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JCARE-CARD研究　予後調査に関するお願い

JCARE-CARD研究
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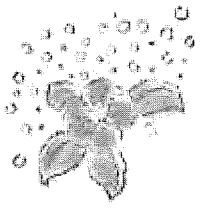

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VI. 発表論文

Circ J 2004; **68:** 1095–1103

Novel Pathophysiological Insight and Treatment Strategies for Heart Failure

— Lessons From Mice and Patients —

Hiroyuki Tsutsui, MD

The ultimate goal of heart failure (HF) treatment is to improve the prognosis of patients. Previous basic, clinical, and population studies have advanced the modern treatment of HF, but efficacy is still limited especially in 'real world' patients. There are 2 approaches to solve this crucial issue. First is the further development of novel therapeutic strategies based on new insight into the pathophysiology of myocardial remodeling and failure. Second is the improvement of the quality of care in routine clinical practice. The basic approach is to develop the treatment of myocardial remodeling by regulating mitochondrial oxidative stress. In the failing heart, oxygen radicals are the result of defects of mitochondrial electron transport, causing mitochondrial DNA damage and functional decline, and further production of oxygen radicals. Oxidative stress causes myocyte hypertrophy, apoptosis, and interstitial fibrosis by activating matrix metalloproteinases, all of which result in myocardial remodeling and failure. Therefore, mitochondrial oxidative stress and DNA damage are good therapeutic targets. The clinical approach is to develop effective strategies of HF management for the 'real world' patients. Readmission because of exacerbation is common in HF patients and further impairs their quality of life. Noncompliance with treatment is the most common precipitating factor for readmission. Regular medical follow-up and social support are important components that should be included in the disease management program of HF patients. These basic and clinical approaches are needed to establish new and effective treatment strategies for Japanese patients with HF. (*Circ J* 2004; **68:** 1095–1103)

Key Words: Heart failure; Mitochondria; Mortality; Oxidative stress; Readmission; Remodeling

Congestive heart failure (HF) is a leading cause of morbidity and mortality in industrialized countries[1] and is also a growing public health problem, mainly because of the aging of the population and the increased prevalence of HF in the elderly. Previous basic, clinical, and population studies have advanced the modern treatment of HF, but efficacy is still limited in the 'real world'. There are 2 approaches to solve this crucial issue. First is the further development of therapeutic strategies based on a novel insight into the pathophysiology of myocardial remodeling and failure. Second is the improvement of quality of care in routine clinical practice.

Basic Approach: Novel Pathophysiological Insight and Treatment Strategies of Myocardial Remodeling by Regulating Oxidative Stress

Mechanisms and Consequences of Oxidative Stress in HF

Reactive oxygen species (ROS) such as superoxide anions ($\cdot O_2^-$) and hydroxy radicals ($\cdot$OH) cause the oxidation of membrane phospholipids, proteins, and DNAs[2] and have been implicated in a wide range of pathological conditions including ischemia–reperfusion injury, neurodegenerative diseases, and aging. Under physiological conditions, their toxic effects can be prevented by scavenging enzymes such as superoxide dismutase (SOD), glutathione peroxidase (GSHPx), and catalase, as well as by other nonenzymatic antioxidants. However, when the production of ROS becomes excessive, oxidative stress may have a harmful effect on the functional and structural integrity of biological tissue; for example, ROS cause contractile failure and structural damage in the myocardium. The importance of oxidative stress with respect to the pathophysiology of left ventricular (LV) remodeling and failure responsible for HF progression is continuing to emerge.

Increased ROS Production Within the Failing Myocardium

Recent experimental and clinical investigations have suggested that the generation of ROS increases in chronic HF[3–6] Lipid peroxides and 8-iso-prostaglandin F2α, which are the major biochemical consequences of ROS generation, are elevated in the plasma and pericardial fluid of patients with HF and also positively correlate with the severity of HF[3,4] However, these findings provide only indirect evidence of ROS generation in the failing hearts and it is difficult to quantify the amount of ROS in the intact biological system because they are unstable and rapidly react with unoxidized adjacent molecules, thus having a very short half life. The only method of directly quantifying ROS in biological tissue is electron spin resonance (ESR) spectroscopy. Using ESR combined with the nitroxide radical, 4-hydroxy-2,2,6,6-tetramethyl-piperidine-N-oxyl (hydroxy-TEMPO), as a spin probe, a definitive and direct demonstration of enhanced generation of ROS in the

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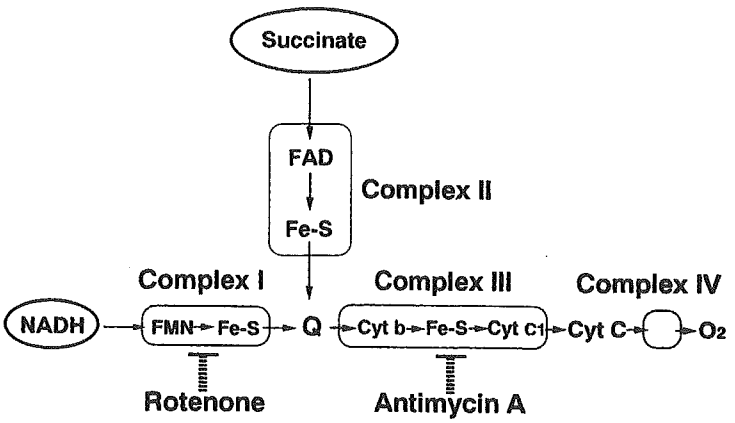

Fig 1. Components of the respiratory chain in mitochondria. FAD, flavin adenine nucleotide; FMN, flavin mononucleotide; Fe-S, iron-sulfur protein; Q, ubiquinone, Cyt, cytochrome (Reproduced with permission from Ide T, et al. *Circ Res* 1999; **85:** 357–363).

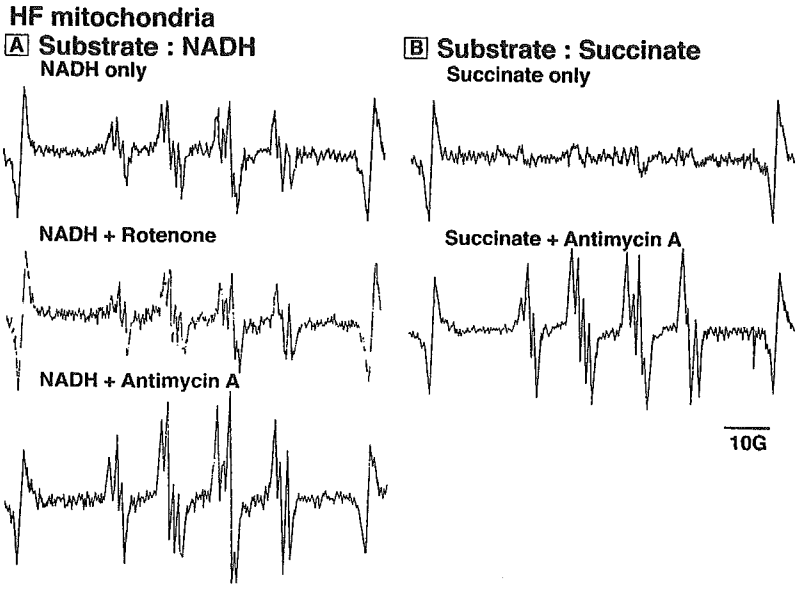

Fig 2. An electron spin resonance (ESR) analysis of 5,5'-dimethyl-1-pyrroline-N-oxide (DMPO) adduct formation in heart failure (HF) mitochondria in the presence of NADH (A) and succinate (B). (A) The reaction mixture consisted of submitochondrial particles obtained from the HF heart (2 mg protein/ml), NADH (200 μmol/L) with alcohol dehydrogenase (9 U/ml) to regenerate NADH or succinate (10 mmol/L), and DMPO in phosphate buffered saline, pH 7.4. Note that the DMPO-OOH signals were amplified in the presence of antimycin A (200 μmol/L), but not in the presence of rotenone (200 μmol/L). (B) Similar to NADH, when succinate was reacted with the mitochondria, the DMPO-OOH signals were enhanced in the presence of antimycin A. Instrumental conditions: X-band (9.43 GHz) ESR; microwave power 10 mW; field modulation width 0.063 mT; sweep time 5 mT/min (Reproduced with permission from Ide T, et al. *Circ Res* 1999; **85:** 357–363).

failing myocardium has been provided[7] $\cdot O_2^-$ is a primary radical that could lead to the formation of other ROS, such as H_2O_2 and $\cdot$OH, in the failing heart. $\cdot$OH could arise from electron exchange between $\cdot O_2^-$ and H_2O_2 via the Harber-Weiss reaction. In addition, $\cdot$OH is also generated by the reduction of H_2O_2 in the presence of endogenous iron by the Fenton reaction. The generation of $\cdot$OH implies a pathophysiological significance of ROS in HF because $\cdot$OH radicals are the predominant oxidant species causing cellular injury.

