Rate Pressure Product and Severely Impaired Systolic Function in Heart Failure Patients (Heart Failure and Severe Systolic Dysfunction)

Ibtesam Ibrahim El-Dosouky and Hala Gouda Abomandour*
Cardiology Department, Faculty of Medicine, Zagazig University, Zagazig, 44519, Egypt
*Corresponding author: Ibtesam Ibrahim El-Dosouky, Lecturer, Cardiology Department, Faculty of Medicine, Zagazig University, Zagazig, 44519, Egypt, Tel: 0020506092608, Fax: 0020502357770; E-mail: ibtesamaldosoky@yahoo.com

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Abstract

Background: Rate Pressure Product (RPP) is an independent index of cardiac work. We aimed to assess the significance of the RPP in patients with chronic Heart Failure (HF) and its relation to their Echocardiographic findings.

Methods: This prospective study included 358 patients with chronic HF 201 (56.1%) HF preserved Ejection Fraction (HFrEF) and 157 (43.9%) HF reduced EF (HFpEF), as 3 groups; average resting RPP 7-10 (n=229), high resting RPP>10 (n=88) and low resting RPP <7 (n=41). NYHA class, Heart Rate (HR), blood pressure, RPP were estimated, S3 and rales were evaluated. Echocardiographic parameters; Left Ventricular End Diastolic (LVED), LV-EF and LV-Stroke Volume Index (SVI) were obtained.

Results: Patients with high RPP had significantly higher incidence of left ventricular hypertrophy, the best EF and the lowest SVI. RPP had significant positive correlations with NYHA class, S3, EF, and EPSS. RPP ≤ 7.75 had 79.2% sensitivity and 70% specificity to predict severely impaired systolic function (EF<30%), (AUC=0.80, p<0.001).

Conclusion: RPP could be a readily available easily measured clinical predictor of low EF; RPP at a cut-off value ≤7.75 could be useful to predict severely impaired LV systolic function. With a new emphasis on incorporation of SVI into diagnostic and follow up approach, hand in hand with the EF specifically in those with LVH.

Keywords: Rate pressure product; HF and reduced EF (HFrEF); Ejection fraction; Stoke volume index

Introduction

Heart failure (HF) is a major health problem worldwide [1]. According to the AHA/ACC Guidelines [2] HF is largely a clinical diagnosis that is based on a careful history and physical examination.” Several criteria have been proposed to diagnose HF; to apply these criteria, cardiac function must be evaluated by appropriate tests as echocardiography that can distinguish between HF with reduced ejection fraction (HFrEF) and HF with preserved ejection fraction (HFpEF) [3,4].

Rate-Pressure Product (RPP) is a valuable marker and one of the commonly used indices of cardiac function, which is frequently adopted as an index of ‘work’ or, more correctly, ‘effort’. Under resting conditions, safer RPP should range between 7 and 10 [5].

Routine serial echocardiography may provide valuable information which could influence the treatment options, as the dependence on the patient complaint only may be deceiving [6].

The aim of this study was to assess the significance of the RPP in patients with chronic heart failure and its relation to the Echocardiographic findings in this group of patients.

Methods

Our study was a prospective cross section case control, single centre study conducted at our cardiology department. It was approved by the ethics committee of our institute.

We selected 358 patients with chronic HF [201 (56.1%) of them had HFrEF and 157 (43.9%) had HFpEF], all were on medical treatment came for follow up in the outpatient clinic; all were in stage C-HF according to the ACC/AHA guide lines for diagnosis of HF [7]. We did not differentiate the patients according to the underlying etiology, we just saw the end result; HF.

Patients with possible active heart disease as myocarditis or infective endocarditis, acute pulmonary edema, acute coronary syndrome, associated heart disease requiring surgical intervention, advanced heart valve disease mainly aortic stenosis or mitral regurgitation more than mild, cardiac arrhythmia including atrial fibrillation or heart block, advanced renal or liver impairment, or those with poor echo window were excluded from the study.

After giving written consents, all participants were subjected to the following: History taking and thorough clinical examination: with special emphasis on NYHA functional classification, heart rate (HR) and blood pressure for: the rate pressure product (RPP=Systolic Blood Pressure (SBP) X (HR)/1000), weight and height for the Body Surface Area (BSA) and Body Mass Index (BMI).
We selected 2 of the most important signs in the Framingham criteria for the diagnosis of heart failure on follow up of our patients who were already diagnosed as HFrEF; S3 and rales [8].

