The Egyptian Journal of Hospital Medicine (January 2023) Vol. 90 (2), Page 3660-3665

Clinical Utility of Echocardiography in Heart Failure Patients with Preserved Ejection Fraction and its Correlation with 24-Hour Blood Pressure Variability

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ABSTRACT

Background: Cardiologists from all around the world are now debating the subject ejection fraction is still preserved in heart failure (HFpEF). HFpEF has a wide range of composite etiology and pathophysiologic processes. While the main worry is diastolic dysfunction, which includes aberrant passive stiffness that is increased while actively relaxing.
Objective: The present study aimed to establish the connection between 24-hour Blood Pressure Variability and tolerance patients with heart failure whose ejection fraction has remained stable should exercise.
Patients and methods: A case control study was conducted on 120 patients with typical symptoms and signs of heart failure, whose left ventricular ejection fraction (LVEF) ≥50% at Zagazig University Hospital from February 2020 to January 2021. The study recruited 80 patients with HFpEF and 40 control subjects. The search strategy targeted subjects with normal echocardiogram. **Results**: HFpEF patients with reduced exercise capacity had higher BPV index values compared with those with good exercise tolerance. Additionally, fractional shortening time (6 Minute Walking Test) was negatively correlated with LAVI, E/e' ratio and left ventricular desynchrony BPV index was very excellent independent predictor of decreased exercise capacity in addition to left ventricular desynchrony. BPV index ≥10.65 mmHg and Ts-SD ≥31.5 were the ideal cut-off values for identifying patients with impaired exercise ability with HFpEF.
Conclusion: Use of BPV along with comprehensive echocardiographic assessment including LAVI and e` as important and feasible tool in diagnosis and people with HFpEFs prognosis.
Keywords: Heart Failure, Blood Pressure, Systolic blood pressure, Diastolic blood pressure, Preserved Ejection Fraction, Case control study, Zagazig University.

INTRODUCTION

Heart failure (HF), which has high rates of morbidity, death, and hospitalization, is a serious public health problem [1]. 50% of hospitalized heart failure (HF) patients have heart failure with preserved ejection fraction (HFpEF), but estimates of the severity of the condition vary due to comorbidity and ill-defined diagnostic criteria, and different types of institutions [2]. Comprehensive echocardiograms were not used in earlier registry studies of the HF epidemiology, and they infrequently described the underlying HF subtype. While HFrEF patients' survival has increased over time as a result of advancements in therapy, HFPEF patients' survival has not changed significantly [3,4]. Due to our limited understanding of its etiology and the lack of solid evidence that any treatment may change its natural course, HFpEF does, in fact, continue to be a difficult disease [5].

Despite having a normal ejection fraction, patients with HFpEF frequently exhibit exercise intolerance and dyspnea. Uncertainty exists regarding the pathophysiology. There is debate concerning the association of the systolic function of the left ventricle (LV) and/or the dyssynchrony of the left ventricle with blood pressure (BP) in those patients. The current study aimed to evaluate the 24-hour variability of blood pressure in people with maintained ejection fraction who have heart failure and the association between that variability and the patients' echocardiographic results and exercise tolerance. Also, in individuals with HFPEF, our study examined the relationship between the left ventricle (LV), fractional shortening time (6 Minute Walking Test: 6MWD), subclinical systolic dysfunction, and dyssynchrony.

PATIENTS AND METHODS

A case control study was conducted on 120 patients with typical symptoms and signs of heart failure, whose left ventricular ejection fraction (LVEF) ≥50% at Zagazig University Hospital from February 2020 to January 2021.

Eighty patients with HFpEF were included, and their data were compared to those of 40 healthy control volunteers.

Patients were recruited when they had left ventricular ejection fraction (LVEF) less than 50% and echocardiography revealed diastolic dysfunction (mitral inflow E/A ratio, e′ measured at the mitral annulus, and e′ ratio), in addition these were signs and symptoms of HF. Those with cognitive impairment, atrial fibrillation, severe hepatic disease, severe renal impairment, hyperthyroidism, arthritis, ankle, knee, or hip injuries, or muscle atrophy were not included in the study. Those who have any problems that could be fatal, such as those whose systolic blood pressure (SBP) is more than 180 mm Hg or whose diastolic blood pressure (DBP) larger than 100 mm Hg, resting heart rate greater than 120, or drug or alcohol addiction, were also ineligible. Those who had recently undergone a myocardial infarction, unstable angina, had a pacemaker implanted, had an enlarged LV dimension, or had valvular heart disease were also rejected.