Decreased antioxidant capacity could further aggravate the ROS accumulation in HF; however, the activities of SOD, catalase, and GSHPx are not decreased in the failing heart[8] which indicates that oxidative stress in HF is primarily caused by enhanced pro-oxidant generation rather than a decline in antioxidant defenses. Moreover, within the failing myocardium the generation of ROS is greater than the scavenging capacity of endogenous antioxidants.

Mitochondria as an Enzymatic Source of ROS Production

Possible cellular sources of ROS generation within the heart include cardiac myocytes, endothelial cells, and neutrophils. Within cardiac myocytes, ROS can be produced by several mechanisms including mitochondrial electron transport, NADPH oxidase, and xanthine dehydrogenase/xanthine oxidase. Mitochondria produce ROS through one electron carrier in the respiratory chain. Under physiological conditions, small quantities of ROS are formed during mitochondrial respiration, which, however, can be detoxified by the endogenous scavenging mechanisms of myocytes.

$\cdot O_2^-$ can be assessed by ESR spectroscopy with 5,5'-dimethyl-1-pyrroline-N-oxide (DMPO) as a spin trap, a standard method of detecting ROS in the biological tissue. The inhibition of electron transport at the sites of complex I and complex III in normal submitochondrial particles results in a significant production of $\cdot O_2^-$.[9] HF mitochondria produce more $\cdot O_2^-$ than normal mitochondria in the presence of NADH, but not when succinate is a substrate, indicating that complex I is the predominant source of such $\cdot O_2^-$ production (Figs 1,2). Furthermore, mitochondria in HF are associated with a decrease in complex I activity. Therefore, mitochondria are the predominant source of ROS in the failing heart, indicating a pathophysiological link between mitochondrial dysfunction and oxidative stress;[10] as has been reported in other disease conditions including aging and neurodegenerative diseases.

Even though mitochondrial electron transport is considered to play an important role in the ROS production in HF, the possibility that other enzymatic sources of ROS generation such as vascular endothelial cells (via xanthine oxidase and/or NADPH oxidase) and activated leukocytes (via

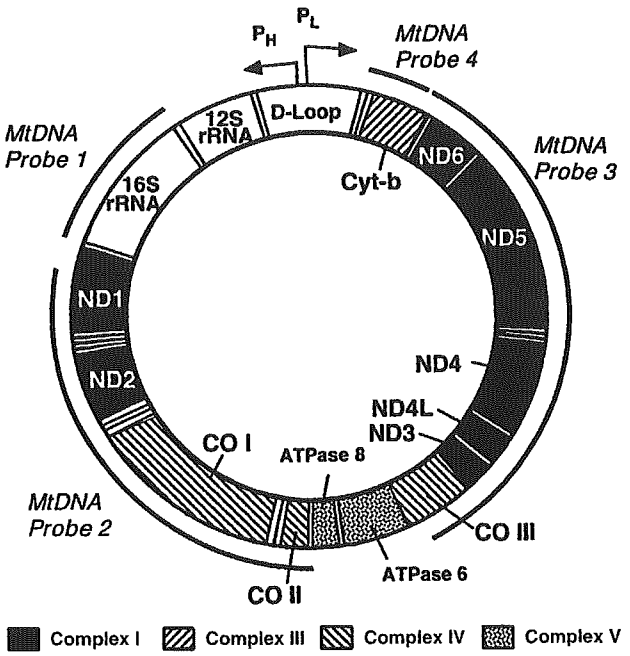

Fig 3. Map of the mitochondrial genome. The 16.3-kilobase mouse mitochondrial genome shows the 13 mRNA, 2 rRNA (12S and 16S), and 21 tRNA coding genes. mRNA genes are shown as areas labeled with the codes of the corresponding electron transport chain complexes I, III, IV, and V. PH and PL refer to the promoters of heavy (H) and light (L) strand transcription, respectively (Reproduced with permission from Ide T, et al. *Circ Res* 2001; **88:** 529–535).

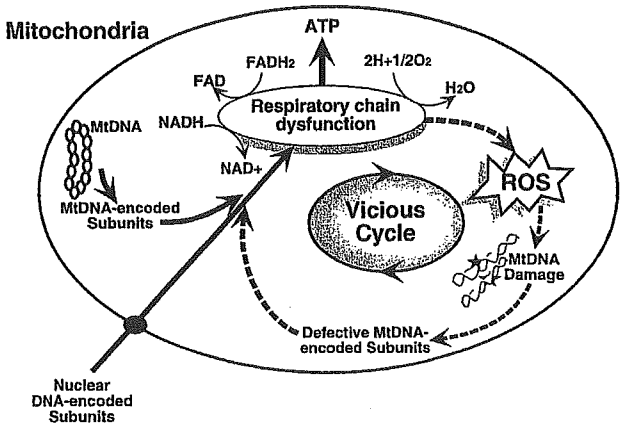

Fig 4. Schematic representation of the intimate link between reactive oxygen species (ROS), mtDNA damage, and respiratory chain dysfunction in the mitochondria. Mitochondrial ROS generation may lead to a catastrophic cycle of mitochondrial functional decline, further ROS generation, and cellular injury (Reproduced with permission from Ide T, et al. *Circ Res* 2001; **88:** 529–535).

NADPH oxidase) could contribute to oxidative stress in HF[11] cannot be completely excluded. In fact, Bauersachs et al have demonstrated that vascular NAD(P)H oxidase is activated in HF.[12] This enzyme system is the major source of ROS in both the endothelium and vascular smooth muscle, which are able to generate ROS in response to angiotensin II, which stimulates the expression of NAD(P)H oxidase. Plasma renin activity as well as tissue ACE activity is activated in HF. Therefore, enhanced formation of angiotensin II may lead to oxidative stress via this enzyme system in HF.

Oxidative Stress and Mitochondrial DNA Damage

ROS can damage mitochondrial macromolecules either at or near the site of their formation. Therefore, in addition to their role as a source of ROS, the mitochondria themselves can be damaged by ROS.

Mitochondria contain closed circular, double-strand DNA of approximately 16.5 kb. Both strands of the mitochondrial DNA (mtDNA) are transcribed. The mitochondrial genome encodes 13 polypeptides involved in oxidative phosphorylation, including 7 subunits (ND1, ND2, ND3, ND4, ND4L, ND5, and ND6) of rotenone-sensitive NADH-ubiquinone oxidoreductase (complex I), 1 subunit (cytochrome b) of ubiquinol-cytochrome c oxidoreductase (complex III), 3 subunits (COI, COII, and COIII) of cytochrome-c oxidase (complex IV), and 2 subunits (ATPases 6 and 8) of complex V along with 22 tRNAs and 2 rRNA (12S and 16S) subunits (Fig 3). The polypeptides are translated by mitochondrial ribosomes and consist of components of the electron transport chain.

The mtDNA could be a major target for ROS-mediated damage for several reasons. First, mitochondria do not have a complex chromatin organization consisting of histone proteins, which may serve as a protective barrier against ROS. Second, mtDNA has limited repair ability against DNA damage. Third, a large amount of the $\cdot O_2^-$ formed inside the mitochondria can not pass through the membranes and, hence, ROS damage may be contained largely within the mitochondria. In fact, mtDNA accumulates significantly higher levels of the DNA oxidation product, 8-hydroxydeoxyguanosine, than nuclear DNA.[13] As opposed to nuclear-encoded genes, mitochondrial-encoded gene expression is largely regulated by the copy number of mtDNA.[14] Therefore, mitochondrial injury is reflected by mtDNA damage as well as by a decline in the mitochondrial RNA (mtRNA) transcripts, protein synthesis, and mitochondrial function.[15,16] It has recently been shown that the increased generation of ROS is associated with mitochondrial damage and dysfunction in the failing heart, characterized by increased lipid peroxidation in the mitochondria, decreased mtDNA copy number, a decrease in the number of mtRNA transcripts, and reduced oxidative capacity because of low complex enzyme activities.[17] Chronic increases in ROS production are associated with mitochondrial damage and dysfunction, which thus can lead to a catastrophic cycle of mitochondrial functional decline, further ROS generation, and cellular injury (Fig 4). Defects of mtDNA may thus play an important role in the development and progression of myocardial remodeling and failure.

