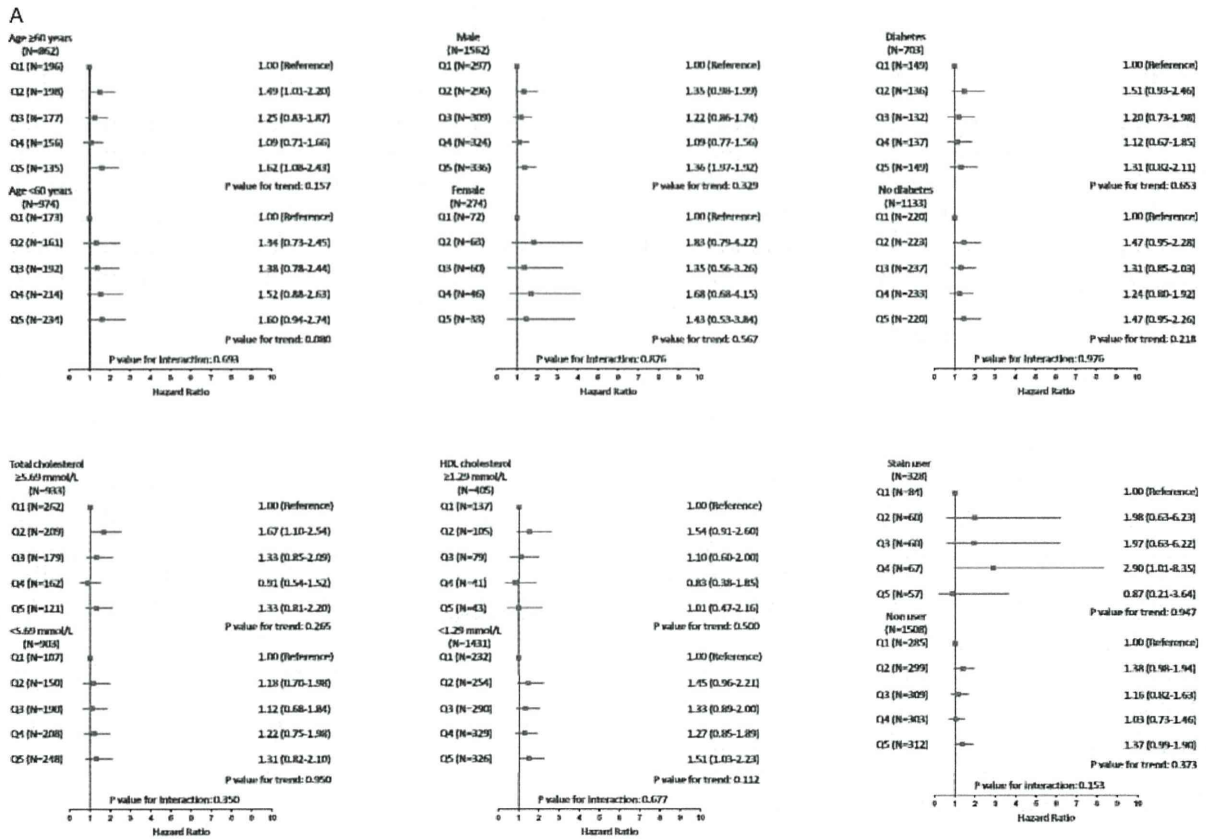

Figure 3 Subgroup analyses of (A) all-cause deaths and (B) cardiac deaths. HDL, high-density lipoprotein. This figure is only reproduced in colour in the online version.

women who receive coronary revascularisation are older and their baseline risk profiles are worse than men.[21 22] These factors might attenuate the significance of the association of triglyceride levels and cardiac mortality in women in our study population. Nevertheless, considering that no significant association was observed between triglyceride levels and cardiac mortality in all subgroups which included small numbers of patients (ie, women, patients with high HDL cholesterol levels and patients receiving statins), the results of analysis within individual subgroups should be interpreted with caution.

