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The safety and efficacy of compression therapy in patients with stable heart failure

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ABSTRACT

Background: Compression therapy is widely used as a therapeutic option for edema; however, concerns regarding its safety in patients with heart failure (HF) arose, particularly due to increased venous return, which increases pulmonary artery blood pressure. This study aimed to investigate the safety of compression therapy in patients with chronic HF.

Methods: This study retrospectively enrolled patients with stable chronic HF who initiated treatment with compression therapy for lower extremity edema. The primary outcome was New York Heart Association (NYHA) class changes after 1 month of compression therapy, and adverse events were evaluated.

Results: We analyzed 101 patients who initiated compression therapy. The number of patients continuing compression therapy at one month was 86. Overall, 61.6 % were female and the median age was 81 years. The proportion of patients with heart failure and preserved ejection fraction (HFpEF) was 50.4 %. Brain natriuretic peptide levels were significantly lower than baseline levels at 1 month, (baseline vs 1 month: 486 (360–696) vs 311 (211–511), $p < 0.001$), with a lower NYHA III prevalence (baseline vs 1 month: 53.5 % vs 32.6 %, $p < 0.001$), without any adverse events related to compression therapy initiation. Additionally, multivariate logistic analysis indicated an association between HFpEF and significant BNP reduction after compression therapy (odds ratio: 4.70; 95 % confidence interval: 1.63–13.6).

Conclusions: Compression therapy was associated with decreased BNP levels and improved symptoms, especially in HFpEF, without any adverse events in stable chronic HF. These findings indicate that compression therapy is safe for patients with stable chronic HF.

1. Introduction

Extracardiac factors, such as venous and lymphatic dysfunction, have garnered attention for their contributions to heart failure (HF) pathogenesis. Rabelo E et al. reported a correlation between HF and venous endothelial dysfunction [1]. Lymphatic dysfunction has been implicated in HF with preserved ejection fraction (HFpEF) and is known to cause leg edema [2]. Addressing leg edema, an extracardiac factor in HF may be effective considering its relevance to congestive manifestations, including lower extremity edema, associated with increased intracardiac pressure.

Leg compression therapy via compression stockings has been widely employed to ameliorate venous and lymphatic dysfunction by improving lymphatic pump function, even in healthy individuals [3–5]. However, concerns regarding its safety in patients with HF have been raised, particularly due to increased venous return, which increases pulmonary artery blood pressure. Therefore, therapy guidelines for venous leg ulcers consider compression stockings an absolute contraindication for those with HF, while HF guidelines do not mention the possibility of worsening HF due to compression therapy [6,7]. Little is known about the safety and efficacy of compression therapy in patients with HF although compression therapy for leg edema in this population

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Table 1
Baseline characteristics with wearing compression therapy after three months.

	Total	Continued compression therapy	Discontinued compression therapy	p value
Number	101	51	50	–
Age	81 (75–85)	81 (75–85)	81 (76–85)	0.81
Female, n (%)	63 (62.4)	36 (70.6)	27 (54.0)	0.09
Body mass index, (kg/m^2)	21.6 (19.5–24.2)	21.6 (19.5–24.4)	21.7 (19.6–24.2)	0.74
Diabetes mellitus, n (%)	42 (41.6)	18 (35.3)	22 (44.0)	0.26
Hypertension, n (%)	56 (55.4)	28 (54.9)	27 (54.0)	0.95
Coronary heart disease, n (%)	33 (32.7)	15 (29.4)	18 (36.0)	0.34
Valve disease, n (%)	30 (29.7)	14 (27.5)	16 (32.0)	0.67
Atrial fibrillation, n (%)	55 (54.5)	31 (60.8)	24 (48.0)	0.03
Pacemaker implantation, n (%)	19 (18.8)	10 (19.6)	9 (18.0)	0.89
Systolic BP[a] (mmHg)	119 (101–129)	121 (103–131)	112 (100–124)	0.05
Diastolic BP[a] (mmHg)	69 (64–78)	69 (63–78)	71 (64–80)	0.43
Heart rate (/min)	76 (67–84)	79 (66–85)	75 (69–84)	0.74
HFpEF[b], n (%)	56 (55.4)	34 (66.7)	22 (44.0)	0.02
LVEF[c] (%)	55 (43–62)	58 (45–63)	51 (41–62)	0.02
Pitting edema scale, n (%)				0.16
0	6 (5.9)	1 (1.9)	5 (10.0)	
1	50 (49.5)	25 (49.0)	25 (50.0)	
2	30 (29.7)	15 (29.4)	17 (34.0)	
3	13 (12.9)	10 (19.6)	3 (6.0)	
4	0 (0)	0 (0)	0 (0)	
NYHA[d], n (%)				0.82
2	45 (44.6)	22 (43.1)	23 (46.0)	
3	56 (55.4)	29 (56.8)	27 (54.0)	
Haemoglobin (g/dL)	11.0 (9.8–13.2)	11.0 (9.8–13.0)	11.9 (9.8–13.6)	0.21
Haematocrit (%)	35.6 (30.4–39.3)	34.2 (30.3–38.9)	36.4 (30.4–41.2)	0.29
eGFR[e] (ml/min/1.73 m^2)	47.9 (36.2–58.1)	48.8 (38.8–60.4)	46.4 (33.7–55.2)	0.22
Uric acid (mg/dl)	6.9 (5.0–9.1)	6.9 (4.9–8.6)	7.0 (5.2–9.4)	0.55
BNP[f] (pg/mL)	479 (350–691)	476 (356–757)	482 (347–604)	0.51
Estimated plasma volume	2274 (1967–2501)	2221 (1933–2389)	2305 (2086–2584)	0.13
Estimated extracellular volume (ml)	11,913 (11239–13341)	11,756 (10630–13322)	12,330 (11800–13354)	0.08
Drug, n (%)				
Loop diuretic, n (%)	99 (98.0)	50 (98.0)	49 (98.0)	0.93
Tolvaptan, n (%)	68 (67.3)	36 (70.6)	32 (74.0)	0.39
ACEi[g] or ARB[h], n (%)	90 (89.1)	47 (92.1)	43 (86.0)	0.54
MRA[i], n (%)	86 (85.1)	41 (80.4)	45 (90.0)	0.37
SGLT2[j] inhibitor, n (%)	50 (49.5)	23 (45.1)	27 (54.0)	0.54