Several factors may be the stimuli for increased ROS in HF. The activation of neurohumoral factors commonly seen in HF, including catecholamines and cardiac sympathetic tone, renin–angiotensin system, cytokines, and nitric oxide (NO), can all contribute to the generation of ROS. If mitochondria are the principle source of ROS in response to cytokines such as tumor necrosis factor α (TNFα) and NO, such stimuli may directly modify mitochondrial electron transport function and lead to $\cdot O_2^-$ production. Generation of ROS, mtDNA decline, and loss of complex activity have been also observed in vitro when cardiac myocytes are exposed to TNFα.[18] The equivalent results observed in vivo and in vitro indicate that TNFα plays an important role in oxidative stress involved in the patho-

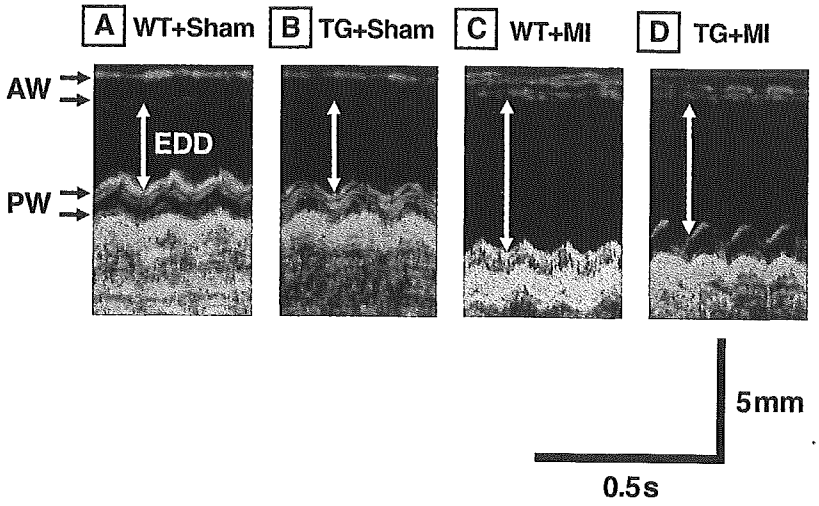

Fig 5. M-mode echocardiograms obtained from wild-type mice (WT)+Sham (A), GSHPx transgenic mice (TG)+Sham (B), WT+MI (C), and TG+MI (D) mice. AW, anterior wall. PW, posterior wall. EDD, end-diastolic diameter (Reproduced with permission from Shiomi T, et al. *Circulation* 2004; **109:** 544–549).

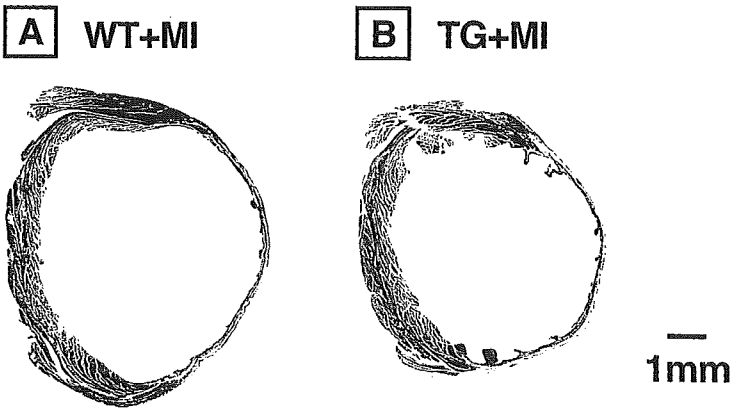

Fig 6. Low-power photomicrographs of Masson-trichrome-stained LV cross-section obtained from WT+MI (A) and TG+MI (B) mice. Scale bar=1 mm (Reproduced with permission from Shiomi T, et al. *Circulation* 2004; **109:** 544–549).

genesis of myocardial remodeling and failure. Further, overexpression of the TNFα gene in mice induces increased ROS production in association with myocardial contractile dysfunction and structural remodeling.[19]

A number of pathogenic mtDNA base substitution mutations, such as missense mutations and mtDNA rearrangement mutations (deletions and insertions), have been identified in patients with mitochondrial diseases.[20] Accumulation of the deleted forms of mtDNA in the myocardium frequently results in either cardiac hypertrophy, conduction block, or HF.[21] Furthermore, there is now a consensus view that mutations of mtDNA and abnormalities in mitochondrial function are associated with common forms of cardiac diseases such as ischemic heart disease[22] and dilated cardiomyopathy.[23] In these conditions, however, the strict causal relationships between abnormalities in mtDNA and cardiac dysfunction have yet to be fully elucidated.[24] Even though the mechanisms by which mtDNA damage arises in these conditions have not been clarified, ROS have been proposed as the primary contributing factor. Direct evidence that mtDNA defects occur not only in a limited small subset of mitochondrial diseases, but also in the more common HF phenotype occurring after myocardial infarction (MI) has been provided and is further supported by studies of mice lacking MnSOD that show an accumulation of oxidative damage of mtDNA and electron transport complexes[25] in association with the development of dilated cardiomyopathy.[26]

ROS can cause an oxidative modification of nucleotides, such as 8-oxo-7,8-dihydrodeoxyguanosine triphosphate (8-oxo-dGTP), which can lead to defects in DNA replication. The misincorporation of 8-oxo-dGTP into DNA is prevented by 8-oxo-dGTPase, which hydrolyzes 8-oxo-dGTP into 8-oxo-dGMP. 8-oxo-dGTPase is highly expressed in cardiac myocytes from the post-MI failing hearts, which suggests that this enzymatic system that prevents oxidative DNA damage may be activated in response to increased oxidative stress.[27]

Oxidative Stress and Myocardial Damage

ROS have direct effects on cellular structure and function and may be integral signaling molecules in myocardial remodeling and failure. ROS result in a phenotype characterized by hypertrophy and apoptosis in isolated cardiac myocytes[28] and have also been shown to activate matrix metalloproteinase (MMP) in cardiac fibroblasts.[29] Myocardial MMP activity is increased in the failing heart[30,31] and furthermore, an MMP inhibitor has been shown to limit early LV dilatation in a murine model of MI.[32] There is a significant improvement in the survival after MI in MMP-2 knockout mice, which is mainly attributable to inhibition of early cardiac rupture and the development of subsequent LV dysfunction.[33] Because MMP can be activated by ROS,[34] one proposed mechanism of LV remodeling is the activation of MMPs secondary to increased ROS production. Sustained MMP activation might therefore influence the structural properties of the myocardium by providing an abnormal extracellular environment with which the

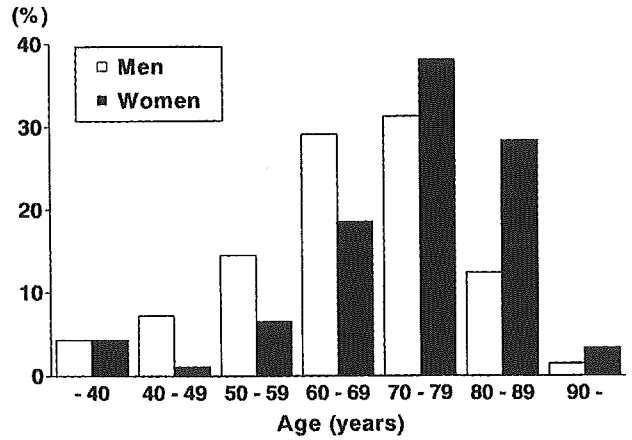

Fig 7. Age distribution of men (open bars) and women (closed bars) hospitalized with congestive heart failure (Reproduced with permission from Tsuchihashi M, et al. *Jpn Circ J* 2000; **64:** 953–959).

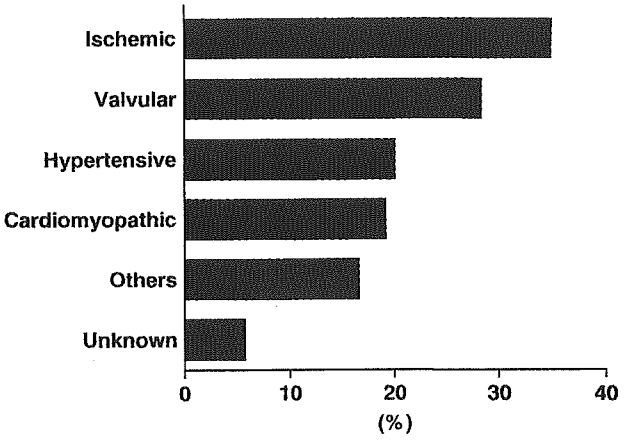

Fig 8. Distribution of the causes of heart failure. Patients could have more than one cause. Numbers denote the percentage of patients to the total number of study patients (Reproduced with permission from Tsuchihashi M, et al. *Jpn Circ J* 2000; **64:** 953–959).

myocytes interact. The ·OH scavenger, dimethylthiourea, inhibits the activation of MMP-2 in association with the development of LV remodeling and failure[35] which raises the interesting possibility that increased ROS after MI may be a stimulus for myocardial MMP activation that might play an important role in the development of HF.