On the other hand, the relationship between triglyceride levels and mortality risks among patients with CAD receiving statin treatment has been investigated in several studies. For instance, Wolfram *et al*[23] reported that, in patients with acute coronary syndrome of whom 98% were on statin treatment, triglyceride levels were not associated with 1-year clinical outcomes. In addition, there was no significant relationship between triglyceride levels and short-term outcome in the Myocardial Ischaemia Reduction with Aggressive Cholesterol Lowering trial.[24] Analyses from the Incremental Decrease in End Point Through Aggressive Lipid Lowering trial and the Treating to New Targets trial showed that triglyceride levels are associated with a risk of cardiovascular events even after adjustment of other lipid parameters, but this relationship was no longer significant when other risk factors were included in further multivariable analysis.[25] In contrast, the Pravastatin or Atorvastatin Evaluation and Infection Therapy-Thrombolysis In Myocardial Infarction (PROVE IT-TIMI) 22 trial showed an independent relationship between triglyceride levels and cardiovascular events outcome, which is consistent with the results of the present study.[26] These conflicting results could be explained by the differences in baseline triglyceride levels across these studies, including ours. In studies which failed to show a significant relationship between triglyceride levels and outcomes,[23–25] patients had relatively low triglyceride levels compared with the PROVE IT-TIMI 22 trial[26] and the present study, suggesting that the degree of hypertriglyceridaemia may affect the effect of adjustment for covariates including other lipid parameters. Nevertheless, these results also indicate that elevated triglyceride levels can be a predictor of worse outcomes even in patients on statin treatment, and further adjunctive intervention for elevated triglyceride levels should be considered.[27]

It remains controversial whether there is a causal relationship between triglyceride levels and CAD morbidity and mortality. The triglyceride level is rather regarded as an important biomarker of cardiovascular disease because of its association with atherogenic remnant particles and apo CIII.[18] Randomised controlled studies on treatment for lowering triglyceride levels could provide a solution to this controversy. However, all available interventions for lowering triglyceride levels such as drugs (eg, fibrates, niacin and statins) and lifestyle modifications also affect the confounding parameters, including LDL cholesterol, HDL cholesterol and insulin resistance,[28–31] so we could not determine the causality in such studies. However, as the condition is characterised by an increased circulating triglyceride level, the triglyceride level can be considered as an interventional target. This hypothesis is supported by a recent report by Tirosh and colleagues[32] who followed 13 953 young men aged 26–45 years for 5.5 years and performed two measurements of fasting triglycerides 5 years apart. There were significant correlations between a good lifestyle and the reduction in triglyceride levels between the two measurements. Evaluation of the change