Values are expressed as mean ± SD or median (25 %–75 %) or number of subjects (percentage).
[a] blood pressure; [b]heart failure preserved ejection fraction; [c]left ventricular ejection fraction; [d]New York Heart Association functional classification; [e]estimated glomerular filtration rate; [f]B-type natriuretic peptide; [g]angiotensin conversion enzyme inhibitor; [h]angiotensin receptor blocker, [i]mineralocorticoid receptor antagonist, [j]Sodium–glucose cotransporter 2; p-value: Wilcoxon signed-rank test.

potentially has positive effects [8].

This study aims to evaluate the safety of compression therapy in patients with stable HF and to investigate the relationship between compression therapy and trends in Brain Natriuretic Peptide (BNP) levels.

2. Methods

2.1. Study population

This retrospective study collected data from patients with stable chronic HF who visited our outpatient department at three centers and received compression therapy through new compression stockings from 2018 to 2021. Indications for leg compression therapy included managing chronic edema and preventing varicose veins, even in cases without evident edema. Medical records of patients were obtained and analyzed. This study defines HF with the criteria established by the Japan Circulation Society Guidelines [9]. The enrollment criteria for this study stipulated that participants must meet the following criteria: 1) a previous hospitalization for HF or a BNP level of $>$ 100 pg/dL, 2) New York Heart Association (NYHA) classification of II or III, 3) no changes in oral medication, including dosage, from one year preceding to three months following the initiation of compression therapy. The study excluded patients undergoing hemodialysis. The Ethical Review Committee of Iwate Medical University approved the study (MH2021-081).

2.2. Study protocol

All data, including laboratory results, echocardiography, electrocardiography, vital signs, medical history, medication status, degree of lower limb edema and exercise tolerance, were extracted from the electronic medical records of patients in the ambulatory care at baseline, as well as after 1 and 3 months of compression therapy. Compliance with compression therapy was evaluated at the same time points. The Edema Grading Scale (https://www.med-health.net/Edema-Grading.html) quantitatively assessed the severity of lower limb edema, scored as 1+: barely detectable depression of 2 mm; 2+: 4-mm deep pit; 3+: 6-mm deep pit; 4+: 8-mm deep pit. HFpEF was diagnosed when the left ventricular ejection fraction (LVEF) was $\geq$ 50 %, calculated using the modified Simpson method [9]. In this retrospective analysis of our patient data, we identified the change in NYHA class at 1 month as the primary endpoint. Correspondingly, changes in BNP levels and the degree of lower limb edema at 1 month, important indicators of cardiac function and fluid status, were analyzed as secondary endpoints. In addition, we assessed compression therapy on HF by measuring changes in BNP levels at baseline, 1 month, and 3 months. The BNP reduction rate was calculated as (baseline BNP - BNP at 1 month)/baseline BNP. A higher BNP reduction rate was defined as $\geq$ 30 % [10]. Ineffective compression therapy was also described as having a BNP reduction rate of $\leq$ 10 %. Body fluid composition was estimated by estimating plasma volume (ePV) using the Kaplan–Hakim formula [11], and calculated extracellular volume (eEV) using the equation “8116.6 * (0.00714 *

Table 2
Transition of a parameter after compression therapy at one month.

