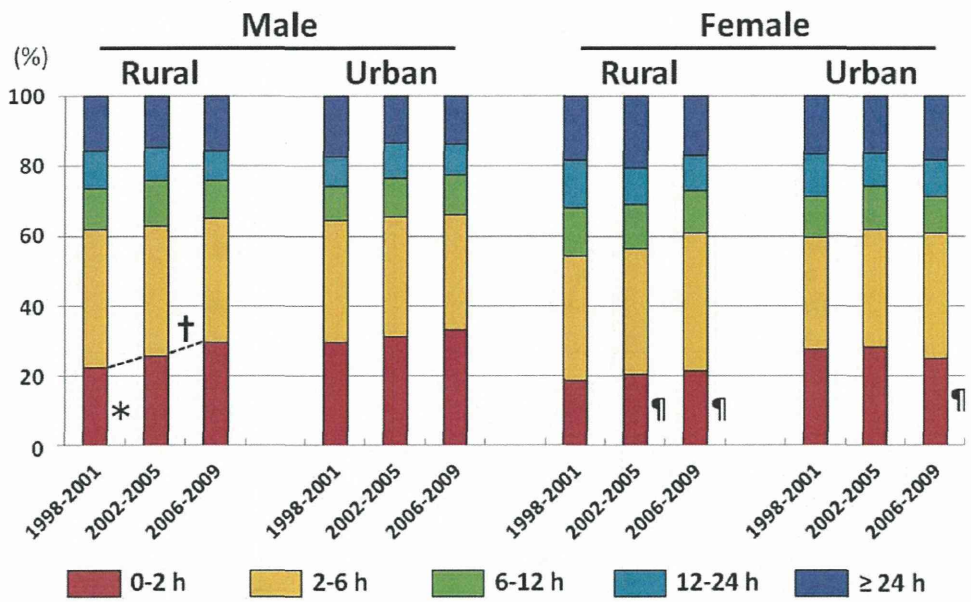

Figure 4. Time interval from the onset of symptoms to hospitalization. The percentage of patients with less than 2 h of elapsing time for hospitalization has significantly increased in rural male patients. The percentage was significantly lower in female patients than in male patients in both areas in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

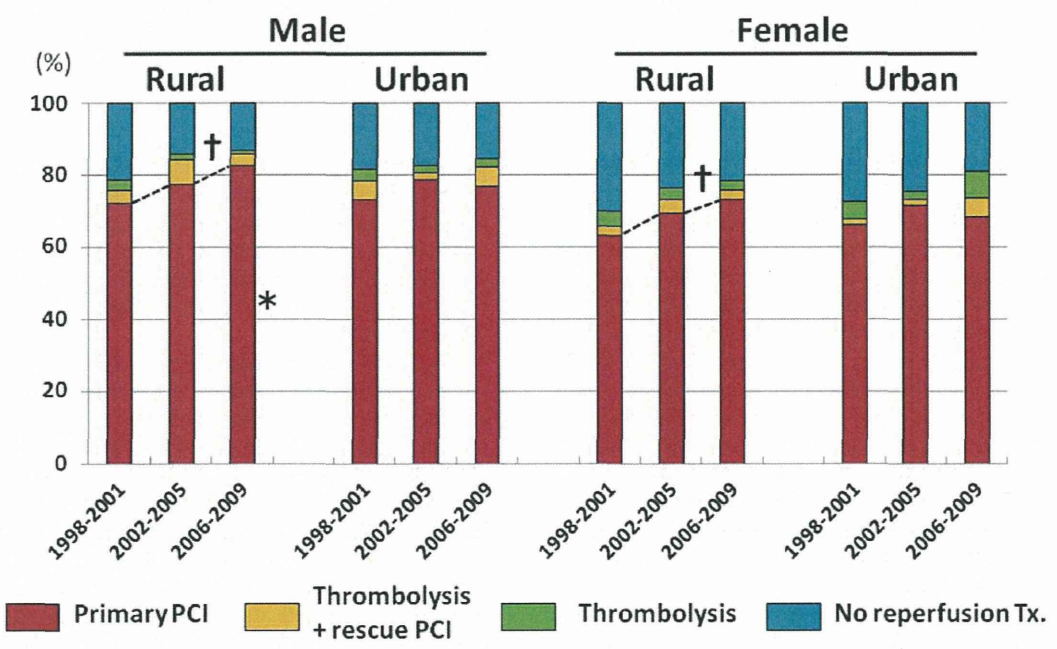

Figure 5. Prevalence of reperfusion therapy for acute myocardial infarction (AMI). The prevalence of primary percutaneous coronary intervention (PCI) steadily increased in the rural area in both sexes. Importantly, the prevalence of PCI was approximately 10% lower in female patients than in male patients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

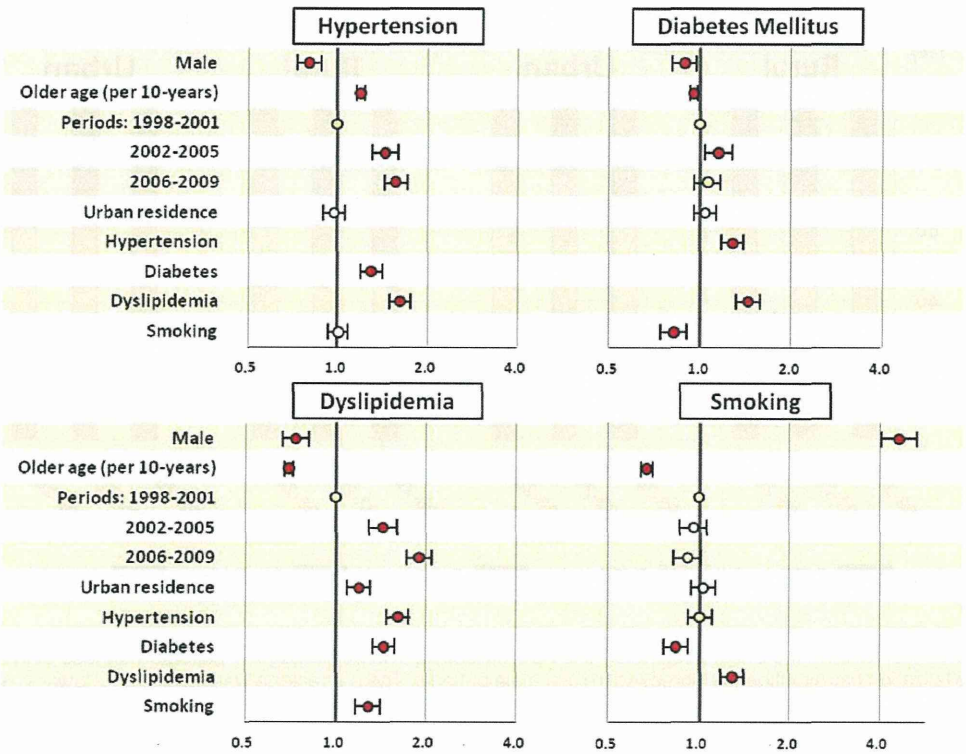

Figure 6. Multivariate analysis of coronary risk factors in acute myocardial infarction (AMI) patients. During the study periods, the prevalence of hypertension and dyslipidemia significantly increased in AMI patients. Hypertension was associated with older age but not with residence, whereas dyslipidemia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

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

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

Regarding the time from the onset of AMI to admission, the percentage of the patients with less than 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-

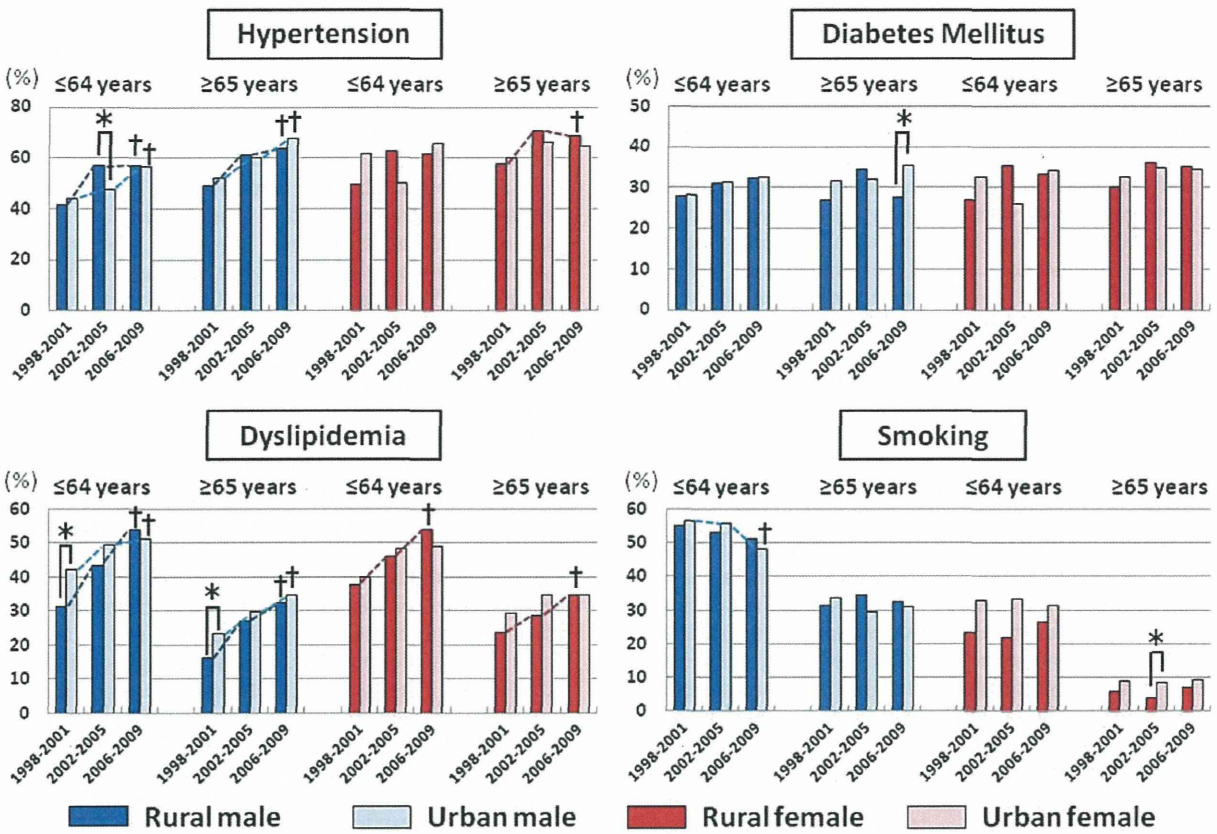

Figure 7. Prevalence of coronary risk factors in acute myocardial infarction (AMI) patients. The prevalence of hypertension and dyslipidemia had a trend of increase in both rural and urban areas. In particular, the prevalence of dyslipidemia in rural male patients aged ≤64 years markedly increased. *P<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 urbanization, life-style changes and the incidence and mortality of AMI in the largest number of patients in Japan.

