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Cardiac rehabilitation in patients with cardiovascular disease leads various hemodynamic parameters obtained using simple non-invasive tests to their appropriate levels

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ABSTRACT

We evaluated whether comprehensive cardiac rehabilitation (CR) in patients with cardiovascular disease (CVD) could improve various hemodynamic parameters obtained using simple non-invasive tests. We analyzed 48 CVD patients with (n = 38, CR group) or without (n = 10, non-CR group) a CR program, and prospectively followed them for 12 months. Various parameters were measured at baseline and after 12 months using 3 simple non-invasive tests: blood pressure (BP) and severity of atherosclerosis [arterial velocity pulse index (AVI) and atrial pressure volume index] were determined using PASESA®, an index of total autonomic nerve activity and a coefficient of variation of the R-R interval (CVRR) were determined using eHEART®, and the total peripheral resistance, stroke volume and cardiac index (CI) were determined using nico®. The main hemodynamic parameters did not change between baseline and 12 months in both groups. Patients in the CR group were divided into higher (H-) and lower (L-) systolic BP (SBP) or AVI according to the average value of SBP or AVI at baseline in the CR group. Patients with H-SBP or H-AVI in the CR group showed a significant reduction of SBP or AVI at 12 months. In addition, patients in the CR group were divided into H- and L- CI or CVRR according to the average value of CI or CVRR at baseline in the CR group. Patients with L-CI or L-CVRR in the CR group significantly improved after 12 months. In conclusion, CR may lead various hemodynamic parameters obtained using simple non-invasive tests to their appropriate levels.

1. Introduction

Comprehensive cardiac rehabilitation (CR) has been shown to improve cardiac function and prognosis in patients with cardiovascular disease (CVD) [1,2]. Recently, we reported that a 3-month CR program significantly decreased blood pressure (BP) [3] and improved atherosclerosis and sympathetic nerve as assessed by 3 simple non-invasive tests: BP and severity of atherosclerosis [arterial velocity pulse index (AVI) and arterial pressure volume index (API)] were determined using PASESA® (AVE-1500, Shisei Datum, Tokyo, Japan), an index of total autonomic nerve activity and a coefficient of variation of the R-R interval (CVRR) were determined using eHEART® (Parama-Tec, Fukuoka, Japan), and absolute and relative differences in BP between arms, pressure rate product (PRP), mean total peripheral resistance index (TPR), stroke volume (SV), and cardiac index (CI) were determined using nico® (Parama-Tec, Fukuoka, Japan) [4]. These 3 easy-to-use devices, PASESA® [5], nico PS-501® (North Parama Inc., Tokyo, Japan) [6] and eHEART® [7], are currently available for clinical use in Japan. We concluded that these simple non-invasive devices may be useful for assessing the effectiveness of CR. In addition, since we followed the patients for only 3 months [4], we considered a longer follow-up period (12 months) in this study. Therefore, we evaluated whether 12 months of comprehensive CR improved various hemodynamic parameters obtained using simple non-invasive tests in patients with CVD.

2. Methods

2.1. Study population and protocol

We enrolled 38 CVD outpatients into a CR program (CR group) and prospectively followed them for 12 months. We compared them to

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10 age-, gender- and body mass index (BMI)-matched CVD patients without CR (non-CR group, standard pharmacological care and no regular exercise habits). This study was approved by the Independent Review Board of Fukuoka University Hospital (#14-3-07) and registered under UMIN000016668. All subjects gave their written informed consent to participate.

2.2. Exercise protocol

The CR group participated in a supervised exercise training program at the hospital's gym for 12 months, with an average of 8 times (4–12 times) a month. Briefly, exercise intensity was chosen at 50% of peak VO_2 according to a cardio pulmonary exercise test (CPX) or Borg's scale 11–13 during exercise. Each session lasted about 1 h and consisted of a warm-up exercise (10 min) followed by 30 min of cycling or walking at the indicated exercise intensity and 20 min of cooling down and stretching. BP and heart rate (HR) were measured at rest and at the end of exercise, and an electrocardiogram [Central Monitor (DS-5700) Fukuda Denshi Co. Ltd., Tokyo, Japan] and Borg's scale were recorded during exercise.

