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Assessment of Heart Rate Variability in Heart Failure Patients

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ABSTRACT

Background: Heart rate variability (HRV) depicts the functional status of the autonomic nervous system and its effects on sinus node. **Objective:** The aim of the study was to analyze heart rate variability (HRV) parameters in patients with heart failure with reduced ejection fraction (HFrEF) and to assess correlation between HRV parameters and functional capacity of the study group (assessed by NYHA class and 6 MWT).
Subjects and Methods: This study included a total of 80 patients with chronic heart failure with reduced ejection fraction, attending at the Outpatient Clinic, Department of Cardiology, Al-Azhar (Al-Hussein) University Hospital. This study was conducted between December 2018 to October 2019. Patients were divided into four groups according to New York Heart association functional classification (NYHA). All patients were subjected to cardiac tests mainly ECGs, Echocardiography and 24 hours Holter monitoring.
Results: High statistically significant difference was found between the four groups regarding HRV parameters (SDNN rMSSD, pNN50 and LF/HF ratio) and 6MWT duration. There was positive correlation between premature ventricular contractions (PVCs) burden and ANS indices (LF/HF).
Conclusion: Disturbed cardiac autonomic function was found in patients with heart failure with reduced ejection fraction (HFrEF). HRV parameters have strong positive correlation with NYHA functional class and with 6MWT distance in patients with HF. Impaired autonomic function was associated with higher PVCs burden even in patients with same NYHA class.
Keywords: Heart Rate Variability, Heart Failure Patients

INTRODUCTION

Heart failure (HF) is a common, progressive, complex clinical syndrome with high morbidity and mortality [1]. It is a phenomenon involving pump failure with subsequent inability to meet the body needs and may involve either right ventricle (RV) or left ventricle (LV) or more often both, which causes an altered pathological condition [2].

Decreased exercise capacity is the main symptom in HF patients; therefore, the physician should provide an estimation of the functional class (New York heart association NYHA) of the patient based on an assessment of the patient's daily activity and the limitations imposed by the patient's symptoms of HF [3]. Subset of HF patients has symptoms out of proportion to the resting hemodynamics and left ventricular ejection fraction (LVEF) [4].

LVEF is well recognized in the adverse clinical outcomes of patients with acute heart failure, however, it loses statistical power when applied to patients with chronic and advanced heart failure. In this setting, RV function determines exercise capacity and survival [5]. Heart failure with reduced ejection fraction (HFrEF) is now the preferred term for HF with LVEF<40% [6].

Chronic heart failure refers to patients with diagnosed heart failure for a period of time (arbitrarily defined as a minimum of 3 months) and follows that these patients have received some heart failure treatment [7].

The incidence and progression of heart failure are associated with an increasing severity of autonomic derangements, specifically a compensatory increase in activity of the sympathetic nervous system and a decrease in activity of the parasympathetic nervous system [8].

Indeed, when the heart dilates, vagal and sympathetic afferent cardiac fibers increase their firing, and this afferent sympathetic excitation leads to the tonic and reflex inhibition of cardiac vagal efferent activity. This phenomenon can be expected to occur whenever the heart dilates in heart failure probably due to the systolic dysfunction. In cases of diastolic dysfunction in which the heart does not dilate, the mechanisms in which the vagal activity is reduced have not been fully determined [9].

There are several compensatory mechanisms that occur as the failing heart attempts to maintain adequate function. These include increasing cardiac output via the Frank–Starling mechanism, increasing ventricular volume and wall thickness through ventricular remodeling, and maintaining tissue perfusion with augmented mean arterial pressure through activation of neurohormonal systems. Although initially beneficial in the early stages of heart failure, all of these compensatory mechanisms eventually lead to a vicious cycle of worsening heart failure [10].

Analysis of heart rate variability on the basis of routine 24-hour Holter recordings has been shown to provide a sensitive measurement of cardiac control by the autonomous nervous system (ANS) [11].

HRV is a non-invasive measure reflecting the variation over time of the period between consecutive heartbeats (RR intervals). In fact, heart rate (HR), which continuously fluctuates over time, is under the influence of control mechanisms aimed at maintaining a dynamic stability called homoeostasis

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[12]. In this equilibrium, the sympathetic stimulation causes acceleration in HR by increasing the firing rate of pacemaker cells in the heart's sino-atrial node, while the parasympathetic system causes deceleration in HR by decreasing of the firing rate of pacemaker cells. Clinical studies have shown reduced HRV in patients with congestive heart failure [13].