	baseline	After 1 month	p value
Number	86	–	–
Age	81 (75–85)	–	–
Female, n (%)	53 (61.6)	–	–
Body mass index, (kg/m^2)	21.6 (19.5–24.4)	21.5 (19.4—–24.2)	< 0.001
Diabetes mellitus, n (%)	32 (37.0)	–	–
Hypertension, n (%)	46 (53.0)	–	–
Coronary heart disease, n (%)	29 (34.0)	–	–
Valve disease, n (%)	27 (31.4)	–	–
Atrial fibrillation, n (%)	49 (57.0)	–	–
Pacemaker implantation, n (%)	15 (17.4)	–	–
Systolic BP[a] (mmHg)	113.5 ± 17.3	114.8 ± 15.4	0.41
Diastolic BP[a] (mmHg)	70 (64–80)	71 (65—–80)	0.57
Heart rate (/min)	77 (68–84)	74 (69—–82)	0.17
HFpEF[b], n (%)	46 (50.4)	–	–
LVEF[c] (%)	51 (41–62)	–	–
Pitting edema scale, n (%)			< 0.001
0	4 (4.7)	23 (26.7)	
1	42 (48.8)	48 (55.8)	
2	30 (34.9)	13 (15.1)	
3	8 (9.3)	2 (2.3)	
4	0 (0)	0 (0)	
NYHA[d], n (%)			< 0.001
1	0 (0)	2 (2.3)	
2	40 (46.5)	56 (65.1)	
3	46 (53.5)	28 (32.6)	
Haemoglobin (g/dL)	11.5 (9.9–13.3)	12.0 (10.4 – 13.8)	< 0.001
Haematocrit (%)	35.7 (30.8–40.7)	36.9 (32.1 – 42.1)	< 0.001
eGFR[e] (ml/min/1.73 m^2)	48.3 (38.5–59.3)	46.0 (36.1 – 56.6)	0.13
Uric acid (mg/dl)	6.9 (5.1–9.0)	6.9 (5.6 – 9.1)	0.07
BNP[f] (pg/mL)	486 (360–696)	311 (200—–511)	< 0.001
Estimated plasma volume	2260 (1974–2532)	2208 (1915 – 2460)	< 0.001
Estimated extracellular volume (ml)	12,329 (11292–13308)	12,198 (11199—–13193)	< 0.001
Drug, n (%)			
Loop diuretic, n (%)	84 (97.7)	–	–
Tolvaptan, n (%)	63 (73.3)	–	–
ACEi[g] or ARB[h], n (%)	79 (91.9)	–	–
MRA[i], n (%)	77 (89.5)	–	–
SGLT2[j] inhibitor, n (%)	43 (50.0)	–	–

Values are expressed as mean ± SD or median (25 %–75 %) or number of subjects (percentage).
[a] blood pressure; [b]heart failure preserved ejection fraction; [c]left ventricular ejection fraction; [d]New York Heart Association functional classification; [e]estimated glomerular filtration rate; [f]B-type natriuretic peptide; [g]angiotensin conversion enzyme inhibitor; [h]angiotensin receptor blocker, [i]mineralocorticoid receptor antagonist, [j]Sodium–glucose cotransporter 2; p-value: the Friedman's test.

height (cm)$^{0.725}$ * weight (kg)$^{0.425}$)–28.2." [12].

2.3. Statistical analysis

Numeric variables were expressed as mean ± standard deviation when displaying normal distribution and median (interquartile range) when exhibiting skewed distribution. Categorical data were presented in frequencies and percentages. The Friedman's test was employed to evaluate temporal changes. The *t*-test and the Kruskal–Wallis test analyzed normally and non-normally distributed continuous variables, respectively, in the case of two-group comparisons. The chi-squared test determined differences in demographic parameter proportions. Logistic regression analysis was conducted for group comparisons stratified by improvement of NYHA classification, improvement of edema scales, and BNP reduction rate for one month. The significant univariate factors adjusted the multivariate model. IBM Statistical Package for the Social Sciences Statistics version 25 for Windows (IBM Corp., Armonk, NY, USA) was used for data processing. Statistically significant differences were set at a *p*-value of < 0.05.

3. Results

3.1. Baseline characteristics

This study initially enrolled 101 patients. Table 1 presents the baseline data for this group. The median age of the participants was 81 years (range: 75–85), with 62.4 % being female. Atrial fibrillation complications were present in 54.5 % of the group. The median LVEF was 55 % (43–62), and HFpEF was 55.4 %. The median BNP level was 479 pg/mL (350–691). The pitting edema scale ranged from 0 to 4, accounting for 5.9 %, 49.5 %, 29.7 %, 12.9 %, and 0 % of patients, respectively. Regarding NYHA classification, 44.6 % of patients were classified as II, and 55.4 % as III. Loop diuretics were administered to almost all patients (98.0 %).

