

Recombinant human brain natriuretic peptide ameliorates venous return function in congestive heart failure

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Abstract

Aims Recombinant human brain natriuretic peptide (rh-BNP) is commonly used as a decongestive therapy. This study aimed to investigate the instant effects of rh-BNP on cardiac output and venous return function in post-cardiotomy patients with congestive heart failure (CHF).

Methods and results Twenty-four post-cardiotomy heart failure patients were enrolled and received a standard loading dose of rh-BNP. Haemodynamic monitoring was performed via a pulmonary artery catheter before and after the administration of rh-BNP. The cardiac output and venous return functions were estimated by depicting Frank-Starling and Guyton curves. After rh-BNP infusion, variables reflecting cardiac congestion and venous return function, such as pulmonary artery wedge pressure, mean systemic filling pressure (Pmsf) and venous return resistance index (VRRi), reduced from 15 ± 3 to 13 ± 3 mmHg, from 32 ± 7 to 28 ± 7 mmHg and from 6.7 ± 2.6 to 5.7 ± 1.8 mmHg min m²/L, respectively. Meanwhile, cardiac index, stroke volume index, and the cardiac output function curve remained unchanged per se. The decline in Pmsf [−13% (−22% to −8%)] and VRRi [−12% (−25% to −5%)] was much greater than that in the systemic vascular resistance index [−7% (−14% to 0%)]. In the subgroup analysis of reduced ejection fraction (<40%) patients, the aforementioned changes were more significant.

Conclusions rh-BNP might ameliorate venous return rather than cardiac output function in post-cardiotomy CHF patients.

Keywords rh-BNP; Venous return; Cardiac output; Congestive heart failure

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Introduction

Patients who undergo cardiac surgery are more likely to develop acute congestive heart failure (CHF) due to pre-operative cardiac dysfunction, acute structural changes, intraoperative myocardial injury, and improper post-operative management.¹ Brain natriuretic peptide (BNP) is an endogenous hormone released by the ventricles² to adjust circulatory pressure, volume distribution, and attenuate congestion progression during CHF.³ Hence, the recombinant human BNP (rh-BNP), a medicine with the same

structure as native BNP, is considered as a decongestant with a significant effect on reducing both right-sided and left-sided filling pressures.^{4,5}

Previous studies performed in cardiac surgical populations demonstrated that empiric post-operative use of rh-BNP brought neither additional risks nor benefits,^{6–8} which implies that a deeper understanding of rh-BNP's role in haemodynamic regulation to guide the use of rh-BNP is needed. However, the physiological therapeutic effects of rh-BNP remain controversial. Early studies showed that rh-BNP caused an increased cardiac output (CO).^{9–12} However, as we have known,

rh-BNP is not an inotrope and does not have a signalling pathway enabling it to enhance myocardial contractility.^{4,11} Furthermore, several subsequent studies conducted on cardiac surgical and paediatric patients reported no changes in CO.^{13–15} The intrinsic explanation for these inconsistencies in CO function is still unclear. Almost all studies reported an attenuation in overhigh filling pressure without decreasing the blood volume returned to the heart (which is usually equal to CO).^{9–15} Therefore, how rh-BNP can affect venous return and alleviate congestion should be investigated further.

Both CO function (Frank-Starling) curve¹⁶ and venous return (Guyton) curve¹⁷ are intuitive methods used to describe the working status of the heart and venous system. This physiological study was designed therefore, to investigate the instant effects of rh-BNP on CO and venous return functions among patients with post-cardiotomy heart failure.

Methods

Patients

This study was approved by the Institutional Review Board (Zhongshan Hospital, Fudan University, Shanghai, China: Number B2020-056), and conducted in a 40-bed cardiac surgical intensive care unit (ICU). Patients were eligible to participate in the study if they met all of the following criteria¹: clinical manifestations suggesting CHF {congestion on chest radiograph, rales on chest auscultation, clinically relevant oedema or an elevated filling pressure [either central venous pressure (CVP) ≥ 12 mmHg or pulmonary artery wedge pressure (PAWP) ≥ 15 mmHg], and an increased N terminal pro BNP [NT-proBNP > 900 pg/mL]},^{2,18,19} weaning failure (failed spontaneous breathing test) and relied on mechanical ventilation,³ haemodynamic monitoring via a pulmonary artery catheter,⁴ decision from the attending physician to use rh-BNP. Exclusion criteria were¹: patients < 18 years old,² pregnant,³ haemodynamic instability (norepinephrine or epinephrine ≥ 0.1 $\mu\text{g}/\text{kg}/\text{min}$),⁴ unable to tolerate postural and positive end-expiratory pressure (PEEP) changes,⁵ arrhythmias, and⁶ severe acute kidney injury [KDIGO stage 3²⁰ or underwent renal replacement therapy (RRT)]. Written informed consent was obtained from patients' legally authorized representatives.