The aim of the current study was to analyze heart rate variability (HRV) parameters in patients with heart failure with reduced ejection fraction (HFrEF) and to assess correlation between HRV parameters and functional capacity of the study group (assessed by NYHA class and 6 MWT).

SUBJECTS AND METHODS

This study included a total of 80 patients with chronic heart failure with reduced ejection fraction, attending at the Outpatient Clinic, Department of Cardiology, Al-Azhar (Al-Hussein) University Hospital. This study was conducted between December 2018 to October 2019.

Ethical approval:

Approval of the ethical committee was obtained. Written informed consent from all the subjects were obtained.

Patients were classified according to New York heart association classification (NYHA classification) into 4 groups:

- **Group I (NYHA I)**: Included 20 patients (No symptoms and no limitation in ordinary physical activity, e.g. shortness of breath when walking, climbing stairs etc.)
- **Group II (NYHA II)**: Included 20 patients (Mild symptoms (mild shortness of breath and/or angina) and slight limitation during ordinary activity).
- **Group III (NYHA III)**: Included 20 patients (Marked limitation in activity due to symptoms, even during less-than-ordinary activity, e.g. walking short distances (20-100 m). Comfortable only at rest).
- **Group IV (NYHA IV)**: Included 20 patients (Severe limitations. Experiences symptoms even while at rest. Mostly bedbound patients).

Inclusion criteria:

Patients diagnosed as heart failure with reduced ejection fraction (HFrEF) with LVEF <40%.

Exclusion criteria:

Refusal of the patients to participate in the study. Any patients with ejection fraction ≥ 40%. Diabetic patients, patients with atrial fibrillation, patients with frequent ectopics ≥ 10% , patients with significant valvular lesions and poor echocardiography window.

All patients were subjected to:

1. Careful history taking from all patient for assessment of heart failure with emphasis on exercise tolerance of the patient, cardiac congestive symptoms, low cardiac output symptoms, other cardiac symptoms and previous diagnostic tests done, mainly ECGs, Echocardiography, nuclear scans, Cardiac CT, CMR and coronary angiography.
2. General and local cardiac examination was done for all patient including (vital signs with JVP, cardiac examination which involve precordial examination to detect clinically heart size, heart sounds, added sound, murmurs and examination of the back). Other systems will also be examined relevant systems were also examined, Respiratory and Musculoskeletal systems.
3. Resting surface 12 leads electrocardiogram (ECG) was done for all patients to studied for:
   - Detection of the rate, rhythm and any recognized supra-ventricular or ventricular activity.
   - QRS morphology, axis and duration.
4. Echocardiography:

   All patients were examined at rest in the left lateral decubitus position to obtain adequate images in different standard views. Standard 2D TTE examination were performed with a "Philips iE33 X Matrix" ultrasound machine using "S5-1" matrix array transducers (Philips Medical Systems, Andover, USA) equipped with STE technology, using a multi frequency (1- 5 MHz). ECG-gated examination mostly used to help us during image acquisition and later analysis.

   Chamber quantification was performed in accordance with the recommendations of the American Society of Echocardiography and the European Association of Cardiovascular Imaging [14,15] the following parameters were taken:

   I. Left ventricular dimensions and volumes
   II. Left ventricular Ejection fraction (LVEF %) was determined using Simpson's biplane volumetry.
5. **24 hours Holter monitoring:**

   The Participants were subjected to 24 hours ambulatory 3-channel Holter. All recordings were edited manually on Schiller MT 200 software package, that can be communicate with Schiller devices (Schiller MT 101).

Data analysis

Analysis of the whole period of 24 hours for detection of:

- Average, maximum and minimum heart rate.
- Detection of the sinus beats template and its number.
- Identification of **Heart Rate Variability (HRV)**
  - Time domain in the form of SDNN>100msec. Thus, the observed cut-off values of 24-h

measures of HRV e.g. SDNN <50 for highly depressed HRV, or SDNN <100 ms for moderately depressed HRV are likely to be broadly applicable. PNN50%=7.5 [16].

- Frequency domain in the form of LF: ranging between 0.04 and 0.15 Hz, HF: ranging from 0.15 to 0.4 Hz [17] and LF/HF ranging from (1.5-2) is considered as balanced ANS [16].

