population is aging rapidly. Figure 1 shows the time-course of aging and population projections between 1950 and 2055, which is assembled using the data reported by the Japanese Cabinet Office (The Status of Aging 2007). As of October 1, 2006, the total population of Japan was 127.8 million and the number of elderly aged 65 or older was 26.6 million, accounting for 21% of the total population. The elderly population is expected to continue to increase rapidly and the percentage of the elderly will reach 35.8 million (27%) in 2055 (The Status of Aging 2007). Life expectancy in Japan at birth has also drastically increased since World War II to 78.6 years for males and 85.5 years for females in 2005 (Life Expectancies at Specified Ages 2006). The Japanese Cabinet Office expects that it will reach 83.7 years for males and 90.3 years for female in 2055. Thus, in the near future, Japanese society will encounter more difficult medical problems due to rapid aging, which other developed countries have never before experienced.

Changing causes of death in Japan

Infectious diseases such as pneumonia, tuberculosis, and gastroenteritis were the leading causes of death in Japan until the mid 1900s. The major health problems in Japanese society have drastically changed since World War II. The morbidity and mortality rates of lifestyle-related diseases such as cancer, heart disease, stroke, and diabetes mellitus have dramatically increased. Approximately 60% of the mortality is now attributed to lifestyle-related diseases (cancer, 31%; ischemic heart disease 16%; cerebrovascular disease 13%; diabetes mellitus 1%; and hypertensive disease 0.6%) and the medical costs for these diseases amounts to 10.2 trillion yen (87.8 billion US dollars), accounting for approximately 30% of the total cost of the Japanese health insurance in 2003 (Exercise and Physical Activity Reference for Health Promotion 2006). Currently, heart disease is the second most frequent cause of death in Japan. Figure 1 shows the trend of the mortality due to heart diseases, which is constructed using the reports of death certificates in Japan (Summary of Vital Statistics 2005). There is a clear trend for the increase in death due to heart disease since 1950s (there was a temporary sharp decline in 1995 due to the tenth revision of the International Classification of Diseases regarding the description of diagnosis in death certificates).

Health insurance system and future economic burden in Japan

In Japan, all citizens are enrolled in the mandatory health insurance system based on employment and residential status. The average number of visits to a doctor per year is 16 in Japan, versus 5.8 visits in the United States (Itoh 2004). As elderly patients tend to visit doctors more frequently and to have more medication or high-cost medical care, medical

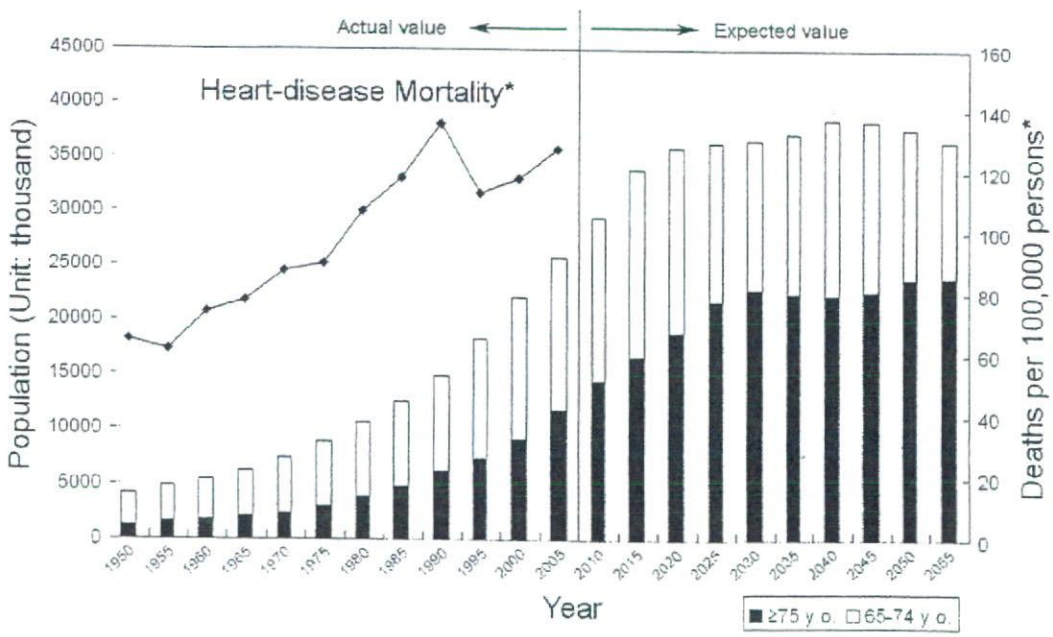


Figure 1 Time-course and future prediction of the increase in elderly population and heart-disease mortality in Japan. Data are based on the Status of Aging and Implementation of Measures for Aging Society in 2005, reported by the Japanese Cabinet.

expenditure for the elderly is already taking one-third of the national health expenditure, and is projected to reach a half of the expenditure by the year 2025 (Itoh 2004). Progressive aging of the society and the consequent increase in the number of patients with CHF will cause more financial burden within Japanese society, which could lower the quality of medical services in the future.

An overview of heart failure studies in Japan

In Japan, medical treatment for patients with CHF is mainly based on the evidence obtained from randomized trials in the United States and Europe. There have been no sufficient randomized treatment trials or prospective cohort studies in Japan to clarify the real characteristics of Japanese patients with CHF or to improve their prognosis and quality of life. The mandatory health insurance system, the shortage of the budget to fulfill mega-trials, and the absence of trained research nurse system may all be responsible for the current situation. This section describes several cohort studies with Japanese CHF patients, major outcomes of the CHART-1 study, and randomized treatment trials for CHF performed with Japanese patients, either those that have already been published or are currently in progress. Finally, racial differences will be discussed, because this issue may also influence the impact of risk factors and/or the effects of treatments for CHF.