Measurements of haemodynamic effects

Throughout the study, patients were sedated with a combination of remifentanyl and midazolam, with the aim of achieving a Richmond Agitation–Sedation Scale²¹ of -5 . Haemodynamic monitoring was conducted by using a pulmonary artery catheter (Swan-Ganz CCOmbo 774F75, Edwards

Lifescience Corporation, Irvine, USA). Pressure transducers were zeroed and fixed at the intersection of the mid-axillary line and the fourth intercostal space. For each enrolled patient, rh-BNP (an alternative drug of nesiritide, produced by Tibet Rhodiola pharmaceutical Inc., Chengdu, China) was prepared at a concentration of 10 $\mu\text{g}/\text{mL}$ and administered as a standard intravenous bolus of 2 $\mu\text{g}/\text{kg}$ (over 15 min) followed by a continuous infusion at a rate of 0.01 $\mu\text{g}/\text{kg}/\text{min}$.

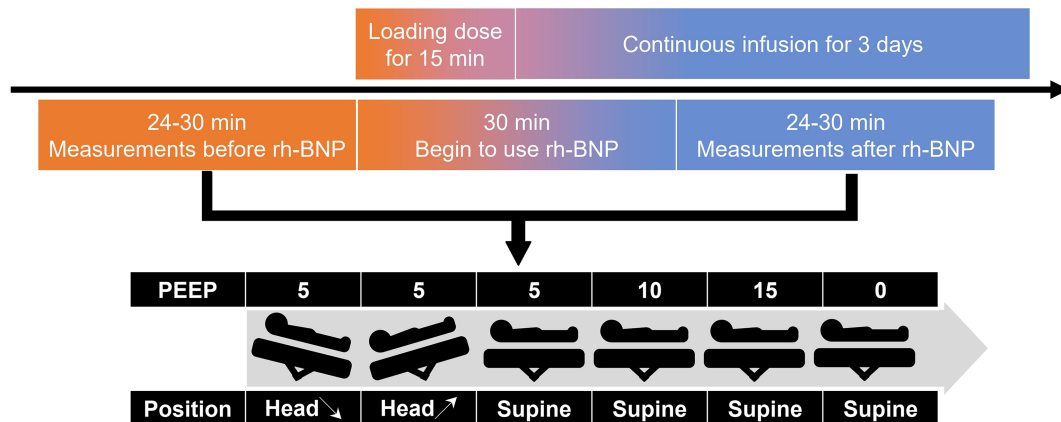
Before using rh-BNP, a set of baseline haemodynamic parameters, including heart rate, CVP, PAWP, systolic blood pressure (SBP), diastolic blood pressure, mean arterial pressure (MAP), pulse pressure, mean pulmonary artery pressure (MPAP), systemic vascular resistance index (SVRI), pulmonary vascular resistance index (PVRI), cardiac index (CI), and stroke volume index (SVI), were recorded. Furthermore, cardiac function and venous return curves were depicted, and their corresponding parameters were calculated based on a detailed protocol. Thirty minutes after initiation of the loading dose, measurements of preceding parameters were repeated. The study protocol was completed within 90 min (Figure 1). During the protocol period, diuretics were withheld while other medications remained unchanged, and the total fluid volume and urine output (UO) were recorded. Furthermore, 1 h UO before and after the initiation of rh-BNP (for 30 min) was also recorded.

The methods of estimating the cardiac output and venous return function

The Frank-Starling curve describes how CO changes with preload²² and the Trendelenburg manoeuvre could be used to simulate changes of the preload.²³ In this section, patients were placed at three different positions (supine and 15° downward or upward bed angulation) but with the same PEEP setting of 5 cmH_2O . For each position, after a 3 min stabilization, CVP and its corresponding CI were recorded. Using these three (CVP, CI) coordinate pairs and a horizontal axis intercept of -2 mmHg, the cardiac function curve was regressed as a logarithmic function ($A \cdot \ln(X + B) + C$).²²

To assess the venous return curve, four gradients of the PEEP settings (0 , 5 , 10 , and 15 cmH_2O) were used to increase intrathoracic pressure, which would further increase the CVP (representing the backward resistance of venous return). Similarly, four (CVP, CI) coordinate pairs were measured to perform a linear regression. Theoretically,
$$\text{VenousReturn} = \frac{\text{Mean systemic filling pressure} - \text{Central Venous Pressure}}{\text{Venous Return Resistance}}$$
 From this, the horizontal axis intercept and the inverse of the slope of the regression line represented the mean systemic filling pressure (Pmsf) and the venous return resistance index (VRRI), respectively.¹⁷

Figure 1 Research flow chart. All patients received a loading dose of 2 µg/kg over 15 min and a continuous infusion of 0.01 µg/kg/min for 3 days. Before and after administration of rh-BNP, some manoeuvres were performed to measure three points induced by postural changes and four points by positive end-expiratory pressure gradients to depict the Frank-Starling and venous return curves before and after using rh-BNP. rh-BNP, recombinant human brain natriuretic peptide.