3.2. Continuation and discontinuation of compression therapy

Within the first month, 15 individuals withdrew from compression therapy. Subsequently, of the 86 participants who continued past the

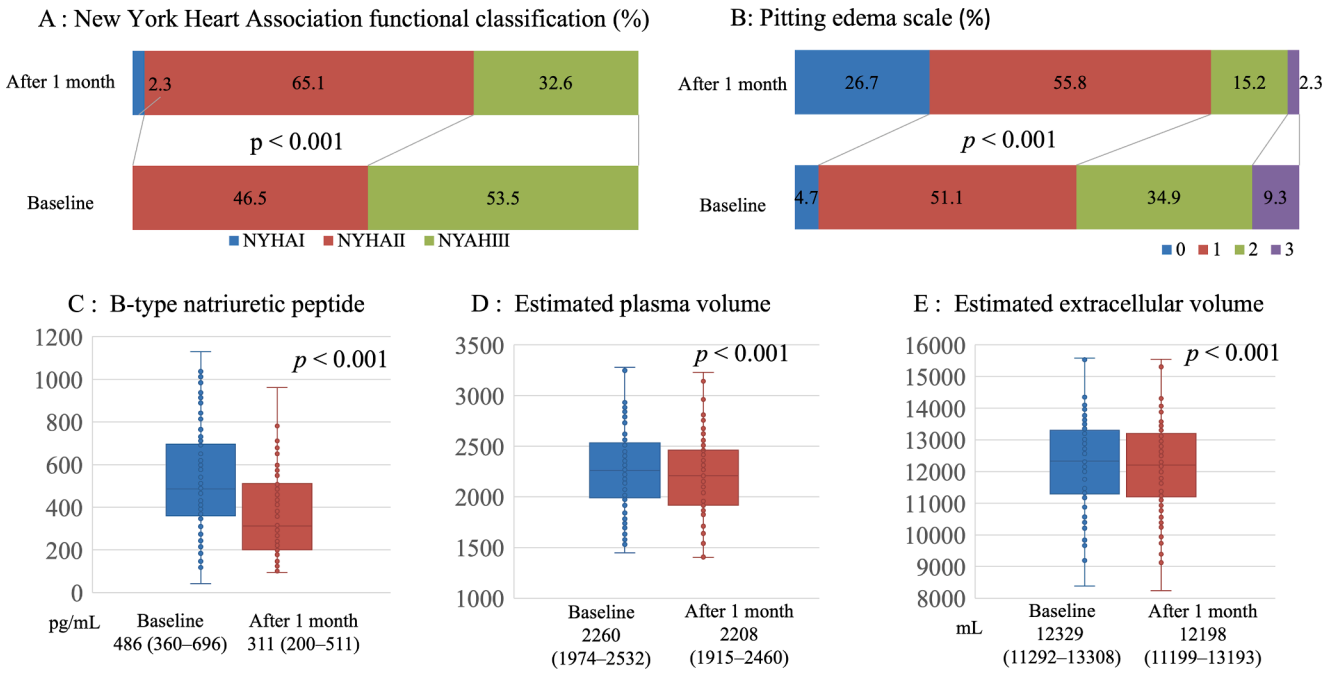

Fig. 1. Transition of clinical parameters after compression therapy for 1 month: (A) The transition of New York Heart Association classification between baseline and 1 month. (B) Pitting edema status between baseline and 1 month. (C) BNP levels transition between baseline and 1 month. (D) Estimated plasma volume transition between baseline and 1 month. (E) Estimated extracellular volume transition between baseline and 1 month.

first month, 33 discontinued the therapy within the next 3 months due to discomfort or difficulty wearing it. Additionally, 2 participants discontinued due to skin complications. These withdrawals total 50 (15 initial + 33 subsequent + 2 for skin complications), leaving 51 individuals (50.5 % of the original cohort) who continued with the compression therapy for the entire study period. Importantly, among these 51 patients, no cases of heart failure symptom deterioration, hospitalization, or the need for adjustment in diuretic therapy were reported. Furthermore, Table 1 compares baseline data between the continuation and discontinuation groups after 3 months, showing a higher LVEF in the continuation group compared to the discontinuation group and a greater prevalence of HFpEF in the continuation group.

3.3. Effects of compression therapy on various parameters after 1 month

Table 2 shows the baseline and the parameter changes in the population that continued compression therapy for one month. The median age of these participants was 81 years (range: 75–85), with 61.6 % being female. Atrial fibrillation complications were noted in 57.0 % of this subgroup, and the median LVEF was 51 % (range: 41–62), with HFpEF present in 50.4 % of patients. The median BNP level was 486 pg/mL (range: 360–696). The pitting edema scale ranged from 0 to 4, accounting for 4.7 %, 48.8 %, 34.9 %, 9.3 %, and 0 % of patients, respectively. Regarding NYHA classification, 46.5 % of patients were classified as II, and 53.5 % as III.

Further, Table 2 provides a comprehensive overview of the baseline and 1-month follow-up data for the population that continued compression therapy. Significant improvements were observed in NYHA classification and pitting edema scale after 1 month of compression therapy (Fig. 1A, 1B). BNP levels also showed a notable reduction (Fig. 1C). Hemoglobin and hematocrit levels increased, while ePV and eEV decreased (Fig. 1D, 1E), suggesting a positive impact on body fluid composition. The estimated glomerular filtration rate did not show significant change.