Received: 27/10/2022
Accepted: 30/12/2022

Based on the findings of the 6MWT, patients were divided into two groups; A population with a lower tolerance for exercise (6MWT distance <300 meter) and a group of good exercise tolerance (6MWT distance ≥ 300 meter).

Standard echocardiography

The American Society of Echocardiography's (ASE) transthoracic M mode, two-dimensional (2-D), pulsed-wave, continuous wave, color-flow, and tissue Doppler imaging (TDI) recommendations were used to evaluate each participant [6]. The experiments were carried out at a depth of 16 cm with a 2 MHz to 4 MHz transducer utilizing the system GE Vivid-7 (GE Vingmed, Norway). A single-lead ECG recording was made continuously throughout the echocardiogram. the left atrial volume index, transmitral blood flow, and mitral annular tissue velocities; the LV structure, which comprises the LV dimensions, wall thickness, and mass index; and the systolic function, which includes the EF, were all statistically evaluated. LV endocardial borders were manually drawn for the apical 4 and 2 chamber views, at end diastole and end systole, and the modified biplane Simpson rule was employed to calculate LV volumes [7].

In order to determine the left atrial volume index, the left atrial volume was measured from the apical 2 and 4 chamber views using the biplane area-length technique (LAVI). The E/e′ value was measured from the septal and lateral sites of the mitral annulus and the average was obtained. Mitral inflow velocity was evaluated by pulsed wave Doppler from the apical 4-chamber view, by positioning the sample volume at the tip of the mitral leaflets. E/e′ ratio was calculated as E wave divided by E/e′ [8].

Ethics Approval:

The protocol of the present study was approved by both the Institutional Review Board [IRB] and the local ethics committee at Zagazig University's Faculty of Medicine. Before enrolling, each participant completed an informed consent form. This study was executed according to the code of ethics of the World Medical Association (Declaration of Helsinki) for studies on humans.

Statistical Analysis

The coding, entry, and analysis of historical data, fundamental clinical examinations, laboratory investigations, and outcome measurements were all done use the Excel programme. The collected data were introduced and statistically analyzed by utilizing the Statistical Package for Social Sciences (SPSS) version 20 for windows. Qualitative data were defined as numbers and percentages. Chi-Square test and Fisher's exact test were used for comparison between categorical variables as appropriate. Quantitative data were tested for normality by Kolmogorov-Smirnov test. Normal distribution of variables was described as mean and standard deviation (SD), and independent sample t-test was used for comparison between groups. P value ≤0.05 was considered to be statistically significant.

RESULTS

Regarding left ventricular dyssynchrony, the results showed that all systolic asynchrony parameters were significantly higher among patients with HFpEF when compared with healthy control subjects; Ts-SD-6 and Ts-SD-12 **(Table 1)**.

Table 1. LV Dyssynchrony parameters comparison between HFpEF patients and control.

Variable	Patients (n. 80)	Control (n. 40)	t-test	P-value
Ts-6	67.5 ± 29.25	49.6 ± 21.5	8.671	0.00**
Ts-SD-6	30.20 ± 9.38	21.62 ± 3.27	6.667	0.00**
Ts-12	95.7 ± 41.8	42.7 ± 13.5	8.671	0.00**
TS-SD-12	33.53 ± 11.36	13.56 ± 4.17	6.667	0.00**

Table 2 showed that all ambulatory blood pressure monitoring parameters are significantly elevated in patients with HFpEF in comparison to control subjects**.**

Table 2. Ambulatory blood pressure monitoring data comparison between HFpEF patients and control.