Data collection

Upon patient inclusion, demographic information, comorbidity, and intraoperative information were recorded. Echocardiographic parameters [left ventricular ejection fraction (LVEF), tricuspid annular plane systolic excursion (TAPSE), left atrial diameter, left ventricular end-diastolic diameter, and left ventricular end-systolic diameter] and laboratory parameters (cardiac troponin T, NT-proBNP, creatinine, blood urea nitrogen, bilirubin, albumin and lactate) of the same day were also collected. All study patients were followed up until hospital discharge or death, to record clinical outcomes, such as RRT rate, length of mechanical ventilation, length of ICU stay, length of hospital stay, and hospital mortality.

Data analysis

The number of patients included in similar haemodynamic studies ranges from 15 to 25.^{24–26} Therefore, an initial target of 30 cases was set for this study and an interim analysis was conducted when 80% of the target (24 cases) was reached, at which point the decision was made to terminate enrolment based on the significance of the results. Data were presented as the means ± standard deviations (if normally distributed) or medians with interquartile ranges [IQR] (if non-normally distributed) for continuous variables, and total numbers with percentages for categorical variables. Comparisons were made using Student's *t*-test or Wilcoxon rank-sum test for continuous variables, and the Fisher's exact test for categorical variables, as appropriate. To describe the overall effects of rh-BNP, integrated CO and venous return curves were depicted based on the mean values of equation coefficients. Furthermore, we compared the characteristics and therapeutic effects of rh-BNP between patients with LVEF ≤ or >40%,

namely heart failure with reduced EF (HFrEF) or mildly reduced and preserved EF (HFmrEF and HFpEF).^{27,28} All statistical tests were two-tailed, and a value of $P < 0.05$ indicated statistical significance. Statistical analyses were performed using R, version 3.6.2 (R Foundation for Statistical Computing, Vienna, Austria).

Results

Patients

During the study period (June 2020 to April 2021), 24 patients were included and of them, 20 (83%) received aortic/mitral/tricuspid valve surgery, and four patients (17%) underwent coronary artery bypass surgery, and their characteristics are presented in *Table 1*. On the day of rh-BNP administration, the LVEF, TAPSE, and NT-proBNP were 50% (IQR: 36–62), 13 mm (IQR 11–17), and 2622 ng/mL (IQR 1506–9966), respectively. During the ICU stay, five patients (21%) received RRT and only one (4%) died. The length of mechanical ventilation, ICU stay, and hospital stay were 3 days (IQR 2–9), 10 days (IQR 6–16) and 20 days (IQR 12–31), respectively. Among those patients, 10 (42%) had HFrEF. Patients with HFrEF had larger left ventricular diameters. They also appeared to have a trend of higher NT-proBNP and blood urea nitrogen, despite the lack of statistical significance.

Haemodynamic parameters

The haemodynamic parameters before and after the administration of rh-BNP were measured and are summarized in *Table 2*. During the study period, fluid volume and UO were 73 ± 22 and 85 ± 27 mL, respectively. After the loading dose of rh-BNP, the heart rate (84 ± 16 to 85 ± 17 beat/min, $P = 0.091$), CI

Table 1 Baseline clinical, surgical, laboratory, echocardiographic characteristics and clinical outcomes by ejection fraction

	All patients (n = 24)	HFrEF (n = 10)	HFmrEF or HFpEF (n = 14)	P value
Pre-operative characteristics				
Age (years)	60 ± 14	67 ± 13	59 ± 15	0.688
Male, n (%)	16 (67)	9 (90)	7 (50)	0.079
Body mass index (kg/m ²)	22 ± 3	23 ± 3	22 ± 3	0.192
Coronary artery disease, n (%)	6 (25)	4 (40)	2 (14)	0.192
Diabetes, n (%)	6 (25)	1 (10)	5 (36)	0.341
Chronic kidney disease, n (%)	3 (13)	2 (20)	1 (7)	0.550
Hypertension, n (%)	9 (38)	4 (40)	5 (36)	1.000
NYHA class III–IV, n (%)	12 (50)	6 (60)	7 (50)	0.697
Operative information				
Re-do surgery, n (%)	6 (25)	1 (10)	5 (36)	0.341
Cardiopulmonary bypass time (min)	142 ± 42	143 ± 42	141 ± 44	0.941
Aortic cross-clamping time (min)	84 ± 35	92 ± 32	76 ± 36	0.302
Information on the day of using rh-BNP				
Time-point of rh-BNP administration (h)	41 (20–68)	34 (20–87)	41 (22–100)	0.558
LVEF (%)	50(36–62)	34(29–37)	62(56–65)	<0.001
TAPSE (mm)	13 (11–17)	12 (10–16)	15 (11–17)	0.291
Left atrial diameter (mm)	45 (42–49)	45 (44–50)	43 (41–49)	0.187
LVEDD (mm)	47 (44–59)	60 (47–69)	44 (41–48)	0.039
LVESD (mm)	33 (29–45)	42 (38–58)	29 (26–32)	0.008
cTnT (ng/mL)	0.58 (0.41–1.38)	0.78 (0.53–1.80)	0.52 (0.41–0.91)	0.219
NT-proBNP (ng/mL)	2622 (1506–9966)	7897 (1955–14 485)	2192 (1291–4578)	0.057
Creatinine (μmol/L)	121 (98–198)	158 (105–254)	115 (84–151)	0.171
BUN (mmol/L)	10 (8–16)	14 (9–22)	10 (7–12)	0.050
Bilirubin (μmol/L)	20 (14–33)	16 (14–20)	27 (18–47)	0.049
Albumin (g/L)	37 (34–38)	37 (35–38)	36 (33–37)	0.262
Lactate (μmol/L)	1.3 (1.2–1.6)	1.3 (1.2–1.7)	1.4 (1.2–1.5)	0.637
Clinical outcomes				
Renal replacement therapy, n (%)	5 (21)	4 (29)	1 (10)	0.358
Length of mechanical ventilation (day)	3 (2–9)	4 (3–14)	3 (2–7)	0.472
Length of ICU stay (day)	10 (6–16)	11 (9–15)	8 (5–16)	0.428
Length of hospital stay (day)	20 (12–31)	22 (14–28)	18 (12–33)	0.445
Hospital mortality, n (%)	1 (4)	1 (10)	0 (0)	0.417

