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RESEARCH ARTICLE

The effect of cardiac rehabilitation on blood pressure, and on left atrial and ventricular functions in hypertensive patients

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Abstract

Purpose: Hypertension is associated with left ventricular (LV) hypertrophy, impaired LV relaxation, and left atrial (LA) enlargement. Cardiac rehabilitation (CR) improves clinical outcomes in a broad spectrum of cardiac disease. The aim of our study was to determine the effect of CR on blood pressure (BP), and on LA and LV functions in hypertensive patients.

Methods: Thirty consecutive hypertensive patients who would undergo CR program, and 38 hypertensive patients who refused to undergo CR program were included. All patients underwent ambulatory BP monitoring and transthoracic echocardiography, which were repeated after completion of the CR program, or 12 weeks later in the control group. LA and LV functions were assessed by both speckle tracking and 3-dimensional echocardiography. N-terminal pro-brain natriuretic peptide (NT-proBNP) levels were assessed before and after CR.

Results: Although initial ambulatory BP values and NT-proBNP levels were similar between the groups, daily, day-time, and night-time BP and NT-proBNP were significantly lower in the CR group after rehabilitation. LA reservoir strain and LV global longitudinal strain of the CR group significantly increased after CR while no significant increase was observed in controls.

Conclusion: CR improves LA and LV strain while lowering BP and should be encouraged in routine management of hypertensive patients.

KEYWORDS

cardiac rehabilitation, hypertension, left atrium, left ventricle, speckle tracking echocardiography

1 | INTRODUCTION

Arterial hypertension remains a major cause of mortality and morbidity worldwide.[1] Despite remarkable advances in treatment and management, hypertensive patients are still at risk for future cardiac events.[2-4] Hypertension-mediated organ damage is becoming increasingly apparent with wider use of imaging.[5] Some types of hypertension-mediated organ damage can be reversed by antihypertensive treatment, especially when initiated early. However, some may become irreversible with long-standing hypertension despite improved blood pressure control.[6,7] Chronically increased left ventricular (LV) workload in hypertensive patients can result in LV hypertrophy, impaired LV relaxation, and left atrial (LA) enlargement, leading to heart failure with preserved ejection fraction.

Lifestyle changes including salt restriction, cessation of smoking, moderation of alcohol consumption, healthy diet, and maintaining an

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ideal body weight with regular physical activity are recommended to all hypertensive patients and to patients with high-normal blood pressure.[8-10] Cardiac rehabilitation (CR) is a structured program including exercise, lifestyle modification, psychosocial support, and education, adapted to the individual conditions of each patient. CR is associated with improved clinical outcomes in a broad spectrum of cardiac disease.[11-13]

The aim of this study was to evaluate the effect of CR on blood pressure, and on LA and LV functions in hypertensive patients.

2 | PATIENTS AND METHODS

This investigation conformed with the principles outlined in the Declaration of Helsinki. The study was approved by the local ethics committee. All participants gave written informed consent before inclusion.

The patients were selected among those who were referred to a CR program between January and June 2017. One hundred consecutive hypertensive patients who were older than 18 years, had normal sinus rhythm, and controlled blood pressure were invited to this prospective study. After exclusion of patients with secondary hypertension (2 patients with primary hyperaldosteronism and 1 patient with pheochromocytoma), grade 3 hypertension (21 patients), moderate or severe valvular pathology (6 patients), functional limitation for physical exercise (2 patients), the remaining 68 patients with grade 1 or grade 2 essential (primary) hypertension were included in the study.

All patients were evaluated in terms of demographic characteristics, concomitant diseases, and cardiovascular risk factors. Hypertension was defined as systolic and/or diastolic blood pressure ≥140/90 mm Hg, previously diagnosed hypertension, or use of any antihypertensive medications. Grading of hypertension was based on the European Society of Cardiology guidelines for arterial hypertension.[8] The assessment and management of the patients were also in accordance with the 2018 ESC/ESH Guidelines for the management of arterial hypertension.[8] Office blood pressure treatment target ranges were 130 or lower (if tolerated) in patients aged 18 to 65 years, and 130 to 139 in patients aged 65 to 79 years. The antihypertensive drugs the patients were taking were noted. All the patients were taking at least one antihypertensive drug, and no change was made in their medications throughout the study. Diabetes mellitus was defined as fasting plasma glucose levels of more than 126 mg/dL in at least two consecutive measurements, previously diagnosed diabetes, or use of antidiabetic medications such as oral antidiabetic agents or insulin. Dyslipidemia was defined as serum total cholesterol ≥200 mg/dL, serum triglyceride ≥150 mg/dL, low-density lipoprotein cholesterol ≥130 mg/dL, previously diagnosed hyperlipidemia, or the use of lipid-lowering medication.

Detailed physical examination was performed. Body mass index (BMI) was calculated. Complete blood count and biochemical tests (fasting glucose, lipid levels, creatinine, N-terminal pro-brain natriuretic peptide [NT-ProBNP] and high-sensitive C-reactive protein [hs-CRP]) were obtained. All patients underwent ambulatory blood pressure monitoring and transthoracic echocardiography.

After initial examination, all patients were recruited to a CR program of 30 sessions for 10 weeks. Thirty patients accepted to participate in the program while 38 patients did not accept due to various reasons (23 patients refused as they were working and could not take excuse from work three times a week for 10 weeks, 11 patients refused due to difficulty in transportation to the rehabilitation center, and 4 patients refused due to living in another city), and they were included as control group.

