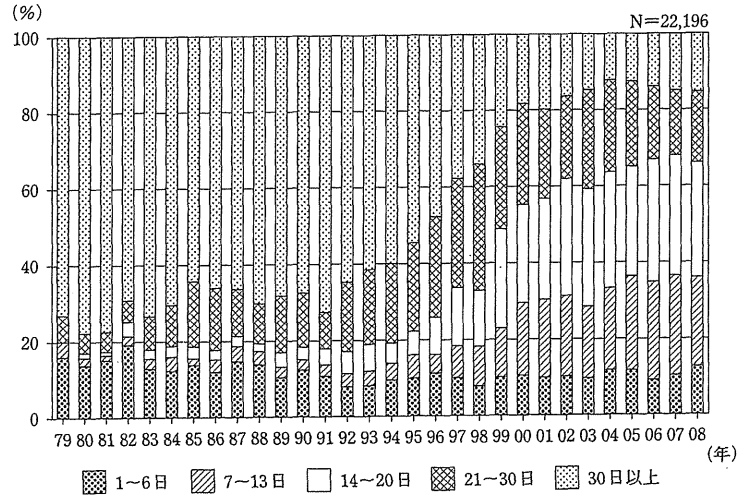

図 12　入 院 期 間（文献 1)から改変引用）

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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REVIEW ARTICLE

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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

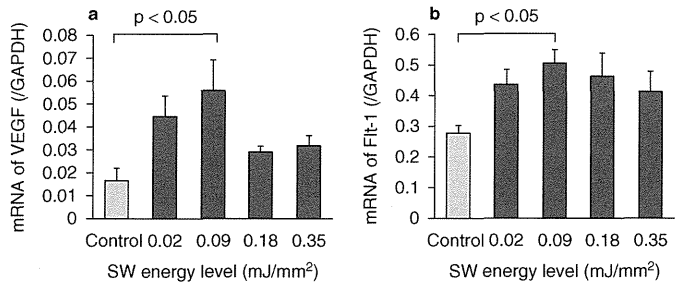

Fig. 1. Effects of shock wave (SW) therapy on mRNA expression in human umbilical vein endothelial cells (HUVECs) *in vitro*. SW treatment up-regulated mRNA expression as a proportion of glyceraldehyde dehydrogenase (GAPDH) mRNA expression of (**a**) vascular endothelial growth factor (VEGF) and (**b**) 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.

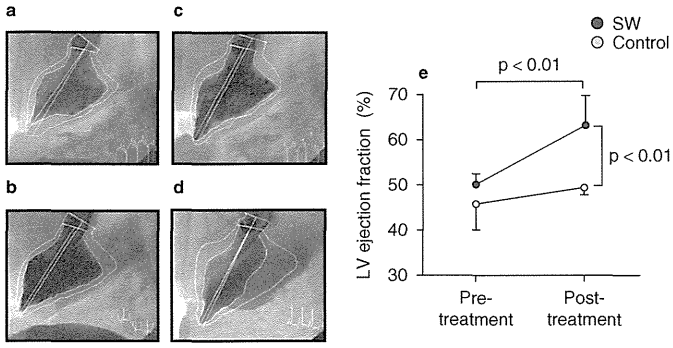

Fig. 2. Effects of shock wave (SW) therapy on left ventricular (LV) function in pigs *in vivo*. The extracorporeal cardiac SW therapy improved ischemia-induced myocardial dysfunction *in vivo* as evaluated by left ventriculography. Four weeks after the implantation of an ameroid constrictor, LV wall 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

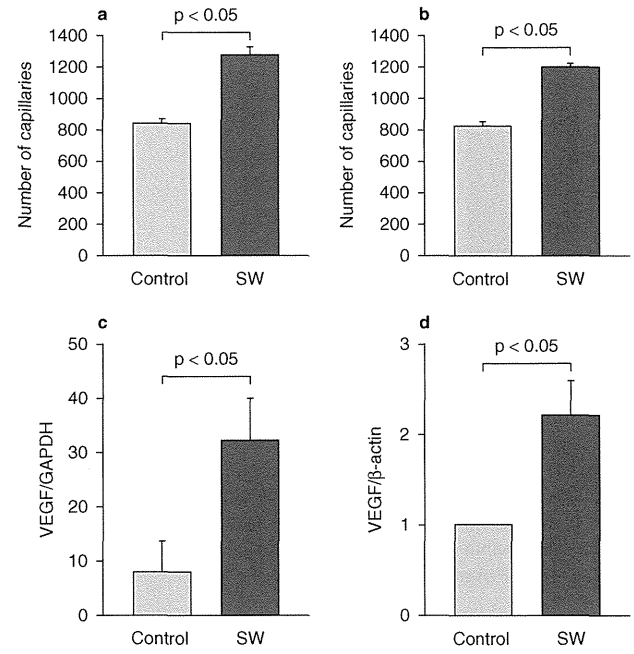

Fig. 3. Effects of shock wave (SW) therapy on capillary density and vascular endothelial growth factor (VEGF) expression in the ischemic myocardium in pigs *in vivo*. The extracorporeal cardiac SW therapy increased the density of factor VIII-positive capillaries and VEGF expression in the ischemic myocardium. 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.

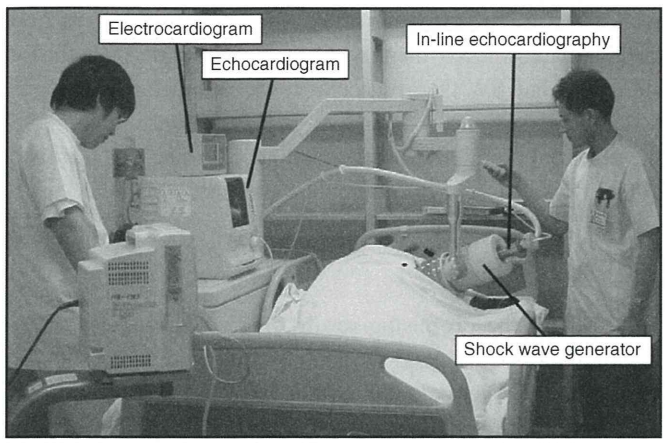

Fig. 4. Extracorporeal cardiac shock wave (SW) therapy in action in a patient with severe coronary artery disease. The machine is equipped with a SW generator and in-line echocardiography. The SW generator is attached to the chest wall of the patient when used. The SW pulse is easily focused on the ischemic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

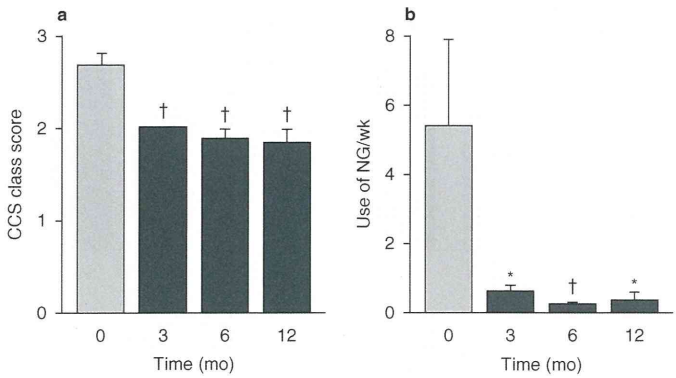

Fig. 5. Effects of extracorporeal cardiac shock wave (SW) therapy on symptoms and the use of nitroglycerin. Extracorporeal cardiac SW therapy significantly improved (**a**) the Canadian Cardiovascular Society (CCS) class scores and (**b**) number of nitroglycerin (NG) uses per week in patients with severe 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

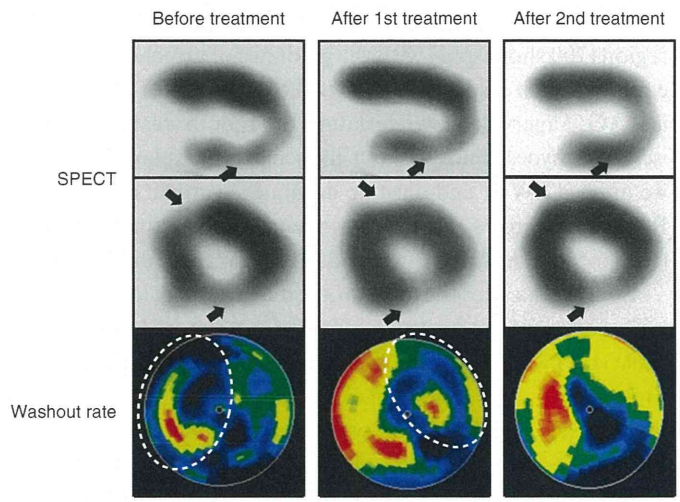

Fig. 6. Effects of extracorporeal cardiac shock wave (SW) therapy on myocardial perfusion in patients with severe angina pectoris. Dipyridamole stress thallium-201 single photon emission computed tomography (SPECT) imaging and polar map in a patient with severe three-vessel coronary artery disease before 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.