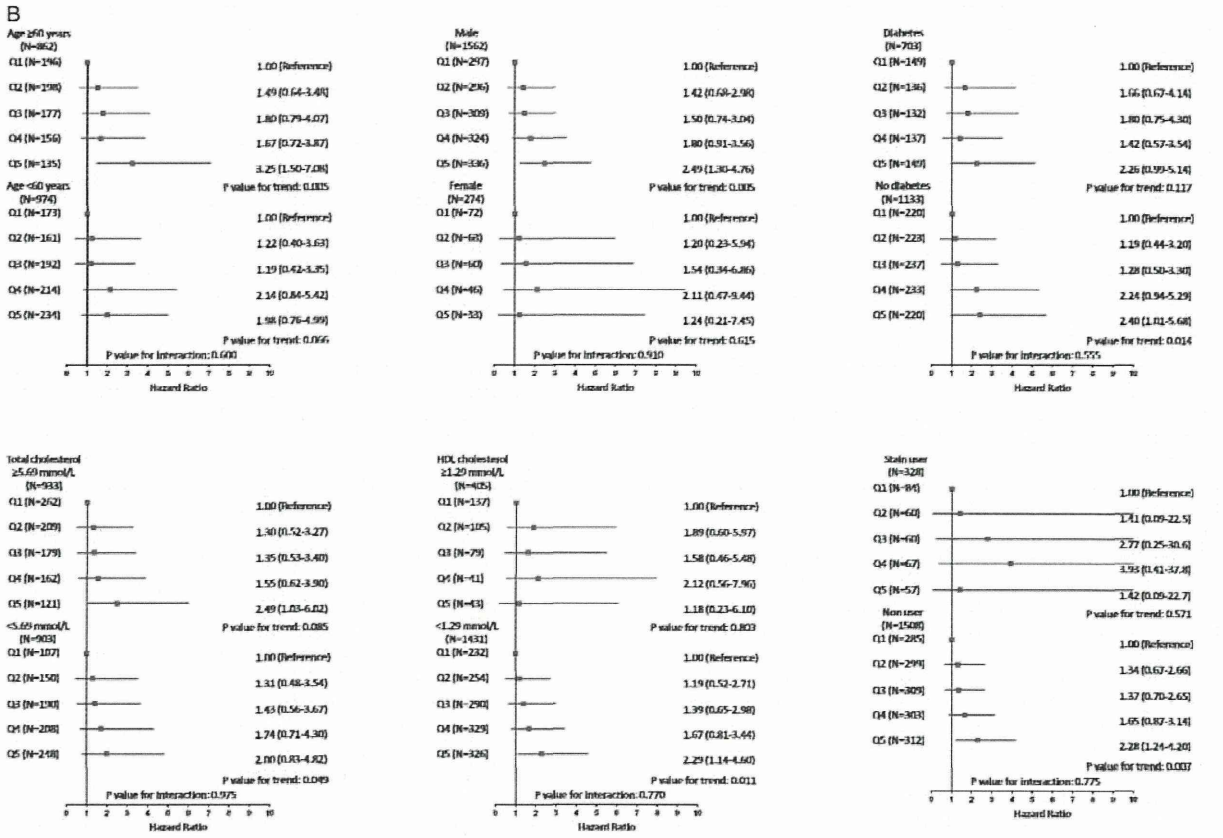

Figure 3 Continued.

in triglyceride levels over the first 5 years and incident CAD in the next 5.5 years showed a direct correlation between increases in triglyceride levels and the risk of CAD. These findings suggest a causal relationship between increased triglyceride level and CAD morbidity and mortality.

The present study has several limitations. First, balloon angioplasty was the only PCI used in all patients and 51.1% of the CABG procedures involved an arterial graft. It is difficult to determine whether the use of stents and arterial grafts could have improved the results in the recent era of revascularisation and to evaluate the relative importance of improvements in both operator skills and adjunctive drug therapy. Further investigation is needed to clarify whether triglyceride levels will affect the long-term mortality in the stent and arterial bypass era. Second, assessment of data only of patients who achieved complete revascularisation also introduced potential selection bias in terms of the overall mortality rate which should be taken into account. Third, several groups recently reported that the non-fasting triglyceride level is a superior predictor of cardiovascular risk than fasting levels.[33 34] If we can use non-fasting triglyceride levels as a predictor of cardiovascular morbidity and mortality in patients with CAD, it would have greater clinical applications as it is easier to obtain non-fasting than fasting triglyceride levels. Further studies and discussions regarding the importance of non-fasting triglyceride levels in the secondary prevention of CAD are therefore needed.

Conclusions

Fasting triglyceride levels were associated with an increase in cardiac mortality over a 10-year period after complete coronary revascularisation. This association was observed even after adjustment for the total and HDL cholesterol levels together with other covariates.

Contributors HD had full access to all data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Conception and design: HD, TK, KM. Acquisition of data: KK, NK, MO, ST. Analysis and interpretation of data: HD, TK, NY. Drafting of the manuscript: TK, NY. Critical revision of the manuscript for important intellectual content: HD, KM, AA. Final approval of the version to be published: HD, KM, KK, NK, MO, ST, AA.

Competing interests None.

Ethics approval Ethics approval was obtained from Juntendo University ethics committee.

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Mortality risk of triglyceride levels in patients with coronary artery disease

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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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See page 917 for disclosure information.

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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 $P < .05$.