Biochemistry tests, ambulatory blood pressure monitoring, and transthoracic echocardiography were repeated during the week following the CR program completion, or 12 weeks after initial evaluation as for the control group.

2.1 | Twenty-four-hour ambulatory blood pressure measurement

A Mobil O Graph ambulatory blood pressure monitor, V20 (IEM, Stolberg, Germany) was used for Holter monitoring of daily, daytime and nighttime blood pressure. Measurements were done every 30 minutes from 6 AM to 10 PM and every 60 minutes from 10 PM to 6 AM The cuff was placed around the nondominant arm of patients. Patients were instructed to carry out their usual activities during the day, to go to bed not later than 11 PM and arise not before 7 PM, and to record their activities in a diary (time of going in and out of bed, as well as exercise times during the day). They were instructed to keep their arm still during measurements. Holter measurements were performed during working days (Monday-Friday). Recordings were considered valid if there were at least 24 valid blood pressure measurements at day-time and at least 6 at night-time. If the recording was invalid, the patients were asked to undergo for a repeat Holter monitoring the following day.

During monitoring, patients in whom nighttime mean systolic blood pressures decreased by 10% or more were defined as dippers, and patients with a nighttime mean systolic blood pressures decrease <10% were defined as nondippers. The patients with reverse dipping patterns (nocturnal rise in nighttime blood pressure) or extreme dipping (nocturnal fall in night-time blood pressure greater than 20%) were included in the nondipper group. Blood pressure load was calculated and noted as the percentage of measured values, which were more than 140/90 mm Hg in daytime and more than 120/80 mm Hg in nighttime.

2.2 | Echocardiographic evaluation

All patients and controls underwent a detailed transthoracic echocardiographic examination by a single experienced cardiologist with an Epiq 7 echocardiography device (Philips Medical Systems, Andover, Massachusetts) with its S5-1 transducer (3.5 MHz) for two-dimensional (2D) measurements and its X5-1 transducer (1-3 MHz) for three-dimensional (3D) measurements. Patients were positioned in the left lateral decubitus position. Standard M-mode, 2D, Doppler and

color-coded tissue Doppler images (TDI) were obtained during breath-hold, stored in cine loop format from three consecutive beats, and transferred to a workstation for further offline analysis. Gain settings, filters, and pulse repetition frequency were adjusted to optimize color saturation; a color Doppler frame scanning rate of 100 to140 Hz was used for color TDI images, and grayscale images were acquired at a frame rate of 44 to 82 frames/s. Conventional echocardiographic measurements were performed in accordance with the recommendations of the American Society of Echocardiography guidelines.[14,15]

The LA and LV functions were also assessed by speckle tracking echocardiography (STE) as previously described.[16,17] All images were recorded at a rate of at least 50 frames per second to allow for reliable operation of the software. Myocardial strain was calculated by measuring the change of position of the speckles within a myocardial segment during the cardiac cycle. The assessment of LV global longitudinal strain (GLS) was performed by applying 2D STE to the apical two-, three-, and four-chamber views of the LV. The LV was divided into six segments in each apical view. The value of LV GLS was derived from the average of the six segmental peak systolic longitudinal strain values from each apical views. LA endocardial border was manually traced in apical four-chamber view by composing the six segments. After segmental tracking quality analysis and manual adjustment when required, the strain curves were generated by the software for each atrial segment. The longitudinal LA wall deformation was assessed by measuring the peak values for strain during the contractile, reservoir, and conduit phases (Figure 1). The software used the QRS complex (R-R gating) as the initiation of strain calculation. When the R wave is used, all strain values are positive, and there are two peaks that correspond to reservoir function (first peak between R wave and T wave), and to the atrial contractile function (starting on the P wave), respectively. The difference between the reservoir phase strain and the atrial contraction strain values reflects conduit function.

Real-time 3D echocardiography was performed with acquisition of "full-volume" real-time pyramidal volumetric datasets along four consecutive cardiac cycles. Individuals were instructed to hold their breath and images were coupled with electrocardiographic recordings. Apical two-chamber and four-chamber views were extracted from the pyramidal data set during expiration. LA cavity was included in the pyramidal scan volume. Data sets were digitally stored and analyzed using QLAB software version 9.1 (Philips Medical systems, Andover, Massachusetts). Anatomical landmarks used to calculate LA volumes were manually identified as follows: lateral, septal, anterior, and inferior points of the mitral annulus, and the fifth point at the apex of the LA. Points determined to represent the pulmonary vein ostia or LA appendages were excluded from the measurement. The LA internal endocardial border of each frame was defined by automated processing and manually adjusted for pulmonary vein ostia and LA appendage exclusion. From these data, a three dimensional model of LA volume was generated. The following LA volumes and functions were measured: (a) LA maximum volume (Vmax): at end systole, the time at which the atrial volume was the largest just before the mitral valve opening; (b) LA minimum volume (Vmin): at end diastole, the time at which the atrial volume was at its nadir before mitral valve closure; and (c) LA volume before atrial contraction (Vpre A): the last frame before mitral valve reopening or at the time of the P wave on electrocardiogram (Figure 2). From these three volumes, the following measurements were selected as indices of LA function and calculated as follows: (a) LA total stroke volume (TSV): Vmax–Vmin; (b) LA total emptying fraction (TEF): TSV/Vmax × 100; (c) LA active stroke volume (ASV): Vpre A-Vmin; (d) LA active emptying fraction (AEF): ASV/Vpre A × 100; (e) LA expansion index (EI): TSV/Vmin × 100; (f) LA passive stroke volume (PSV): Vmax – Vpre A; and (g) LA passive emptying fraction (PEF): (Vmax – Vpre A)/Vmax × 100. LA volumes (LAV) were indexed to the body surface area to obtain LA volume indexes (LAVI). Accordingly, TEF and EI were assumed to reflect atrial reservoir function, AEF was assumed to reflect atrial pump function, and PEF was assumed to reflect atrial conduit function.[18]

