

● 図 1 心筋エネルギー代謝

心筋細胞は脂肪酸、ブドウ糖、乳酸を燃料とし、主要なATPをミトコンドリアでの酸化的リン酸化によって生成している

2) 心筋細胞内での代謝過程

ブドウ糖は心筋細胞内に取り込まれ解糖系により分解され、2分子のピルビン酸を生じる。ピルビン酸はミトコンドリアに流入し、ミトコンドリア膜に存在するピルビン酸脱水素酵素の作用によりアセチル CoA に変換される。脂肪酸は心筋細胞内に流入後アシル CoA に生成され、カルニチンと結合してアシルカルニチンとなり、ミトコンドリア内に移動して再びアシル CoA とカルニチンに分かれる。その後アシル CoA はβ酸化によりアセチル CoA に分解される。

3) ミトコンドリア内での酸化的リン酸化

このようにしてブドウ糖や脂肪酸から生成されたアセチル CoA は TCA 回路に入り、さまざまな中間代謝産物に変換され、その過程で NADH や FADH₂ といった還元型の補酵素が産生される。これらの補酵素由来の電子は電子伝達系を流れる。その際、電子の持つエネルギーによりミトコンドリアの内膜から外へ H⁺ が移動し、膜を隔てて H⁺ イオン勾配が生じる。この H⁺ イオン勾配が ADP リン酸化の駆動力となり、ATP が産生される。この過程を **酸化的リン酸化** と呼ぶ。好気性条件下では、ブドウ糖 1 分子から ATP 32 分子（うち解糖系由来の ATP は 2 分子）が産生され、脂肪酸の 1 例としてパルミチン酸 1 分子から ATP 105 分子が産生されると考えられている。ATP は心筋細胞内でクレアチンキナーゼの作用によりクレアチンと結合し、クレアチンリン酸の形でエネルギーを蓄える。収縮や Ca²⁺ サイクリングの維持、イオンの能動輸送に必要な ATP はクレアチンリン酸から供給される。

3 病的な心筋のエネルギー代謝

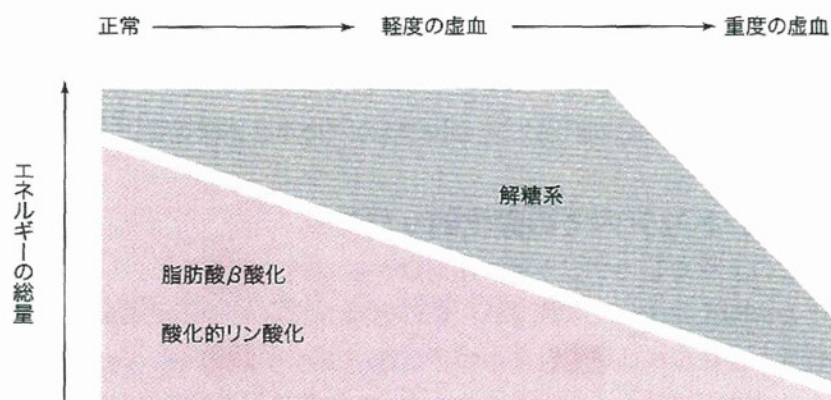
高血圧や心筋症などにより病的な肥大を起こした心臓には、遺伝子情報のリプログラミングが起こり、エネルギー代謝は胎生型へ変化する。すなわちミトコンドリアでの酸化的リン酸化が低下し、主なエネルギー源は脂肪酸からブドウ糖に移行し、ブドウ糖を解糖系で燃焼させ、ATPの合成を行うようになる。この代謝変化は心筋酸素消費を抑え、一過性には適応現象となるが、やがてATPの産生不足から収縮不全を来すようになる。

また、虚血性心疾患において冠血流が障害されると、心筋に十分な酸素の供給が得られず、脂肪酸の β 酸化は障害され、ミトコンドリアでの酸化的リン酸化が低下し、解糖系が促進される。この解糖系促進は、酸素に依存しないATPを供給し心筋を維持しようとする生体の防御機構である。しかし、嫌気性条件下ではピルビン酸がTCA回路に入らず、乳酸が産生され、細胞内に乳酸が蓄積し血中へと放出される。さらに重症の虚血では、ブドウ糖運搬の低下とグリコーゲンの枯渇、乳酸や H^+ イオンの蓄積などにより解糖系も阻害される(図2)。

このような病的な心筋の脂肪酸代謝からブドウ糖代謝への移行を非侵襲的に画像化可能としたものが ^{18}F -フルオロデオキシグルコース(^{18}F -FDG)を利用した陽電子放射型断層撮影(PET)である。PETの詳細については別項を参照されたい。

● memo 冠静脈洞血中乳酸濃度

好気性条件では心筋で消費される乳酸が、嫌気性条件では心筋に蓄積し放出され、心筋虚血時には冠動脈よりも冠静脈洞の乳酸濃度が高値を示す。この現象を利用し、冠動脈と冠静脈洞の血中乳酸値を測定し心筋虚血の有無の判定に利用することが可能である。



● 図2 心筋虚血に対する代謝応答

正常時には脂肪酸を主な燃料とし酸化的リン酸化によってATPを生成しているが、虚血になるとブドウ糖を主な燃料として利用し、解糖系にてATPを生成する。重度の虚血になるとブドウ糖の運搬も低下し、解糖系も機能しなくなる

● memo ^{18}F -FDG PET

^{18}F -FDGはブドウ糖のアナログであり、心筋のブドウ糖利用状態の評価に用いられる。心筋血流および収縮が低下した領域でブドウ糖代謝が保持されているいわゆる「冬眠心筋」の検出が可能であり、冬眠心筋は血行再建術が施行された場合、心機能改善が期待できる。

4 おわりに

心臓のエネルギー代謝のバランスは心疾患の発症や進展と密接に関連している。ブドウ糖、脂肪酸代謝経路やATP産生経路は、今後心疾患治療の標的となる可能性が高いと考えられる。

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Effect of the Great East Japan Earthquake on Cardiovascular Diseases

– Report From the 10 Hospitals in the Disaster Area –

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Background: We reported an increased occurrence of cardiovascular diseases (CVDs) after the Great East Japan Earthquake by examining ambulance records, but it had to be confirmed by cardiologists.

Methods and Results: We enrolled patients admitted to the cardiology department of the 10 hospitals in the disaster area from 4 weeks prior to 15 weeks after March 11 in the years 2008–2011 (n=14,078). The weekly occurrence of several CVDs, including heart failure (HF), pulmonary thromboembolism (PTE) and infectious endocarditis (IE), was sharply and significantly increased after the Earthquake.

Conclusions: The Disaster caused significant increases in the occurrence of HF, PTE and IE. (*Circ J* 2013; **77**: 490–493)

Key Words: Cardiovascular disease; Disasters; Great East Japan Earthquake

We examined ambulance records from Miyagi prefecture and reported that the occurrence of cardiovascular diseases (CVDs), including heart failure (HF), acute coronary syndrome (ACS), stroke, and cardiopulmonary arrest, had increased after the Great East Japan Earthquake (magnitude 9.0 on March 11, 2011).¹ However, because the ambulance records were made in the emergency rooms by doctors who were not always cardiologists, our findings had to be confirmed by cardiologists in the disaster area. Furthermore, we did not examine the incidence of pulmonary thromboembolism (PTE), infectious endocarditis (IE) or takotsubo cardiomyopathy in that previous study because those diagnoses require a professional approach.¹

In this study, we examined the medical records made by cardiologists to determine whether the occurrence of CVDs,

including HF, acute myocardial infarction (AMI), PTE, IE and takotsubo cardiomyopathy, had increased after the Earthquake.

Methods

The ethical committees of Tohoku University Hospital and participating hospitals approved the protocol of the present study.