Echocardiographic evaluation: Comprehensive 2D and Doppler Echocardiographic studies were performed on the commercially available ultrasound equipment (Vivid-9, GE Healthcare) according to the American Society of Echocardiography guidelines [9].

Interventricular Septum (IVS), posterior wall thickness, left ventricular end diastolic dimension (LVEDd) and left ventricular end systolic dimension (LVESd) were obtained from the parasternal long-axis view, at the mitral valve leaflet tips [9].

Left ventricular ejection fraction (LVEF) was measured by the modified biplane Simpson's rule. The LV systolic function is normal if ejection fraction is >55%, and considered as mildly impaired if EF is 54-45 moderately impaired if EF is 44-30 and severely abnormal if ejection fraction is <30% [10].

LV end diastolic volume (LVEDV) and LV end systolic volume (LVESV) were obtained from apical four- and two-chamber views, with accurate tracing of endocardial borders. LV Outflow Tract (LVOTd) Diameter was measured in the parasternal long axis view in early systole. LV outflow tract time velocity integral (LVOT vti) was measured in the apical long axis view using pulsed wave Doppler with the sample volume just below the region of flow convergence, approximately 5 mm apically from the aortic valve and in parallel with blood flow.

LV stroke volume (LV-SV) was calculated by: the Doppler method (SV=LVOT area [3.4 × LVOT diameter] × LVOT vti) and by the cube formula (SV=LVEDD3-LVESD3) for comparison with the Doppler method and then indexed to the BSA for the SVI.

Degree of LV diastolic dysfunction was also evaluated according to the latest guidelines.

We divided our patients (358) into 3 groups according to the resting RPP [5]:
- Average resting RPP 7-10 (n=229)
- High resting RPP>10 (n=88)
- Low resting RPP<7 (n=41).

Statistical analysis
Collected data were analyzed using SPSS software statistical package for social science version 19 (SPSS, Inc. Chicago, IL, USA). Data were reported as mean ± SD for continuous variables or number and percentage for categorical variables. Data were tested for normality using the Kolmogorov-Smirnov test. Means were compared using ANOVA test. Categorical data were compared using the chi-squared test. Pearson and spearman correlations were used to detect the relations between different study parameters. Receiver Operating Characteristics (ROC) analysis was used to determine the cut-off values with associated sensitivity and specificity. p value was considered significant if <0.05.

Results
Baseline demographic and clinical characteristics of the study groups are in Table 1, with high prevalence of those with an average RPP, who were younger (47.9 ± 16.1 years old) compared to the other groups (p<0.05).

<table>
<thead>
<tr>
<th>Variables</th>
<th>Average RPP (n=229)</th>
<th>High RPP (n=88)</th>
<th>Low RPP (n=41)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y (mean ± SD)</td>
<td>47.9 ± 16.1</td>
<td>59.1 ± 12.4</td>
<td>58.1 ± 10.4</td>
<td>A#H, A#L, &lt;0.05</td>
</tr>
<tr>
<td>Gender (M/F%)</td>
<td>(39/61%)</td>
<td>(48/52%)</td>
<td>(75.6/24.4%)</td>
<td>L#H, L#A, &lt;0.001</td>
</tr>
<tr>
<td>S3 (%)</td>
<td>(84%)</td>
<td>(70%)</td>
<td>(93%)</td>
<td>L#H&lt;0.05</td>
</tr>
<tr>
<td>Rales (%)</td>
<td>(6%)</td>
<td>(1%)</td>
<td>(26%)</td>
<td>L#H, L#A&lt;0.05</td>
</tr>
<tr>
<td>NYHA class:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I (%)</td>
<td>(56.4%)</td>
<td>(98.7%)</td>
<td>(7.5%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>II&amp;III (%)</td>
<td>(43.6%)</td>
<td>(1.3%)</td>
<td>(72.5%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>BMI (mean ± SD)</td>
<td>26.1 ± 3.5</td>
<td>27.2 ± 2.8</td>
<td>25.6 ± 2.8</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>HR. bpm (mean ± SD)</td>
<td>74 ± 9.4</td>
<td>87.5 ± 9.8</td>
<td>81 ± 11</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>SBP.mmHg (mean ± SD)</td>
<td>118.3 ± 10.6</td>
<td>139.4 ± 12.6</td>
<td>98 ± 8.1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>DBP.mmmHg (mean ± SD)</td>
<td>72.5 ± 6.8</td>
<td>85.2 ± 7.5</td>
<td>60.6 ± 2.3</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>RPP (mean ± SD)</td>
<td>8.3 ± 0.9</td>
<td>12 ± 2.1</td>
<td>5.9 ± 0.5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>PP mmHg (mean ± SD)</td>
<td>44.5 ± 9.7</td>
<td>56.4 ± 11.1</td>
<td>37 ± 8.5</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