BUN, blood urea nitrogen; cTnT, cardiac troponin T; HFmrEF, heart failure with mildly reduced ejection fraction; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; ICU, intensive care unit; LVEDD, left ventricular end-diastolic diameter; LVEF, left ventricular ejection fraction; LVESD, left ventricular end-systolic diameter; NT-proBNP, N terminal prohormone of brain natriuretic peptide; TAPSE, tricuspid annular plane systolic excursion.

(3.0 ± 0.5 to 3.0 ± 0.6 L/min/m², $P = 0.542$) and SVI (37 ± 8 to 36 ± 9 mL/m², $P = 0.208$) remained unchanged. Whereas CVP (12 ± 3 to 11 ± 3 mmHg, $P < 0.001$), PAWP (15 ± 3 to 13 ± 3 mmHg, $P < 0.001$), MAP (73 ± 8 to 66 ± 7 mmHg, $P < 0.001$) and MPAP (25 ± 6 to 22 ± 6 mmHg, $P < 0.001$) decreased significantly. The percent changes were -8% (IQR 11 to -5), -13% (IQR 22 to -8), -8% (IQR 13 to -3), and -9% (IQR: 13 to -5) for CVP, PAWP, MAP, and MPAP, respectively. However, we only observed a reduction in SVRI (21.1 ± 6 to 19.4 ± 4.9 mmHg min m²/L, $P = 0.004$) rather than PVRI (mmHg min m²/L, $P = 0.199$). The declines in CVP and PAWP were 8% (IQR 5 to 11) and 13% (IQR 6 to 18). Besides, we also observed a slight increase of UO after the loading dose of rh-BNP in both subgroups.

Frank-Starling and venous return curves

The instant effects of rh-BNP on the function of CO and venous return are shown in *Figure 2*. Three points induced by postural changes and four points by PEEP gradients were used to depict the CO function (Frank-Starling) and venous return (Guyton) curves before and after the use of rh-BNP

(*Figure 2A*). The averaged effects of rh-BNP are presented in *Figure 2B* where (i) the CO function curves did not change after rh-BNP treatment; (ii) the intercept of the X-axis and the inverse of the slope of the venous return curves decreased significantly. Prior to rh-BNP, the Pmsf was 32 ± 7 mmHg, which was much higher than the values for patients without heart failure (16 to 23 mmHg).^{29–31} After rh-BNP treatment, this value reduced to 28 ± 7 mmHg ($P = 0.002$). Besides, the parameter for the resistance to venous return, VVRI, was also significantly reduced from 6.7 ± 2.6 to 5.7 ± 1.8 mmHg min m²/L ($P = 0.002$) and the reduction in VVRI and SVRI was 12% (IQR 5 to 25) and 7% (IQR 0 to 14), respectively. Furthermore, the reduction in venous return pressure gradient (Pmsf-CVP) was 13% (IQR 1 to 23), which was very close to the VVRI.

