Table. Clinical Characteristics and Outcome of the Study Population

	Rural area			P value for trend	Urban area			P value for trend
	1998–2001 (n=2,145)	2002–2005 (n=2,699)	2006–2009 (n=2,807)		1998–2001 (n=1,529)	2002–2005 (n=1,508)	2006–2009 (n=1,682)	
Male								
Age (years)	66.2±12.4*	67.0±12.9*	66.7±12.7	0.373	65.0±12.7	65.2±12.9	65.9±12.9	0.046
Age-adjusted incidence of AMI (/10^5 persons/year)								
All	42.3±3.8*	47.2±3.2	47.3±2.5	0.274	55.1±4.7	49.3±10.9	47.9±4.1	0.163
<45 years old	4.9±0.9	5.8±0.7	6.9±1.2	0.018	5.1±0.7	5.7±0.5	6.0±2.7	0.460
45–64 years old	66.6±6.3*	83.2±5.5	88.9±14.9	0.016	91.2±4.9	85.9±21.0	83.7±8.2	0.402
65–74 years old	170.2±32.9	186.3±39.2	179.3±17.8	0.679	228.2±18.1	208.1±56.3	180.1±15.6	0.065
≥75 years old	253.5±47.0*	261.1±62.9	250.8±33.4	0.937	355.0±48.0	277.8±73.4	308.0±19.7	0.207
Hypertension (%)	46.1	59.5*	60.9	<0.001	48.2	54.3	63.0	<0.001
Diabetes mellitus (%)	27.5	32.9	29.5*	0.265	30.6	31.6	34.1	0.070
Dyslipidemia (%)	22.4*	34.1*	41.4	<0.001	32.2	39.0	42.0	<0.001
Smoking (%)	40.6	42.1	40.6	0.956	44.0	41.8	38.6	0.008
In-hospital mortality (%)	7.6	6.8	7.8	0.832	8.8	5.7	8.7	0.997
Female								
Age (years)	74.1±9.7	76.1±11.1	75.3±11.4	0.017	74.4±10.4	74.6±12.0	75.3±11.4	0.224
Age-adjusted incidence of AMI (/10^5 persons/year)								
All	11.5±2.4*	13.6±1.1	13.2±1.0	0.202	15.1±1.2	11.9±2.0	12.4±2.4	0.077
<45 years old	0.2±0.4	0.4±0.2	0.7±0.5	0.114	0.2±0.2	0.5±0.3	0.5±0.7	0.297
45–64 years old	10.5±4.2	13.7±3.1	18.1±4.1	0.102	10.1±1.6	11.0±2.2	16.1±7.1	0.102
65–74 years old	54.5±1.8*	65.0±8.4	56.4±4.4	0.602	84.5±5.8	55.3±6.5	48.9±9.1	<0.001
≥75 years old	100.8±17.4*	135.7±14.9	120.8±7.9	0.076	165.9±13.9	131.4±19.4	129.8±17.2	0.016
Hypertension (%)	55.8	69.3	67.5	<0.001	60.2	63.5	65.0	0.137
Diabetes mellitus (%)	29.3	36.1	35.1	0.032	32.5	33.2	34.5	0.510
Dyslipidemia (%)	25.8	30.9	38.6	<0.001	31.0	37.1	37.7	0.039
Smoking (%)	8.9	6.6*	10.6	0.163	12.1	13.4	14.1	0.383
In-hospital mortality (%)	12.3	11.1	14.5	0.254	14.4	15.3	14.1	0.892

Values are mean±SD or n (%). *P<0.05 for the difference between rural and urban areas. AMI, acute myocardial infarction. Study population was divided into 2 groups according to the residence: inside (urban area) and outside Sendai City (rural area).

tion form gradually over the last 30 years. Thus, although the incidence of AMI and related data (time of onset, age and sex) are available for the last 30 years, the date on the pre-hospital management, infarction site, coronary risk factors, reperfusion therapies, duration of hospitalization and in-hospital outcome are only available for the last 10–20 years, which were analyzed in the present study.

Data Analysis

In the present study, we have registered a total of 19,921 patients with AMI (male/female 14,290/5,631) over the last 20 years after the municipal merger in 1988. In particular, we have focused on the patients registered between 1998 and 2009 (total, 12,491; male/female, 8,969/3,522), who were divided into 2 groups according to their residences; inside (urban area, n=4,719) and outside Sendai City (rural area, n=7,651), after excluding the patients whose residences were unknown (n=159). We also divided the total observational period of 12 years into the 3 periods: 1998–2001, 2002–2005 and 2006–2009. To calculate the sex- and age-adjusted incidence of AMI (/100,000 person/years), we applied the direct standardization method using the age distribution of the Japanese population from the 2000 census,[5] as the standard population. In addition, in order to clarify the age-specific trend, we categorized the age at AMI onset into the 4 groups: ≤44 (young), 45–64 (middle-aged), 65–74 (old) and ≥75 years old (high-old).[15]

Results are expressed as mean±SD. Linear trends were examined for continuous variables by using analysis of variance (ANOVA) with repeated measures or the Jonckheere-Terpstra trend test as appropriate, and for categorical variables by using the chi-square test for trend. Differences in mean values were examined with a t-test, Mann-Whitney test or chi-square test as appropriate. Multiple logistic regression analysis was used to examine determinants of risk factor prevalence in AMI patients. Variables used for analysis included: sex, age at onset of AMI (per 10 years), study periods (1998–2001, 2002–2005 and 2006–2009), residence (rural vs. urban), and other risk factors. The odds ratios (ORs) and 95% confidence intervals (95%CI) were calculated. A P-value less than 0.05 were considered to be statistically significant. All statistical analyses were performed using the statistical software SPSS version 18 for Windows.

Results

Over the last 20 years, the incidence of AMI (/100,000 persons/year) significantly increased in both the rural and the urban areas in the Miyagi prefecture (2.1- and 1.3-fold, respectively, both P<0.001) (**Figure 1A**). Furthermore, the extent of the increase in AMI incidence was greater in the rural area than in the urban area, finally exceeding that in the urban area after 2000. These changes were accompanied with rapid aging

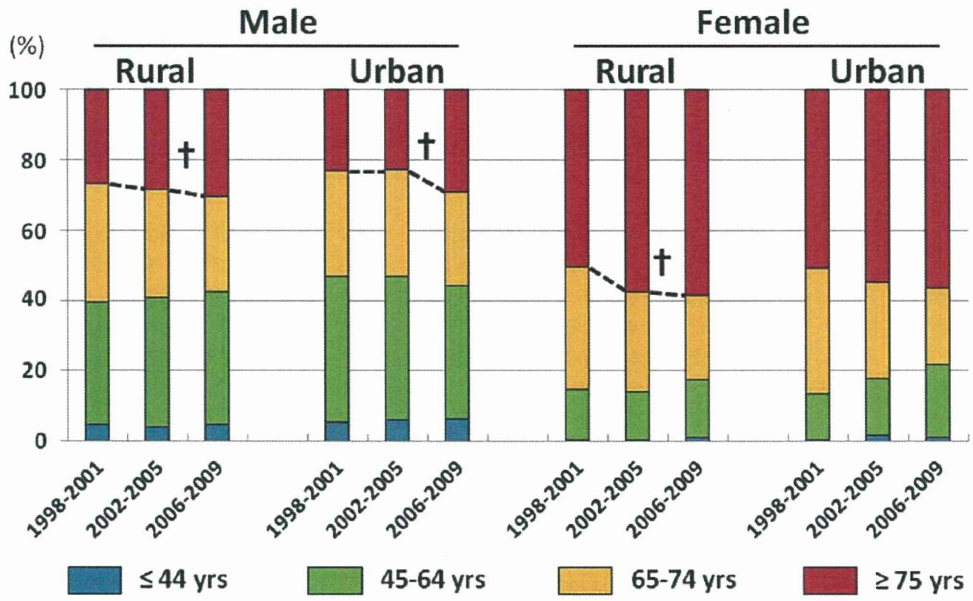

Figure 2. Age-distribution of acute myocardial infarction (AMI) patients. The percentage of high-old patients (≥75 years old) was markedly higher in female patients than in the patients in the rural and urban areas and has been increasing significantly in male patients in both areas and rural female patients. †P<0.05 for linear trend.

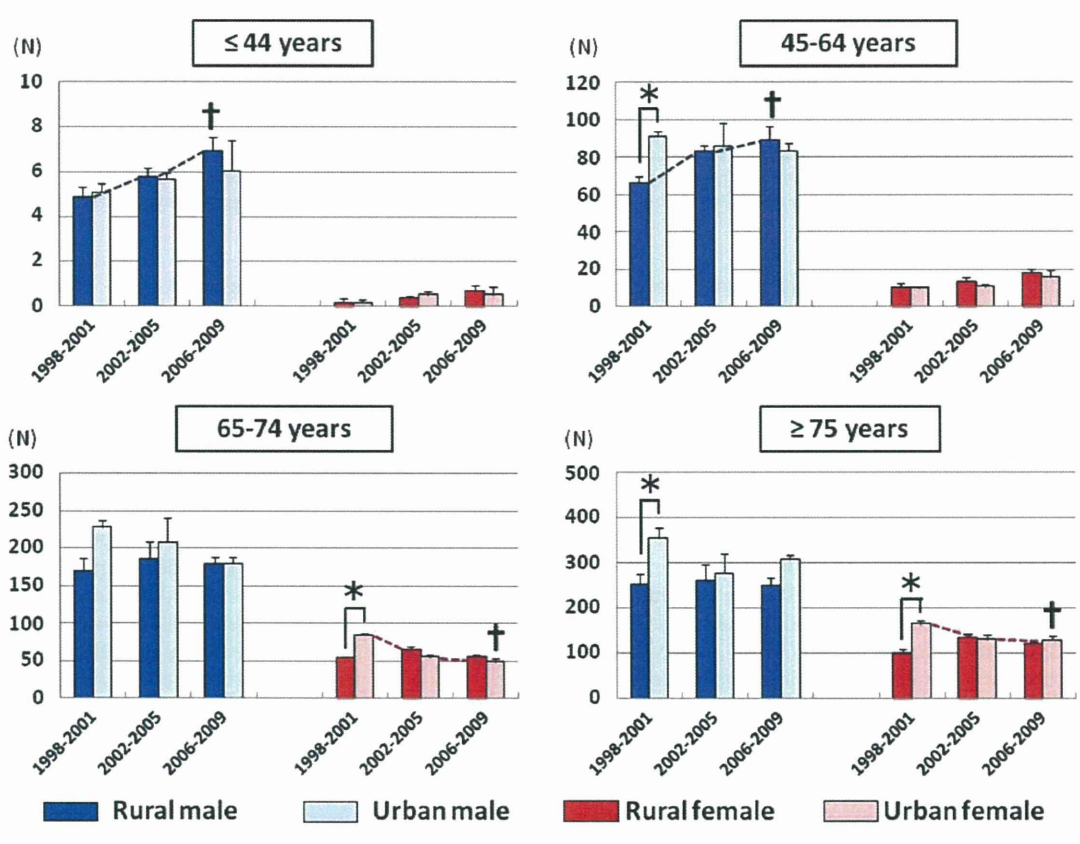

Figure 3. Age-specific incidence of acute myocardial infarction (AMI) (/100,000 persons/year). The significant increase in the age-adjusted incidence of AMI was noted in <44 and 45–64 year old rural male patients, and the significant decrease was noted in 65–74 and >75 year old urban female patients. Values are presented as mean±SE. *P<0.05 for the difference between rural and urban areas. †P<0.05 for linear trend.