- **Supraventricular arrhythmia.**
- **Ventricular arrhythmia** and identifiable grading of ventricular arrhythmia risk according to the Lown's grade into:
  - 0 = no ventricular premature beats (VPBs).
  - 1 = < 30 VPBs/hour.
  - 2 = >30 VPBs/hour.
  - 3 = multiform VPBs.
  - 4a = repetitive VPBs – couplets.
  - 4b = repetitive VBPs - runs of ventricular tachycardia.
  - 5 = early VPBs i.e. R on T [18].

6. **Six Minute walk test** was done for all patients to determine the total distance covered as a measure of the functional capacity of the patients [19].

Statistical analysis

Recorded data were analyzed using the statistical package for social sciences, version 20.0 (SPSS Inc., Chicago, Illinois, USA). Quantitative data were expressed as mean± standard deviation (SD). Qualitative data were expressed as frequency and percentage.

The following tests were done:

- Independent-samples t-test of significance was used when comparing between two means.
- Chi-square (x^2) test of significance was used in order to compare proportions between two qualitative parameters.
- The confidence interval was set to 95% and the margin of error accepted was set to 5%. The p-value was considered significant as the following:
- Probability (P-value)
- P-value <0.05 was considered significant.
- P-value <0.001 was considered as highly significant.
- P-value >0.05 was considered insignificant.

RESULTS

Table (1): Comparison between the four groups as regard patients' demographic and clinical data**.**

		NYHA I	NYHA II	NYHA III	NYHA IV	Test	p. value
Age (year)	Mean ± S. D	51.80 ± 9.07	50.00 ± 7.98	51.75 ± 9.03	52.05 ± 7.82	F: 0.246	0.864
BMI (kg/m^2)	Mean ± S. D	23.00 ± 3.28	22.45 ± 3.41	25.25 ± 2.75	27.00 ± 2.18	F: 10.186	0.001*
Gender	Male (%)	10 (50%)	11 (55%)	11 (55%)	10 (50%)	X^2: 0.201	0.978
Smoking	Yes (%)	7 (35%)	9 (45%)	10 (50%)	9 (45%)	X^2: 0.965	0.810

Table (2): Comparison between the four groups as regard LVEDD, LVESD, LVEDV, LVESV and EF, showing no statistically significant difference between the four groups.

		NYHA I	NYHA II	NYHA III	NYHA IV	Test	p. value
EF	Mean ± S. D	30.70 ± 6.31	32.87 ± 5.49	33.61 ± 5.19	32.07 ± 5.29	F:0.986	0.404
LVEDD	Mean ± S. D	7.02 ± 0.61	6.99 ± 0.72	6.97 ± 0.81	7.02 ± 0.70	F:0.028	0.994
LVESD	Mean ± S. D	5.97 ± 0.57	5.83 ± 0.61	5.82 ± 0.76	5.92 ± 0.66	F:0.994	0.871
LVEDV	Mean ± S. D	259.39 ± 50.37	254.88 ± 55.47	256.88 ± 67.85	260.49 ± 58.15	f:0.037	0.990
LVESV	Mean ± S. D	179.80 ± 39.95	171.21 ± 39.61	171.58 ± 51.82	177.63 ± 44.39	F:0.191	0.902

Table (3): Comparison between the four groups as regard sex minute walk test (6MWT), showing statistically significant difference between the four groups.

		Range	Mean ± S. D	F. test	p. value
6MWT	NYHA I	378 – 531	467.05 ± 46.70	335.899	0.001*
	NYHA II	231 – 452	390.20 ± 58.25		
	NYHA III	75 – 213	165.65 ± 41.46		
	NYHA IV	34 – 175	71.70 ± 30.31		

Table (4): Comparison between the four groups as regard HRV parameters (SDNN, rMSDD, PNN50, LF\HF), showing statistically significant difference between the four groups .

		NYHA I	NYHA II	NYHA III	NYHA IV	Test	p. value
SDNN	Mean ± S. D	99.05 ± 23.76	85.65 ± 9.75	67.45 ± 10.22	42.15 ± 8.55	F:57.972	0.001
PNN50	Mean ± S. D	9.84 ± 6.96	3.90 ± 1.49	3.67 ± 3.53	0.66 ± 0.37	F:18.672	0.001
Rmssd	Mean ± S. D	62.90 ± 35.57	38.20 ± 7.61	33.25 ± 15.11	18.75 ± 7.26	F:16.838	0.001
LF\HF	Mean ± S. D	2.58 ± 0.62	3.33 ± 0.81	4.45 ± 0.69	5.05 ± 1.06	f:37.271	0.001

Table (5): Correlation between 6MWTD with MSSD,LF\HF,pNN50,SDNN,EF, showing a Positive correlation and significant between 6MWT D with rMSSD,LF/HF ratio, SDNN and PNN50and no correlation between 6MWT D and LVEF % that is statistically non significant

With	6 MWT D	
	R	P
rMSSD	0.545	0.001*
LF / HF	- 0.739	0.001*
PNN50	0.559	0.001*
SDNN	0.787	0.0011*
EF	- 0.081	0.476

Table (6): Correlation between PVCs burden with LF\HF, showing moderate Positive correlation and significant between PVCs burden with LF/HF ratio.