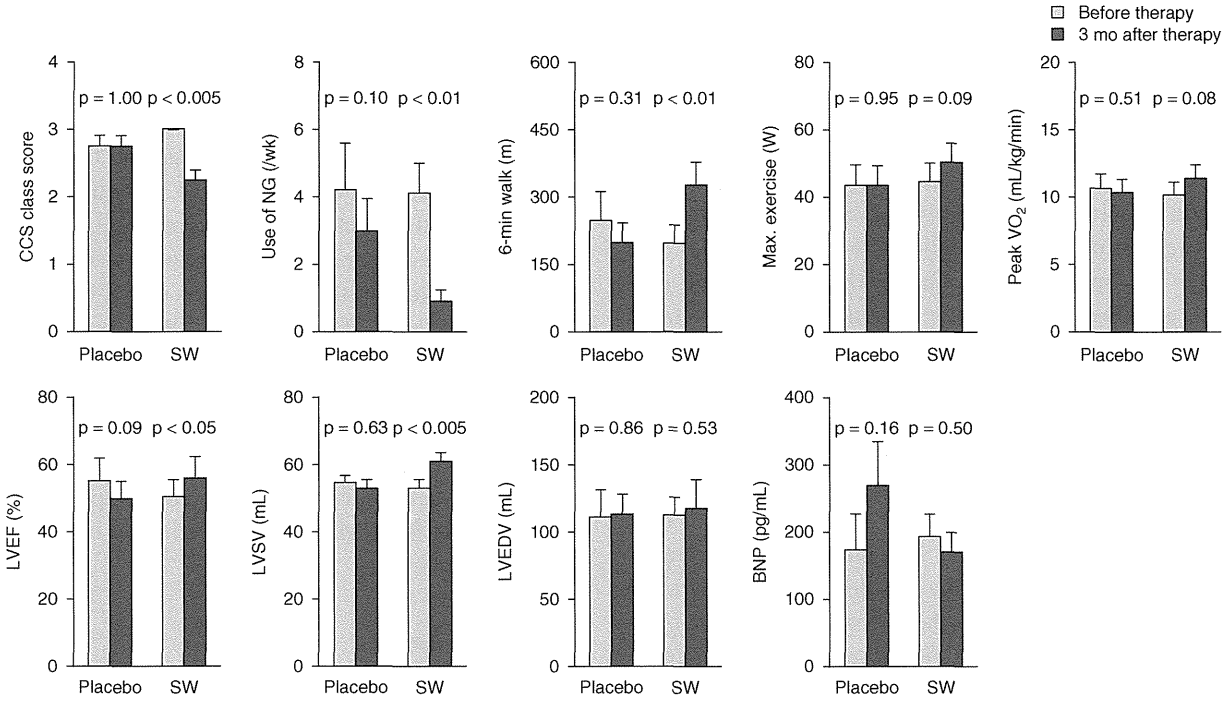

Fig. 7. Effects of extracorporeal cardiac shock wave (SW) therapy in patients with severe angina pectoris in the placebo-controlled and double-blind study. **BNP** = brain natriuretic peptide; **CCS** = Canadian Cardiovascular Society; **LVEDV** = left ventricular (LV) end-diastolic volume; **LVEF** = 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.

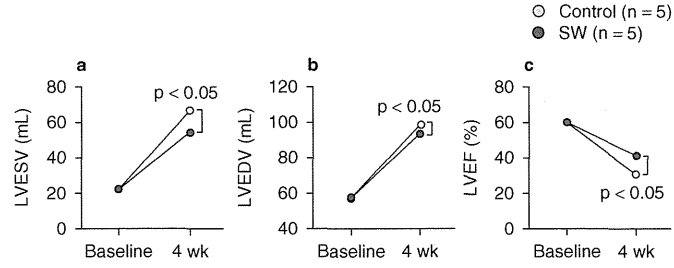

Fig. 8. Effects of extracorporeal cardiac shock wave (SW) therapy on left ventricular (LV) remodeling in pigs *in vivo*. SW therapy significantly ameliorated LV remodeling characterized by the increase in (**a**) LV end-systolic volume (LVESV) and (**b**) end-diastolic volume (LVEDV) and (**c**) reduced 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.

Acknowledgments

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ORIGINAL ARTICLE
Epidemiology

Trends in Acute Myocardial Infarction Incidence and Mortality Over 30 Years in Japan:

Report From the MIYAGI-AMI Registry Study

Toru Takii, MD; Satoshi Yasuda, MD; Jun Takahashi, MD; Kenta Ito, MD; Nobuyuki Shiba, MD; Kunio Shirato, MD; Hiroaki Shimokawa, MD; on behalf of the MIYAGI-AMI Study Investigators

Background: Worldwide, the rate of aging is highest in Japan, especially the female population. To explore the trends for acute myocardial infarction (AMI) in Japan, the MIYAGI-AMI Registry Study has been conducted for 30 years since 1979, whereby all AMI patients in the Miyagi prefecture are prospectively registered.

Methods and Results: In 1979–2008, 22,551 AMI patients (male/female 16,238/6,313) were registered from 43 hospitals. The age-adjusted incidence of AMI (/100,000 persons/year) increased from 7.4 in 1979 to 27.0 in 2008 (P<0.001). Although control of coronary risk factors remained insufficient, the rates of ambulance use and primary percutaneous coronary intervention (PCI) have increased, and the overall in-hospital mortality (age-adjusted) has decreased from 20.0% in 1979 to 7.8% in 2008 (P<0.0001). However, the in-hospital mortality remains relatively higher in female than in male patients (12.2% vs 6.3% in 2008). Female patients were characterized by higher age and lower PCI rate.

Conclusions: The MIYAGI-AMI Registry Study demonstrates the steady trend of an increasing incidence, but decreasing mortality, for AMI in Japan over the past 30 years, although the female population still remains at higher risk for in-hospital death, despite improvements in the use of ambulances and primary PCI. (*Circ J* 2010; **74:** 93–100)

Key Words: Acute myocardial infarction; Aging; Gender; Risk factors

Acute myocardial infarction (AMI) is a major cause of morbidity and mortality worldwide. In the United States, nearly 1 million patients suffer from AMI each year.[1] In the past decades, industrialization, urbanization, and associated life-style changes have taken place worldwide as the population grows older in association with the epidemics of obesity and metabolic syndrome. Especially in Japan, these changes have become more evident because the rate of aging is the highest in the world and the westernization of lifestyle has progressed rapidly.[2] In order to estimate the trends in the burden of disease, particularly that of AMI, it is important to monitor and track the incidence and mortality of AMI in the same community for a long time. Indeed, the World Health Organization Monitoring Trends and Determinants in Cardiovascular Disease (WHO-MONICA) project reported the prevalence and case-fatality rate in 21 countries,[3] but Japan was not included. Moreover, in Japan, there have been few studies specifically for AMI and most of them have included a small number of annual events with a relatively short monitoring period.[4–7]

