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ORIGINAL ARTICLE

Differences in hemodynamic responses between intravenous carperitide and nicorandil in patients with acute heart failure syndromes

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Abstract While recent guidelines for the treatment of acute heart failure syndromes (AHFS) recommend pharmacotherapy with vasodilators in patients without excessively low blood pressure (BP), few reports have compared the relative efficiency of vasodilators on hemodynamics in AHFS patients. The present study aimed to assess the differences in hemodynamic responses between intravenous carperitide and nicorandil in patients with AHFS. Thirty-eight consecutive patients were assigned to receive 48-h continuous infusion of carperitide (n = 19; 0.0125–0.05 μg/kg/min) or nicorandil (n = 19; 0.05–0.2 mg/kg/h). Hemodynamic parameters were estimated at baseline, and 2, 24, and 48 h after drug administration using echocardiography. After 48 h of infusion, systolic BP was significantly more decreased in the carperitide group compared with that in the nicorandil group (22.1 ± 20.0 % vs 5.3 ± 10.4 %, P = 0.003). While both carperitide and nicorandil significantly improved hemodynamic parameters, improvement of estimated pulmonary capillary wedge pressure was greater in the carperitide group (38.2 ± 14.5 % vs 26.5 ± 18.3 %, P = 0.036), and improvement of estimated cardiac output was superior in the nicorandil group (52.1 ± 33.5 % vs 11.4 ± 36.9 %, P = 0.001). Urine output for 48 h was greater in the carperitide group, but not to a statistically significant degree (4203 ± 1542 vs 3627 ± 1074 ml, P = 0.189). Carperitide and nicorandil were differentially effective in improving hemodynamics in AHFS patients. This knowledge may enable physicians in emergency wards to treat and manage patients with AHFS more effectively and safely.

Keywords Acute heart failure · Hemodynamics · Natriuretic peptide · Nicorandil

Introduction

Acute heart failure syndromes (AHFS) are characterized by a gradual or rapid change in the signs and symptoms of heart failure, resulting in the need for urgent treatment [1, 2]. Several recent sets of guidelines for the management of AHFS have suggested that vasodilator therapy should be considered for AHFS patients with a high to normal blood pressure (BP) on admission and should be avoided in those with a low BP [3].

Among the currently available vasodilators, natriuretic peptide preparations such as carperitide and nesiritide (recombinant human atrial and brain natriuretic peptide, respectively) achieve significant reduction of venous and ventricular filling pressures with subsequent rapid improvement of dyspnea or orthopnea [4–6]. Carperitide has been approved for AHFS in Japan, and it was recently reported that signs and symptoms were improved by carperitide therapy in approximately 80 % of AHFS patients with an adequate systolic BP [7, 8].

Nicorandil (*N*-(2-hydroxyethyl)nicotinamide nitrate) has nitrate-like properties, activates adenosine triphosphate-sensitive potassium channels, and results in balanced venous and arterial vasodilation [9, 10]. Nicorandil has also recently been approved for AHFS in Japan, and our prior study suggested that intravenous administration of nicorandil produces optimal benefits in improving hemodynamics in

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AHFS, as determined by results of noninvasive echocardiographic hemodynamic evaluation [11].

While recent guidelines for the treatment of AHFS recommend pharmacotherapy with vasodilators in patients without excessively low BP, these guidelines do not specifically address the strategy for early medical treatment, because there is limited evidence on the efficacy of the pharmacological agents currently used for AHFS. In addition, few reports have compared the relative efficiency of vasodilators on hemodynamics in AHFS patients. Therefore, the present study aimed to assess the differences in hemodynamic responses between carperitide and nicorandil in patients with AHFS.

Patients and methods

Patients

The study group consisted of 38 consecutive hospitalized patients with AHFS referred to the cardiac intensive care unit at Tokyo Women's Medical University Hospital, who were successfully and accurately assessed for hemodynamic parameters by transthoracic Doppler echocardiography before initial administration of carperitide or nicorandil between May 2008 and August 2010. The diagnosis of heart failure was made based on modified Framingham criteria [12, 13]. In brief, heart failure was diagnosed based on satisfaction of two major criteria or one major and two minor criteria. Acute heart failure syndrome was also defined as the new onset of decompensated heart failure or decompensation of chronic, established heart failure meeting the above criteria and sufficient to warrant hospitalization [1]. We excluded patients who had (1) acute coronary syndrome, (2) moderate to severe valvular heart disease, (3) severe renal insufficiency (serum creatinine >2.0 mg/dl), (4) systolic arterial BP <90 mmHg, (5) pulmonary arterial hypertension with a relevant precapillary component, (6) acutely unstable clinical status not permitting a period of hemodynamic assessment before intravenous vasodilator administration, (7) poor echo window or nonoptimal Doppler signal, or (8) any condition that would contraindicate use of a vasodilator. The study was carried out according to the principles of the Declaration of Helsinki, and the study protocol was approved by the institutional ethics committee. All participating patients gave written informed consent before enrollment.

