001
Plasma BNP on hospital admission, pg/ml	871.3 ± 970.2	851.4 ± 843.7	900.8 ± 1132.5	0.003

HF, heart failure; COPD, chronic obstructive pulmonary disease; VT, ventricular tachycardia; VF, ventricular fibrillation; PCI, percutaneous coronary intervention; CABG, coronary artery bypass grafting; NYHA, New York Heart Association; LV, left ventricular; EDD, end-diastolic dimension; ESD, end-systolic dimension; EF, ejection fraction; BNP, B-type natriuretic peptide.

study that includes physiological and psychosocial aspects must be conducted.

In conclusions, there were several differences with respect to clinical characteristics and treatment between males and females with HF. However, the effect of sex on outcomes was not found during long-term follow-up. Further investigation is needed to reveal novel mechanisms, therapeutic strategies, and effective management in males and females.

The authors of this manuscript have certified that they comply with the Principles of Ethical Publishing in the International Journal of Cardiology [6].

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Original article

Rationale and design of the Japanese Heart Failure Outpatients Disease Management and Cardiac Evaluation (J-HOMECARE)

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Heart failure;
Disease management;
Psychological status;
Prognosis;
Quality of life

Summary
Background: Although many studies have demonstrated the efficacy of disease management programs on mortality, morbidity, quality of life (QOL), and medical cost in patients with heart failure (HF), no study has focused on psychological status as an outcome of disease management. In addition, very little information is available on the effectiveness of disease management programs in other areas than the USA and Europe.
Methods: The Japanese Heart Failure Outpatients Disease Management and Cardiac Evaluation (J-HOMECARE) is a randomized controlled trial in which 156 patients hospitalized with HF will be randomized into usual care or a home-based disease management arm receiving comprehensive advice and counseling by visiting nurses during the initial 2 months and telephone follow-up for the following 4 months after discharge. This study evaluates depression and anxiety (Hospital Anxiety and Depression Scale), mortality, readmission due to HF, and QOL (Short Form-8). Data are collected during index hospitalization and then 2, 6, and 12 months after discharge. This study started in December 2007, and the final results are expected in 2011.
Conclusion: The J-HOMECARE will provide important information on the efficacy of disease management for psychological status as well as the effective components of disease management for patients with HF. (ClinicalTrials.gov number, NCT01284400).

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[1] See Appendix A.

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Introduction

Heart failure (HF) is one of the leading causes of death and hospitalization in developed countries. It is often associated with multiple co-morbidities and complications, as well as impaired quality of life (QOL). Although many therapeutic options have reduced mortality and morbidity in patients with HF [1–4], frequent re-hospitalization due to worsening HF, low QOL [5], and psychological problems remain a critical issue [6]. Our previous studies demonstrated that poor follow-up as well as psychosocial distress such as anxiety was an independent predictor associated with hospitalization due to worsening HF [7,8].

To improve outcomes of HF patients, a variety of disease management programs have been developed and tested over the past 25 years [9–11]. These programs include HF clinics, home-based intervention, and tele-monitoring. The key components of all of these interventions were education and counseling, symptom monitoring by a nurse, accessibility of healthcare provider in case of problems, optimization of medication, and social support service after discharge. They have been reported to decrease rehospitalization due to worsening HF, increase time to first major event, decrease medical costs, and improve QOL [12]. However, some studies have failed to support these positive findings, by reporting negative or inconclusive results [13,14]. In addition, the differences in national healthcare systems raise questions about the suitability and comparability of these programs in different countries. To the best of our knowledge, no trials have been conducted to evaluate the effect of disease management programs in other countries other than the USA, Europe, and Australia. Moreover, almost all previous studies have evaluated the effects of disease management on mortality, readmission due to HF, QOL, and medical costs. Even though psychosocial distress, including depression and anxiety, is common among patients with HF and is a high risk for mortality and morbidity in HF [8,15], there is no trial to assess the efficacy of disease management programs for the psychosocial status of HF patients.

The Japanese Heart Failure Outpatients Disease Management and Cardiac Evaluation (J-HOMECARE) is a randomized controlled trial to evaluate the efficacy of home-based disease management programs compared with usual care in improving psychosocial status, mortality, HF hospitalization, and QOL in Japanese HF patients.

Study design

Overview

J-HOMECARE is a multicenter, randomized, efficacy trial designed to evaluate the efficacy of home-based disease management programs on psychosocial status and QOL as well as mortality and morbidity as compared to usual care in Japanese HF patients. This study has been approved by the Ethics Committee of Hokkaido University Graduate School of Medicine. Recruited patients with HF were randomized into usual care and home-based disease management groups between December 2007 and March 2010. Patients undergo their respective J-HOMECARE treatment for 6 months and are then followed up for an additional 6 months. All data collection was scheduled to end in March 2011.

Study objectives

The primary objective of J-HOMECARE is to determine the effectiveness of interventions, as compared to that of usual care, on psychological status, including depression and anxiety, in HF patients. The secondary objective is to determine the effectiveness of interventions, compared to that of usual care, on all-cause death, cardiac death, sudden cardiac death, readmission due to decompensated HF, and QOL.

Study patients and baseline assessment

The process of the trial is shown in Fig. 1. All study candidates are required to have had a hospital admission for HF with symptoms and signs of HF and a pre-existing history of chronic HF [New York Heart Association (NYHA) II–IV]. Eligible patients must be at least 18 years of age. Reasons for exclusion from the study are as follows: end-stage HF defined as requiring mechanical support or continuous intravenous inotropic support; a serious life-threatening illness with a life-expectancy of <6 months; stroke within the last 3 months; cognitive dysfunction; substance abuse or psychotic disorder; patients whose physician or nurses refused access.

After informed consent has been obtained from eligible patients, they are randomized on a 1:1 basis, to either usual care or a home-based disease management program.

Baseline and all annual examinations consist of: (1) clinical characteristics including height, body weight, pulse, and blood pressure; (2) etiology of HF; (3) risk factors such as hypertension, diabetes mellitus, dyslipidemia, smoking habits, and/or alcohol drinking habits; (4) comorbidities such as prior myocardial infarction (MI), atrial fibrillation, ventricular arrhythmias, hyperuricemia, chronic kidney disease, anemia, stroke, chronic obstructive pulmonary disease, locomotor disability, prior percutaneous coronary intervention (PCI) or coronary artery bypass graft (CABG); (5) severity of HF [NYHA functional class, brain natriuretic peptide (BNP)], and echocardiography; (6) treatment at hospital discharge; and (7) a questionnaire assessing depression, anxiety, QOL, and physical activity (Table 1).

Intervention protocol

Enrolled patients receive comprehensive discharge education using a booklet provided by a cardiologist, nurse, dietitian, or pharmacist. This booklet provides knowledge and information on pathophysiology, medical treatment, diet, physical activity, lifestyle modification, self-measurement of body weight, self-monitoring of worsening HF, and emergency contact methods (Fig. 2). Follow-up assessments were performed 1, 2, 6, and 12 months after discharge.

A home-based disease management program consists of home visit by nurse to provide symptom monitoring, education, and counseling and telephone follow-up by nurse in addition to routine follow-up by cardiologist (Table 2). A home visit is made within 14 days after discharge from