To assess intraobserver variability, 10 subjects were randomly selected and LV GLS and LA reservoir and conduit strain measurements were repeated by the same investigator who performed all of the strain calculations for the study data. The intraobserver variability for STE analysis was 1.8%, 2.9%, and 2.3% for LV and LA reservoir and conduit strains respectively, in our study.

2.3 | Cardiac rehabilitation program

The CR program included supervised exercise training together with education about prevention from cardiovascular diseases. Advices for lifestyle modifications including a healthy, balanced diet with salt restriction, cessation of smoking, moderation of alcohol consumption, maintaining an ideal body weight with regular physical activity, regular sleep, and dealing with stress were given to each patient, and adherence to these advices was checked each week by a trained nurse.

All patients underwent exercise tolerance test in CR unit. Exercise capacities of patients were assessed with a cycle ergometer Ergoselect 2 model 600 with Opticare software program (Ergoline, Bitz, Germany). Patients were asked to wear comfortable training clothes, not to eat or drink 3 hours prior to their arrival, and stop smoking before the test. Target and maximum heart rate were calculated using Karvoneen formula ([Maximal heart rate – resting heart rate] × Intensity% + resting heart rate) individually for each patient according to his or her age and gender. At the beginning of the test, cycling with 30 W of pedal load and 15 W increment was applied every two minutes with constant pedaling speed of 55 to 65 cycles per minute. The test was stopped if patients reached their target heart rate or wanted to stop due to fatigue. Maximal energy consumption (kcal/min), maximal oxygen consumption in mL/min/kg or the metabolic equivalent of task (MET) (ml/kg/min), maximum pedal load in Watts, total distance, heart rate, and blood pressure values before and after the test were recorded. The data were used to develop individualized rehabilitation program of patients in CR and as a follow-up criterion of fitness parameters.

Initially, the ratio of maximum load to patient's body weight (Watt/kg) was calculated. This ratio was used as an indicator of physical fitness. The values lower than 1.4 W/kg indicated an untrained