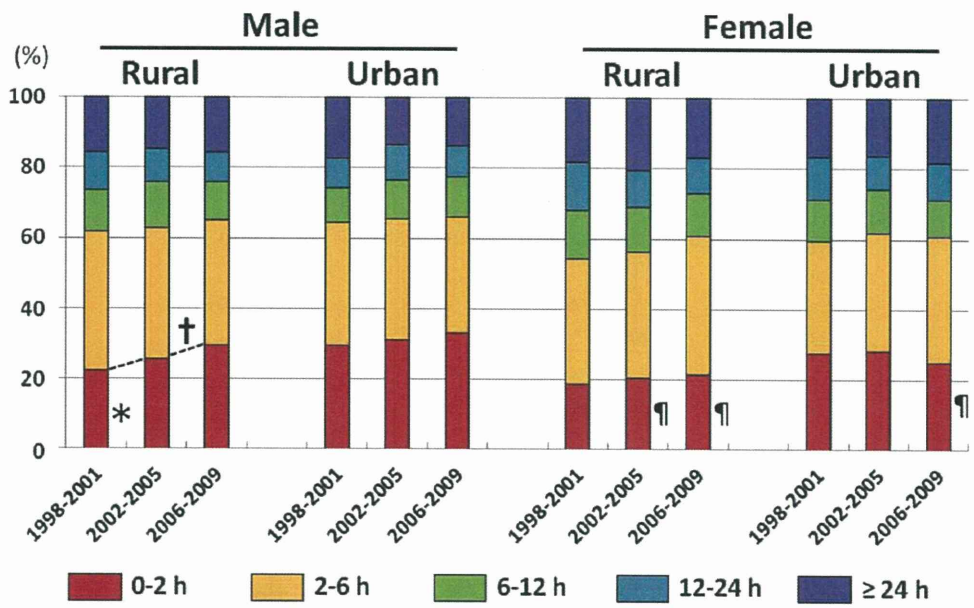

Figure 4. Time interval from the onset of symptoms to hospitalization. The percentage of patients with less than 2 h of elapsing time for hospitalization has significantly increased in rural male patients. The percentage was significantly lower in female patients than in male patients in both areas in 2006–2009. *P<0.05 for the difference between rural and urban areas. ¶P<0.05 for the difference between the sexes in the same rural or urban areas. †P<0.05 for a linear trend.

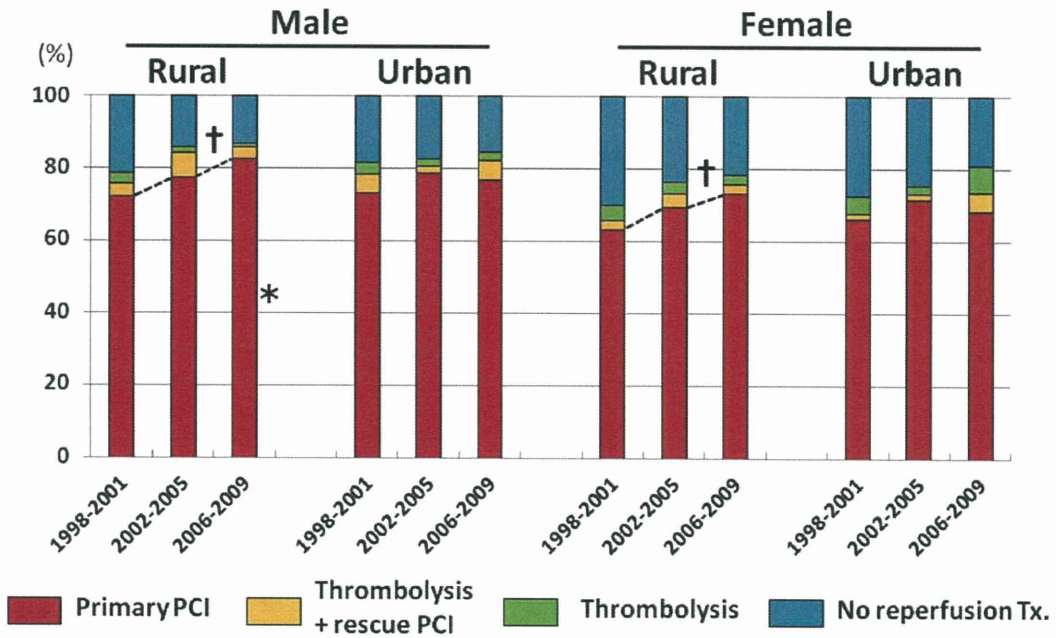

Figure 5. Prevalence of reperfusion therapy for acute myocardial infarction (AMI). The prevalence of primary percutaneous coronary intervention (PCI) steadily increased in the rural area in both sexes. Importantly, the prevalence of PCI was approximately 10% lower in female patients than in male patients in both rural and urban areas. *P<0.05 for the difference in male patients between rural and urban areas. †P<0.05 for linear trend.

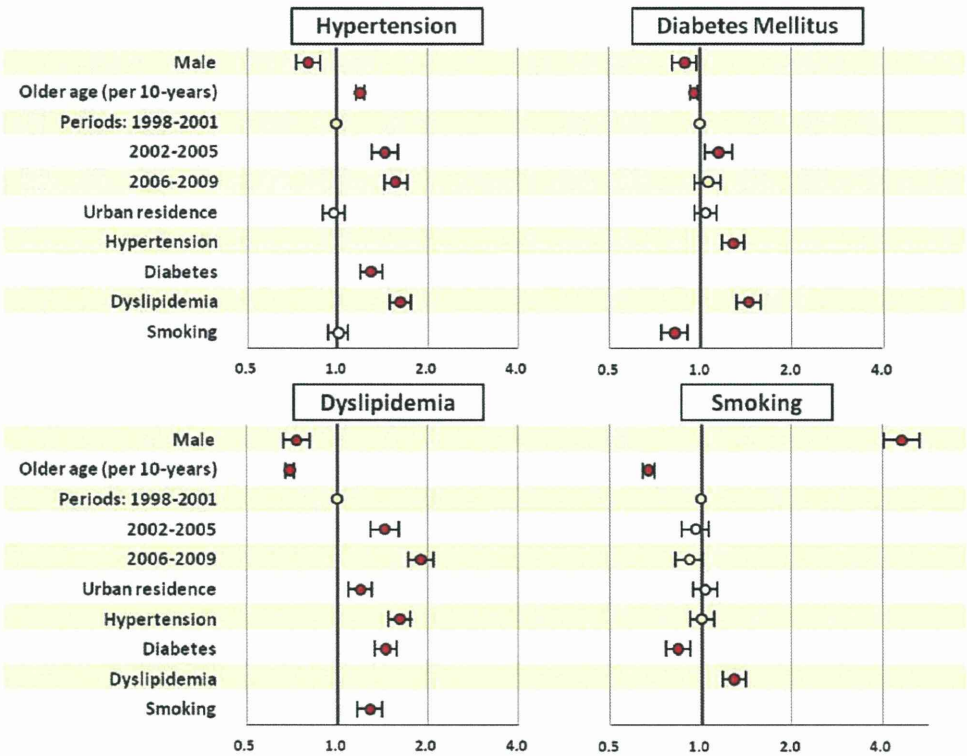

Figure 6. Multivariate analysis of coronary risk factors in acute myocardial infarction (AMI) patients. During the study periods, the prevalence of hypertension and dyslipidemia significantly increased in AMI patients. Hypertension was associated with older age but not with residence, whereas dyslipidemia was associated with younger age and urban residence. Smoking was associated with male sex and younger age. The odds ratios and 95% confidence intervals for factors are shown with red circles for P<0.05.

in both areas in the Miyagi prefecture (**Figure 1B**). Following age adjustment (**Figure 1C**), the incidence of AMI in the rural area increased significantly (P<0.001), whereas that in the urban area decreased significantly (P<0.001) in the recent 10-year period (between 1998 and 2009). In contrast, in-hospital mortality significantly decreased in both areas (both P<0.001), but to a greater extent in the rural area (0.5-fold in the rural area and 0.9-fold in the urban area) (**Figure 1D**). In 1998–2001, there was no significant difference in in-hospital mortality between the rural and urban male patients (P=0.263), and in-hospital mortality remained low (~8%) from 1998–2001 to 2006–2009 in both the rural and urban male patients (rural: P=0.832; urban: P=0.997) (**Table**). Importantly, in-hospital mortality of the female patients in both the rural and the urban areas remained doubled compared with the male patients during the study period (**Table**).

The clinical characteristics of the AMI patients in the present study are shown in **Table**. The female patients were approximately 10 years older than the male patients and approximately a half of them were ≥75 years-old in 1998–2001 in both areas, with a significant further increase in the rural area (male, P<0.001; female, P<0.001) and such a trend in the urban area (male, P=0.054; female, P=0.176) (**Figure 2**). In 1998–2001, the age-adjusted incidence of AMI was significantly lower in the rural area than in the urban area for both sexes (male, P=0.019; female, P=0.035) (**Table**). However, the difference between the 2 areas became insignificant in 2006–2009 for both sexes (male, P=0.824; female, P=0.530). When investigating the age-specific trend, the significant increase in the age-adjusted incidence of AMI was noted in the young (<44 years-old) and middle age (45–64 years-old) male patients only in the rural area (young, P=0.018; middle age, P=0.016), and the significant decrease was noted in the old (65–74 years-old) and high-old (>75 years-old) female patients in the urban area (old, P<0.001; high-old, P=0.016) (**Table**, **Figure 3**).