An HMG-CoA reductase inhibitor, fluvastatin, inhibits the production of MMPs at a concentration as low as 5 μmol/L in vitro[36] Chronic fluvastatin therapy for post-MI mice can improve their survival and inhibit the development of cardiac remodeling and failure[37] These effects are associated with attenuation of the increase in myocardial MMPs, MMP-2 and MMP-13, in the noninfarcted LV, the site of ongoing remodeling, which was significantly attenuated in the fluvastatin-treated animals[37]

Oxidative Stress and Skeletal Muscle Dysfunction

Oxidative stress could be the mechanistic basis also for muscle fatigue and reduced exercise tolerance in HF patients[38] a notion supported by a positive correlation between ROS and exercise intolerance in these patients[39] Further, production of ROS was increased in skeletal muscle homogenates obtained from a murine model of HF and the increased ROS were identified as ·OH originating from $\cdot O_2^-$, which was associated with a concomitant increase in the oxidation of lipids[40] These results are consistent with those of previous reports that the oxidative capacity is reduced and O_2 utilization is inadequate in skeletal muscle mitochondria from HF patients[41] Skeletal muscle mitochondria from HF are associated with a decrease in the activities of complex I and complex III[40] As has been shown in the failing heart[9] defects in electron transfer function may lead to ROS production and thus ROS may play an important role in the muscle atrophy commonly seen in HF patients through the induction of apoptosis. In addition, ROS impair myoplasmic Ca^{2+} homeostasis and inhibit oxidative energy production in the mitochondria, both of which may contribute to the muscle contractile dysfunction. An attempt to attenuate oxidative stress would improve, to some extent, the exercise capacity of patients with HF.

Novel Therapeutic Strategies of HF Targeting Oxidative Stress

Oxidative stress is now considered to play an important role in the development and progression of myocardial remodeling and failure. Based on this novel paradigm, it is expected that novel therapeutic strategies of HF can be developed. A growing body of evidence suggests that antioxidants exert protective and beneficial effects in experimental HF[35,42–45] An antioxidant, vitamin E, prevented the transition from hypertrophy to failure in a guinea pig model of ascending aortic constriction[43] In addition, probucol, a lipid-lowering as well as potent antioxidant agent, had protective effects against pacing-induced HF[44] and adriamycin-induced cardiomyopathy[45]

The first line of defense against ROS-mediated cardiac injury comprises several antioxidant enzymes including SOD, catalase, and GSHPx. Of these, GSHPx is an important enzyme that performs several vital functions. It is a key antioxidant that catalyses 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 ·OH; in addition, GSHPx possesses a higher affinity for H_2O_2 than catalase and is present in relatively high amounts within the heart especially in the cytosolic and mitochondrial compartments[46] These lines of evidence imply the primary importance of GSHPx as a defense mechanism within the heart compared with catalase. Moreover, GSHPx is expected to exert greater protective effects against oxidative damage than SOD because the greater dismutation of $\cdot O_2^-$ by SOD may result in an increase of H_2O_2. Therefore, compared with SOD or catalase, GSHPx is thought to be more effective in protecting cells, tissues, and organs against oxidative damage[47] It has been recently demonstrated that GSHPx overexpression inhibited the development of LV remodeling and failure after MI (Figs 5,6), which might contribute to improved survival[48] These findings not only extend the previous studies that employed antioxidants, but also reveal the major role of ROS in the pathophysiology of post-MI remodeling, which is associated with the attenuation of myocyte hypertrophy, apoptosis, and interstitial fibrosis[48] Further, peroxiredoxin (Prx)-3, one of 6 distinct Prx family members identified in mammals and which can scavenge H_2O_2, may also exert

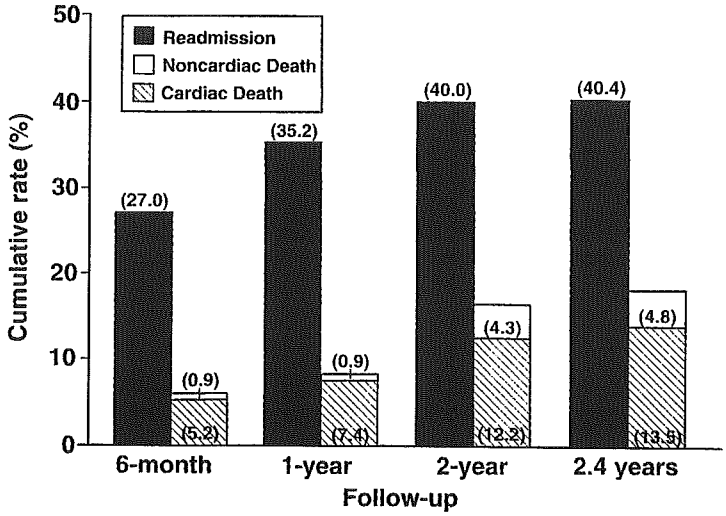

Fig 9. Cumulative rate of readmission, cardiac death, and noncardiac death in all patients with heart failure after discharge (Reproduced with permission from Tsuchihashi M, et al. *Am Heart J* 2001; **142:** e7).

protective effects against myocardial oxidative damage because it is specifically located in the mitochondria.[49]

Oxidative stress is involved not only in HF, but also in other cardiovascular diseases such as atherosclerosis and hypertension. Therefore, therapeutic strategies to modulate this maladaptive response should be the goal of future extensive investigation and such therapies, designed to interfere with oxidative stress, especially within the mitochondria, could have a broader application.

Clinical Approach: Management of 'Real World' Patients With HF

The clinical characteristics, drug therapy, and prognosis of patients with HF have been well described by both community-based[50–53] and hospital-based studies;[54–56] as well as by clinical trials of HF treatment.[57–60] However, these studies have been performed mainly in the United States and Europe and very little information is available in Japan. Results may not be directly translatable from one country to another that has a different population with a different health care system because variations in the population and quality of care may be important cofactors in the interactions among disease severity and outcome.[61] Furthermore, race is an important determinant of certain clinical outcomes in cardiovascular diseases.[62,63]

'Real World' Patients With HF

The characteristics of consecutive patients in Fukuoka who were hospitalized and discharged with HF during 1997 were assessed and their status followed through December 1999.[64] The study institutions included 5 cardiology units (1 university hospital and 4 nearby hospitals) serving as primary, secondary, and tertiary referral medical centers for cardiovascular patients.

Age Distribution The mean age was 69±14 years (range 16–92), and 70% of patients were >65 years of age. Overall, 60% were men and 40% women. The number of patients with HF increased with advancing age (Fig 7) and women especially, were found to be mostly older than 70 years.

Causes of HF Ischemic heart disease was the dominant cause and was involved in one-third of the cases (Fig 8), which is comparable to that reported in recent studies in Europe, but is lower than those in the clinical trials in which a large proportion of patients (60–75%) was attributed to an ischemic cause.[65] Another unique feature is that hypertensive heart disease was found in 20%, which is comparable to that observed in the studies in Sweden (17%)[55] and Italy (15%);[54] but is lower than that recognized in the population-based studies. Hypertension is still an important causative and contributing factor for HF and the importance of its treatment has been also supported by the recent evidence that effective antihypertensive therapy can reduce the incidence of HF.[57,66]

HF With Preserved Systolic Function A high proportion of patients had relatively preserved LV systolic function[67] and half of the patients with definite HF who underwent echocardiography had a normal ejection fraction (>50%), indicating the contribution of diastolic dysfunction in the pathogenesis of HF.[68] Patients with preserved systolic function were more often women and there was a higher prevalence of cardiac hypertrophy. At follow-up, cumulative survival probabilities were similar between patients with preserved systolic function and those with systolic dysfunction. Further, readmission rates were also comparable between those with preserved and depressed systolic function. In light of these findings, an effective therapeutic strategy for this subset of patients needs to be established.

Prognosis The patient population hospitalized with HF had a relatively good survival prognosis; the 1-year mortality rate being 8.3% (Fig 9).[64] In contrast to the relatively low mortality, rates of readmission for HF were as high as 40%, which is comparable with prior studies showing a 3- to 6-month readmission rate of 30–50%.[69–71] The most commonly identified cause for hospital readmission was lack of compliance with medical and dietary treatment.[72] Further studies to identify the independent factors contributing to hospital readmission have demonstrated that patients with a previous history of hospitalization for HF, longer hospital stay, and a history of hypertension are at increased risk for readmission, and that socioeconomic factors, including poor follow-up visits, poor professional support, and unemployment, are also potentially important predictors of HF-related readmission.[72]

Nationwide Survey of HF Patients in Japan

Even though previous studies have provided a valuable insight into the effective treatment strategies for HF pa-

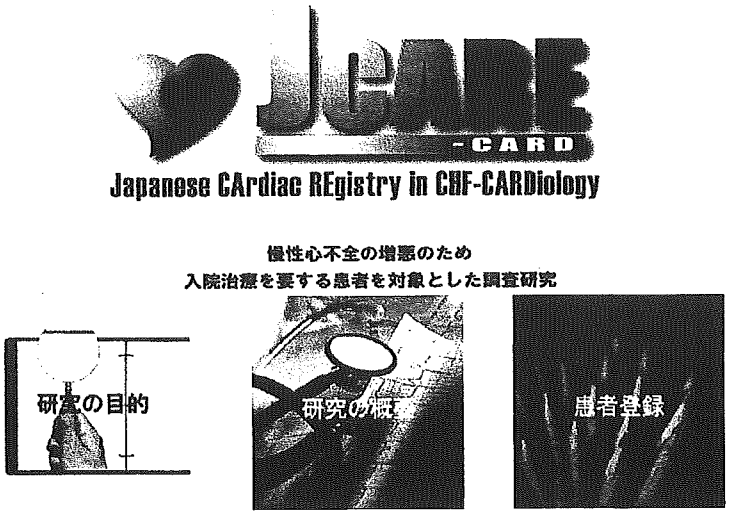

Fig 10. JCARE-CARD (http://www.jcare-card.jp/). Homepage images for the patient registration.