**Table 1:** Baseline demographic and clinical characteristics of the study groups. RPP: Rate Pressure Product; y: years; SD: Standard Deviation; M: Males; F: Females; S3: 3rd heart Sound; NYHA: New York Heart Association (NYHA) Functional Classification; BMI: Body Mass Index; HR: Heart Rate; SBP: Systolic Blood Pressure; DBP: Diastolic Blood Pressure; PP: Pulse Pressure; A: group of Average RPP; L: group of Low RPP; H: group of High RPP; #: versus.
There was male predominance in patients with lower RPP (75.6/24.4%) compared to the other groups (p<0.001).

Patients with low RPP had significantly higher prevalence of S3 (93%), compared with high RPP group (70%), p<0.05.

Patients with low RPP had significantly higher prevalence of rales (26%), p<0.05, limiting dyspnea (NYHA class II and III) (72.5%), p<0.001 compared with the other groups.

Eccent was consistently higher with decreasing the RPP; it was the lowest in patients with high RPP (8.5 ± 1.3 mm) and the highest in patients with low RPP (11.3 ± 4.3 mm), p<0.001 and so the LVESd was the biggest in patients with low RPP (60.1 ± 15.1 mm) compared to the other groups, p<0.001 (Table 2).

<table>
<thead>
<tr>
<th>Variables</th>
<th>Average RPP (n=229)</th>
<th>High RPP (n=88)</th>
<th>Low RPP (n=41)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>LVEDd. mm (mean ± SD)</td>
<td>47.7 ± 9.6</td>
<td>50.5 ± 10.3</td>
<td>48.8 ± 12.8</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>LVESd. mm (mean ± SD)</td>
<td>45.8 ± 16.9</td>
<td>44.5 ± 13.1</td>
<td>60.1 ± 15.1</td>
<td>L#A, L#H&lt;0.001</td>
</tr>
<tr>
<td>EPSS. mm (mean ± SD)</td>
<td>10.2 ± 3</td>
<td>8.7 ± 1.6</td>
<td>11.4 ± 4.3</td>
<td>H#A&lt;0.05, H#H&lt;0.05</td>
</tr>
<tr>
<td>EF% (mean ± SD)</td>
<td>52.2 ± 13.3</td>
<td>51.4 ± 10.6</td>
<td>37 ± 8.8</td>
<td>L#A and L#H&lt;0.001</td>
</tr>
<tr>
<td>SVI (HF/EF) mL/m²/beat (mean ± SD)</td>
<td>42.9 ± 18.5</td>
<td>37.8 ± 8.7</td>
<td>40.2 ± 18.3</td>
<td>H#R and H#N&lt;0.05</td>
</tr>
<tr>
<td>HFrEF&lt;30%</td>
<td>47%</td>
<td>0</td>
<td>0.244</td>
<td>L#H, L#A&lt;0.05</td>
</tr>
<tr>
<td>HFrEF&gt;30%</td>
<td>48.1%</td>
<td>0.557</td>
<td>0.732</td>
<td>L#H, L#A&lt;0.05</td>
</tr>
<tr>
<td>HFrEF</td>
<td>47.2%</td>
<td>0.443</td>
<td>0.224</td>
<td>L#H, L#A&lt;0.05</td>
</tr>
<tr>
<td>LVH (n%)</td>
<td>(11%)</td>
<td>(51.5%)</td>
<td>(10%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Conc. (n%)</td>
<td>(1%)</td>
<td>(42.4%)</td>
<td>(10%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Eccent. (n%)</td>
<td>-0.01</td>
<td>(9.1%)</td>
<td>0</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

SVI measured in patients with HFrEF was lower in patients with high RPP 37.8 ± 8.7 compared with that in average RPP group 42.9 ± 18.5 and low RPP group 40.2 ± 18.3 mL/m²/beat, p<0.05.

RPP had a significant positive correlation with the EF (r=0.3, p<0.05) and negative correlations with the NYHA class (r=-0.73, p<0.001), presence of S3 (r=-0.2, P=0.04) and the EPSS (r=-0.22, P=0.01).

EF had significant negative correlations with; NYHA class (r=-0.6), presence of S3 (r=-0.4) and presence of rales (r=-0.52), p<0.001.