Regarding the time from the onset of AMI to admission, the percentage of the patients with less than 2h of elapsing time at admission was significantly lower in the rural area than in the urban area for the male patients in 1998–2001 (P<0.001) (**Figure 4**). However, the difference became insignificant in 2006–2009 (P=0.051), accompanied with the significant increase in the percentage in the rural area (rural, P<0.001; urban, P=0.082). Importantly, in the rural female patients, the percentage of patients with less than 2h of elapsing time at admission remained at a low level (~20%), and the difference between the sexes in the rural area became greater from 1998–2001 (P=0.086) to 2006–2009 (P<0.001). In contrast, the difference between the sexes in the urban area was significant in 2006–2009 (P=0.04). Moreover, the prevalence of primary PCI in the female patients was lower by ~10% compared with the male patients in both areas (**Figure 5**). In the male patients, the prevalence of primary PCI significantly increased only in the rural area from 1998–2001 to 2006–2009 (rural, P<0.001; urban, P=0.054), and a similar trend was also noted in the female patients (rural, P<0.001; urban, P=0.176).

Multivariate analysis of the coronary risk factors in AMI patients showed that the prevalence of hypertension and dys-

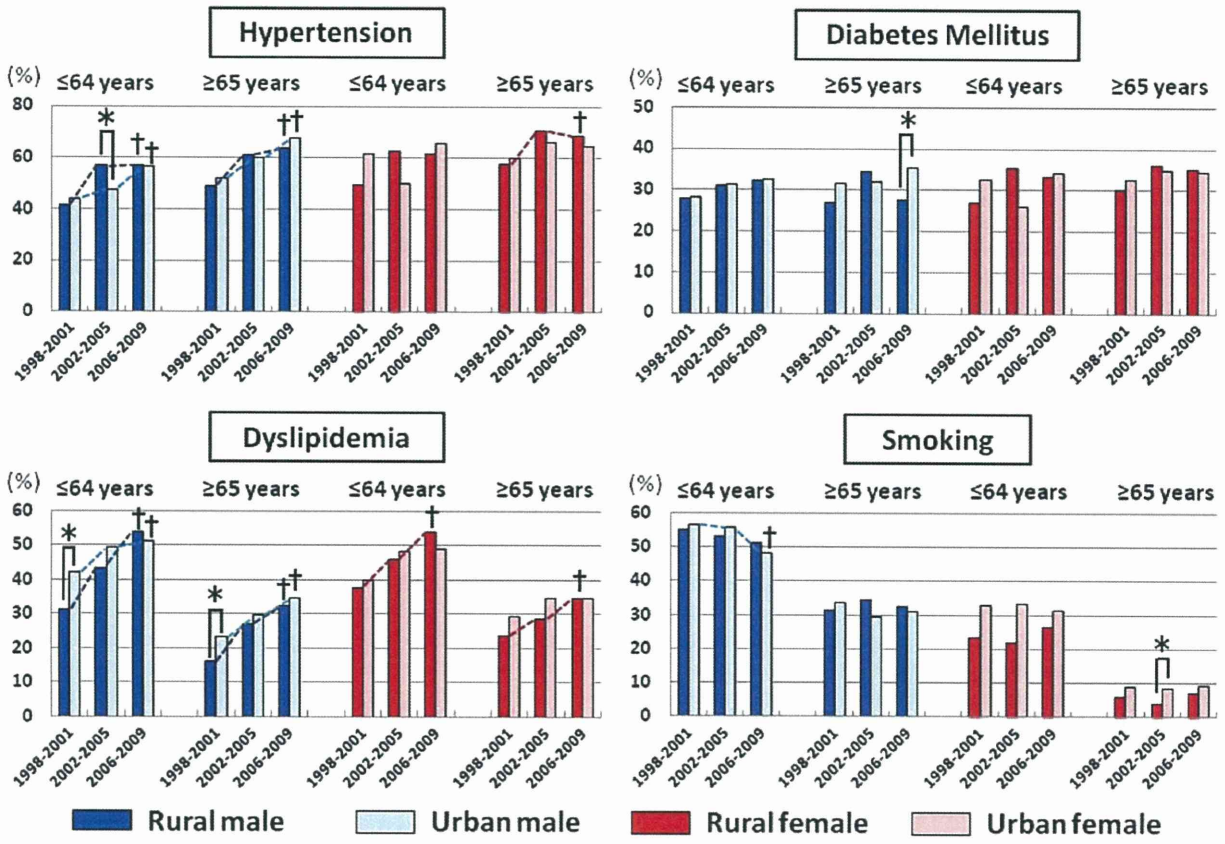

Figure 7. Prevalence of coronary risk factors in acute myocardial infarction (AMI) patients. The prevalence of hypertension and dyslipidemia had a trend of increase in both rural and urban areas. In particular, the prevalence of dyslipidemia in rural male patients aged ≤64 years markedly increased. *P<0.05 for the difference between rural and urban areas. †P<0.05 for linear trend.

lipidemia significantly increased and that of diabetes tended to increase (**Figure 6**). Hypertension was associated with older age but not with residence, whereas dyslipidemia was associated with younger age and urban residence. Although the prevalence of dyslipidemia in the male patients was significantly lower in the rural area than in the urban area in 1998–2001, it significantly increased in the rural area and the difference between the 2 areas became insignificant in 2006–2009 (**Table**). Moreover, the progressive increase in the prevalence of dyslipidemia was noted in both areas for both sexes with a more sharp increase in the rural area (**Figure 7**). Smoking was associated with male sex and younger age, but not with residence (**Figure 6**), and the prevalence of smoking largely remained unchanged in both areas for both sexes (**Figure 7**).

Discussion

The novel findings of the present study were that the incidence of AMI increased more rapidly in the rural area than in the urban area, with rapid aging in both areas. Moreover, the incidence of AMI in the rural male patients ≤64 years-old was increased along with the marked increase in the prevalence of dyslipidemia in Japan. Although in-hospital mortality from AMI markedly decreased in both areas over the last 20 years, it remained relatively high in female patients than in male patients in both areas. To the best of our knowledge, this is the first study that demonstrates the association between urbanization, life-style changes and the incidence and mortality of AMI in the largest number of patients in Japan.

Comparison of the Incidence of AMI Between Rural and Urban Areas

Although in the United States and European countries, the incidence of CAD has been declining in the last decades,[1,2,4] the present study demonstrates that the incidence of AMI has been rapidly increasing in both the rural and urban areas over the last 20 years, with a more noted increase in the former than in the latter. However, this tendency has disappeared following age adjustment in recent years only in the urban area, which implied that the increased tendency in the incidence of AMI in the rural area might be not be associated with rapid aging alone in recent years.

There were few studies that addressed the difference in the incidence of CAD between rural and urban areas in Japan. The Akita-Osaka study is the community-based survey, where the residents of the Yao City, Osaka prefecture (an urban community with a total census population of 23,552 in 2000) and those of Ikawa Town, Akita prefecture (a rural community with a total census population of 6,116 in 2000) were compared during the period of 1964–2003.[12] In this study, significant increases in the age-adjusted incidence of AMI and sudden cardiac death were noted in Yao City (in male patients from 1980 to 2003) but not in Ikawa City in both sexes.[12] The present study confirmed the results of the Akita-Osaka study

in the rural and urban areas of the same Miyagi prefecture. The Yamagata AMI Registry study provided more recent data and an age-specific trend in the period of 1993–2007.[17] The population density of the Yamagata prefecture was 133/km^2 in 2000, which was comparable with that of the rural area in the present study.[15] In this study, the age-adjusted incidence of AMI in the male but not that in the female patients significantly increased. In particular, the male population who were younger than 65 years old showed a marked increase in AMI, a consistent finding with the present results for the rural area. These results indicate that the incidence of AMI has been increasing in the younger male population in the rural areas of Japan. Taken together, unlike the trend in Western countries, it appears that the incidence of AMI has been increasing in Japan to a greater extent in the rural area than in the urban area over the last 20 years and has been associated with rapid aging.

Decreasing In-Hospital Mortality and Improvement in Critical Care

In the present study, the in-hospital mortality from AMI significantly decreased in both the urban and the rural areas over the last 20 years. The present study also demonstrates that primary PCI was performed more frequently in the rural area than in the urban area, along with the shortening in the elapsing time from the onset to hospitalization. The recent progress in critical care might have beneficial effects, overcoming the rapid aging in AMI patients.

In the most recent 10 year period, the in-hospital mortality remained at a low level in male patients, whereas in female patients, the mortality remained doubled compared with the male patients in both the rural and the urban areas. It was previously reported that the poorer outcome of the female AMI patients could be caused by multiple factors, including higher age, higher risk profiles, longer elapsing time from the onset to hospitalization, higher incidence of Killip class ≥2, and less frequent use of primary PCI.[18–20] Indeed, in the present study, the female patients were approximately 10 years older than the male patients and half of them were older than 75 years and needed a longer time from the onset of AMI to hospitalization in the both areas in 2006–2009. These points might have limited the use of primary PCI with a resultant poor outcome for the female AMI patients in the present study.

Changes in the Prevalence of Coronary Risk Factors in AMI Patients

The WHO-MONICA studies, as well as several Japanese cohort studies, demonstrated that the incidence of cardiovascular diseases increased and were associated with the clustering of risk factors.[21–23] In the present study, the prevalence of hypertension and dyslipidemia in AMI patients significantly increased in both the rural and urban areas. Importantly, there was a significant difference in the prevalence of dyslipidemia between the rural and urban areas with a marked increase noted in the rural area, especially in those male patients aged ≤64 years. Indeed, previous studies demonstrated that dyslipidemia is an independent risk factor in male but not in female patients,[17,24] and in the Yamagata-AMI Registry study, the increased prevalence of dyslipidemia in the younger male patients with AMI was also associated with an increased incidence of AMI.[17] In the Miyagi prefecture, the intake of animal fat was significantly higher in the rural than in the urban area in 2000 (rural 20.7 g/day vs. urban 23.4 g/day, $P<0.05$).[25] Moreover, in Japan, fat intake and serum levels of total cholesterol were higher in the urban than in the rural areas in 1966; however, the difference in cholesterol levels between the 2 areas became smaller in 1966–1985 along with the influence of Westernization of food habits in the rural area.[8] Taken together, it might indicate that the increase in the incidence of AMI in younger male patients in the rural area was likely to be associated with the marked increase in the prevalence of dyslipidemia.