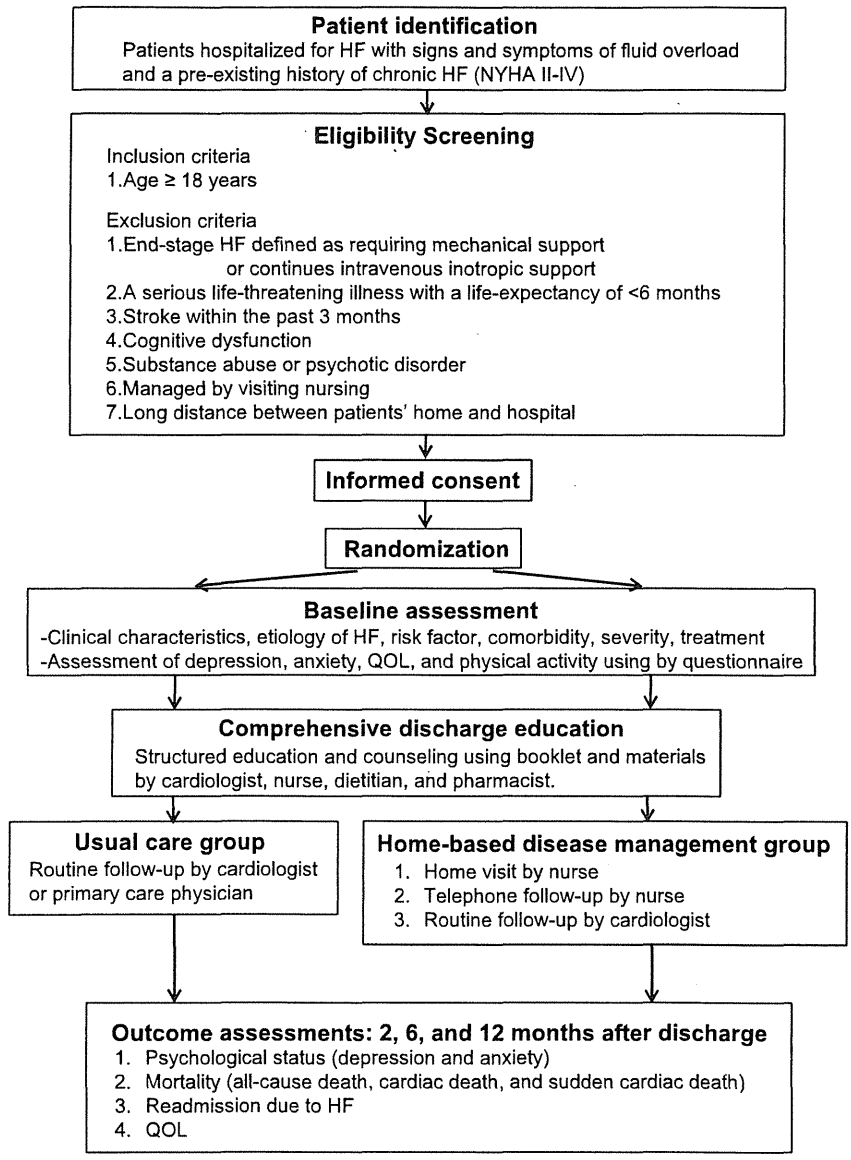

Figure 1 Study protocol of J-HOMECARE. HF, heart failure; NYHA, New York Heart Association; QOL, quality of life.

the hospital. The nurse visits the patient's home to assess how the patient is coping in the home environment, HF status, general health status, adherence to medication, lifestyle modification, daily activity, and social support needs (Table 3). Home visits are made once per two weeks until 2 months after discharge. After the conclusion of home visiting, the nurse conducts telephone follow-up once a month until 6 months after discharge (Fig. 3). Nurses monitor HF symptoms, patient's general health status, and the need of other health and social support (Table 4). The

Table 1 Questionnaires used in the J-HOMECARE study.

	Assessment schedule	Questionnaire
Depression	Baseline, 1, 3, 6, and 12 months	Hospital Anxiety and Depression Scale
Anxiety	Baseline, 1, 3, 6, and 12 months	Hospital Anxiety and Depression Scale
Quality of life	Baseline, 1, 3, 6, and 12 months	Medical outcome study Short Form-8
Physical activity	Baseline, 1, 3, 6, and 12 months	Specific activity scale

Table 2 Components and contents of the home-based disease management program during home visits.

Components	Contents
Coping in the home environment	Advice on how to adapt patients' current lifestyle to accommodate recommended changes Assessment and support of mismatch between physical disability and home environment
HF status	Assessment of HF-related symptoms, daily weight, and vital signs Consultation with cardiologist, if needed
General health status	Assessment of comorbidity, psychosocial response, and activity of daily living Consultation with cardiologist or other health professional, if needed
Adherence to medication	Assessment of coping with regimen Advice on effective coping strategy Assessment of side effects Support to caregiver's optimal monitoring for patient's adherence Consultation with pharmacist or cardiologist, if needed
Lifestyle modification	Advice on sodium restriction, fluid restriction, alcohol restriction, and smoking cessation Consultation with dietician or cardiologist
Daily activity	Assessment of work, daily, and leisure activity
Social support needs	Assessment of inadequate social support and social isolation Consultation with social worker, if needed

HF, heart failure.

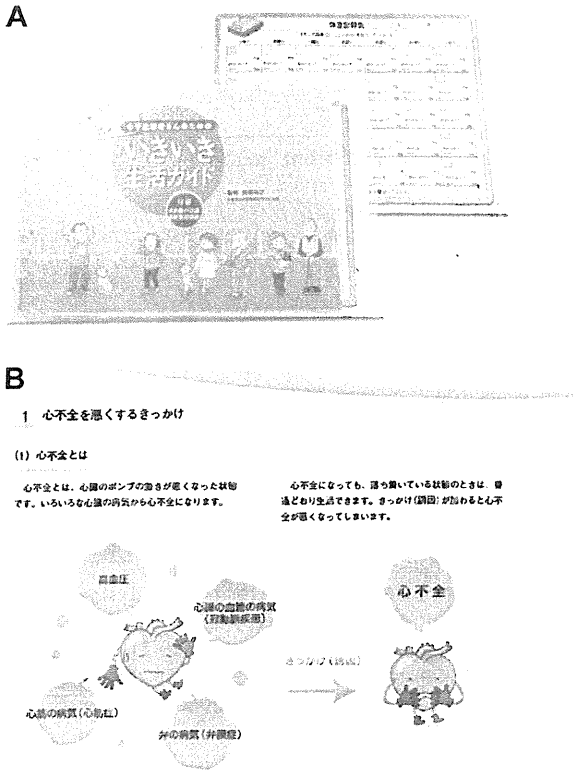

Figure 2 Photos of patient education booklet. (A) Booklet and check list of body weight. (B) A page of the booklet.

nurse consults a multidisciplinary team during the intervention period to optimize her advice for each patient. This multidisciplinary team consists of a cardiologist, dietician, pharmacist, and social worker. Other healthcare professionals are consulted, as required.

Patients in the control group receive usual care and follow-up. After hospital discharge, patients assigned to the usual care group continue to receive routine management by the cardiologist. No extra follow-up by a HF nurse or multidisciplinary team is provided. Patients are treated according to the current guidelines for HF management by standard medications.

Endpoints

The primary end point is the change in psychological status including depression and anxiety. We assess the change in the prevalence of depression and anxiety and the change in the score of the Hospital Anxiety and Depression Scale (HADS) from baseline to 12 months after discharge [16]. A change in the QOL score is assessed by the Short Form-8. Patients' QOL, psychological status, and physical activity are assessed in the outpatient clinic or by mail at 2, 6, and 12 months after discharge (Table 1).

The secondary endpoint is the time to the first event (all-cause death, cardiac death, sudden cardiac death, or hospitalization for HF). Hospitalization for HF is defined as an unplanned overnight stay in a hospital (different dates for admission and discharge) due to progression of HF or directly related to HF. Data are collected by chart reviews or interview to the patient.

Statistical analysis and sample size

All analyses are conducted according to the intention-to-treat principle. Data from all randomized patients will be analyzed according to the treatment assignment. Baseline characteristics will be compared between the 2 treatment arms to assess covariate balance, and any imbalances will be adjusted in multivariate models. To meet the primary objective of the study, the primary endpoint, the change

Table 3 Check list of patient status during home visit.

Vital Sign	Blood pressure	___/___mmHg
	Heart rate	___/min
	Breaths per minute	___/min
Heart failure symptoms	Dyspnea/Shortness of breath	Yes/No
	Paroxysmal nocturnal dyspnea	Yes/No
	Orthopnea	Yes/No
	Cough/Sputum	Yes/No
	Fatigue	Yes/No
	Oliguria/Nocturia	Yes/No
	Coldness of limbs	Yes/No
	Palpitation	Yes/No
	Edema	Yes/No
	Anorexia	Yes/No
	Insomnia	Yes/No
Body weight	Self-measurement of body weight	Yes/No*
	Body weight	___/kg
	Body weight change from baseline	___/kg
Life style modification	Adherence to sodium or fluid restriction	Yes/No*
	Excessive activity	Yes/No*
	Physical or mental stress	Yes/No*
	Infection prevention	Yes/No*
	Alcohol restriction	Yes/No*
	Smoking cessation	Yes/No*
Adherence to medical regimen	Poor	Yes*/No
	If yes, name and number of missed drugs	
Social support	Need for additional specialized care	Yes*/No
	Need for other social resources	Yes*/No
Report to primary physician	Need for additional education or support	Yes*/No
	Appointment of next clinic visit	Yes/No
	Need for immediate emergency room/clinic visit	Yes/No

* Require additional education or support for patient or families/caregivers.

in psychological status between baseline to 12 months after discharge, will be evaluated using the paired *t*-test, and multivariate modeling will be analyzed using logistic regression. To assess the secondary endpoint, event rates of death and readmission over time will be summarized using Kaplan–Meier survival curves, and differences in these curves by the intervention will be analyzed using the Mantel–Haenszel (log-rank) test. In addition, a Cox proportional hazard model will be fitted for a multivariate analysis. A *p*-value below 0.05 will be considered as statistically significant and the incidence curves will be considered to be confirmed as different.