Variable	Patients (n. 80)	Control (n. 40)	t-test	P-value
SD day systolic readings	12.45 ± 4.06	8.26 ± 0.97	6.782	0.00**
SD day diastolic readings	9.34 ± 2.89	6.70 ± 1.29	6.498	0.00**
SD night systolic readings	11.51 ± 3.92	8.37 ± 0.80	6.003	0.00**
SD night diastolic readings	9.02 ± 2.45	7.21 ± 0.95	5.565	0.00**
BPV index	11.01 ± 3.72	7.95 ± 0.92	6.111	0.00**

The percentage of abnormal 6MWT among patients was 41.2%, while no subject had abnormal test among controls **(Table 3).** Comparing the 6MWT distance between HFpEF patients and controls, it was shown that the 6MWT distance was significantly reduced in HFpEF patients.

Table 3. 6 MW distance comparison between HFpEF patients and control.

Variable		Patients (n. 80)	Control (n. 40)	t-test	P-value
6 MW distance		386.68 ± 125.0	534.39 ± 8.15	7.967	0.00**
Reduced	N	33	0	31.44	0.00**
	%	41.2%	0.0%		
Normal	N	47	58		
	%	58.8%	100.0%		
Total	N	80	58	---	
	%	100.0%	100.0%		

As regards left ventricular dyssynchrony parameters, **table 4** shows that Ts SD and Te SD were significantly higher among HFpEF with reduced 6 MWTD.

Table 4. LV Dyssynchrony parameters comparison between patients with abnormal 6MWT versus those with normal 6MWT.

Variable	Patients with reduced exercise tolerance (N=33)	Patients with good exercise tolerance (N=47)	t-test	P-value
Ts-6	81.3 ± 45.5	48.5 ± 13	8.671	<0.001
Ts-SD-6	39.54±4.65	15.68±5.08	6.667	<0.001
Ts-12	115.9 ± 53.5	73.2 ± 30.5	8.671	<0.001
TS-SD-12	58.96±6.81	23.63±5.43	6.667	<0.001

Ts = time to peak tissue velocity; Ts-SD-12 = standard deviation of Ts of the 12 LV segments; Ts-12 = maximal difference in Ts between any 2 of the 12 LV segments; Ts-SD-6 = standard deviation of Ts of the 6 basal LV segments; Ts-6 = maximal difference in Ts between any 2 of the 6 basal LV segments.

Table 5 represents the ABPM data among patients with reduced 6MWTD compared with those with normal 6MWTD. SD day systolic readings, SD day diastolic readings, SD night systolic readings, SD night diastolic readings and BPV index were significantly higher among HFpEF patients with reduced 6 MWTD.

Table 5. Ambulatory blood pressure monitoring data comparison between patients with abnormal 6MWT versus those with normal 6MWT.

Variable	Patients with reduced exercise tolerance (N=33)	Patients with good exercise tolerance (N=47)	t-test	P-value
SD day systolic readings	17.66 ± 1.58	8.79 ± 1.36	26.750	<0.001
SD day diastolic readings	12.42 ± 0.67	7.18 ± 1.57	17.949	<0.001
SD night systolic readings	15.66 ± 2.19	8.59 ± 1.39	17.637	<0.001
SD night diastolic readings	11.57 ± 1.18	7.23 ± 1.20	15.977	<0.001
BPV index	14.85 ± 1.92	8.31 ± 1.78	15.636	<0.001

BPV index could efficiently predict reduced exercise tolerance in patients with HFpEF with a cut-off value of ≥10.65 mmHg, which had the highest area under the curve (AUC= 0.979, with sensitivity of 95.0%; specificity, 98.3%; and 95% confidence interval [CI] = 0.937 - 0.995; P<0.001) **(Figure 1).** Furthermore, Ts-SD-12 could efficiently predict reduced exercise tolerance in patients with HFpEF with a cut-off value of ≥42.5 msec. which had the highest area under the curve (AUC= 0.97, with sensitivity of 90.0%%; specificity, 97.5% and 95% confidence interval [CI] = 0.931 - 0.985; P<0.001) **(Figure 1)**. LAVI could efficiently predict reduced exercise tolerance in patients with HFpEF with a cut-off value of ≥34.5 mmHg, which had the highest area under the curve (AUC=0.925, with sensitivity of 90%; specificity, %; and 97.5% confidence interval [CI] = 0.87.5 -0. 915; P<0.001) **(Figure 1)**.