The present study also demonstrates the increase in the prevalence of hypertension in AMI patients. In the Tohoku district, including the Miyagi prefecture, the prevalence of hypertension was relatively higher compared with other parts of Japan,[12,26] and thus more careful and strict control of risk factors is needed.

The prevalence of smoking remained high not only in the urban areas but also in the rural areas. In particular, in the younger male patients, the prevalence of smoking (~50%) was higher compared with the general Japanese population (36.8% in males and 9.1% in females in 2008).[27] Importantly, in the younger urban female patients, it remained more than 30%; 3 times higher than in the general Japanese population.

Study Limitations

Several limitations should be mentioned for the present study. First, although in the Miyagi prefecture, almost all AMI patients are transferred to our participating hospitals via the established emergency medical system, we cannot completely confirm that all patients have been registered in our registry. Second, while the MIYAGI-AMI Registry Study has been conducted over 20 years, the diagnosis of AMI has been changing.[28] In the present study, the diagnosis was made on the basis of the WHO-MONICA criteria with creatine kinase (CK).[16] Indeed, troponins are widely used in recent clinical practice and are more sensitive and specific biomarkers of myocyte necrosis than CK,[29] which might affect the results. Third, this study is an observational study and cannot reach the cause-effect relationship. Moreover, we did not examine the prevalence of risk factors in control subjects and did not collect the data of medical treatment for prevention, thus we were unable to precisely estimate the influence of risk factors on the incidence of AMI. Finally, in the present study, we did not examine the long-term mortality but only examined in-hospital mortality. The increasing incidence of decreasing in-hospital mortality from AMI in the Japanese population has apparently resulted in the recent increase in the number of patients with ischemic heart failure, as recently demonstrated in our heart failure cohort study, the CHART-1 and the CHART-2 studies.[30,31] Thus, a more effective strategy to improve the management of post-infarction heart failure needs to be developed.

Conclusions

Our MIYAGI-AMI Registry Study demonstrates that urbanization and life-style changes have been associated with the incidence and mortality of AMI in Japan, although sex differences still remain to be improved.

Acknowledgments

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Extracorporeal Shock Wave Therapy for Ischemic Cardiovascular Disorders

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Contents

Abstract

Ischemic heart disease is the leading cause of death and a major cause of hospital admissions, with the number of affected patients increasing worldwide. The current management of ischemic heart disease has three major therapeutic options: medication, percutaneous coronary intervention (PCI), and coronary artery bypass grafting (CABG). However, the prognosis for patients with severe ischemic heart disease without indications for PCI or CABG still remains poor due to the lack of effective treatments. It is therefore crucial to develop alternative therapeutic strategies for severe ischemic heart disease. Extracorporeal shock wave (SW) therapy was introduced clinically more than 20 years ago to fragment kidney stones, which has markedly improved the treatment of urolithiasis. We found that a low-energy SW (about 10% of the energy density used for urolithiasis) effectively increases the expression of vascular endothelial growth factor (VEGF) in cultured endothelial cells. Based on this *in vitro* study, we initiated *in vivo* studies and have demonstrated that extracorporeal cardiac SW therapy with a low-energy SW up-regulates the expression of VEGF, induces neovascularization, and improves myocardial ischemia in a porcine model of chronic myocardial ischemia, without any adverse effects *in vivo*. On the basis of promising results in animal studies, we performed a series of clinical studies in patients with severe coronary artery disease without indication for PCI or CABG, including, firstly, an open trial followed by a placebo-controlled, double-blind study. In both studies, our extracorporeal cardiac SW therapy improved symptoms, exercise capacity, and myocardial perfusion in patients with severe coronary artery disease. Importantly, no procedural complications or adverse effects were noted. The SW therapy was also effective in ameliorating left ventricular remodeling after acute myocardial infarction (MI) in pigs and in enhancing angiogenesis in hind-limb ischemia in rabbits. Based on these animal studies, we are also conducting clinical studies in patients with acute MI and in those with peripheral artery disease. Thus, our extracorporeal cardiac SW therapy appears to be an effective, safe, and non-invasive angiogenic approach in cardiovascular medicine and its indication could be extended to a variety of ischemic diseases in the near future. In this article, we briefly summarize our work in animals and humans, and discuss the advantages and perspectives of our extracorporeal SW therapy.

1. Introduction

Ischemic heart disease is the leading cause of death and a major cause of hospital admissions, with the number of affected patients increasing worldwide.[1] The current management of ischemic heart disease has three major therapeutic options: medication, percutaneous coronary intervention (PCI), and coronary artery bypass grafting (CABG). However, the prognosis for patients with severe ischemic heart disease without indications for PCI or CABG still remains poor due to the lack of effective treatments. Therefore, it is crucial to develop alternative therapeutic strategies for severe ischemic heart disease. During this decade, a variety of regenerative therapies, such as gene and cell therapies, have been investigated.[2-12] However, most of these regenerative therapies are invasive in nature. In addition, although many of these therapies have been shown to be effective in animal models, their efficacy and safety have not yet been fully established in clinical trials.[13-20]

Extracorporeal shock wave (SW) therapy was introduced clinically more than 20 years ago to fragment kidney stones, and has markedly improved the treatment of urolithiasis. Extracorporeal SW lithotripsy with high-energy SW is also indicated for gallstones and pancreatic and salivary stones. We have previously reported that low-energy cardiac SW therapy effectively induces neovascularization and improves myocardial ischemia in a porcine model of chronic myocardial ischemia.[21,22] Based on the promising results from animal studies, we first reported that low-energy cardiac SW therapy significantly improved symptoms and myocardial perfusion and reduced the use of nitroglycerin.[23] In this article, we briefly summarize our work in animals and humans, and discuss the advantages and perspectives of our low-energy SW therapy for ischemic diseases.

2. *In vitro* Study

SW is a longitudinal acoustic wave that propagates through water or soft tissue as ultrasound does. In contrast to ultrasound, SW is a single pressure pulse with a short needle-like positive spike <1 μsec in duration and up to 100 MPa in amplitude, followed by a tensile wave of several μsec with lower amplitude. We and others demonstrated that low-energy SW enhances nitric oxide (NO) production[24] and the expression of vascular endothelial growth factor (VEGF) and its receptor, fms-related tyrosine kinase 1 (Flt-1), in cultured human umbilical vein endothelial cells (HUVECs) *in vitro* (figure 1).[21]

Importantly, we demonstrated that the expression of VEGF peaked at 0.09 mJ/mm^2 in cultured endothelial cells, at approximately 10% of the energy used for lithotripsy treatment in the clinical setting (figure 1).[21] Subsequently, Yip et al.[25] reported that low-energy SW applied to bone-marrow-derived mononuclear cells (BMDMNCs) enhanced VEGF production from BMDMNCs and their differentiation into endothelial phenotype cells.[25] In addition, Nurzynska et al.[26] reported that low-energy SW activated proliferation and differentiation in cardiac primitive cells. Tamma et al.[27] also reported that SW induced the proliferation and differentiation of osteoblasts and reduced their secretion of pro-osteoclastogenic factors.

SW exerts a 'cavitation effect' (a μm-sized violent collapse of bubbles inside and outside the cells)[28] and was shown to induce localized stress on cell membranes that resembles shear stress,[29] due to the localized nature of the physical forces generated by cavitation.[30] Several biochemical effects of SW have been reported including hyperpolarization, Ras activation, non-enzymatic NO synthesis, and induction of stress fibers and intercellular gaps.[31-33] However, detailed intracellular mechanisms of SW action remain to be elucidated.

3. Extracorporeal Cardiac Shock Wave (SW) Therapy for Angina Pectoris

3.1 Animal Studies

Based on our *in vitro* study, we examined whether low-energy SW could ameliorate myocardial ischemia in a porcine model *in vivo*. A porcine model of chronic myocardial ischemia was made by placing an ameroid constrictor at the proximal segment of the left circumflex (LCX) coronary artery. This gradually induced a total occlusion of the artery with sustained myocardial dysfunction but without myocardial infarction in 4 weeks.[21] At 4 weeks after the implantation of the ameroid

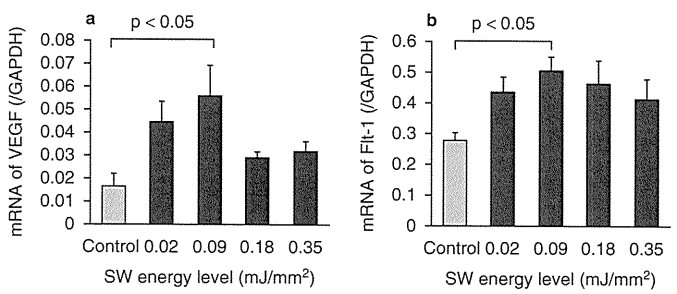

Fig. 1. Effects of shock wave (SW) therapy on mRNA expression in human umbilical vein endothelial cells (HUVECs) *in vitro*. SW treatment up-regulated mRNA expression as a proportion of glyceraldehyde dehydrogenase (GAPDH) mRNA expression of (**a**) vascular endothelial growth factor (VEGF) and (**b**) VEGF receptor, Flt-1, with a maximum effect noted at 0.09 mJ/mm^2, a level that is approximately 10% of that used for urinary lithotripsy. Results are expressed as mean ± SEM (n = 10 in each group). From Nishida et al.,[21] with permission.