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To explore the actual trend for AMI reflecting "real-world" practice in Japan, we have been conducting the MIYAGI-AMI Registry Study for 30 years since 1979, whereby all AMI patients in the Miyagi prefecture have been prospectively registered and there has been a relatively stable population over those years.[8,9]

Methods

The MIYAGI-AMI Registry Study

The Miyagi prefecture is located in northeastern Japan and has had a relatively stable population of approximately 2 million over the last 30 years (2,054,000 in 1979 and

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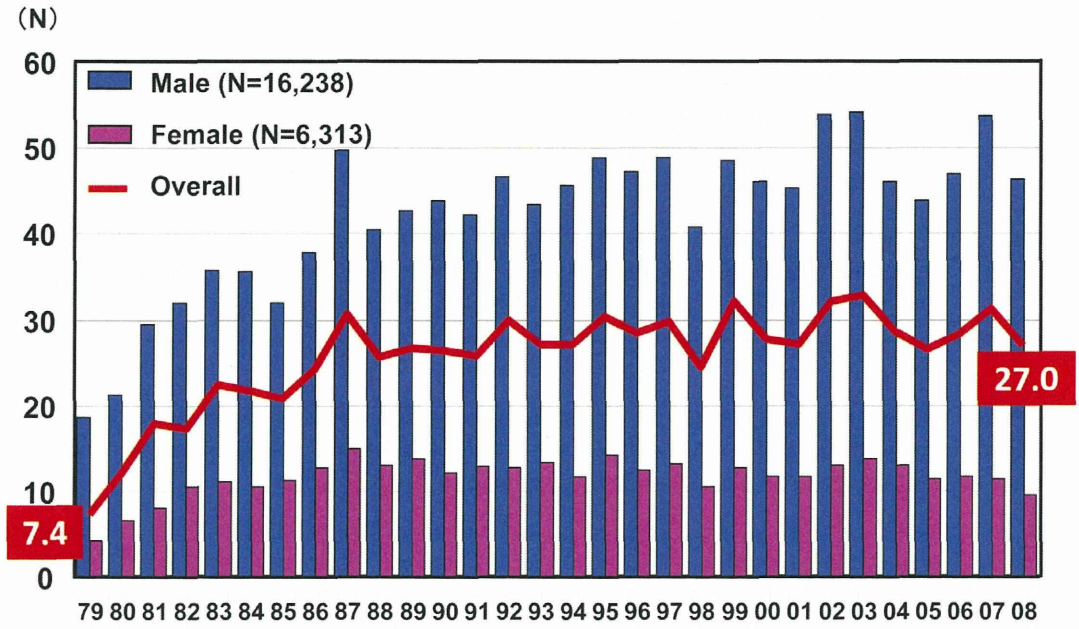

Figure 1. Age-adjusted incidence (/100,000 persons/year) of acute myocardial infarction has increased over the last 30 years, especially evident in the male population.

2,340,000 in 2008). The MIYAGI-AMI Registry Study is a prospective, multicenter, observational study. Details of data collection have been published previously.[8,9] Briefly, this registry was established in 1978 and the 43 major hospitals with a coronary care unit and/or cardiac catheterization facilities in the Miyagi prefecture have been participating (Appendix 1). In our study, almost all the patients with AMI were finally admitted to 1 of the 43 participating hospitals in the Miyagi prefecture, enabling us to precisely examine the practice for AMI. This study was approved by the Institutional Review Board of Tohoku University Graduate School of Medicine, under the condition that personal data are protected at all times.

Diagnosis of AMI was made by the individual cardiologists in charge, based on the WHO-MONICA criteria.[3] Generally, it was based on the findings of typical chest pain symptoms, ECG changes and increased serum levels of cardiac enzymes (ie, creatine phosphokinase, aspartate aminotransferase and lactate dehydrogenase).

The registration form included the date and time of symptom onset, age, sex, pre-hospital management (eg, use of ambulance, time interval from the onset of symptoms to admission), infarction site, coronary risk factors (hypertension, diabetes mellitus, dyslipidemia, and smoking), reperfusion therapies (eg, thrombolysis or percutaneous coronary intervention (PCI)), duration of hospitalization and in-hospital outcome (eg, in-hospital mortality). In the Miyagi-AMI Registry Study, we have revised the registration form step by step over the past 30 years. Thus, although the incidence of AMI and related data (time of onset, age and sex) are available for those 30 years, the date of pre-hospital management, infarction site, coronary risk factors, reperfusion therapies, duration of hospitalization, and in-hospital outcome are available for the past 10–20 years.

In the Miyagi-AMI Registry Study, the decision of reperfusion was made by the individual cardiologists in charge. Primary PCI has been commonly performed since 1992, according to the protocol of each hospital. Thrombolysis was performed with intravenous administration of urokinase (480–960×10^3 IU for 30 min) or alteplase (290–435×10^3 IU/kg for 60 min) or with intracoronary administration of alteplase (maximum 6.4×10^6 IU) or urokinase (maximum 960×10^3 IU).[2,3] Rescue PCI was performed when thromolysis was unsuccessful in terms of symptoms, ECG changes and/or coronary blood flow.

Data Analysis

In the present study, we registered a total of 22,551 patients with AMI (males/females 16,238/6,313) who were hospitalized between 1979 and 2008. Sex- and age-adjusted incidence rates of AMI per 100,000 person-years were calculated. To adjust the age distribution differences among the periods, we applied the direct method using the Japanese population from the 2000 census,[10] as the standard population.

Results are expressed as mean±SD. Trend in age-adjusted incidence, age-adjusted in-hospital mortality, and use of ambulance were assessed using the Cochran-Armitage trend test.[11,12] Age and therapy differences were estimated by the χ^2-test. These analyses were carried out with SAS software version 9.1 (SAS Institute, Inc, Cary, NC, USA). P-values <0.05 were considered to be statistically significant.

Results

The overall age-adjusted incidence of AMI (/100,000 persons/year) markedly increased by 3.6-fold, from 7.4 in 1979 to 27.0 in 2008 (P<0.001) (**Figure 1**). The average age of the male and female AMI patients in the whole period was 65±13 and 75±11 years, respectively. In males, the age-adjusted incidence of AMI (/100,000 persons/year) significantly increased by 2.5-fold, from 18.7 in 1979 to 46.4 in 2008 (P<0.0001), whereas in females, it tended to be increased by

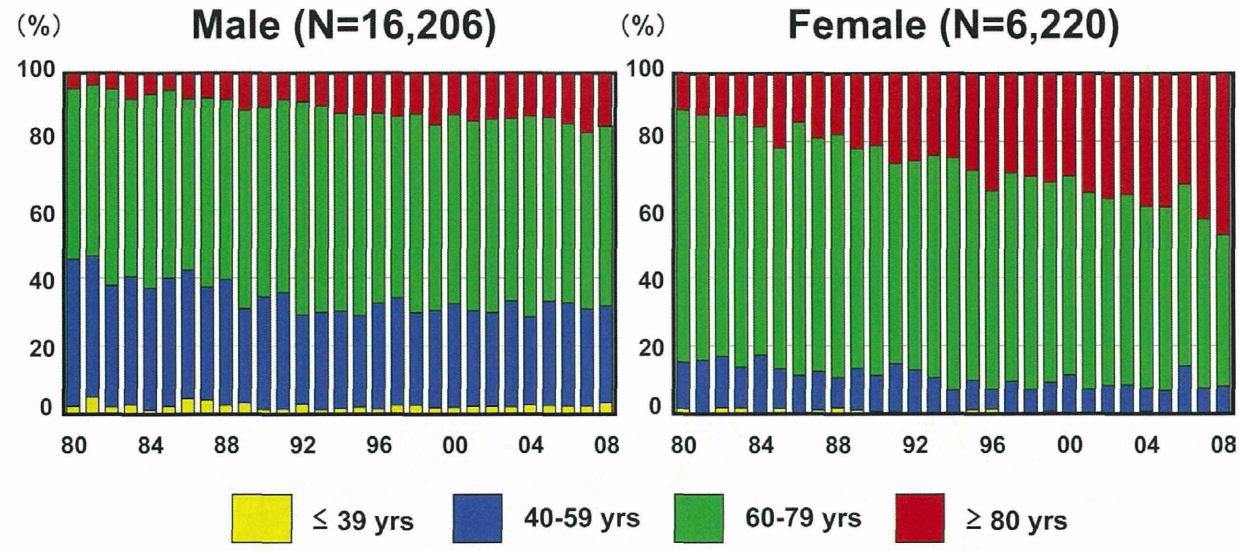

Figure 2. Serial changes in the age distribution of patients with acute myocardial infarction. The increasing prevalence of elderly patients is evident, especially females.