Prospective cohort studies in Japan

There are few multi-institutional prospective cohort studies with CHF patients in Japan (Table 1). The Chronic Heart Failure Analysis and Registry in the Tohoku District (CHART)-1 study was the first cohort study in Japan, including more than 1,000 Japanese patients with stable CHF, who were registered at 26 hospitals in the Tohoku district with a population of approximately 9.8 million (Shiba et al 2004). The CHART-1 study was initiated in February 2000 and was completed in December 2005. The total number of CHF patients enrolled was 1,278 and the mean follow-up period was 3.5 years. Details of design and the main outcome will be presented at the following part in this article. The Japanese Cardiac Registry of Heart Failure in Cardiology (JCARE-CARD) is a registry of hospitalized patients with worsening CHF at 164 hospitals throughout the country between January 2004 and June 2005 (Tsutsui et al 2006). Death and hospital admission of the patients were followed through 2006 with the mean follow-up period of at least 1 year. Results of this study will appear in the near future. The Japanese Cardiac Registry of

Table 1 Multicenter prospective cohort study for patients with chronic heart failure in Japan

Study [Reference]	Study population	Age, years (Mean)	Total enrollment	Heart failure stage/NYHA	Study start Expected completion	Mean follow-up	1-year mortality	Status
CHART-1 Study [Shiba 2004]	Chronic heart failure outpatients/ hospitalized pts.	≥18 (68)	1278	(B) C-D I-IV		3.5 years	7.3%	Published
JCARE-CARD [Tsutsui 2006]	Hospitalized patients with heart failure	≥15	2676	C-D		At least one year		Completed
JCARE-GENERAL [Tsutsui 2007]	Outpatients with heart failure	≥15 (74)	2685	C-D		One year	6.3%	Published
CHART-2 Study	Chronic heart failure High risk for heart failure outpatients/ hospitalized pts.	≥20	10000 (expected)	B-D I-IV	Oct 2006 Sep 2011			Recruiting

Data are retrieved from published papers or the UMIN Clinical Trials Registry (http://www.umin.ac.jp/ctr/index-j.htm)/ClinicalTrials.gov (http://clinicaltrials.gov/).
Abbreviations: NYHA, New York Heart Association; pts, patients.

Heart Failure in General Practice (JCARE-GENERAL) is a registry of outpatients with CHF managed by cardiologists in hospitals and primary care physicians in general practice (Tsutsui et al 2007). Baseline data of totally 2,685 patients were collected during November 2004 and follow-up data were collected for 1 year after the enrolment. During the mean follow-up period of 427 days, the crude mortality rate was 6.7% in patients managed by cardiologists and 5.9% in those managed by general physicians. The Chronic Heart Failure Analysis and Registry in the Tohoku District (CHART)-2 study is currently the largest prospective and hospital-based cohort study with patients with CHF in Japan. This study was designed to investigate the characteristics and prognosis of a total of 10,000 patients with symptomatic CHF (Stage C/D in the ACC/AHA classification) and those with structural heart disease but without signs or symptoms of CHF (Stage-B in the AHA/ACC classification) (Hunt et al 2001). This study will elucidate the incidence and prognostic impact of metabolic syndrome in those patients, especially on the development of the first symptomatic CHF. The CHART-2 study was started in October 2006 and will be completed in September 2011.

The CHART-1 Study

Risk stratification is the first line strategy to improve the prognosis and quality of life of patients with CHF. A number of factors have been found to correlate with the mortality of patients with CHF (Rector et al 1994; Deedwania 2003; Bettencourt et al 2000). The CHART-1 study was started to register patients with stable CHF in February 2000 to clarify the characteristics and prognosis and to seek for prognostic factors in Japanese CHF patients (Shiba et al 2004, 2005). Patients were enrolled when at least one of the following criteria was met: (1) left ventricular ejection fraction (LVEF) <50%, (2) left ventricular end-diastolic dimension >55 mm, or (3) at least one episode of congestive heart failure. Patients less than 18 years old or those with clinically unstable conditions were excluded. Baseline data, including laboratory findings, results of echocardiography, and medical treatments for CHF, were recorded and annual surveillance was performed until the end of 2005.

Characteristics and prognosis of patients with CHF in Japan.

A total of 1,278 patients were enrolled in the CHART-1 cohort. The mean age of the study population was 68.3 years, and male accounted for 66% of the total study population. The prevalence of diabetes mellitus and hypertension was 19% and 47%, respectively. Other baseline characteristics of patients are shown in Table 2. Ischemic etiology accounted for only 25% and the percentage of patients older than 65 years was 66%. Patients with preserved systolic function (defined as LVEF >50%) accounted for 45% of the total population. During the mean follow-up period of 3.5 years, all-cause mortality rate at 1-, 2-, and 3-year was 7%, 16%, and 22%, respectively (Figure 2). Multivariate Cox analysis showed that several covariates, such as age, diabetes mellitus, ventricular tachycardia, serum level of B-type natriuretic peptide (BNP), rural residence, and NYHA functional class, were significantly associated with all-cause mortality (Shiba et al 2004). Figure 3 shows the Kaplan-Meier analyses of freedom from all-cause mortality in patients stratified by serum level of BNP or LVEF. Patients with higher BNP concentration had a significantly poorer prognosis (Watanabe et al 2005), however, the prognostic impact was not significantly different between patients with 200–500 pg/mL of BNP level and those with >500 pg/mL (Figure 3A). The all-cause mortality of patients with preserved systolic function (LVEF > 50%) was not significantly different than that of patients with

Table 2 Baseline characteristics of the Japanese patients in the CHART-1 study

No. of patients	1,278
Follow-up period (years)	3.5 ± 1.7
Age (years)	68.3 ± 13.4
≤39	3.7%
40–64	30.2%
65–74	32.8%
≥75	33.3%
Male (%)	66.0%
NYHA	
I	19.7%
II	63.0%
III	16.5%
IV	0.8%
Underlying disease	
Coronary artery disease	25.4%
Valvular heart disease	26.4%
Left ventricular hypertrophy	14.0%
Non-ischemic cardiomyopathy	28.6%
Other	5.6%
Left ventricular ejection fraction (%)	51.1 ± 15.9
<30%	11.7%
30–50%	43.7%
>50%	44.6%
Hypertension	47.4%
Diabetes	18.9%
Dyslipidemia	16.7%
Atrial fibrillation	41.8%
Ventricular tachycardia	20.1%
History of heart failure admission	23.4%

Abbreviations: NYHA, New York Heart Association.

moderately decreased LVEF (30%–50%). However the prognosis of those with severely low LVEF (<30%) was the lowest with frequent episodes of sudden cardiac death (Figure 3B). The 3-year incidence of sudden death was higher in patients with LVEF <30% than those with LVEF ≥30% (15% vs 4%, respectively, $p < 0.001$). Primary prevention of sudden cardiac death with an implantable cardioverter defibrillator in those patients should be recommended when they meet the criteria in the authorized guidelines (Watanabe et al 2006). Recently, anemia has been emphasized as an important prognostic predictor in patients with CHF (Ezekowitz et al 2003). Our data also showed that anemia was significantly associated with all-cause mortality, cardiac-cause mortality, and sudden death in patients with diastolic CHF (Tada et al 2007), as well as in those with systolic CHF, as reported by other researchers (O'Meara et al 2006).

