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Novel Pathophysiological Insight and Treatment Strategies for Heart Failure
~Lessons From Mice and Patients~

Running head: Pathophysiology and treatment of heart failure

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Abstract

Our ultimate goal of heart failure (HF) treatment is to improve the prognosis of patients. Previous basic, clinical, and population sciences have advanced the modern treatment of HF. However, its efficacy is still limited especially in the "real world" patients. There are two approaches to solve this crucial issue. First is the further development of novel 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. Our basic approach is to develop the therapeutic strategy of myocardial remodeling by regulating mitochondrial oxidative stress. In the failing hearts, oxygen radicals are produced by the defects of mitochondrial electron transport. They cause mitochondrial DNA damage and functional decline, leading to the 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. Our clinical approach is to develop the effective strategies of HF management for the "real world" patients. Readmission due to the exacerbation is common in HF patients and further impairs the quality of life. Noncomplicance to the treatment is the most common precipitating factor for readmission. Regular medical follow-up and social support are important components which should be included in the disease management program of HF patients. These basic and clinical approaches are needed to establish the novel and most effective treatment strategies for Japanese patients with HF.

Congestive heart failure (HF) is a leading cause of morbidity and mortality in industrialized countries.[1] 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. Previous basic, clinical, and population sciences have advanced the modern treatment of HF. However, its efficacy is still limited especially in the "real world" patients. There are two 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 such scavenging enzymes as superoxide dismutase (SOD), glutathione peroxidase (GSHPx), and catalase as well as by other non-enzymatic antioxidants. However, when the production of ROS becomes excessive, oxidative stress might have a harmful effect on the functional and structural integrity of biological tissue. ROS cause contractile failure and structural damage in the myocardium. The importance of oxidative stress is increasingly emerging with respect to a pathophysiological mechanism of left ventricular (LV) remodeling and failure responsible for HF progression.

Increased ROS Production Within the Failing Myocardium

Recent experimental and clinical investigations have suggested the generation of ROS to increase in chronic HF. [3-6] Lipid peroxides and 8-iso-prostaglandin F2α, which are the major biochemical consequences of ROS generation, have been shown to be elevated in plasma and pericardial fluid of patients with HF and also positively correlated to the severity of HF. [3,4] However, all of these findings have provided only indirect evidence of ROS generation in the failing hearts. It is difficult to quantify the amount of ROS in the intact biological system since they are unstable and rapidly react with unoxidized adjacent molecules and thus their half life is very short. The only method to directly quantify 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, we first provided a definitive and direct demonstration of enhanced generation of ROS in the failing myocardium.[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 myocardium. $\cdot OH$ 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 means of the Fenton reaction. The generation of $\cdot OH$ implies a pathophysiological significance of ROS in HF since $\cdot OH$ radicals are the predominant oxidant species causing cellular injury.

The decreased antioxidant capacity could further aggravate the ROS accumulation in HF. However, the activities of SOD, catalase, and GSHPx were not decreased in the failing hearts. [8] These results thus indicate that oxidative stress in HF is primarily due to the enhancement of prooxidant generation rather than to the decline in antioxidant defenses. Moreover, the generation of ROS is greater than the scavenging capacity of endogenous antioxidants within the failing myocardium.

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 carriers 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 using ESR spectroscopy with 5,5'-dimethyl-1-pyrroline-N-oxide (DMPO) as a spin trap, a standard method to detect ROS in the biological tissue. The inhibition of electron transport at the sites of complex I and complex III in the 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 succinate as a substrate, indicating that complex I is the predominant source of such $\cdot O_2^-$ production (**Figure 1 and 2**). Furthermore, HF mitochondria are associated with a decrease in complex I activity. Therefore, mitochondria are the predominant source of ROS in failing hearts, 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, we could not completely exclude 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 NADPH oxidase) could contribute to oxidative stress in HF.[11] 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. They 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, an 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 the role of mitochondria as a source of ROS, the mitochondria themselves can be damaged by ROS.

Mitochondria contain closed circular, double-strand DNA of ~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 (**Figure 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 a limited repair activity against DNA damage. Third, a large part of $\cdot O_2^-$ which is 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] We have recently shown that the increased generation of ROS was associated with mitochondrial damage and a dysfunction in the failing hearts, which were characterized by an increased lipid peroxidation in the mitochondria, a decreased mtDNA copy number, a decrease in the number of mtRNA transcripts, and a reduced oxidative capacity due to 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 (**Figure 4**). MtDNA defects may thus play an important role in the development and progression of myocardial remodeling and failure.