Protocol

After baseline hemodynamic measurements were recorded, patients were assigned to receive 48 h of continuous infusion of carperitide (0.0125–0.05 μg/kg/min) or nicorandil (0.05–0.2 mg/kg/h) [11, 14]. We used nicorandil between May 2008 and June 2009, and carperitide between July 2009 and August 2010. The doses of carperitide or nicorandil were adjusted according to the condition and systolic BP of each individual patient. Use of intravenous vasodilators or inodilators with the study drug was not permitted. However, prior use of intravenous bolus injection or additional bolus injection of diuretics was permitted. All patients were allowed to continue oral medications used before admission, including diuretics, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, β-blockers, and digoxin. Hemodynamic measurements were obtained at baseline, and 2, 24, and 48 h after the start of carperitide or nicorandil administration.

Hemodynamic assessment

Hemodynamic evaluation was performed using a cuff sphygmomanometer and transthoracic Doppler echocardiography. Systemic BP was measured noninvasively by a cuff sphygmomanometer. Echocardiographic studies were performed using commercially available ultrasound equipment. A complete M-mode, two-dimensional Doppler study was performed, in the left lateral decubitus or supine position, using standard parasternal, apical, and subcostal approaches. The methods of the noninvasive echocardiographic hemodynamic evaluation have been described previously [11] and are summarized here. Mean right atrial pressure (RAP) was estimated from the inferior vena cava diameter and its degree of respirophasic change [15]. Pulmonary artery systolic pressure (PASP) is equivalent to right ventricular systolic pressure in the absence of obstruction to flow between the right ventricle and pulmonary artery. An estimate of PASP was obtained by adding an estimate of RAP to the systolic transtricuspid pressure gradient [16, 17]. This gradient was estimated by application of the modified Bernoulli equation to the peak velocity of the continuous-wave Doppler tricuspid regurgitation signal. Pulmonary artery end-diastolic pressure is frequently used as an estimate of pulmonary capillary wedge pressure (PCWP). Application of the modified Bernoulli equation to the end-diastolic velocity of the continuous-wave Doppler pulmonary regurgitation signal, and adding to this an estimate of RAP, provided an estimation of PCWP [16, 18]. Estimated cardiac output (CO) was calculated as the product of heart rate, velocity time integral at the left ventricular outflow tract, and the area of the left ventricular outflow tract [19, 20]. Outflow tract diameter was measured with digital calipers in the parasternal long-axis view. All echocardiographic data were obtained by an experienced sonographer and interpreted by two experienced echocardiographers unaware of the patients' participation in the study.

End points

The protocol-specified analyses concerned the hemodynamic effects of carperitide or nicorandil administration in patients with AHFS. The primary end point of the study was the absolute change from baseline in estimated PCWP during carperitide or nicorandil administration. Secondary end points included changes in estimated PASP, estimated CO, and systolic BP. Urine output was measured for 48 h after the start of carperitide or nicorandil administration, and the total dose of intravenous furosemide for 48 h was measured. B-type natriuretic peptide and serum creatinine levels before and after carperitide or nicorandil administration were also measured.

Statistical analysis

Analyses were performed using SAS System version 9.1 software (SAS Institute, Cary, NC, USA). Data are presented as means with standard deviations and frequencies. The Student's *t* test was used to compare groups with respect to normally distributed continuous variables. The Chi-square test or Fisher's exact test (when an expected value was <5) was used to compare nominally scaled variables. For multiple paired time effect comparisons, Dunnett's multiple comparison method was applied. Two-tailed *P* values of less than 0.05 were considered significant.

Results

Baseline characteristics

The baseline demographic, clinical, and hemodynamic characteristics of the 19 patients treated with carperitide and 19 patients treated with nicorandil are shown in Table 1. Before administration of study drugs, no significant differences were observed between the two groups. All patients had dyspnea at rest or New York Heart Association class IV symptoms at the time of infusion, and had clinical evidence of fluid overload.

Table 1 Baseline characteristics of the study patients treated with carperitide or nicorandil

	Carperitide (n = 19)	Nicorandil (n = 19)	P value
Men, n (%)	14 (74)	14 (74)	0.999
Age, years	73 ± 11	69 ± 16	0.398
Ischemic etiology, n (%)	8 (42)	10 (53)	0.516
Medical history, n (%)			
Prior hospitalization for heart failure	9 (47)	12 (63)	0.328
Hypertension	13 (68)	12 (63)	0.732
Diabetes mellitus	7 (37)	8 (42)	0.740
Chronic obstructive pulmonary disease	6 (32)	2 (11)	0.232
Left ventricular ejection fraction, %	34 ± 13	35 ± 15	0.945
Heart rate, beats/min	88 ± 23	76 ± 15	0.073
Blood urea nitrogen, mg/dl	35 ± 17	27 ± 17	0.165
Creatinine, mg/dl	1.4 ± 0.6	1.2 ± 0.5	0.319
Uric acid, mg/dl	7.4 ± 2.3	6.3 ± 1.8	0.181
B-type natriuretic peptide, pg/ml	1083 ± 1131	1741 ± 1265	0.100
Baseline hemodynamic parameters			
Systolic BP, mmHg	141 ± 26	131 ± 31	0.294
Diastolic BP, mmHg	73 ± 15	73 ± 17	0.921
Estimated PASP, mmHg	56 ± 10	51 ± 12	0.217
Estimated PCWP, mmHg	27 ± 5	24 ± 9	0.169
Estimated CO, l/min	3.8 ± 1.3	3.7 ± 1.1	0.845