Study Population and Participating Hospitals

We enrolled all patients admitted to the cardiology department of the 10 hospitals in Miyagi prefecture from 4 weeks prior to 15 weeks after the Earthquake in 2011 and in the corresponding periods in 2008, 2009 and 2010 (n=14,078). We also col-

Received December 24, 2012; revised manuscript received January 5, 2013; accepted January 7, 2013; released online January 18, 2013 Time for primary review: 3 days

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ISSN-1346-9843 doi:10.1253/circj.CJ-12-1594

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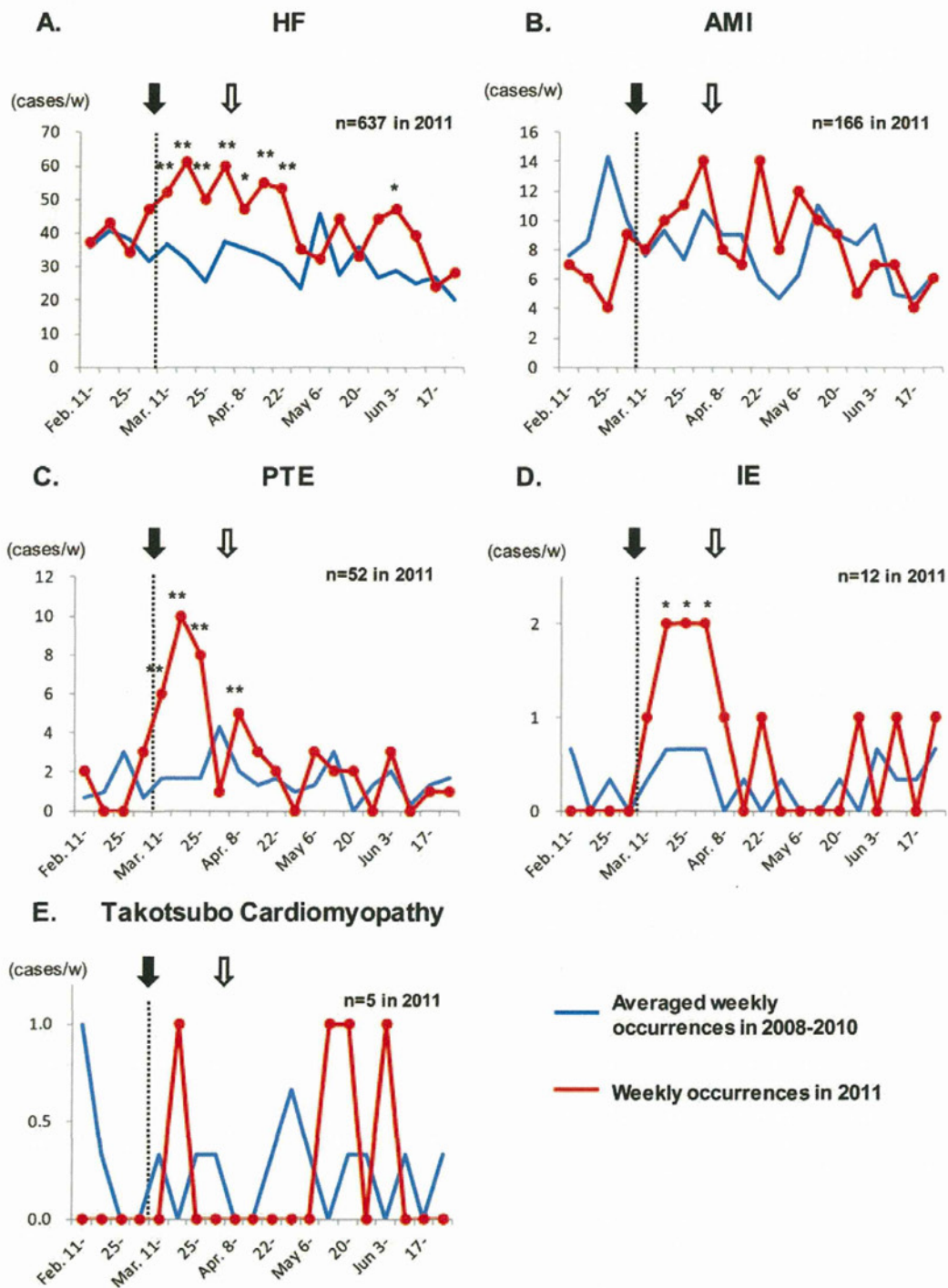


Figure 1. Weekly occurrence of cardiovascular diseases: (A) heart failure (HF), (B) acute myocardial infarction, (C) pulmonary thromboembolism (PTE), (D) infectious endocarditis (IE) and (E) takotsubo cardiomyopathy. HF, PTE and IE were significantly increased after the Earthquake. * $P < 0.05$, ** $P < 0.01$. Black arrows indicate the occurrence of the Great East Japan Earthquake (magnitude 9.0, March 11, 2011), and white arrows indicate the largest aftershock (magnitude 7.2, April 7, 2011).

lected additional information about the date of admission, sex and age of the patients from the medical insurance database. We defined the 3 hospitals facing the Pacific Ocean as those in the seacoast area with direct assault by the tsunamis, and the remaining 7 hospitals as those in the inland (remote) area.

Definition of the Diseases

All definitive diagnoses of the patients were confirmed at discharge by cardiologists and classified according to the International Statistical Classification of Diseases and Related Health Problems, 10th revision (ICD-10). We also collected the diag-

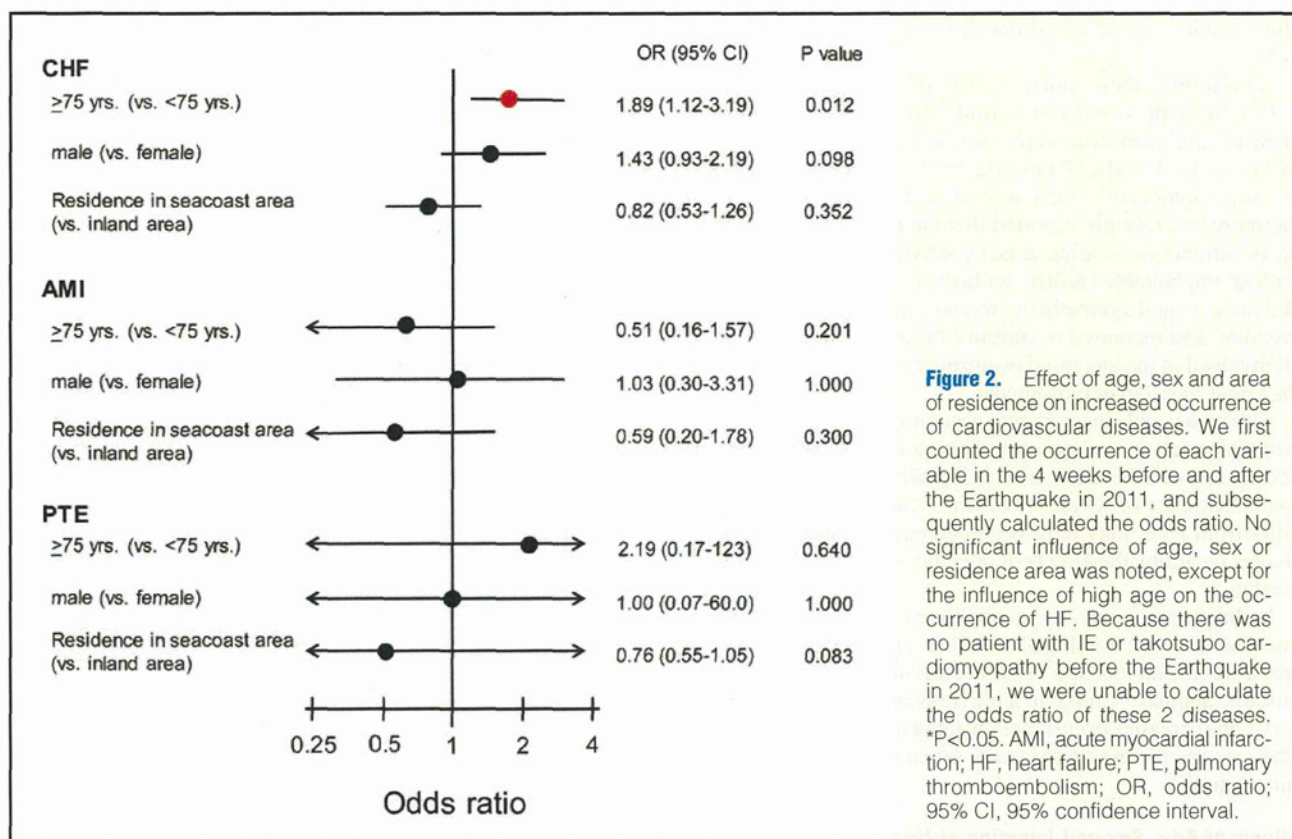


Figure 2. Effect of age, sex and area of residence on increased occurrence of cardiovascular diseases. We first counted the occurrence of each variable in the 4 weeks before and after the Earthquake in 2011, and subsequently calculated the odds ratio. No significant influence of age, sex or residence area was noted, except for the influence of high age on the occurrence of HF. Because there was no patient with IE or takotsubo cardiomyopathy before the Earthquake in 2011, we were unable to calculate the odds ratio of these 2 diseases. * $P < 0.05$. AMI, acute myocardial infarction; HF, heart failure; PTE, pulmonary thromboembolism; OR, odds ratio; 95% CI, 95% confidence interval.

nosis at discharge from the medical insurance database as the ICD-10 code, comprising I-50.0 (HF), I-21.0–I-21.9 (AMI), I-26.0–I-26.9 (PTE), I-33.0–I-33.9 (IE) and takotsubo cardiomyopathy (I-51.8).