Comparison of the Incidence of AMI Between Rural and Urban Areas

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

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

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

Decreasing In-Hospital Mortality and Improvement in Critical Care

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

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

Changes in the Prevalence of Coronary Risk Factors in AMI Patients

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

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

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

Study Limitations

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

Conclusions

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

Acknowledgments

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Enhancement of Cardiac Performance by Bilevel Positive Airway Pressure Ventilation in Heart Failure

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ABSTRACT

Background: Recent studies have reported the clinical usefulness of positive airway pressure ventilation therapy with various kinds of pressure support compared with simple continuous positive airway pressure (CPAP) for heart failure patients. However, the mechanism of the favorable effect of CPAP with pressure support can not be explained simply from the mechanical aspect and remains to be elucidated.

Methods and Results: In 18 stable chronic heart failure patients, we performed stepwise CPAP (4, 8, 12 cm H_2O) while the cardiac output and intracardiac pressures were continuously monitored, and we compared the effects of 4 cm H_2O CPAP with those of 4 cm H_2O CPAP plus 5 cm H_2O pressure support. Stepwise CPAP decreased cardiac index significantly in patients with pulmonary arterial wedge pressure (PAWP) <12 mm Hg (n = 10), but not in those with PAWP ≥ 12 mm Hg (n = 8). Ventilation with CPAP plus pressure support increased cardiac index slightly but significantly from 2.2 ± 0.7 to 2.3 ± 0.7 L min^{-1} m^{-2} ($P = .001$) compared with CPAP alone, regardless of basal filling condition or cardiac index.

Conclusions: Our results suggest that CPAP plus pressure support is more effective than simple CPAP in heart failure patients and that the enhancement might be induced by neural changes and not simply by alteration of the preload level. (*J Cardiac Fail 2012;18:912–918*)

Key Words: Noninvasive positive pressure ventilation, cardiac output, hemodynamic, chronic heart failure.

Noninvasive positive pressure ventilation (NIPPV) has been widely used as an effective and safe treatment for acute[1] as well as chronic heart failure.[2–5] Particularly, NIPPV with inspiratory pressure support (PS) and positive end-expiratory pressure (PEEP), such as bilevel positive airway ventilation (fixed PS levels) and adaptive servoventilation (ASV; varying PS levels), has gained popularity rapidly as an effective therapy for improving the symptoms and prognosis even in patients with the most severe chronic heart failure,[6] independent from the apnea hypopnea index.[7] Although many researchers and clinicians think that the favorable effects of ASV are attributable to the continuous positive airway pressure (CPAP)[4,6,7] that ameliorates pulmonary congestion in addition to its ability to stabilize abnormal breathing, such as Cheyne-Stokes respiration, the fundamental physiologic significance of adding PS to CPAP in the treatment of heart failure patients has not been fully elucidated. As for the efficacy of CPAP, Bradley et al[8] already demonstrated that 5 cm H_2O CPAP decreased cardiac output in heart failure patients with pulmonary arterial wedge pressure (PAWP) <12 mm Hg and increased cardiac output in those with PAWP ≥ 12 mm Hg. On the other hand, Lenique et al[9] reported no change in cardiac output or stroke volume but improvement of lung compliance as well as lung and respiratory resistance, and reduction of work of breathing by 10 cm H_2O CPAP in 9 acute heart failure patients with mean baseline PAWP of 26.7 mm Hg. These findings indicate that CPAP treatment at some pressure levels may not be effective or safe, depending on the conditions of individual heart failure patients. Recently, acute studies on the hemodynamic or neural responses to ASV performed at CPAP of 5 cm H_2O with minimal PS of 3 cm H_2O in awake heart failure patients showed an increase in cardiac output measured by ultrasound cardiography[10] as well as a decrease in muscle sympathetic nerve activity[11] in patients with unstable respiration. These results seem to contradict the findings of Bradley et al's[8] study, in which approximately one-half of the patients

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with PAWP <12 mm Hg showed a decrease in cardiac output by CPAP. Therefore, 2 questions arise. First, does the addition of PS to a certain level of CPAP confer additional favorable hemodynamic effect(s), besides restoration of normal breathing pattern, compared with CPAP without PS? Second, is there a specific safe level of end-expiratory pressure below which cardiac output does not decrease in most chronic heart failure patients? To clarify these issues, we designed an investigation that compared the effects of CPAP at different pressure levels and compared the effect of 1 level of CPAP alone with the same level of CPAP plus PS in chronic heart failure patients with various PAWP levels.

Methods

Among patients who were admitted to our hospital for the treatment of acute heart failure, the following patients were recruited in the present study: ejection fraction (EF) <60%, New York Heart Association (NYHA) functional status III or IV, an indication of cardiac catheter examination to clarify clinical status, and clinical condition stabilized after conventional medical treatment for heart failure for ≥5 days. We excluded patients with residual myocardial ischemia or severe pulmonary disease and those who were considered mentally unsuitable for long study. Eventually, 18 patients participated in this study after giving full informed consents, comprising 11 patients with cardiomyopathy, 2 with ischemic heart disease, and 5 with valvular heart disease. The clinical characteristics of the patients are presented in Table 1.

We performed positive airway pressure ventilation using the BiPAP Auto-SV Advanced system (Philips Respironics, Murrysville, Pennsylvania, USA) with full face mask at our catheter laboratory with the patients awake, using fixed PEEP and fixed PS. The Swan-Ganz catheter was inserted via a right supraclavical approach. Hemodynamic parameters were monitored with the use of this catheter for continuous cardiac output measurement (Vigilance; Edwards Lifesciences, Irvine, CA). The changes in temperature brought by continuous thermal energy emitted by the thermal filament on the catheter were used to calculate cardiac output with the use of thermodilution principles. Peripheral blood pressure was also continuously monitored through an arterial line inserted from the radial artery. Arterial oxygen saturation (SpO_2) was continuously measured percutaneously with the use of an RMC-3000 (Nihon Koden, Tokyo, Japan), and central venous oxygen saturation (SvO_2) was intermittently measured by direct collection of blood sample from the catheter. Twelve-lead electrocardiography was monitored in the usual manner.

In each patient, after hemodynamic parameters were stabilized, we recorded baseline data without positive airway pressure (PAP), and then initiated CPAP initially at 4 cm H_2O, increasing stepwise to 8 cm H_2O and 12 cm H_2O every 5 minutes, during which the hemodynamic data were recorded continuously. The data averaged for the last 2.5 minutes in each step was used for evaluation. After the above studies, we returned CPAP to 4 cm H_2O for 5 minutes and then added 5 cm H_2O PS to the 4 cm H_2O CPAP (bilevel PAP) for 5 minutes, and measured hemodynamic parameters during the 2 ventilation modes.

This study was approved by an Institutional Review Committee at Saiseikai Futsukaichi Hospital.

Statistics

For the analysis of hemodynamic responses to stepwise increase in CPAP from 4 cm H_2O to 12 cm H_2O, the subjects were divided into 2 groups based on the basal PAWP pressure: PAWP <12 mm Hg and PAWP ≥12 mm Hg (Table 1). The differences in hemodynamic responses between the 2 groups were compared using 2-way repeated analysis of variance (ANOVA). The comparisons between CPAP 0 cm H_2O and 4, 8, or 12 cm H_2O were analyzed by 1-way repeated ANOVA followed by Bonferroni correction, and the difference between CPAP plus PS and CPAP alone was analyzed with the use of paired Student *t* test. Statistical analysis was performed with the use of SPSS software (SPSS, Chicago, IL). Data are expressed as mean ± D. A *P* value of <.05 was considered to be significant.

Results

The demographic and clinical characteristics of all patients and patients stratified by PAWP are presented in Table 1. Compared with patients with PAWP <12 mm Hg (n = 10), patients with PAWP ≥12 mm Hg (n = 8) had significantly greater height, greater body weight, an larger left ventricular dimensions at end-diastole (LVDd) and end-systole (LVDs).

Stepwise increase of CPAP decreased cardiac index (CI) in patients with PAWP <12 mm Hg (n = 10) and the decrease was significant at 12 cm H_2O CPAP, whereas all CPAP increments did not change CI significantly in patients with PAWP ≥12 mm Hg (n = 8; Table 2; Fig. 1).

In all patients (n = 18), stepwise increase of CPAP significantly decreased CI at 12 cm H_2O CPAP. Stepwise CPAP increase did not change aortic pressure heart rate or calculated systemic arterial and pulmonary arterial resistances, but significantly elevated pulmonary artery pressure (PulAP) at 12 cm H_2O CPAP, pulmonary artery wedge pressure (PAWP) 12 cm H_2O of CPAP, and right atrial pressure (RAP) at 8 cm H_2O and 12 cm H_2O CPAP (Table 2).

In the comparison between CPAP with 5 cm H_2O of PS (CPAP + PS: expiratory PAP [EPAP]/inspiratory PAP [IPAP] = 4/9 cm H_2O) and CPAP without PS (EPAP/IPAP = 4/4 cm H_2O), CPAP + PS increased CI significantly compared with CPAP without PS in all subjects, regardless of basal PAWP or CI (ΔCI [CPAP + PS value − CPAP value]: 0.2 ± 0.2 L min^{-1} m^{-2}; *P* = .001; Table 3; Fig. 2). This increase in CI by CPAP + PS was not different between patients with PAWP ≥12 mm Hg and those with PAWP <12 mm Hg (*P* = .673). No significant differences between CPAP + PS and CPAP without PS were detected for changes in RAP, PAWP, SpO_2, SvO_2, and heart rate (Table 3; Fig. 3). However, significant decreases were observed for changes in mean aortic pressure (AoP), PulAP, systemic arterial resistance, and pulmonary arterial resistance (Table 3; Fig. 3).