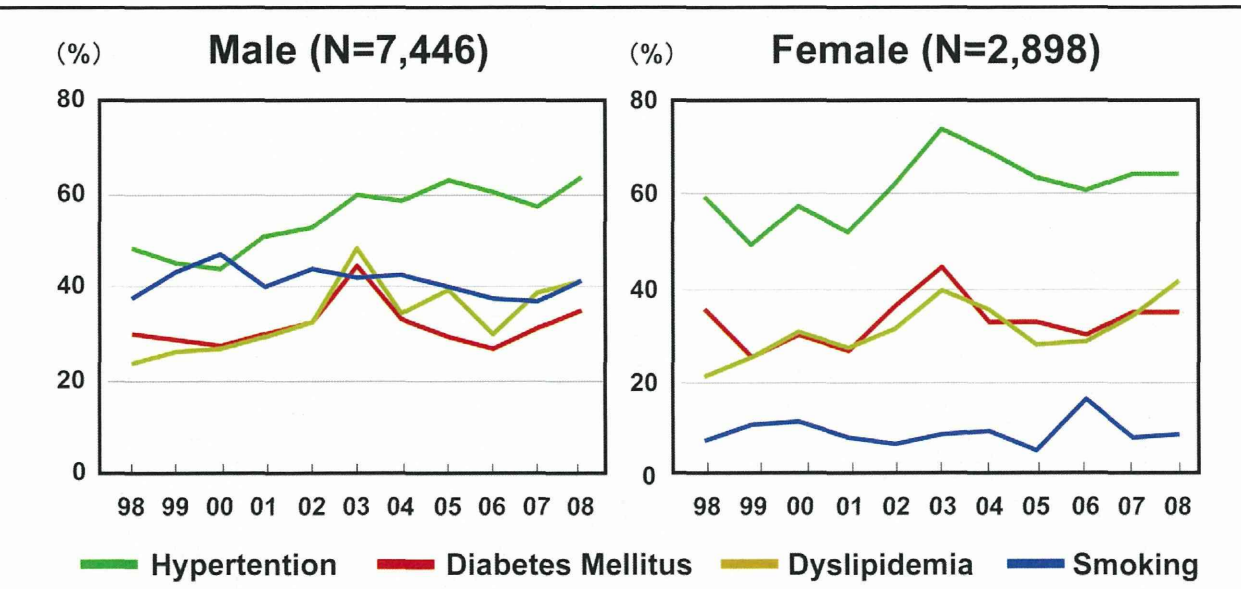

Figure 3. Prevalence of coronary risk factors in patients with acute myocardial infarction. It is evident that the control of all 4 major coronary risk factors is insufficient.

2.3-fold, from 4.2 in 1979 to 9.6 in 2008, but did not reach a statistically significant level (P=0.15).

The distribution of age significantly changed with the increased population of elderly patients, especially that of ≥80-year-old patients, in both sexes (both P<0.001) (**Figure 2**). Moreover, the prevalence of hypertension, diabetes mellitus, and dyslipidemia also significantly increased over time in both sexes (all P<0.01) (**Figure 3**). Smoking habit also remained at ~40% in male and ~10% in female patients (**Figure 3**). The peak time of onset of AMI remained in the early morning (**Figure 4**), and the distribution of the infarct site was the anterior wall in 45%, inferior/posterior wall in 43%, and other in 12%.

Over the past 30 years, the use of ambulances significantly increased from 47% in 1980 to 64% in 2008 (P<0.0001) (**Figure 5**). Along with this increased use, the overall in-hospital mortality has markedly decreased from 20% in 1979 to 8% in 2008 (P<0.0001) (**Figure 5**). However, the in-hospital mortality of female patients remained relatively higher than for male patients over the past 30 years (6.3% in males and 12.2% in females in 2008) (**Figure 5**).

Use of primary PCI has dramatically increased from 20% in

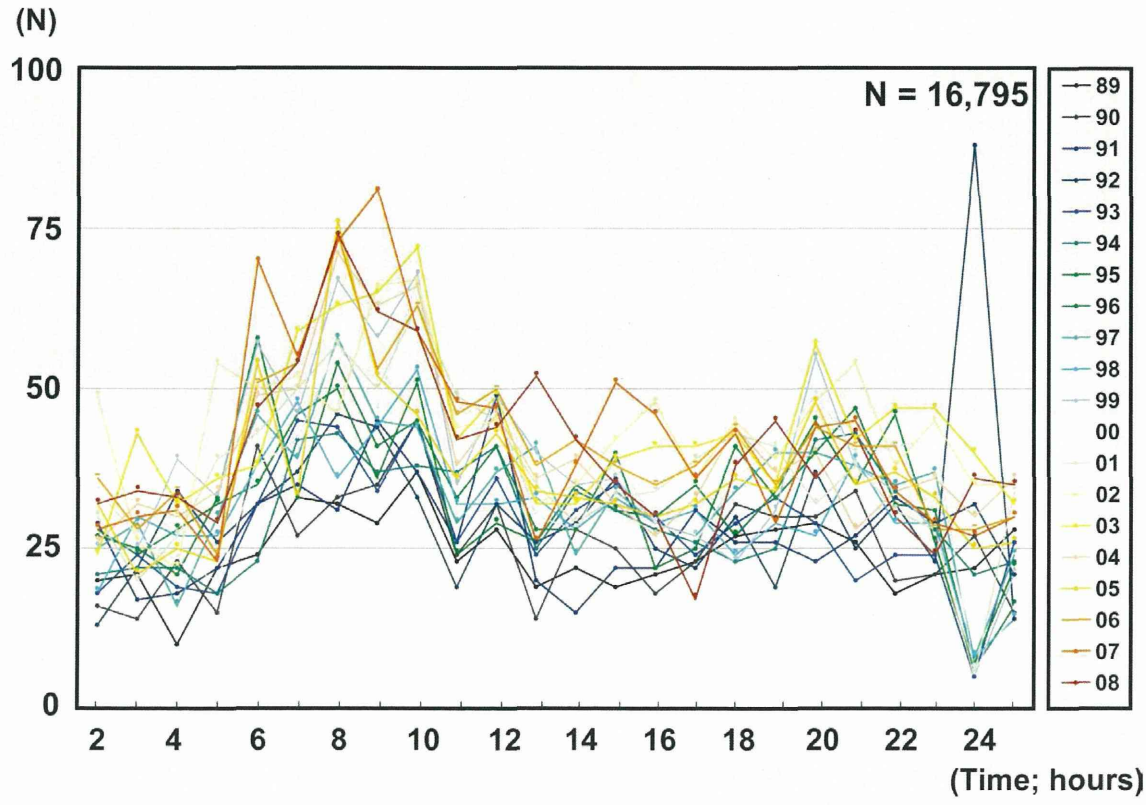

Figure 4. Peak time of onset of acute myocardial infarction has remained in the early morning.