The sample size is based on the assumption that the disease management program will produce a 30% reduction in the primary outcome, relative to the control usual care arm, from the results of previous similar trials for patients with MI or HF [17,18]. Previous nurse-led, behavioral intervention studies improved scores for depression and anxiety by a range of 30–40% [17,18]. It was calculated that 156 subjects (78 in each group) will be required to detect a 30% reduction in events (power of 80%, alpha of 0.05) in the disease management group, and dropouts and losses were estimated to be approximately 20% over the duration of the trial.

Discussion

J-HOMECARE is designed to determine the efficacy of disease management on psychosocial status in HF patients. Depression is known to obstruct active participation in lifestyle modification and symptom recognition required for taking appropriate action in case of worsening symptoms [19]. Moreover, depression and anxiety increase risks of mortality and readmission in patients with HF [8,20]. However, psychosocial problems are both underestimated and undertreated in HF patients [21,22]. Nurse-led intervention in MI patients has been reported to reduce psychological distress [23], whereas no previous studies have evaluated their effectiveness in disease management programs for psychological disorders in HF. If this study proves their effectiveness for psychological disorders, they could play an important role in improving psychosomatic symptoms, and could eventually improve clinical outcomes.

The significance of J-HOMECARE conducted in Japan is also designed to determine the clinical value of a disease management program across the country and healthcare system. With a rapidly growing aging population in developed countries, this trial will be able to explain how these management programs can be effective for universal strate-

Table 4 Components and contents of the home-based disease management program in telephone follow-up.

Components	Contents
HF status	Assessment of HF-related symptoms, daily weight Consultation with cardiologist, if needed
General health status	Assessment of comorbidity, psychosocial response, and activity of daily living Consultation with cardiologist or other health professional, if needed
Adherence to medication	Assessment of coping with regimen Assessment of side effects Support to caregiver's optimal monitoring for patient's adherence Consultation with pharmacist or cardiologist, if needed
Lifestyle modification	Advice on sodium restriction, fluid restriction, alcohol restriction, and smoking cessation Consultation with dietician or cardiologist, if needed
Social support needs	Assessment of inadequate social support and social isolation Consultation with social worker, if needed

HF, heart failure.

gies for HF, regardless of the differences in ethnicity and healthcare systems.

In J-HOMECARE, visiting nurses provide advice and counseling regarding coping in the home environment, healthcare and social support, and future healthcare needs for 3 months after discharge. Based on previous studies, the elements of disease management programs for HF consist of 4 categories: (1) symptom monitoring; (2) therapeutic modification; (3) patient education; and (4) patient adherence [24,25]. In a growing aging population, elderly patients living with HF have complex problems, such as living alone, having an elderly caregiver, or having a mismatch between disability in the instrumental activities of daily living (IADL) and life circumstances. These problems interfere with their adherence to and maintenance of optimized medical treatment [26]. Therefore, the comprehensive advice and support of J-HOMECARE may play an important role in enhancing the various elements of disease management programs.

In conclusion, J-HOMECARE is a multicenter, randomized trial analyzing the impact of home-based disease management programs on the psychological status as well as prognosis and QOL of HF patients in Japan. It is the first trial carried out in Japan to analyze the effect of disease management on clinical outcomes for Japanese patients and is expected to prove its effectiveness in disease management irrespective of the national health service system. Moreover, our intervention has both multidisciplinary and comprehensive features including continuing support to manage patients' complex problems and enhance their self-care and adherence. Results from this trial will help healthcare providers to determine the effective components of an HF management program.

Funding

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Conflict of interest

Hiroyuki Tsutsui has received research support from Novartis and honoraria for lectures from Shionogi, Daiichi Sankyo, Tanabe-Mitsubishi, Novartis, MSD, Pfizer, Takeda.

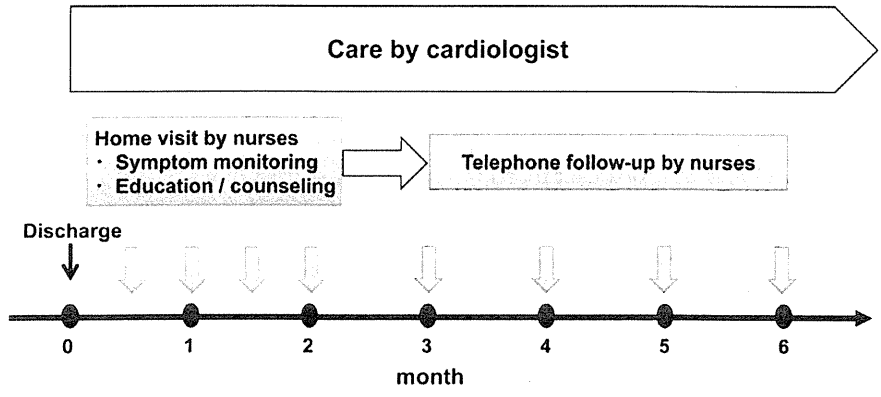

Figure 3 Algorithm of home-based disease management.

Appendix

Steering Committee

Hiroyuki Tsutsui (Chair), Miyuki Tsuchihashi-Makaya (Co-chair).

Endpoint Adjudication Committee

Members: Takayuki Inomata, Shintaro Kinugawa, Kenichi Sugioka.
Assistant: Mayumi Koasa.

Data and Safety Monitoring Committee

Members: Hisashi Kai, Tomomi Ide.
Assistant: Erina Ninomiya.

Investigators:

Hisashi Matsuo, Toru Kaji, Yoshiko Nishino, Reiko Omi, Noboru Asai, Mizue Takahashi, Shigeo Kakinoki, Chika Takagi, Kazuhiko Nagai, Miki Takeuchi, Shuko Uchionbou, Shigeru Takechi, Atsuko Namikoshi, Masumi Sakurada, Masumi Furuya, Yuki Heishi.

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ORIGINAL ARTICLE

Lower aerobic capacity was associated with abnormal intramuscular energetics in patients with metabolic syndrome

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Lower aerobic capacity is a strong and independent predictor of cardiovascular morbidity and mortality in patients with metabolic syndrome (MetS). However, the mechanisms are not fully elucidated. We tested the hypothesis that skeletal muscle dysfunction could contribute to the lower aerobic capacity in MetS patients. The incremental exercise tests with cycle ergometer were performed in 12 male patients with MetS with no habitual exercise and 11 age-, sex- and activity-matched control subjects to assess the aerobic capacity. We performed ^{31}phosphorus-magnetic resonance spectroscopy (MRS) to assess the high-energy phosphate metabolism in skeletal muscle during aerobic exercise. Proton-MRS was also performed to measure intramyocellular lipid (IMCL) content. Peak oxygen uptake (peak VO_2; 34.1 ± 6.2 *vs.* 41.4 ± 8.4 ml kg^{-1} min^{-1}, $P<0.05$) and anaerobic threshold (AT; 18.0 ± 2.4 *vs.* 23.1 ± 3.7 ml kg^{-1} min^{-1}, $P<0.01$) adjusted by lean body mass were lower in MetS patients than control subjects. Phosphocreatine (PCr) loss during exercise was 1.5-fold greater in MetS, suggesting reduced intramuscular oxidative capacity. PCr loss was inversely correlated with peak VO_2 ($r=-0.64$) and AT ($r=-0.60$), respectively. IMCL content was threefold higher in MetS and was inversely correlated with peak VO_2 ($r=-0.47$) and AT ($r=-0.52$), respectively. Moreover, there was a positive correlation between IMCL content and PCr loss ($r=0.64$). These results suggested that lean-body aerobic capacity in MetS patients was lower compared with activity-matched healthy subjects, which might be due to the reduced intramuscular fatty acid oxidative metabolism.
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Keywords: energy metabolism; exercise; metabolic syndrome; muscles

INTRODUCTION

The drastic increase in the number of obese patients with insulin resistance has become a medical and public health crisis in industrialized countries. Metabolic syndrome (MetS) characterized by insulin resistance and obesity contributes to the enhanced risk of developing atherosclerotic cardiovascular disease and type 2 diabetes.[1,2]

Lower aerobic capacity is an independent predictor of all-cause mortality in patients with insulin resistance and type 2 diabetes.[3] Moreover, aerobic capacity is more powerful predictor of mortality than other established risk factors of cardiovascular diseases.[4] Therefore, improving the aerobic capacity is of great importance in MetS patients. In general, the aerobic capacity is adjusted by body weight and tends to be low in obese subject such as MetS patients because of weight gain primarily due to increased fat mass. However, it has not been fully clarified whether lean-body aerobic capacity is impaired in patients with MetS.