Several possible factors might be involved as 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 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 could be observed also in vitro when cardiac myocytes were exposed to TNFα.[18] The equivalent results observed between in vivo and in vitro indicate that TNFα plays an important role in oxidative stress in the pathogenesis of myocardial remodeling and failure. Further, overexpression of TNFα gene induced the increase in ROS production in association with the myocardial contractile dysfunction and structural remodeling in mice.[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] An

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 in 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 to be the primary contributing factor. We have provided direct evidence that mtDNA defects occur not only in a limited small subset of mitochondrial diseases but also in a more common HF phenotype occurring after myocardial infarction (MI). This is further supported by the studies on mice lacking MnSOD which 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. We have demonstrated that 8-oxo-dGTPase was highly expressed in the cardiac myocytes from the post-MI failing hearts, thus suggesting that this enzymatic system preventing 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] ROS have also been shown to activate matrix metalloproteinase

(MMP) in cardiac fibroblasts.[29] Myocardial MMP activity is increased in the failing hearts.[30,31] Further, an MMP inhibitor has been shown to limit early LV dilatation in a murine model of MI.[32] We have shown the significant improvement in the survival after MI in MMP-2 knockout mice, which was mainly attributable to the inhibition of early cardiac rupture and the development of a 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 myocytes interact. We have demonstrated that ·OH scavenger, dimethylthiourea, inhibits the activation of MMP-2 in association with the development of LV remodeling and failure.[35] These data raise the interesting possibility that increased ROS after MI can be a stimulus for myocardial MMP activation, which 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 administration of statin into post-MI mice can improve the survival and inhibit the development of cardiac remodeling and failure.[37] These effects were associated with the attenuation of an increase of myocardial MMPs, MMP-2 and MMP-13, in the noninfarcted LV, the site of ongoing remodeling, which was significantly attenuated in 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] This notion is supported by a positive correlation between ROS and exercise intolerance in these patients.[39] Further, we demonstrated that the production of ROS was increased in the skeletal muscle homogenates obtained from a murine model of HF and increased ROS were

identified as $\cdot OH$ originating from $\cdot O_2^-$, which was associated with a concomitant increase in the oxidation of lipids.[40] These results are consistent with the previous studies 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 hearts,[9] the defects in electron transfer function may lead to the ROS production. 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 the 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 proved to play an important role in the development and progression of myocardial remodeling and failure. Based on this novel paradigm, we expect that novel therapeutic strategies of HF could 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 the guinea pig model of ascending aortic constriction.[43] In addition, probucol, 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 mechanism against ROS-mediated cardiac injury comprises several antioxidant enzymes including SOD, catalase, and GSHPx. Among these antioxidants, GSHPx is an important enzyme that performs several vital functions. GSHPx is a key antioxidant which 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 $\cdot OH$. GSHPx possesses a higher affinity for

H_2O_2 than catalase. Further, it 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 to catalase. Moreover, GSHPx is expected to exert greater protective effects against oxidative damage than SOD because 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] We have recently demonstrated that GSHPx overexpression inhibited the development of LV remodeling and failure after MI (**Figure 5 and 6**), which might contribute to the improved survival.[48] These findings not only extended the previous observation that employed antioxidants, but also revealed the major role of ROS in the pathophysiology of post-MI remodeling. These effects were 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 which can scavenge H_2O_2, may also exert 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 various cardiovascular diseases including atherosclerosis and hypertension. Therefore, therapeutic strategies to modulate this maladaptive response should definitely become a target for future extensive investigation and therapies designed to interfere with oxidative stress, especially within the mitochondria, could have a broader application.

Clinical Approach
Management of the "Real World" Patients with HF

The clinical characteristics, drug therapy, and prognosis of patients with HF have been well described by a number of 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. The previous results may not be directly translatable from one country to another which has different population with different health care system since 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]

The "Real World" Patients with HF

We assessed the characteristics of patients consecutively hospitalized and discharged with HF during 1997 and the status of these patients was followed through December 1999. 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 in Fukuoka with 1.3 million inhabitants.[64]

Age Distribution

The mean age was 69±14 years (range 16 to 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 (**Figure 7**). Especially, women were found mostly in older than 70 years.

Causes of HF

Among HF patients, ischemic heart disease was the dominant cause and was involved in one thirds of the cases (**Figure 8**). This value is comparable to that reported in recent studies in Europe, but is lower than those in the clinical

trials that large proportion of patients (60-75%) was attributed to ischemic cause [65] Another unique feature is that hypertensive heart disease was found in 20%. This figure is comparable to that observed in the study in Sweden (17%)[55] and that in Italy (15%), [54] but 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 the effective antihypertensive therapy can reduce the incidence of HF.[57,66]

HF with Preserved Systolic Function

The high proportion of patients had relatively preserved LV systolic function.[67] The half of patients with definite HF who had echocardiography had 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 had 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 preserved and depressed systolic function. In light of these findings, effective therapeutic strategy for this subset of patients needs to be established.