Statistical Analysis

We used a Poisson regression model to assess differences in the variables between 2011 and the previous 3 years.¹ Furthermore, as previously reported,¹ we calculated the odds ratio with the 4-week occurrence in 2011 before and after the Earthquake in terms of age (<75 or ≥75 years), sex, and area of residence (inland vs. seacoast). Continuous variables are expressed as mean ± SD. All statistical analyses were performed using R 2.15.0 (www.r-project.org/). All P values were 2-sided, and $P < 0.05$ was considered to be statistically significant.

Results

The number of patients enrolled in the study for 2008, 2009, 2010 and 2011 was 3,190, 3,582, 3,752 and 3,554, respectively. In 2011, the prevalence of male sex was significantly lower (62.2%, 61.75, 59.95 and 58.8% in 2008, 2009, 2010 and 2011, respectively, $P = 0.014$) and age (years) was significantly higher (68.8 ± 13.9 , 69.5 ± 13.9 , 70.4 ± 14.2 , and 71.2 ± 14.2 in 2008, 2009, 2010 and 2011, respectively, $P < 0.05$).

The weekly occurrence of each of HF, PTE and IE was significantly increased after the Earthquake (Figures 1A,C,D). We also noted a mild but insignificant peak of the weekly occurrence of AMI after the Earthquake (Figure 1B). There were very few cases of takotsubo cardiomyopathy, even after the Earthquake (Figure 1E). The significant increase in the weekly occurrence of HF was prolonged for 7 weeks after the Earth-

quake in 2011 (Figure 1A), whereas the time course of PTE showed a second peak at the largest aftershock (magnitude 7.2 on April 7, 2011).

The subgroup analyses showed that among the 3 factors examined (age, sex, and area of residence), only higher age (>75 years) significantly influenced the occurrence of HF but not that of AMI or PTE (Figure 2). Because there was no patient with IE or takotsubo cardiomyopathy for 4 weeks before the Earthquake in 2011, we were unable to calculate the odds ratio of either disease.

Discussion

In the present study of cardiologists records, as compared with our recent study using ambulance records,¹ we were able to demonstrate the following: (1) a sharp and sustained (over 7 weeks) increase in the occurrence of HF after the Earthquake, (2) a sharp but transiently increased occurrence of both PTE and IE after the Earthquake, and (3) a tendency for the occurrence of AMI to be increased, but not that of takotsubo cardiomyopathy, after the Earthquake.

Increased Occurrences of CVD

The present study demonstrated a significant increase in the occurrence of both HF and PTE, consistent with the findings of our recent study¹ and another study,² and of IE, which was a novel finding not reported previously.^{3–8}

The Earthquake forced many people in the Miyagi prefecture to take shelter and/or to live without daily necessities, services, and medicines. Disaster situations can increase the occurrence of CVDs through physical and mental stresses.⁹ Furthermore, a prolonged stressful situation can suppress the immune sys-

tem,¹⁰ leading to increased rates of infectious diseases, such as IE.

Activation of the sympathetic nervous system of people involved in the present disaster would have elevated both blood pressure and heart rate, as previously reported.^{9,11} The report by Satoh et al has also demonstrated that self-monitored blood pressure significantly increased after the Earthquake.¹² Furthermore, we recently reported that the Earthquake increased the occurrence of ventricular tachyarrhythmias among patients with an implantable cardiac defibrillator.¹³ Thus, we consider that an activated sympathetic nervous system, elevated blood pressure, and increased occurrence of tachyarrhythmias were all involved in the increased occurrence of HF during and after the Great East Japan Earthquake.

Although people in temporary accommodation were supplied with information and compression stockings, the increased occurrence of PTE after the Earthquake was not prevented.³ The occurrence of severe PTE, with resultant improved mortality from PTE, may have been decreased; however, further studies regarding the effects of preventive practice for PTE are needed.

In the present study, the occurrence of AMI also tended to increase after the Earthquake, and in our recent study there was a significant increase in the occurrence of ACS (AMI plus unstable angina).¹ Unlike in a previous report,³ we did not observe an increased occurrence of takotsubo cardiomyopathy. The reasons for the discrepancy remains to be examined in future studies.

Effects of Age, Sex and Location of Hospitals on CVDs

In the present study, no significant influence of age, sex or area of residence was noted for CVDs, except for the influence of higher age on the occurrence of HF, which suggested that the Earthquake had a greater effect on elderly people.

Although the tsunami directly and seriously affected the sea-coast area, the increased occurrence of CVDs after the Earthquake was comparable between the seacoast and inland areas. Similar indirect effects of a disaster on CVD occurrence were reported after the World Trade Center Disaster in 2001, whereby the blood pressure of people in Mississippi was equally elevated as in those in New York City.¹⁴ These results indicate that life-threatening events, such as a great earthquake, can trigger CVDs even in remote areas.

The limitations of this study include the lack of detailed patient data, such as clinical characteristics and underlying heart disease. In order to prospectively observe the long-term prognosis of the patients, we are following the HF patients in a cohort in the Tohoku area,¹⁵ which had been established 2.5 years before the Earthquake.

Conclusions

The Great East Japan Earthquake Disaster significantly in-

creased the occurrence of CVDs, including HF, PTE and IE. Elderly patients with HF were significantly more affected by the Earthquake.

Acknowledgments

This work was supported by the contribution of the Japanese Circulation Society.

Disclosures

None.

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Urbanization, Life Style Changes and the Incidence/In-Hospital Mortality of Acute Myocardial Infarction in Japan

– Report From the MIYAGI-AMI Registry Study –

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on behalf of the MIYAGI-AMI Study Investigators

Background: It remains to be examined whether urbanization and lifestyle changes are associated with the incidence and mortality from acute myocardial infarction (AMI) in Japan.

Methods and Results: A total of 19,921 AMI patients (male/female 14,290/5,631) registered by the MIYAGI-AMI Registry Study from 1988 to 2009 were divided into 2 groups according to their residences; inside (urban area, n=7,316) and outside (rural area, n=11,402) of Sendai City. From 1988 to 2009, the incidence of AMI (/100,000 persons/year) increased more rapidly in the rural area (24.2 to 51.4) than in the urban area (31.3 to 40.8) ($P<0.001$), with rapid aging in both areas. Moreover, from 1998 to 2009, the age-adjusted incidence of AMI in young (<44 years) and middle-aged (45–64 years) male patients (both $P<0.05$) in the rural area increased significantly, along with a markedly increased prevalence of dyslipidemia ($P<0.001$). Although in-hospital mortality from AMI decreased in both areas over the last 20 years (both $P<0.001$), it remained relatively higher in female than in male patients and was associated with higher age of the onset, longer elapsing time for admission and lower prevalence of primary coronary intervention in female patients in both areas.