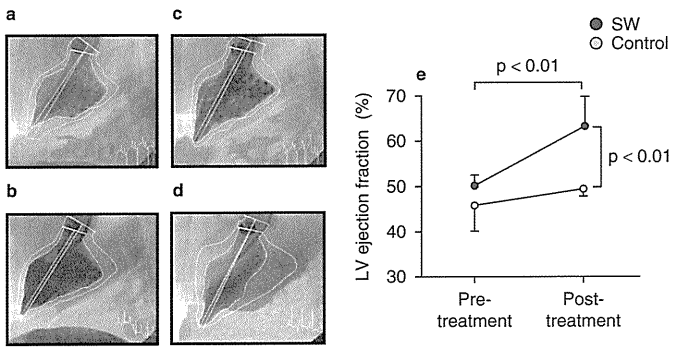

Fig. 2. Effects of shock wave (SW) therapy on left ventricular (LV) function in pigs *in vivo*. The extracorporeal cardiac SW therapy improved ischemia-induced myocardial dysfunction *in vivo* as evaluated by left ventriculography. Four weeks after the implantation of an ameroid constrictor, LV wall motion of the LCX (posterolateral) region was reduced in both (**a**) the control and (**c**) the SW group (before SW therapy). Eight weeks after the implantation of an ameroid constrictor, no significant change in LV wall motion was noted in the control group (**b**), whereas marked recovery was noted in the SW group (**d**). (**e**) SW therapy normalized LV ejection fraction in the SW group but not in the control group. Results are expressed as mean±SEM (n=8 in each group). From Nishida et al.,[21] with permission.

constrictor, we performed extracorporeal SW therapy to the ischemic myocardium three times during the first week (n=8), whereas animals in the control group (n=8) received the same anesthesia procedures three times a week but without the SW treatment. Based on our *in vitro* experiments, we applied low-energy SW (0.09 mJ/mm^2) to nine spots in the ischemic LCX region (200 shots/spot) with the guidance of an echocardiogram equipped with a specially designed SW generator (Storz Medical AG, Tägerwilen, Switzerland). In order to treat the targeted ischemic myocardium without inducing ventricular arrhythmia, we applied SW at end-diastole during the cardiac cycle with an R-wave-triggered system. We evaluated cardiac function before (baseline) and at 4 and 8 weeks after the ameroid implantation.

Four weeks after the implantation of an ameroid constrictor, wall motion of the posterolateral (LCX) region in the left ventricle (LV) was reduced in both the control and the SW groups to the same extent (figure 2a,c). However, 4 weeks after the SW therapy, left ventriculography showed marked improvement of LV wall motion only in the SW group (figure 2b,d). The SW therapy normalized the LV ejection fraction in the SW group but not in the control group (figure 2e). In this study, the SW treatment normalized global and regional myocardial function as well as regional myocardial blood flow in the chronic ischemic region, evaluated using colored microspheres (Dye-Trak, Triton Technology) and spectrophotometry. In addition, the SW therapy increased capillary density and up-regulated VEGF expression in the ischemic myocardium *in vivo* (figure 3). Importantly, no procedural complications or adverse effects, such as tissue injury, hemorrhage, or arrhythmia, were noted during or after the SW therapy. These results suggest that the low-energy cardiac SW therapy activates the endogenous angiogenic system in pigs *in vivo*.[21] This was the first report to demonstrate the potential usefulness of extracorporeal cardiac SW therapy as a non-invasive treatment for chronic myocardial ischemia.

3.2 Clinical Studies

Based on the promising results in animal studies, we performed the first clinical trial of extracorporeal cardiac SW therapy in an open-labeled manner.[23] We performed cardiac SW therapy (200 shots/spot at 0.09 mJ/mm^2 for 20–40 spots, three times a week/series) in nine patients with end-stage coronary artery disease (CAD) with no indication for PCI or CABG (55–82 years old, five men and four women). During the therapy, the patients lay on the bed in a supine position without any anesthesia (figure 4). Importantly, our SW therapy significantly improved symptoms and reduced nitroglycerin use

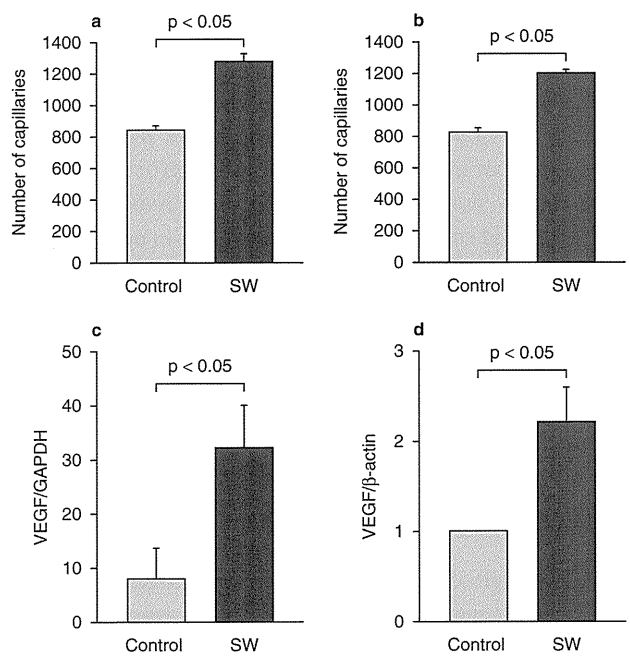

Fig. 3. Effects of shock wave (SW) therapy on capillary density and vascular endothelial growth factor (VEGF) expression in the ischemic myocardium in pigs *in vivo*. The extracorporeal cardiac SW therapy increased the density of factor VIII-positive capillaries and VEGF expression in the ischemic myocardium. Capillary density was significantly greater in the SW group than in the control group in both (**a**) the endocardium and (**b**) the epicardium. The (**c**) mRNA expression and (**d**) protein levels of VEGF as proportions of glyceraldehyde dehydrogenase (GAPDH) mRNA expression and β-actin, respectively, were significantly higher in the SW group than in the control group. Results are expressed as mean±SEM (n=6 in each group). From Nishida et al.,[21] with permission.

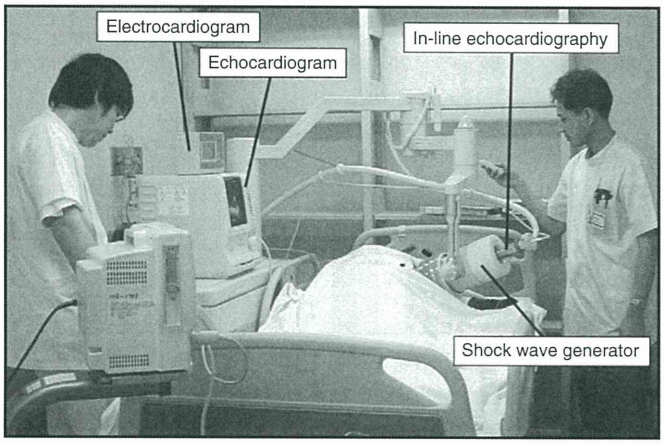

Fig. 4. Extracorporeal cardiac shock wave (SW) therapy in action in a patient with severe coronary artery disease. The machine is equipped with a SW generator and in-line echocardiography. The SW generator is attached to the chest wall of the patient when used. The SW pulse is easily focused on the ischemic myocardium under the guidance of echocardiography. There is no need for anesthesia or sedatives.

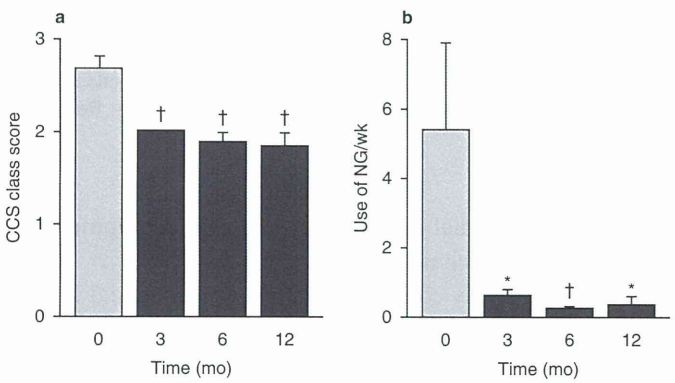

Fig. 5. Effects of extracorporeal cardiac shock wave (SW) therapy on symptoms and the use of nitroglycerin. Extracorporeal cardiac SW therapy significantly improved (**a**) the Canadian Cardiovascular Society (CCS) class scores and (**b**) number of nitroglycerin (NG) uses per week in patients with severe angina pectoris. Results are expressed as mean ± SEM. * $p < 0.05$, † $p < 0.01$ vs 0 month (statistically analyzed by a *post hoc* test after one-way ANOVA). From Fukumoto et al.,[23] with permission.

(figure 5) and improved myocardial perfusion as assessed by dipyridamole stress thallium scintigraphy only in the ischemic area treated with the SW therapy (figure 6). These beneficial effects of the SW therapy persisted for at least 12 months. No procedural complications or adverse effects were noted. These results indicated that our extracorporeal cardiac SW therapy was a safe, effective, and non-invasive therapeutic strategy for severe ischemic heart disease.[23] Following our initial report, several clinical studies with positive results were reported worldwide.[34-37] To confirm the usefulness and safety of our SW therapy, we performed a second clinical trial in a randomized and placebo-controlled manner. In this second trial, again we were able to demonstrate that the low-energy SW therapy not only improved symptoms and reduced nitroglycerin use, but also improved LV function (figure 7), establishing cardiac SW therapy as an effective and safe angiogenic strategy for severe ischemic heart disease.[38] As described above, extracorporeal cardiac SW therapy improved the quality of life in patients with angina pectoris. However, it is still not known whether our SW therapy improves the long-term prognosis of those patients. Further studies are needed.

4. Extracorporeal Cardiac SW Therapy for Acute Myocardial Infarction

The development of emergent reperfusion therapy has dramatically reduced the mortality of patients with acute myocardial infarction (AMI). However, LV remodeling following AMI, which leads to heart failure, sudden cardiac death, and poor prognosis,[39] still needs to be addressed. It was reported that capillary density in the border zone is negatively correlated with infarct size 1 month after AMI, suggesting the importance of adequate growth of the capillary microvasculature.[40] It is highly expected that enhancing neovascularization in the

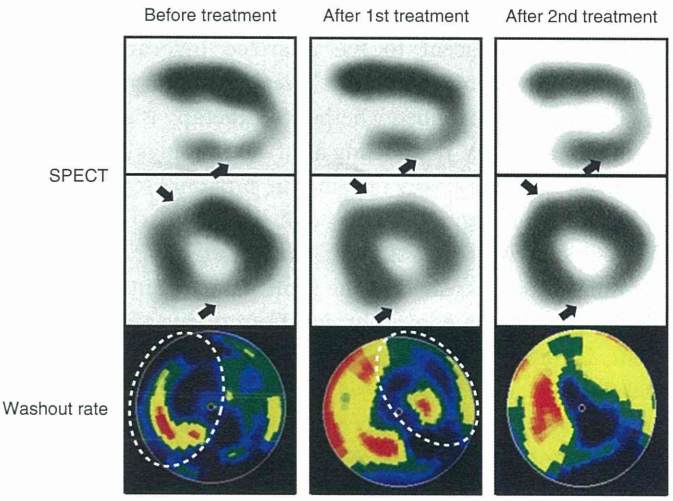

Fig. 6. Effects of extracorporeal cardiac shock wave (SW) therapy on myocardial perfusion in patients with severe angina pectoris. Dipyridamole stress thallium-201 single photon emission computed tomography (SPECT) imaging and polar map in a patient with severe three-vessel coronary artery disease before and after SW therapy. The results clearly demonstrated that SW therapy ameliorated myocardial perfusion only where SW was applied; in the anteroseptal wall after the first treatment and in the lateral wall after the second treatment (arrows) in a step-wise manner after the staged SW treatment. The areas treated with SW therapy are indicated with dotted lines. From Fukumoto et al.,[23] with permission.