2.3. Data collection

Patient characteristics including age, gender, BMI, prevalence of hypertension (HTN), dyslipidemia (DL) and diabetes mellitus (DM) and medications were assessed at baseline. Patients who had a current systolic BP (SBP)/diastolic BP (DBP) ≥140/90 mm Hg or who were receiving antihypertensive therapy were considered to have HTN. DM was defined using the Japan Diabetes Society Criteria or if the patient was being treated with an oral hypoglycemic agent or insulin. Patients with low-density lipoprotein cholesterol ≥140 mg/dl, triglyceride ≥150 mg/dl, and/or high-density lipoprotein cholesterol <40 mg/dl, or who were receiving lipid-lowering therapy, were considered to have DL. Ischemic heart disease (IHD) was defined as lumen diameter stenosis >50% in at least 1 major coronary artery as determined by coronary angiography and as diagnosed by old myocardial infarction. Heart failure was assumed based on the medical history, including medications and cardiac function. Medications included β-blocker, calcium channel blocker (CCB), angiotensin II receptor blocker (ARB)/angiotensin converting enzyme inhibitor (ACE-I) and diuretic. Various parameters were obtained using PASESA® [5], nico PS-501® [6] and eHEART® [7] at baseline and after 12 months.

2.4. CPX

Patients underwent symptom-limited CPX using a cycle ergometer with respiratory gas exchange analysis at baseline. The testing consisted of an initial 2 min of rest, 1 min of warm-up at 0 W, and full exercise under a ramp protocol with increments of 10 W/min. Expired gas analysis was performed throughout testing on a breath-by-breath basis, and work rate at anaerobic threshold (AT), volume of oxygen uptake (VO_2) at AT, O_2 pulse at AT, peak VO_2, minimum ventilation (VE)/volume of exhaled carbon dioxide (VCO_2), VE vs. VCO_2 slope, peak Gas exchange data were collected.

2.5. Measurements of parameters of arterial stiffness using PASESA®

We wrapped a cuff around the left upper arm of sitting patients and measured the brachial BP oscillometrically using PASESA® after at least 5 min of rest [4,5]. AVI, API, SBP, DBP and HR were collected.

2.6. Evaluation of various hemodynamic parameters using nico PS-501®

We wrapped cuffs around both the right and left upper arms of sitting patients. The nico PS-501® is a noninvasive BP-monitoring device based on the Korotkoff sound method. The PS-501® measures BP at the upper arm between 30 and 280 mm Hg and HR between 30 and 180 beat/min. Inflation is performed by an automatic pump system and deflation is controlled by an automatic pressure-release valve. Bilateral brachial PRP, SV, CI, and mean TPR were analyzed by a nico PS-501® [4,6]. We calculated absolute (|rt. BP − lt. BP|) and relative (rt. BP − lt. BP) differences in SBP and DBP between arms. Mean TPR was calculated by average of rt. TPR and lt. TPR.

2.7. Measurement of HRV using eHEART®

Beat-to-beat HR data in the supine position were continuously recorded for 5 min using eHEART® after at least 5 min of rest. This equipment is convenient and both rapid and simple to use, and 5 min of recording was sufficient for an analysis. Five minutes has been shown to be sufficient for short-term HRV analysis [7]. In addition, Bigger recommended that high-frequency (HF) power should be based on at least 1 min of recording, while low-frequency (LF) power required at least 2.5 min [8]. Using eHEART®, we evaluated parameters of heart rate variability (HRV), such as CVRR, HF, LF, and the ratio of LF to HF (LF/HF) [4,9]. The fluctuations of R-R intervals were integrated on the HF band (0.15–0.40 Hz) and the LF band (0.05–0.15 Hz). HRV was expressed as the power of the LF and HF components and the LF/HF power ratio.

2.8. Statistics

Statistical analysis was performed using the using the statistical software R (version 3.3.2). Data are expressed as the mean ± standard deviation or number (%). Categorical and continuous variables were compared between the groups by a chi-square analysis and *t*-test, respectively. The Spearman Rank Correlation Coefficient was used to evaluate associations between the groups. A value of $p < 0.05$ was considered significant.

3. Results

3.1. Patient characteristics at baseline in the non-CR and CR groups

Table 1 shows the patient characteristics at baseline in the non-CR and CR groups. In the CR group, the percentages (%) of male, HTN, DM, DL, IHD and heart failure were 56%, 62%, 15%, 74%, 39% and 37%, respectively. There were no significant differences in patient characteristics except for % ARB/ACE-I between the groups. % ARB/ACE-I in the CR group was significantly higher than that in the non-CR group.