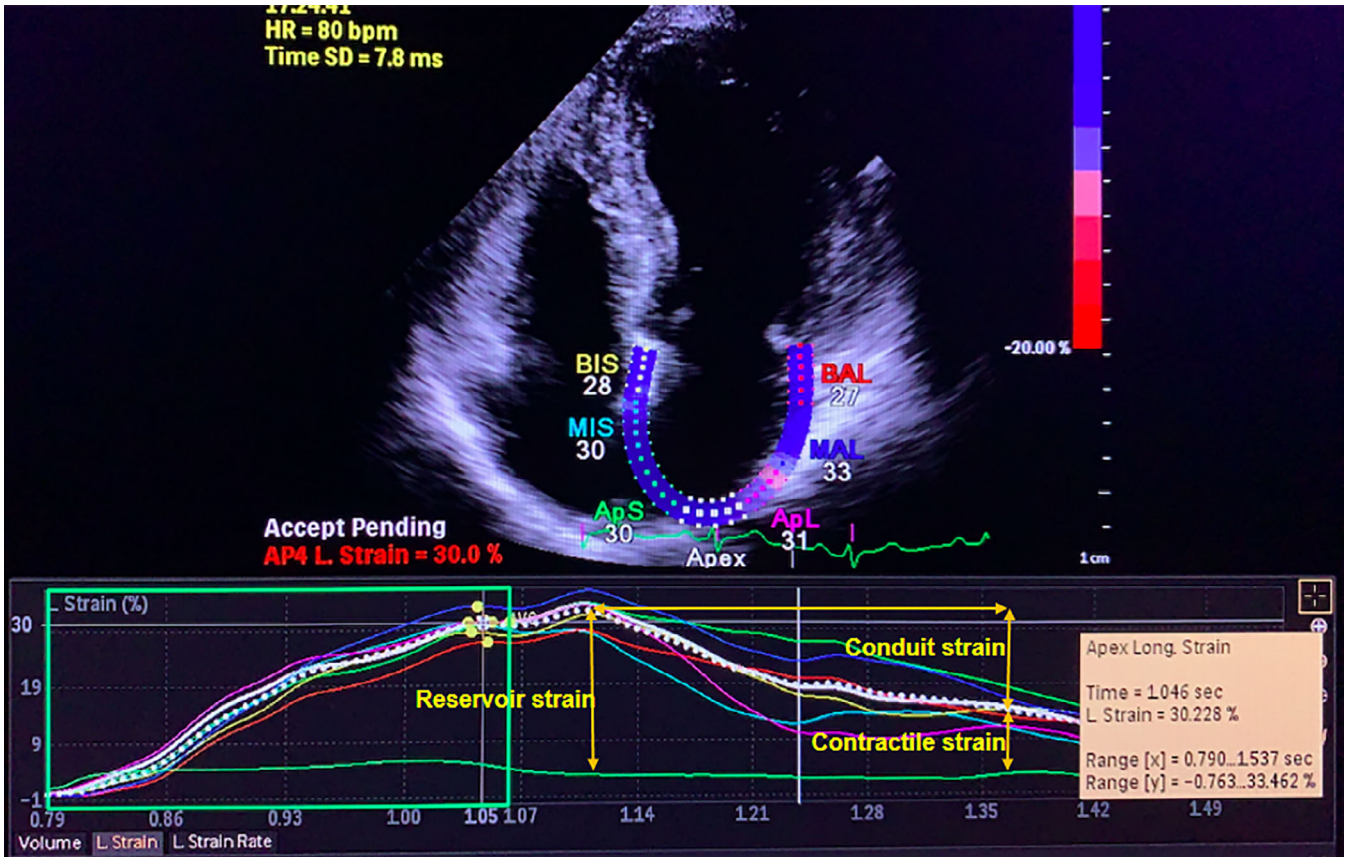

FIGURE 1 Left atrial longitudinal strain curve depicting phasic reservoir (peak), conduit, and contractile strain

person or patients with moderate to high risk for cardiac complications during physical stress, according to the recommendations of the American Heart Association.[19] If the ratio was lower than 1 W/kg, patients started the program with low-intensity intermittent training to provide a better compliance with the program. When the ratio was 1.4 and over, exercise program was continued with constant heart rate (endurance training) method. Individual exercise programs were revised by weekly assessments depending on improvements in physical fitness.

Each training session included reduced-load warming and cooling periods for five minutes. In the intermittent training program, the patients performed low load for 1 minute and maximum load for 1 minute consecutively for 20 minutes. In constant heart rate method, the maximal load at target heart rate was recorded with the exercise testing and the patients exercised without exceeding target heart rate. The target heart rate was kept constant by changing the load automatically.

After cycle ergometer training, each exercise session was finished with stretching and strengthening exercises. Biceps, triceps, deltoid, quadriceps, hamstrings, abductor muscle groups were trained in muscle strengthening program. Strengthening exercises were planned with calculation of 1 repetition maximum method. Maximum load which could be hold by three different large muscle groups of lower and upper extremities was determined. Each muscle was strengthened with 3 × 10 repetitive isotonic contractions with up to 75% resistance of 1 repetition maximum.

CR program was performed 3 days per week for 10 weeks in the hospital. After the program, the patients were encouraged to perform aerobic exercises by themselves during their daily life.

2.4 | Statistical analysis

All statistical tests were performed with the Statistical Package for the Social Science 20.0 for Windows (IBM-SPSS, Chicago, Illinois). Continuous variables were checked for normal distribution by the Kolmogorov-Smirnov test and presented as mean ± SD, while categorical variables were expressed as numbers and percentages. chi-square test or McNemar test was used to compare categorical variables. Student *t*-test or paired sample test were used to compare continuous variables with normal distribution while Mann-Whitney *U*-test or Wilcoxon test were used to compare the continuous variables without normal distribution. Correlation analysis was performed by Spearman's correlation tests. $P < .05$ was considered statistically significant.

3 | RESULTS

The study included 68 consecutive hypertensive patients who were referred to a CR program. Thirty of the patients who accepted to undergo CR program formed the CR group while the remaining