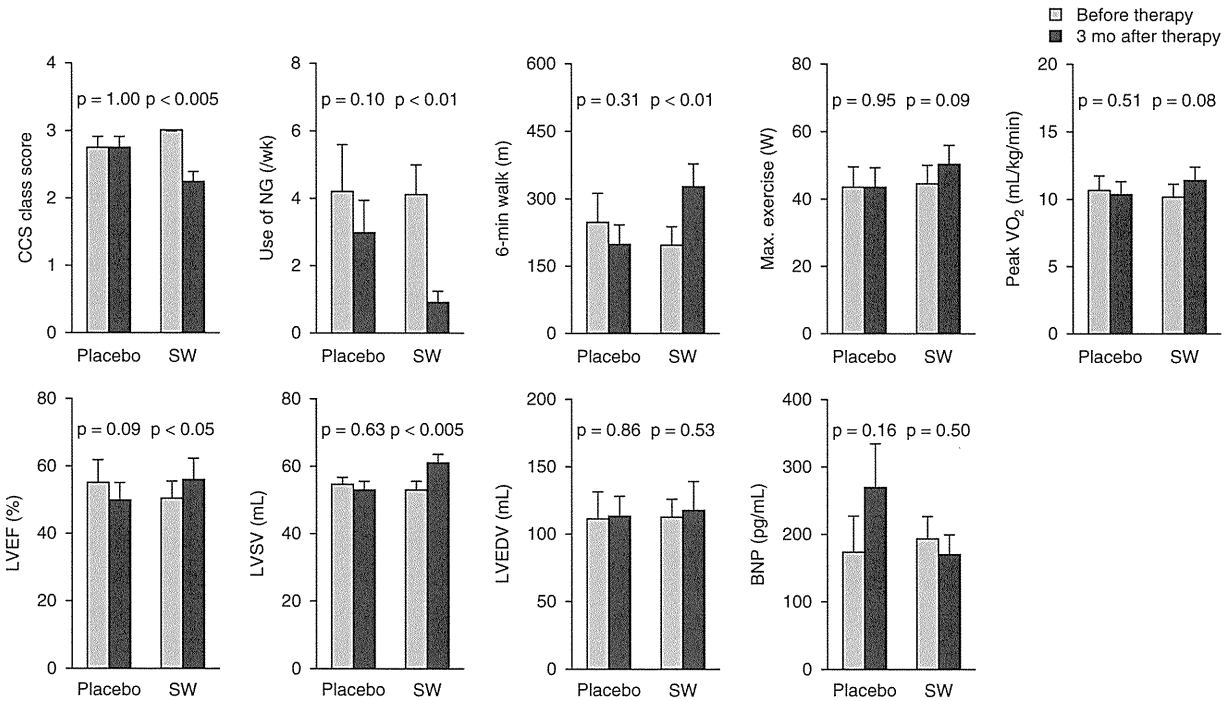

Fig. 7. Effects of extracorporeal cardiac shock wave (SW) therapy in patients with severe angina pectoris in the placebo-controlled and double-blind study. **BNP** = brain natriuretic peptide; **CCS** = Canadian Cardiovascular Society; **LVEDV** = left ventricular (LV) end-diastolic volume; **LVEF** = LV ejection fraction; **LVSV** = LV stroke volume; **max. exercise** = maximum exercise capacity in watts (W); **NG** = nitroglycerin; **peak VO_2** = peak oxygen uptake. Results are mean ± SE (n = 8 in each group). From Kikuchi et al.,[38] with permission.

border zone adjacent to the infarcted myocardium could ameliorate the progression of LV remodeling in patients with AMI. Thus, we examined whether SW therapy is also effective in ameliorating LV remodeling after AMI in pigs *in vivo*. AMI was created by surgically excising the proximal segment of the LCX.[41] Low-energy SW therapy (200 shots/spot at 0.09 mJ/mm^2, three times a week) was started 3 days after AMI. The remaining animals were treated in the same manner but without the SW treatment as a control group. Four weeks after the treatment, LV ejection fraction, LV end-systolic volume, and LV end-diastolic volume were significantly improved in the SW group compared with the control group (figure 8). Furthermore, regional myocardial blood flow and number of capillaries in the border zone were significantly improved in the SW group compared with the control group. Again, no procedural complications or adverse effects were noted. These results suggest that our extracorporeal cardiac SW therapy is an effective and non-invasive therapy for ameliorating LV remodeling after AMI. This is the first report to demonstrate the usefulness and safety of extracorporeal cardiac SW therapy as a non-invasive treatment of AMI. We were also able to confirm the beneficial effects and safety of cardiac SW therapy in another porcine model of myocardial ischemia/reperfusion (90-minute ischemia) to mimic the clinical setting.[42]

We are currently conducting the first clinical trial in AMI patients who have been successfully treated with PCI, in order to examine whether our cardiac SW therapy combined with PCI ameliorates LV remodeling and dysfunction after AMI in humans.

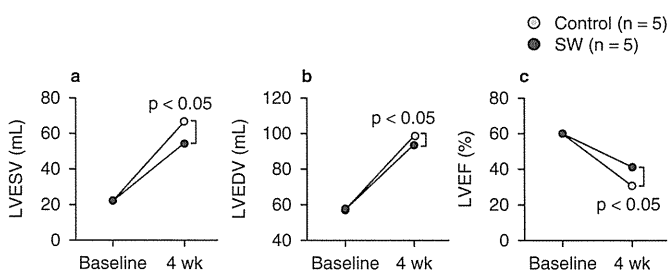

Fig. 8. Effects of extracorporeal cardiac shock wave (SW) therapy on left ventricular (LV) remodeling in pigs *in vivo*. SW therapy significantly ameliorated LV remodeling characterized by the increase in (**a**) LV end-systolic volume (LVESV) and (**b**) end-diastolic volume (LVEDV) and (**c**) reduced LV ejection fraction (LVEF) in a porcine model of AMI. From Uwatoku et al.,[41] with permission.

5. SW Therapy for Other Ischemic Disorders

Peripheral arterial disease (PAD) is often associated with cardiovascular diseases as a part of systemic atherosclerosis, and its associated morbidity is rapidly increasing worldwide.[43-45] Thus, we examined the effects of our SW therapy on hind-limb ischemia in rabbits.[46] Hind-limb ischemia was induced by surgical excision of the entire unilateral femoral artery. One week after the operation, we started the SW therapy (200 shots/spot at 0.09 mJ/mm^2) to the ischemic region three times a week for 3 weeks. Four weeks after the operation, blood flow, blood pressure, and capillary density were all significantly increased in the SW group compared with the control group.[46]

Based on favorable results in animal studies, we are conducting a clinical study in patients with PAD with intermittent claudication (Fontaine stage II) and those with critical limb ischemia (Fontaine stage III and IV). During the therapeutic procedure, patients lie in a prone position without any anesthesia. SWs are applied to the ischemic calf muscle three times a week for 3 consecutive weeks (200 shots/spot at 0.05 mJ/mm^2 for 40 spots). Walking ability and peripheral blood flow are evaluated at 4, 8, 12, and 24 weeks after the SW therapy.

Recently, the beneficial effects of low-energy SW therapy have also been reported in other ischemic disorders, including the skin flap model in rodents[47,48] and in patients with refractory chronic skin ulcers.[49,50] Also, low to high energy levels of SW are widely used for the treatment of certain orthopedic conditions, such as bone non-unions, tendinosis calcarea, epicondylitis, and calcaneal spur.[51,52] In the orthopedic field, SW therapy is reported to affect the expression of several chemokines and matrix metalloproteinases with resultant anti-inflammatory effects.[24,47,53,54] These findings suggest that multiple signaling pathways are involved in mediating the beneficial effects of the SW therapy.

6. Advantages of Extracorporeal Cardiac SW Therapy

A major advantage of our extracorporeal cardiac SW therapy is its non-invasive nature without any adverse effects. If necessary, we are able to repeatedly treat patients with SW therapy as no surgery or anesthesia is required for the treatment. This is an important factor in determining the clinical usefulness of angiogenic therapies, especially in elderly patients. The combination of cell therapy and SW therapy could be one potential approach. Indeed, enhanced expression of multiple angiogenic factors, such as VEGF and stromal-derived factor 1 (SDF-1), is crucial for the recruitment and incorporation of endothelial progenitor cells (EPCs).[55-61] Also, it was reported that the activation of the SDF-1/CXCR4 axis is essential for the retention of pro-angiogenic stem cells in peripheral organs, although the up-regulation of VEGF is sufficient to mobilize stem or progenitor cells from the bone marrow to the systemic circulation.[56,60] Thus, it is possible that SW therapy enhances the incorporation of circulating EPCs by up-regulating the expression of SDF-1 in ischemic myocardium. This notion has been supported by a recent report showing that the addition of SW therapy enhances the effectiveness of cell-based angiogenic therapy.[62] In this study, low-energy SW therapy was employed to treat hind-limb ischemia in rats in combination with cell-based therapy, where the expression of stromal-derived factor 1 (SDF-1) and recruitment of endothelial progenitor cells by SW therapy were enhanced.[62] In addition, it has been recently reported that the beneficial effects of cell therapy were enhanced by pretreating BMDMNCs with SW before implantation into the infarct area.[63]

7. Conclusions

Extracorporeal low-energy SW therapy appears to be an effective, safe, and non-invasive approach to ischemic heart disease, and its use could be extended to a variety of other ischemic disorders in the near future. The beneficial effects of SW may be mediated by the enhancement of several intrinsic angiogenic systems, although the precise mechanisms remain to be elucidated.