The work rate at AT, VO_2 at AT, and O_2 pulse at AT at baseline and after 1 year were 41 ± 12 (23–62) and 42 ± 10 (16–66) watts, 13.8 ± 2.1 and 13.6 ± 2.4 ml/kg/min, 9.0 ± 1.7 and 8.8 ± 1.9 ml/beats, respectively. In addition, the peak VO_2, minimum VE/VCO_2, VE vs. VCO_2 slope, and peak Gas exchange at baseline and after 1 year were 16.6 ± 3.2 and 17.3 ± 3.6 ml/kg/min, 32 ± 3.2 and 33 ± 3.7 L, 29 ± 3.6 and 30 ± 3.7, and 1.0 ± 0.1 and 1.0 ± 0.1, respectively. There were no significant changes in these parameters between baseline and after 1 year.

Next, the patients were divided into 2 groups according to the average work rate at AT at baseline: higher work rate at AT at baseline (H-work rate group) and lower work rate at AT at baseline (L-work rate group). The work rate at AT after 1 year (38 ± 7 watts) significantly improved compared to that at baseline (32 ± 7 watts) ($p = 0.01$) in the L-work rate group, but not in the H-work rate group.

3.2. Determination of various parameters including BP, PR and arterial stiffness using PASESA® in the non-CR and CR groups

There were no significant differences in parameters obtained using PASESA® at baseline between the non-CR and CR groups, as shown in

Table 1
Patient characteristics at baseline in the non-CR and CR groups.

	Non-CR group (n = 10)	CR group (n = 38)
Age, y.	62 ± 13	70 ± 12
Gender (male), n (%)	3 (30)	22 (56)
BMI, kg/m^2	22.2 ± 3.6	23.9 ± 2.8
HTN, %	4 (40)	24 (62)
DM, %	1 (10)	6 (15)
DL, %	4 (40)	29 (74)
CVD		
IHD, %	2 (20)	15 (39)
Heart failure, %	5 (50)	14 (37)
PAD, %	0 (0)	5 (13)
Others, %	3 (30)	4 (10)
NYHA classification		
I/II/III/IV, n (%)	8 (80)/2 (20)/0 (0)/0 (0)	33 (85)/3 (8)/2 (5)/0 (0)
LVEF, %	61 ± 13	60 ± 12
Medication		
ARB/ACE-I, %	3 (30)	29 (74)*
Diuretic, %	3 (30)	10 (26)
β-Blocker, %	3 (30)	19 (49)
CCB, %	5 (50)	15 (39)

BMI, body mass index; HTN, hypertension; DM, diabetes mellitus; DL, dyslipidemia; CVD, cardiovascular disease; IHD, ischemic heart disease; PAD, peripheral arterial disease; NYHA, New York Heart Association; LVEF, left ventricular ejection fraction; ARB/ACE-I, angiotensin II receptor blocker/angiotensin converting enzyme inhibitor; CCB, calcium channel blocker.

* $p < 0.05$ vs. non-CR group.

Fig. 1A–D. In both groups, SBP, HR, AVI and API at 12 months were not significantly different from those at baseline. In the CR group, DBP at 12 months was significantly less than that at baseline. The patients in the CR group were divided into 2 groups according to the average value of SBP at baseline in the CR group: higher SBP (H-SBP, n = 18) and lower SBP (L-SBP, n = 20) (Fig. 2A). In the H-SBP group, SBP after 12 months was significantly lower than that at baseline.

Next, we divided the patients in the CR group into 2 groups according to the average value of AVI in the CR group: H-AVI (n = 16) and L-AVI (n = 22) (Fig. 2B). Again, AVI after 12 months was significantly lower than that at baseline in the H-AVI group, whereas AVI after 12 months was significantly higher than that at baseline in the L-AVI group.

The patients in the non-CR group were also divided into 2 subgroups according to the average values of SBP or AVI at baseline: H-SBP or H-AVI group and L- SBP or L-AVI group. In the H-SBP and H-AVI subgroups in the non-CR group, there were no significant changes in SBP or AVI between baseline and after 12 months (data not shown).