With	LF / HF	
	R	P
PVCs burden	0.464	0.0001*

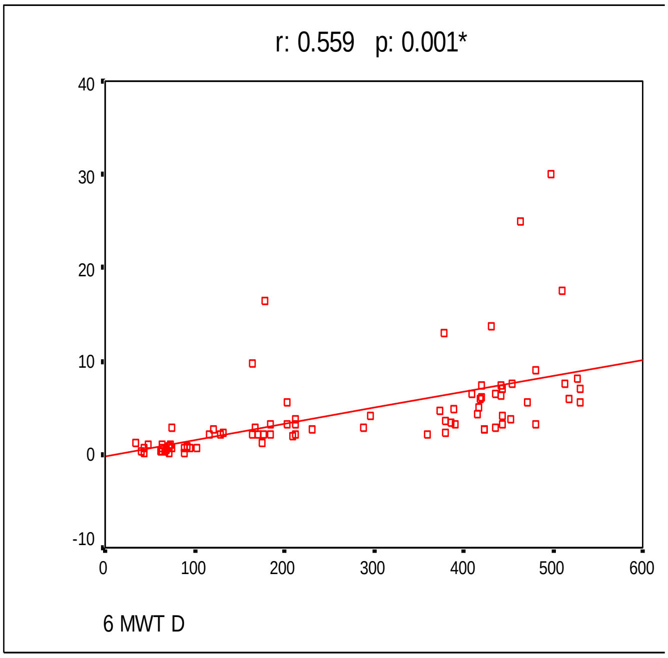

Fig. (1): Scatter plot between 6MWT D and PNN50 in patients groups.