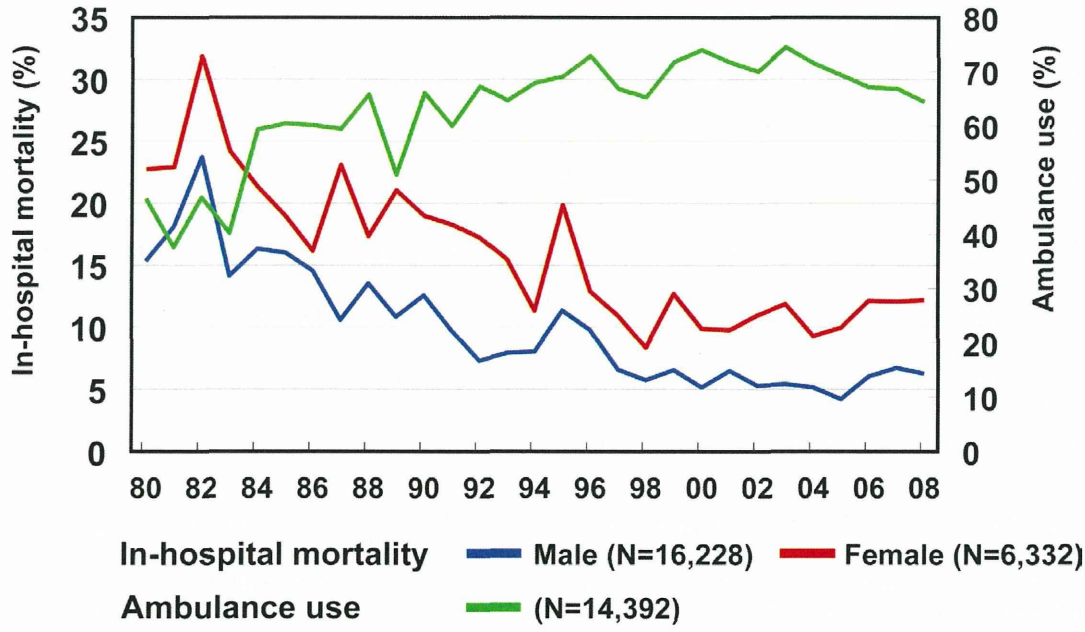

Figure 5. Age-adjusted in-hospital mortality (/100,000 persons/year) and ambulance use. Together, with the increased use of ambulances, in-hospital mortality has dramatically decreased; however, female patients still are at higher risk than male patients.

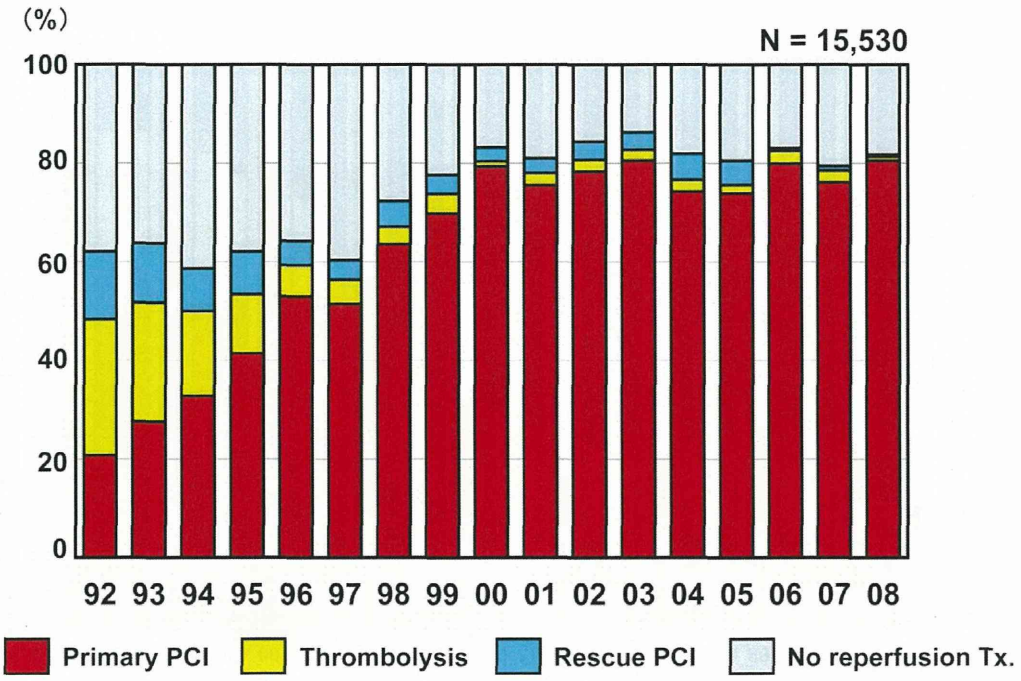

Figure 6. Prevalence of reperfusion therapy (Tx) for acute myocardial infarction. The prevalence of primary percutaneous coronary intervention (PCI) has increased, especially in the past 10 years.

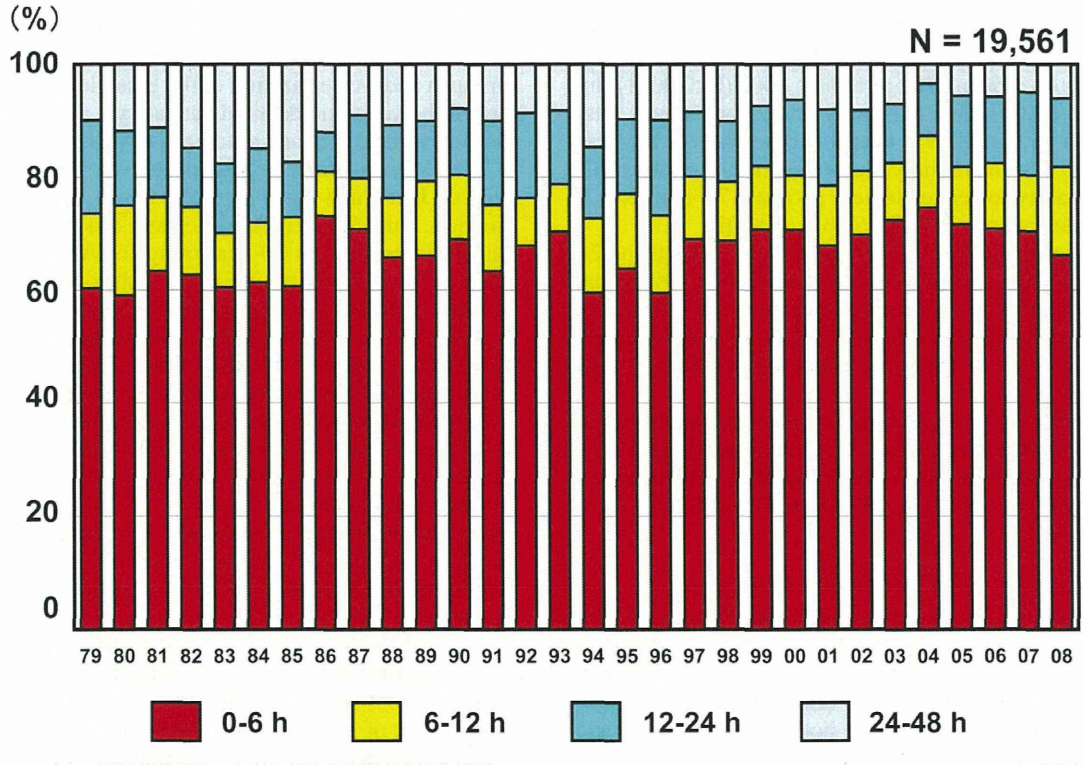

Figure 7. Time interval from the onset of symptoms to admission shows no change.