Discussion

The main result of this study is that cardiac output was increased when low-level PS (5 cm H_2O) was added to

Table 1. Demographic and Clinical Characteristics of All Patients and Patients Stratified by PAWP

	All	PAWP <12 mm Hg	PAWP ≥12 mm Hg	*P* Value
n	18	10	8	
Age (y)	69.4 ± 12.7	74.0 ± 13.4	63.6 ± 9.5	.084
Male/Female	11/7	5/5	6/2	.280
Height (cm)	159.0 ± 7.7	155.8 ± 8.4	163.0 ± 4.5	.044
Weight (kg)	52.0 ± 9.6	46.6 ± 8.5	58.7 ± 6.1	.004
LVDd (mm)	54.9 ± 6.6	52.1 ± 6.8	58.4 ± 4.7	.042
LVDs (mm)	44.4 ± 7.9	40.8 ± 7.8	48.9 ± 5.7	.027
IVS (mm)	10.1 ± 2.7	9.9 ± 2.9	10.5 ± 2.4	.620
PW (mm)	10.8 ± 2.6	11.1 ± 2.0	10.5 ± 3.4	.670
LAD (mm)	45.3 ± 8.6	43.0 ± 8.9	48.3 ± 7.9	.210
AOD (mm)	19.0 ± 9.3	18.0 ± 9.3	20.1 ± 9.7	.652
EF (%)	38.8 ± 14.2	43.5 ± 12.0	32.9 ± 15.2	.117
Cardiomyopathy (n)	11	6	5	.763
Ischemic heart disease (n)	2	2	0	.248
Valvular heart disease (n)	5	2	3	.655

PAWP, pulmonary artery wedge pressure; LVDd, left ventricular dimension at end-diastole; LVDs, left ventricular dimension at end-systole; IVS, interventricular septum; PW, left ventricular posterior wall thickness; LAD, left atrial dimension; AOD, aortic dimension; EF, ejection fraction.

P values are for the difference between PAWP <12 mm Hg and PAWP ≥12 mm Hg accoding to unpaired Student *t* test or chi-square test.

low-level CPAP (4 cm H_2O), regardless of the basal PAWP level or cardiac output, and this increase was accompanied by a decrease in peripheral arterial resistance. Furthermore, we found that CPAP produced a pressure-dependent decrease in cardiac index: Cardiac index decreased significantly when the CPAP level was elevated to 12 cm H_2O in patients with PAWP <12 mm Hg, but did not change at all CPAP levels in patients with PAWP >12 mm Hg, which partially contradicted the findings reported by Bradley et al.[8]

Table 2. Basal Values and Changes of Hemodynamic Parameters During Stepwise CPAP Increases

			Change in Value Relative to Baseline Value			
		Basal Value at CPAP 0 cm H_2O	At CPAP 4 cm H_2O	At CPAP 8 cm H_2O	At CPAP 12 cm H_2O	*P* value
CI (mL min^{-1} m^{-2})	All	2.4 ± 0.8	−0.1 ± 0.3	−0.2 ± 0.3	−0.3 ± 0.5*	
	PAWP <12	2.6 ± 0.8	−0.1 ± 0.3	−0.3 ± 0.3	−0.5 ± 0.4*,†	.195
	PAWP ≥12	2.1 ± 0.8	−0.1 ± 0.4	−0.1 ± 0.4	−0.1 ± 0.4	
AoP (mm Hg)	All	89.2 ± 17.2	−1.0 ± 6.0	−2.7 ± 7.1	−3.1 ± 9.0	
	PAWP <12	90.6 ± 20.3	−0.4 ± 7.7	−3.0 ± 8.5	−4.9 ± 8.6	.731
	PAWP ≥12	86.8 ± 12.5	−2.0 ± 1.9	−2.2 ± 5.0	−0.2 ± 9.8	
PulAP (mm Hg)	All	20.8 ± 9.1	−0.1 ± 2.7	0.9 ± 3.4	3.1 ± 3.3*,†	
	PAWP <12	17.0 ± 4.8	−0.1 ± 2.6	1.5 ± 2.7	4.1 ± 2.9*,†	.454
	PAWP ≥12	25.6 ± 11.1	−0.1 ± 3.1	0.1 ± 4.2	1.8 ± 3.4	
PAWP (mm Hg)	All	12.3 ± 7.8	0.3 ± 2.2	1.7 ± 3.0	3.6 ± 4.1*,†	
	PAWP <12	6.8 ± 2.3	0.3 ± 1.4	2.2 ± 3.2	3.6 ± 4.0*	.778
	PAWP ≥12	19.1 ± 6.7	0.3 ± 3.0	1.0 ± 2.9	3.6 ± 4.6	
RAP (mm Hg)	All	7.2 ± 7.8	1.5 ± 1.5	2.8 ± 2.2*	4.5 ± 2.9*,†	
	PAWP <12	3.6 ± 2.1	1.5 ± 0.7	2.9 ± 2.0*	4.3 ± 2.1*,†	.956
	PAWP ≥12	12.4 ± 10.2	1.4 ± 2.2	2.7 ± 2.6	4.7 ± 3.9*	
Systemic arterial resistance (dyne s^{-1} m^{-5})	All	2,008.9 ± 785.6	−110.7 ± 203.5	−70.0 ± 273.5	7.5 ± 428.7	
	PAWP <12	2,133.3 ± 908.7	−110.9 ± 262.6	−53.9 ± 288.6	16.1 ± 439.6	.890
	PAWP ≥12	1,809.1 ± 570.7	−110.4 ± 59.4	−95.6 ± 278.0	−6.4 ± 461.3	
Pulmonary arterial resistance (dyne s^{-1} m^{-5})	All	336.1 ± 319.1	−28.6 ± 86.6	−27.3 ± 93.7	11.3 ± 113.6	
	PAWP <12	333.1 ± 172.0	−36.3 ± 57.2	−19.1 ± 77.4	43.8 ± 84.1	.586
	PAWP ≥12	340.3 ± 476.6	−17.0 ± 124.4	−41.0 ± 123.2	−42.9 ± 142.6	
SpO_2 (%)	All	97.0 ± 1.9	0.3 ± 0.8	0.5 ± 1.3	0.9 ± 1.1	
	PAWP <12	97.2 ± 2.2	0.1 ± 0.9	0.1 ± 1.6	0.6 ± 1.0	.201
	PAWP ≥12	96.8 ± 1.7	0.5 ± 0.8	0.9 ± 0.8	1.3 ± 1.2*	
SvO_2 (%)	All	65.3 ± 9.3	−0.1 ± 1.2	−0.6 ± 3.2	−1.8 ± 3.4	
	PAWP <12	66.7 ± 5.5	−0.4 ± 1.4	−1.7 ± 3.1	−2.8 ± 2.1*	.078
	PAWP ≥12	63.6 ± 12.8	0.3 ± 1.0	0.8 ± 3.0	−0.6 ± 4.3	
HR (/min)	All	73.9 ± 10.8	−1.2 ± 4.3	−0.2 ± 5.2	1.1 ± 6.3	
	PAWP <12	77.2 ± 9.2	−1.3 ± 3.1	−1.0 ± 4.5	0.0 ± 6.2	.569
	PAWP ≥12	70.3 ± 11.8	−1.0 ± 5.7	0.6 ± 6.0	2.3 ± 6.8	

CPAP, continuous positive airway pressure; PAWP, pulmonary artery wedge pressure (mm Hg); AoP, mean aortic pressure; PulAP, pulmonary artery pressure; RAP, right atrial pressure; SpO_2, arterial oxygen saturation; SvO_2, venous oxygen saturation; HR, heart rate.

P values are for the difference in response to stepwise CPAP increase between 2 groups according to 2-way repeated ANOVA.

*Significant difference compared with 0 cm H_2O CPAP, analyzed by 1-way repeated ANOVA followed by Bonferroni correction with significance accepted at $P < .05$.

†Significant difference compared with 4 cm H_2O CPAP, analyzed by 1-way repeated ANOVA followed by Bonferroni correction with significance accepted at $P < .05$.

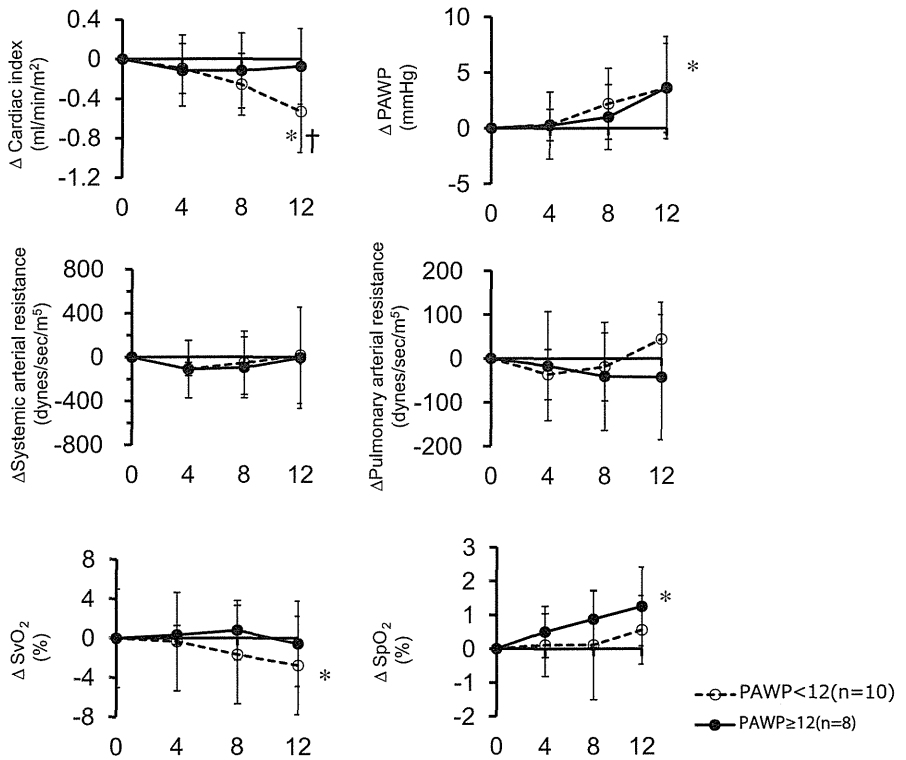

Fig. 1. Changes in hemodynamic parameters during stepwise CPAP increase in patients with PAWP <12 mm Hg (*open circles*) and PAWP ≥ 12 mm Hg (*solid circles*). Stepwise increase of CPAP from 4 cm H_2O to 12 cm H_2O decreased cardiac index significantly in patients with PAWP <12 mm Hg, but did not change cardiac index in patients with PAWP ≥ 12 mm Hg. Stepwise increase in CPAP did not change systemic arterial resistance or pulmonary arterial resistance in both groups but elevated PAWP. CPAP, continuous positive airway pressure; PAWP, pulmonary artery wedge pressure; SpO_2, arterial oxygen saturation; SvO_2, venous oxygen saturation. *Significant difference compared with 0 cm H_2O CPAP, analyzed by 1-way repeated ANOVA followed by Bonferroni correction with significance accepted at $P < .05$. †Significant difference compared with 4 cm H_2O CPAP, analyzed by 1-way repeated ANOVA followed by Bonferroni correction with significance accepted at $P < .05$.