Comparison between patients with HFrEF and HFmrEF or HFpEF

The instant haemodynamic changes were more significant in HFrEF patients when compared with HFmrEF and HFpEF patients (*Table 2* & *Figure 2C,D*). The main haemodynamic

Table 2 The comparisons of haemodynamic parameters and urine output before and after using rh-BNP

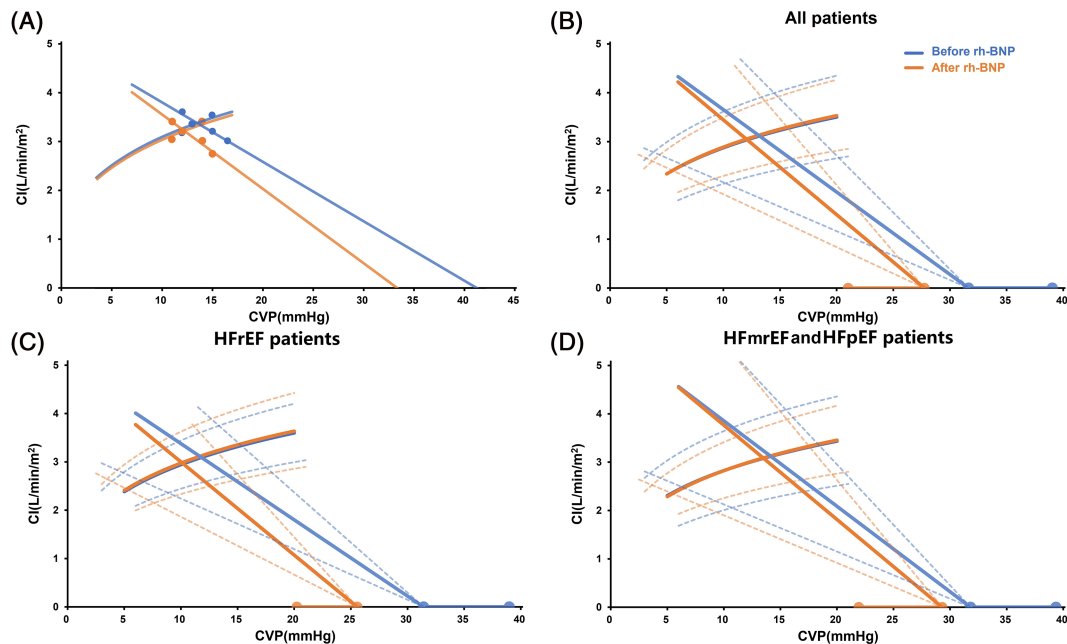
Parameters	All patients (n = 24)			HFREF (n = 10)			HFmrEF or HFpEF (n = 14)		
	Before rh-BNP	After rh-BNP	Percent change (%)	Before rh-BNP	After rh-BNP	Percent change (%)	Before rh-BNP	After rh-BNP	Percent change (%)
HR (beat/min)	84 ± 16	85 ± 17	1 (0 to 1)	89 ± 18	90 ± 18	1 (0 to 1)	80 ± 15	82 ± 15	0 (-1 to 3)
CVP (mmHg)	12 ± 3	11 ± 3*	-8 (-11 to -5)	11 ± 2	10 ± 2*	-9 (-11 to -8)	14 ± 4†	12 ± 4*	-7 (-11 to -2)
PAWP (mmHg)	15 ± 3	13 ± 3*	-13 (-22 to -8)	16 ± 4	13 ± 4*	-17 (-24 to -13)	14 ± 3	12 ± 3*	-10 (-12 to -7)
Pmsf (mmHg)	32 ± 7	28 ± 7*	-13 (-18 to -6)	31 ± 8	26 ± 5*	-18 (-22 to -13)	32 ± 8	29 ± 7*	-10 (-15 to -4)†
Pmsf-CVP (mmHg)	19 ± 7	17 ± 6*	-13 (-1 to -23)	21 ± 9	16 ± 6*	-24 (-11 to -30)	18 ± 7	17 ± 6	-6 (-17 to 9)†
SBP (mmHg)	113 ± 13	105 ± 13*	-4 (-13 to -1)	110 ± 14	102 ± 14*	-5 (-11 to -2)	116 ± 13	107 ± 12*	-3 (-13 to 1)
DBP (mmHg)	55 ± 7	51 ± 6*	-8 (-11 to -2)	54 ± 8	50 ± 5*	-9 (-11 to -3)	56 ± 7	51 ± 7*	-8 (-11 to -2)
MAP (mmHg)	73 ± 8	66 ± 7*	-8 (-13 to -3)	70 ± 8	64 ± 6*	-10 (-11 to -5)	75 ± 7	68 ± 7*	-8 (-14 to -2)
PP (mmHg)	58 ± 14	54 ± 13*	-3 (-15 to 4)	55 ± 17	52 ± 14	-5 (-14 to 2)	60 ± 13	56 ± 12	-2 (-14 to 6)
MPAP (mmHg)	25 ± 6	22 ± 6*	-9 (-13 to -5)	26 ± 4	23 ± 4	-11 (-15 to -6)	24 ± 7	22 ± 7*	-7 (-10 to -5)
SVRI (mmHg min m ² /L)	21.1 ± 6	19.4 ± 4.9*	-7 (-14 to 0)	20.6 ± 5.2	19.3 ± 4.3*	-3 (-9 to 0)	21.5 ± 6.7	19.5 ± 5.5*	-10 (-15 to -1)
PVRI (mmHg min m ² /L)	3.3 ± 1.3	3.4 ± 1.3	1 (-2 to 8)	3.2 ± 1	3.3 ± 0.9	0 (-2 to 9)	3.4 ± 1.7	3.5 ± 1.7	1 (-3 to 5)
VRI (mmHg min m ² /L)	6.7 ± 2.6	5.7 ± 1.8*	-12 (-25 to -5)	7.2 ± 3.2	5.5 ± 1.9*	-22 (-32 to -12)	6.3 ± 2.2	5.8 ± 1.8*	-7 (-16 to 1)†
CI (L/min/m ²)	3.0 ± 0.5	3.0 ± 0.6	-2 (-6 to 5)	3.0 ± 0.5	2.9 ± 0.6	-1 (-6 to 2)	3.0 ± 0.5	3.0 ± 0.6	-2 (-6 to 7)
SVI (mL/m ²)	37 ± 8	36 ± 9	-2 (-7 to 2)	35 ± 8	33 ± 8	-2 (-7 to 0)	38 ± 8	37 ± 9	-2 (-6 to 5)
UO (mL/kg/h)	0.92 ± 0.27	1.03 ± 0.34*	13 (7 to 24)	0.82 ± 0.24	0.95 ± 0.30*	22 (2 to 27)	0.99 ± 0.27	1.09 ± 0.36*	12 (8 to 15)