Treatment of patients with CHF in Japan

Treatments with angiotensin converting enzyme inhibitors (ACEI), angiotensin II receptor blockers (ARB), or β-blockers are recommended to improve prognosis and quality of life for patients with CHF (Hunt et al 2001). However it has previously been reported that such evidence-based treatments might not be sufficiently used in patients who should have had benefits of such medications (Masoudi et al 2003). The

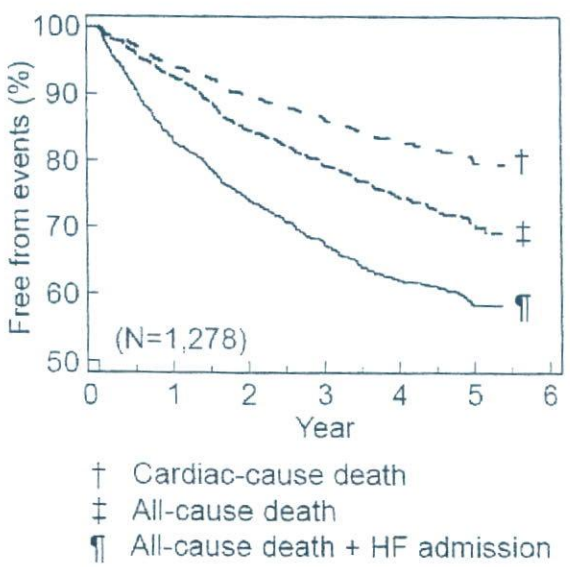


Figure 2 Prognosis of the Japanese patients with CHF in the CHART-1 study. Copyright © 2004. Reproduced with permission from Shiba N, Watanabe J, Shinozaki T, et al. 2004. Analysis of chronic heart failure registry in the Tohoku district: third year follow-up. *Circ J*. 68:427–34.
Abbreviations: HF, heart failure.

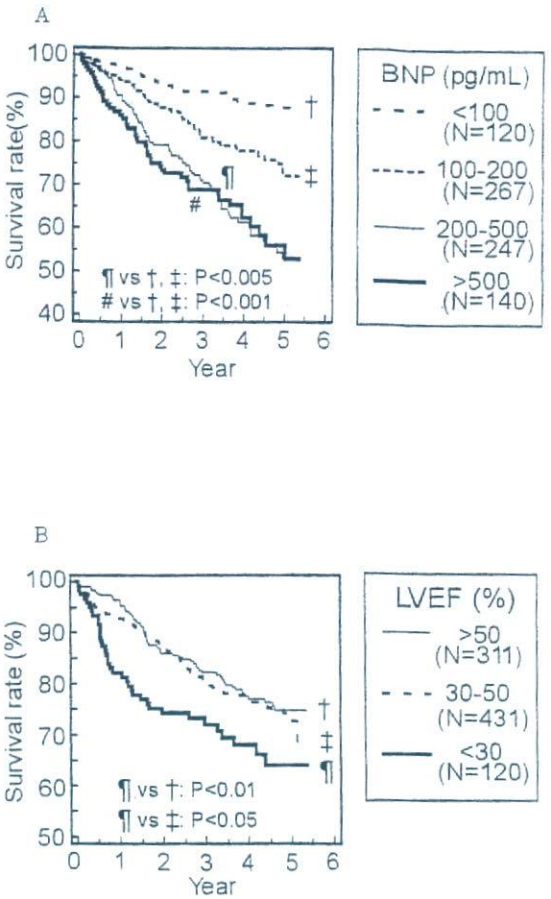


Figure 3 Kaplan-Meier curves of freedom from all-cause death stratified by (A) BNP and (B) LVEF in the CHART-1 study.
Abbreviations: BNP, B-type natriuretic peptide; LVEF, left ventricular ejection fraction.

overall usage rate of ACEI/ARB or β-blocker in patients enrolled in the CHART-1 study was 70% and 28%, respectively (Figure 4). The penetration rate of these medications was relatively lower in female patients, elderly patients, and those with valvular heart disease or preserved LVEF, and this trend was more evident for the treatment with β-blocker than ACEI/ARB (Figure 4). These results suggest that future clinical trials are still necessary for such minorities who have not usually been enrolled in major randomized treatment trials for CHF.

Clinical outcomes of Japanese patients with CHF

Figure 5 showed survival curves of placebo groups in randomized treatment trials for CHF performed in Western countries, superimposed with the result obtained in our CHART-1 study with Japanese CHF patients. One-year all-cause mortality of patients with mild-moderate CHF (NYHA