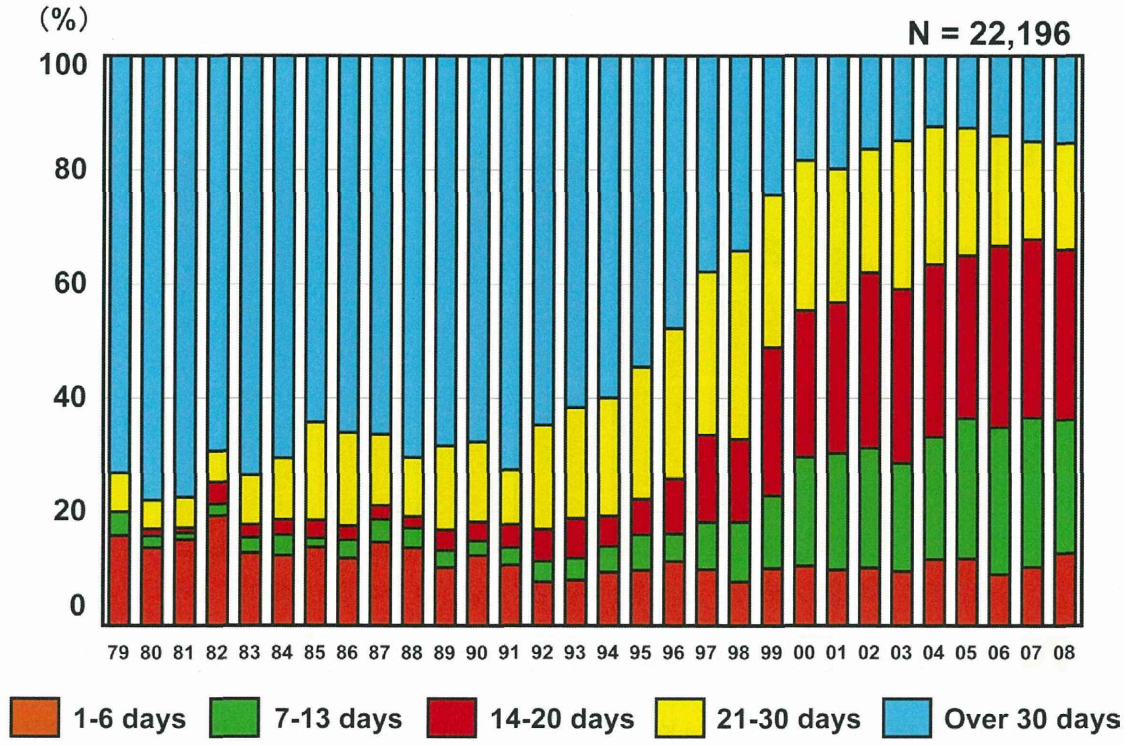

Figure 8. Hospitalization for acute myocardial infarction has been dramatically shortened.

1992 to 80% in 2008 (P<0.0001) (**Figure 6**). In contrast, the prevalence of patients without reperfusion therapy significantly decreased from 38% in 1992 to 18% in 2008 (P<0.0001). In-hospital mortality was significantly lower for patients with primary PCI (5%, n=8,693) than for those without it (17%, n=254) (P<0.01). Importantly, the prevalence of primary PCI was significantly lower for female patients (71%, n=2,412) than for male patients (80%, n=6,061) (P<0.01).

In 1979, approximately 30% of patients had more than 12 h from the onset of AMI to hospitalization, while 60% of patients were hospitalized within 6 h after the onset (**Figure 7**). This tendency for the majority of AMI patients to be hospitalized within 6 h was fairly consistent throughout the study period (**Figure 7**).

Finally, the duration of hospital stay has significantly shortened over the past 30 years; the prevalence of discharge within 20 days after the onset of AMI significantly increased from 20% in 1979 to 66% in 2008 (P<0.0001) (**Figure 8**).

Discussion

The data from the 30-year MIYAGI-AMI Registry Study demonstrates that there is the steady trend of increasing incidence, but decreasing mortality, for AMI in Japan and that the female population still remains at higher risk for in-hospital mortality, despite progress in both patient transfer and reperfusion therapy.

Increasing Incidence of AMI

There have been few studies regarding the incidence of AMI in Japan and most were performed between the 1960s and 1980s.[4,13,14] Their results were conflicting as they reported either a declining or flattened[4,13,14] trend in the incidence of AMI. After the 1990s, the rate of aging has been the highest in Japan and westernization of the lifestyle has rapidly accelerated; however, no detailed data are yet available regarding the actual incidence and outcome of AMI.

The Miyagi prefecture is located on the Pacific Ocean side of Japan and has a typical balance of urban and rural districts. Our MIYAGI-AMI Registry Study provides important insights into the 30-year trend for AMI in Japan from 1979 to 2008. As shown in **Figure 1**, the overall age-adjusted incidence of AMI (/100,000 persons/year) increased from 7.4 in 1979 to 27.0 in 2008, indicating a steady trend of increasing incidence of AMI. The incidence of AMI was male-predominant (males 46.4 vs females 9.6 in 2008), a consistent finding with the Takashima AMI registry (males 100.7 vs females 35.7 in 1999–2001)[5] and the Niigata and Nagaoka study (males 41.9 vs females 5.3 in 1994–1996).[6] However, the current incidence of AMI in Japan is still lower than that in North America and Europe; the incidence of AMI for males (/100,000 persons/year) is 824 in Finland, 823 in United Kingdom, 605 in Canada, 508 in the United States, 314 in France, and 270 in Italy.[15]

Age is a most important risk factor for the development of cardiovascular diseases and accompanying clinical events. In the present study, the aging of the population is evident; the number of aged patients, especially that of ≥80-year-old patients, increased significantly in the past 30 years (**Figure 2**). Even a relatively short-term survey (1992–2001) of Medicare in 4 US states demonstrated that the age of AMI patients is older and that the proportion of the population >85 years old has increased.[16] These findings indicate the urgent need for evidence-based management strategies applicable to increas-

ingly elderly AMI patients.[17]

Insufficient Control of Coronary Risk Factors

The WHO-MONICA studies, as well as the Japanese epidemiological studies, have previously shown that the risk of cardiovascular diseases increases with clustering of risk factors, such as hypertension, hyperlipidemia and diabetes mellitus.[18–20] The present study demonstrates that the control of major coronary risk factors is still insufficient in Japan (**Figure 3**), which could largely account for the increasing incidence of AMI. The westernization of lifestyle and the high rate of aging in Japan are apparent causative factors for the trend. Furthermore, the prevalence of smoking still remains high at ~40% in male patients with AMI, although it has been reported that the smoking rate has declined by 20% in the general Japanese population.[21,22]

Higher Risk for Females for In-Hospital Mortality of AMI

One of the important findings in the present study is that the in-hospital mortality still remains relatively higher for female patients than for male patients (**Figure 5**). A similar trend has been reported from the American Heart Association Heart Disease and Stroke Statistics.[23] Several factors could be involved in the sex difference in in-hospital mortality, including higher age, longer time elapsed from onset to hospitalization, and low prevalence of PCI in female AMI patients. Indeed, in the present study, the average age of the female patients was 10 years older than that of the male patients. The older age of female patients at the time of admission may further limit the use of several therapies,[24] which could have been the case in the present study. In addition, the incidence of death from procedural complications, such as vascular and hemorrhagic complications, is greater in females.[25] Thus, more attention should be paid to these factors when treating female AMI patients.

Unchanged Time of Onset and Infarct Site

It has been repeatedly demonstrated that the onset of AMI peaks early in the morning in both Japan[26] and Western countries.[27,28] The present study not only confirmed this point but also demonstrated that such a tendency has remained unchanged for the past 30 years in Japan (**Figure 4**). These results suggest that the triggering mechanism(s) for AMI has remained unchanged despite the increasing incidence of the disease.

The present study also demonstrated that the AMI site has unchanged in the last 30 years. Although anterior AMI is associated with worse outcome, as compared with inferior AMI,[29] the present result indicates that the improvement of morality is likely to be related to factors other than the AMI site.