The determinants of aerobic capacity are multifactorial, but aerobic capacity is generally believed to be impaired in the presence of abnormalities in skeletal muscle energy metabolism,[5] and energy metabolism largely depends on mitochondrial function.[6] Indeed, it has been shown that mitochondrial ATP production in skeletal muscle is impaired in insulin-resistant offspring of patients with type 2 diabetes,[7] which raises the possibility that mitochondrial oxidative phosphorylation in skeletal muscle might be impaired in MetS. However, it has not been determined whether lower aerobic capacity is associated with skeletal muscle dysfunction in these patients.

Insulin resistance is characterized not only by abnormal glucose metabolism but also by abnormal fatty acid metabolism, which leads to the ectopic fat accumulation.[8] It has been reported that intramyocellular lipid (IMCL) content is inversely correlated with insulin sensitivity in humans.[9] IMCL content is determined by the balance between the uptake of free fatty acid into skeletal muscle cells and fatty acid β-oxidation within the mitochondria.[10] Thus, abnormal fatty acid

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metabolism within the mitochondria can reduce the production of energy from fatty acid, which in turn might impair aerobic capacity in MetS. However, the significance of IMCL in the skeletal muscle energy metabolism and aerobic capacity in MetS is not fully elucidated.

Therefore, the purpose of this study was to determine (1) whether lean-body aerobic capacity, skeletal muscle energy metabolism and IMCL content are abnormal in MetS patients, and (2) whether these abnormalities are related to each other.

METHODS

Subjects

A total of 12 sedentary Japanese male patients with MetS, diagnosed by physical checkups at Hokkaido University Hospital or neighboring hospitals on the basis of International Diabetes Federation criteria, were studied. All subjects underwent a physical examination and assessment of medical history. They also underwent electrocardiograms and cardiac ultrasounds. Patients with cardiovascular disease, peripheral artery disease, pulmonary disease, stroke and orthopedic disease who had difficulty performing exercise testing were excluded. Patients receiving insulin or antidiabetic drugs were also excluded. Six patients were treated with antihypertensive drugs, including calcium antagonists in four patients, β-blockers in three patients, angiotensin receptor blockers in three patients and diuretics in one patient. One hypercholesterolemic patient was taking atorvastatin. A total of 11 age-, sex- and activity-matched healthy subjects were also studied as control subjects. The protocol was approved by the Medical Ethics Committee of Hokkaido University Hospital, and written informed consent was obtained from all participating subjects.

Clinical and anthropometric measurements

Body weight, height, waist circumference, blood pressure and heart rate were measured, and body mass index (body weight/(height)^2, kg m^{-2}) was calculated. Whole-body fat mass and lean body mass (LBM) were measured by an air displacement plethysmograph (the BOD POD Body Composition System; Life Measurement Instruments, Concord, CA, USA).

Daily physical activity

To monitor the level of physical activity during daily life, movement-related calorie consumption and steps were measured for 1 week using a pedometer equipped with an accelerometer (Lifecorder Plus, Suzuken, Nagoya, Japan), as described previously.[11]

Blood biochemistry

Peripheral blood samples were collected after 10 h of fasting. Blood glucose, plasma insulin, glycohemoglobin A1c, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, triglyceride and free fatty acid were measured. The homeostasis assessment model of insulin resistance was also calculated.[12]

Aerobic capacity

All subjects exercised on an upright electromechanical ergometric bicycle (Aerobike 75XLII, Combi Wellness, Tokyo, Japan) using a ramp protocol (25 W min^{-1}). As an index of perceived effort, the rating of perceived exertion was evaluated with the 10-point Borg scale immediately after the exercise was finished. Respiratory gas analysis was performed with a breath-by-breath apparatus (Aeromonitor AE-300S, Minato Medical Science, Osaka, Japan). The anaerobic threshold (AT) was determined by the V-slope method as described previously.[13] AT could not be measured in one patient with MetS because of technical difficulties. To eliminate the influence of the differences in body composition between groups, the absolute values of peak oxygen uptake (peak VO_2) and AT were adjusted by LBM as well as body weight.

Skeletal muscle energy metabolism by ^{31}phosphorus-magnetic resonance spectroscopy

Muscle strength was initially determined by the one repetition maximum (1-RM) measurement, which measured the maximum weight that could be lifted 5 cm above ground, as described previously.[14] The 1-RM was determined by a successful plantar flexion without any assistance from other body parts (for example, thigh). The 1-RM measurement was designed using increments of 10 kg until 60–80% of the perceived maximum. Then, the load was gradually increased by 1–5 kg weight until the subject was not able to maintain proper form or to completely lift the weight. The final acceptable weight was determined as 1-RM. The calf flexor muscle cross-sectional area at the level of the muscle belly was also measured using magnetic resonance imaging.

Measurements of ^{31}phosphorus-magnetic resonance spectroscopy (^{31}P-MRS) in the calf flexor muscle were performed by a 1.5-T superconducting magnet (Magnetom Vision VB33G, Siemens, Erlangen, Germany), as described previously.[14] A unilateral plantar flexion exercise with a constant load of 20% 1-RM was performed for 4 min with 0.67 Hz on the original apparatus. The spectra of high-energy phosphate metabolites were acquired at rest and every 30 s during exercise at an echo time of 1 ms and repetition time of 2000 ms. Phosphocreatine (PCr) was standardized as [PCr]/([PCr]+[Pi]), where [PCr] indicates the concentration of PCr and [Pi] indicates the concentration of inorganic phosphate (Pi). The maximal degree of PCr change (PCr loss) during exercise was calculated as: PCr loss=$(PCr_{rest}-PCr_{peak})/PCr_{rest}$. The intramuscular pH was calculated from changes in the chemical shifts of Pi relative to PCr as described previously.[15]

IMCL content by proton-MRS

IMCL content in the resting tibialis anterior muscle at the level of the muscle belly of the calf was measured after the blood correction at fasting state using proton-MRS, as described previously.[16] Magnetic resonance images were acquired using a clinical 1.5-T whole-body scanner system (Signa Horizon LX, GE Medical Systems, Milwaukee, WI, USA), and a standard head coil (28 cm diameter) was used for detection. Transverse T_1-weighed magnetic resonance images (echo time/repetition time=8.5/400 ms) were acquired to determine the placement of the proton-MRS voxels. The voxel volume was $10\times10\times10$ mm^3. Localized proton spectra were obtained by a point-resolved spectroscopy sequence with echo time/repetition time=30/3000 ms and 64 averages with water suppression. Unsuppressed water spectra were also acquired as an internal standard. Spectra were processed using the SAGE software package (GE Medical Systems). Quantification of IMCL and extramyocellular lipid was carried out to compare the intensity of $(CH_2)_n$ at 1.3 and 1.5 p.p.m. resonance with the water resonance intensity at 4.7 p.p.m. IMCL and extramyocellular lipid were quantified relative to muscle water as described previously.[16]

Statistical analysis

Data are expressed as means ± s.d. Student's unpaired *t*-tests were performed to compare means between patients with MetS and control subjects. Correlations were examined by linear regression analysis using the least-square method. Statistical significance was defined as $P<0.05$.

RESULTS

Characteristics of the study subjects

Age of control subjects and MetS patients were similar (Table 1). Body weight, body mass index, percent fat and waist circumference were significantly higher in patients with MetS compared with control subjects; however, there was no significant difference in LBM between groups. There was no significant difference in blood pressure between groups; however, some patients with MetS were treated with antihypertensive drugs. The daily physical activity, assessed by movement-related calorie consumption and steps, was comparable between groups.

Blood biochemistry

As expected, fasting blood glucose, plasma insulin, homeostasis assessment model of insulin resistance, glycohemoglobin A1c and triglycerides were significantly higher in MetS (Table 2). By contrast, no significant difference was found in high-density lipoprotein cholesterol, low-density lipoprotein cholesterol and free fatty acid.

Table 1 Characteristics of the study subjects

	Control	*MetS*
N	11	12
Age, years	49±10	49±10
Body weight, kg	65.6±8.2	80.7±11.5*
Body mass index, $kg\,m^{-2}$	22.5±2.0	27.2±3.3*
Waist circumference, cm	80.8±6.3	95.6±8.7*
Percent fat, %	21.2±4.5	29.0±4.6*
LBM, kg	51.6±5.1	56.4±9.0
Systolic blood pressure, mm Hg	122.9±12.8	135.0±16.5
Diastolic blood pressure, mm Hg	77.0±9.1	81.0±11.6
Steps, steps per day	7185±1835	7353±2180
MCC, kcal per day	215±66	238±65

Abbreviations: LBM, lean body mass; MCC, movement-related calorie consumption; MetS, metabolic syndrome.
Data are means±s.d. *$P<0.01$ *vs.* control subjects.