3.3. Evaluation of various hemodynamic parameters obtained using nico PS-501® in the non-CR and CR groups

There were no significant differences in parameters obtained using nico PS-501® at baseline between the non-CR and CR groups, as

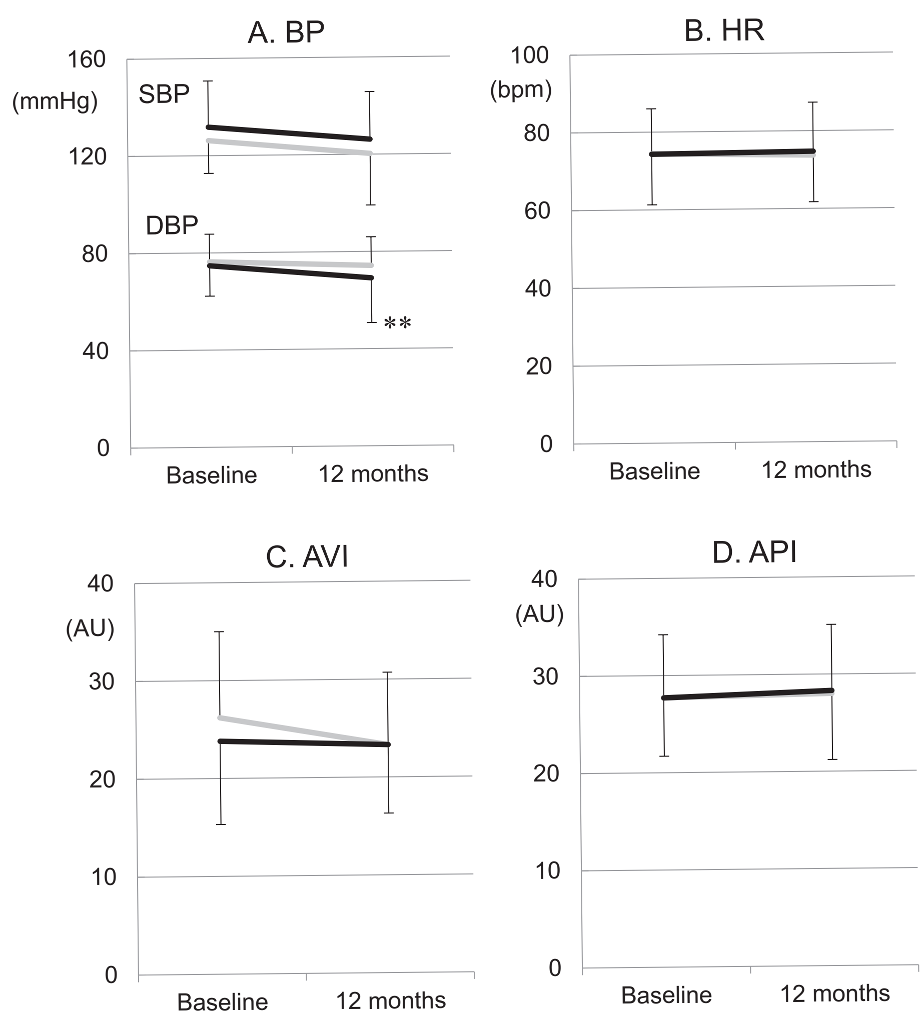

Fig. 1. BP (A), HR (B), AVI (C), and API (D) obtained using PASESA® in the non-CR and CR groups. SBP, systolic blood pressure; DBP, diastolic BP; HR, heart rate; AVI, arterial velocity pulse index; API, atrial pressure volume index; bpm, beats per minute; AU, arbitrary units. Black and gray lines indicate the CR and non-CR groups, respectively. **$p < 0.01$ vs. at baseline.