Values are mean ± SD

BP blood pressure, *CO* cardiac output, *PASP* pulmonary artery systolic pressure, *PCWP* pulmonary capillary wedge pressure

Acute hemodynamic effects of carperitide

After 2 h of carperitide infusion, estimated PCWP was reduced from 27.3 ± 5.0 to 21.0 ± 4.4 mmHg ($P < 0.05$ by Dunnett's multiple comparison method), and was sustained for 48 h to 16.8 ± 4.7 mmHg ($P < 0.05$, Fig. 1a). Estimated PASP was also reduced from 55.5 ± 10.3 to 46.4 ± 8.2 mmHg ($P < 0.05$) after 2 h of carperitide infusion, and was sustained for 48 h to 40.2 ± 12.4 mmHg ($P < 0.05$, Fig. 1b). There was no change in estimated CO over 48 h of carperitide infusion (3.8 ± 1.3 to 4.0 ± 1.8 l/min, *P* not significant; Fig. 1c). Systolic BP was decreased after 2 h of carperitide infusion (140.8 ± 26.3 to 131.4 ± 24.4 mmHg, $P < 0.05$), and was sustained for 48 h (109.1 ± 33.8 mmHg, $P < 0.05$; Fig. 1d). The average dose of intravenous carperitide was 0.022 ± 0.013 μg/kg/min.

Acute hemodynamic effects of nicorandil

After 2 h of nicorandil infusion, estimated PCWP was reduced from 24.0 ± 8.8 to 19.8 ± 7.4 mmHg ($P < 0.05$), and was sustained for 48 h to 17.2 ± 6.3 mmHg ($P < 0.05$, Fig. 1a). Estimated PASP was also reduced from 51.1 ± 11.6 to 43.8 ± 10.9 mmHg ($P < 0.05$) after 2 h of nicorandil infusion, and was sustained for 48 h to 39.4 ± 7.7 mmHg ($P < 0.05$, Fig. 1b). A significant increase in estimated CO was observed at 2 h, from 3.7 ± 1.1 to 4.5 ± 1.3 l/min ($P < 0.05$). This increase in estimated CO was sustained for 48 h to 5.5 ± 1.7 l/min ($P < 0.05$, Fig. 1c). There was a significant decrease in systolic BP after 48 h of

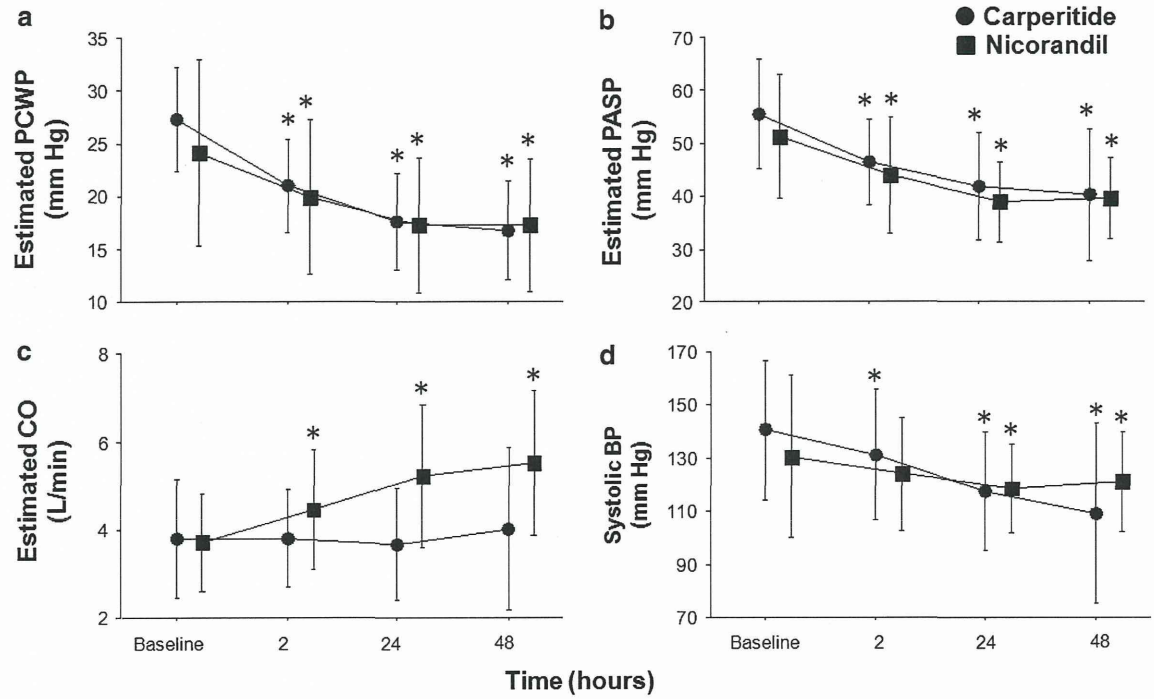

Fig. 1 Changes in estimated PCWP (**a**), estimated PASP (**b**), estimated CO (**c**), and systolic BP (**d**) during 48-h carperitide or nicorandil infusion. *$P < 0.05$ versus baseline by Dunnett's multiple comparison method. *BP* blood pressure, *CO* cardiac output, *PASP* pulmonary artery systolic pressure, *PCWP* pulmonary capillary wedge pressure

nicorandil infusion (130.9 ± 30.5 to 121.5 ± 18.7 mmHg, $P < 0.05$; Fig. 1d). The average dose of intravenous nicorandil was 0.161 ± 0.054 mg/kg/h.