Improvement of Critical Care and In-Hospital Care for AMI

The present study demonstrated the overall in-hospital mortality (age-adjusted) has significantly reduced from ~20% in 1979 to 12.2% in 2008. The duration of hospital stay was also significantly shortened over the past 30 years (**Figure 8**), during which the paradigm of AMI management has shifted from a conservative strategy to an interventional strategy.[30] In fact, in the present study, use of primary PCI has been increasing from 20% in 1992 to ~80% in 2008 (**Figure 6**), and in-hospital mortality was lower in patients who underwent primary PCI than in those who did not. The progress in reperfusion therapy, especially that of primary PCI, appears to have contributed to the reduction in in-hospital mortality and hospital stay, as previously reported from this registry.[8,9]

Currently, approximately half of AMI patients in the Western countries are transported to hospital by ambulance.[31,32] The present study demonstrated the ambulance use in Japan has increased to ~70% in the past 10 years (**Figure 5**). Because the majority of AMI patients in the past 30 years were hospitalized within 6 h (**Figure 7**), the increased use of ambulances may not have directly contributed to the shortened interval from onset of symptoms to hospitalization. However, the increased use of ambulances should have resulted in increased use of primary PCI with a resultant improvement in the in-hospital mortality.

The increasing incidence of, but decreasing in-hospital mortality from, AMI in Japan may have resulted from the recent increase in the number of patients with ischemic heart failure, as reported in the Chronic Heart Failure Analysis and Registry in the Tohoku District (CHART) registry study.[33] For surviving AMI patients, it is important to understand the underlying risk factors that lead to secondary cardiac events.[34] Indeed, a more effective strategy to improve the management of post-infarction heart failure needs to be developed.[33,34]

Conclusions

Our MIYAGI-AMI Registry Study demonstrates that over the past 30 years in Japan, there has been a steady trend of increasing incidence, but decreasing mortality, for AMI in the Japanese population, although female patients are still at higher risk for in-hospital mortality than male patients, a result in which both positive (eg, increased use of ambulance and primary PCI) and negative factors (eg, insufficient control of coronary risk factors and aging of the whole society) may be involved.

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Appendix 1

List of Participating Hospitals

Fukaya Hospital, Hiroshi Akiho, MD; Hikarigaoka Spellman Hospital, Tomofumi Mimata, MD; Ishinomaki Municipal Hospital, Kenjirou Akai, MD; Ishinomaki Red-Cross Hospital, Hiroyasu Sukegawa, MD; JR Sendai Hospital, Masao Kuroha, MD; Katta General Hospital, Hiroyuki Kanno, MD; Kesen-numa Hospital, Kazunori Ogata, MD; Kurihara Central Hospital, Seiji Komatsu, MD; Tohoku Rosai Hospital, Tatsuya Komaru, MD; Marumori National Health Insurance Hospital, Masataka Otomo, MD; Miyagi Eastern Cardiovascular Institute, Toru Naganuma, MD; Miyagi Cancer Center, Nobuo Tomisawa, MD; Miyagi Cardiovascular and Respiratory Center, Noboru Osawa, MD; Mori Hospital, Akio Mori, MD; Nagamachi Hospital, Hidetoshi Mitobe, MD; Nishitaga National Hospital, Shigenori Kitaoka, MD; NTT EAST Tohoku Hospital, Aki Yamada, MD; Oizumi Memorial Hospital, Yoshirou Koiwa, MD; Osaki Citizen Hospital, Tetsuya Hiramoto, MD; Saito Hospital, Keiji Otsuka, MD; Saka General Hospital, Atsushi Obata, MD; Sanuma Municipal General Hospital, Hiroshi Ishii, MD; Sendai Cardiovascular Center, Shin-ya Fujii, MD; Sendai City Hospital, Tetsuo Yagi, MD; Sendai Kosei Hospital, Taiichirou Meguro, MD; Sendai Medical Center, Tsuyoshi Shinozaki, MD; Sendai Open Hospital, Masaharu Kanazawa, MD; Sendai Public Health Insurance Hospital, Yoshichika Oikawa, MD; Sendai Red-Cross Hospital, Yuji Konno, MD; Sendai Tokushukai Hospital, Kimihiko Ogata, MD; Sen-en General Hospital, Ryouichi Hashiguchi, MD; Shichigashuku National Health Insurance Clinic, Takahiro Nagashima, MD; Shiogama City Hospital, Jun Goto, MD; South Miyagi Medical Center, Kan-ichi Inoue, MD; Tohoku Kosai Hospital, Mitsumasa Fukuchi, MD; Tohoku University Hospital, Department of Cardiovascular Medicine, Hiroaki Shimokawa, MD; Department of Cardiovascular Surgery, Kouichi Tabayashi, MD; Department of Gastroenterology, Toru Shimosegawa, MD; Tohoku Welfare and Pension Hospital, Yoshiaki Katahira, MD; Tome Public Hospital, Munehiko Ishii, MD.

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NOTE

Association of plasma B-type natriuretic peptide levels with obesity in a general urban Japanese population: the Suita study

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Abstract. The inverse association between plasma B-type natriuretic peptide (BNP) levels and body mass index (BMI) has been reported in Western populations. Here we analyzed the relationship between plasma BNP and obesity in a general urban Japanese population. We recruited 1,759 subjects without atrial fibrillation or history of ischemic heart disease aged 38-95 years (mean age ± standard deviation 64.5 ± 10.9 years, 56.1% women, mean BMI 22.8 ± 3.1 kg/m^2) from the participants in the Suita Study between August 2002 and December 2003. In multivariable regression analyses adjusted for age, systolic blood pressure, pulse rate, serum creatinine, left ventricular hypertrophy in ECG, the inverse relationships between BNP levels and BMI (kg/m^2) was found in both sexes (both $p<0.001$). Multivariable-adjusted mean plasma BNP levels in the group of BMI<18.5, 18.5≦BMI<22, 22≦BMI<25, and 25≦BMI were 23.4, 17.9, 14.0 and 13.0 pg/mL, respectively (trend $p<0.001$). The negative association of body fat (percentage and mass), skin fold thickness, or waist circumference with BNP levels was observed in both sexes ($p<0.01$). Among the obesity indices, body fat mass is most tightly associated with BNP. In conclusion, plasma BNP was inversely associated with obesity-related markers such as body fat mass, skinfold thickness and waist circumferences after adjusted for relevant covariates in a Japanese population.

Key words: BNP, BMI, Body fat mass, Japanese

B-TYPE natriuretic peptide (BNP) is a cardiac hormone, synthesized in, processed in and secreted from heart [1]. The secretion of BNP is stimulated in heart failure along with its severity. Plasma BNP is clinically utilized to diagnose the existence or the severity of the cardiac failure [2]. BNP levels are affected by demographic variables such as age, gender, and clinical characteristics such as hypertension [3, 4], atrial fibrillation [5], and renal function [6].

Several recent studies have suggested that obesity, as indexed elevated body mass index (BMI), also affects BNP levels, with lower circulating levels in those with higher BMI in subjects with and without heart failure [7-12]. In addition, the Dallas Heart Study revealed that BNP is closely associated with lean mass than with fat mass [8]. However, these studies were mostly conducted in Western countries, where BMI is much higher than in other parts of the world. It is not unclear whether this relationship could apply in a general Japanese population whose BMI levels are lower than in Western countries [13].

Therefore, the aim of the present study is to evaluate the association between BMI and BNP levels in a general urban Japanese population. To further elucidate the mechanisms of the relationship between obesity and BNP levels, we examine the relationship between BNP levels and various obesity related factors such as lean body mass, body fat mass, skin fold thickness, and waist circumferences.

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Methods

Study Sample

The Suita Study [14-16], an epidemiological study of cerebrovascular and cardiovascular disease, was based on a random sampling of 15,200 (30–79 years of age at enrollment) Japanese residents of Suita. They were all invited, by letter, to attend regular cycles of follow-up examination (every 2 years). Subjects were recruited into the Suita Study between August 2003 and December 2004 in this study (n=2,007). Subjects with chronic atrial fibrillation at time of referral (n=40) and history of ischemic heart disease (n= 97) were excluded. After applying this exclusion, 1,759 individuals were included in this analysis. The study design was approved by the institutional review board of the National Cardiovascular Center. Informed consent was obtained from all subjects.