Our result that cardiac output increased when 5 cm H_2O PS was added to 4 cm H_2O CPAP in most patients with chronic congestive heart failure is a novel finding, and it may provide a clue to explain why PAP treatment with the use of devices such as ASV is almost uniformly effective even in severe heart failure. We found that systemic and pulmonary arterial resistances decreased under the condition of CPAP + PS. These changes may be attributed to attenuation of the enhanced sympathetic nervous activity (SNA) in the heart failure condition through neural reflex induced by regular inflation of the lung. This mechanism was also suggested by the study by Harada et al,[11] in which a decrease in variation of tidal volume in heart failure patients by ASV was accompanied by instantaneous decrease in muscle SNA. SNA synchronizes with central inspiratory motor activity, and activation of pulmonary vagal afferents that reflexively inhibits sympathetic nerve discharge determines the net effect of the respiratory modulation on

Table 3. Hemodynamic Parameters During CPAP (4 cm H_2O) Alone and CPAP (4 cm H_2O) with 5 cm H_2O Pressure Support (PS)

	CPAP Alone	CPAP+PS	*P* Value
CI (mL min^{-1} m^{-2})	2.2 ± 0.7	2.3 ± 0.7	.001
AoP (mm Hg)	87.4 ± 14.5	84.3 ± 13.8	.002
PulAP (mm Hg)	22.0 ± 8.7	21.0 ± 8.4	.021
PAWP (mm Hg)	12.5 ± 7.4	12.3 ± 7.8	.673
RAP (mm Hg)	7.3 ± 7.0	7.5 ± 6.8	.482
Systemic arterial resistance (dyne s^{-1} m^{-5})	2263.0 ± 828.4	1995.9 ± 746.4	.001
Pulmonary arterial resistance (dyne s^{-1} m^{-5})	362.1 ± 282.9	298.1 ± 252.3	.003
SpO_2 (%)	97.5 ± 2.0	97.9 ± 1.6	.104
SvO_2 (%)	66.6 ± 67.5	67.5 ± 8.8	.211
HR (/min)	73.4 ± 12.0	73.2 ± 10.0	.853

CPAP, continuous positive airway pressure; CI, cardiac index; AoP, mean aortic pressure; PulAP, pulmonary artery pressure; PAWP, pulmonary artery wedge pressure; RAP, right atrial pressure; SpO_2, arterial oxygen saturation; SvO_2, venous oxygen saturation; HR, heart rate.
P values are for the difference between 2 groups according to paired Student *t* test.

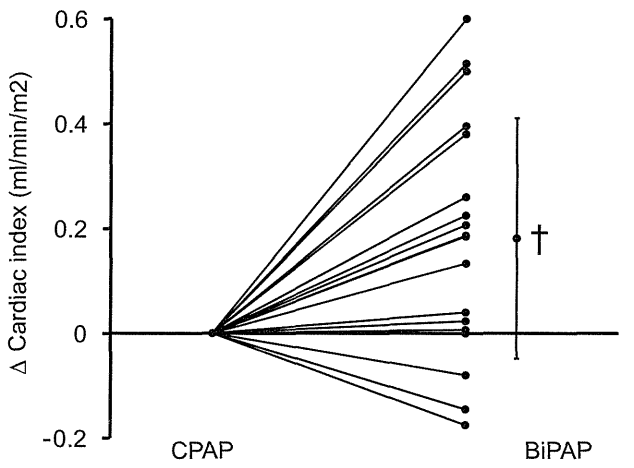

Fig. 2. Relative changes in cardiac index by bilevel PAP (CPAP + pressure support) compared with CPAP without pressure support. Bilevel PAP increased cardiac index significantly compared with CPAP alone. BiPAP, bilevel positive airway pressure; CPAP, continuous positive airway pressure; PAWP, pulmonary arterial wedge pressure. $^{\dagger}P < .01$; significant difference compared with 4 cm H_2O CPAP alone.

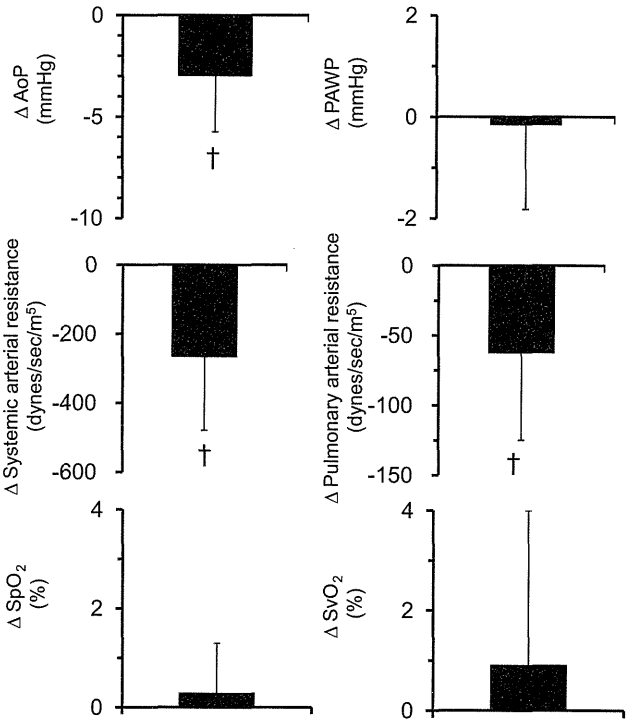

Fig. 3. Relative changes in hemodynamic parameters by bilevel PAP (CPAP + pressure support) compared with CPAP without pressure support. No significant differences in PAWP, SpO_2, and SvO_2 were observed between CPAP and bilevel PAP, but systemic arterial resistance and pulmonary arterial resistance were reduced significantly by bilevel PAP compared with CPAP. AoP, aortic pressure; CPAP, continuous positive airway pressure; PAWP, pulmonary arterial wedge pressure; SpO_2, arterial oxygen saturation; SvO_2, venous oxygen saturation. $^{\dagger}P < .01$; significant difference compared with 4 cm H_2O CPAP.

SNA.[11] Our results are supported by Oldenburg et al,[12] who reported that NIPPV decreased blood pressure but did not increase HR in 61 consecutive heart failure patients. These effects might be caused by a decrease in sympathetic tone, as was speculated in our study, and the decrease in blood pressure should be safe and might be beneficial to the patient. Because we did not examine the respiratory pattern in our patients, we can not compare this point. However, the decrease in systemic arterial resistance might support a decrease in sympathetic outflow also in our patients. If the neural response of decreased SNA truly occurs with the addition of PS to a low basal CPAP, this may imply that bilevel PAP therapy including ASV would be more comfortable for patients compared with simple CPAP, and this might explain the higher adherence rate for ASV and consequently higher clinical efficacy of ASV treatment compared with CPAP.[13]

Earlier studies using the same type of bilevel PAP reported various results. Becker et al[14] reported that bilevel PAP of 5/10 cm H_2O and 10/15 cm H_2O decreased cardiac output to a greater extent than CPAP of 5 cm H_2O and 10 cm H_2O in obstructive sleep apnea patients with normal cardiac function, but Acosta et al[15] reported that bilevel PAP of 3/5 cm H_2O increased cardiac output as measured by echocardiography. The difference in patient background between studies may be the main source of the difference in findings. Chadda et al[16] studied the hemodynamic and respiratory effects of CPAP and NIPPV (5 cm H_2O CPAP plus 5 cm H_2O PS) in patients with acute pulmonary edema and found that NIPPV did not change cardiac output significantly compared with 5 cm H_2O CPAP. Their study, however, was performed in acute patients with orthopnea, which may account for the difference from our results.

Our finding that low-level CPAP does not deteriorate the hemodynamic state in the majority of chronic heart failure patients suggests that a low level of CPAP should be recommended when the condition of the patient's cardiac filling pressure has not been determined before initiation of NIPPV or is expected to fluctuate after NIPPV is started. Our group has recently reported that an EPAP as low as 6 cm H_2O is sufficient to treat even patients with very severe pulmonary edema.[1] Therefore, when NIPPV is used aiming solely at treating heart failure or pulmonary congestion, a low end-expiratory pressure (4–8 cm H_2O) is adequate and safer, and pressures higher than this level may not be necessary or may even be harmful sometimes. This result also suggests that when a severe heart failure patient has both obstructive as well as central apnea, complete resolution of airway obstruction might better be attained by combined use of NIPPV and another device, such as oral appliance, to avoid using a high level of PAP.

As for the discrepancy between our result using 4–8 cm H_2O CPAP (no change in cardiac index) and that of Bradley et al[8] using 5 cm H_2O CPAP (decreased cardiac output) in patients with PAWP <12 mm Hg, we have no clear

explanation except that the differences in patient population and measuring device might have some effects.

Study Limitations

The present study has some limitations. First, the number of patients was small and did not represent a wide spectrum of heart failure severity. However, with this study population we were able to observe the differential effect of high CPAP on higher and lower PAWP levels similar to the results of Bradley et al.[8] Therefore, we consider that a larger number of patients is not necessary to reconfirm this result. Also, we demonstrated a robust favorable effect of adding PS to CPAP compared with CPAP without PS in our patients, including 11 with PAWP <12 mm Hg. Therefore, we do not consider it necessary to increase the number of patients to improve the accuracy of the result. However, the small number of subjects precluded multivariate analyses to identify other confounding factors. Also, the small number becomes a problem when comparing patients with PAWP <12 mm H_2O and those with PAWP ≥ 12 mm H_2O. Further study recruiting a larger number of patients is certainly required to confirm the findings.