Conclusions: These results demonstrate that urbanization and lifestyle changes have been associated with the incidence and mortality from AMI, although sex differences still remain to be improved. (*Circ J* 2012; **76**: 1136–1144)

Key Words: Acute myocardial infarction; Aging; Life-style; Risk factors; Sex

The incidence and mortality from coronary artery disease (CAD) has been declining in the United States and European countries.^{1–4} These declines have been attributed to the control of risk factors (eg, hypertension, dyslipidemia and smoking) and the improvement in critical care (eg, coronary revascularization therapy).^{5–7} In contrast to the Western countries, in Japan, a highly developed and racially homogeneous country that is rapidly aging, total cholesterol levels and the prevalence of obesity have been increasing as a result of lifestyle Westernization influence since the 1960s.^{8,9} However, the mortality from CAD has been declining and has remained much lower compared with other Western countries from 1960 to 2000.^{9–11} Importantly, there are some differences in lifestyle between people living in rural and urban areas in Japan. Indeed, it was reported that people in urban areas had

greater intakes of fat and cholesterol than those in rural areas in Japan.⁸ However, only a few studies have previously addressed the difference in the incidence and mortality from CAD between the rural and urban areas in Japan.^{8,12}

In order to explore the annual trend for acute myocardial infarction (AMI) in Japan, we have been conducting the MIYAGI-AMI Registry Study for more than 30 years since 1979, where almost all AMI patients in the Miyagi prefecture have been prospectively registered.^{10,13,14} The Miyagi prefecture, which is located in northeastern Japan, includes Sendai City, one of the 19 government-designed cities, and has a typical balance of urban and rural areas in Japan. Sendai City merged with neighboring municipalities in 1987–1988 and the population of Sendai City increased to 1,008,130 in 2000, which accounted for approximately 40% of the population of

Received October 26, 2011; revised manuscript received December 12, 2011; accepted January 5, 2012; released online February 18, 2012
Time for primary review: 14 days

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ISSN-1346-9843 doi:10.1253/circj.CJ-11-1233

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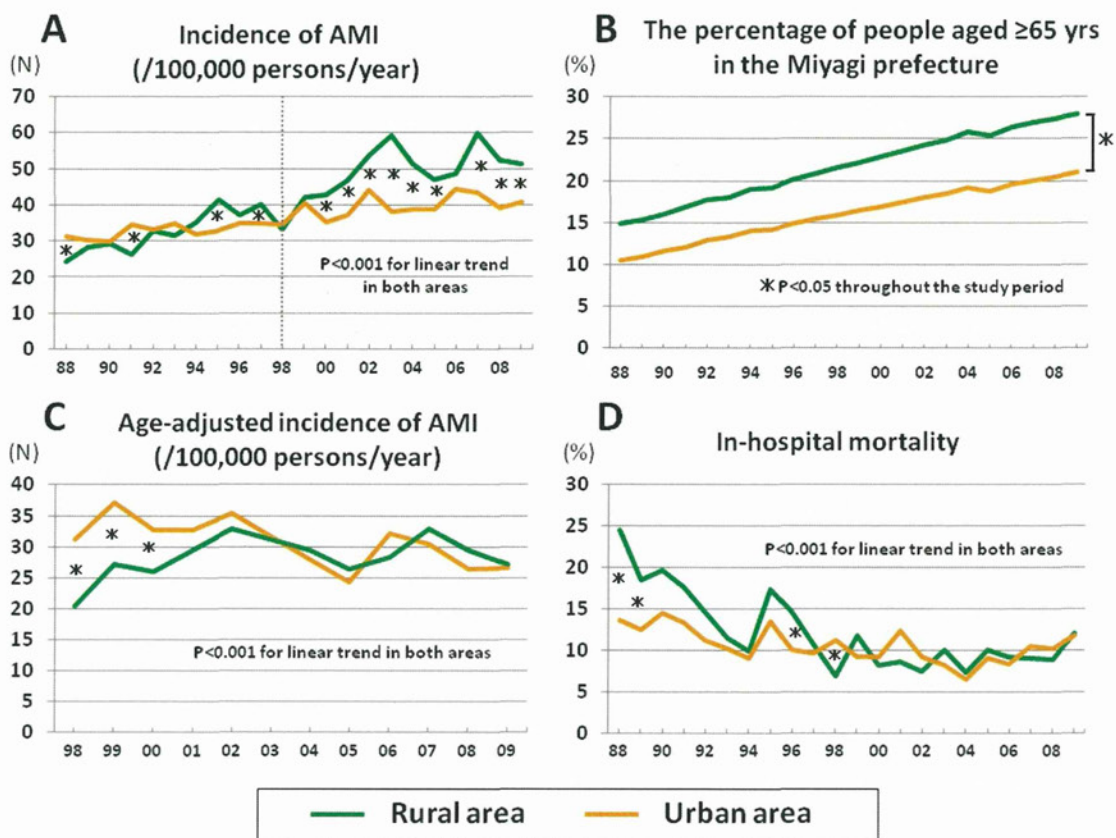


Figure 1. The 20-year trend of acute myocardial infarction (AMI) in the Miyagi prefecture. (A) The incidence of AMI (/100,000 persons/year) has significantly increased in both areas (both $P<0.001$) with a greater extent in the urban area over the last 20 years, accompanied with rapid aging in both areas (B). (C) The age-adjusted incidence of AMI (/100,000 persons/year) in the rural area increased significantly ($P<0.001$), whereas that in the urban area decreased significantly ($P<0.001$) in the recent 10 years (between 1998 and 2009). (D) In-hospital mortality (%) decreased and remained at a low level in the past 10 years in both areas. * $P<0.05$ for the difference between the rural and the urban areas.

the Miyagi prefecture, which was 2,365,320 in 2000. The population density of Sendai City (1,279/km² in 2000) has been much higher than that of any other parts of the Miyagi prefecture (209/km² in 2000).¹⁵

In the present study, we examined whether urbanization and lifestyle changes were associated with the incidence and mortality from AMI, with special reference to the difference between the urban and rural areas in our MIYAGI-AMI Registry Study.

Methods

The MIYAGI-AMI Registry Study

The MIYAGI-AMI Registry Study is a prospective, multi-center and observational study. As previously reported,^{10,13,14} this registry was established in 1979 and all 43 hospitals with a coronary care unit and/or cardiac catheterization facility in the Miyagi prefecture have been participating (Appendix 1). In the Miyagi prefecture, almost all AMI patients are transferred to one of those participating hospitals via the emergency medical service. 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.

In the MIYAGI-AMI Registry Study, the diagnosis of AMI and decision to use reperfusion therapy were made by individual cardiologists in charge. Diagnosis of AMI was made based on the WHO-MONICA criteria.¹⁶ Briefly, it was based on the finding of typical severe chest pain accompanied by abnormal ECG changes and increased serum levels of cardiac enzymes (ie, creatine phosphokinase, aspartate amino transferase and lactate dehydrogenase). Coronary thrombolysis was performed with intravenous administration of urokinase (480–960×10³ IU for 30 min) or alteplase (290–435×10³ IU/kg for 60 min) or with intracoronary administration of urokinase (maximum 960×10³ IU) or alteplase (maximum 6.4×10⁶ IU). Rescue percutaneous coronary intervention (PCI) was performed when thrombolysis was unsuccessful. Primary PCI has been widely performed in the Miyagi prefecture since 1992, as reported previously.^{10,13,14}

The registration form of the MIYAGI-AMI Registry includes 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 and/or PCI), and in-hospital outcome (eg, in-hospital mortality). In our MIYAGI-AMI Registry Study, we have revised the registra-