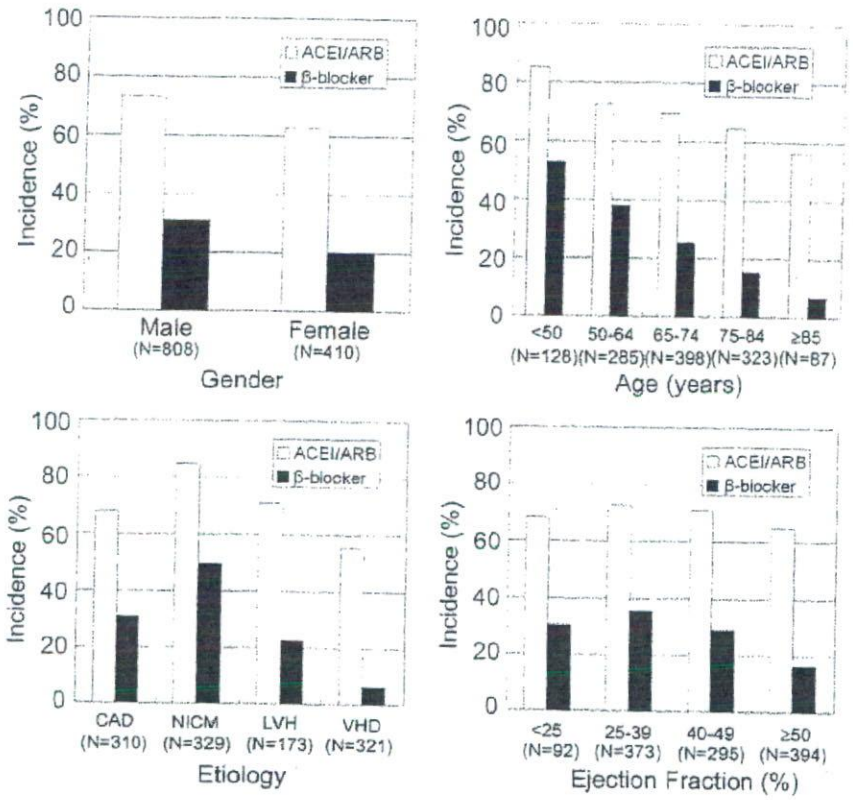


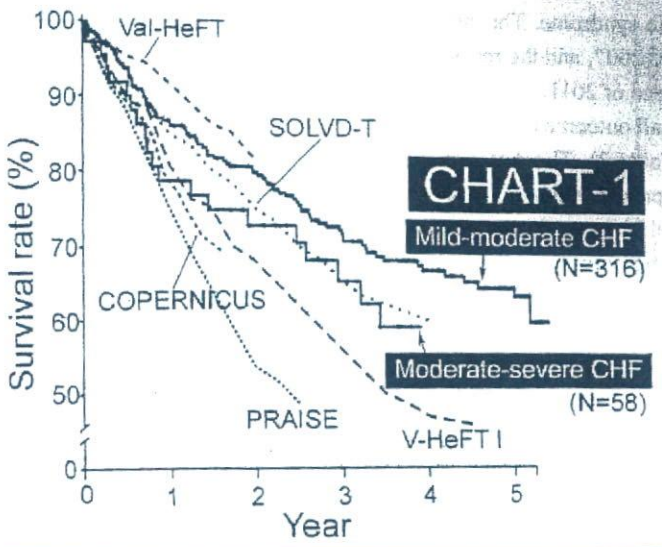
Figure 4 Prevalence of the use of renin-angiotensin inhibitors and β-blockers in the CHART-1 study. Copyright © 2007. Reproduced with permission from Shiba N, Takahashi J, Matsuki M. 2007. The CHART Study (Japanese). *Naika*, 99:410–14.
Abbreviations: ACEI, angiotensin-converting-enzyme inhibitor; ARB, angiotensin II receptor blocker; CAD, coronary artery disease; NICM, non-ischemic cardiomyopathy; LVH, left ventricular hypertrophy; VHD, valvular heart disease.

II–IV and LVEF ≤40%) or moderate-severe CHF (NYHA III–IV and LVEF ≤35%) was 13% and 21%, respectively. Importantly, as is evident in Figure 5, the prognosis of Japanese patients with CHF was equally poor compared with Western CHF patients. Since the Japanese society is aging rapidly, a sharp increase in the number of CHF patients will be inevitable in the near future in Japan, as CHF is a disease of the elderly. Figure 6 shows the event rate in CHF patients based on age at the entry, demonstrating that elderly Japanese patients with CHF had an increased incidence of cardiac death and a combination of cardiac death and admission due to congestive CHF. This is because elderly CHF patients have a higher rate of combined risk factors, such as anemia, chronic kidney disease, hypertension, and atrial fibrillation. Appropriate prevention strategies against the development and progression of CHF should be undertaken in Japan.

Major CHF treatment trials in Japan

There are 2 published randomized treatment trials for CHF patients in Japan (Table 3). The Multicenter Carvedilol Heart Failure Dose Assessment (MUCHA) trial enrolled 174 patients with mild to moderate CHF to seek for the efficacy and optimum dose of carvedilol, with 3 treatment arms, including placebo, 5 and 20 mg of the β-blocker in daily dose (Hori et al 2004). During the 24–48 weeks of the treatment period, carvedilol achieved dose-related improvement of the rate of death or cardiovascular hospitalization to 25%, 9%, and 5% in the placebo, 5 mg, and 20 mg group, respectively ($p = 0.002$). The Assessment of Response to Candesartan in Heart Failure in Japan (ARCH-J) study investigated the efficacy of candesartan (8 mg once daily) in comparison with the placebo in 305 patients with symptomatic CHF (Matsumori et al 2003). During the 6-month follow-up period, fatal cardiovascular events occurred in 2 patients in each treatment group and the incidence of progression of CHF was 7% and 22% in the candesartan and the placebo group, respectively ($p = 0.0004$).

We have recently initiated a large outcome study with olmesartan in CHF patients, termed The Supplemental Benefit of Angiotensin II Receptor Blocker in Hypertensive



	Mild-moderate CHF	Moderate-severe CHF
N	316	58
NYHA	II-IV	III-IV
Ejection Fraction (Mean)	≤40% (31.1±6.6%)	≤35% (25.8±5.8%)
Age	66.3±13.3 years	67.2±12.9 years
Male	69.4%	64.4%
Coronary Artery Disease	35.3%	32.2%

Figure 5 Comparison of the prognosis of patients with CHF between Western clinical trials and the CHART-1 study. Copyright © 2007. Reproduced with permission from Shiba N, Takahashi J, Matsuki M. 2007. The CHART Study (Japanese). *Naika*, 99:410–14.
Abbreviations: HYHA, New York Heart Association.

Patients with Stable Heart Failure Using Olmesartan (SUPPORT trial), which is currently the largest outcome study in Japan (Table 3). The purpose of our SUPPORT trial is to examine whether an ARB, olmesartan, in addition to conventional treatment, reduces the mortality and morbidity of hypertensive patients with stable CHF. The primary endpoint is a combined event of all-cause death, nonfatal acute myocardial infarction, nonfatal stroke, and hospital admission due to congestive heart failure. We also aim to evaluate the beneficial effect of olmesartan on the

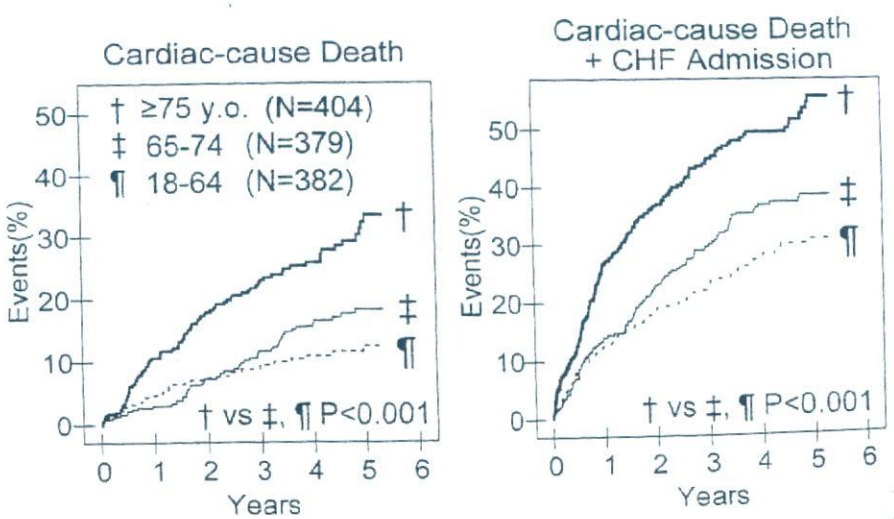


Figure 6 Prognosis of elderly patients with CHF in the CHART-1 study. Copyright © 2007. Reproduced with permission from Shiba N, Takahashi J, Matsuki M. 2007. The CHART Study (Japanese). *Naika*, 99:410–14.
Abbreviations: CHF, congestive heart failure.

progression of metabolic syndrome. The entry of patients was started in November 2007, and the results of the study will be obtained by the end of 2011.