Second, we examined only 1 level of CPAP and 1 level of PS to study the effect of additional PS. We limited the number of pressure levels, because the total study time per patient would be too long for chronic heart failure patients if we had studied more pressure levels. Also, the order of measurement was fixed and PS addition was performed after the stepwise CPAP study. The order by which the studies were performed might have some effect on the result of additional PS on cardiac output. Further study with a different protocol with special emphasis on this point, examining various CPAP or PS levels performed in a random order, is necessary to more precisely elucidate the best way of applying ASV or bilevel PAP.

Third, in the case that NIPPV affects the severity of tricuspid regurgitation, the cardiac output measured by Vigilance would be affected, because calculation of cardiac output in this system is based on thermodilution principles. However, the mean effect should be the same in all patients, and therefore the deviation from the true value may be similar overall.

Conclusion

In terms of clinical application in heart failure patients, our study shows that PAP therapy with ≤ 8 cm H_2O EPAP is safe, whereas caution has to be exercised when using EPAP at a higher level, owing to the risk of lowered cardiac output. Safe therapy can be obtained by initiating with a low level of EPAP (4 cm H_2O), confirming safety, and then adding a low level of PS. Because central apnea tends to be more common in patients with higher PAWP, CPAP treatment may be safer and more effective in this type of patients. However, a high EPAP is not recommended for all patients with central apnea, because some may have low PAWP, and careful monitoring is necessary. Although checking PAWP in all heart failure patients is ideal, it is not practical in the clinical setting. We propose to estimate the PAWP status from clinical findings and initiate PAP with caution.

In conclusion, we demonstrated unfavorable effect of CPAP when used at >8 cm H_2O in patients with lower PAWP. This fact has to be taken into account for safer treatment of heart failure patients, especially those with a less congestive status. We showed a consistent increase in cardiac output by bilevel PAP in heart failure patients, suggesting a favorable effect of PS through improvement of neural control and proposing a new concept for using PS in the treatment of heart failure patients.

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Disclosures

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Original article

Effect of cardiac rehabilitation on muscle mass, muscle strength, and exercise tolerance in diabetic patients after coronary artery bypass grafting

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ABSTRACT

Background: The effects of cardiac rehabilitation (CR) on muscle mass, muscle strength, and exercise tolerance in patients with diabetes mellitus (DM) who received CR after coronary artery bypass grafting (CABG) have not been fully elucidated.
Methods: We enrolled 78 consecutive patients who completed a supervised CR for 6 months after CABG (DM group, $n = 37$; non-DM group, $n = 41$). We measured mid-upper arm muscle area (MAMA), handgrip power (HGP), muscle strength of the knee extensor (Ext) and flexor (Flex), and exercise tolerance at the beginning and end of CR.
Results: No significant differences in confounding factors, including age, gender, ejection fraction, or number of CR sessions, were observed between the two groups. At the beginning of CR, the levels of Ext muscle strength and peak VO_2 were significantly lower in the DM group than in the non-DM group. At the end of CR, significant improvement in the levels of muscle strength, HGP, and exercise tolerance was observed in both groups. However, the levels of Ext muscle strength, HGP, peak VO_2, thigh circumference, and MAMA were significantly lower in the DM group than in the non-DM group. In addition, no significant improvement in thigh circumference and MAMA was observed in the DM group. At the end of CR, the levels of thigh circumference and MAMA correlated with Ext and Flex muscle strength as well as with HGP. Percent changes in the levels of Ext muscle strength were significantly correlated with those of MAMA and hemoglobin A1c.
Conclusions: These data suggest that improvement in muscle strength may be influenced by changes in muscle mass and high glucose levels in DM patients undergoing CR after CABG. A CR program, including muscle mass intervention and blood glucose control, may improve deterioration in exercise tolerance in DM patients after CABG.

Introduction

Patients with diabetes mellitus (DM) are at increased risk of coronary artery disease (CAD) [1]. Patients with DM are at 2–4 times higher risk of developing CAD and mortality due to CAD compared with non-DM patients [2]. Patients with CAD are treated by lifestyle modification, medical therapy, and coronary revascularization such as percutaneous coronary intervention and coronary artery bypass grafting (CABG). However, the benefits of revascularization are less and the risks and complications are greater than those in non-DM patients. Previous studies have also reported a high incidence of bypass graft dysfunction and a high mortality even in DM patients who underwent CABG [3].

Cardiac rehabilitation (CR) has numerous benefits such as modification of risk factors and prevention of future cardiovascular events [4]. Improvement in peak VO_2 after CR reduced cardiovascular morbidity and mortality in patients with CAD [5]. However, a previous study demonstrated that the presence of DM was a negative factor for improvement in peak VO_2 [6]. Another report showed a significant inverse relationship between fasting blood glucose

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levels and changes in peak VO_2 in CR participants with DM after coronary events [7]. Park et al. reported that a low level of muscle strength was a predictor of physical limitation, and diabetes was associated with a low level of skeletal muscle strength and deterioration in quality [8]. We recently reported that muscle strength and exercise tolerance were significantly lower in DM patients than non-DM patients at the beginning of CR after CABG [9]. However, the effects of CR on muscle mass, muscle strength, and exercise tolerance in DM patients undergoing CR after CABG has not been fully elucidated. The aim of this study was to investigate the effects of CR on muscle mass, muscle strength, and exercise tolerance in DM patients who received CR after CABG.

Methods

Subjects

We enrolled 78 consecutive patients who completed a supervised CR for 6 months after CABG at Juntendo University Hospital from July 2002 to February 2005. The patients were divided into 2 groups: those with DM (DM group, $n=37$) and those without DM (non-DM group, $n=41$), according to the guidelines of the Japan Diabetes Society (JDS), which includes history of medical treatment, fasting plasma glucose $\geq$ 126 mg/dl or casual plasma glucose $\geq$ 200 mg/dl, and hemoglobin (Hb) A1c $\geq$ 6.1% [10]. All patients participated in the CR program 6–8 days after CABG. All subjects gave written informed consent and the ethical committee of the institution approved this study.

Rehabilitation protocol

The CR program consisting of warm-up stretching, aerobic exercise, resistance training, and cool-down, was scheduled once or twice a week for 6 months, as described previously [11,12]. Aerobic exercise consisted of a cycle ergometer, treadmill, and walking on an indoor track with a total duration of approximately 60 min exercise intensity was prescribed individually at the anaerobic threshold (AT) level, as measured by an ergometer test using expiratory gas analysis or a rating of 11–13 on a standard Borg's perceived exertion scale. Resistance training, which was gradually added to the exercise program at least 6 weeks after participation, included sit-ups, back kicks and front raises, squats, and push-ups, using the patient's own weight. This training consisted of 1–2 sets of 10–15 repetitions for each muscle group with 3–5 min rest between sets. Patients were encouraged to perform home-based aerobic exercise twice a week for more than 20 min at a rating of 11–13 of perceived exertion on Borg's scale. All subjects were instructed to follow the phase II diet of the American Heart Association at the beginning of CR. An educational program regarding CAD and its risk factors at baseline was also provided for each subject by physicians, nurses, and dietitians.

Measurements

We assessed body composition, muscle strength, and exercise tolerance at the beginning and end of CR. Anthropometric parameters were assessed using body mass index (BMI), waist size, thigh circumference, triceps skin fold thickness measured on the dominant hand, and mid-upper arm circumference. Thigh circumference was measured directly below the gluteal fold of the right thigh according to WHO standards [13]. Mid-upper arm muscle area (MAMA) was calculated according to a standard method [14]. The percentages of body fat and lean body weight were measured by BOD POD® (Life Measurement, Inc., Concord, CA, USA), as described previously [11,12]. The power of the thigh muscles was measured using the Cybex770 system (Cybex Division of Lumex, Ronkonkoma, NY, USA), as also reported previously [11,12]. The isokinetic peak torques of the knee extensor (Ext) and flexor (Flex) muscles were measured at 60°/s, and those were adjusted by body weight according to the following formula: strength (Nm) $\times$ 100/kg body weight. Handgrip power (HGP) in the dominant hand was also measured. To measure peak oxygen consumption (peak VO_2) and oxygen uptake at the AT, patients underwent ergometer testing (Corival 400, Lobe B.V., Groningen, Netherlands) using an expiratory gas analysis machine (Vmax-295, SensorMedics Co., Yorba Linda, CA, USA). After a period of resting, warm-up was performed for a few minutes at 20 W, followed by ramp loading (15 W/min) until subjective exhaustion, progressive angina, ST-segment depression ($\geq$2 mm), or sustained tachyarrhythmia. The point of AT was determined by the "V-slope" method.

Statistical analyses

The results are expressed as mean $\pm$ standard deviation and were analyzed using the StatView software (Version 5.0J for Windows, SAS Institute, Cary, NC, USA). Comparisons between the DM and non-DM groups were performed by Student's *t*-test. Data at baseline and after 6 months of CR were compared for each patient by paired *t*-test to evaluate the singular effects of CR. Correlation coefficients were determined by linear regression analysis. Statistical significance of correlation coefficients was determined by the method of Fisher and Yates. A *p*-value of less than 0.05 was considered significant.

Results

Characteristics of CR subjects

The clinical characteristics of the subjects are presented in Table 1. Thirty-seven patients were diagnosed as having DM. No significant differences with regard to age, gender, coronary risk factors, number of diseased vessels, ejection fraction, or physiological variables, were observed between the DM and non-DM groups. Thirty-six patients received complete revascularization using the off-pump operation. One patient who had received re-CABG was in the DM group. No significant differences in the concomitant use of drugs, including antiplatelets, calcium channel blockers, β-blockers, angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, or statins, were observed between the two groups. In the DM group, 24 patients (65%) and 13 patients (35%)

Table 1
Clinical characteristics of the study subjects.