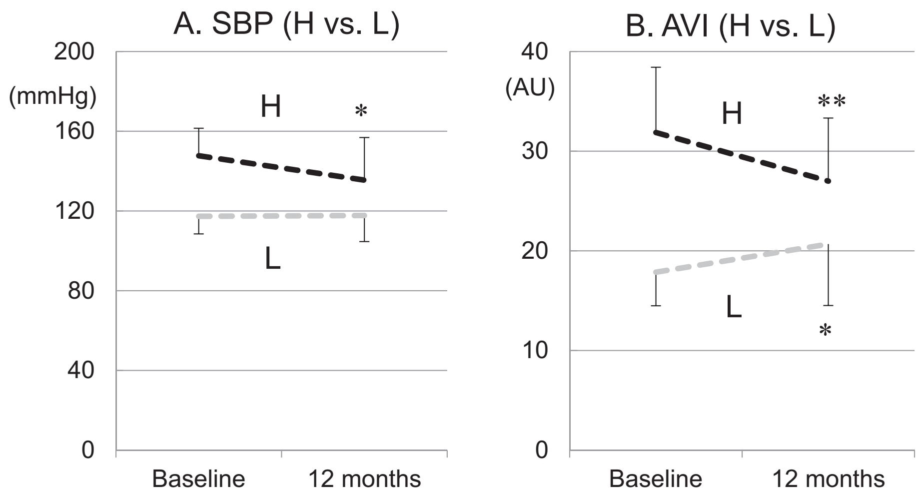

Fig. 2. SBP in the higher (H)-SBP and lower (L)-SBP groups in the CR group (A). AVI in the H-AVI and L-AVI groups in the CR group (B). SBP, systolic blood pressure; AVI, arterial velocity pulse index; AU, arbitrary units. Dotted black and gray lines indicate the H and L groups in the CR group, respectively.**p < 0.01, *p < 0.05 vs. at baseline.

shown in Table 2. Three and 4 patients have the missing data of TPR and SV or CI, respectively. There were no significant changes in the absolute or relative differences in SBP or DBP between arms after 12 months compared to baseline between the groups. In addition, there were no significant changes in PRP or CI between baseline and after 12 months in either group. Mean TPR and SV in the CR group significantly improved after 12 months.

Table 2
Evaluation of various hemodynamic parameters using nico PS-501® in the non-CR and CR groups.

	Non-CR group (n = 10)		CR group (n = 38)	
	Baseline	1 year	Baseline	1 year
SBP absolute, mm Hg	2.0 ± 3.1	4.0 ± 3.0	3.3 ± 4.2	5.5 ± 5.3
Relative, mm Hg	1.4 ± 3.4	2.8 ± 4.1	−0.1 ± 5.3	0.5 ± 7.6
DBP absolute, mm Hg	5.6 ± 5.3	3.8 ± 2.6	4.9 ± 8.6	3.3 ± 3.1
Relative, mm Hg	2.4 ± 7.3	0.8 ± 3.5	−0.9 ± 9.9	−0.1 ± 4.5
PRP, bpm * mm Hg	9630 ± 2422	9874 ± 2775	10,026 ± 2206	9641 ± 1795
Mean TPR, mm Hg/L/min	1637 ± 353	1484 ± 265	1387 ± 550	1196 ± 487*
SV, mL	64.8 ± 7.2	68.7 ± 11.1	72.6 ± 13.4	77.6 ± 13.3*
CI, L/min/m^2	3.2 ± 0.5	3.3 ± 0.4	3.3 ± 0.6	3.5 ± 0.6

SBP, systolic blood pressure; DBP, diastolic blood pressure; PRP, pressure rate product; TPR, total peripheral resistance; SV, stroke volume; CI, cardiac index.
* p < 0.05 vs. at baseline in the CR groups.

The patients in the CR group were divided into 2 groups according to the average value of mean TPR, SV, or CI at baseline in the CR group: H-TPR (n = 13) and L-TPR (n = 22), H-SV (n = 19) and L-SV (n = 15), and H-CI (n = 14) and L-CI (n = 20) groups, respectively (Fig. 3). In the H-TPR group, mean TPR after 12 months was significantly lower than that at baseline (Fig. 3A). In each of the L-SV and L-CI groups, SV and CI after 12 months were significantly higher than those at baseline (Fig. 3B, C). The patients in the non-CR group were also divided into 2 subgroups according to the average values of SV or CI at baseline: H-SV or H-CI group and L-SV or L-CI group. In the L-SV and L-CI subgroups in the non-CR group, there were no significant changes in SV or CI between baseline and after 12 months (data not shown).

3.4. Measurement of HRV using eHEART® in the non-CR and CR groups

Fig. 4A–D shows the parameters of HRV. There were no significant differences in parameters obtained using eHEART® at baseline between the non-CR and CR groups. LF/HF after 12 months was significantly higher than that at baseline in the CR group (Fig. 4C).