CI, cardiac index; CVA, central venous pressure; DBP, diastolic blood pressure; HFmrEF, heart failure with mildly reduced ejection fraction; HFpEF, heart failure with preserved ejection fraction; HFREF, heart failure with reduced ejection fraction; HR, heart rate; MAP, mean arterial pressure; MPAP, mean pulmonary artery pressure; PAWP, pulmonary artery wedge pressure; Pmsf, mean systemic filling pressure; PP, pulse pressure; PVRI, pulmonary vascular resistance index; SBP, systolic blood pressure; SVI, stroke volume index; SVRI, systemic vascular resistance index; VRI, the resistance index to venous return; UO, Urine output.

*P < 0.05 for comparison between pre- and post- nesiritide.

†P < 0.05 for comparison between patients with HFREF and HFpEF.

Figure 2 The cardiac output function and venous return curves. (A) An example of plotting venous return curves and cardiac output function curves. (B, C and D) The instant effects of rh-BNP on cardiac output function and venous return function curves for all patients, patients with HFrEF or HFmrEF and HFpEF. The blue and orange lines indicated the status before and after using rh-BNP. The solid lines or curves were the averaged effects while the dashed lines and line segments represented the standard deviation. CI, cardiac index; CVP, central venous pressure; HFmrEF, heart failure with mildly reduced ejection fraction; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; rh-BNP, recombinant human brain natriuretic peptide.



parameters, such as CVP, MAP, CI, SVI, SVRI, MPAP, and PVRI, showed a similar tendency in both subgroups. Despite very close Pmsf (31 ± 8 vs. 32 ± 8 mmHg, $P = 0.841$) before using rh-BNP, Pmsf decreased more dramatically in HFrEF patients [percent change: -18% (IQR 22 to -13) vs. -10% (IQR 15 to -4), $P = 0.022$]. The reduction in the VRR1 was also greater in patients with HFrEF [percent change: -22% (-32 to -12) vs. -7% (-16 to 1), $P = 0.026$]. Moreover, in patients with HFrEF, the reduction in the VRR1 was much larger than that in the SVRI [percent change: -22% (-32 to -12) vs. -3% (-9 to 0), $P = 0.041$].

Comprehensive interpretation of the role of recombinant human brain natriuretic peptide on systemic circulation