Differences in hemodynamic responses between carperitide and nicorandil

Percent changes in hemodynamic parameters from baseline after 48 h of carperitide or nicorandil infusion are shown in Fig. 2. Systolic BP decreased significantly more in the carperitide group than in the nicorandil group (22.1 ± 20.0 % vs 5.3 ± 10.4 %, $P = 0.003$). The improvement in estimated PCWP was superior in the carperitide group to that of the nicorandil group (38.2 ± 14.5 % vs 26.5 ± 18.3 %, $P = 0.036$), while the improvement in estimated CO was greater in the nicorandil group than in the carperitide group (52.1 ± 33.5 % vs 11.4 ± 36.9 %, $P = 0.001$). There were no significant differences between the two groups with respect to changes in diastolic BP, heart rate, and estimated PASP. Urine output from baseline to 24 h of study-drug infusion was significantly greater in the carperitide group than in the nicorandil group (2353 ± 939 vs 1708 ± 566 ml, $P = 0.015$). Urine output for 48 h of study-drug infusion was also greater in the carperitide group than in the

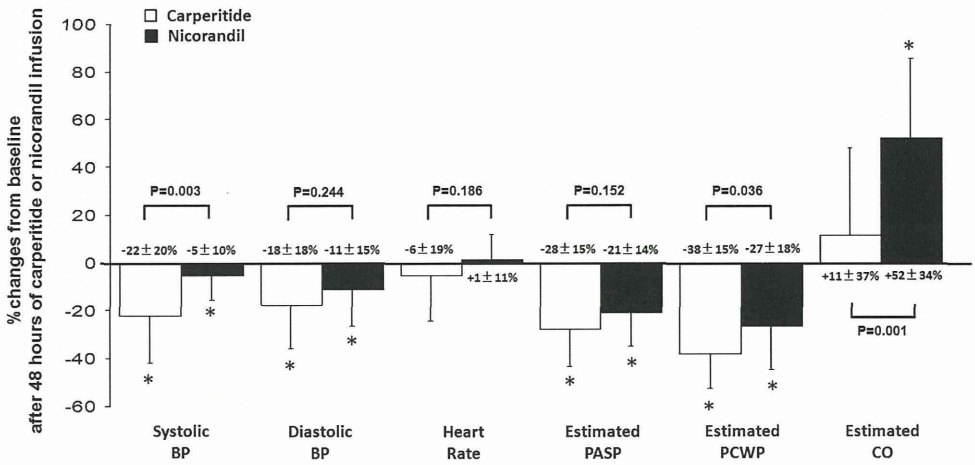

Fig. 2 Percent changes in systolic BP, diastolic BP, heart rate, estimated PASP, estimated PCWP, and estimated CO after 48-h carperitide or nicorandil infusion (versus baseline). *$P < 0.05$ versus baseline by Dunnett's multiple comparison method. *BP* blood pressure, *CO* cardiac output, *PASP* pulmonary artery systolic pressure, *PCWP* pulmonary capillary wedge pressure

nicorandil group (4203 ± 1542 vs 3627 ± 1074 ml), and the total dose of intravenous furosemide for 48 h tended to be smaller in the carperitide group than in the nicorandil group (29.0 ± 35.9 vs 40.2 ± 31.1 mg), but this was not statistically significant ($P = 0.189$ and $P = 0.313$, respectively). A trend for a more favorable change in creatinine level was observed in the carperitide group compared with the nicorandil group (+9.8 ± 27.3 % vs +16.8 ± 76.0 %), and the improvement in B-type natriuretic peptide levels was greater in the nicorandil group than in the carperitide group (−53.3 ± 32.2 % vs −45.3 ± 30.8 %); however, these differences were not statistically significant ($P = 0.709$ and $P = 0.439$, respectively).

Adverse events

Hypotension (systolic BP <90 mmHg) during 48 h of carperitide infusion was observed in three patients, which was successfully managed with dose reduction of this drug. There were two episodes of headache during the 48-h nicorandil infusion, which were successfully managed with a nonsteroidal anti-inflammatory drug. There were no episodes of recurrent dyspnea or arrhythmia in both groups. Infusion was therefore continued for 48 h in all study patients.

Discussion

In this study, we assessed the difference in hemodynamic response between carperitide and nicorandil in patients with AHFS. While both carperitide and nicorandil significantly improved hemodynamic parameters, the improvement in estimated PCWP was greater in the carperitide group and the improvement in estimated CO was superior in the nicorandil group. The carperitide group had a trend toward a higher urine output and lower total dose of intravenous furosemide over 48 h compared with the nicorandil group.