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特集／心筋梗塞診療の最新情報

我が国の心筋梗塞コホート研究

宮城県心筋梗塞対策協議会

安田　聡　瀧井　暢
伊藤　健太　下川　宏明

緒　言

「宮城県心筋梗塞対策協議会」は，昭和54年(1979年)に当時の東北大学第一内科 故・瀧島任名誉教授が中心となり，宮城県の救急医療の一環として，緊急性が特に高い急性心筋梗塞症に適切に対処しその予後を改善することを目的に設立された。1979年当時を振り返ってみると，アメリカ合衆国と中華人民共和国が国交樹立(1月)，イギリス・保守党の党首サッチャーが先進国初の女性首相に就任(5月)，日本シリーズ(11月)では広島対近鉄第7戦の江夏の21球が語り草となった時代であった。

この協議会は，宮城県の主要循環器診療施設が参加し県下の急性心筋梗塞症例のほぼ全例を前向きに登録している点，平成20年度で30年に及ぶ長期間の登録になった点，の2つの意味で全国的にも大変特徴のある臨床疫学研究となっている。急性心筋梗塞症の診断はWHO-MONIKA基準に準じ各施設毎に，症状・心電図変化・血液学的検査・画像検査により総合的に行われた。本稿では，宮城県心筋梗塞対策協議会で得られた知見について，1979年から2008年までの30年間の年次推移を中心に紹介する[1]。

Ⅰ．宮城県推計人口の推移と総登録患者数

1979年から2008年までの宮城県推計人口の推移を示す(図1)。1979年は205.4万人，2008年は234.9万人と，この30年間で約10%の増加にとどまっている。したがって，約200万人とほぼ安定した人口動態の中での調査結果であるといえる。過去30年間に県下の43施設から登録された急性心筋梗塞総数は22,551症例(男16,236例/女6,313例)に及ぶ。登録された急性心筋梗塞患者の年齢は，男性65±13[SD]歳に対して女性75±11歳と，女性がより高齢であった。

Ⅱ．心筋梗塞発症率の推移

官報等でも死亡診断書からの死亡率のデータは報告されているが，“発症頻度”に関する本邦データは極めて少なく，欧米の発症頻度との比較がこれまで困難であった。本研究により，本邦において，過去30年間心筋梗塞の発症数は明らかに増加傾向にあることが初めて示された。図2に年齢補正後のデータを示す。1979年には人口10万人あたり7.4人の発症率であったが，2008年には27.0人と3.6倍に増加していた。特に男性では増加が著しく，1979年には年間18.7人であったのに対して，2008年には年間46.4人と，約2.5倍となった。一方，女性では，1979年には年間4.2人であったのに対して2008年には年間9.6人であった。国内の他の研究と比較してみる。滋賀県の高島町研究(1990～2001)

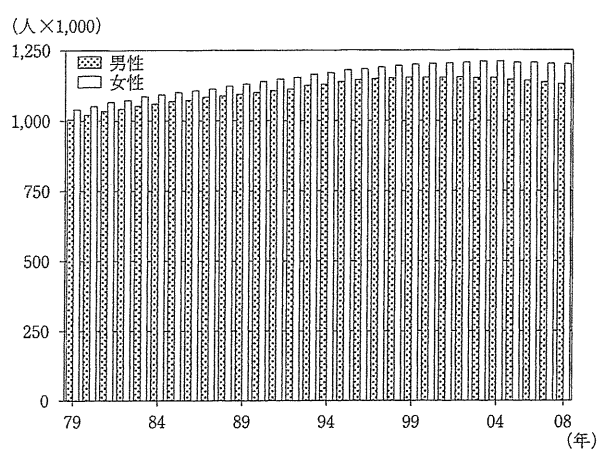

図1　宮城県推計人口推移(文献1)より改変引用)

東北大学大学院医学系研究科循環器内科学分野・
宮城心筋梗塞対策協議会

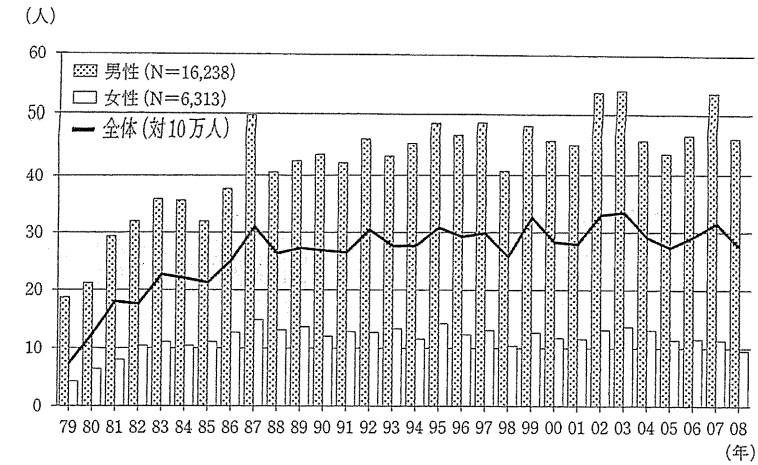

図　2　　心筋梗塞発症頻度（年齢補正データ）
（文献1）から改変引用）

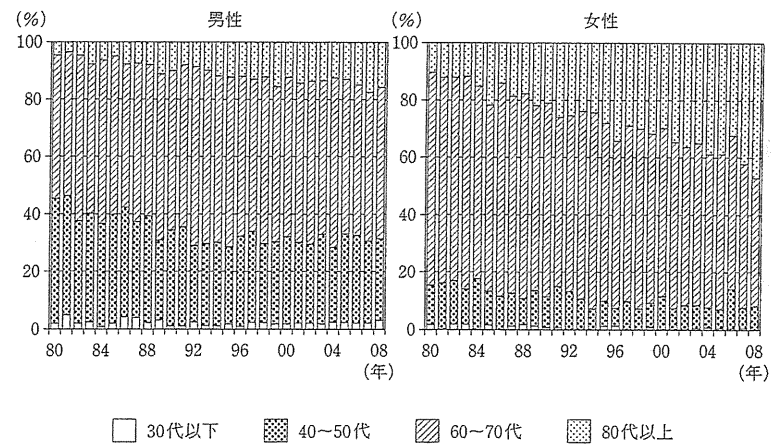

図　3　　登録症例の年齢構成（文献1）から改変引用）

では[2]，男性100.7人，女性35.7人，新潟県の長岡市研究（1994～1996）では[3]，男性41.9人，女性5.3人といずれも男性優位の発症率であり，同年代の発症率は，宮城県では滋賀県・高島町に比し低率，新潟県・長岡市研究とほぼ同等という結果であった。

発症率はこの30年間で増加しているが，その頻度を北米やヨーロッパのデータと比較すると，依然として低率であることがわかる[4]：フィンランド，824；英国，823；カナダ，605；アメリカ，508；フランス，314；イタリア，270。

Ⅲ．高　齢　者　の　増　加

図3に，性別，年齢階層別の変遷を示す。39歳以下，40～59歳，60～79歳，80歳以上と4つの階層に分けて検討したところ，30年間に心筋梗塞罹患患者の高齢化，特に女性では80歳以上の症例が占める割合が急速に増加していることが明らかになった（図4）。米国4州での保険データ解析（1992～2001）[5]でも80歳代の症例増加が報告されているが，世界的にも有数の長寿

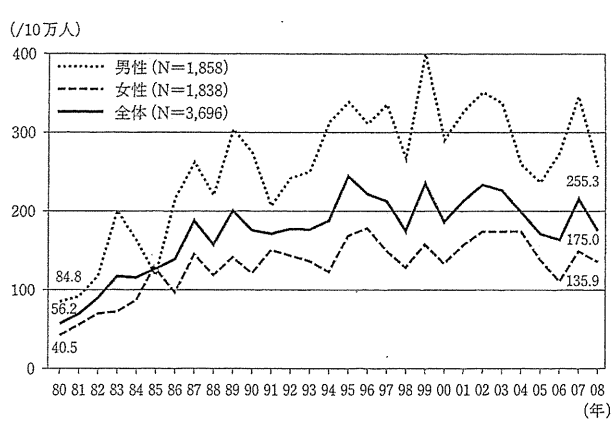

図　4　　80歳以上患者の心筋梗塞発症頻度
（文献1）から改変引用）

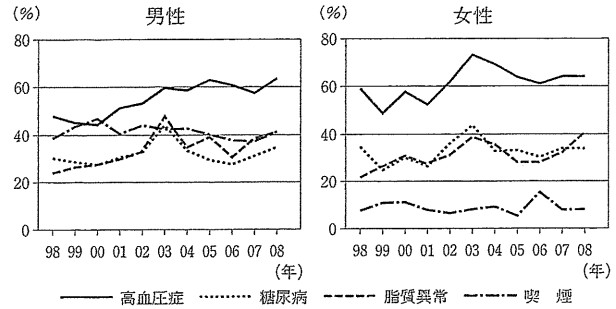

図 5　動脈硬化危険因子合併の推移
(文献1)から改変引用)

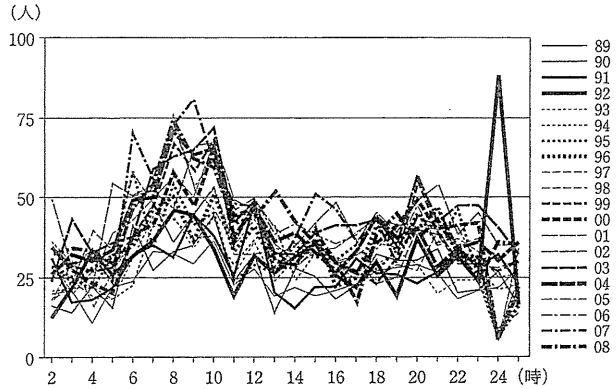

図 6　心筋梗塞発症時間の年次推移
(文献1)から改変引用)