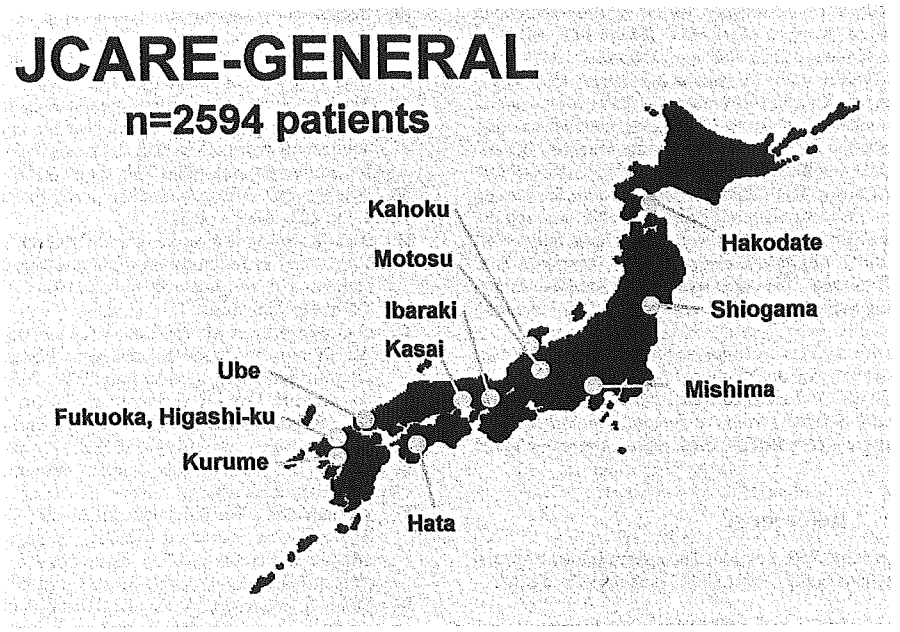

Fig 11. JCARE-GENERAL. Location of the nationwide study areas in Japan.

tients in Japan;[64,67,72] the generality of the results has been questioned because the investigation was conducted in a small number of patients. Furthermore, the participating hospitals were not representative of all cardiology units in the geographic area. However, the aim was to obtain a realistic picture of the characteristics of patients with HF admitted to hospital cardiology units rather than a precise evaluation of the prevalence of HF as an epidemiological study.

It is of critical importance to analyze the realistic data of HF patients on a nationwide basis, and to form a database for future investigations. For this purpose, a nationwide survey has been started by the Japanese Cardiac Registry (JCARE) investigators with the support of the Japanese Circulation Society and the Japanese Society of Heart Failure. One survey during 2004 focused on the demographic and clinical characteristics, treatment strategies, and long-term outcomes of patients admitted to hospitals in Japan because of the worsening of HF symptoms (JCARE-CARD; Fig 10). Another survey evaluated the demographic and clinical characteristics, treatment drugs, and long-term outcomes of patients with HF treated at outpatient clinics (JCARE-GENERAL; Fig 11). The primary goals of JCARE study are (1) to characterize the nationwide contemporary features of HF patients and (2) to delineate the independent predictors of prognosis in 'real world' patients with HF in Japan.

Effective Strategies of Treatment and Management for HF

There is an urgent need to develop and establish more effective strategies to prevent the progression and exacerbation of HF. Based on the findings obtained from preliminary surveys of 'real world' patients with HF, systematic patient management that coordinates care in the hospital, outpatient, and home settings is expected to reduce morbidity. It is also important to employ interventions that can prevent readmission especially for high-risk patients.

Conclusions

Both basic and clinical approaches are needed to improve the prognosis of patients with HF. First is the development of novel therapeutic strategies based on the new insight into the pathophysiology of myocardial remodeling and failure. One approach is to regulate mitochondrial oxidative stress. Second is the improvement of quality of care in routine clinical practice. These approaches need to be continued to establish new and effective treatment strategies for Japanese patients with HF.

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特別寄稿

慢性心不全の実態からみた治療のあり方
―臨床疫学研究からのレッスン―

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Key words：chronic heart failure, diastolic heart failure, readmission, clinical epidemiology, observational study

How to Treat the "Real World" Patients with Heart Failure : Lessons from the Epidemiological Study

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〈**Abstract**〉
Previous basic, clinical, and population sciences have advanced the modern treatment of heart failure. However, its efficacy is still limited especially in the "real world" patients. The clinical characteristics and prognosis of patients with heart failure have been described by a number of previous studies, which have been performed mainly in the United States and Europe. Very little information is available on this issue in Japan. We determined the clinical characteristics and prognosis of 230 patients consecutively hospitalized with HF at 5 teaching hospitals in Fukuoka, Japan in 1997. Patients were elderly and made up of a larger population of women especially at a higher age. The major causes of heart failure were ischemic, valvular, and hypertensive ; 35% of HF patients had a normal ejection fraction by echocardiography, in which heart failure might be mainly attributable to diastolic dysfunction. Readmission due to the exacerbation of heart failure is common. Noncomplicance to the treatment is the most common precipitating factor for readmission. Regular medical follow-up and social support are important for the disease management program of heart failure. A nationwide survey of the "real world" patients needs to be performed in Japan to establish the most effective and efficient treatment strategies.

はじめに

人口の高齢化・生活習慣の欧米化に伴う虚血性心疾患の増加により慢性心不全患者は増加の一途を辿っているが，今後さらに増加していくと予想される．欧米では，このような患者の増加は，臨床上の問題のみならず医療経済も含んだ社会問題として捉えられ，その効果的治療法や予防法の確立を目的とした大規模な登録研究や臨床試験が行われている．しかしながら，わが国では循環器領域において世界に通用する多施設を対象とした疫学研究データがきわめて乏しいため，このような患者の数，臨床像，治療内容，予後などの実態は全く分かっていない．欧米で行われた研究結果をそのまま人種も年齢構成も異なる日本人の患者にあてはめることができないのは言うまでもなく，

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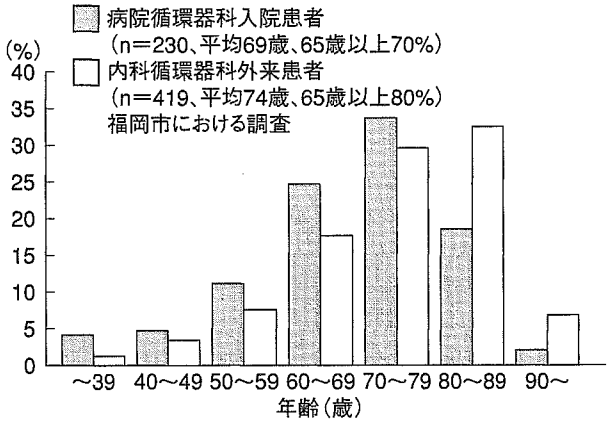