Nicorandil has a double cellular mechanism of action, acting both as an adenosine triphosphate-sensitive potassium channel activator and exhibiting a nitrate-like effect, which may explain its combined arterial and venous vasodilatory effects [9, 10, 21–23]. Dilation of the arterial resistance vessels reduces afterload and allows the left ventricle to eject more blood. The nitrate-like effect is primarily believed to affect the venous system and increase venous capacitance, and reduces congestion. This double effect might explain the hemodynamic effects observed in this study, i.e., a reduction in estimated PCWP and increase in estimated CO.

Carperitide is a cyclic peptide consisting of 28 amino acid residues and is called α-human atrial natriuretic peptide, which was isolated from the human atrium, and identified and synthesized by genetic recombination [24]. Carperitide has been clinically used for the management of AHFS, because of its pharmacological actions of vasodilation that reduce both preload and afterload, as well as having a natriuretic action [5, 25]. In addition, carperitide inhibits the renin–angiotensin–aldosterone and sympathetic nervous systems, which are believed to be related to the development, sustenance, and progression of heart failure [26, 27]. Therefore, carperitide may have a mechanism of action related to the pathology of AHFS. The reduction in systolic BP and PCWP observed in this study might have resulted from the vasodilator effect of carperitide. Furthermore, volume (preload) reduction by the natriuretic action of carperitide could have contributed to hemodynamic differences between carperitide and nicorandil observed in this study, i.e., the greater reduction in systolic BP and PCWP and no improvement of CO in the carperitide group. In fact, urine output over 24 h was significantly greater in the carperitide group than in the nicorandil group, although the total dose of intravenous furosemide tended to be smaller in the carperitide group. Further studies are required to investigate the exact mechanism responsible for the differences in hemodynamic responses between carperitide and nicorandil observed in this study.

Early management of AHFS is critical, but the current guidelines do not address the early clinical assessment and treatment of this syndrome. Recently, two or three categories of early-phase AHFS have been suggested by numerous researchers, mainly according to the patient's BP at the time of presentation [28, 29]. One type of AHFS is characterized by an elevation in systolic BP. High BP rapidly develops, and is related to high filling pressures and increased sympathetic tone; this results in the redistribution of systemic fluids and the activation of neurohormonal factors. Symptoms in these patients usually develop abruptly, and patients suffer pulmonary rather than systemic congestion. This type of heart failure is referred to as "vascular" failure or "hypertensive" AHFS [28, 29]. The other type of heart failure is characterized by normal or low BP. These patients show symptoms that gradually develop over several days, and have significant systemic congestion. This type of heart failure is referred to as "cardiac" failure or "normotensive–hypotensive" AHFS [28, 29]. Since vasodilators are not recommended as first-line therapy in hypotensive AHFS, vasodilation therapy is recommended in hypertensive and normotensive AHFS. In the current study, systolic BP and filling pressures (i.e., PCWP) had a greater decrease in the carperitide group than in the nicorandil group. In addition, a previous study revealed that a cutoff value of >120 mmHg for systolic BP had a sensitivity of 94 % and a specificity of 86 % for predicting

a good response to initial carperitide therapy [30]. Furthermore, the neurohormonal effect of carperitide, such as inhibition of the sympathetic nervous system, could attenuate the activation of neurohormonal factors in hypertensive AHFS. Using carperitide as first-line treatment in hypertensive AHFS could thus lead to favorable results. By contrast, the improvement in CO was greater and the change in systolic BP was smaller in the nicorandil group than in the carperitide group in the present study. Therefore, using nicorandil as a first-line treatment in normotensive AHFS could lead to favorable results. On the other hand, carperitide showed a tendency to have better diuretic activity, and the choice of carperitide could be useful for the treatment of normotensive AHFS with excessive volume overload under close monitoring to avoid hypotension. Furthermore, a recent case report describes the efficiency of a combination of low-dose carperitide and nicorandil in patients with AHFS and borderline BP (i.e., low to normal) [31]. The choice of vasodilators in normotensive AHFS patients, who are often difficult to manage, is controversial. This remains an important area of future research.

Limitations

The results of the present study have several limitations in the methodology. First, this was a single-center study with a small sample size. In addition, our study population was specifically selected to represent patients in whom echocardiography could be accurately performed in the urgent phase of AHFS. Second, we used transthoracic Doppler echocardiography to assess hemodynamic parameters in the study population. Pulmonary artery catheterization yields valuable hemodynamic findings, including filling pressures and CO, in patients with AHFS. However, it is invasive, and is associated with complications such as pneumothorax, infection, arrhythmias, and bleeding. Previous studies have suggested that this invasive procedure neither decreases risk of overall in-hospital mortality or length of stay, nor confers benefit in critically ill patients [32, 33]. By contrast, Doppler echocardiography is currently the primary clinical method for noninvasive measurement of hemodynamic parameters, and may obviate the need for invasive catheterization [16]. Numerous previous investigations have demonstrated that results of noninvasive Doppler techniques are highly reproducible and accurate in the assessment of RAP, pulmonary artery pressures, PCWP, and CO [20, 34, 35]. Third, we did not study the effects of intravenous administration of carperitide or nicorandil on symptoms. Furthermore, the end points used were not true end points such as morbidity and mortality, and were instead surrogate scales. Other limitations include a lack of an appropriate evidence-based titration regimen for carperitide or nicorandil. Because of these limitations, our results must be considered preliminary. Further well-designed, larger-scale studies would be useful for extending our findings to yield more practical guidelines for AHFS in settings closely resembling those of daily clinical practice.