Table 2 Blood biochemistry

	Control	*MetS*
N	11	12
Blood glucose, $mg\,dl^{-1}$	90.4±7.4	110.0±17.2†
Insulin, $\mu l\,U\,ml^{-1}$	4.7±2.1	13.7±7.6†
HOMA-IR	1.0±0.5	3.8±2.2†
HbA1c, %	5.2±0.3	5.6±0.6*
HDL cholesterol, $mg\,dl^{-1}$	62.3±15.0	52.8±11.6
LDL cholesterol, $mg\,dl^{-1}$	109.7±29.6	129.7±31.7
Triglyceride, $mg\,dl^{-1}$	95.6±48.3	160.4±71.8*
FFA, $mEq\,l^{-1}$	0.47±0.23	0.53±0.20

Abbreviations: FFA, free fatty acid; HbA1c, glycohemoglobin A1c; HDL, high-density lipoprotein; HOMA-IR, homeostasis assessment model of insulin resistance; LDL, low-density lipoprotein; MetS, metabolic syndrome.
Data are means±s.d. *$P<0.05$ and †$P<0.01$ *vs.* control subjects.

Table 3 Aerobic capacity

	Control	*MetS*
N	11	12
RPE	7.6±1.5	7.4±1.5
Peak respiratory exchange ratio	1.27±0.10	1.21±0.09
Peak VO_2/BW, $ml\,kg^{-1}\,min^{-1}$	31.9±5.7	23.9±4.7†
Peak VO_2/LBM, $ml\,kg^{-1}\,min^{-1}$	41.4±8.4	34.1±6.2*
AT/BW, $ml\,kg^{-1}\,min^{-1}$	18.9±4.0	12.7±1.2†
AT/LBM, $ml\,kg^{-1}\,min^{-1}$	23.1±3.7	18.0±2.4†
Peak workload, W	185.8±32.8	163.1±36.2

Abbreviations: AT, anaerobic threshold; BW, body weight; LBM, lean body mass; MetS, metabolic syndrome; peak VO_2, peak oxygen uptake; RPE, rating of perceived exertion. Data are means±s.d. *$P<0.05$ and †$P<0.01$ *vs.* control subjects.

Aerobic capacity

The rating of perceived exertion and peak respiratory exchange ratio were comparable between groups (Table 3). Peak VO_2 and AT adjusted by body weight were significantly lower in MetS patients, even when normalized to LBM, they were significantly lower in patients with MetS, suggesting that lean-body aerobic capacity was impaired in MetS. No significant difference was found in peak workload between groups.

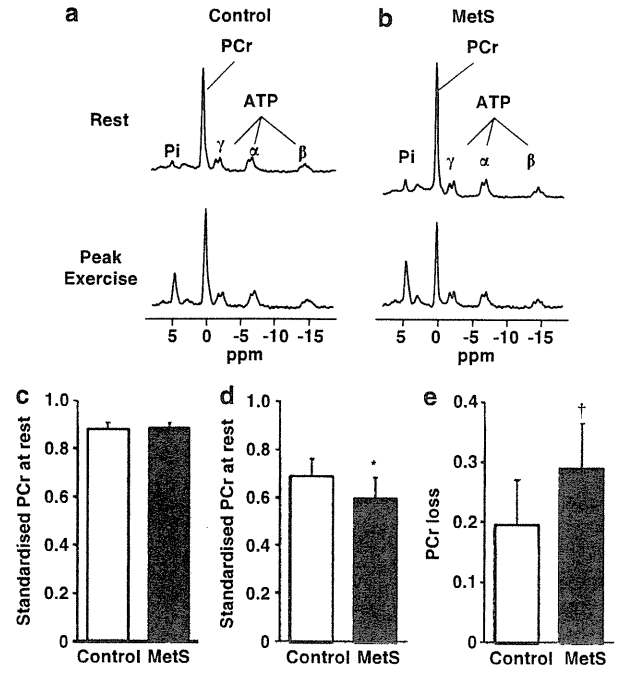

Figure 1 Representative ^{31}phosphorus-magnetic resonance spectra at rest (upper panel) and peak plantar flexion exercise (lower panel) in the calf muscle of a control subject (**a**) and a MetS patient (**b**). The summary data of standardized PCr at rest (**c**), peak exercise (**d**) and PCr loss (**e**) from control subjects (n=11) and MetS patients (n=12). *$P<0.05$ and †$P<0.01$ *vs.* control subjects. MetS, metabolic syndrome; PCr, phosphocreatine; Pi, inorganic phosphate.

High-energy phosphate metabolism in skeletal muscle

There was no significant difference in the muscle strength (1-RM; 40.5±6.9 kg for control *vs.* 43.2±6.0 kg for MetS) or muscle mass (muscle cross-sectional area; 53.4±7.4 cm^2 for control *vs.* 56.4±8.8 cm^2 for MetS) between groups. The representative spectra of ^{31}P-MRS are shown in Figures 1a and b. Spectra of ^{31}P-MRS at rest were similar in the two groups. The PCr level was lower and the Pi level was higher in a MetS patient than in a control subject at peak exercise. By contrast, no alteration in ATP level during exercise was found in either group. The summary data are shown in Figures 1c–e. There was no significant difference in the standardized PCr at rest between groups (0.88±0.03 for control *vs.* 0.89±0.02 for MetS; Figure 1c), whereas the standardized PCr at peak exercise was significantly lower in patients with MetS compared with control subjects (0.60±0.09 *vs.* 0.69±0.08, $P<0.05$; Figure 1d). Accordingly, PCr loss, difference in standardized PCr between resting and peak exercise, was significantly greater in MetS patients than in control subjects (0.20±0.08 *vs.* 0.29±0.08, $P<0.01$; Figure 1e). There was no decrease in the intramuscular pH during plantar flexion exercise in either group.

To examine whether lean-body aerobic capacity is related to high-energy phosphate metabolism in skeletal muscle, the indices of lean-body aerobic capacity were plotted against PCr loss within the same individuals. Peak VO_2 and AT normalized to LBM were inversely correlated with PCr loss (Figures 2a and b).

IMCL content

Figure 3a shows the representative spectra of proton-MRS. IMCL content was significantly greater in MetS patients than in control

subjects (5.1 ± 1.5 *vs.* 1.7 ± 1.0 mmol per kg wet weight, $P<0.01$; Figure 3b). IMCL was significantly correlated with body weight ($r=0.67$, $P<0.01$), body mass index ($r=0.74$, $P<0.01$), percent fat ($r=0.71$, $P<0.01$), waist circumference ($r=0.78$, $P<0.01$), fasting blood glucose ($r=0.44$, $P<0.05$), plasma insulin ($r=0.62$, $P<0.01$), homeostasis assessment model of insulin resistance ($r=0.61$, $P<0.01$) and triglyceride ($r=0.57$, $P<0.01$).

To examine whether IMCL content is related to lean-body aerobic capacity or high-energy phosphate metabolism in skeletal muscle, IMCL content was plotted against peak VO_2 and AT adjusted by LBM or PCr loss within the same individuals. Peak VO_2 and AT adjusted by LBM were inversely correlated with IMCL content (Figures 3c and d). Moreover, PCr loss was positively correlated with IMCL content (Figure 3e).

DISCUSSION

The present study demonstrated for the first time that the lean-body aerobic capacity in MetS patients with no habitual exercise was lower compared with activity-matched control subjects and was inversely correlated with high-energy phosphate metabolism in skeletal muscle. Furthermore, IMCL content was increased in MetS patients and, importantly, was inversely correlated with the aerobic capacity as well as insulin sensitivity. The correlation between IMCL content and impairment of high-energy phosphate metabolism in skeletal muscle might reflect the impaired fatty acid oxidation in skeletal muscle of MetS patients. Therefore, our data suggest that the impaired intramuscular fatty acid oxidative metabolism might contribute to the lower lean-body aerobic capacity in MetS patients.