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

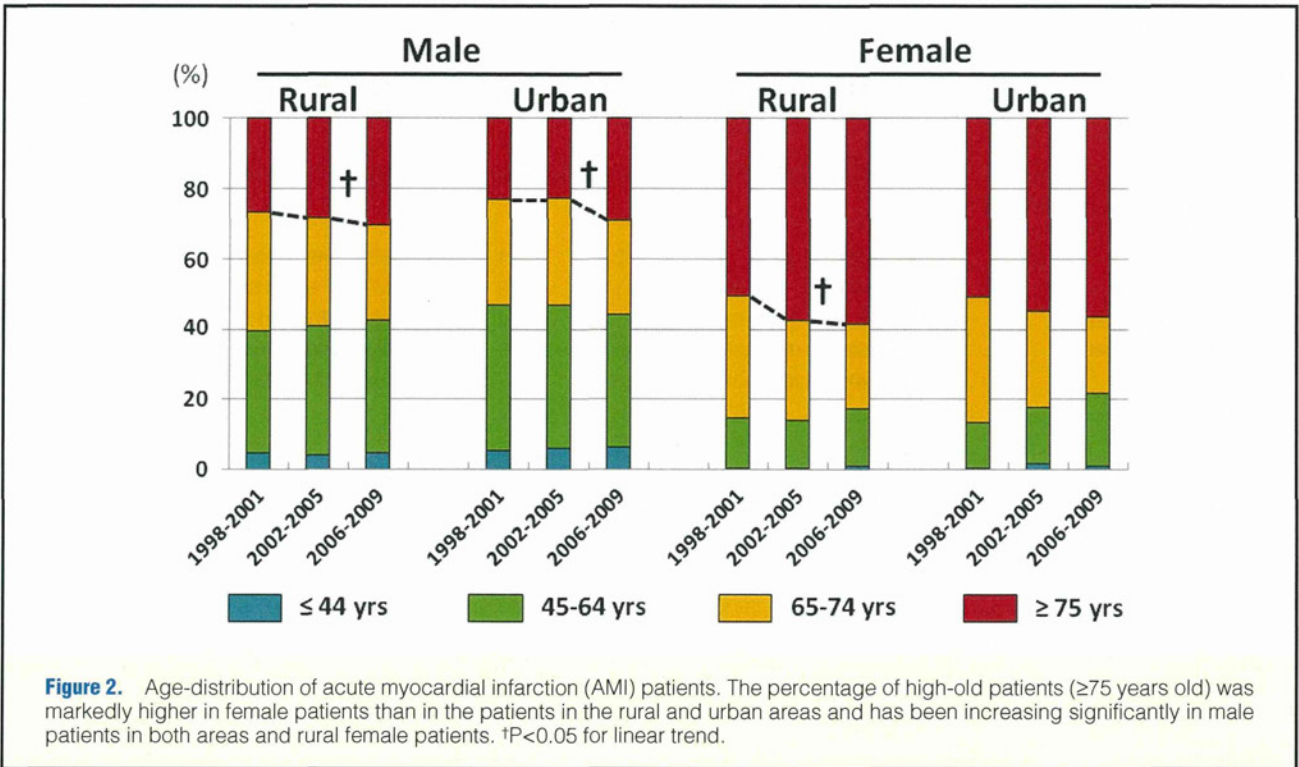


Figure 2. Age-distribution of acute myocardial infarction (AMI) patients. The percentage of high-old patients (≥ 75 years old) was markedly higher in female patients than in the patients in the rural and urban areas and has been increasing significantly in male patients in both areas and rural female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

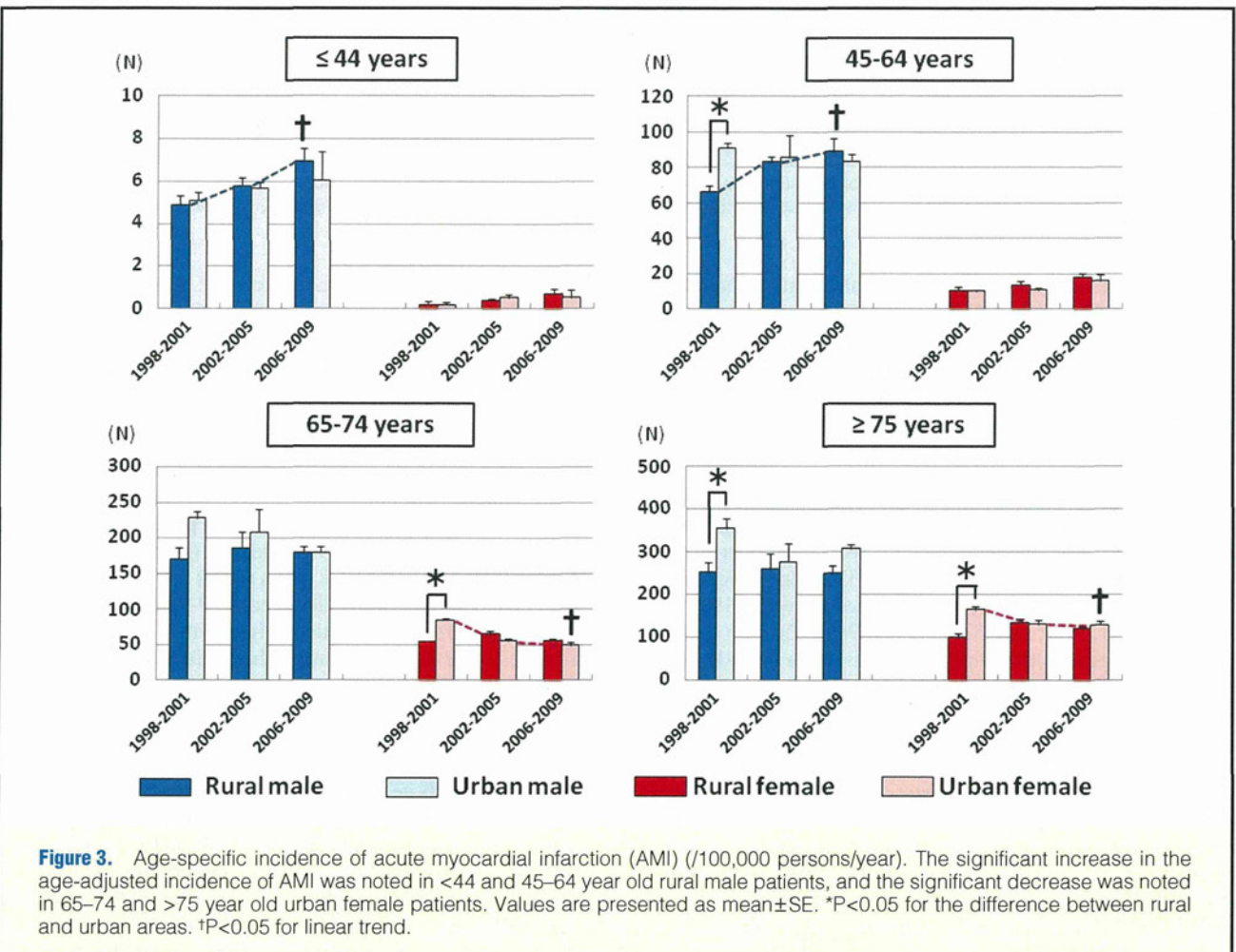


Figure 3. Age-specific incidence of acute myocardial infarction (AMI) (/100,000 persons/year). The significant increase in the age-adjusted incidence of AMI was noted in < 44 and $45-64$ year old rural male patients, and the significant decrease was noted in $65-74$ and > 75 year old urban female patients.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

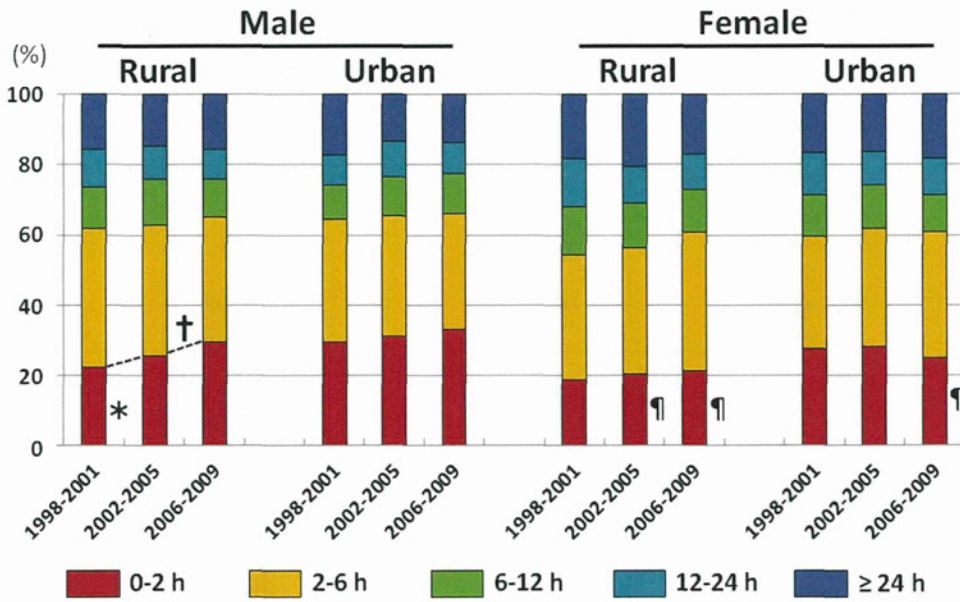


Figure 4. Time interval from the onset of symptoms to hospitalization. The percentage of patients with less than 2h of elapsing time for hospitalization has significantly increased in rural male patients. The percentage was significantly lower in female patients than in male patients in both areas in 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.