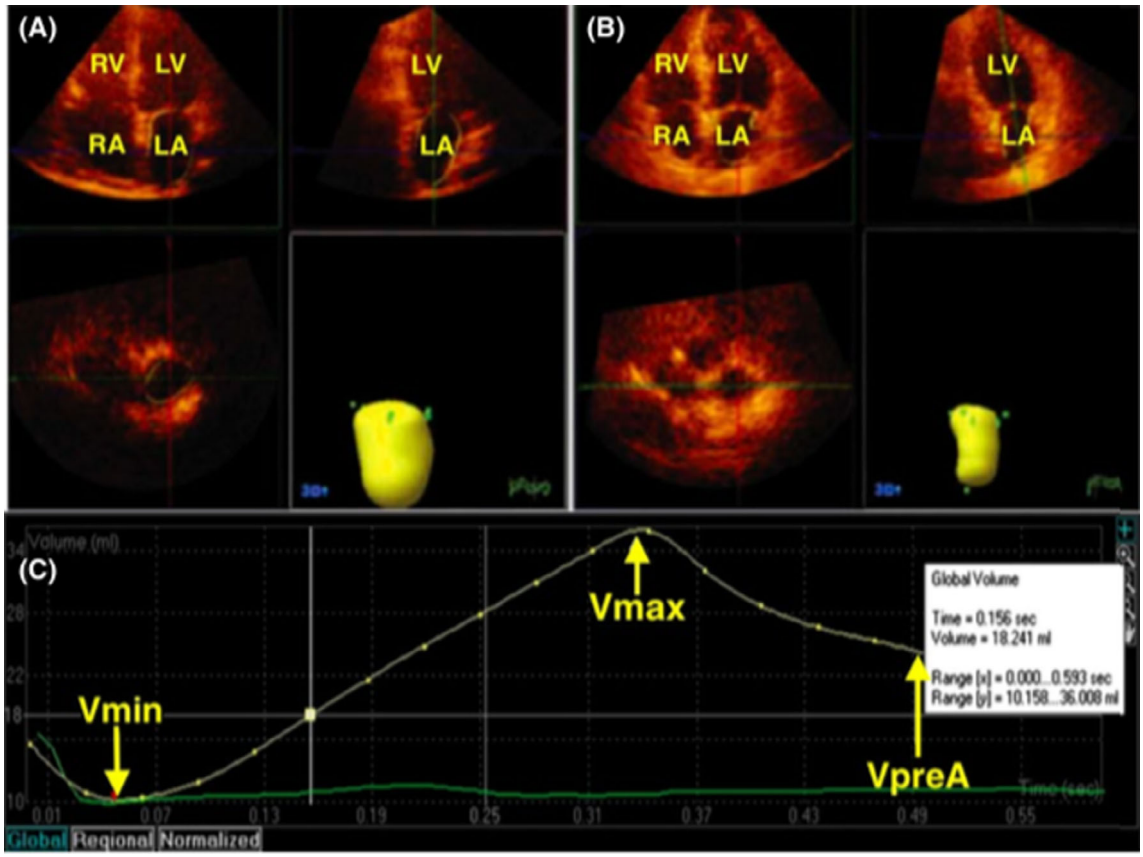

FIGURE 2 Left atrial volume quantification by real-time three-dimensional echocardiography of maximum (A) and minimum (B) left atrial volumes and time-volume curve (C). Vmax: maximum volume; Vmin: minimum volume; and Vpre A: left atrial volume before atrial contraction

TABLE 1 The characteristics of the study patients

	Cardiac rehabilitation group (n = 30)	Controls (n = 38)	P
Female	21 (70%)	21 (55%)	.214
Age (years)	55.9 ± 8.1	56.5 ± 9.0	.768
Coronary artery disease	5 (17%)	2 (5%)	.129
Diabetes mellitus	8 (27%)	5 (13%)	.160
Hyperlipidemia	8 (27%)	7 (18%)	.416
Smoking	10 (33%)	9 (24%)	.379
Medications			
Body mass index (kg/m^2)	31.14 ± 4.53	29.03 ± 4.70	.066
Angiotensin converting enzyme or angiotensin receptor blocker	27 (90%)	35 (92%)	1.00
Calcium channel blocker	14 (47%)	15 (39%)	.552
Diuretics	18 (60%)	22 (58%)	.861
Beta blocker	8 (27%)	6 (16%)	.271

Note: Values are provided as number (percentage) for categorical variables, and mean ± SD for quantitative variables.

38 patients who refused to participate in the program formed the control group. The characteristics and biochemical variables of the patients are shown in Tables 1 and 2, respectively. There was no significant difference in the patients' characteristics between groups. Although the initial NT-ProBNP levels were similar, NT-ProBNP levels decreased significantly with CR program and the CR group had significantly lower NT-ProBNP levels after CR than controls.

TABLE 2 The biochemical variables and body mass index of the patients

	Cardiac rehabilitation group (n = 30)			Controls (n = 38)				
	Before rehabilitation	After rehabilitation	P1[a]	Baseline	At the 12th week	P2[b]	P3[c]	P4[d]
Glucose (mg/dL)	113 ± 44	108 ± 35	0.236	114 ± 43	115 ± 45	0.422	0.608	0.120
Creatinine (mg/dL)	0.73 ± 0.27	0.77 ± 0.31	0.141	0.80 ± 0.20	0.81 ± 0.17	0.674	0.221	0.564
Total cholesterol (mg/dL)	216 ± 40	213 ± 37	0.761	219 ± 39	213 ± 39	0.112	0.391	0.868
LDL cholesterol (mg/dL)	135 ± 33	131 ± 33	0.525	134 ± 35	131 ± 31	0.612	0.736	0.908
HDL cholesterol (mg/dL)	48 ± 9	51 ± 11	0.115	50 ± 9	54 ± 12	0.098	0.498	0.389
Hb (g/dL)	13.4 ± 1.4	13.5 ± 1.5	0.543	13.4 ± 1.4	13.6 ± 1.8	0.431	0.868	0.742
NT-proBNP (pg/mL) mean	119 ± 137	102 ± 132	0.016	126 ± 105	121 ± 125	0.178	0.214	0.009
median (IQR)	86 (134)	69 (89)		98 (119)	89 (127)			
(25th-75th percentile)	(22-156)	(29-118)		(28-147)	(31-158)			
hs-CRP (mg/L)	6.5 ± 4.6	4.1 ± 3.5	0.070	5.8 ± 2.9	5.0 ± 3.3	0.236	0.317	0.265
BMI (kg/m^2)	31.14 ± 4.53	30.12 ± 4.41	<0.001	29.03 ± 4.70	29.01 ± 4.11	0.913	0.066	0.285

Note: Values are provided as mean ± SD.
Abbreviations: BMI, body mass index; Hb, hemoglobin; HDL, high density cholesterol; hs-CRP, high-sensitive C-reactive protein; IQR, interquartile ranges; LDL, low density cholesterol; NT-proBNP, N terminal pro-brain natriuretic peptide.
[a]P1 denotes statistical difference in the biochemical variables before and after cardiac rehabilitation in cardiac rehabilitation group.
[b]P2 denotes statistical difference in the biochemical variables at baseline and 12 weeks later in control group.
[c]P3 denotes statistical difference between biochemical variables of cardiac rehabilitation group before cardiac rehabilitation and biochemical variables of controls at baseline.
[d]P4 denotes statistical difference between biochemical variables of cardiac rehabilitation group after cardiac rehabilitation and biochemical variables of controls at 12 weeks.