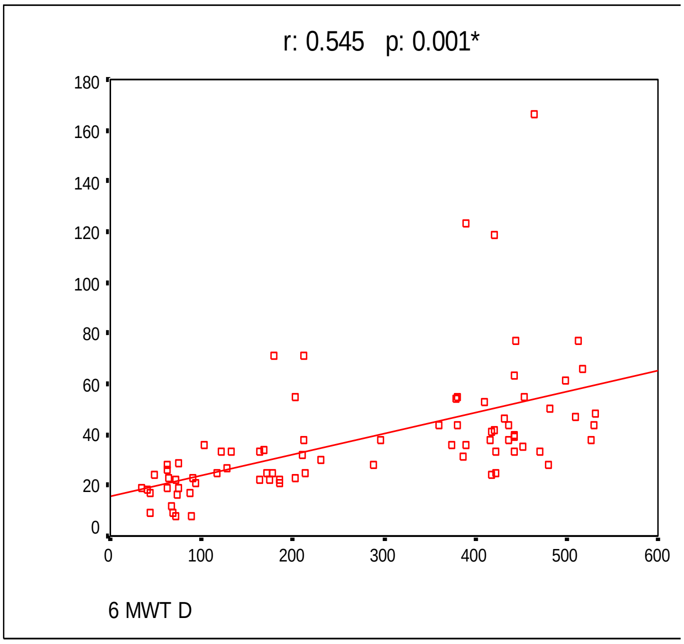

Fig. (2): Scatter plot between 6MWT D and rMSSD in patients' group

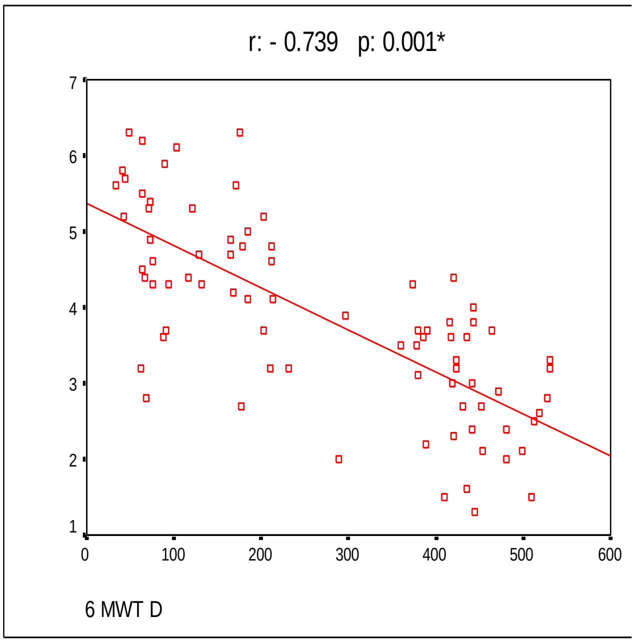

Fig. (3): Scatter plot between 6 MWT D and LF/HF ratio in patients groups

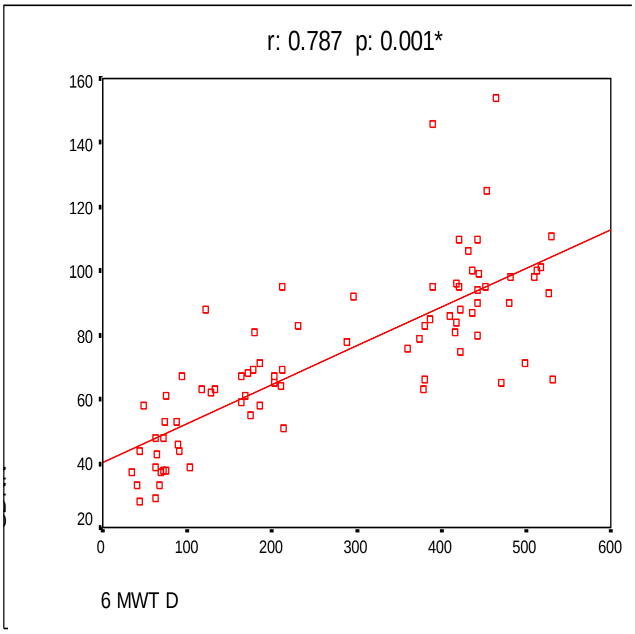

Fig. (4): Scatter plot between 6MWT D and SDNN in patients group.

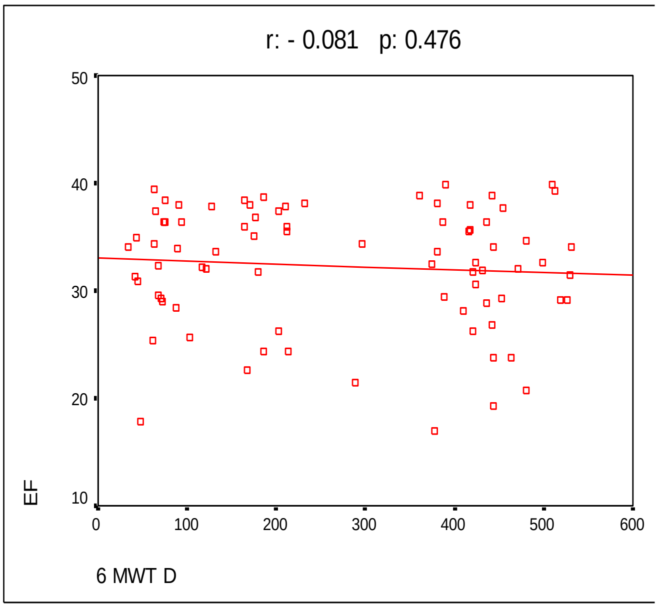

Fig. (5): Scatter plot between 6 MWT D and EF in patients groups

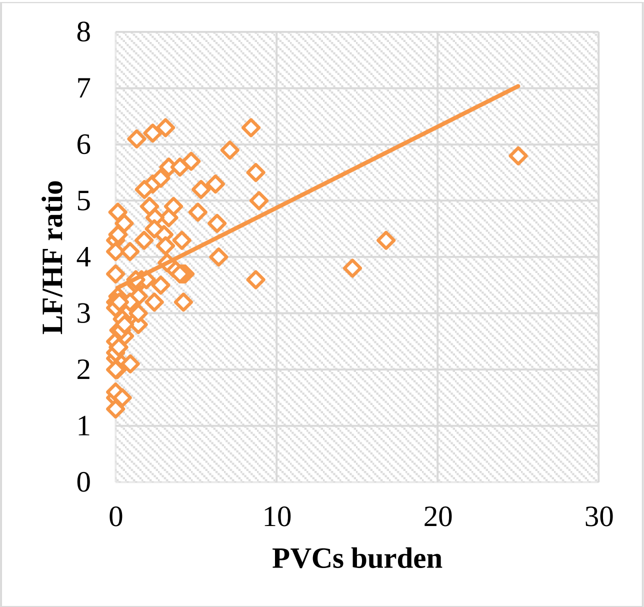

Fig . (6): scatter plot between PVCs burden andLF\HF ratio in patients groups.