The patients in the CR group were divided into 2 groups according to the average value of CVRR at baseline in the CR group: H-CVRR (n = 14) and L-CVRR (n = 24) (Fig. 5). CVRR after 12 months was significantly higher than that at baseline in the L-CVRR group, but significantly lower than that at baseline in the H-CVRR group.

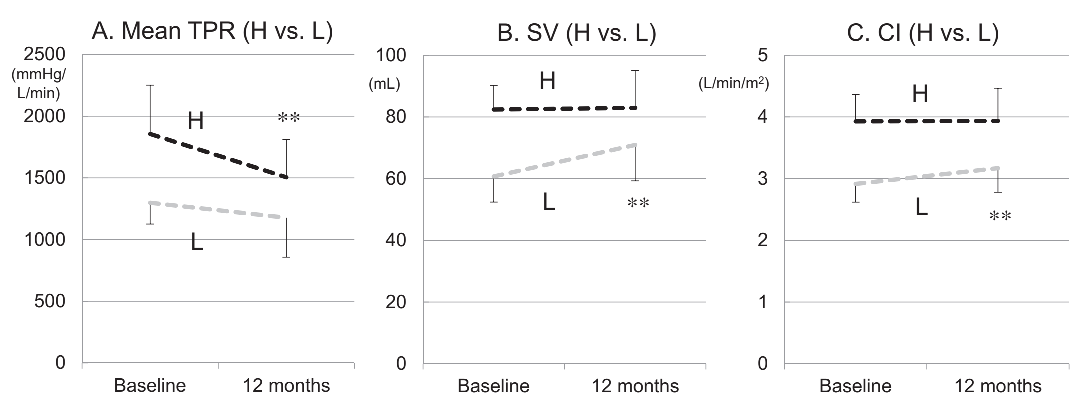

Fig. 3. A) Mean TPR in the higher (H)-TPR and lower (L)-TPR groups in the CR group. B) SV in the H-SV and L-SV groups in the CR group. C) CI in the H-CI and L-CI groups in the CR group. TPR, SV and CI were obtained using nico® in the CR group. Dotted black and gray lines indicate the H and L groups in the CR group, respectively. TPR, total peripheral resistance index; SV, stroke volume; CI, cardiac index. **p < 0.01 vs. at baseline.