	DM	Non-DM	*p*-Value
N	37	41	
Age (year)	63.5 ± 10	64.1 ± 9	NS
Male (%)	29 (78)	39 (95)	NS
Hypertension (%)	22 (61)	30 (73)	NS
Dyslipidemia (%)	28 (76)	31 (76)	NS
Current smoker (%)	17 (49)	21 (53)	NS
Familial history (%)	11 (26)	9 (26)	NS
History of MI (%)	2 (5)	0 (0)	NS
History of PCI (%)	2 (5)	0 (0)	NS
History of previous CABG (%)	1 (3)	0 (0)	NS
Diseased vessels			
LMT (%)	9 (25)	2 (5)	NS
3VD (%)	18 (48)	28 (68)	NS
1–2VD (%)	10 (27)	11 (27)	NS
Ejection fraction (%)	59.7 ± 16	65.3 ± 12	NS
Off-pump CABG (%)	36 (97)	41 (100)	NS
Exercise in hospital (times)	16 ± 14	18 ± 14	NS

Data are presented as the mean value ± SD. DM, diabetes mellitus; MI, myocardial infarction; PCI, percutaneous coronary intervention; CABG, coronary arterial bypass grafting; LMT, left main trunk; VD, vessel disease.

were treated with oral anti-diabetic agents and insulin, respectively. No significant differences were observed between the two groups in exercise duration in the CR program (data not shown). No subject in either group showed any worsening of symptoms or had cardiovascular events during the 6 months of the study.

Serum lipid profiles and glucose parameters

Serum lipid profiles and glucose parameters at baseline and the end of CR are presented in Table 2. Fasting blood glucose and HbA1c levels before and after CR were significantly higher in the DM group than in the non-DM group (both $p < 0.05$). Lipid profiles were not significantly different between the two groups at both baseline and the end of CR.

Anthropometric parameters

The anthropometric parameters at baseline and after CR in both groups are presented in Table 3. The anthropometric parameters at baseline were not significantly different between the two groups. In the non-DM group, waist circumference (from 84.5 ± 7.8 to 82.2 ± 6.7 cm, $p < 0.05$) was significantly decreased, and thigh circumference (from 48.9 ± 4.1 to 50.7 ± 3.7 cm, $p < 0.05$), arm forced circumference (from 29.0 ± 2.6 to 30.0 ± 2.4 cm, $p < 0.05$), mid-upper arm muscle circumference (from 25.7 ± 2.5 to 26.5 ± 2.4 cm, $p < 0.05$), and MAMA (from 53.2 ± 10.3 to 56.5 ± 10.0 cm^2, $p < 0.05$) were significantly increased. In the DM group, waist circumference (from 83.4 ± 8.3 to 80.2 ± 5.7 cm, $p < 0.05$) was significantly decreased, however, thigh circumference, arm forced circumference, mid-upper arm muscle circumference, and MAMA were not significantly altered. At the end of CR, thigh circumference (47.3 ± 2.5 cm vs. 50.7 ± 3.7 cm, $p < 0.05$), arm forced circumference, (28.4 ± 1.6 cm vs. 30.0 ± 2.4 cm, $p < 0.05$), mid-upper arm muscle circumference (25.0 ± 1.8 cm vs. 26.5 ± 2.4 cm, $p < 0.05$), and MAMA (49.9 ± 7.1 cm^2 vs. 56.5 ± 10.0 cm^2, $p < 0.05$) were significantly lower in the DM group than in the non-DM group.

Exercise tolerance and muscle strength

Exercise tolerance and muscle strength at baseline and after CR in each group are presented in Table 4. At the beginning of CR, the levels of peak VO_2 (13.7 ± 4.0 ml kg^{-1} min^{-1} vs. 16.0 ± 4.7 ml kg^{-1} min^{-1}, $p < 0.05$) and thigh muscle strength (136.3 ± 42.7 Nm kg^{-1} × 100 vs. 162.7 ± 47.9 Nm kg^{-1} × 100, $p < 0.05$) were significantly lower in the DM group than in the non-DM group. No significant differences in HGP (28 ± 9 kg vs. 31 ± 9 kg, NS) were observed between the two groups. At the end of CR, both groups showed significant improvements in exercise tolerance and muscle strength. Improvements in exercise tolerance and muscle strength were identical in the DM and non-DM groups. However, the levels of peak VO_2 (19.4 ± 3.8 ml kg^{-1} min^{-1} vs. 22.9 ± 5.4 ml kg^{-1} min^{-1}, $p < 0.05$) and AT (11.3 ± 2.2 ml kg^{-1} min^{-1} vs. 13.3 ± 3.4 ml kg^{-1} min^{-1}, $p < 0.05$) were still significantly lower in the DM group than in the non-DM group. The levels of thigh Ext muscle strength (164.1 ± 43.3 Nm kg^{-1} × 100 vs. 193.3 ± 51.9 Nm kg^{-1} × 100, $p < 0.05$) and HGP (30 ± 7 kg vs. 35 ± 8 kg, $p < 0.05$) were also significantly lower in the DM group than in the non-DM group.

Correlations between muscle mass, muscle strength, and HbA1c

At the end of CR, the values for thigh muscle strength were correlated with thigh circumference ($r = 0.44$, $p < 0.01$) and MAMA ($r = 0.37$, $p < 0.05$) (Fig. 1). The values of HGP were correlated with thigh circumference ($r = 0.52$, $p < 0.01$), and MAMA ($r = 0.48$, $p < 0.05$) (Fig. 1). The same trends were observed at the beginning of CR [9]. Moreover, the percent change in Ex muscle strength was

Table 2
Comparison of glucose, lipid, and other parameters between the DM and non-DM groups.

	DM group ($n = 37$)		Non-DM group ($n = 41$)	
	Baseline	After	Baseline	After
Fasting blood glucose (mg/dl)	143 ± 57	167 ± 68	103 ± 14	112 ± 20
HbA1c (%) (JDS)	7.0 ± 1.3	7.2 ± 1.4	5.1 ± 0.4	5.2 ± 0.5
LDL-C (mg/dl)	116 ± 37	97 ± 22	124 ± 40	89 ± 16
HDL-C (mg/dl)	48 ± 15	50 ± 14	51 ± 12	49 ± 12
TG (mg/dl)	161 ± 97	168 ± 191	149 ± 66	158 ± 97
Creatinine (mg/dl)	1.4 ± 2.3	1.1 ± 1.3	0.8 ± 0.2	0.8 ± 0.2
CRP (mg/dl)	0.6 ± 1.4	0.6 ± 1.3	0.2 ± 0.2	0.7 ± 2.0

Data are presented as the mean value ± SD. DM, diabetes mellitus; HbA1c, hemoglobin A1c; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; TG, triglycerides; CRP, C-reactive protein.
$^{*}p < 0.05$ compared with at baseline.
$^{**}p < 0.05$ compared with the DM group at baseline.
$^{\#}p < 0.05$ compared with the DM group after 6 months.

Table 3
Comparison of anthropometric parameters between the DM and non-DM groups.

	DM group ($n = 37$)		Non-DM group ($n = 41$)	
	Baseline	After	Baseline	After
Body mass index (kg m^{-2})	23.3 ± 2.7	22.6 ± 1.9	23.4 ± 2.9	23.7 ± 2.5
Lean body weight (kg)	48.4 ± 9.8	45.2 ± 5.2	49.4 ± 7.7	49.6 ± 7.3
Waist circumference (cm)	83.4 ± 8.3	80.2 ± 5.7*	84.5 ± 7.8	82.2 ± 6.7*
Thigh circumference (cm)	47.2 ± 4.3	47.3 ± 2.5	48.9 ± 4.1	50.7 ± 3.7$^{*,\#}$
Arm forced circumference (cm)	28.3 ± 2.7	28.4 ± 1.6	29.0 ± 2.6	30.0 ± 2.4$^{*,\#}$
Mid-upper arm muscle circumference (cm)	24.9 ± 2.4	25.0 ± 1.8	25.7 ± 2.5	26.5 ± 2.4$^{*,\#}$
Mid-upper arm muscle area (cm^2)	49.7 ± 9.5	49.9 ± 7.1	53.2 ± 10.3	56.5 ± 10.0$^{*,\#}$

Data are presented as the mean value ± SD. DM, diabetes mellitus.
* $p < 0.05$ compared with at baseline.
$^{\#}$ $p < 0.05$ compared with the DM group after 6 months.

Table 4
Comparison of exercise tolerance and muscle strength between the DM and non-DM groups.

	DM group ($n=37$)		Non-DM group ($n=41$)	
	Baseline	After	Baseline	After
Anaerobic threshold (ml kg^{-1} min^{-1})	8.3 ± 1.6	11.3 ± 2.2*	9.7 ± 2.7	13.3 ± 3.4*,#
Peak VO_2 (ml kg^{-1} min^{-1})	13.7 ± 4.0	19.4 ± 3.8*	16.0 ± 4.7**	22.9 ± 5.4*,#
Anaerobic threshold workload (W)	34 ± 15	52 ± 21*	39 ± 20	66 ± 22*,#
Peak workload (W)	73 ± 23	107 ± 21*	81 ± 29	124 ± 29*,#
Knee extension (Nm kg^{-1} × 100)	136.3 ± 42.7	164.1 ± 43.3*	162.7 ± 47.9**	193.3 ± 51.9*,#
Knee flexion (Nm kg^{-1} × 100)	80.0 ± 26.7	102.4 ± 30.3*	91.2 ± 29.2	115.1 ± 30.7*
Power of hand grip (kg)	28 ± 9	30 ± 7*	31 ± 9	35 ± 8*,#

Data are presented as the mean value ± SD. DM, diabetes mellitus.
* $p<0.05$ compared with at baseline.
** $p<0.05$ compared with the DM group at baseline.
# $p<0.05$ compared with the DM group after 6 months.