3.4. Association of NYHA classification and edema scale changes with one month of compression therapy

Table 3 displays the results of a univariate logistic regression analysis, which evaluated factors associated with improvement in NYHA class and edema scale following one month of compression therapy. While factors contributing to improvement in NYHA classification were not identified, the analysis indicated that heart failure with preserved ejection fraction (HFpEF) was the only factor associated with edema improvement, exhibiting an odds ratio (OR) of 11.7 (95 % confidence interval [CI]: 1.05–31.2).

3.5. Factors affecting B-type natriuretic peptide reduction rates in compression therapy for 1 month

The proportion of participants in the higher BNP reduction rate group (BNP reduction rate: ≥0.3) was 45.3 %, while that in the lower BNP reduction rate group (BNP reduction rate: <0.3) was 54.7 %. Table 3 shows the comparison between the groups. The median values were the cut-off for ePV and eEV. Female proportion, atrial fibrillation prevalence, systolic blood pressure, and HFpEF were higher in the higher BNP reduction rate group compared to the lower BNP reduction rate group ($p = 0.03$, $p = 0.01$, $p = 0.01$, and $p < 0.001$, respectively). The pitting edema scale was also lower in the higher BNP reduction rate group ($p = 0.02$). Table 4 presents the logistic analysis results. Univariate analysis revealed significant associations for the higher BNP reduction group with female gender (OR: 2.78, 95 % CI: 1.11–6.96), atrial fibrillation (OR: 3.15, 95 % CI: 1.27–7.78), systolic blood pressure (OR: 1.03, 95 % CI: 1.01–1.06), HFpEF (OR: 6.46, 95 % CI: 2.48–16.8), and pitting edema scale of ≥ 2 (OR: 3.07, 95 % CI: 1.27–7.43) (Table 3). The multivariate analysis identified a significant association between HFpEF and a higher BNP reduction rate (OR: 4.70, 95 % CI: 1.63–13.6). The multivariate analysis revealed no significant differences between the higher BNP reduction rate group and other factors (Table 5.)

Table 3
Correlates of improvement NYHA classification and edema scale for one month using univariate logistic regression analysis.

Variable	Improvement NYHA classificationOR (95 %CI)	p value	Improvement edema scaleOR (95 %CI)	p value
Age	1.04 (0.97–1.11)	0.38	1.13 (0.93–1.20)	0.13
Female	1.49 (0.49–2.76)	0.42	0.99 (0.25–3.89)	0.98
Body mass index	0.95 (0.86–1.04)	0.29	0.91 (0.79–1.13)	0.35
Diabetes mellitus	1.36 (0.56–3.29)	0.81	1.12 (0.27–4.74)	0.88
Hypertension	0.58 (0.14–2.40)	0.46	0.77 (0.47–2.13)	0.49
Coronary heart disease	2.88 (0.63–13.2)	0.17	3.05 (0.79–8.45)	0.20
Valve disease	1.56 (0.70–1.93)	0.63	1.64 (0.78–1.89)	0.51
Atrial fibrillation	5.81 (0.89–12.5)	0.09	3.98 (0.88–17.7)	0.07
Pacemaker implantation	0.83 (0.64–1.94)	0.78	0.74 (0.52–2.06)	0.65
Systolic BP[a] (mmHg)	1.03 (0.98–1.09)	0.27	0.96 (0.91–1.03)	0.30
Diastolic BP[a] (mmHg)	1.00 (0.93–1.08)	0.96	1.02 (0.93–1.16)	0.68
Heart rate (/min)	1.01 (0.94–1.05)	0.97	0.98 (0.91–1.05)	0.75
HFpEF[b], n (%)	2.44 (0.42–14.3)	0.32	11.7 (1.05–31.2)	0.04
Pitting edema scale ≧ 2	3.34 (0.90–12.4)	0.07	–	–
NYHA[c] classification = 3	–	–	0.88 (0.63–1.29)	0.85
Haemoglobin (g/dL)	0.48 (0.13–1.81)	0.28	0.45 (0.19–1.78)	0.31
Haematocrit (%)	1.34 (0.85–2.11)	0.21	1.53 (0.90–2.39)	0.28
eGFR[d] (ml/min/1.73 m^2)	1.07 (0.96–1.06)	0.78	0.98 (0.93–1.02)	0.25
Uric acid (mg/dl)	0.84 (0.60–1.20)	0.35	0.78 (0.57–1.08)	0.13
BNP[e] (pg/mL)	1.00 (0.98–1.07)	0.13	1.00 (0.99–1.00)	0.50
Estimated plasma volume of > 2260	2.21 (0.79–3.46)	0.19	1.39 (0.53–3.02)	0.37
Estimated extracellular volume of > 12329 ml	1.04 (0.78–1.68)	0.46	0.84 (0.47–1.57)	0.33

The cut-off for estimated plasma volume and estimated extracellular volume were medium values.
The multivariate model was adjusted by the significant univariate factors.
[a] blood pressure; [b]heart Failure preserved ejection fraction; [c]New York Heart Association functional classification; [d]estimated glomerular filtration rate; [e]B-type natriuretic peptide.