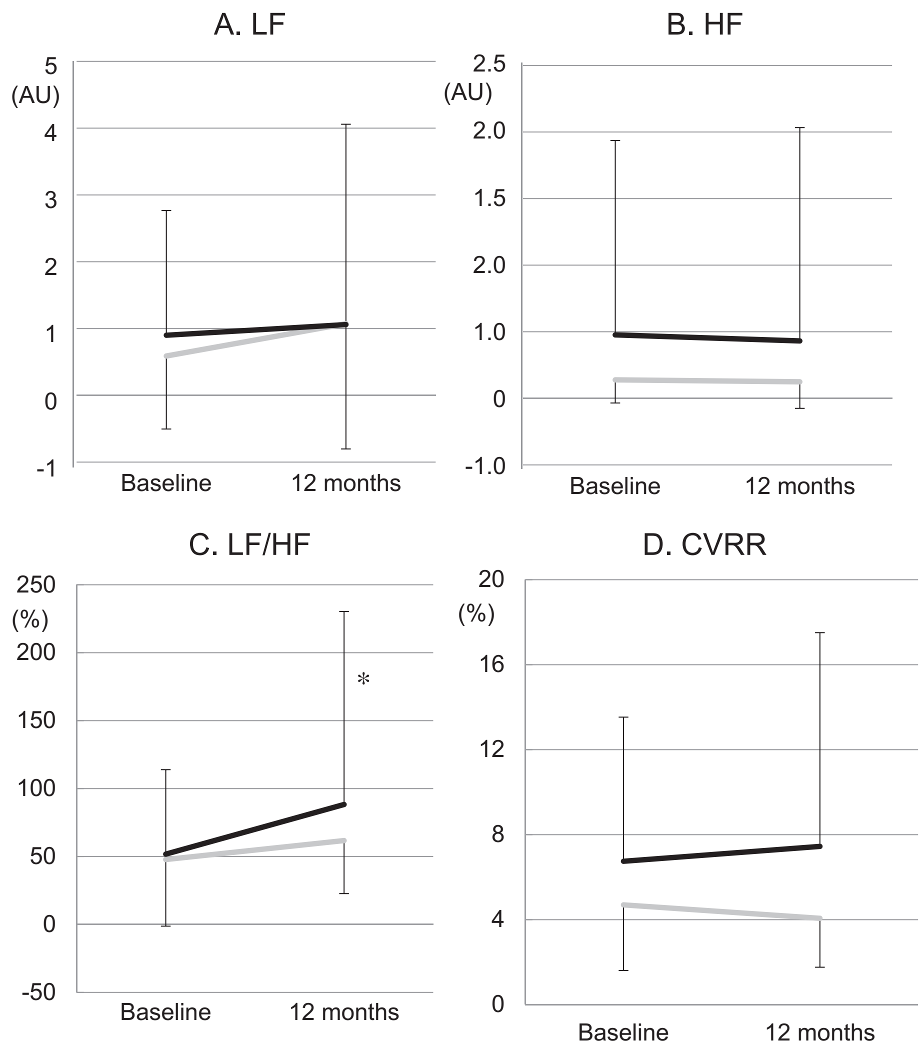

Fig. 4. LF (A), HF (B), LF/HF (C) and CVRR (D) obtained using eHEART® in the non-CR and CR groups. LF, low-frequency; HF, high-frequency; LF/HF, the ratio of LF to HF; CVRR, the coefficient of variation of the R-R interval; AU, arbitrary units. Black and gray lines indicate the CR and non-CR groups, respectively. *p < 0.05 vs. at baseline.

3.5. Associations between ΔAVI and ΔSBP or ΔCI and Δmean TPR in the CR group (Δ = the value after 12 months minus the value at baseline)

Fig. 6 shows the associations between ΔAVI and ΔSBP or Δmean TPR and ΔCI in the CR group. ΔAVI was positively correlated with ΔSBP ($r = 0.501$ $p = 0.001$), and ΔmeanTPR was negatively correlated with ΔCI ($r = -0.645$ $p < 0.001$).

4. Discussion

In this prospective study, we assessed the effectiveness of a 12-month CR program using 3 simple, non-invasive devices (PASESA®, nico PS-501®, eHEART®). First, various parameters, such as SBP, AVI, API, CI, and CVRR, did not change between baseline and 12 months in both the CR and non-CR groups. Interestingly, patients with H-SBP or H-AVI in the CR group, but not those with L-SBP or L-AVI, showed a significant reduction of SBP or AVI, respectively, at 12 months. Patients in the CR group with H-TPR, L-SV, L-CI, or L-CVRR showed significant improvements in their parameters after 12 months.

Based on the results obtained with PASESA®, DBP in the CR group showed a significant reduction after 12 months, and CR produced a significant reduction of SBP after 12 months in patients with higher

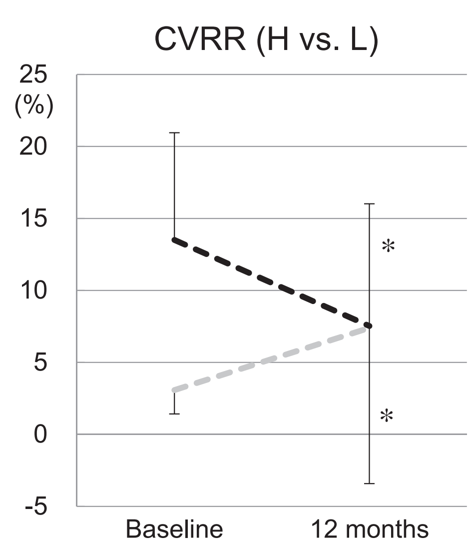

Fig. 5. CVRR in the higher (H)-CVRR and lower (L)-CVRR groups in the CR group. CVRR, the coefficient of variation of the R-R interval. Dotted black and gray lines indicate the H and L groups in the CR group, respectively. *p < 0.05 vs. at baseline.