The aerobic capacity was lower in patients with MetS, which was supported by the reduced peak VO_2 and AT (Table 3). The lower aerobic capacity in MetS was not merely due to the increased body weight and fat mass, because peak VO_2 was significantly reduced in these patients even after adjusted by LBM (Table 3). Moreover, all subjects enrolled in the present study had usual physical activity, and their daily physical activity was comparable between the two groups (Table 1). Therefore, physical activity did not affect the difference in aerobic capacity between groups in this setting, although physical activity is one of the most important factors for aerobic capacity. Previous studies have demonstrated that peak VO_2 was decreased in patients with type 2 diabetes.[17] However, these studies were not designed to strictly match the physical activity between control subjects and patients with type 2 diabetes. The present study clearly demonstrated that the lean-body aerobic capacity in patients with MetS was lower than that in activity-matched healthy subjects.

In the present study, PCr loss was greater in MetS patients than that in control subjects (Figure 1e). PCr always works as an energy buffer, which can be converted to ATP to compensate for impaired oxidative phosphorylation or glycolysis and maintain the ATP level constant during exercise. The intramuscular pH in the calf flexor muscle did not significantly fall during plantar flexion exercise in either group because of low-intensity exercise, indicating that oxidative metabolism was mainly observed in our ^{31}P-MRS study, although glycolysis was also a source of ATP production. Therefore, the greater PCr loss in MetS patients (Figure 1e) suggests the impairment of intramuscular high-energy phosphate metabolism assessed by, at least in part, oxidative phosphorylation in mitochondria. This finding was consistent with the previous studies that skeletal muscle biopsy samples from patients with insulin resistance and type 2 diabetes demonstrated mitochondrial dysfunction or reduced gene expression involved in mitochondrial oxidative phosphorylation.[18,19] Moreover, the present

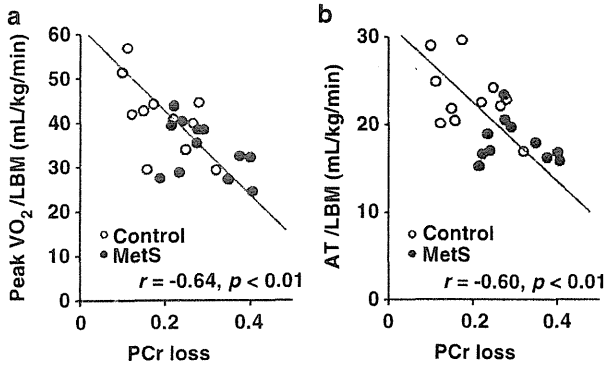

Figure 2 (**a**, **b**) Association between lean-body aerobic capacity and intramuscular high-energy phosphate metabolism. AT, anaerobic threshold; LBM, lean body mass; PCr, phosphocreatine; peak VO_2, peak oxygen uptake.

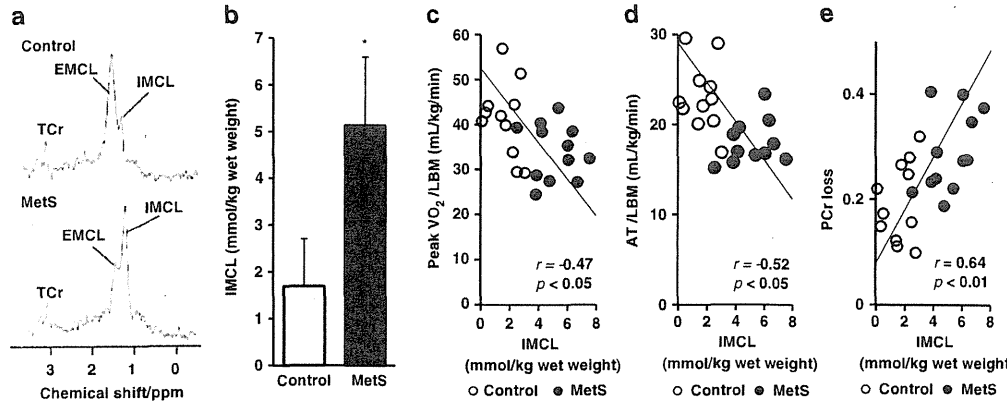

Figure 3 Representative proton-magnetic resonance spectra in the resting tibialis anterior muscle (**a**) of a control subject (upper panel) and a MetS patient (lower panel), and the summary data of IMCL content (**b**) from control subjects ($n=11$) and MetS patients ($n=12$). (**c**–**e**) The association between IMCL and lean-body aerobic capacity or high-energy phosphate metabolism in skeletal muscle. *$P<0.01$ *vs.* control subjects. EMCL, extramyocellular lipid; IMCL, intramyocellular lipid; MetS, metabolic syndrome; TCr, total creatine.

study demonstrated for the first time that peak VO_2 and AT normalized to LBM were closely correlated with PCr loss (Figures 2a and b). In contrast, muscle strength and muscle mass were comparable between groups. Therefore, skeletal muscle energy metabolism is a major determinant of aerobic capacity in MetS patients.

IMCL content was increased in MetS patients compared with control subjects (Figure 3b). An imbalance of uptake and oxidation of fatty acid could lead to lipid accumulation within skeletal muscle in the setting of insulin resistance.[20] Insulin resistance has been characterized by the reduced capacity of fatty acid oxidation in skeletal muscle rather than by the rate of fatty acid uptake into skeletal muscle in obese subjects with insulin resistance.[21] Moreover, a state of metabolic inflexibility in skeletal muscle, which is characterized by lower rate of fatty acid oxidation during fasting conditions and impaired glucose oxidation on insulin stimulation, could contribute to the accumulation of IMCL.[22] Taken together, the increased IMCL content in patients with MetS may directly reflect the impaired fatty acid oxidation in skeletal muscle, which is consistent with our finding that IMCL content was correlated with impairment of high-energy phosphate metabolism (Figure 3e). Interestingly, IMCL content was inversely correlated with the lean-body aerobic capacity (Figures 3c and d). These findings suggest that the energy production within the mitochondria and the energy substrate supply to the mitochondria are decreased in skeletal muscle, and that this decrease might lead to the lower aerobic capacity in patients with MetS.

In the present study, IMCL content was correlated with insulin resistance, such as fasting blood glucose, insulin and homeostasis assessment model of insulin resistance, as previously described.[9] Blaak *et al.*[23] showed that the fatty acid oxidation was impaired in skeletal muscle from patients with type 2 diabetes. They concluded that the impairment of fatty acid oxidation could be a cause of insulin resistance and type 2 diabetes, and not merely a consequence. Importantly, the impaired fatty acid oxidation can lead to the accumulation of specific IMCL intermediates, including long-chain fatty acyl-CoA, diacylglycerol and ceramide, as well as IMCL.[24] Recent studies have revealed that the accumulation of IMCL intermediates might impair insulin signaling[25] and the mitochondrial function.[26] Therefore, IMCL might have a major role in the pathogenesis of insulin resistance.

There are limitations in the present study that should be acknowledged. First, peripheral blood flow was not measured in the study subjects. As vasodilation is impaired in patients with insulin resistance and diabetes,[27] the impaired aerobic capacity that we observed might be due to the decreased blood flow to skeletal muscle. However, Hallsten *et al.*[28] demonstrated that the peripheral blood flow to skeletal muscle in obese and insulin-resistant subjects was not lower than that in controls, even during exercise. Therefore, skeletal muscle blood flow is not likely to have influenced the aerobic capacity in MetS patients in the present study. Second, the correlation between the aerobic capacity and the skeletal muscle energy metabolism was not significant when the analysis was performed only within MetS patients. As the range of aerobic capacity in MetS patients was small, we could not detect a significant correlation.

In conclusion, the present study demonstrated that the lean-body aerobic capacity was impaired in MetS patients with no habitual exercise compared with activity-matched control subjects. This result is likely due to the impaired intramuscular fatty acid oxidative metabolism. These findings provide new insights into the pathophysiology regarding the lower aerobic capacity in MetS, which might be useful for its therapeutic treatment.