Conclusions

Carperitide and nicorandil were differentially effective in improving hemodynamics in patients with AHFS. An improvement in estimated PCWP and urine output was greater in the carperitide group than in the nicorandil group, while an improvement in estimated CO was superior in the nicorandil group, suggesting a natriuretic action of carperitide and an arterial vasodilatory effect of nicorandil. Knowledge of these differences may enable physicians in emergency wards to treat and manage AHFS patients more effectively and safely.

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Conflict of interest None.

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Original article

Impact of clustered depression and anxiety on mortality and rehospitalization in patients with heart failure☆

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ABSTRACT

Background: Anxiety is often present in patients with depression. The aim of this study was to evaluate the impact of clustered depression and anxiety on mortality and rehospitalization in hospitalized patients with heart failure (HF).

Methods: A total of 221 hospitalized patients with HF, who completed the questionnaires, were analyzed in this prospective study (mean age 62 ± 13 years; 28% female). One-third patients had implanted cardiac devices. Depression was defined as a Zung Self-Rating Depression Scale index score of ≥60 and anxiety was defined as a State-Trait Anxiety Inventory score of ≥40 (male) or ≥42 (female). The primary outcome was the composite of death from any cause or rehospitalization due to worsened HF and refractory arrhythmia.

Results: Of the 221 HF patients, 29 (13%) had depression alone, 80 (36%) had anxiety alone, and 46 patients (21%) had both depression and anxiety. During an average follow-up of 41 ± 21 months, patients with depression alone and those with clustered depression and anxiety were at an increased risk of the primary outcome [hazard ratio (HR) 2.24, 95% confidence interval (CI): 1.17–4.28, $p = 0.01$ and HR 2.75, 95% CI: 1.51–4.99, $p = 0.01$, respectively] compared to patients with no symptoms. Multivariate analysis after adjusting for age, gender, New York Heart Association functional class, B-type natriuretic peptide, device implantation, renal dysfunction, and left ventricular dysfunction showed clustered depression and anxiety, but not depression alone or anxiety alone, was an independent predictor of the primary outcome (HR 1.96, 95% CI: 1.00–3.27, $p = 0.04$).

Conclusions: Our results showed that clustered depression and anxiety were associated with worse outcomes in patients with HF.

Introduction

Heart failure (HF) is caused from most types of heart diseases and is a chronic and progressive condition that is a major cause of morbidity and mortality [1]. The psychological issues, particularly emotional distress including depression and anxiety, are common in patients with HF [1–5]. Several studies have focused on the role of depression and suggested that depression is a possible risk factor for adverse outcomes in patients with HF [4–7]. The prevalence of depression is reported to be approximately 15–40% in patients with HF, and depression is independently associated with poor outcomes [5–13]. A meta-analysis showed that depression is common among patients with HF, and substantially higher rates of clinically significant depression are present among patients with more severe HF [4].

There have been fewer studies regarding anxiety in patients with HF. A previous report showed that 18.4% of patients with

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HF had an anxiety disorder [14]. Another report showed that the score for anxiety symptoms was higher in patients with HF than in healthy controls [15]. However, this issue has remained controversial [1]. In some studies, no association has been found between anxiety symptoms and cardiac events in patients with HF [16–19].

Recently, van den Broek et al. [20] focused on the impact of clustering psychosocial risk factors on clinical outcomes in patients with implantable cardioverter defibrillators (ICDs) and showed that ICD patients with both anxiety and Type D personality were at an increased risk of ventricular arrhythmia. In that study, the risk factors were clustered because psychological risk factors often occurred together, but not individually, and the clustering of psychological risk factors may pose a high-risk factor for clinical events than would a single risk factor in cardiac patients [20,21]. Although depression and anxiety have been discussed separately as psychological factors, they frequently cluster within a patient [22]. The signs and symptoms of anxiety are often present in patients with depression, and the two conditions may play a partial role in a pathophysiological process of HF [23]. Some studies have shown that the clustered depression and anxiety worsened patients' health status following myocardial infarction or percutaneous coronary intervention [24,25]. From this viewpoint, clustered depression and anxiety may be clinically valuable as an indicator of psychological distress in patients with HF. However, a few studies have investigated this issue. The aim of this study was to evaluate the effect of clustered depression and anxiety on mortality and rehospitalization in patients with HF.

Methods

We conducted a substudy of the prospective observational study comprising hospitalized patients with cardiovascular disease, who were admitted to the Cardiology Department of Tokyo Women's Medical University Hospital between June 2006 and April 2008. Patients with dementia, delirium, or other conditions (e.g. unconsciousness, intensive care, and end stage of another life-threatening disease) that make completing self-reported written questionnaires difficult were excluded. Among them, 221 patients with a New York Heart Association (NYHA) functional class ≥2 on admission, who were diagnosed with HF, and who completed the questionnaires were included in this study (Fig. 1). The details of the study have been reported elsewhere [26]. The protocol was approved by the institutional review board of Tokyo Women's Medical University. All patients gave written informed consent.