TABLE 3 Ambulatory blood pressure values of the patients

	Cardiac rehabilitation group (n = 30)			Controls (n = 38)				
	Before rehabilitation	After rehabilitation	P1[a]	Baseline	At the 12th week	P2[b]	P3[c]	P4[d]
Daily systolic BP (mm Hg)	130 ± 11	126 ± 9	0.006	130 ± 10	129 ± 12	0.845	0.808	0.046
Daily diastolic BP (mm Hg)	82 ± 8	78 ± 7	<0.001	82 ± 10	80 ± 9	0.087	0.945	0.063
Day-time systolic BP (mm Hg)	132 ± 12	128 ± 9	0.024	132 ± 12	131 ± 10	0.612	0.900	0.079
Day-time diastolic BP (mm Hg)	84 ± 8	80 ± 7	0.002	85 ± 11	84 ± 11	0.847	0.690	0.045
Night-time systolic BP (mm Hg)	126 ± 12	121 ± 10	0.005	123 ± 10	124 ± 9	0.774	0.178	0.427
Night-time diastolic BP (mm Hg)	77 ± 8	73 ± 8	0.003	77 ± 10	75 ± 11	0.098	0.957	0.154
Daily systolic BP load (%)	34 ± 23	26 ± 21	0.026	30 ± 22	30 ± 24	0.899	0.528	0.425
Daily diastolic BP load (%)	33 ± 22	25 ± 18	0.008	38 ± 28	34 ± 22	0.064	0.368	0.023
Day-time systolic BP load (%)	32 ± 25	24 ± 20	0.027	29 ± 25	27 ± 29	0.102	0.777	0.287
Day-time diastolic BP load (%)	32 ± 22	25 ± 18	0.039	36 ± 28	31 ± 26	0.177	0.477	0.048
Night-time systolic BP load (%)	47 ± 34	33 ± 31	0.023	35 ± 28	37 ± 29	0.584	0.114	0.805
Night-time diastolic BP load (%)	38 ± 27	28 ± 25	0.010	43 ± 31	37 ± 31	0.071	0.529	0.041
Nondipper (n-%)	23 (76.7%)	17 (%56.7)	0.210	28 (73.7%)	26 (68.4%)	0.500	0.778	0.318

Note: Values are provided as mean ± SD.
Abbreviations: BP, blood pressure.
[a]P1 denotes statistical difference in the ambulatory blood pressure measures before and after cardiac rehabilitation in cardiac rehabilitation group.
[b]P2 denotes statistical difference in the ambulatory blood pressure measures at baseline and 12 weeks in control group.
[c]P3 denotes statistical difference between the ambulatory blood pressure measures of cardiac rehabilitation group before cardiac rehabilitation and ambulatory blood pressure measures of controls at baseline.
[d]P4 denotes statistical difference between the ambulatory blood pressure measures of cardiac rehabilitation group after cardiac rehabilitation and ambulatory blood pressure measures of controls at 12 weeks.

There were significant decreases in daily, day-time, and night-time systolic and diastolic blood pressure means and loads after CR while no significant change was observed in the control group (Table 3). Although the number of nondippers decreased in the CR group, the difference did not reach statistical significance.

TABLE 4 Conventional echocardiographic variables of the patients

	Cardiac rehabilitation group (n = 30)			Controls (n = 38)				
	Before rehabilitation	After rehabilitation	P1[a]	Baseline	At the 12th week	P2[b]	P3[c]	P4[d]
LVD (mm)	49 ± 3	45 ± 4	0.528	45 ± 3	47 ± 3	0.765	0.446	0.512
LVS (mm)	29 ± 3	27 ± 3	0.698	27 ± 3	27 ± 3	0.808	0.488	0.910
IVS (mm)	12 ± 2	11 ± 1	0.003	11 ± 1	11 ± 1	0.760	0.020	0.655
PW (mm)	11 ± 1	11 ± 1	0.113	10 ± 1	11 ± 1	0.482	0.025	0.517
LVEDV (mL)	87 ± 15	87 ± 17	0.649	88 ± 30	88 ± 26	0.711	0.829	0.898
LVESV (mL)	37 ± 8	36 ± 8.	0.596	36 ± 15	36 ± 17	0.914	0.973	0.602
LVEF (%)	57 ± 6	59 ± 5	0.100	59 ± 5	60 ± 5	0.393	0.195	0.254
LVMI (g/m^2)	104 ± 27	97 ± 22	<0.001	93 ± 18	92 ± 19	0.793	0.036	0.062
E wave (m/s)	0.8 ± 0.1	0.8 ± 0.2	0.626	0.7 ± 0.2	0.7 ± 0.2	0.522	0.123	0.618
A wave (m/s)	0.8 ± 0.1	0.8 ± 0.1	0.166	0.8 ± 0.2	0.8 ± 0.1	0.788	0.196	0.950
E wave deceleration time (ms)	199 ± 30	193 ± 38	0.321	205 ± 34	198 ± 31	0.412	0.474	0.528
e' wave (cm/s)	9.7 ± 2.9	9.6 ± 2.5	0.855	9.8 ± 3.1	9.6 ± 3.4	0.799	0.779	0.904
a' wave (cm/s)	11.7 ± 1.9	11.1 ± 2.2	0.064	12.2 ± 2.4	11.9 ± 2.2	0.337	0.394	0.245
s' wave (cm/s)	8.9 ± 1.7	8.6 ± 1.6	0.253	9.3 ± 0.1	9.2 ± 0.1	0.554	0.766	0.244
E/e' lateral	8.1 ± 3.0	8.0 ± 2.6	0.513	7.5 ± 2.3	7.7 ± 2.5	0.695	0.186	0.418