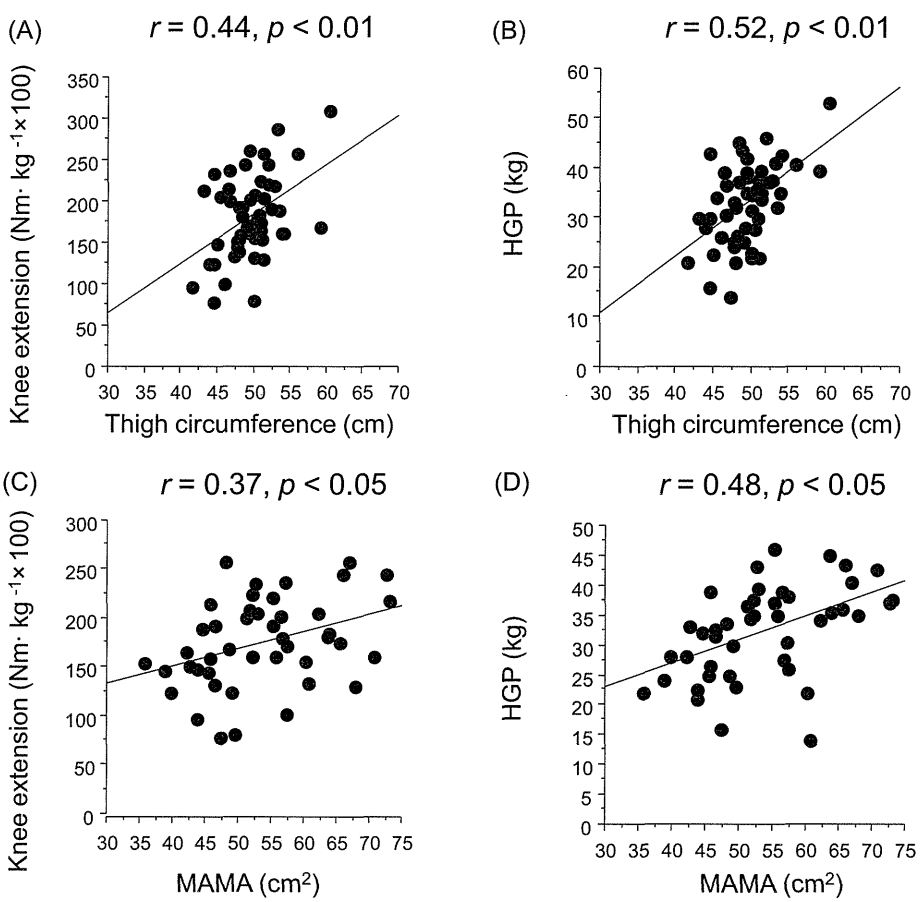

Fig. 1. Correlations between muscle strength and muscle mass. At the end of cardiac rehabilitation, the levels of muscle strength of thigh were correlated with thigh circumference ($r=0.44$, $p<0.01$) (A) and MAMA ($r=0.37$, $p<0.05$) (C). The values of HGP were correlated with thigh circumference ($r=0.52$, $p<0.01$) (B), and MAMA ($r=0.48$, $p<0.05$) (D). MAMA, mid-upper arm muscle area; HGP, hand grip power.

correlated with MAMA ($r=0.47$, $p<0.005$) and HbA1c ($r=-0.41$, $p<0.05$) (Fig. 2).

Discussion

In the present study, we demonstrated that: (1) the levels of muscle strength and exercise tolerance at the beginning and end of CR were significantly lower in the DM group than in the non-DM group; (2) exercise tolerance and muscle strength after CR were significantly improved in both groups; (3) muscle mass was significantly increased after CR in the non-DM group, but not in the DM group; and (4) percent change in muscle strength was correlated with that of HbA1c in patients undergoing CR after CABG. Our group and others previously reported a relationship between muscle strength and peak VO_2 in patients with cardiovascular disease [15,16]. However, to the best of our knowledge, this is the first report to simultaneously demonstrate the effects of CR on muscle mass, muscle strength, and exercise tolerance, and to compare DM and non-DM patients undergoing CR after CABG.

CR is described as a class I recommendation in most contemporary cardiovascular clinical practice guidelines. Following CR, patients show increased exercise tolerance and muscle strength, which have proven to be the strongest predictors of the risk of death among subjects both with and without known cardiovascular disease [17,18]. Boulé et al. reported in a meta-analysis that

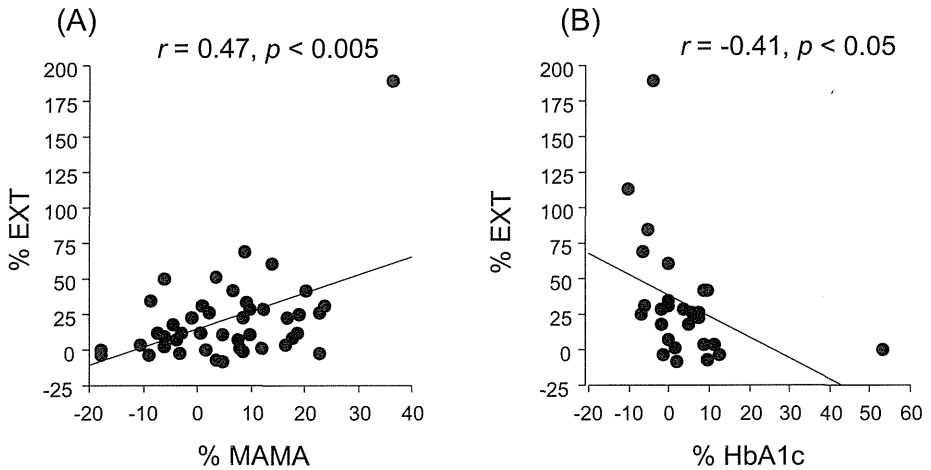

Fig. 2. Correlations between percent change in muscle strength and those in MAMA and HbA1c. A significant relation between the percent change in the muscle strength and those in MAMA was observed ($r = 0.47$, $p < 0.005$) (A). A significant inverse relation between the percent change in the muscle strength and those in HbA_1c was observed ($r = -0.41$, $p < 0.05$) (B). % EXT, percent change of knee extension; % MAMA, percent change of mid-upper arm muscle area; % HbA_1c, percent change of hemoglobin A_1c.

structured exercise training in DM patients achieved an 11.8% increase in peak VO_2 [19]. This is particularly important, because an improvement in peak VO_2 of 1.44 ml kg^{-1} min^{-1} was equivalent to a 7.9% reduction in overall mortality [20]. Moreover, exercise has many potential benefits, including not only improving exercise tolerance, but also improving glucose metabolism, insulin signaling, lipid profile, endothelial function, and blood pressure, reducing vascular inflammation and facilitating weight maintenance [7]. Either aerobic or resistance training alone improves glycemic control in DM patients, however, a combination of both may be more beneficial for improving risk factors than each alone [18]. Williams et al. have reported a combination of aerobic and resistance training exercise improved through neuromuscular adaptation, muscle fiber hypertrophy, and increased muscle oxidative capacity [21]. A previous study demonstrated the beneficial effects of resistance training on muscle mass and strength in chronic heart failure [18]. We also reported that CR with aerobic and resistance training had beneficial effects not only on the modification of metabolic risk factors, but also on improvement in exercise tolerance and muscular strength in patients with metabolic syndrome following CABG [12].

Levels of exercise tolerance and muscle strength were lower in DM than in non-DM patients in the present study. A previous report showed that endothelial dysfunction associated with high glucose levels is caused by the increased production of vasoconstrictor prostanoids as a consequence of protein kinase C activation [22]. Other studies have demonstrated that DM patients have impaired metabolism of both glucose and fatty acids in skeletal muscles. In addition, the bioenergetic capacity of skeletal muscle mitochondria was found to be impaired in DM patients [23]. We previously observed a significant inverse relationship between fasting glucose levels and thigh muscle strength at the beginning of CR in DM patients after CABG [9].

The DM group showed no increase in muscle mass such as MAMA and thigh circumference (Table 3), both of which correlated with thigh muscle strength and HGP (Fig. 1). Vergès et al. reported that the effects of CR on exercise capacity were significantly lower in DM than in non-DM patients, and the response to CR was influenced by blood glucose levels [7]. Moreover, we showed a significant inverse relationship between percent change for HbA1c and that for thigh muscle strength in the DM group (Fig. 2). Park et al. demonstrated that functional muscle quality was relatively low in DM patients. Furthermore, long duration of diabetes and poor glycemic control were associated with deterioration in muscle quality. Diabetes with poor glycemic control is related to the presence and severity of peripheral neuropathy and inflammatory cytokines, which have detrimental effects on muscle function [8]. Chronic hyperglycemia induces a condition of oxidative stress that is causally involved in the development of skeletal muscle depletion [24]. The increased production of reactive oxygen species induced by hyperglycemia has also been suggested to be involved in the redox regulation of glucose transport in skeletal muscle [25]. Hyperglycemia leads to the production of Amadori products between glucose and reactive amino groups of serum proteins [26]. These products undergo further irreversible reactions to form advanced glycation end products that promote insulin resistance and trigger inflammation, which leads to diabetic vascular complications [26]. The DM group had 11.0 ± 6.7 years' duration of DM history in the present study, and the prevalence of microvascular complications, including retinopathy, nephropathy, and neuropathy was 38%. These data may explain the mechanisms by which improvements in muscle mass and strength, and exercise tolerance, were impaired in the DM group. Thus, not only exercise but also glycemic control may be important in improving muscle structure.

Several studies have shown a U-shaped association between BMI and mortality. Increased risk was independent of abdominal and general obesity, and lifestyle and cardiovascular risk factors such as blood pressure and lipid levels were related to early cardiovascular morbidity and mortality. Additionally, Heitmann et al. reported that this risk was related more to thigh than waist circumference [13]. A study in a cohort of community-dwelling Japanese elderly demonstrated that low arm muscle area was an independent risk factor for 2-year mortality [27]. We would like to clarify whether arm muscle area after CR can predict morbidity and mortality in DM patients after CABG.

There are some limitations to the present study. First, because this was a single-center study with a small sample size, studies of larger sample size are required to confirm these findings. Second, the exercise session at the outpatient clinic was encouraged once a week with at least 2 exercise sessions at home. However, while the mean number of CR sessions in hospital was 16–18 times, we have no data regarding home-based exercise frequency and intensity for either group, and we need to assess the effects of exercise frequency and intensity in a future study. The program used in this study may not have been sufficiently rigorous to alter parameters such as glucose control and lipid profiles. Third, we enrolled patients undergoing CR after CABG. Therefore, the results may not necessarily be representative of all DM patients with CAD. In a future study,

we need to investigate DM patients undergoing percutaneous intervention and/or those with acute coronary syndrome. Finally, we need to investigate whether different treatments, including intensive glucose control and a combination of aerobic and resistance training, can enhance muscle mass and ameliorate future cardiovascular events and long-term mortality in DM patients after CABG.