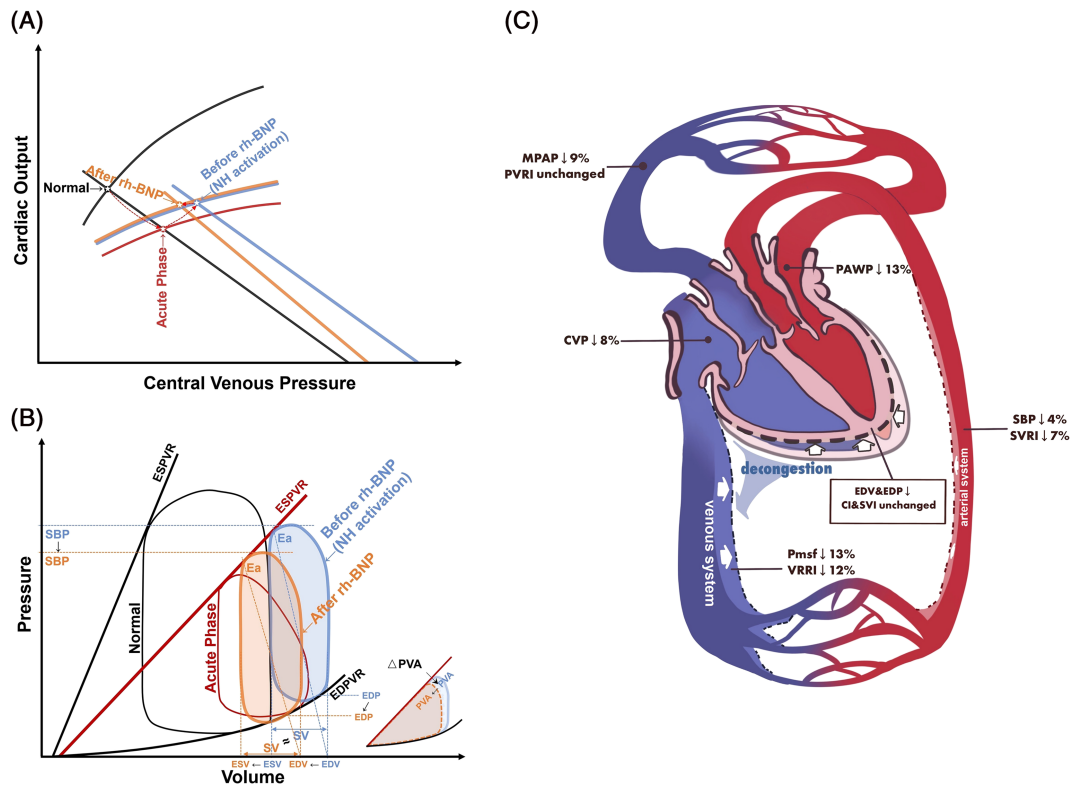
Combined with the method of pressure–volume analysis,³² we made rational extrapolations for the comprehensive effects of rh-BNP on systemic circulatory system (Figure 3A,B). During the immediate aftermath of heart injury, the cardiac function curve fell to its lowest point and the P–V loop narrowed and shifted to the right and downwards (red curves), resulting in low CO and SBP but high end-diastolic volume (EDV) and filling pressures. After this, neuro-hormonal activation caused a modest increase in con-

tractility and shifted the venous return curve significantly rightward (blue curves). This led to a compensatory increase in SBP at the expense of further increasing EDV and filling pressure, the potential energy (represents the residual energy stored in the myofilaments at the end of systole that is not converted to external work³²) and pressure–volume area (linearly related to total mechanical energy³³) increased accordingly. After the use of rh-BNP, the CO function curve remained unchanged while both the Pmsf and VRR1 decreased, shifting the working condition of the heart to the orange point with the same CO but lower CVP. However, the P–V loop moved left and downwards lowering EDV and end-systolic volume,²⁵ thus reducing the potential energy and pressure–volume area, at a price of slightly decreased SBP.

Discussion

To the best of our knowledge, this is the first study to investigate the instant therapeutic effects of rh-BNP on CO and venous return function in mechanically ventilated post-operative heart failure patients. Our work demonstrated that rh-BNP (i) did not alter the CO function (ii) but ameliorated the venous return function by decreasing the systemic filling pressure and resistance to venous return.

Figure 3 The schematic picture of the mechanism of rh-BNP's effects. (A and B) Different stages of acute heart failure and receiving rh-BNP illustrated by cardiac output–venous return relation and pressure–volume relation. The black, red, blue, and orange curves indicate normal, acute phase, before and after rh-BNP, respectively. (C) The comprehensive effects of rh-BNP. CI, cardiac index; CVP, central venous pressure; EDP, end-diastolic pressure; EDPV, end-diastolic volume; EDV, end-diastolic volume; ESV, end-systolic volume; ESVPR, end-systolic pressure–volume relationship; MPAP, mean pulmonary artery pressure; PAWP, pulmonary artery wedge pressure; Pmsf, mean systemic filling pressure; PVA, pressure–volume area; PVRI, pulmonary vascular resistance index; SBP, systolic blood pressure; SV, stroke volume; SVI, stroke volume index; SVRI, systemic vascular resistance index; VVRI, venous return resistance index.



Effects of recombinant human brain natriuretic peptide on cardiac output function

It is widely acknowledged that BNP is not an inotrope^{4,11} and in our study, neither the value of CO nor the CO function curve changed after infusion of rh-BNP. This finding is consistent with other studies based on cardiac surgical population.^{13,14} Moreover, a physiological study performed on patients who underwent left heart catheterization and echocardiography demonstrated that rh-BNP did not improve cardiac contractility or functional parameters (CO, LVEF and $-dP/dt$, etc.).³⁴ However, a number of earlier stage researches have reported an increment in CO^{9–12} and of note, the population in these studies had higher baseline blood pressure or vascular resistance, indicating an overhigh afterload, which was probably due to the enhanced autonomic tone and over-activation of the renin–angiotensin–aldosterone system in the acute phase of heart failure.³⁵ Under this circumstance, reducing vascular resistance may shift upwards the CO function curve and therefore improve CO. On the contrary, among

the cardiac surgical population, we should not anticipate that the use of rh-BNP will improve CO.