Note: Values are provided as mean ± SD.

Abbreviations: A, late diastolic mitral flow velocity; a', late diastolic velocity of the lateral mitral annulus; E, early diastolic mitral flow velocity; e', early diastolic velocity of the lateral mitral annulus; IVS, interventricular septum thickness; LVD, left ventricular end-diastolic diameter; LVEDV, left ventricular end-diastolic volume; LVEF, left ventricular ejection fraction; LVESV, left ventricular end-systolic volume; LVS, left ventricular end-systolic diameter; PW, posterior wall thickness; s', systolic velocity of the lateral mitral annulus.

[a]P1 denotes statistical difference in the conventional echocardiographic variables before and after cardiac rehabilitation in cardiac rehabilitation group.

[b]P2 denotes statistical difference in the conventional echocardiographic variables at baseline and 12 weeks in control group.

[c]P3 denotes statistical difference between the conventional echocardiographic variables of cardiac rehabilitation group before cardiac rehabilitation and the conventional echocardiographic variables of controls at baseline.

[d]P4 denotes statistical difference between the conventional echocardiographic variables of cardiac rehabilitation group after cardiac rehabilitation and the conventional echocardiographic variables of controls at 12 weeks.

TABLE 5 Speckle tracking echocardiography (STE) and 3D echocardiographic variables of the patients

	Cardiac rehabilitation group (n = 30)			Controls (n = 38)				
	Before rehabilitation	After rehabilitation	P1[a]	Baseline	At the 12th week	P2[b]	P3[c]	P4[d]
LAVmax (mL)	52.3 ± 14.7	50.5 ± 14.1	0.333	47.5 ± 9.9	46.8 ± 8.9	0.576	0.113	0.482
LAVmin (mL)	20.2 ± 9.4	19.5 ± 9.4	0.602	18.1 ± 5.7	18.8 ± 7.2	0.660	0.252	0.396
LAVpreA (mL)	32.1 ± 13.3	32.6 ± 13.9	0.757	31.5 ± 7.5	32.3 ± 8.7	0.590	0.829	0.913
LA TSV (mL)	31.5 ± 8.4	31.0 ± 8.4	0.623	29.4 ± 7.9	30.1 ± 6.1	0.477	0.291	0.408
LA TEF (%)	62.6 ± 10.4	62.5 ± 9.8	0.943	61.8 ± 9.1	60.9 ± 9.6	0.648	0.743	0.538
LA PSV (mL)	20.2 ± 6.7	18.2 ± 5.6	0.232	16.1 ± 7.6	17.6 ± 5.8	0.305	0.114	0.402
LA PEF (%)	40 ± 12.5	37.1 ± 11.7	0.263	33.5 ± 11.9	35.5 ± 8.9	0.318	0.064	0.196
LA ASV (mL)	11.7 ± 5.9	13.1 ± 7.2	0.209	13.5 ± 5.3	13.1 ± 5.0	0.890	0.194	0.868
LA AEF (%)	36.8 ± 11.8	39.8 ± 11.9	0.992	42.5 ± 13.2	40.6 ± 12.7	0.788	0.074	0.760
Expansion index	155.7 ± 76.4	158 ± 65.2	0.753	162 ± 66.6	162 ± 71.6	0.908	0.398	0.557
LA reservoir strain (%)	31.4 ± 8.8	34.7 ± 9.6	0.020	34.9 ± 10	33.7 ± 14.6	0.546	0.133	0.818
LA conduit strain (%)	13.9 ± 6	15.9 ± 8.9	0.149	17.2 ± 7.6	18.4 ± 7.6	0.391	0.064	0.098
LVGLS (%)	19.8 ± 2.5	20.7 ± 2.2	0.002	20.0 ± 1.8	20.4 ± 2.1	0.105	0.634	0.239

Notes: Values are provided as mean ± SD.

Abbreviations: LA AEF, left atrium active emptying fraction; LA ASV, left atrium active stroke volume; LA PEF, left atrium passive emptying fraction; LA PSV, left atrium passive stroke volume; LA TEF, left atrium total emptying fraction; LA TSV, left atrium total stroke volume; LAVmax, Left atrium maximum volume; LAVmin, left atrium minimum volume; LAVpreA, left atrium volume before atrial contraction; LVGLS, left ventricular global longitudinal strain.

[a]P1 Denotes statistical difference in the STE and 3D echocardiographic variables before and after cardiac rehabilitation in cardiac rehabilitation group.