Routine physical examination, 12-lead surface ECG, several blood chemical variables and plasma BNP measurements were performed. A physician or nurse interviewed each patient personal history of cardiovascular disease, including angina pectoris and/or myocardial infarction. Blood pressure was measured after at least 5 minutes of rest in a sitting position. Systolic and diastolic blood pressures (SBP and DBP) were the means of two measurements by well-trained doctors (recorded at least 1 min apart) [16]. BMI was calculated as weight in kilograms divided by height in meters squared. Waist circumference was measured in a standing position at the umbilical level by well-trained technicians [15]. Lean body mass and body fat mass were calculated by the bioelectrical impedance analyzer [17]. Brachial triceps and subscapular skin fold thickness was measured using keys calipers by trained physician epidemiologists with standard methods.

Measurement of BNP

Blood sample was collected into tubes containing EDTA. Plasma BNP was measured by validated and commercially available immunoassay kit (Shionogi, Osaka, Japan). The measurable range of the BNP assay is 4.0 to 2000 pg/mL. Average intra- and inter-assay coefficients of variation were 3.7% and 4.5%, respectively.

Statistical Analyses

Continuous data are presented as means ± standard deviations (SDs) for normally distributed variables and as medians (interquartile range) in case of skewed distribution. Categorical data are presented as numbers and percentage. Comparison of clinical characteristics between patients each BMI category were performed using Kruskal-Wallis test for continuous data and χ^2 test for categorical data. Variables with skewed distributions underwent logarithmic transformation to create normal distributions. The value less than the lower detection limit of the BNP assay (BNP < 4.0 pg/mL) were found 9.0% of all subjects. For analyses examining continuous BNP levels, we treated lower detection limit of the BNP assay for 4.0 pg/mL and performed multivariable linear regression with log-transformed BNP as the dependent variables. Covariates examined for inclusion in the multivariable models were age, sex, systolic blood pressure, pulse rate, serum creatinine, and left ventricular hypertrophy (LVH) in ECG. Sex-specific regression analyses were also performed. In additional models, we replaced the continuous BMI variable with BMI categories (BMI<18.5, 18.5 ≦ BMI< 22, 22 ≦ BMI < 25, and 25 kg/m^2 ≦ BMI). The results of the multivariable analyses were also used to examine the relations of BMI category to adjusted plasma BNP levels. Since models used log-transformed dependent variables, we exponentiated the β coefficient for BMI to characterize its multiplicative effect on absolute plasma BNP levels. Because of the skewed nature of the BNP distributions and potential violations of assumptions inherent in the least-squares model, we used multivariable logistic regression analyses to analyze correlations of normal plasma BNP levels (BNP<18.4 pg/mL). We estimated odds ratios for having normal BNP levels according to BMI category, with lowest BMI individuals as the referent group. Odds ratios were adjusted for the same covariates used in the linear models.

All data were analyzed with the JMP version 6.0 (SAS Corporation, Cary, NC, USA) statistical software package.

Results

Baseline Characteristics

The clinical characteristics of study population (mean ± SDs age 64.5 ± 10.9 years, mean BMI 22.8 ± 3.1 kg/m^2, 56.1% women) stratified by BMI category are listed in Table 1. Increasing BMI was associated with an increased likelihood of being men; higher systolic blood pressure, and lower BNP levels.

Table 1 Baseline characteristics stratified by BMI: the Suita Study.

	BMI<18.5 (n=139)	18.5 ≦ BMI<22 (n=590)	22 ≦ BMI<25 (n=642)	25 ≦ BMI (n=388)	*p* value
Age, y	65.6 ± 11.5	64.2 ± 11.5	64.7 ± 10.6	64.0 ± 10.3	0.471
Men, %	28.1	35.3	50.5	51.8	<0.001
Smoking (ever), %	88.5	82.5	72.0	74.7	<0.001
Alcohol (ever), %	97.1	97.5	96.3	97.2	0.658
Hypertension, %	23.7	23.4	37.1	48.7	<0.001
Diabetes Mellitus, %	4.3	4.1	8.9	13.7	<0.001
Dyslipidemia, %	11.5	21.7	26.3	30.7	<0.001
Left ventricular hypertrophy, %	7.2	10.0	11.4	7.2	0.119
Height, cm	157.2 ± 8.0	157.3 ± 8.0	159.0 ± 9.3	158.7 ± 8.9	0.003
Weight, kg	43.2 ± 5.1	50.9 ± 5.8	59.4 ± 7.3	68.5 ± 9.4	<0.001
Skinfold thickness, mm	21.1 ± 6.8	26.5 ± 7.5	31.3 ± 8.9	37.9 ± 11.4	<0.001
Body fat mass, kg	7.9 ± 1.8	12.3 ± 2.3	16.1 ± 2.6	22.1 ± 4.5	<0.001
Lean body mass, kg	35.4 ± 4.9	38.6 ± 5.9	43.3 ± 8.0	46.4 ± 8.9	<0.001
Waist circumference, cm	71.6 ± 5.0	78.9 ± 5.3	86.5 ± 5.1	94.6 ± 6.6	<0.001
Systolic blood pressure, mmHg	117 ± 21	120 ± 18	125 ± 19	131 ± 19	<0.001
Diastolic blood pressure, mmHg	71 ± 11	74 ± 10	76 ± 10	80 ± 10	<0.001
Pulse rate, bpm	68 ± 10	67 ± 10	67 ± 9	67 ± 10	0.252
Serum creatinine, mg/dL	0.69 ± 0.21	0.68 ± 0.17	0.71 ± 0.16	0.72 ± 0.23	<0.001
Fasting plasma glucose, mg/dL	93 ± 18	94 ± 15	100 ± 21	105 ± 22	<0.001
HbA1c, %	5.4 ± 0.8	5.3 ± 0.5	5.5 ± 0.7	5.6 ± 0.8	<0.001
Triglyceride, mg/dL	80 ± 55	92 ± 55	109 ± 72	133 ± 86	0.722
Total cholesterol, mg/dL	208 ± 31	210 ± 32	211 ± 33	211 ± 32	<0.001
HDL cholesterol, mg/dL	73 ± 17	64 ± 15	59 ± 14	54 ± 13	<0.001
BNP, pg/mL	23.2 (14.7, 41.8)	18.6 (9.0, 32.6)	14.5 (7.5, 26.0)	13.2 (6.4, 24.2)	<0.001

Results presented are mean ± SD for continuous variables or percentage for categorical variables.
BNP levels are presented as median (25th, 75th percentile).
Comparison of clinical characteristics between patients each BMI category were performed using Kruskal-Wallis test for continuous data and χ^2 test for categorical data.

When BNP level was categorized by quartile (data not shown), increasing BNP levels was associated with an increased likelihood of being women and older; lower BMI, and pulse rate; an increased likelihood of having LVH; and higher systolic blood pressure.

Association between BMI and BNP Levels

Results of multivariable regression models are shown in Table 2. After adjustment for age, systolic blood pressure, pulse rate, serum creatinine, and LVH, BMI was inversely associated with plasma BNP levels, with 5% decrease associated with each 1 unit increase in BMI in both sexes (p<0.001 for both). There was also a progressive decrease in plasma BNP levels with increasing BMI category. In men, highest BMI group (BMI ≧ 25) had 29% lower plasma BNP levels compared with lowest BMI group (BMI < 18.5) (p<0.001). In women, highest BMI group (BMI ≧ 25) had 23% lower plasma BNP levels compared with lowest BMI group (BMI < 18.5) (p<0.001). Multivariable-adjusted mean levels of plasma BNP were shown in Fig. 1 for each BMI category. For both sexes, adjusted BNP levels decreased in a stepwise fashion across categories of increasing BMI (p<0.001 for trend for all comparisons).

For logistic regression analysis, the BNP levels were considered as a categorical variable, pooling the subjects into two distinct groups: <18.4 pg/mL (nor-