Effects of recombinant human brain natriuretic peptide on venous return function

In the acute phase of heart failure, the compensatory mechanism transferred unstressed volume (mainly in the venous system³⁶) to stressed volume (functional circulating blood volume) in order to ameliorate the reduction of CO, which contributes to a congestive state.^{32,37} rh-BNP has a widely recognized physiological effect of reducing cardiac filling pressures (both CVP and PAWP) and by studying these post-cardiotomy heart failure patients, we found that rh-BNP could also significantly reduce Pmsf and VVRI. Moreover, rh-BNP induced a greater decline in VVRI than in SVRI (especially among HFrEF patients), implying a greater increase in venous compliance. In contrast, nitroglycerin, a vasodilator frequently used in heart failure treatment, only

reduced the Pmsf rather than the VRRl.³⁸ It is also important to note that, according to the VAMC study, nitroglycerin caused a delay and smaller decline in CVP and PAWP than rh-BNP.⁵

Effects of recombinant human brain natriuretic peptide on pulmonary circulation system

In the present study, we also observed a significant decrease in pulmonary artery pressure, which may introduce a misconception that rh-BNP can exert similar effects to those of pulmonary hypertension drugs. However, we should note that there is actually no significant change in pulmonary circulatory resistance and that the reduction in pulmonary artery pressure is more attributable to a reduction in backward left atrial pressure. Several well-performed physiological studies published in recent years have also confirmed that rh-BNP reduces pulmonary artery pressure but does not alter pulmonary circulatory resistance.^{25,26,34}

Effects of recombinant human brain natriuretic peptide on short-term urine output

Negative fluid balance may also have an effect on filling pressure, and this study also found a slight degree of acute increase in UO, although it was not the primary study objective. The actual fluid balance during the 90 min measurement period was very small, so this small increase in UO cannot explain the dramatic effect on venous return with rh-BNP. There is still some controversy about the diuretic effect of rh-BNP. Elkayam *et al.* found that although rh-BNP increased renal artery diameter, there was no significant increase in renal blood flow due to reduced perfusion pressure.²⁶ The NAPA study showed that even a low dose of rh-BNP regimen (0.01 µg/kg/min without bolus for at least 24 h) could lead to an increase in UO.¹⁴ Another study performed on a paediatric population also confirmed that the use of rh-BNP was associated with a trend toward a significant increase in UO.³⁹ However, Gottlieb *et al.* suggested that a greater UO during the use of rh-BNP was more attributable to concomitant diuretic use.⁴⁰

A summary of the comprehensive effects of recombinant human brain natriuretic peptide on the circulatory system

To help to elucidate the instant effects of rh-BNP on circulatory pressure and volume distribution, we plotted a diagram of circulatory system changes as seen in *Figure 3C* and found (i) slight dilatation of the arterial system (small reductions in SBP and SVRI); (ii) significant dilatation of the venous system

(larger reduction in Pmsf and VRRl), which increased venous capacity to buffer the redundant blood volume; (iii) unchanged CO with reduced heart volume (preload)²⁵ and filling pressures, as a result of a gradual transfer of the blood volume from the overfilled heart to the enlarged venous bed; and (iv) blood volume returning to the heart did not increase. As we know, the *venous return = pressure gradient/resistance*. In this study, the pressure gradient showed a similar or greater decline when compared with the VRRl, leading to a balanced or very small reduction in venous return; and (iv) unchanged pulmonary vasculature despite a decreased pulmonary pressure.

The main function of the venous system is to contain blood (the main blood reservoir) and to collect blood flowing through the tissues and transport it back to the heart.²² For patients with post-cardiotomy CHF, we postulate that the rh-BNP could rapidly transfer the overfilled blood from the heart to the venous bed, thereby reduce filling pressures and improve the workload of heart. The excess fluid in the venous bed is then excreted gradually by the diuretic effect of rh-BNP, or by supplementing diuretics. Therefore, we recommend against prophylactic or empiric use of rh-BNP in cardiac surgical population. Conversely, rh-BNP should only be administered in patients with evidence about congestion.

Limitations

There are several limitations in our study. Firstly, it was conducted in a single centre and cardiac surgical population. Secondly, the CVP or PAWP were not very high in some patients, however, the Pmsf was above 20 mmHg for all the study population. Thirdly, receiving invasive mechanical ventilation under deep sedation allowed us to perform the measurements required for this study; however, it may limit the range of study population. Fourth, we did not measure the diameter of the heart which may represent a deficiency in the study design. Finally, based on our technical conditions, we were not able to measure the P-V loop directly. However, based on previous studies, we can still make a reasonable extrapolation about the heart volume changes.

Conclusions

In this study, we found that rh-BNP might ameliorate venous return function (reducing both systemic filling pressure and resistance to venous return) rather than CO function in mechanically ventilated post-cardiotomy heart failure patients. This study provides a more detailed interpretation of rh-BNP's effects on haemodynamic profiles in CHF patients, which will facilitate clinicians to make the decision regarding the appropriate use of rh-BNP.

Conflict of interest

The authors declare that there is no conflict of interest.

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