3.6. Comparison of BNP levels in patients continuing and discontinuing compression therapy at 3 months

A significant reduction in BNP levels was observed compared to the baseline measurements at 1 and 3 months in the continuing compression therapy group. However, no significant difference was observed between BNP levels at 1 and 3 months (baseline vs. after 1-month, $p < 0.001$; baseline vs. after 3 months, $p < 0.001$; after 1 month vs after 3 months, $p = 0.37$, Fig. 2A). Conversely, a significant reduction in BNP levels at 1 month was observed in the groups where participants discontinued compression therapy between 1 and 3 months, but this increased again at 3 months (baseline vs after 1 month, $p < 0.001$; baseline vs after 3 months, $p = 0.52$, after 1 month vs after 3 months, $p < 0.001$, Fig. 2B).

4. Discussion

The present study demonstrated that leg compression therapy showed an association with NYHA classification change, BNP level reduction, and edema scale change at 1 month among patients with HF. Moreover, compression therapy withdrawal after 1 month was associated with increased BNP levels during follow-up. Logistic analysis revealed that compression therapy might be associated with lowering BNP levels among patients with HFpEF. Compression therapy did not cause major complications, but the 3-month persistence was very low, with only half of the patients persisting for 3 months. Substantial gaps remain in our understanding of the full spectrum of effectiveness and safety of compression therapy in heart failure, highlighting the necessity for further, ideally prospective, research.

Safety concerns about compression therapy include the sudden displacement of a large volume of blood from the veins of the lower extremities, as compression may increase intracardiac pressure and precipitate pulmonary edema [13]. Previous studies have revealed that compression therapy for patients with NYHA class III and IV HF increases pulmonary capillary wedge pressure and right atrial pressure in the short term but does not affect cardiac output as assessed using the Swan–Ganz catheter [14]. Conversely, previous research has indicated that a short term increase in cardiac return, despite the increase in right-side heart pressure, does not significantly alter left-side heart function [15]. Moreover, atrial natriuretic peptide levels have been reported to immediately increase after lower limb compression therapy in patients with HF of NYHA class II with leg edema and decrease to baseline after 10 min [16]. These findings suggested that compression therapy rapidly

Table 4
Comparison baseline characteristics by B-type natriuretic peptide reduction rate for one month.

BNP reduction rate, %	≧0.3	<0.3	p value
Number	39	47	–
Age	83 (75–288)	81 (76–283)	0.07
Female, n (%)	29 (74.4)	24 (51.1)	0.03
Body mass index, (kg/m2)	21.6 (19.5–24.4)	21.5 (19.4–24.2)	0.65
Diabetes mellitus, n (%)	13 (33.3)	19 (40.4)	0.50
Hypertension, n (%)	22 (56.4)	24 (51.1)	0.63
Coronary heart disease, n (%)	15 (38.5)	14 (29.8)	0.43
Valve disease, n (%)	13 (33.3)	14 (29.8)	0.72
Atrial fibrillation, n (%)	28 (71.8)	21 (44.7)	0.01
Pacemaker implantation, n (%)	6 (15.4)	9 (19.1)	0.65
Systolic BP[a] (mmHg)	122 (106–131)	112 (99–121)	0.01
Diastolic BP[a] (mmHg)	72 (64–82)	69 (64–77)	0.36
Heart rate (/min)	79 (66–86)	75 (69–83)	0.80
HFpEF[b], n (%)	30 (76.9)	16 (34.0)	< 0.001
LVEF[c] (%)	59 (51–63)	44 (38–57)	0.004
Pitting edema scale, n (%)			0.02
0	0 (0)	6 (12.8)	
1	16 (41.0)	26 (55.3)	
2	17 (43.6)	13 (27.7)	
3	6 (15.4)	2 (4.3)	
4	0 (0)	0 (0)	
NYHA[d], n (%)			0.42
2	20 (51.3)	20 (42.6)	
3	19 (48.7)	27 (57.4)	
Haemoglobin (g/dL)	11.0 (9.8–12.9)	12.1 (9.9–13.9)	0.14
Haematocrit (%)	34.8 (31.5–38.5)	36.6 (30.2–42.6)	0.24
eGFR[e] (ml/min/1.73 m^2)	48.9 (39.5–60.3)	47.7 (36.3–57.5)	0.55
Uric acid (mg/dl)	6.9 (4.9–8.2)	6.5 (5.2–9.5)	0.32
BNP[f] (pg/mL)	476 (385–691)	495 (317–731)	0.47
Estimated plasma volume of > 2260, n (%)	18 (46.2)	25 (53.2)	0.19
Estimated extracellular volume of > 12329 ml, n (%)	16 (41.0)	27 (57.4)	0.66