There are 5 other small outcome trials that are currently in progress in Japan (Table 3). The Assessment of Beta-Blocker Treatment in Japanese Patients with Chronic Heart Failure (J-CHF) and the Japanese Diastolic Heart Failure Study (J-DHF) are investigating the effects of carvedilol in patients with systolic CHF and those with diastolic CHF, respectively. Another objective of J-CHF is to determine the optimum dose of carvedilol and to elucidate the differences in clinical characteristics between responders and nonresponders to the β-blocker. The Pitavastatin Heart Failure Study (PEARL study) is designed to evaluate the efficacy of pitavastatin for CHF with mild hypercholesterolemia. The Japanese Multicenter Evaluation of Long- versus short-acting Diuretics in Congestive Heart Failure (J-MELODIC) is designed to compare the effects of furosemide and azosemide in patients with CHF and to test the hypothesis that long-acting diuretics are superior to short-acting ones in those patients. The Japanese Heart Failure Outpatients Disease Management and Cardiac Evaluation Study (J-HOMECARE) was designed to evaluate the benefit of disease management program for prognosis, psychological status and quality of life of patients with CHF.

There are 2 large trials that have investigated the role of valsartan in Japanese patients with cardiovascular disease including CHF (Table 4). The Japanese Investigation of Kinetic Evaluation in Hypertensive Event and Remodeling Treatment (JIKEI-HEART) Study was designed to investigate whether concomitant treatment with valsartan in addition to conventional treatment improves the prognosis of Japanese patients with hypertension, ischemic heart disease, or congestive heart failure. The results of this study have recently been published (Mochizuki et al 2007). After a median follow-up period of 3.1 years, the incidences of stroke, transient ischemic attack, angina pectoris, and CHF were significantly lower in patients treated with valsartan compared with those with the conventional treatment. However, the benefit of the add-on valsartan treatment in a sub-population with CHF, which accounted for 11% of the total population, has not been published yet. The Add-on Effects of Valsartan on Morbi-Mortality (KYOTO-HEART) study was designed to assess the add-on effect of valsartan on the conventional treatment in terms of the morbidity and mortality in Japanese hypertensive patients with high risks of cardiovascular diseases including CHF (Table 4).

Many of the randomized clinical trials performed in Japan utilize the prospective randomized open blinded endpoint (PROBE) design, as an alternative to the randomized double-blind placebo-controlled design (Tables 3 and 4). This is mainly because the PROBE study tends to be more cost effective and its open-labeled medication may minimize ethical considerations (Hansson et al 1992).

Racial difference in morbidity and mortality due to cardiovascular diseases

Several researchers have suggested that cardiovascular risk factors have different prognostic impact among different populations. The Seven Countries Study Research Group showed a substantial heterogeneity among populations in terms of the death rate due to coronary artery disease, even at a similar level of blood pressure (Van den Hoogen et al 2000). The proportion of deaths attributable to cardiovascular disease has also been reported to vary among different cohorts even at the similar serum cholesterol level. The long-term follow-up for 25 years for 12,763 men in 16 cohorts in Europe, the United States, and Japan showed that the risk factors of cardiovascular disease, such as insufficient physical activity and high serum cholesterol level, were not significantly associated with all-cause death in several countries including Japan (Menotti et al 2001). Since these differences cannot be explained by other baseline characteristics, smoking habits, or genetic difference, environmental and/or behavioral factors may play an important role in the development of cardiovascular diseases. The Ni-Hon-San Study, which compared cardiovascular disease rates and risk factors in Japanese men living in Japan, Hawaii, and California, showed that the mortality rate due to coronary artery disease was lowest in Japanese men living in Japan, whereas it was highest in those living in California (Benfante 1992). Racial differences may also influence the effect of medical treatment for CHF. Several studies demonstrated that genetic polymorphisms and/or a difference in β1-receptor sensitivity, which are frequently observed in the Japanese population, might change the pharmacokinetics or the clinical effect of medical drugs, such as ACEI and β-blockers (Kubota et al 2000; Xie et al 2001; Ranade et al 2002).

Future direction for the management of CHF in Japan

CHF is a slowly progressive disease from stage A to stage D unless appropriately treated as described in the ACC/AHA guidelines (Hunt et al 2001). The strategy to manage CHF has been changing recently from treatment to prevention

Table 3 Multicenter randomized clinlical trials for patients with chronic heart failure in Japan

Trial [Reference]	Design	Age, years (Mean)	Comparison	Total enrollment	HF stage NYHA	Study start Expected completion	Mean follow-up	Primary outcome *Published main outcome	Status
MUCHA Trial [Hori 2004]	RDBPC	20–79 (60)	Carvedilol 5 mg Carvedilol 20 mg Placebo	174	C-D II-III		24–48 weeks	Dose-related improvement of HF with carvedilol*	Published
ARCH-J [Matsumori 2003]	RDBPC	≥20 (64)	Candesartan Placebo	305	C-D II-III		6 months	Slowing progression of HF with candesartan*	Published
J-CHF	PROBE	20–79	Carvedilol; 2.5 mg, 5 mg, or 20 mg	480 (exp.)	C-D II-III	Jul 2003 Dec 2009		Cardiovascular mortality Hospitalization for HF	Recruiting
J-DHF	PROBE	≥20	Carvedilol Control	800 (exp.)	C-D	May 2004 Mar 2011		Cardiovascular mortality Hospitalization for HF	Recruiting
SUPPORT Trial	PROBE	20–79	Olmesartan Standard therapy	1000 (exp.)	C-D II-IV	Nov 2006 Sep 2011		Combination of mortality/AMI/Stroke/admission due to HF	Recruiting
PEARL Study	RO	20–79	Pitavastatin Control	500 (exp.)	C-D II-III	Jul 2006 Jul 2010		Cardiac mortality Hospitalization for HF	Recruiting
J-MELODIC	PROBE	≥20	Furosemide Azosemide	300 (exp.)	C-D II-III	Jun 2006 Mar 2010		Cardiovascular mortality Hospitalization for HF	Recruiting
J-HOMECARE	RO	N/A	Education/counseling Control	300 (exp.)	C-D	Dec 2006 Dec 2008		Mortality Readmission for HF	Recruiting

Data are retrieved from published papers or the UMIN Clinical Trials Registry (http://www.umin.ac.jp/ctr/index-j.htm)/ClinicalTrials.gov (http://clinicaltrials.gov/).
Abbreviations: RDBPC, randomized double-blind placebo-controlled design; NYHA, New York Heart Association; HF, heart failure; PROBE, prospective randomized open blinded end-point design; exp., expected; AMI, acute myocardial infarction, RO; randomized open-label design.

Table 4 Multicenter randomized clinlical trials for patients with cardiovascular risks including CHF in Japan

Trial [Reference]	Design	Study population	Age, years (Mean)	Comparison	Total enrollment	Study start Expected completion	Duration	Primary outcome *Published main outcome	Status
JIKEI-Heart Study [Mochizuki 2007]	PROBE	Hypertension coronary disease heart failure	20–79 (65)	Valsartan Standard therapy	3081		3.1 years	Prevention of cardiovascular events with additional valsartan*	Published
KYOTO-HEART Study	PROBE	Hypertension with one or more risk factors including heart failure	20–79	Valsartan Standard therapy	3000 (exp.)	Jan 2004 Oct 2007		Combination of stroke/AMI/CHF etc.	Recruiting

Data are retrieved from published papers or the UMIN Clinical Trials Registry (http://www.umin.ac.jp/ctr/index-j.htm) / ClinicalTrials.gov (http://clinicaltrials.gov/).
Abbreviations: PROBE, prospective randomized open blinded end-point design; exp., expected; AMI, acute myocardial infarction; CHF, congestive heart failure.