図 1 年齢分布（文献 1 より引用改変）

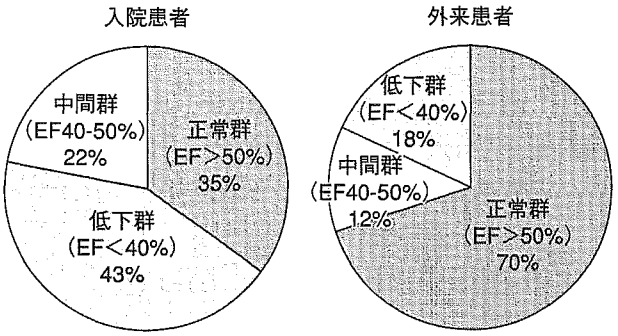

図 3 左室駆出率の内訳（文献 1 より引用改変）

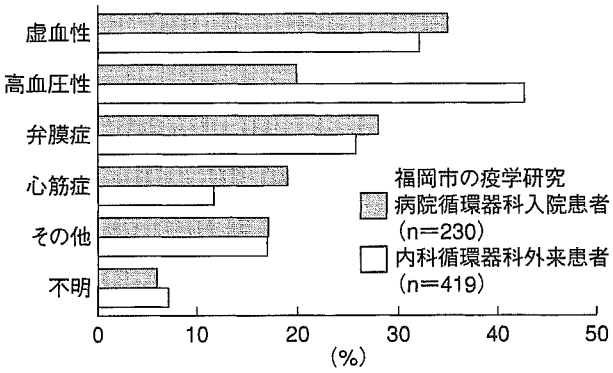

図 2 原因疾患（文献 1 より引用改変）

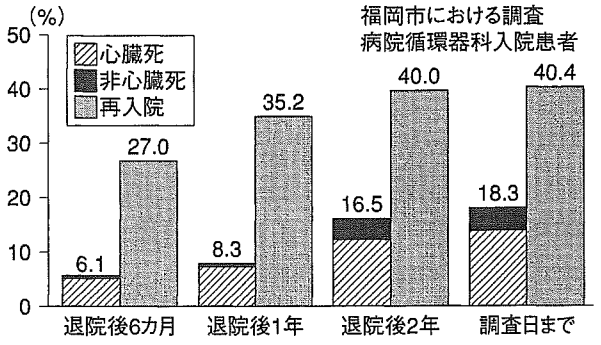

図 4 長期予後(死亡と再入院)（文献 1 より引用改変）

わが国独自の研究が必要である．

さらに，近年，数多くの大規模臨床試験により ACE 阻害薬や β 遮断薬が慢性心不全患者の予後を改善することが明らかにされてきた．このような薬物療法の進歩は慢性心不全の治療効果の向上に寄与してきたと考えられる．しかし一方で，疫学研究では慢性心不全患者の予後の改善は十分でないことも報告されている．その理由の 1 つとして，大規模臨床試験の患者は，年齢や基礎疾患などが実際の患者と大きく異なっており，一部の患者しか反映していないことが指摘されている．大規模臨床試験の結果から得られたエビデンスを実際の診療に役立てるためには，大規模な臨床データを解析する登録研究により患者の実態（real world）を知ることがきわめて重要である．

本稿では，我々が行ってきた慢性心不全患者を対象とした臨床疫学研究[1~3]をふまえ，慢性心不全治療のあり方を概説する．

慢性心不全患者の実態 —福岡市における研究から—

我々が福岡市において行ってきた臨床疫学研究によると慢性心不全患者のほとんどは 70~80 歳と高齢であり（図 1），その主たる原因疾患は，虚血性心疾患と高血圧，弁膜症である（図 2）．左室駆出率は入院患者の 35%，外来患者の 70%で正常に保たれており，拡張不全による心不全はまれではない（図 3）．入院患者の 1 年死亡率は 8.3%であり，再入院率は 35.2%にも達する（図 4）．

慢性心不全患者の実態からみた治療の留意点

慢性心不全患者の実態をふまえ，その治療にお

いて留意すべき点を列挙すると以下のようにまとめられる．

1）現在の慢性心不全治療ガイドラインは65歳未満を対象とした大規模臨床試験に基づいており，今後は高齢者を対象としたガイドラインを確立していく必要がある．

2）心不全の発症と進行を予防するためには，原因疾患としての高血圧や虚血性心疾患等の予防や治療がきわめて重要である．

3）拡張不全の治療ガイドラインの確立が必要である．

4）再入院に対しては，薬物治療だけでは不十分であり，疾患管理が必要である．

慢性心不全にて入院治療を受けた患者において，心エコーによる左室駆出率が50%以上と正常に保たれている患者が全体の35%を占めるという我々の成績[2]は，欧米の従来の研究とほぼ同様であった．収縮機能が正常な心不全患者は一般的に高齢で，女性が多く，高血圧や左室肥大が多く認められる．治療薬剤の選択については，高血圧が多いためかCa拮抗薬の使用率が高く，一方，収縮不全では，利尿薬とACE阻害薬の使用率が高かった．このような患者の予後について，Framingham研究では，駆出率が低下した患者は正常な患者と比較して予後が不良であると報告されている[4]一方，米国Olmsted郡の研究では，駆出率が低下した患者と維持された患者とで予後に有意差は認められなかった[5]．我々の対象患者を駆出率維持群（EF＞50%），中間群（40～50%），低下群（EF＜40%）の3群に分けて，生存率と心不全増悪による入院率を検討したところ，有意差は認めなかった[2]．

拡張不全に対する薬物治療については，CHARM-Preserved試験でアンジオテンシンII受容体拮抗薬カンデサルタンが，心不全増悪による入院に対して抑制効果のあることが示された[6]が，現在さらにI-PRESERVE試験，ACE阻害薬はPEP-CHF試験，β遮断薬はSENIORS試験といった大規模臨床試験が進行中である．今後これらの試験の結果をふまえ，拡張不全の治療ガイドラインが確立されることが期待される．

表　心不全増悪の誘因
（文献3より引用改変）

塩分・水分制限の不徹底	33（%）
感染症	20
過労	12
治療薬服用の不徹底	11
不整脈	11
精神的または身体的ストレス	5
心筋虚血	5
コントロール不良の高血圧	4
合併疾患の増悪	4

慢性心不全患者は心不全増悪による再入院を繰り返しやすい．再入院の誘因は，塩分・水分制限や服薬の不徹底など治療コンプライアンス不良，過労，精神的または身体的ストレスなど非医学的因子のほうが多い（表）．再入院の規定因子を明らかにするために，再入院患者と非再入院患者とを比較したところ，患者背景には両群で差がなく，左室駆出率や入院時のNYHAクラス，退院時の薬物療法も有意差がなかった[3]．心不全増悪による再入院の独立した規定因子は，外来への通院頻度，心不全による入院の既往，入院期間，専門的介護を受けていないことなどであった．さらに規定因子の数が多いほど，再入院率および死亡率が高かった．このような結果から，慢性心不全の増悪による再入院に対しては，患者管理が重要であると予測される．

実際，欧米においては慢性心不全患者に対する疾病管理の有用性を検討した臨床試験の結果が報告されている．プログラムは，具体的には患者教育などを含む総合的管理，心不全専門外来による管理，在宅治療，電話による管理などがある．いずれの疾病管理プログラムにおいても，再入院を約40～50%減少させることが報告されており，その効果は薬物治療の約20～30%より大きい．

わが国における大規模臨床疫学研究の推進

わが国において慢性心不全患者の臨床像や治療などの実態が知られていないという現実は，効果的かつ効率的治療を見出し，適切な治療を構築し

ていくうえで，きわめて重大な問題である．

我々は，慢性心不全の増悪のため入院治療を要する患者を全国レベルで登録して大規模なデータベースを構築し，その解析から，患者背景，治療，予後を解析する「慢性心不全の増悪のため入院治療を要する患者を対象とした調査研究（JCARE-CARD研究）」を計画立案し，2004年より着手した．本研究では，2004年1月から1年間にわたり全国の日本循環器学会研修施設のうち研究への協力が可能な施設（2004年2月9日現在410施設）において心不全の増悪のために入院治療を行った患者を前向きに登録するものである．慢性心不全の定義はFramingham研究の診断基準を用いる．登録時調査として1）年齢，性別，2）心不全増悪の誘因(医学要因，社会環境要因など)，3）入院期間，4）基礎疾患（虚血，高血圧，心筋症，弁膜症，不明，その他），5）合併疾患（高血圧，糖尿病，高脂血症，脳血管障害，腎不全），6）慢性心房細動，7）重症度，8）心機能評価（心エコーおよびBNP），9）退院時治療：薬剤，手術(弁手術，冠動脈バイパス術など)を登録する．さらに予後調査（1〜2年後）として1）死亡（入院中さらに退院後の全死亡と心血管死）2）剖検，3）心不全増悪による再入院，4）持続性心室頻拍または心室細動を調査する．患者登録は，ユーザー名とパスワードを付与された各施設の医師がホームページ（http://www.jcare-card.jp/）から直接行う（図5）．

本研究は，患者に対して介入は行わない登録観察研究である．したがって，患者の不利益・危険性はないが，研究計画の立案，倫理委員会の審査，対象者からの同意取得，匿名性，インターネットにおけるデータ登録，データの管理体制において十分な倫理的配慮を行った．

本研究の特色は，第一に，急性増悪にて入院治療を必要とした心不全患者を，全国規模で登録した大規模データベースを用いて解析する点である．全国規模で多数かつ幅広い重症度の患者を登録するため，より実際の患者像を反映した解析が可能となる．第二に，心不全患者の臨床病態，治療内容，とくに投薬，長期予後に関するデータを集積し，解析することによって，患者の生命予後ばかりでなく心不全の増悪を防止し，さらには生活の質（QOL）を改善する治療法を探索し，確立することを目指す．