Values are expressed as mean ± SD or median (25 %–75 %) or number of subjects (percentage).
p-value: Kruskal–Wallis test or chi-squared test.
[a] blood pressure; [b]heart Failure preserved ejection fraction; [c]left ventricular ejection fraction; [d]New York Heart Association functional classification; [e]estimated glomerular filtration rate; [f]B-type natriuretic peptide; [g]angiotensin conversion enzyme inhibitor; [h]angiotensin receptor blocker, [i]mineralocorticoid receptor antagonist, [j]Sodium–glucose cotransporter 2;

Table 5
Correlates of higher B-type natriuretic peptide reduction rate (≧0.3) for one month using logistic regression analysis.

Variable	Univariate analysisOR (95 %CI)	p value	multivariate analysisOR (95 %CI)	p value
Age	1.03 (0.99–1.06)	0.17	–	–
Female	2.78 (1.11–6.96)	0.029	2.39 (0.73–7.86)	0.15
Body mass index	0.95 (0.86–1.04)	0.29	–	–
Diabetes mellitus	1.36 (0.56–3.29)	0.50	–	–
Hypertension	0.81 (0.34–1.89)	0.62	–	–
Coronary heart disease	1.47 (0.60–3.62)	0.40	–	–
Valve disease	1.74 (0.79–1.88)	0.51	–	–
Atrial fibrillation	3.15 (1.27–7.78)	0.013	1.70 (0.60–4.84)	0.32
Pacemaker implantation	0.77 (0.25–2.39)	0.65	–	–
Systolic BP[a] (mmHg)	1.03 (1.01–1.06)	0.018	1.02 (0.98–1.05)	0.29
Diastolic BP[a] (mmHg)	1.02 (0.98–1.06)	0.34	–	
Heart rate (/min)	1.00 (0.96–1.04)	0.99	–	
HFpEF[b], n (%)	6.46 (2.48–16.8)	< 0.001	4.70 (1.63–13.56)	0.004
Pitting edema scale ≧ 2	3.07 (1.27–7.43)	0.013	2.19 (0.78–6.15)	0.14
NYHA[c] classification = 3	0.70 (0.30–1.65)	0.42	–	–
Haemoglobin (g/dL)	0.85 (0.70–1.03)	0.10	–	–
Haematocrit (%)	0.95 (0.89–1.02)	0.16	–	–
eGFR[d] (ml/min/1.73 m^2)	1.01 (0.98–1.03)	0.55	–	–
Uric acid (mg/dl)	0.92 (0.77–1.10)	0.36	–	–
BNP[e] (pg/mL)	1.00 (0.99–1.01)	0.26	–	–
Estimated plasma volume of > 2260	1.33 (0.57–3.11)	0.52	–	–
Estimated extracellular volume of > 12329 ml	0.51 (0.22–1.22)	0.13	–	–

The cut-off for estimated plasma volume and estimated extracellular volume were medium values.
The multivariate model was adjusted by the significant univariate factors.
[a] blood pressure; [b]heart Failure preserved ejection fraction; [c]New York Heart Association functional classification; [d]estimated glomerular filtration rate; [e]B-type natriuretic peptide.

increases the cardiac volume load. However, the volume overload via compression therapy would only temporarily be induced and with a reversible alteration in patients with stable HF. Previous research revealed that hANP demonstrated a temporary but significant elevation, rapidly returning to its initial value on average 10 min after compression, in the cohort with venous insufficiency and coinciding HF [17]. Similarly, we found no adverse event following the start of compression therapy initiation although our results were based on a small number of patients, and BNP levels were decreased in participants with stable HF. These findings would support the safety and efficacy of compression therapy in patients with stable HF with careful utilization.

Interestingly, a previous study revealed that surgery for varicose veins by removing the dysfunctional vein of the lower extremities was associated with decreased BNP levels through improvements in venous insufficiency, even in patients without HF [18]. Compression therapy potentially improves venous insufficiency and reduces BNP levels in the same physiological mechanism [3]. The study results may be related to improved venous dysfunction by compression therapy.

Central lymphatic dysfunction increases central venous pressure, but whether the same applies to peripheral lymphatic dysfunction remains unclear [19]. Rossitto, G. et al. indicated that reduced lymphatic reserve may represent a novel therapeutic target in patients with HFpEF [2]. Compression therapy supports lymphatic function [4,5]; thus, the association between lymphatic dysfunction and HFpEF may be related to our results that compression therapy was more associated with BNP level reduction among patients with HFpEF than HF with reduced ejection fraction.