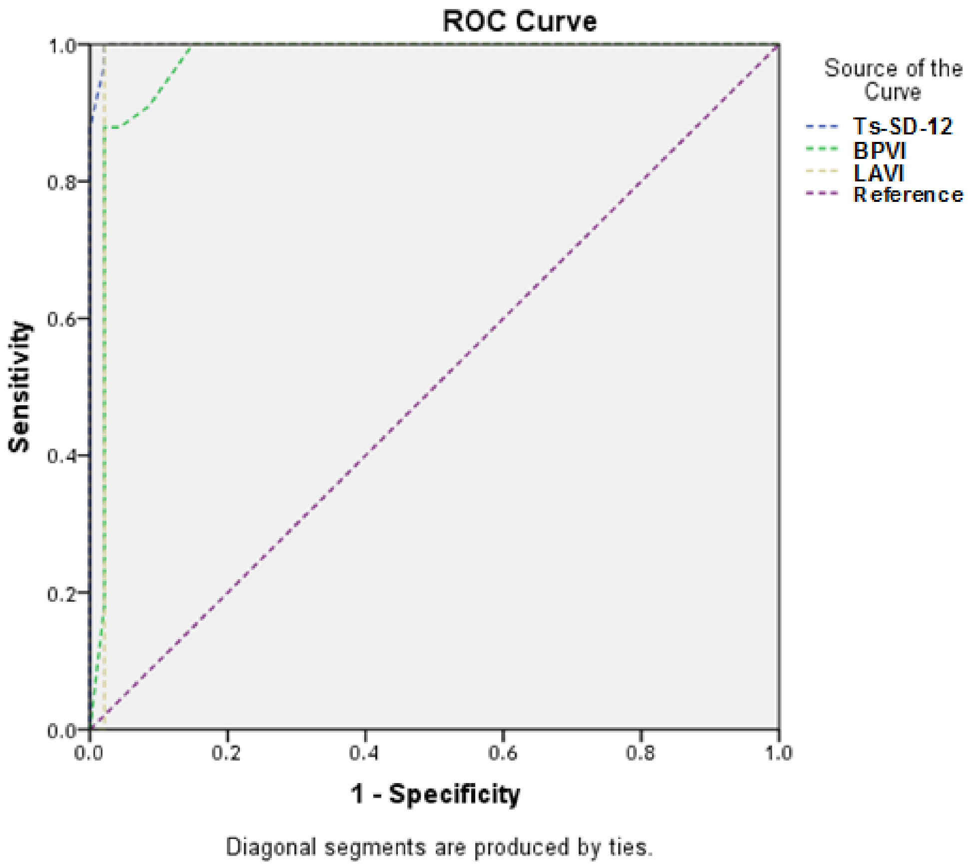

Figure 1. ROC curve analyses for prediction of reduced exercise tolerance in HFpEF patients and each of Ts-SD-12, BPVI and LAVI.

At multivariate logistic regression analysis, showed that LAVI (P<0.03), Ts-SD-12 (P<0.001) and BPV index (P<0.001) were significant independent predictors for reduced 6MWT in patients with HFpEF (**Table 6**).

Table 6. Multivariate logistic regression for independent predictors for reduced 6MWT.

Variable		Wald	P-value	OR	95% confidence interval	
					Lower	Upper
	Obesity	2.095	0.102	1.527	0.815	7.528
	LAVI	3.135	<0.03	3.254	1.254	11.528
	E/e	2.145	0.108	1.507	0.854	12.524
	Ts SD-12	4.856	<0.001	4.927	2.145	10.635
	Ts SD-6	2.536	0.0745	3.386	0.985	13.362
	BPV index	5.051	<0.00	5.019	1.859	10.874

LAVI: Left atrial volume index; Ts-SD-12: standard deviation of Ts of the 12 LV segments; Ts SD-6: standard deviation of Ts of the 6LV segments BPV: blood pressure variability.

DISCUSSION

According to our research, there is a significant link between variations in blood pressure and left ventricular function dyssynchrony. In addition, the BPV index and LV dyssynchrony showed a strong connection. It's interesting to note that in patients with HFpEF, both LV dyssynchrony and BPV index were independent predictors of decreased exercise tolerance.