さらに，全国の指定された約10地域の内科・循環器科の診療を行っているすべての医療機関の外来において慢性心不全患者をすべて登録し，その患者背景，治療内容，予後を調査する「地域住民の中で外来治療を受けている慢性心不全患者を対象とした調査研究（JCARE-GENERAL研究）」を計画・立案し，2003年より進行中である（図6）．登録対象患者は外来治療を受けている慢性心不全患者である．慢性心不全の定義はヨーロッパの慢性心不全治療ガイドラインの診断基準に準じて「心不全症状（息切れや倦怠感など）と徴候（ラ音や浮腫など）があり，それらが他の疾患によるものでない患者」で，「心機能障害を有する患者」とした．2003年11月を中心に，全国9地域で1カ月間にわたり外来受診した慢性心不全患者を全例前向きに登録した．登録には手帳サイズの調査票を用いた．調査項目は，年齢，性別，基礎疾患（虚血，高血圧，心筋症，弁膜症，不明，その他），心房細動，慢性心不全の既往，投薬内容（ACE阻害薬，ARB，β遮断薬，利尿薬，ジギタリス，Ca拮抗薬，アスピリン，スタチン），心エコー所見(可能な患者のみ)とした．予後調査項目(1年後)は，生死と心不全増悪による入院である．この研究では，幅広い重症度の患者の臨床像や治療と予後との相関を明らかにすることができる．さらに，指定された地域の住民の中で慢性心不全患者をもれなく登録することによって，慢性心不全の有病率と発症率を推定することも可能である．

JCARE研究により日本人の患者の実態を明らかにできるばかりでなく，実際の患者像に即した臨床マーカーや治療法の有効性判定，治療効果の規定因子の解析など無作為コントロール試験では得られない情報を提供できるものと期待される．JCARE研究は，将来的には，ゲノムデータも収集し，遺伝子多型解析により疾患関連遺伝子・薬剤感受性遺伝子・副作用関連遺伝子の探索・同定を行う．さらに，臨床データと一体化することによっ

JCARE-CARD（慢性心不全入院患者）
全国における病院型コホートのコンソーシアムの形成

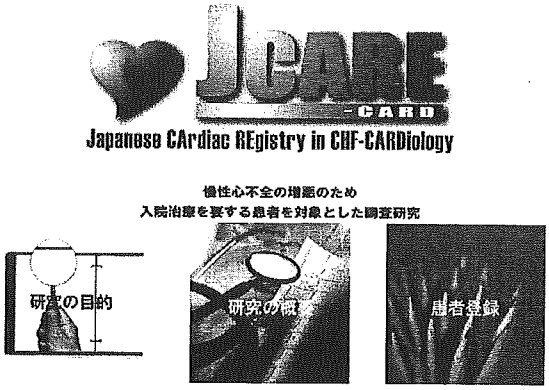

図 5　JCARE-CARD 研究

JCARE-GENERAL（慢性心不全外来患者）
全国における地域型コホートのコンソーシアムの形成

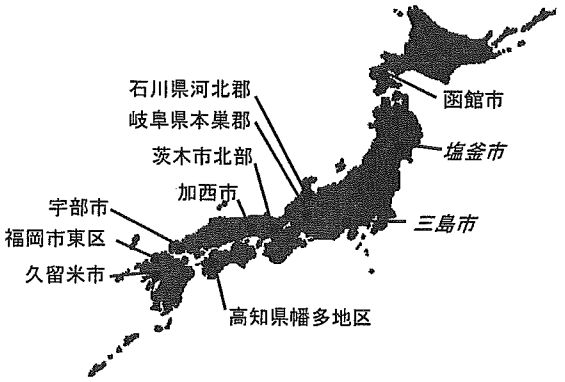

図 6　JCARE-GENERAL 研究

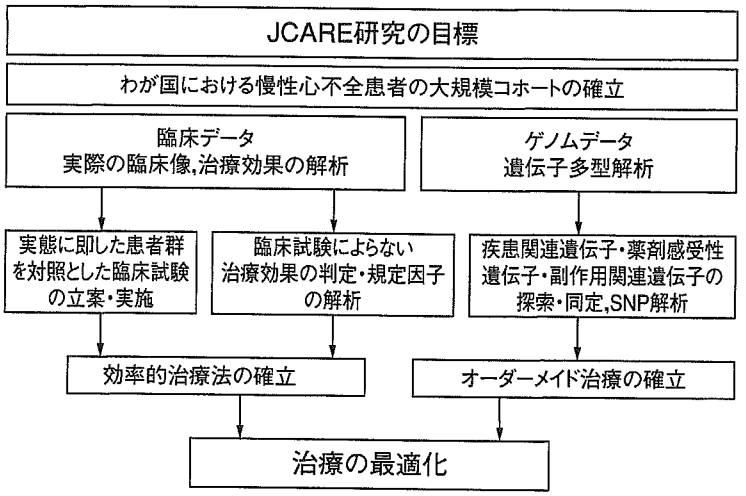

図 7　JCARE 研究の概要

て，慢性心不全患者を対象とした臨床ゲノム疫学データベースの構築をめざすものである．その解析により，日本人の患者の実態にあった効果的・効率的な治療やオーダーメイド治療が可能となることが期待される（図 7）．

ま と め

慢性心不全の治療は，近年得られてきたエビデンスにより大きな進歩を遂げてきた．しかしながら，エビデンスの根拠となる大規模臨床試験の対象患者は，実際の患者のごく一部の患者を反映しているにすぎない．さらに現在の治療でもまだ効果は不十分である．今後，全国レベルで慢性心不全患者の実態を明らかにし，わが国独自のエビデンスをふまえ，さらに効果的な心不全治療法の確立と患者にあった効率的治療法の選択をめざしていくことが必要である．

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Lecture

解　説

慢性心不全治療における患者管理*

眞茅みゆき**　筒井裕之**

Key Words：disease management, heart failure, treatment, readmission, QOL

はじめに

慢性心不全患者は高齢者が多く，その生命予後が不良であるばかりでなく，心不全増悪による再入院を反復する．再入院には不整脈・心筋虚血・感染症などの医学的要因ばかりでなく，治療コンプライアンス不良や身体的・精神的ストレスなどが密接に関与する．慢性心不全に対する薬物治療の効果を最大限引き出し，再入院を減少させ，症状・生活の質(QOL)を改善するには，患者および家族教育・治療コンプライアンスの向上・病状モニタリング・服薬管理・看護師や薬剤師も加えた治療体制などを含む患者管理(disease management)がきわめて重要である．

本稿では，慢性心不全患者の治療において患者管理が必要とされる背景，その有効性と具体的な方法について概説する．

慢性心不全患者における再入院

慢性心不全は高血圧，虚血性心臓病，心筋症など器質的心疾患の終末像であるが，その患者の多くは入・退院を繰り返す高齢者である．このような患者は増加の一途を辿っており，今後さらに増加していくと予想される．近年とくに，入退院を繰り返す高齢の慢性心不全患者が心臓救急の現場で著しく増加しており，有効な対策

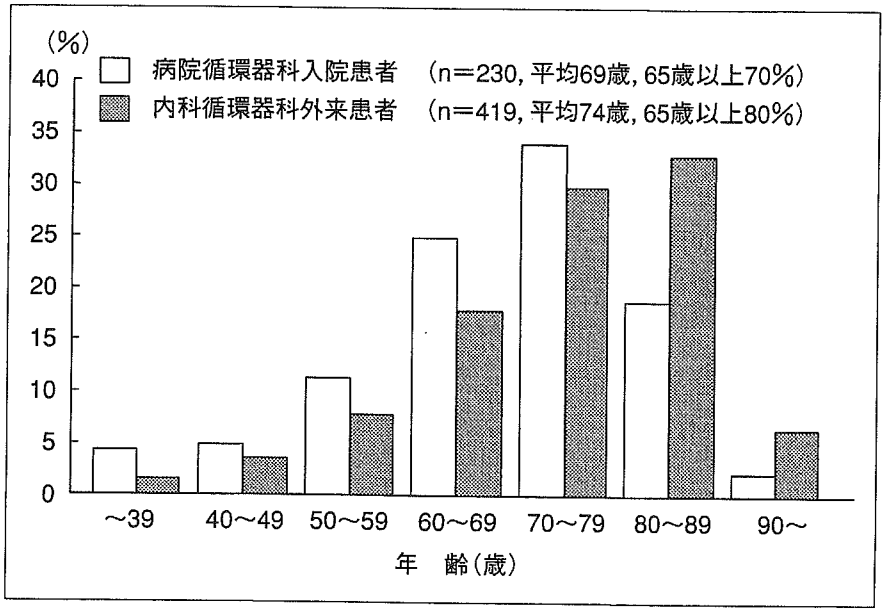

図1　年齢分布

* Disease management in heart failure treatment.