(Bansal et al 2006). Japanese CHF patients have several different profiles compared with Western CHF patients as follows; (*a*) the prevalence of CHF of ischemic origin is lower, (*b*) the percentage of elderly population is remarkably high, and (*c*) the penetration rate of evidence-based medicine, such as ACEI/ARB or β-blockers, is not sufficiently high yet. The current situation of the management of CHF in Japan is probably caused by the fact that the number of randomized treatment trials for Japanese patients is not enough yet. Given the expected future increase in Japanese patients with CHF, effective prevention strategy is necessary. Our on-going CHART-2 and SUPPORT studies will enable us to obtain effective strategies to improve the management of CHF in Japan.

Conclusions

The prevalence of CHF will rapidly increase in the next decades in many industrialized countries, including Japan. Large cohort studies with CHF patients are useful for risk stratification and determination of preventive measures for the disorder. Large-scale, randomized treatment trials also are needed, especially in Japan, in order to obtain further evidence to improve the management of patients with CHF.

Acknowledgments

Active investigators of the CHART studies were described in the paper previously published (Shiba et al 2004) and at the website of the Tohoku Heart Failure Association (see http://tohoku.cardiovascular-medicine.jp). The CHART-1 study was supported by the research grants from the Ministry of Health, Labor and Welfare and Gonryo Medical Foundation. We are grateful for the assistance of research nurses who are working at the Tohoku Heart Failure Association; Mika Matsuki, Shizuka Osaki, Kiriko Yukishita, Yuuko Kidoguchi, Miho Hotta, Haruka Kohno, and Keiko Nishiura.

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特別講演

心臓リハビリテーションの有用性を考える
—血管生物学の立場から—

東北大学大学院医学系研究科 循環器病態学分野　下川宏明（しもかわひろあき）

〔心臓リハビリテーション（JJCR） 13（1）：13-17，2008〕

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はじめに

心臓リハビリテーションは，従来，急性心筋梗塞後の心機能を含む身体機能回復を目指した運動療法として発達してきたが，最近では，その包括する内容や対象とする疾患も多岐にわたるようになってきた．すなわち，包括する内容としては，従来の運動による身体的機能回復に加えて，生活習慣病の是正・精神的支援・復職指導・疾患に対する啓蒙活動が加わり，対象とする疾患も，従来の急性心筋梗塞から，最近では，狭心症・慢性心不全・肺高血圧症・術後患者までその対象が拡大されてきている．

心臓リハビリテーションの目的は，（1）身体機能の向上による生活の質（QOL）の改善と，（2）生命予後の改善（二次予防）の二つがある．その効用も多岐に及び，①体重や血圧の是正，②血管機能（内皮・平滑筋）の改善，③代謝因子（インスリン感受性・脂質等）の改善，④動脈硬化の進展抑制，⑤自律神経系の正常化，が挙げられる．

本稿では，筆者の専門（循環器内科学，血管生物学）の立場から，心臓リハビリテーションの有用性について，特に，血管機能に及ぼす効果について述べる．また，心臓リハビリテーションの補助療法としても効果が期待できる低出力体外衝撃波を用いた心臓の血管新生療法についても紹介する．

心臓リハビリテーションと血管機能

虚血性心臓病の治療には，現時点では大きく分けて，①薬物療法，②冠動脈インターベンション，③冠動脈バイパス術，の3つがある．冠動脈インターベンションや冠動脈バイパス術は，冠動脈狭窄に起因する心筋虚血を改善することにより，確かに患者のQOLを改善するが，特に冠動脈インターベンションの場合は，その他の部位の冠動脈の血管機能を改善はしない．急性心筋梗塞の大部分は非有意冠狭窄病変の破綻や潰瘍形成により閉塞性冠血栓が生じることにより発生する．したがって，いつどの冠動脈部位に生じるかわからない急性心筋梗塞を予防するには，日頃から，生活習慣の改善や薬物療法により，血管機能（内皮・平滑筋）を太い冠動脈から末梢の微小循環まで，できるかぎり正常に保つという視点が極めて重要である（図1）．この意味で，心臓リハビリテーションは，薬物を用いずに，血管機能を改善しうる，いわば第4の治療法とみなすこともできる（図1）．

1．血管由来弛緩因子

定期的な運動が慢性心不全患者の内皮機能を改善させ，その改善度は最大酸素摂取量の改善度と相関することが知られている[1,2]．「内皮機能」にも多種類あるが，内皮由来弛緩因子（endothelium-derived relaxing factors；EDRFs）による血管弛緩反応で評価することが多い．このEDRFsには，主として，プロスタサイクリン（prostaglandin I_2；PGI_2），一酸化窒素（nitric oxide；NO），内皮由来過分極因子（endothelium-derived hyperpolarizing factor；EDHF）の3種類が存在することが知られている[3]．我々は一連の研究により，NOは太い血管のトーヌス調節に重要な役割を果たしているが，血管径が細くなるほどEDHFの関与が大きくなることを示した（図2）[3]．