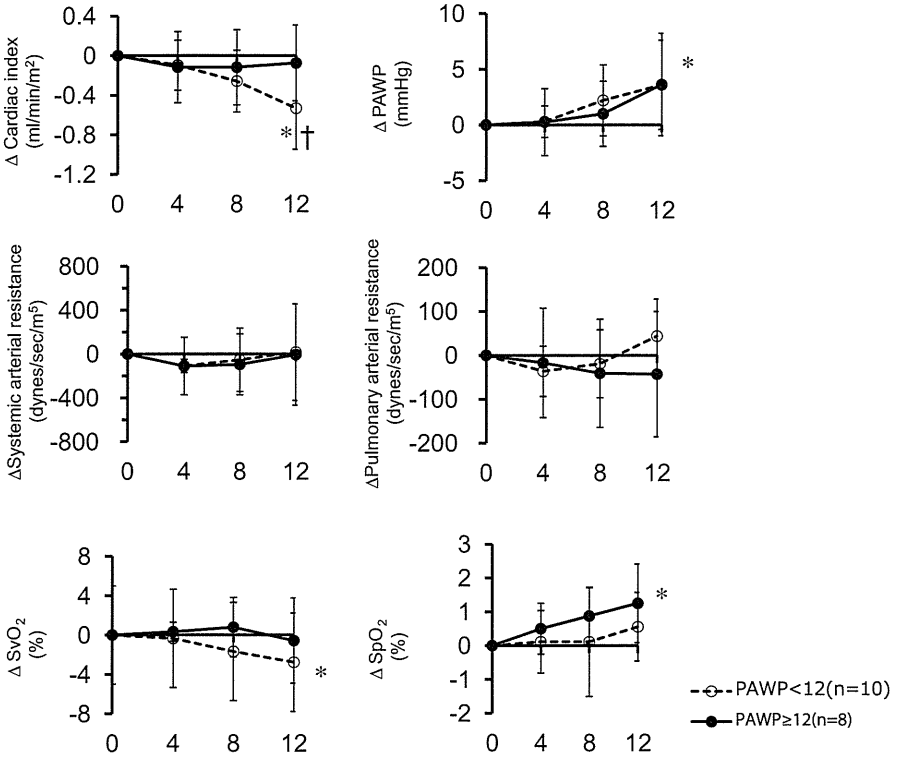

Fig. 1. Changes in hemodynamic parameters during stepwise CPAP increase in patients with PAWP <12 mm Hg (*open circles*) and PAWP ≥12 mm Hg (*solid circles*). Stepwise increase of CPAP from 4 cm H_2O to 12 cm H_2O decreased cardiac index significantly in patients with PAWP <12 mm Hg, but did not change 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.

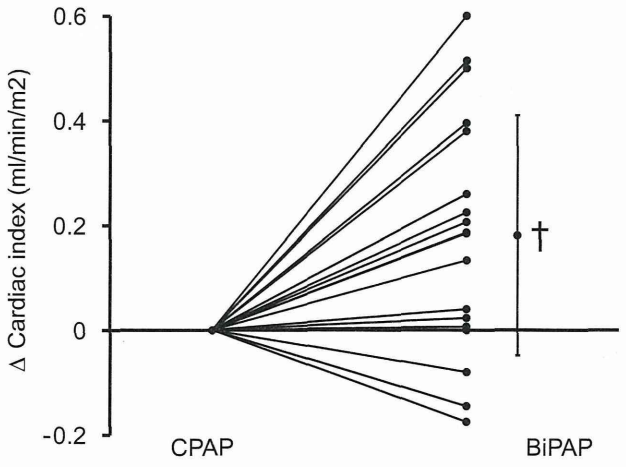

Fig. 2. Relative changes in cardiac index by bilevel PAP (CPAP + pressure support) compared with CPAP without pressure support. Bilevel PAP increased cardiac index significantly compared with CPAP alone. BiPAP, bilevel positive airway pressure; CPAP, continuous positive airway pressure; PAWP, pulmonary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

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.

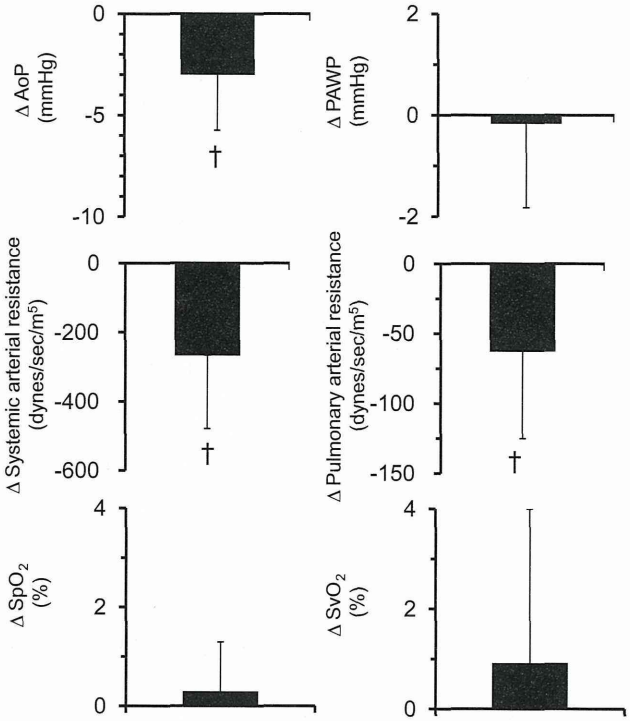

Fig. 3. Relative changes in hemodynamic parameters by bilevel PAP (CPAP + pressure support) compared with CPAP without pressure support. No significant differences in PAWP, SpO_2, and SvO_2 were observed between CPAP and bilevel PAP, but systemic arterial resistance and pulmonary arterial resistance 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.

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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