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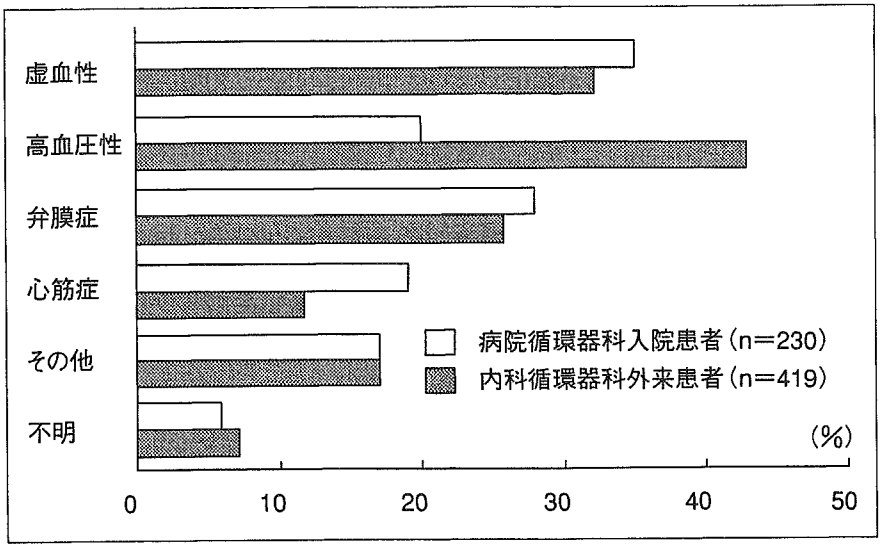

図2　基礎心疾患

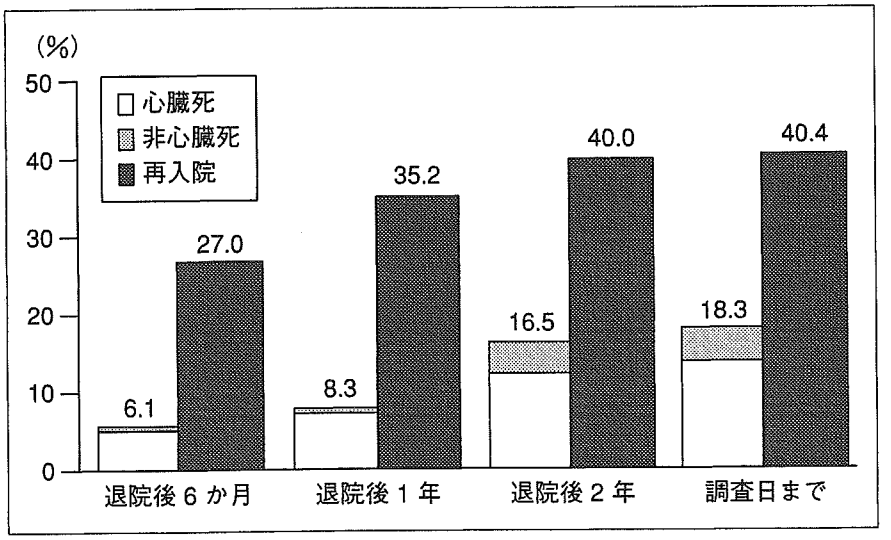

図3　退院後死亡率・再入院率

表1　心不全増悪による再入院の誘因

	%
塩分・水分制限の不徹底	33
感染症	20
過労	12
治療薬服用の不徹底	11
不整脈	11
身体的・精神的ストレス	5
心筋虚血	5
コントロール不良の高血圧	4
合併疾患の増悪	4

(文献[3]より改変引用)

を打ち出すことが急務となっている．

欧米では，このような慢性心不全患者の増加は，臨床上の問題のみならず医療経済も含んだ大きな社会問題として捉えられ，その効果的治療法や予防法の確立を目的とした大規模な登録研究や臨床試験が行われている．しかしながら，わが国では慢性心不全を対象とした疫学研究がきわめて乏しいため，このような患者の数，臨床像，治療および予後などの実態は不明である．

われわれは，福岡市内の5つの循環器科を有する医療機関(病床数20～60床)において，1997年1年間に自宅へ退院した慢性心不全患者230名を登録し，患者背景(年齢，性別)，臨床的特徴(基礎心疾患，重症度，心エコー所見など)を調査した．さらに，平均2.4年間経過観察し，その間の死亡(死亡の原因)と心不全増悪による再入院を調査した．また，福岡市東区において外来

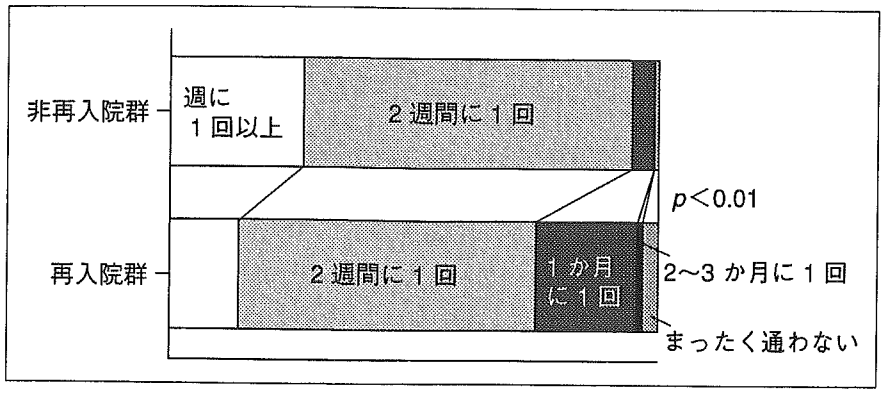

図4　退院後外来受診の頻度

治療を受けている慢性心不全患者419名についても調査した．その結果，慢性心不全の入院患者の平均年齢は69歳であり，65歳以上の高齢者が70％を占めた(図1)．外来患者はさらに高齢であった．慢性心不全の基礎疾患としては，虚血性心疾患や高血圧性心疾患が多かった(図2)．また，退院後1年死亡率が8％であるのに対し，心不全の増悪による再入院が35％ときわめて高率であった[1)2)](図3)．

心不全増悪による再入院に関与する因子

心不全増悪による再入院の誘因を検討すると，塩分・水分制限の不徹底が33％ともっとも多く，過労，治療薬服用の不徹底，身体的または精神的ストレスなどの予防可能な因子が上位を占め，感染症・不整脈・心筋虚血・高血圧などの医学的要因よりむしろ多かった(表1)．さらに，心不全増悪による再入院の規定因子を明らかにするために，再入院81例と非再入院149例で，患者因子(年齢，性)，医学的因子(基礎疾患，心房細動，NYHA分類，左室駆出率，心不全の入院歴，入院期間，高血圧・糖尿病・腎不全・脳血管疾患などの合併症，薬物療法)，および社会環境因子(就労，収入状況，独居，介護者，在宅看護・介護サービス，外来受診頻度)の関与をロジスティック回帰分析により解析すると，「退院後外来受診が少ない」「心不全の入院歴あり」「入院期間が長い」「在宅療養サービスの利用なし」「就労なし」「高血圧の既往あり」などで再入院が多かった．受診頻度が月0〜1回の患者は，それ以上の患者より再入院のリスクが約5倍高かった[3)](図4)．

このような慢性心不全患者の実態は，医療専門職による退院後の十分なフォローアップや支援が，心不全患者の再入院の予防においてきわめて重要であることを示唆している．

慢性心不全治療における患者管理の有効性

欧米では1990年代半ばから，心不全患者を対象として患者管理の予後に対する有効性を検証する介入試験が行われてきた．その結果，患者教育，治療コンプライアンスの向上，訪問や電話などによる患者モニタリング，治療薬の調節，看護師による管理などの患者管理が慢性心不全患者の予後の改善に有効であることが報告されている．とくにRichらの報告は，患者管理の有効性を示した最初の画期的研究と位置づけられている．この研究では高齢心不全患者を対象に，多職種による退院前患者教育の強化，退院後の社会資源の積極的活用，退院後の訪問看護や電話によるフォローアップを行った介入群と，通常の治療を受けた対照群に分け，退院後90日の再入院率，生存率，QOL，医療コストへの効果を検討した．その結果，介入群は対照群に比較し再入院率が50％減少し，QOLスコアが改善し，医療費も低かった[4)]．さらにStewartらは，循環器専門看護師による退院後の定期的な在宅訪問によって，症状のモニタリングや服薬・食事に関する患者教育を行うhome-based intervention (HBI)により再入院率が50％減少し，医療機関に通院する日数が1/2に抑えられたと報告した[5)]．さらに，平均4.2年追跡した結果，HBIにより死亡または再入院が減少することも報告されてい