EDHFの本体は長年不明のままであり論争が続いて

Key words：血管内皮，血管平滑筋，内皮由来弛緩因子，運動，ずり応力

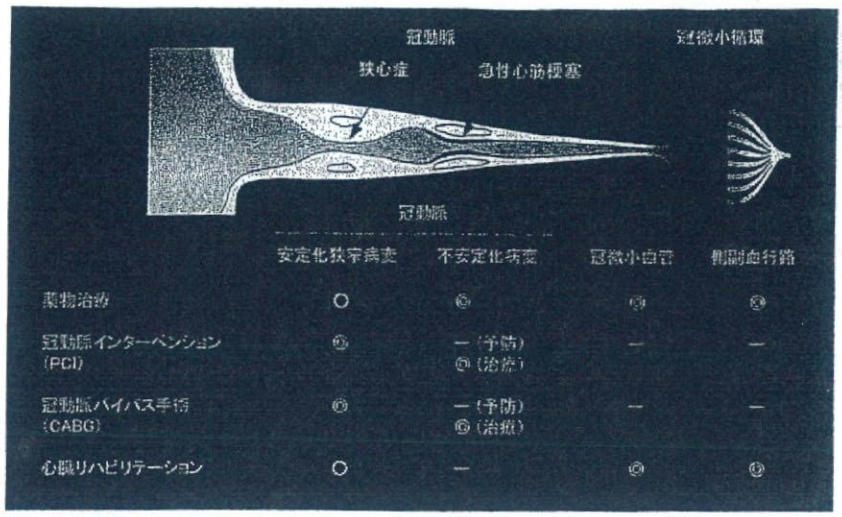

図1　虚血性心疾患の病態と治療法

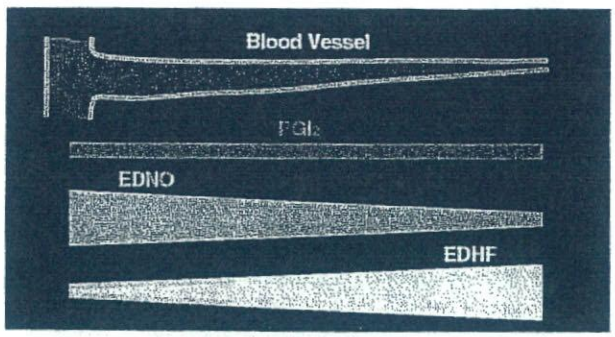

図2　内皮由来弛緩因子の血管径による役割の違い

いるが，実際に複数のEDHFが存在している可能性がある．我々は，EDHFとNOとは異なる物質であるが，動脈硬化危険因子による障害のされ方や治療による改善のされ方に共通点が多いことに着目し，EDHFの本体の少なくとも一つが内皮型NO合成酵素（eNOS）から生理的濃度で産生される過酸化水素（H_2O_2）であることを，マウス[4]，次いでブタ[5]およびヒト[6]において同定した．続いて，eNOS由来のsuperoxide anionsが内皮Cu, Zn-SODにより$EDHF/H_2O_2$に変換されていることを，マウス[7]およびヒト[8]において明らかにした（図3）．続いて，eNOS欠損マウスでも完全にはEDHF反応が消失しないところから，他の2つのNO合成酵素（神経型nNOS，誘導型iNOS）の代償的関与を疑い，これを検討する目的で，3つのNO合成酵素を完全に欠損するマウスを作製した[9]．このNOSs完全欠損マウスは胎生致死ではなかったが，生殖率や寿命が大きく低下していた[9]．このマウスでEDHF反応を検討したところ，同反応が完全に消失していた[10]．このことから，内皮のNOSs系は，太い動脈ではNO産生系として働き，細い動脈では$EDHF/H_2O_2$産生系として働いていることが明らかになった（図4）．心臓リハビリテーションの冠循環への効用を考える場合，こうした血管径による差異も考慮する必要がある．

我々は，一連の研究により，$EDHF/H_2O_2$が冠循環において自動調節能（autoregulation）[11]，虚血再灌流障害の防止[12]，代謝性冠拡張[13]に重要な役割を果たしていることを明らかにした．

2．心臓リハビリテーションと血管内皮機能

内皮機能が心血管イベントの独立した重要な危険因子であることが，現在広く知られている[14]．薬物および非薬物治療の重要な目標の一つが，内皮機能の改善であるといっても過言ではない．長期の運動はヒト内胸動脈においてeNOSを活性化させ，その機序としてAktリン酸化の亢進が関与していることが示されている[15]．また，慢性心不全患者の骨格筋において，長期の運動がCu,Zn-SODの発現を亢進させることも示されている[16]．このような知見は，心臓リハビリテーションが，冠動脈内皮機能としてのNOによる反応も$EDHF/H_2O_2$による反応も改善させていることを示唆する．実際に，長期の運動により，マウスではeNOS発現増加を介して内因性のH_2O_2産生が亢進することが示され，冠動脈狭窄病変を有したブタ冠循環においては，狭窄末梢の微小冠動脈の内皮機能がH_2O_2依存性に改善することが最近示された[17]．したがって，心臓リハビリテーションは，低下した冠動脈内皮機能を，太い冠動脈ではNO依存性に，微小冠動脈ではH_2O_2依存性に改善させる可能性がある．この点に関しては，今後ヒトでの検討が必要

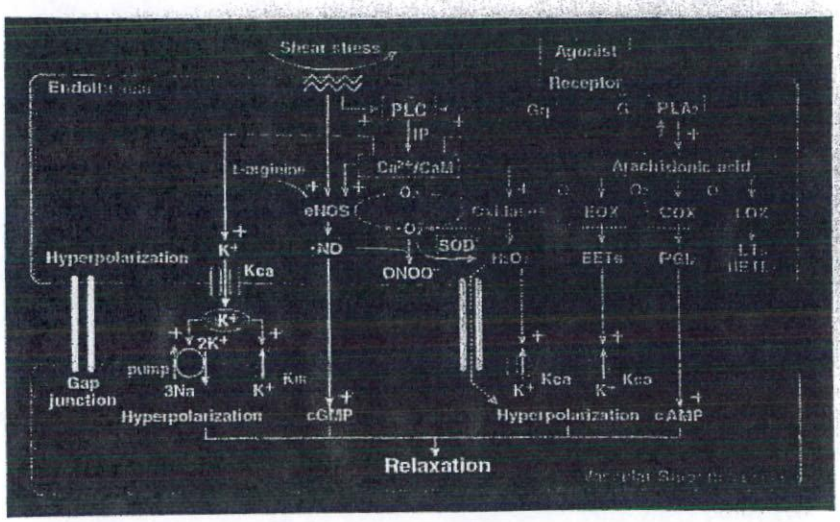

図3　EDHF/H_2O_2説に基づく内皮由来弛緩因子の新しい概念
（文献3：Shimokawa H et al より引用）

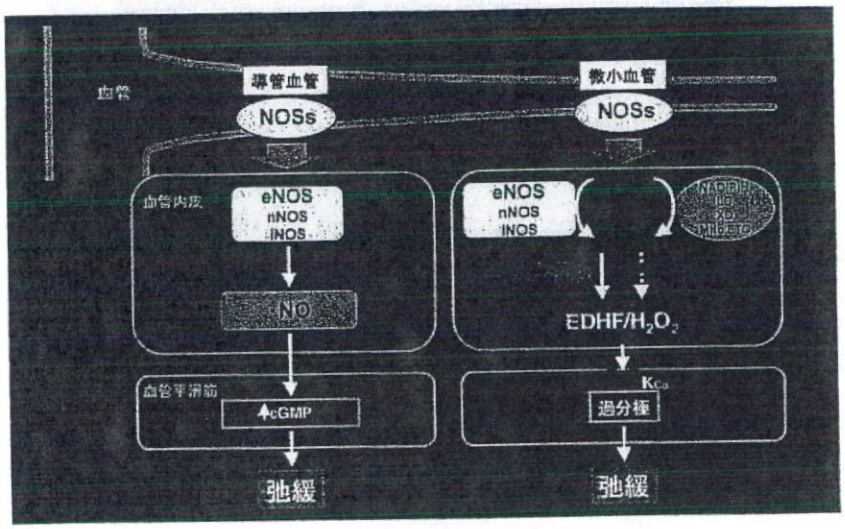

図4　血管径による内皮NO合成酵素系の機能の違い

である（図5）.