Our results agree with **Lee *et al.*** [9] who demonstrated that due to the strong correlation between LV diastolic mechanical dyssynchrony and the degree of diastolic dysfunction and filling pressure, diastolic dyssynchrony may be a contributing factor for acute ischemia and HFpEF in individuals with acute coronary syndromes (i.e., E/e'). It's interesting that in that study, there was no indication of such a connection for systolic mechanical dyssynchrony. Conversely, the observational study conducted by **Biering-Sørensen *et al.*** [10]**,** which revealed that, According to speckle-tracking echocardiography, As LV mechanical dyssynchrony is not a reliable indicator of worsening, mechanical dyssynchrony is not anticipated to be a significant mechanism generating HFpEF outcomes in this condition. This contradiction was answered by others who looked at patients HFpEF participants in the Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist (TOPCAT) experiment who were also whose dyssynchrony was evaluated by strain analysis prior to randomization. Also, they stated that due to non-DICOM imaging format, missing views, and subpar picture quality, strain analysis was not possible in 55% of TOPCAT echocardiographic trials. Moreover, a significant portion of the study sample lacked deformation data from the apical 4- and 2-chamber views as well as strain data from the parasternal short axis view due to a variety of missing data.

However, prior research revealed that improvements in LV filling and filling pressures associated with CRT are typically merely the outcome of enhanced hemodynamics of load-dependent parameters seen in individuals with an aberrant baseline hemodynamic profile [11].

Patients with HFpEF have described Relationship between exercise-induced torsional dyssynchrony and decreased functional capacity by **Tan *et al*.** [12]. Even though it makes perfect sense and logical sense, evaluating heart mechanics and hemodynamics while exercising is rarely done in conditions where symptoms brought on by exercise predominate. This is also the justification behind the stricter guidelines that are now in place for exercise diastology testing in symptomatic people whose resting examination results are insufficient to prove the existence of high LV filling pressures [6].

It was discovered that decreased early diastolic relaxation as measured by 'E/e was most strongly associated with increased LV dyssynchrony. Even in a sample of patients with substantially intact LVEF, the association was still present.

By disrupting temporal variability Systolic dysfunction, which interferes with the normally closely synchronised link between systolic shortening and subsequent diastolic lengthening, may be a significant pathophysiological factor in HFpEF [13]. Dyssynchrony can cause systolic shortening to decrease as it progresses; an increase in diastolic filling pressure has been demonstrated [14].

Studies made specifically for this purpose require looking at the prognostic significance of mechanical dyssynchrony (induced by exercise or existent at rest) in individuals with HFpEF.

Impairment of exercise capacity in HFpEF patients is complex when taken as a whole. We hypothesize that comorbid conditions feed persistent systemic inflammatory states, which in turn encourage extracellular matrix deposition in the left ventricle, which has the fatal consequences of elevated resting left ventricular filling pressures and the inability to respond to exercise by increasing cardiac output.

In order to decrease the likelihood of LV remodeling and diastolic LV dysfunction in persons at risk of diastolic LV dysfunction or with overt HFpEF, our latest study emphasizes the significance of regulating both systolic and diastolic blood pressure as modifiable risk factors. The risk of drastically reducing diastolic blood pressure, which could expose the myocardium to ischemia and eventually functional decline, should be contrasted with the danger of overusing antihypertensive drugs.

LIMITATIONS:

The study has a number of restrictions. First off, the tiny sample size in this study resulted in insufficient power for the analysis. Second, because safety concerns prevented stopping the use of the antihypertensive drugs, ABPM was carried out while they were being taken. Finally, we used discontinuous 24 h-ABPM approaches to quantify the rate of BP variations. These techniques are unable to accurately measure short-term BP fluctuations and can only offer limited insight into slow and relatively "long-term" BP oscillations. Fourth, the evaluated echocardiographic phenotypes are not endpoints. These echocardio-graphic abnormalities have, however, been linked to negative outcomes in long-term investigations.

CONCLUSION

Use of BPV along with Comprehensive echocardiographic assessment including LAVI and e` as important and feasible tool in diagnosis and prognosis of HFpEF patients, abnormal BPV was associated with worse outcomes and poor exercise capacity.

Sources of funding: This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Conflicts of interest: There are no conflicts of interest, according to the authors.

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