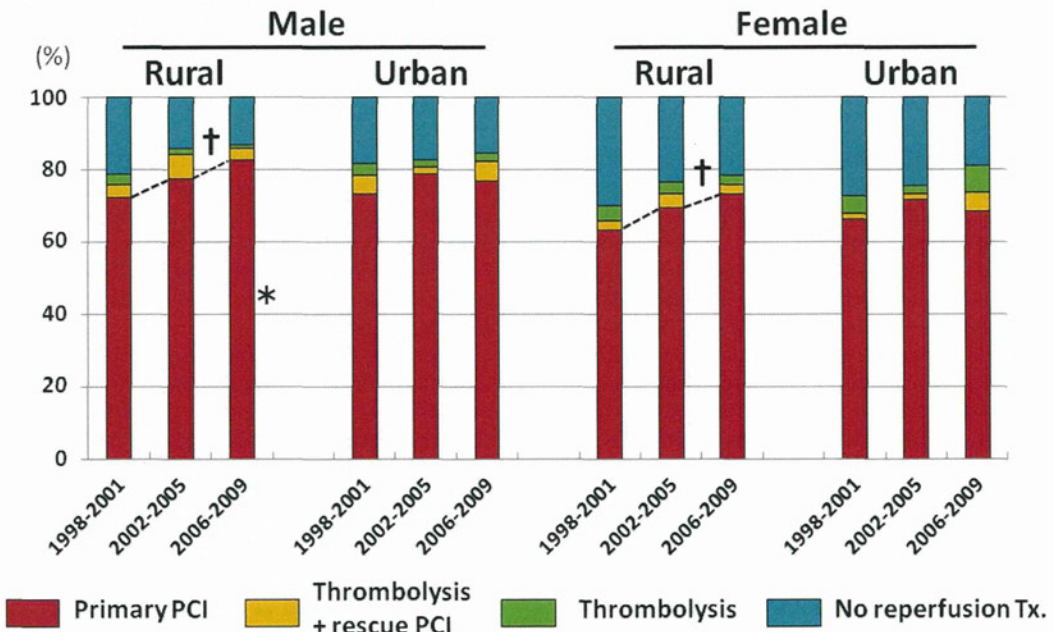
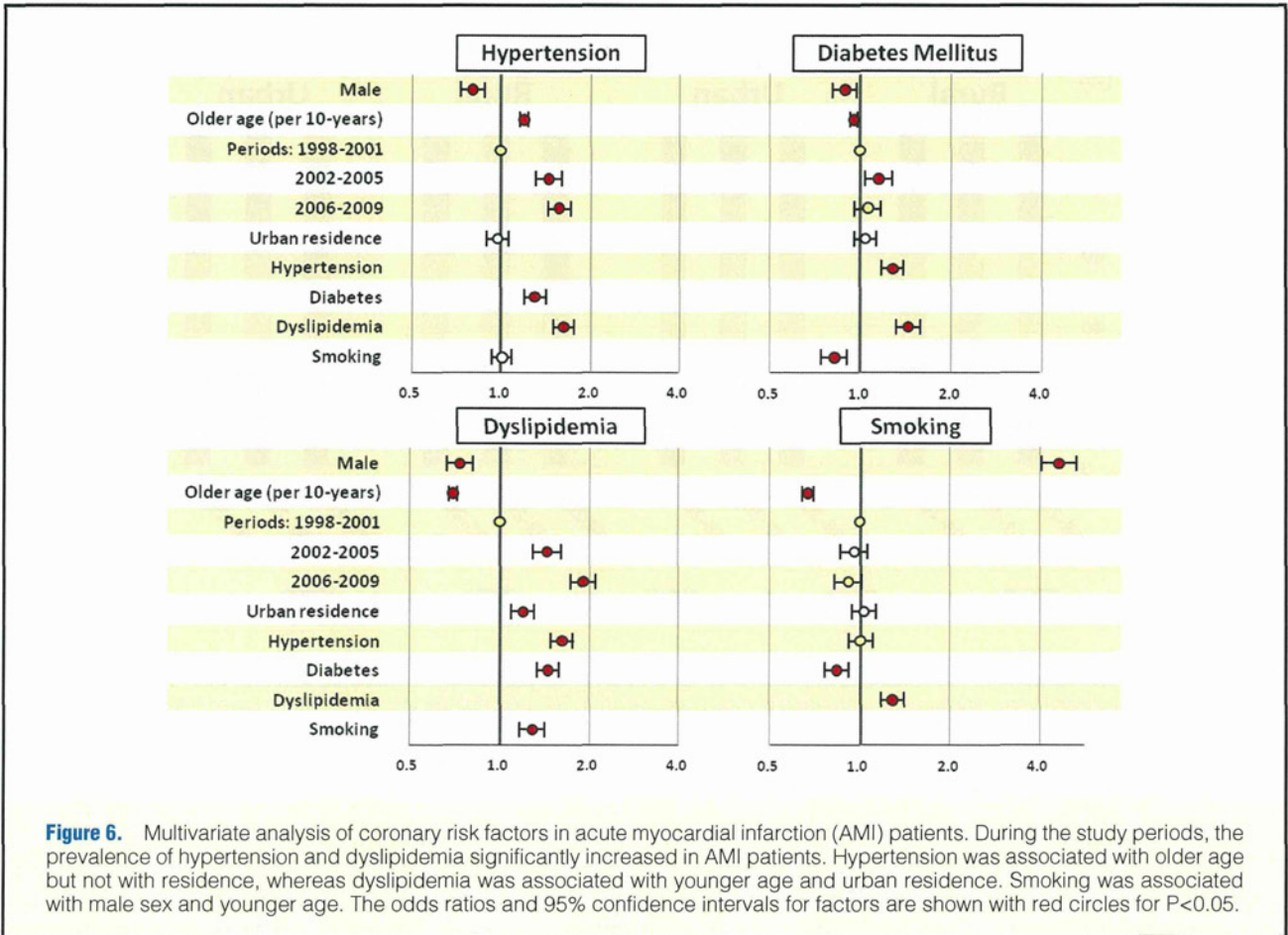


Figure 5. Prevalence of reperfusion therapy for acute myocardial infarction (AMI). The prevalence of primary percutaneous coronary intervention (PCI) steadily increased in the rural area in both sexes. Importantly, the prevalence of PCI was approximately 10% lower in female patients than in male patients 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.



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 in-

crease 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 2 h 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 2 h 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-