NYHA class had a significant positive correlation with presence of rales (r=0.75). ROC analysis showed that RPP at a cut-off value ≤7.75 had a sensitivity of 79% and a specificity of 70% for prediction of severely impaired LV systolic function (EF<30%), (AUC=0.8, p<0.001 at 95% CI of 0.72-0.88) (Figure 1).

**Discussion**

HF is the consequence to cardiac adaptive dynamic processes such as cardiac apoptosis, angiogenesis, fibrosis, and hypertrophy. However, this relevant point to discuss, shows that the cardiac remodelling during HF is the resulting final process of multiple epigenetics, molecular and cellular processes involving different phases of cardiac adaptive response to pathogenic alterations of pre-load and post-load [11] and then leading to substantial alterations in mechanical cardiac muscle properties (diastolic and systolic altered cardiac properties) [12].

Current Guidelines for diagnosis and management of chronic HF only support repeated measurement of Ejection Fraction (EF) through echocardiography depending on changes in clinical status using the subjective NYHA functional classification rather than objective evidence [2]. This may give a misleading impression of improvement in patients with HF [13]. On the other hand, improvements in EF may be associated with worsening NYHA due to other causes as, primary pulmonary disorders; anemia, fatigue, and physical unfitness [14],...
routine serial echocardiography may provide valuable information which could influence the treatment options [6].

Myocardial oxygen consumption is the most important indicator of heart load [15]. The rate-pressure product (heart rate × systolic BP) strongly correlates with myocardial oxygen consumption [5]. RPP at rest could be as a useful marker of cardiac dysfunction as on exercise, it may be more strongly associated with cardiac disease [16].

We hypothesized that determination of cardiac oxygen consumption in patients with heart failure can give good information on the myocardial function status on initial evaluation and on follow up; to interpret symptoms (NYHA function class) which are subjective with the objective parameters either clinical or by echocardiography.

Our results showed that patients with the lowest RPP had more advanced degree of heart failure presented clinically as; advanced NYHA function class, higher incidence of rales and S3 on examination associated with lower SBP and DBP, in agreement with Kowalczys et al. [17], Voors et al. [18] and the Uszko-Lencer et al. [19].

In our study, the RPP had a significant positive correlation with the EF and a significant negative correlation with the EPSS, in agreement with Kowalczys et al. [17], the SVI was the lowest in those with the best EF who had also the highest HR, this could be explained as follow; elevated resting HR commonly associated with pathological mechanisms due to an increase in oxygen demand with impaired pump function resulting in reduction of stroke volume [20], with increased risk for HF worsening [21,22]. Some studies considered EF as a suboptimal measure of left ventricular systolic function [23,24]. The hemodynamic states of patients with HF may be over-simplified when divided into HFrEF and HfP EF depending only on the EF (EF). LV pump performance (SVI) may differ, at a certain level of LV systolic function, depending on LV mass [25]. In agreement with this fact, our patients with higher RPP had higher incidence of LVH (mainly concentric LVH). Concentric LVH can act as a compensatory mechanism that normalizes the contractile stress and the total contractile force. However, if contractile stress remains reduced, the contractile force will be inadequate and result in a fall in stroke volume despite the preserved EF [26].

No cut-off values for those with HFrEF “above or below” which, these patients will suffer. The present study found that RPP at a cut-off value ≤7.75 can predict severely impaired LV systolic function (EF<30%).

**Study Limitations**

Small sample size from a single centre. No data from long term follow up. The study included those in sinus rhythm; we did not study the SVI in detail. Being diabetic and its relation to the type of HF was not discussed.

**Conclusion**

RPP could be a readily available easily measured clinical predictor of low EF; RPP at a cut-off value ≤7.75 could be useful to predict severely impaired LV systolic function. With a new emphasis on incorporation of SVI into diagnostic and follow up approach, hand in hand with the EF specifically in those with LVH.

**Recommendation**

Larger long term follow up study to detect the prognostic relevance of the RPP, including those not in sinus rhythm and its relation to different types of diabetes mellitus. Addition of the objective values of the functional capacity of the patients such as peak VO2 could be of value. HF biomarkers as BNP, and new HF biomarkers as ST2 protein might be used to evaluate different diagnostic stages of HF, such as different response to the HF therapies in both conditions of HFrEF and HfP EF [27] and may be of value when added to improve accuracy.

**Acknowledgment**

all colleagues who helped us to end this work.

**References**