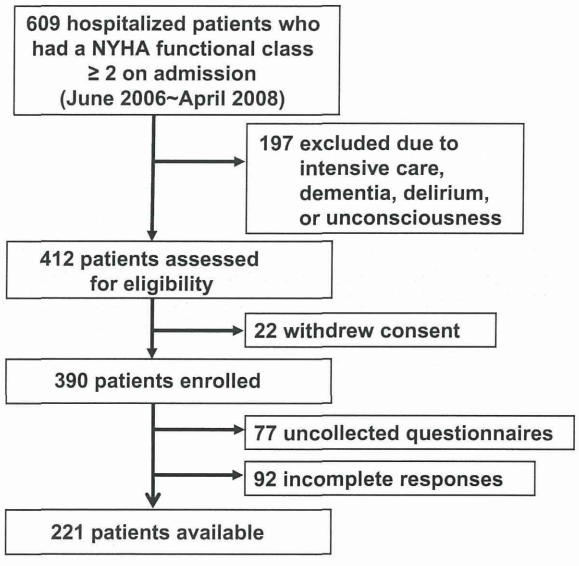

Fig. 1. The flow diagram of study subjects. NYHA, New York Heart Association.

Assessment of depression and anxiety

The majority of patients received the psychological questionnaires within 3 days (2 ± 1 days) after their admission to the hospital. For patients who initially required intensive treatment, these questionnaires were received after their transfer to the general cardiology ward. The Zung Self-Rating Depression Scale (SDS) was used to screen for depression and to measure the severity of the depression in a number of settings [27–31]. The Zung SDS is a self-reported scale containing 20 questions that assess the psychological and somatic symptoms. The Zung SDS score has been reported to be a primary discriminating variable in distinguishing depressed from non-depressed persons and indicates likelihood ratio positive for major depression as 3.3 [95% confidence interval (CI): 1.3–8.1] and likelihood ratio negative as 0.35 (95% CI: 0.2–0.8) [29]. The Zung SDS score has also been used to assess depression in clinical studies on cardiovascular diseases [32–36]. A cutoff index score of 60 has been shown to detect clinical depression while avoiding an abundance of false positives in sick patients [37–40]. In this study, depression was defined as a Zung SDS index score of ≥60.

The State-Trait Anxiety Inventory (STAI) was used to measure anxiety symptoms [41]. In this study, only the state-scale measurement was used because state anxiety is characterized as a temporary change in each patient's emotional state due to medical illness or other external cause, the measurement has also been used in clinical studies on cardiovascular diseases [16,20,42]. The STAI comprises 20 items, and each item is scored on a four-point scale from 1 (not at all) to 4 (very much so). The STAI scores range from 20 to 80, with higher scores indicating greater levels of anxiety. Anxiety was defined as a score of ≥40 (male) or ≥42 (female) [43,44].

Follow-up

After discharge, patients were seen as outpatients at our hospital or their general practitioner's clinic at 1- to 3-month intervals until October 2011. Patients receiving pacing device therapy, including pacemakers, cardiac resynchronization therapy (CRT), and ICD, were also followed every 3–6 months at our pacemaker/ICD clinic. The information about deceased patients was obtained from the medical records, family members, their general practitioners, and the admitting hospital.

Clinical outcomes

The primary outcome was the composite of death from any cause and rehospitalization due to worsened HF and refractory arrhythmia from the time of enrollment to the first event. Worsened HF was defined by signs and symptoms, such as dyspnea, rales, and ankle edema, as well as by the need for treatment with diuretics, vasodilators, positive inotropic drugs, or an intra-aortic balloon pump. Refractory arrhythmia was defined as supraventricular or ventricular tachyarrhythmia that required external defibrillation or pacing, intravenous antiarrhythmics, such as amiodarone and nifekalant, catheter ablation, or implantation of an ICD, or bradyarrhythmia that required implantation of a pacemaker. Both supraventricular and ventricular arrhythmias are common in patients with HF, and cause symptoms, hemodynamic instability, and morbidities such as stroke and sudden death. Therefore, we included rehospitalization for refractory arrhythmia in

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the primary endpoint. The second outcome was death from any cause.

Data analysis

The data are presented as either mean ± standard deviation (SD) or number of patients. We created four groups on the basis of depression and anxiety: (1) depression alone, (2) anxiety alone, (3) clustered depression and anxiety, and (4) no symptoms (no depression nor anxiety). Baseline clinical data were compared between the groups using analysis of variance (ANOVA). The Cox proportional hazards model was used to assess the relationship of depression, anxiety, and the cluster of both with clinical outcomes. We first assessed the unadjusted relationship of the following variables at discharge with the primary outcome: female gender, age ≥65 years, NYHA functional class, plasma B-type natriuretic peptide (BNP) concentration >250 pg/ml [45,46], implantation of an ICD/CRT with a defibrillator (CRT-D), left ventricular ejection fraction (LVEF) ≤35%, estimated glomerular filtration rate (eGFR) by the Modification of Diet in Renal Disease formula [47] <60 ml/min/1.73 m^2, depression, anxiety, and clustered depression and anxiety. Then, we assessed the relationship of depression, anxiety, and the cluster of both with the primary outcome after controlling for gender, age ≥65 years, NYHA functional class, BNP >250 pg/ml, implantation of an ICD/CRT-D, LVEF ≤35%, and eGFR <60 ml/min/1.73 m^2. The cumulative event-free rates were calculated using the Kaplan–Meier method. The data analyses were performed with SPSS (Statistical Package for the Social Sciences) statistical software (version 11.01, SPSS Inc., Chicago, IL, USA). A p-value of <0.05 was considered significant.