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Oxidative stress and heart failure

Hiroyuki Tsutsui, Shintaro Kinugawa and Shouji Matsushima

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Review

Oxidative stress and heart failure

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Tsutsui H, Kinugawa S, Matsushima S. Oxidative stress and heart failure. *Am J Physiol Heart Circ Physiol* 301: H2181–H2190, 2011. First published September 23, 2011; doi:10.1152/ajpheart.00554.2011.—Oxidative stress, defined as an excess production of reactive oxygen species (ROS) relative to antioxidant defense, has been shown to play an important role in the pathophysiology of cardiac remodeling and heart failure (HF). It induces subtle changes in intracellular pathways, redox signaling, at lower levels, but causes cellular dysfunction and damage at higher levels. ROS are derived from several intracellular sources, including mitochondria, NAD(P)H oxidase, xanthine oxidase, and uncoupled nitric oxide synthase. The production of ROS is increased within the mitochondria from failing hearts, whereas normal antioxidant enzyme activities are preserved. Chronic increases in ROS production in the mitochondria lead to a catastrophic cycle of mitochondrial DNA (mtDNA) damage as well as functional decline, further ROS generation, and cellular injury. ROS directly impair contractile function by modifying proteins central to excitation-contraction coupling. Moreover, ROS activate a broad variety of hypertrophy signaling kinases and transcription factors and mediate apoptosis. They also stimulate cardiac fibroblast proliferation and activate the matrix metalloproteinases, leading to the extracellular matrix remodeling. These cellular events are involved in the development and progression of maladaptive myocardial remodeling and failure. Oxidative stress is also involved in the skeletal muscle dysfunction, which may be associated with exercise intolerance and insulin resistance in HF. Therefore, oxidative stress is involved in the pathophysiology of HF in the heart as well as in the skeletal muscle. A better understanding of these mechanisms may enable the development of novel and effective therapeutic strategies against HF.

heart failure; remodeling; oxidative stress; reactive oxygen species; mitochondria

HEART FAILURE (HF) is defined as a complex clinical syndrome that can result from any structural or functional cardiac disorder that impairs the ability of the ventricle to fill with or eject blood (18, 36). Cardiac manifestations of HF are fluid retention, which leads to pulmonary congestion and peripheral edema, as well as low output, which may limit exercise capacity (18, 36). HF is a leading cause of morbidity and mortality in industrialized countries (30, 31, 104, 110). It is also a growing public health problem, mainly because of aging of the population and the increase in the prevalence of HF in the elderly (109).

The major causes of HF are myocardial infarction (MI), hypertension, cardiomyopathy, and valvular heart disease (109). Following MI, the heart usually adapts through a pathophysiological process known as "cardiac remodeling," which involves changes in the structure and function of cardiac myocytes as well as the extracellular matrix in the noninfarcted myocardium. These changes lead to substantial alterations in the shape and volume of the heart and progressive ventricular dilatation and impairment of pump function (24, 78). The mechanisms responsible for the development and progression of HF are the subject of intensive investigation. Alterations of various signaling pathways, including the sympathetic nervous and renin-angiotensin-aldosterone systems have been shown to exert profound effects on the phenotype of the failing myocardium (67). In parallel to these basic findings, a number of clinical studies as well as registry data demonstrated the clinical benefits of medications targeting on these systems such as angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers, aldosterone antagonists, and β-blockers on the clinical outcomes of HF patients (15a, 29, 75, 80, 81, 103, 105). Despite these extensive studies, the fundamental mechanisms responsible for the development and progression of HF have not yet been fully elucidated.

Over the past several decades, clinical and experimental studies have provided substantial evidence that oxidative stress, defined as an excess production of reactive oxygen species (ROS) relative to antioxidant defense, is enhanced in HF (9, 34, 35, 62). Excessive ROS cause cellular dysfunction, protein and lipid peroxidation, and DNA damage and can lead to irreversible cell damage and death, which have been implicated in a wide range of pathological cardiovascular conditions. The importance of oxidative stress is increasingly emerging with respect to a pathophysiological mechanism of cardiac remodeling responsible for the development and progression of HF (100). Specifically, ROS can directly impair contractile function by modifying proteins central to excitation-contraction coupling. Moreover, ROS activate a broad variety of hypertrophy signaling kinases and transcription factors and

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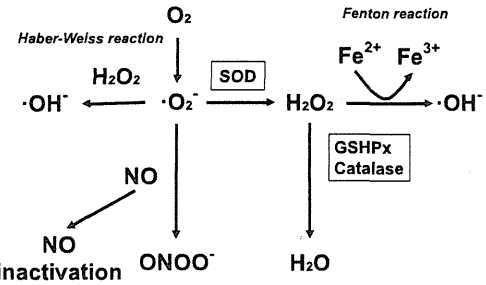

Fig. 1. Reactions underlying the generation and degradation of reactive oxygen species. A small amount of $O_2^{\cdot -}$ is normally produced as a byproduct of the use of molecular oxygen during mitochondrial oxidative phosphorylation. $O_2^{\cdot -}$ is inactivated by either nitric oxide (NO) or superoxide dismutase (SOD). A family of SOD enzymes rapidly converts $O_2^{\cdot -}$ to H_2O_2, which is itself broken down by glutathione peroxidase (GSHPx) and catalase to water. Under pathological conditions, the single-electron reduction of H_2O_2 may lead to the formation of highly reactive OH radicals, either via the Fenton reaction in the presence of iron or via Haber-Weiss reaction by reacting with $O_2^{\cdot -}$. Furthermore, the reaction of $O_2^{\cdot -}$ with NO results in the inactivation of cytoprotective NO and the formation of peroxynitrite ($^{\bullet}ONOO^-$).

mediate apoptosis. They also stimulate cardiac fibroblast proliferation and activate the matrix metalloproteinases (MMPs), leading to the extracellular matrix remodeling. These cellular events are involved in the development and progression of maladaptive myocardial remodeling and failure.

Generation of ROS and Antioxidants

The balance between ROS production and their removal by antioxidant systems is the "redox state." Oxidative stress is defined as an excess production of ROS relative to the levels of antioxidants. ROS are oxygen-based chemical species with high reactivity. They include free radicals, such as superoxide ($O_2^{\cdot -}$) and hydroxyl radical ($^{\bullet}OH$), and nonradicals capable of generating free radicals, such as hydrogen peroxide (H_2O_2) (Fig. 1). $O_2^{\cdot -}$ is a primary radical that could lead to the formation of other ROS, such as H_2O_2 and $^{\bullet}OH$. $^{\bullet}OH$ is also generated by the reduction of H_2O_2 in the presence of endogenous iron by means of the Fenton reaction. In addition, $^{\bullet}OH$ could arise from electron exchange between $O_2^{\cdot -}$ and H_2O_2 via the Harber-Weiss reaction. Furthermore, when both $O_2^{\cdot -}$ with NO are synthesized within a few cell diameters, they will combine spontaneously to form peroxynitrite ($^{\bullet}ONOO^-$) by a diffusion-limited reaction (74).

NO is necessary for normal cardiac physiology in the regulation of cardiac function, including coronary vasodilatation, inhibition of platelet and neutrophil adhesion and activation, and modulation of cardiac contractile function (100). NO also has a protective role against the ischemic and/or failing heart. This protective role is mediated by several mechanisms, including the stimulation of soluble guanylyl cyclase, which leads to a decrease of the concentration of intracellular Ca^{2+}, and the inhibition of oxidative stress. Therefore, $O_2^{\cdot -}$ can exert cytotoxic effects not only due directly to $O_2^{\cdot -}$ itself but are mediated by the inactivation of cytoprotective NO and the formation of highly reactive oxidant $^{\bullet}ONOO^-$, which is produced following interaction of NO with $O_2^{\cdot -}$ (Fig. 1).

Diverse specific and nonspecific antioxidant defense systems exist to scavenge and degrade ROS to nontoxic molecules. Under physiological conditions, their toxic effects can be prevented by such scavenging enzymes as superoxide dismutase (SOD), glutathione peroxidase (GSHPx), and catalase, as well as by other nonenzymatic antioxidants (Fig. 1). GSHPx is a key antioxidant that catalyzes the reduction of H_2O_2 and hydroperoxides. It not only scavenges H_2O_2 but also prevents the formation of other more toxic radicals such as $^{\bullet}OH$. GSHPx possesses a higher affinity for H_2O_2 than catalase. Furthermore, it is present in relatively high amounts within the heart, especially in the cytosolic and mitochondrial compartments (57). These lines of evidence imply the primary importance of GSHPx as a defense mechanism within the heart. Moreover, GSHPx is expected to exert greater protective effects against oxidative damage than SOD because greater dismutation of $O_2^{\cdot -}$ by SOD may result in an increase of H_2O_2. In fact, the mice with GSHPx gene overexpression were more resistant to myocardial oxidative stress as well as remodeling and failure (65, 94).

When the production of ROS exceeds the capacity of antioxidant defense, oxidative stress has a harmful effect on the functional and structural integrity of biological tissue (Fig. 2). Specifically, in the heart, excess ROS can cause myocardial remodeling, including contractile dysfunction and structural alterations.

Oxidative stress has also been suggested as major mechanisms causing endothelial dysfunction not only in atherosclerosis but also in HF (56). Clinical studies suggested that endothelial dysfunction was independently associated with adverse long-term outcomes in patients with HF (47).