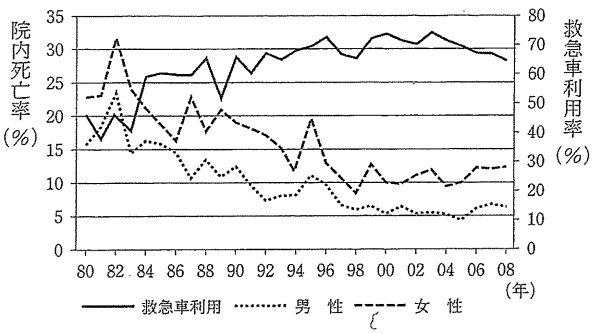

図 7　院内死亡率(心臓死)と救急車利用率
(文献1)から改変引用)

国である我が国からのデータとして，世界的にも注目される結果であると思われる。

Ⅳ. 冠危険因子の推移

宮城心筋梗塞対策協議会では1998年より冠危険因子についてもデータ収集を追加するようになった。高血圧症，糖尿病，脂質異常症，喫煙のいずれの冠危険因子も1998年以降増加傾向にあることが明らかになった（図5）。図3に示したように，患者の高齢化とともに危険因子の重複が進んだこと，日本人のライフスタイルが変化したこと（西洋化）が，関連しているものと推測される。また，我が国の喫煙歴は近年約20%にまで低下していることが報告されているが，心筋梗塞患者，特に男性ではその喫煙率は依然として約40%と高率であり，今後更なる啓発活動が必要と考えられる。

Ⅴ. 発症時間と梗塞部位

心筋梗塞発症が早朝に多いことは国内・国外からの単年度研究により報告されている[6)-8)]。この30年間のライフスタイルの変化が発症時間に何らかの影響を及ぼしている可能性について，時間帯毎の発症数を年度別に比較検討した（図6）。その結果，年度を問わず，概ね6時～10時までの午前中の時間帯に心筋梗塞発症が多いことがわかる。また，梗塞部位に関しても経年的な変化は認められず，前壁心筋梗塞45%，後下心筋梗塞43%，その他が12%であった。

Ⅵ. 院　内　死　亡　率

発症数の増加（図2）と患者高齢化（図3）の一方で，急性期死亡率（30日以内の院内死亡率）は，1979年の20%から2008年の8%に，全体として劇的に改善しているということも今回の解析により明らかになった（図7）。救急車の利用率も，発足当時は約40%であったが，近年では約70%に増加していることがわかる。一方で2008年データにおいても，女性の死亡率は男性の約2倍である（男12% vs. 女6%）という問題点も明らかになった。

Ⅶ. 再灌流療法の普及と男女差

心筋梗塞治療の最大のブレークスルーは再灌流療法にあることはいうまでもない。宮城県心筋梗塞対策協議会においても，1992年より再灌流療法に関する調査が追加され，その重要性を裏付けるデータが明らかになった（図8）。当初は再灌流療法の施行率は約60%，その方法も血栓溶解療法が主体であったが，1996～7年以降は，冠動脈インターベンション（PCI）による血行再建術が急速に普及しており，宮城県の心筋梗塞診療体制が大きく変わった時期であると考えられる。1992年当時PCI施行率は約20%であったが，近年では約80%に達していることがわかる。年齢や他の合併症の問題でPCI非適

応ないし未施行となった患者群も想定しなければならないが，院内死亡率はPCI施行例（n＝8,693）5％に対して，未施行例（n＝254）17％と，PCI施行例で1/3以下であった。また，男性ではPCI施行症例が80％（n＝6,061）であったの対して，女性では71％（n＝2,412）と有意に低率であり（図10），図7で示した女性患者の院内死亡率の高さとの関連性が示唆される。

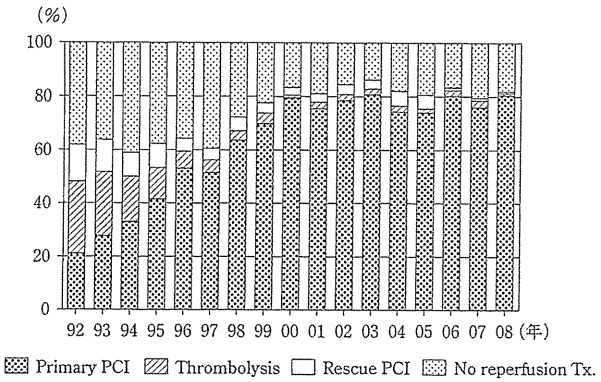

図 8　治療内容（再灌流療法の有無と内訳）（文献1）から改変引用）

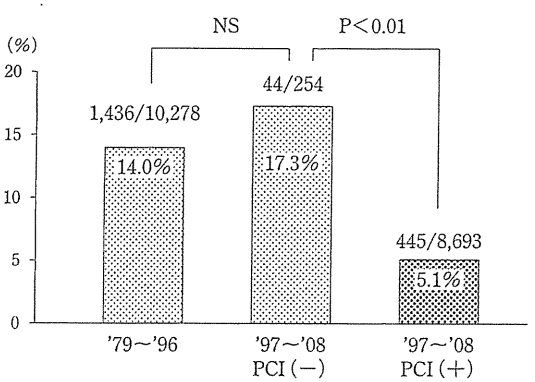

図 9　院内死亡率（心臓死）と冠動脈インターベンション（PCI）との関係（文献1）から改変引用）

女性の心筋梗塞患者では様々な理由で，再灌流療法の恩恵に必ずしも預かっていない現状があり，今後その対策について協議会でも検討をしていく必要があると考えられる。

Ⅷ. 発症から入院までの時間

図11に発症から入院までの時間を示す。6時間以内の入院症例は約60％を占めるものの，この30年間，その割合はほぼ一定でPCIが宮城県において普及してきた1996～7年前後でも大きな差異は認められなかった。アメリカ心臓協会（AHA）のガイドラインでは，「発症から120分以内の再灌流療法」が急性心筋梗塞患者の予後改善のために推奨されている。発症後の時間経過について，今後より詳細な検討解析が必要と思われる。

Ⅸ. 入　院　期　間

図12に入院期間の推移を示す。再灌流療法の普及とともに入院期間も短縮し，20日以内の入

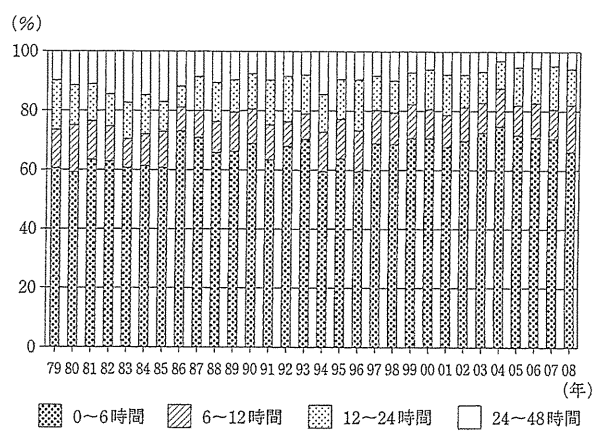

図 11　発症から入院までの時間（文献1）から改変引用）

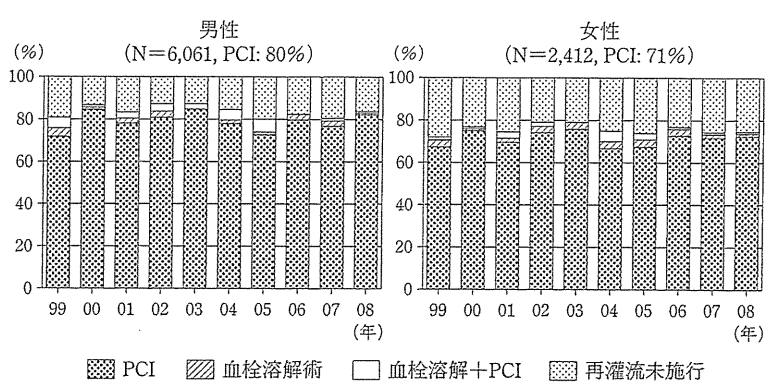

図 10　治療内容（男女比較）（文献1）から改変引用）

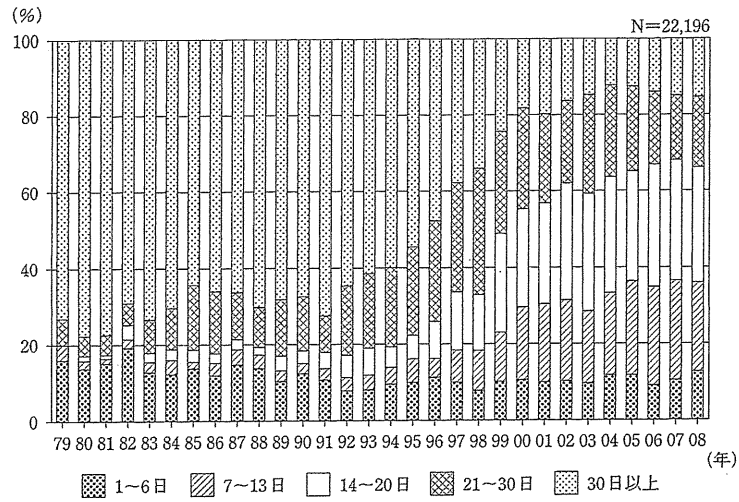

図 12　入 院 期 間（文献1)から改変引用）

院は1979年当時20%にとどまっていたものの2008年には66%に増加していることがわかる。入院期間については2000年以降概ね20日以内が主体となっており，入院後診療についてはほぼ確立されてきているものと推測される。

X. ま と め

1）過去30年間，心筋梗塞の発症数は明らかに増加傾向にあるものの，急性期死亡率は全体として劇的に改善してきている。
2）救急車利用率の増加，冠動脈インターベンションの普及が顕著な一方で，危険因子の管理は未だ十分ではない現状が明らかになった。
3）再灌流療法時代においても女性の死亡率は男性に比し依然として高率であり，その対策が重要であると考えられた。

結 語

30年間に及ぶ宮城県心筋梗塞対策協議会の調査結果から，我が国の急性心筋梗塞診療の実態が明らかになった。設立当時の理念（＝急性心筋梗塞患者の救命率向上）を実践していくために，早期受診・治療を可能とする診療体制を構築していくことが今後ますます重要であると考えられる。また2010年3月11日に東日本大震災が宮城県を中心に発生した。未曾有の大災害が，心筋梗塞の発症にどのような影響を及ぼし得るのか，本協議会での30年データとの比較からその答えが得られるものと思われる。

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