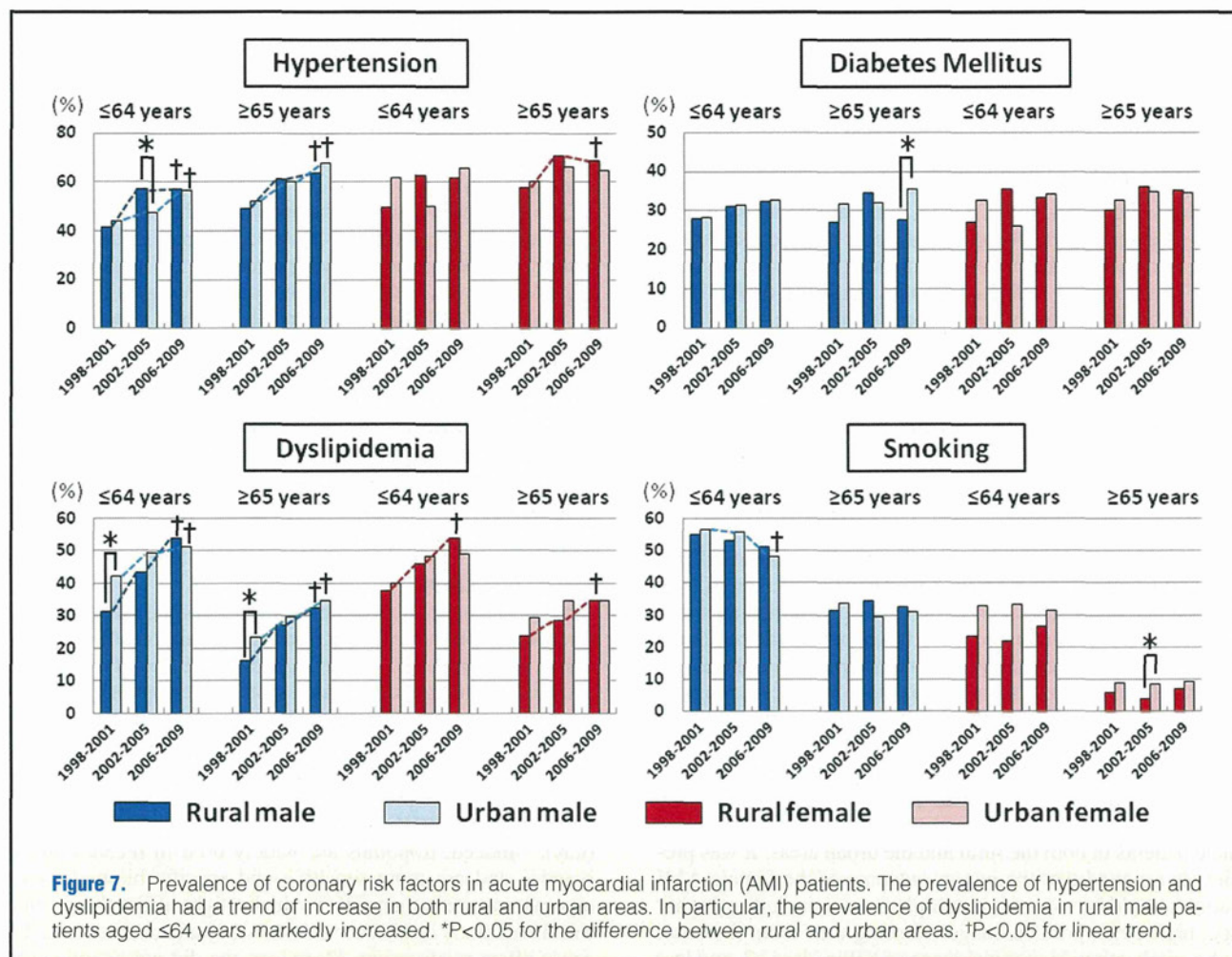


Figure 7. Prevalence of coronary risk factors in acute myocardial infarction (AMI) patients. The prevalence of hypertension and dyslipidemia had a trend of increase in both rural and urban areas. In particular, the prevalence of dyslipidemia in rural male patients aged ≤ 64 years markedly increased.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

tion, 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/km² 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 ($\sim 50\%$) 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

This study was supported, in part, by the grants-in-aid from the Sendai City, the Miyagi Prefecture and the Miyagi Medical Association and the grants-in-aid [H22-Shinkin-004] from the Japanese Ministry of Education, Culture, Sports, Science, and Technology, Tokyo, Japan. We thank all the collaborators in the MIYAGI-AMI Registry Study (Appendix 1). We also thank Ayako Tsunoda for excellent secretarial assistance.

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Appendix 1. List of Participating Hospitals and Investigators

Fukaya Hospital, Akiho H, MD.
 Hikarigaoka Spellman Hospital, Shimura S, MD.
 Ishinomaki Medical Association; Ishinomaki Municipal Hospital, Akai K, MD.
 Ishinomaki Red-cross Hospital, Sukegawa H, MD.
 JR Sendai Hospital, Honda H, MD.
 Katta General Hospital, Kanno H, MD.
 Kesen-numa Hospital, Ogata K, MD.
 Kurihara Central Hospital, Komatsu S, MD.
 Labour Welfare Corporation Tohoku Rosai Hospital, Komaru T, MD.
 Marumori National Health Insurance Hospital, Otomo M, MD.
 Miyagi Eastern Cardiovascular Institute, Kikuchi Y, MD.
 Miyagi Cancer Center, Owada N, MD.
 Miyagi Cardiovascular and Respiratory Center, Osawa N, MD.
 Mori Hospital, Mori A, MD.
 Nagamachi Hospital, Mitobe H, MD.
 Nishitaga National Hospital, Kitaoka S, MD.
 NTT EAST Tohoku Hospital, Yamada A, MD.
 Oizumi Memorial Hospital, Koiwa Y, MD.
 Osaki Citizen Hospital, Hiramoto T, MD.
 Saito Hospital, Otsuka K, MD.
 Saka General Hospital, Watanabe K, MD.
 Sendai Cardiovascular Center, Fujii S, MD.
 Sendai City Hospital, Yagi T, MD.
 Sendai Kosei Hospital, Meguro T, MD.
 Sendai Medical Center, Shinozaki T, MD.
 Sendai Open Hospital Sendai City Medical Center, Kato A, MD.
 Sendai Public Health Insurance Hospital, Oikawa Y, MD.
 Sendai Red-cross Hospital, Wakayama M, MD.
 Sendai Tokushukai Hospital, Fukuchi M, MD.
 Sen-en General Hospital, Hashiguchi R, MD.
 Shichigashuku National Health Insurance Clinic, Nagashima T, MD.
 Shiogama City Hospital, Goto J, MD.
 South Miyagi Medical Center, Inoue K, MD.
 Tohoku Kosai Hospital, Suzuki S, MD.
 Tohoku University Hospital,
 Department of Cardiovascular Medicine, Shimokawa H, MD.
 Department of Cardiovascular Surgery, Saiki Y, MD.
 Department of Gastroenterology, Shimosegawa T, MD.
 Tohoku Welfare and Pension Hospital, Katahira Y, MD.
 Tome Citizen Hospital, Izuma M, MD.
 Toyama Clinic on Tome City, Ishii M, MD.

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)

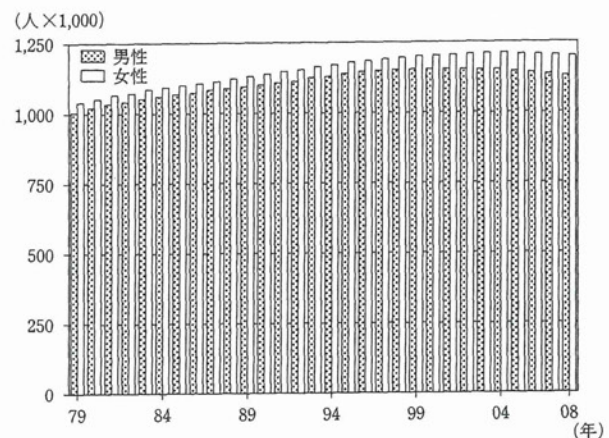


図1 宮城県推計人口推移(文献1)より改変引用)

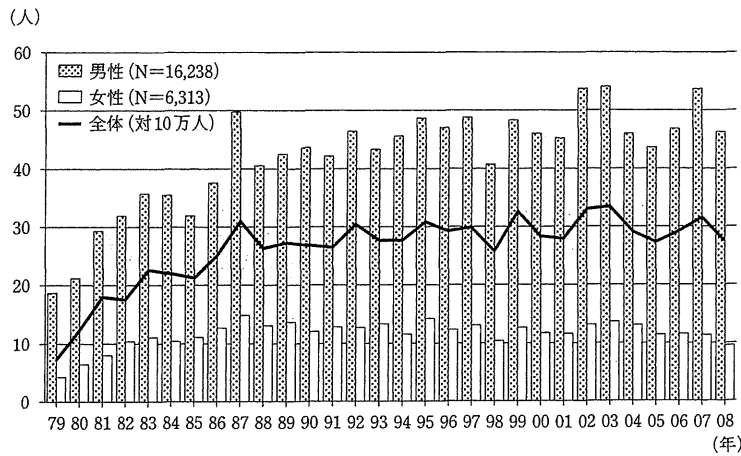


図 2 心筋梗塞発症頻度 (年齢補正データ) (文献1)から改変引用)