DISCUSSION

Decreased exercise capacity is the main symptom in HF patients; therefore, the physician should provide an estimation of the functional class (New York heart association NYHA) of the patient based on an assessment of the patient's daily activity and the limitations imposed by the patient's symptoms of HF **[3]**.

The incidence and progression of heart failure are associated with an increasing severity of autonomic derangements, specifically a compensatory increase in activity of the sympathetic nervous system and a decrease in activity of the parasympathetic nervous system**[8]**.

In our study we evaluated 80 patients diagnosed with heart failure with reduced ejection fraction attending Cardiology Department, Al-Hussein University Hospital. Patients were divided according to New York heart association classification (NYHA classification) into 4 groups.

For all patients resting ECG, Echocardiography, 24 Hours Holter monitoring and 6 MWT were done. There was reduction in HRV parameters (SDNN. rMSSD and pNN50%) in the all study groups.

These findings were in agreements with those of previously described by **Kishi** **[20]**, when he described heart failure as an autonomic nervous dysfunction and **Musialik-Łydka *et al.*** **[21]** who investigated 105 patients with CHF (88 males, 17 females, mean age 54+/-12 years); 77 patients had ischaemic cardiomyopathy, and 28 - dilated cardiomyopathy and The control group consisted of 30 gender- and age-matched healthy subjects and concluded that significant reduction in HRV in HF patients than in controls.

These findings were also in agreements with those of **Saul *et al.*** **[22]** who studied HRV using 24-h Holter ECG recordings to generate time and frequency domain HRV Indices in 21 healthy adults and 25 CHF sufferers (NHYA grade III–IV) The CHF group displayed significantly low SDNN values and had significantly reduced power in all frequency domains.

There was statistically significant difference between the groups (NYHA I to IV) in all HRV parameters including SDNN, PNN50, rMSSD, LF\HF ratio.

This comes in agreement with the findings of **Casolo *et al.*** **[23]** who evaluated 80 patients with CAD. They divided the patients into four groups of equal number based upon the New York Heart Association functional classification (NYHA) and displayed a progressive and significant increase in heart rate and a contemporary decrease in HRV was observed with the advancing severity of CHF. Class IV patients had the smallest HR variation; the spectral composition in this group was barely detectable. The decrease in time domain measures of HRV followed the increase in NYHA Class in a progressive and regular pattern.

These findings were also in agreements to **Musialik-Łydka *et al.*** **[21]**, they found that Patients with NYHA class II had higher values of SDNN and pNN50 than those in class III or IV.

Moreover **Hua *et al.*** **[24]** used HRV parameters to predicted NYHA classification of the patient and concluded that HRV indices carry both high specificity and sensitivity for detection of NYHA class of patients with HFrEF. They concluded also that heart failure is associated with autonomic dysfunction that shows negative correlation with functional capacity.

Effect of exercise on improving HRV parameters was studied by **Abolahrari-Shirazi *et al.*** **[25]**, they concluded that Exercise training is safe and feasible in post percutaneous coronary intervention patients, even in those with reduced ejection fraction. In a seven-week period, exercise training was effective in improving HRV in heart failure patients after percutaneous coronary intervention.

There was a positive correlation between premature ventricular contractions (PVCs) burden and sympathetic indices (HR and LF/HF).

This comes in agreement with the findings of **He *et al.*** **[26]**, who evaluated 160 consecutive patients with idiopathic PVCs (10 PVCs per hour assessed by Holter ECG)(PVCs were divided) and 31 healthy controls, they divided the patients with idiopathic PVCs into 73 fast rate-dependent(F-PVC),56 slow rate-dependent (S-PVC), and 31 HR-independent PVC (I-PVC) based on the relationship between hourly PVC density and hourly HR and concluded that Hourly PVC density was positively correlated with sympathetic indices (HRandLF/HF) In F-PVC group.

CONCLUSION

Disturbed cardiac autonomic function was found in patients with heart failure with reduced ejection fraction (HFrEF). HRV parameters have strong positive correlation with NYHA functional class and with 6MWT distance in patients with HF. Impaired autonomic function was associated with higher PVCs burden even in patients with same NYHA class.

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