[b]P2 Denotes statistical difference in the STE and 3D echocardiographic variables at baseline and 12 weeks in control group.

[c]P3 Denotes statistical difference between the STE and 3D echocardiographic variables of cardiac rehabilitation group before cardiac rehabilitation and the STE and 3D echocardiographic variables of controls at baseline.

[d]P4 Denotes statistical difference between the STE and 3D echocardiographic variables of cardiac rehabilitation group after cardiac rehabilitation and the STE and 3D echocardiographic variables of controls at 12 weeks.

The conventional, STE, and 3D echocardiographic variables of the patients are given in Tables 4 and 5, respectively. The interventricular septum thickness and LV mass index (LVMI) decreased significantly after CR. Although there was no significant change in 3D LA volumes, LA reservoir strain, and LV GLS increased significantly after CR while there was no significant change in LA and LV strain values in the control group. No significant correlation was found between the final blood pressure values or decrease in blood pressure and strain values.

4 | DISCUSSION

CR improves functional capacity and cardiac function in many cardiac diseases. In our study, we explored the effect of CR on blood pressure, LA, and LV functions in hypertensive patients. We found that CR was associated with lower ambulatory blood pressure measures and NT-proBNP levels, and increased LV GLS and LA reservoir strain.

Exercise training has been shown to significantly reduce blood pressures. In their meta-analysis, Cornellissen et al[20] demonstrated that exercise training was associated with decrease in systolic and diastolic blood pressures. Similarly, Kargarfard et al[21] showed that exercise decreased blood pressures in patients with myocardial infarction and suggested that it was safe to perform exercise training in those patients. Blood pressure reduction with exercise may be associated with baroreceptor resetting related to repeated exposure to the established vasopressor response.[22,23] Another possible mechanism may be the decrease in the resting heart rate with concomitant decrease in catecholamines in circulation such as norepinephrine and endogenous ouabain-like substance with exercise.[24,25] Our study showed that CR was associated with the decrease of both the daytime and night-time systolic and diastolic blood pressures and the blood pressure loads in hypertensive patients. Although we failed to show a significantly improvement in dipping status, the number of nondippers decreased in CR group.

Early subclinical echocardiographic abnormalities are present in systolic and diastolic LV function in hypertensive patients.[26] These changes have been suggested to convey significant incremental prognostic information for risk assessment in hypertensive patients.[27] Beneficial effect of exercise training in medically treated hypertensive patients with LV diastolic dysfunction and improving of myocardial function with aerobic exercises have been demonstrated in previous studies.[28,29] Leggio et al[26] studied the effect of exercise training on systolic-diastolic ventricular dysfunctions in hypertensive patients, and found that exercise training had positive impact on both ventricular systolic and diastolic functions in patients who were pharmacologically treated for hypertension. However, there is lack of data about the effect of CR on LV GLS and LA reservoir and conduit strains in hypertensive patients. In our study, although there were no changes in conventional echocardiographic systolic and diastolic LV variables and 3D LA phasic volumes, CR program significantly increased LV GLS and LA reservoir strain. Similar to our study, Acar et al[30] studied the effect of CR in LV and LA functions in patients with myocardial infarction and found that CR increased the LA strain in patients with myocardial infarction due to functional improvement in LV diastolic functions. Improvement in LV diastolic functions after exercise causes reverse LA remodeling, which improves LA functions afterwards. This may be important in the prevention of atrial fibrillation. Atrial fibrillation is a product of electrical and structural atrial remodeling, autonomic perturbations, impaired myocardial mechanics, and dysmetabolism. Hypertension is associated with a 1.8-fold increase in the risk of developing new-onset atrial fibrillation. The improvement of blood pressure, LV and LA functions by CR may prevent the development of atrial fibrillation in these patients.

NT-ProBNP levels are improved by CR in heart failure patients.[31,32] Even a short-term CR of 15 days was associated with a significant decrease in NT-ProBNP levels in patients who had prior cardiac surgery.[33] Reductions in NT-ProBNP may be explained by the neurohormonal changes and blood pressure reductions with exercise. Exercise training ameliorates the sympatho-vagal balance and reduces catecholamines and brain natriuretic peptides.[34]

4.1 | Study limitations

The major limitation of this study is its small sample size and its single center design. The LA functions and volumes were assessed by speckle tracking and 3D echocardiography. Validation of LV and LA functions and volumes by cardiac magnetic resonance imaging might strengthen our results. We did not randomize the patients into CR group and those who refused to participate into CR program were included as control group. Adherence to medication and lifestyle modifications were not evaluated in patients who refused CR. Adherence might be poor in these patients, which might have affected the study results. Similarly, many patients refused to participate because they were working. Their professional activity, especially if it took precedence over their health, might explain the higher blood pressure compared to patients in the rehabilitation group. Ambulatory blood pressure monitoring and transthoracic echocardiography were repeated within the following week after the CR program and long term effect of CR had not been evaluated. Long-term follow up with larger and randomized sample is needed to determine the clinical relevance of CR and the observed changes in strain.

5 | CONCLUSION

CR is associated with improvement not only in blood pressure control but also in both LV and LA functions, and should be recommended to patients with grade 1 and grade 2 primary hypertension. The prolonged effect of CR on blood pressure and myocardial functions needs to be explored in larger hypertensive cohorts.

CONFLICT OF INTEREST

The authors declare no potential conflict of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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