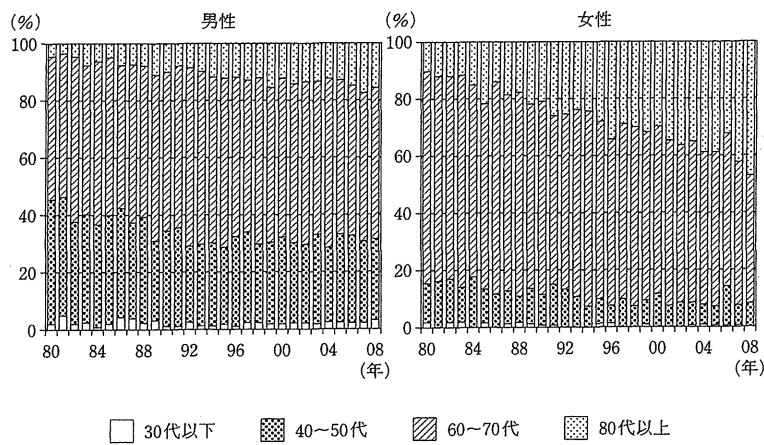


図 3 登録症例の年齢構成 (文献1)から改変引用)

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

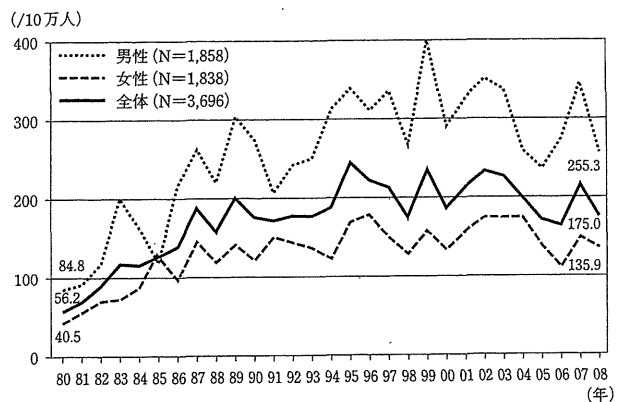


図 4 80歳以上患者の心筋梗塞発症頻度 (文献1)から改変引用)

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

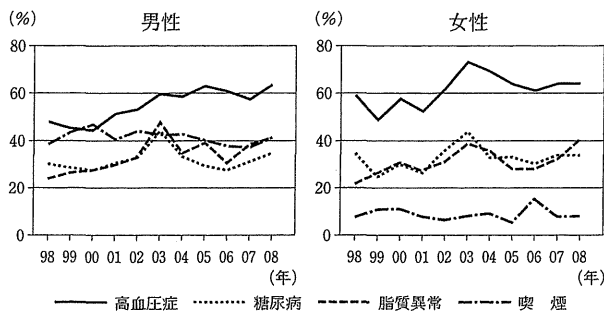


図5 動脈硬化危険因子合併の推移 (文献1)から改変引用)

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、我が国の喫煙率は近年約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%、後下壁心筋梗塞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

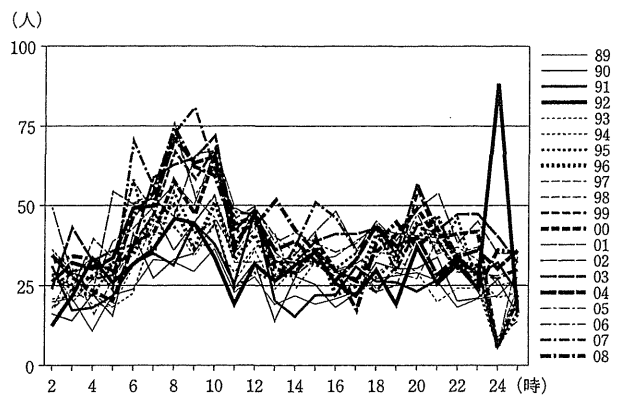


図6 心筋梗塞発症時間の年次推移 (文献1)から改変引用)

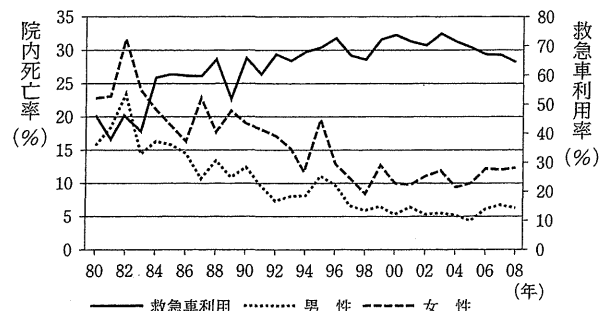


図7 院内死亡率(心臓死)と救急車利用率 (文献1)から改変引用)

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イ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ぬが、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) であったのに対して、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。

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年間で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

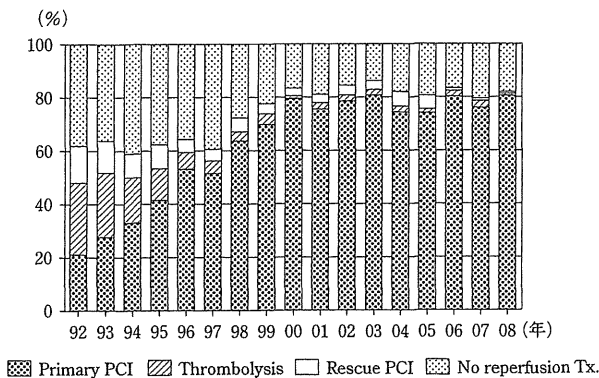


図 8 治療内容 (再灌流療法の有無と内訳) (文献1)から改変引用)

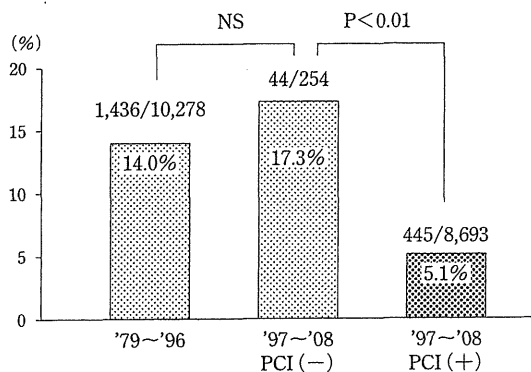


図 9 院内死亡率 (心臓死) と冠動脈インターベンション (PCI) との関係 (文献1)から改変引用)

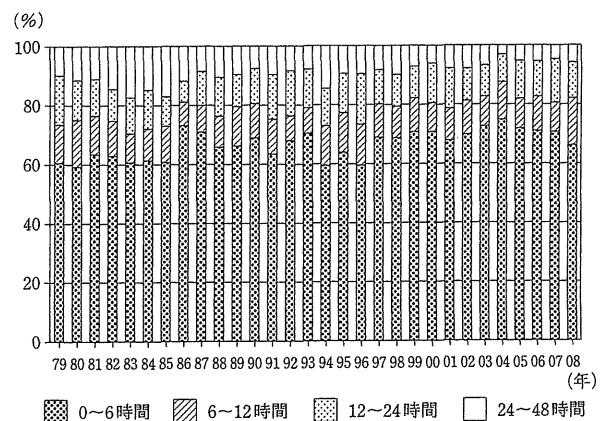


図 11 発症から入院までの時間 (文献1)から改変引用)

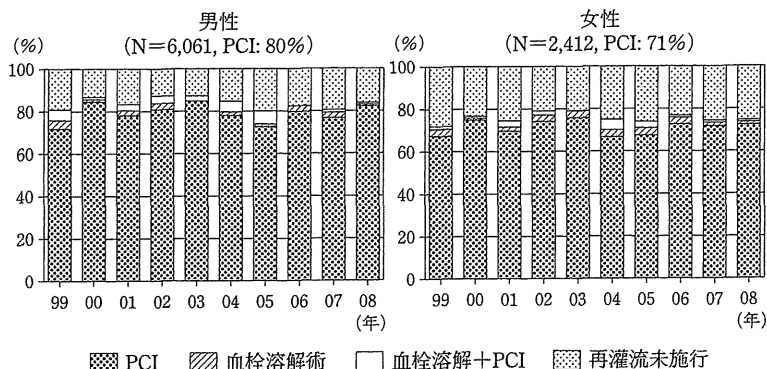


図 10 治療内容 (男女比較) (文献1)から改変引用)