Results

Patients

A total of 221 patients with HF who completed both the Zung SDS and STAI were included in this analysis. More than half of the patients (64%) had a non-ischemic etiology, and one-third had implanted cardiac devices. Five patients (2%) who were diagnosed with major depression by a psychiatrist had taken antidepressants (Table 1). In our sample, none of the patients with depression received non-pharmacological treatment such as cognitive behavior therapy.

Psychological distress and outcomes

Overall, 75 patients (34%) were diagnosed as having depression and 126 patients (57%) as having anxiety. Among them, 29 patients (13%) had depression alone, 80 patients (36%) had anxiety alone, and 46 patients (21%) had both depression and anxiety (Table 1).

During an average follow-up of 41 ± 21 months, 69 patients (31%) met the primary outcome: 31 patients died and 38 patients required rehospitalization due to worsened HF or refractory arrhythmia. Kaplan–Meier curves for the primary outcome in the four groups are shown in Fig. 2. Patients with depression alone and those with clustered depression and anxiety were at an increased risk of the primary outcome [hazard ratio (HR) 2.24, 95% CI: 1.17–4.28, $p = 0.01$ and HR 2.75, 95% CI: 1.51–4.99, $p = 0.01$, respectively] compared to patients with no symptoms. Causes of death and rehospitalization are shown in Table 2. Kaplan–Meier curves for death from any cause are shown in Fig. 3. Patients with clustered depression and anxiety were at an increased risk of death

Table 1
Patient characteristics.

	Depression alone ($n = 29$)	Anxiety alone ($n = 80$)	Depression + anxiety ($n = 46$)	No symptoms ($n = 66$)	p value
Age (years)	61 ± 10	62 ± 14	60 ± 12	62 ± 12	0.18
Female	7 (24%)	22 (28%)	14 (30%)	19 (25%)	0.91
Underlying heart disease					0.01
Coronary artery disease	7 (24%)	20 (25%)	5 (11%)	39 (59%)	
Non-ischemic cardiomyopathy	11 (38%)	23 (29%)	37 (80%)	44 (67%)	
Valvular heart disease	10 (34%)	20 (25%)	2 (4%)	7 (11%)	
Congenital heart disease	0 (0%)	1 (1%)	2 (4%)	2 (3%)	
BNP on admission (pg/ml)	269 (84–709)	275 (4–2254)	349 (8–5271)	152 (4–8454)	0.01
BNP at discharge (pg/ml)	236 (48–826)	242 (18–1478)	288 (15–2326)	120 (5–4926)	0.01
NYHA functional class on admission (II/III/IV)	25/4/0	67/15/0	23/22/1	56/10/0	<0.01
NYHA functional class at discharge (II/III/IV)	27/2/0	77/3/0	30/15/1	64/2/0	<0.01
LVEF (%)	35 ± 10	38 ± 12	35 ± 15	39 ± 16	0.21
eGFR (ml/min/1.73 m^2)	72 ± 36	76 ± 38	70 ± 43	80 ± 38	0.16
Implanted cardiac devices					
Pacemaker/CRT-P	3 (10%)	5 (6%)	7 (15%)	7 (11%)	0.20
ICD/CRT-D	7 (24%)	18 (23%)	15 (33%)	15 (23%)	0.16
Comorbidities					
Hypertension	10 (34%)	31 (39%)	18 (39%)	25 (38%)	0.16
Diabetes	3 (10%)	27 (34%)	11 (24%)	28 (42%)	0.05
Major depression	1 (3%)	0 (0%)	3 (7%)	1 (2%)	0.04
Medications at discharge					
Beta-blockers	21 (72%)	59 (74%)	33 (72%)	43 (65%)	0.76
ACE inhibitors/ARBs	25 (86%)	69 (86%)	42 (91%)	59 (89%)	0.57
Spironolactone/eplerenone	16 (55%)	38 (48%)	30 (65%)	31 (47%)	0.15
Calcium channel blockers	16 (55%)	55 (69%)	19 (41%)	43 (65%)	<0.01
Aspirin	10 (34%)	29 (36%)	15 (33%)	33 (50%)	0.09
Warfarin	16 (55%)	42 (53%)	32 (70%)	22 (33%)	0.11
Amiodarone	11 (38%)	22 (28%)	20 (43%)	9 (14%)	<0.01
Antidepressants	1 (3%)	0 (0%)	3 (7%)	1 (2%)	0.16
Married	26 (90%)	73 (91%)	36 (78%)	64 (97%)	<0.01
Employed	13 (45%)	40 (50%)	13 (28%)	34 (52%)	0.04

Values are n (%) or mean ± SD or median (range).
ACE, angiotensin-converting enzyme; ARB, angiotensin II receptor blocker; BNP, B-type natriuretic peptide; CRT, cardiac resynchronization therapy; CRT-D, CRT with a defibrillator; CRT-P, CRT with a pacemaker; eGFR, estimated glomerular filtration rate; ICD, implantable cardioverter defibrillator; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association.

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