Venous infusion volume is presumed to increase with compression therapy in cases with elevated ePV [11]. Furthermore, patients with elevated eEV are presumed to have a higher presence in the interstitial fluid [12]. This study revealed that eEV and ePV decreased with compression therapy, indicating that body fluid depletion occurred after the start of compression therapy. A venous or lymphatic capacity improvement may reduce eEV and ePV on the extremity leg. Additionally, a randomized controlled trial regarding the efficacy of compression therapy for acute HF has been reported despite a small-scale study [20]. This study suggested that lower extremity leg compression resulted in less intravenous diuretic continuous infusion therapy, which is a greater net reduction in lower extremity edema, reduced patient-assessed HF burden and shorter hospital length of stay, with fewer rates of acute kidney injury [20]. Furthermore, trends toward fewer total days of total diuresis drug, less diuresis escalation, and greater edema reduction were observed in those with compression therapy compared to those without. These findings are reassuring regarding the safety of compression therapy in patients with HF, and further research should address these issues.

5. Limitations

This retrospective and observational design study is inherently susceptible to confounding factors, especially since leg compression therapy was not primarily designed as a treatment for HF. In addition, the study's single-arm design creates significant interpretational limitations. Another critical limitation is the study's small sample size. Nonetheless, our findings suggest that compression therapy poses little risk of harm to stable HF patients, as BNP levels either remained constant or trended downward in nearly all cases, with no severe complications reported. An additional limitation arises from the lack of data regarding the daily duration of compression therapy and the specific pressure applied shortcomings that necessitate further study. Our study population predominantly comprised older females with pre-existing leg edema, thereby introducing a selection bias that challenges the generalizability of our results to the broader HF patient population. Another concern is the tolerability and continuity of compression therapy, even without serious complications. Another concern pertains to the tolerability and continuity of compression therapy, even without serious complications. About half of the patients discontinued the therapy. Therefore, improving the functionality of the equipment and devising ways to enhance continuity are considered essential. Due to these limitations, prospective studies are warranted to clarify the impact of compression therapy on HF. Despite these challenges, this investigation is the first comprehensive study on the use of compression therapy in patients with stable, chronic HF. It can serve as a cornerstone for future research.

6. Conclusion

The present study revealed that compression therapy was associated with a BNP level reduction in patients with stable HF, especially HFpEF, without any adverse events. The efficacy and safety of compression therapy on HF remains not fully understood and should be further explored through large-scale, prospective studies.

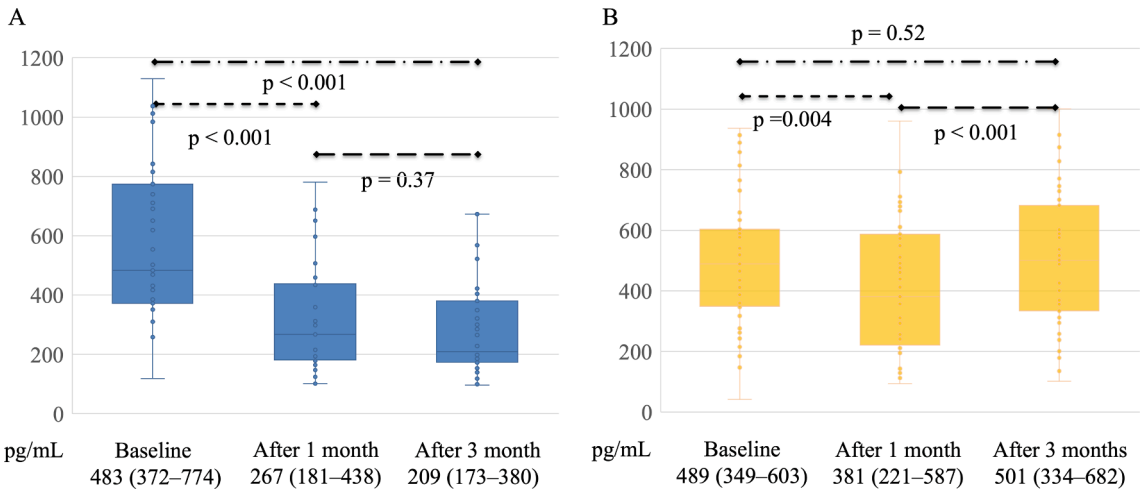

Fig. 2. Transition of B-type natriuretic peptide levels after compression therapy in patients for 3 months (A) who continued compression therapy for 3 months and (B) who withdrew from compression therapy after 1 month.

CRediT authorship contribution statement

Takahito Nasu: Writing, Visualization, Resources, Project administration, Methodology, Investigation, Data curation. **Shingo Matsumoto:** Writing – review & editing, Visualization, Supervision, Resources, Project administration, Methodology, Investigation, Data curation. **Wataru Fujimoto:** Writing – review & editing, Project administration, Methodology, Investigation, Data curation. **Harutomo Numazaki:** Data curation. **Yoshihiro Morino:** Writing – review & editing, Supervision.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Footnotes.

All authors take responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

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