3．心臓リハビリテーションと血管平滑筋機能

血管機能を考える場合，血管平滑筋機能は血管内皮機能と同様に極めて重要である．我々は，一連の基礎的・臨床的研究により，日本人に多い冠動脈攣縮の病態の主体は冠動脈平滑筋の過収縮であり，その分子機構として，Rho-kinaseの活性化が主因になっていることを明らかにした[18]．Rho-kinaseは低分子量G蛋白Rhoの標的分子の一つであり，これが活性化されると，ミオシン脱リン酸化酵素の抑制を介してミオシン軽鎖のリン酸化が亢進し，血管平滑筋の過収縮が惹起される．我々はまた，Rho-kinaseが複数の動脈硬化促進分子を活性化させて動脈硬化を促進すること[19]，その機序の一つとしてeNOSの不活化を惹起することを示した[20]．これらの知見は，ヒトの冠攣縮部位では，血管平滑筋の過収縮に加えて，種々の程度の内皮機能障害がみられる臨床的観察事実をよく説明する．ずり応力がRho/Rho-kinase経路を抑制することが知られており[21]，心臓リハビリテーションがこの経路の抑制を介して，様々な有益な効果を惹起する可能性がある（図6）.

低出力体外衝撃波を用いた重症虚血性心臓病に対する非侵襲性血管新生療法

無症候性心筋虚血を有する患者は，突然死や急性心筋梗塞の発生率が高く予後が悪いことが広く知られている[22]．したがって，心臓リハビリテーションを行う場合，無症候性心筋虚血の有無を事前に精査することは重要であり，また，無症候性心筋虚血の存在が明らかにな

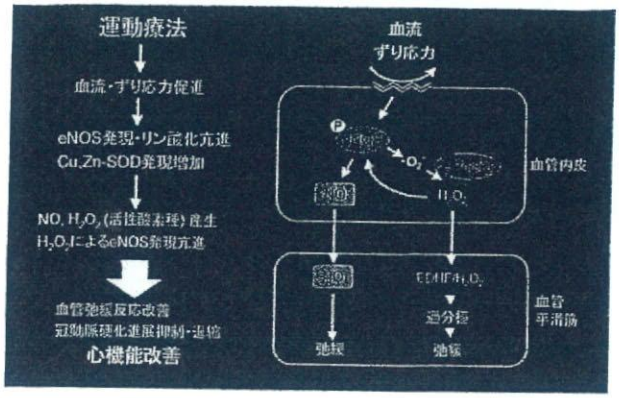

図5　運動療法による内皮機能改善の機序

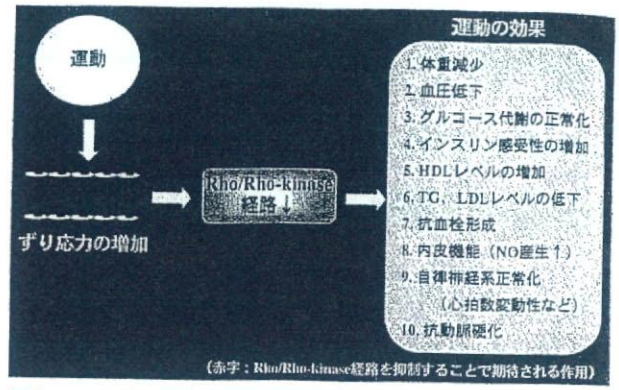

図6　Rho/Rho-kinase 経路抑制を介した運動療法の効果の可能性

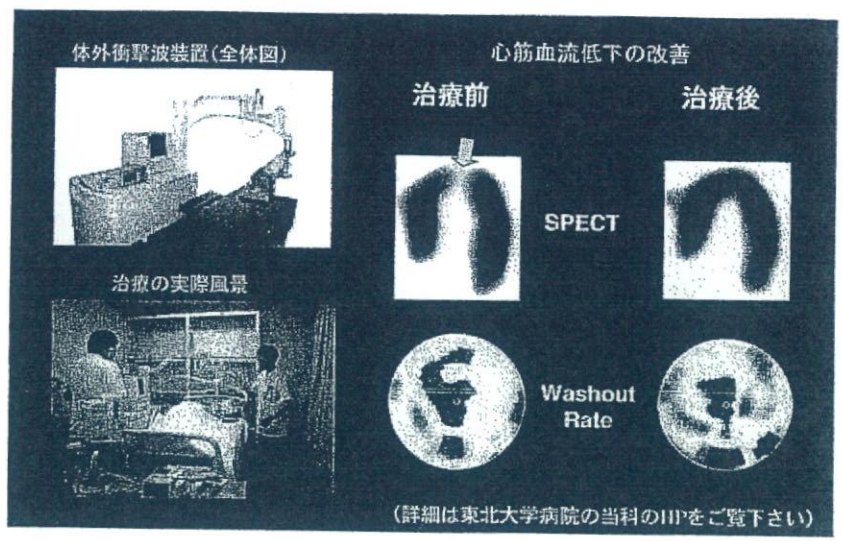

図7　重症虚血性心臓病に対する非侵襲性体外衝撃波療法

れば，それをあらかじめ是正することは重要である．しかし，最近の糖尿病の増加などに伴い，冠動脈インターベンションや冠動脈バイパス手術の適応にならないような重症の虚血性心臓病患者が我が国でも増加してきている．これらの患者に対して，心臓の血管新生を惹起する目的で遺伝子治療や細胞治療が現在先進医療として開発されてきている．

我々は，全く別の発想で，体外から低出力の衝撃波を心筋虚血部位に照射すると，血流や心機能を有意に改善させるほどの血管新生が惹起され，副作用もみられないことを，ヒト由来培養内皮細胞を用いた *in vitro* の研究およびブタの狭心症モデルにおいて確認した[23]．基礎的検討の結果，体外衝撃波の至適レベルは結石破砕治療の10%であること，肺を避けて虚血心筋に照射すれば安全に実施できることを確認した[23]．これを受けて，9名の重症狭心症の患者を対象に第一次の臨床試験を行い，体外衝撃波治療の有効性と安全性を確認した（図7）[24]．現在，この治療法の有効性を検証する目的で，重症狭心症患者を対象としたプラセボ比較二重盲検臨床試験を実施中である．また，動物実験では，本治療が急性心筋梗塞（ブタ）[25]や下肢閉塞性動脈硬化症（ウサギ）にも有効で安全であることを認めている．

本治療法は，冠動脈インターベンションや冠動脈バイパス術が行えないような重症例，あるいはそれらの治療を行っても虚血心筋が残存している症例に対する補助療法としての適応が期待され，心臓リハビリテーションの分野においてもその活用が期待される．

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