Increased ROS in the Failing Heart

A number of experimental and clinical studies have demonstrated the increased generation of ROS in HF (9, 34, 35, 62). The majority of experimental studies using various kinds of animal models of HF, including of our own, were performed in young animals with no coexisting risk factors such as hypertension. However, they have consistently provided substantial evidence that oxidative stress is increased in HF and contributes to its development and progression. Therefore, we consider that oxidative stress is increased not only in patients with

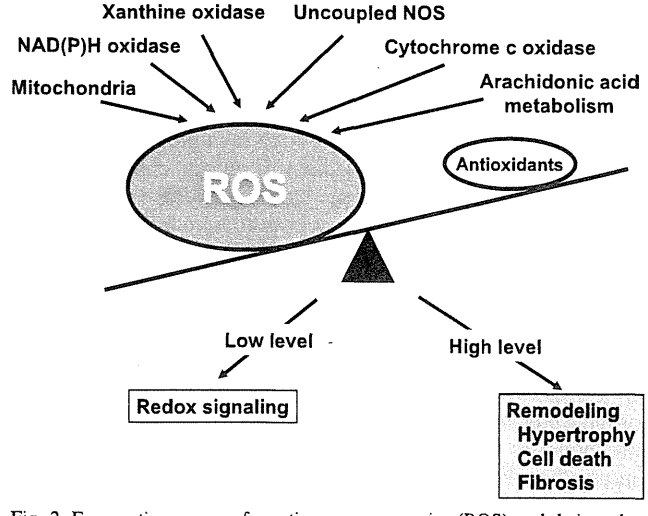

Fig. 2. Enzymatic sources of reactive oxygen species (ROS) and their pathophysiological role. NOS, nitric oxide synthase.

HF but in animal models even though they only mimic the part of clinical HF phenotypes seen in patients. In this review, our studies used mainly two types of animal models of HF: rapid pacing-induced HF in dogs and HF following MI (postinfarct HF) in mice. Both animals show similar structural and functional/hemodynamic characteristics to those in patients with HF. Belch et al. (9) reported that there was a significant negative correlation between malondialdehyde and left ventricular (LV) ejection fraction ($r = -0.35$). Mallat et al. (62) demonstrated that levels of lipid peroxides and 8-iso-prostaglandin $F_{2\alpha}$, the major biochemical markers of ROS generation, were elevated in the plasma and pericardial fluid of patients with HF and also positively correlated with its severity.

Electron spin resonance (ESR) spectroscopy combined with the nitroxide radical 4-hydroxy-2,2,6,6-tetramethyl-piperidine-*N*-oxyl provided a definitive and direct evidence for enhanced generation of ROS within the failing myocardium (38). The generation of $^{\bullet}OH$ implies a pathophysiological significance of ROS in HF because $^{\bullet}OH$ radicals are the predominant oxidant species causing cellular injury.

Oxidative stress results from an imbalance between ROS generation and antioxidant defense mechanisms. Therefore, impaired antioxidant defense mechanisms (SOD, catalase, and GSHPx) or reduced concentrations of endogenous antioxidants (vitamin E, ascorbic acid, and glutathione) can increase ROS levels. Previous studies by Hill and Singal (35) demonstrated that HF subsequent to MI was associated with an antioxidant deficit as well as increased oxidative stress. Furthermore, these changes correlated with the hemodynamic function, suggesting their role in the pathogenesis of cardiac dysfunction (35). In contrast, these was no decrease in the activities of the scavenging enzymes, including SOD and catalase. GSHPx activity was even increased in the heart obtained from pacing-induced HF (107). Our results indicated that oxidative stress in HF might be primarily due to the enhancement of ROS generation rather than to the decline in antioxidant defense within the heart.

Sources of ROS in the Failing Heart

The cellular sources of ROS generation within the heart include cardiac myocytes, endothelial cells, and neutrophils. Within cardiac myocytes, ROS can be produced by several sources, including mitochondria, NAD(P)H oxidase, xanthine oxidase, and uncoupled nitric oxide synthases (NOS) (Fig. 2).

Mitochondria produce ROS through a single electron transport to molecular oxygen in the respiratory chain (Fig. 3). Under physiological conditions, small quantities of ROS are formed during mitochondrial respiration, which, however, can be detoxified by the endogenous scavenging mechanisms. By using ESR spectroscopy with 5,5′-dimethyl-1-pyrroline-*N*-oxide as a spin trap, the inhibition of electron transport at the sites of complex I and complex III in the normal submitochondrial particles resulted in a significant production of $O_2^{\cdot -}$ (39). Mitochondria from the failing heart produced more $O_2^{\cdot -}$ than normal mitochondria in the presence of NADH, indicating that mitochondrial electron transport could be the predominant source of such $O_2^{\cdot -}$ production. Furthermore, the failing mitochondria were associated with a decrease in complex enzyme activity. Therefore, mitochondria are an important source of

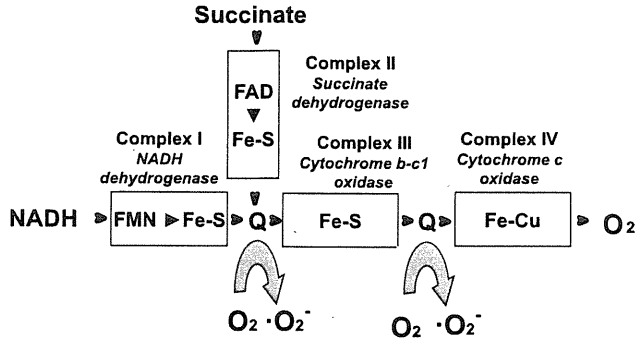

Fig. 3. Mitochondrial electron transport. Localized in the inner mitochondrial membrane, the mitochondrial electron transport chain is formed by a series of cytochrome-based enzymes (complex I: NADH dehydrogenase; complex III: cytochrome b-c_1 oxidase; complex IV: cytochrome oxidase and the smaller molecules coenzyme Q[Q]) that transfer the electrons to molecular oxygen. The transport starts with the transfer of e^- from $NADH^+$ to the iron-sulfur (Fe-S) center of NADH dehydrogenase, which passes them to Q, complex III, cytochrome c, complex IV, and finally to molecular oxygen. $FADH_2$ donates its e^- directly to Q, and the transfer proceeds as above. During this process, the high free energy of the electrons is gradually extracted and converted into ATP. Physiologically, >98% of e^- are tightly coupled with the production of ATP, and only 1–2% "leak" to form $O_2^{\cdot -}$ and are scavenged by mitochondrial SOD. However, when the electron chain transfer is blocked at the level of complex I or III, e^- are inappropriately diverted by one electron reduction directly to O_2, with the resulting formation of a large amount of $O_2^{\cdot -}$. NADH, nicotinamide adenine dinucleotide; FAD, flavin adenine dinucleotide; FMN, flavin mononucleotide.

ROS in failing hearts, indicating a pathophysiological link between mitochondrial dysfunction and oxidative stress (88). Within the mitochondria, most of the oxygen is reduced to water at the respiratory chain. Therefore, when oxygen availability is reduced in conditions such as ischemia or hypoxia, mitochondrial formation of ROS is increased, which can contribute to the induction of myocyte damage or MI (77).

ROS can be generated also via NAD(P)H oxidase and/or xanthine oxidase in the vascular endothelial cells as well as via NAD(P)H oxidase in activated leukocytes. Each member of the NAD(P)H oxidase family contains a catalytic unit termed Nox that forms a heterodimer with a lower-molecular-weight subunit called $p22^{phox}$; this heterodimeric cytochrome is the site of electron transfer from NAD(P)H to molecular O_2, resulting in the formation of $O_2^{\cdot -}$. Five Nox isoforms (Nox1–5) have been identified, each encoded by separate genes and forming the basis of different NAD(P)H oxidases (54). Nox1 and Nox2 require the association of cytosolic regulatory subunits ($p47^{phox}$, $p67^{phox}$, $p40^{phox}$, and Rac) with the cytochrome to activate $O_2^{\cdot -}$ production. In contrast, Nox4 activation does not require these cytosolic subunits. Nox1 is highly expressed in vascular smooth muscle cells but not in cardiac myocytes or endothelial cells. In contrast, Nox2 is abundantly expressed in cardiac myocytes, endothelial cells, and fibroblasts. Nox4 is the most widely expressed isoform in endothelial cells, cardiac myocytes, and fibroblasts. Importantly, NADPH oxidase activity has been shown to be significantly increased by several stimuli that are relevant to the pathophysiology of HF, e.g., mechanical stretch, angiotensin II, endothelin-1, and tumor necrosis factor-α, acting both through posttranslational modification of oxidase regulatory subunits and transcriptional pathways (58). Bauersachs et al. (7) demonstrated increased vascular NAD(P)H oxidase activities and $O_2^{\cdot -}$ production in HF.