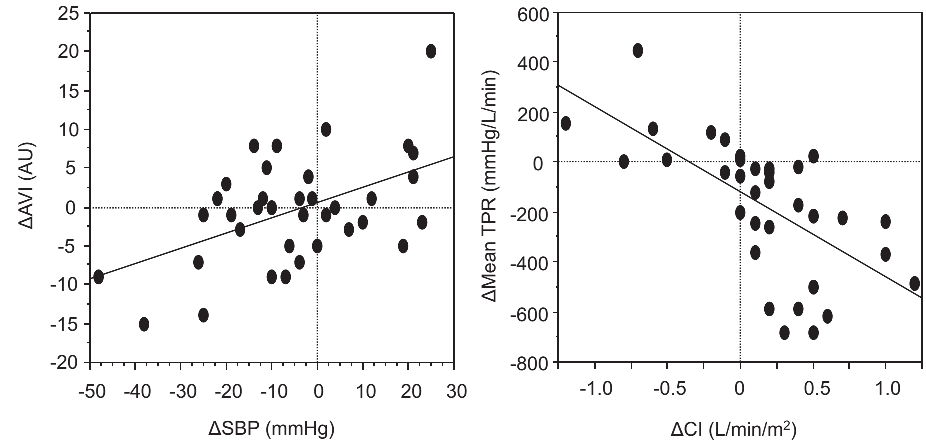

Fig. 6. Associations between ΔAVI and ΔSBP or ΔTPR and ΔCI in the CR group (Δ = the value after 12 months minus the value at baseline). AU, arbitrary units.

levels of SBP. This is reasonable because it is now well-recognized that exercise training in patients with uncontrolled BP reduces BP [10,11]. In addition, a reduction of AVI, which reflects central arterial stiffness [12], was observed in patients with higher levels of AVI in the CR group. Since ΔAVI was positively correlated with ΔSBP in the CR group, a reduction of SBP by CR may improve arterial stiffness.

A nico PS-501® can be used to perform bilateral BP measurements with a synchronal method [5]. In this study, the differences in BP between arms showed a wide variation among patients and we did not identify any clinically significant changes. Mean TPR and SV were significantly improved in the CR group. Although CR did not have beneficial effects on CI in all patients in the CR group, patients in the CR group with L-CI showed significant improvements in their parameters after 12 months. Since BP was calculated by TPR and CI, and since ΔCI was negatively correlated with Δmean TPR in the CR group, a reduction of mean TPR by CR may improve CI.

CVRR in the CR group as assessed by eHEART® was not significantly improved in all patients in the CR group. Patients with H-CVRR in the CR group showed significant improvements in their parameters after 12 months. HRV can provide information on the progression of focal CV atherosclerosis [13]. In the present study, we also confirmed that CR improved parasympathetic modulation. On the other hand, in patients in the CR group with L-CVRR, CVRR significantly increased after 12 months. Six patients in the CR group with L-CVRR had DM, whereas none of the patients in the CR group with H-CVRR had DM. Since the patients with DM showed lower CVRR, CR may have improved CVRR in patients in the CR group with L-CVRR.

There were no significant changes in CPX parameters between baseline and after 1 year. The work rate at AT after 1 year significantly improved compared to that at baseline in the L-work rate group, but not in the H-work rate group. Thus, 2 times/week (8 times a month) of CR in this study may have been enough to improve physical activities in the L-work rate group, although CR programs generally consist of 3 times/week [14]. In addition, when exercise training was initially performed 3 times a week for 8 weeks and then twice a week for 1 year in patients with heart failure, the patients showed improved functional capacity and quality of life [15].

The present study has several limitations. First, this study was at a single center and had a relatively small sample size. Second, there was no randomized prospective follow-up and that initially no sample calculation was performed. Third, the patients received different doses and kinds of medications. Forth, we did not measure the levels of norepinephrine, epinephrine and dopamine in blood to analyze the mechanisms of the beneficial effects of CR. Therefore, a large controlled study should be performed to confirm that CR improves BP, AVI, TPR, SV, CI and CVRR, which can be determined non-invasively.

In conclusion, CR may lead various hemodynamic parameters obtained using simple non-invasive tests to their appropriate levels.

Conflict(s) of interest/disclosure(s)

K.S. is a Chief Director and S.M. is a Director of NPO Clinical and Applied Science, Fukuoka, Japan. K.S. has an Endowed Department of "Department of Molecular Cardiovascular Therapeutics" supported by MSD, Co. LTD. S.M. belongs to the Department of Molecular Cardiovascular Therapeutics supported by MSD, Co. LTD.

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