Prognosis

Our patient population hospitalized with HF had a relatively good survival prognosis; the 1-year mortality rate being 8.3 % (**Figure 9**).[64] In contrast to the relatively low mortality, rates of readmission for HF were as high as 40%. This value was comparable to those in prior studies (a 3- to 6-month readmission rate 30 to 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 for the hospital readmission have

demonstrated that patients with a previous history of hospitalization due to 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 no occupation, are also potentially important predictors of HF-related readmission.[72]

The Nationwide Survey of HF Patients in Japan

Even though our previous studies have provided a valuable insight into the effective treatment strategies for HF patients,[64,67,72] the generality of our results is questioned because our investigation was conducted in a small number of patients. Furthermore, the participating hospitals are not representative of all cardiology units in the geographic area. However, the aim of our previous preliminary studies are to obtain a realistic picture of the characteristics of patients with HF admitted to the 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 is now 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 focused on the demographic and clinical characteristics, treatment strategies, and long-term outcomes in patients admitted to the nationwide hospitals in Japan due to the worsening of HF symptoms during 2004 (JCARE-CARD; **Figure 10**). The other survey evaluated the demographic and clinical characteristics, treatment drugs, and long-term outcomes in patients with HF treated at the outpatient settings (JCARE-GENERAL; **Figure 11).** The primary goal of JCARE study is 1) to characterize the nationwide contemporary features of HF patients and 2) to delineate the independent predictors of prognosis in the "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 our preliminary survey of the "real world" patients with HF, systematic patient management that coordinates care in the hospital, outpatient, and home settings is expected to reduce the morbidity of these patients. 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 further development of novel therapeutic strategies based on a novel insight into the pathophysiology of myocardial remodeling and failure. Our approach is to develop the therapeutic strategy of myocardial remodeling by regulating mitochondrial oxidative stress. Second is the improvement of quality of care in routine clinical practice. These approaches need to be continued to establish the novel and most effective treatment strategies for Japanese patients with HF.

Acknowledgments

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Figure legends

Figure 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. Mitochondrial electron transport complex I is a potential source of oxygen free radicals in the failing myocardium Circ Res 85:357-363,1999)

Figure 2   An ESR analysis of 5,5'-dimethyl-1-pyrroline-*N*-oxide (DMPO) adduct formation in 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. Mitochondrial electron transport complex I is a potential source of oxygen free radicals in the failing myocardium Circ Res 85:357-363,1999)

Figure 3   Map of the mitochondrial genome. The 16.3-kilobase mouse mitochondrial genome is diagrammed showing the 13 mRNA, 2 rRNA (12S and 16S), and 21 tRNA coding genes. mRNA genes are shown as the 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.

Mitochondrial DNA damage and dysfunction associated with oxidative stress in failing hearts following MI. Circ Res 88:529-535,2001)

Figure 4   Schematic representation of an intimate link between 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. Mitochondrial DNA damage and dysfunction associated with oxidative stress in failing hearts following MI. Circ Res 88:529-535,2001)

Figure 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. Overexpression of glutathione peroxidase prevents left ventricular remodeling and failure after myocardial infarction in mice. Circulation 109:544-549,2004)

Figure 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. Overexpression of glutathione peroxidase prevents left ventricular remodeling and failure after myocardial infarction in mice. Circulation 109:544-549,2004)

Figure 7   Age distribution of men (open bars) and women (closed bars) hospitalized with congestive heart failure. (Tsuchihashi M et al. Clinical characteristics and prognosis of consecutively hospitalized patients with congestive heart failure: A study in Fukuoka, Japan. Jpn Circ J 64:953-959, 2000)

Figure 8   Distribution of causes of heart failure. Patients could have more than one cause. Numbers denote the percentage of patients to the total number of study patients. (Tsuchihashi M et al. Clinical characteristics and prognosis of consecutively hospitalized patients with congestive heart failure: A study in Fukuoka, Japan. Jpn Circ J 64 : 953-959, 2000)

Figure 9   Cumulative rate of readmission, cardiac death, and noncardiac death in all patients with heart failure after discharge. (Tsuchihashi M et al. Medical and socioenvironmental predictors of hospital readmission in patients with congestive heart failure. Am Heart J 142:e7,2001)

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

Figure 11   JCARE-GENERAL. The nationwide location of study areas in Japan.
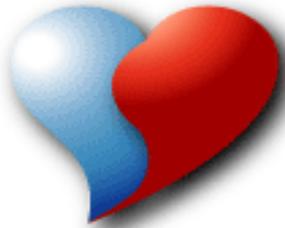
JCARE
-CARD

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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

研究の目的

研究の概要

患者登録