Conclusions

Patients with DM had lower muscle strength and lower exercise tolerance than non-DM patients at the beginning of CR after CABG. Both groups showed improved exercise tolerance and muscle strength after undergoing CR. However, DM patients had lower muscle mass, lower muscle strength, and lower exercise tolerance than non-DM patients at the end of CR. Moreover, improvement in muscle strength may be influenced by changes in muscle mass and high glucose levels in DM patients. Further studies are needed to assess whether a CR program including muscle mass intervention and aggressive glucose control would improve muscle mass and ameliorate future cardiovascular events in DM patients after CABG.

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ORIGINAL ARTICLE

Mortality risk of triglyceride levels in patients with coronary artery disease

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ABSTRACT

Objective The association between triglyceride level and the risk of coronary artery disease (CAD) remains controversial. In particular, the prognostic significance of triglyceride levels in established CAD is unclear. We aimed to assess the relationship between triglyceride levels and long-term (>10 years) prognosis in a cohort of patients after complete coronary revascularisation.

Design Observational cohort study.

Setting Departments of cardiology and cardiovascular surgery in a university hospital.

Patients Consecutive patients who had undergone complete revascularisation between 1984 and 1992. All patients were categorised according to the quintiles of fasting triglyceride levels at baseline.

Main outcome measures The risk of fasting triglyceride levels for all-cause and cardiac mortality was assessed by multivariable Cox proportional hazards regression analyses.

Results Data from 1836 eligible patients were assessed. There were 412 (22.4%) all-cause deaths and 131 (7.2%) cardiac deaths during a median follow-up of 10.5 years. Multivariable analyses including total and high-density lipoprotein cholesterol and other covariates revealed no significant differences in linear trends for all-cause mortality according to the quintiles of triglyceride (p for trend=0.711). However, the HR increased with the triglyceride levels in a significant and dose-dependent manner for cardiac mortality (p for trend=0.031). Multivariable analysis therefore showed a significant relationship between triglyceride levels, when treated as a natural logarithm-transformed continuous variable, and increased cardiac mortality (HR 1.51, p=0.044).

Conclusions Elevated fasting triglyceride level is associated with increased risk of cardiac death after complete coronary revascularisation.

Several epidemiological studies have investigated the relationships between serum triglyceride levels and morbidity and mortality rates of coronary artery disease (CAD).[1–4] However, the evidence for elevated triglyceride levels as an independent risk factor for CAD remains controversial because there is no uniformity in data obtained in large epidemiological studies. There is a concern that adjustment for other abnormal lipid profiles, such as high-density lipoprotein (HDL) cholesterol levels, attenuates the relationship between triglycerides and CAD because there is an inverse correlation between triglyceride levels and HDL cholesterol levels. Nevertheless, meta-analyses have shown that serum triglyceride levels are an independent risk factor for morbidity and mortality rates of CAD in primary prevention.[5–8]

Unlike primary prevention, there are few data on the long-term prognostic significance of triglyceride levels in secondary prevention of CAD. The relationship between triglyceride levels and mortality risk after complete coronary revascularisation has not been established. We aimed to assess the relationship between triglyceride levels and long-term prognosis in a cohort of patients with CAD after complete coronary revascularisation.

METHODS

Subjects

We analysed data from consecutive patients who had undergone coronary revascularisation, including percutaneous coronary intervention (PCI) and coronary artery bypass grafting (CABG), at Juntendo University Hospital (Tokyo, Japan) between January 1984 and December 1992. We included patients who had achieved complete revascularisation—that is, patients in whom no unbypassed major vessels had a stenosis of ≥50%.[9 10] Patients with an untreated neoplasm at baseline and those with associated complex cardiac procedures such as valve replacement or aneurysm repair at the time of surgical revascularisation were excluded. The study was approved by the institute's internal review board and was performed according to the principles expressed in the Declaration of Helsinki and the ethics policy of the institute.

Data collection and definitions of variables

Demographic data including age, gender, body mass index (BMI), coronary risk factors, medication use, revascularisation procedure-related factors and comorbidities were prospectively collected. Blood samples were obtained in the early morning after an overnight fast. Hypertension was defined as systolic blood pressure ≥140 mm Hg and diastolic blood pressure ≥90 mm Hg or treatment with antihypertensive medications. Diabetes mellitus (DM) was defined as fasting plasma glucose level of ≥6.99 mmol/l or treatment with oral hypoglycaemic drugs or insulin injections. A current smoker was defined as a patient who smoked at the time of complete revascularisation or who had quit smoking within 1 year prior to the procedure. Patients with isolated PCI had achieved complete revascularisation by PCI without bypass grafting.

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Outcomes

The follow-up period ended on 30 September 2000. Survival data were collected by establishing serial contact with the patients or their families or from the medical records of deceased patients or those who continued to be followed up at our hospital. Information about the circumstances and date of death was obtained from the families of patients in cases where the patient died at home, and details of the events or the cause of death was supplied by other hospitals or clinics where the patients were admitted. Mortality data were categorised according to the causes of death (eg, all-cause or cardiac deaths) using the International Classification of Diseases, Ninth Revision codes 410–414, 785.51 and 798.

Statistical analysis

For the main analysis, all patients were categorised according to the quintiles of triglyceride levels. Continuous variables are expressed as mean±SD and categorical data are tabulated as frequencies and ratios. Differences between the baseline characteristics of patients within each triglyceride category were analysed by analysis of variance for continuous variables and the Cochrane–Armitage test for trend for proportions. To determine whether the results differed with the cut-off points, we performed secondary analyses in which triglyceride levels were treated as a natural logarithm-transformed continuous variable.

Cumulative mortalities were plotted using Kaplan–Meier curves and differences between quintiles of triglyceride levels were determined using log-rank tests. p Values for log-rank trend tests were also estimated. Cox proportional hazard models were used to compute HR and 95% CI for each quintile of triglyceride level using the lowest quintile as the reference group. Linear trend analyses were performed by using linear contrast coefficients (−2, −1, 0, 1, 2) in Cox proportional hazard models. The assumption of proportional hazards was assessed using a log-minus-log survival graph. Models were initially adjusted for age and gender (Model 1). To determine the role of triglycerides independent of other lipid markers, we adjusted the models for total and HDL cholesterol levels (Model 2). Furthermore, multivariable models were adjusted for non-HDL and HDL cholesterol levels (Model 3) and for BMI, presence of hypertension, presence of DM, current smoking, family history of CAD, prior myocardial infarction (MI), prior stroke, presence of atrial fibrillation, under dialysis, left ventricular ejection fraction, number of diseased vessels, presence of an arterial bypass to left anterior descending artery, presence of a left main trunk lesion, whether complete revascularisation was achieved by isolated PCI and use of drugs (aspirin, angiotensin-converting enzyme (ACE) inhibitors, β-blockers, statins, fibrates and niacin) in addition to the variables used in Model 2 (Model 4). To avoid overadjustment, the latter covariates were added only if they were significant predictors of death from all-cause or cardiac death at an α level of 0.1. Finally, multivariable models were further adjusted for non-HDL cholesterol levels plus the same variables as in Model 4 other than total cholesterol (Model 5).

To assess the potential heterogeneity of the effect of triglyceride levels on cardiac mortality we performed subgroup analyses. The subgroups included age groups (cut-off 60 years), gender, presence/absence of DM, total cholesterol (cut-off 5.69 mmol/l), HDL cholesterol (cut-off 1.29 mmol/l) and use of statins. The first-order interactions in multivariable Cox proportional hazards models were examined by entering interaction terms between triglyceride levels and the abovementioned subgroup variables. We also determined the effect of triglyceride levels on cardiac mortality in each subgroup.

A p value of <0.05 was considered statistically significant unless indicated otherwise. All data were analysed using SAS V.9.2 (SAS Institute, Cary, North Carolina, USA).

RESULTS

We assessed data from 1836 eligible patients who had undergone complete coronary revascularisation during the study period. Baseline and clinical event data were fully documented during a median follow-up period of 10.5 years. All patients underwent PCI with simple balloon angioplasty; no patient received stent implantation since stents were not available when complete revascularisation was achieved. All CABG procedures were performed using a conventional cardiopulmonary bypass; arterial grafts were used in 51.4% of cases. None of the patients had type 1 DM. During the follow-up period 412 patients (22.4%) died from any cause and 131 patients (7.2%) died from cardiac causes.

The baseline characteristics of patients by quintiles of triglyceride levels are shown in table 1. Patients with high triglyceride levels were likely to be young, male and current smokers with a high BMI and total cholesterol level, a low HDL cholesterol level and frequently had prior MI. Among patients with high triglyceride levels, a smaller percentage of patients underwent revascularisation by isolated PCI, a high percentage were taking aspirin and a low percentage were taking statins.

The cumulative survival curves of patients according to the quintiles of triglyceride levels are shown in figure 1. Patients with high triglyceride levels were more likely to have high cumulative cardiac mortality rates (figure 1B) but they did not show any trend to high cumulative all-cause mortality (figure 1A).

The results of Cox proportional hazard regression analyses for all-cause and cardiac mortality are summarised in figure 2. Linear trends for all-cause mortality according to the quintiles of triglyceride levels were not significant in any models except for Model 1. However, among each quintile of triglyceride level in all models, HR increased significantly with the triglyceride levels in a dose-dependent manner for cardiac mortality.

The results of Cox proportional hazard regression analyses, in which triglyceride levels were treated as natural logarithm-transformed continuous variables, are also shown in figure 2. For all-cause mortality, only Model 1 showed a significant association between logarithm-transformed triglyceride level and mortality. However, for cardiac mortality, all models showed significant associations between these two factors.

We also conducted a subgroup analysis separately from the age, gender, presence of DM, total and HDL cholesterol levels and the use of statins for all-cause and cardiac death. Although associations of triglyceride level with mortality were more prominent in men, patients with low HDL and patients not receiving statins, all p values for interaction were not significant (figure 3).

DISCUSSION

In this study we made several important findings that provide insights into the relationship between triglyceride levels and cardiovascular diseases. First, we found that patients in the highest triglyceride quintile had a significantly greater risk of cardiac mortality than those in the lowest triglyceride quintile. Further, HR increased with the triglyceride quintile in a significant and dose-dependent manner, and high logarithm-transformed triglyceride levels were associated with increased long-term cardiac