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Evaluation of Perfusion and Function in Cardiac Radionuclide Imaging in Cases of Heart Failure with Mid-Range Ejection Fraction

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ABSTRACT

Objective: Heart failure with mid-range ejection fraction (HFmrEF) poses a significant clinical challenge due to its diverse etiology and variable prognosis. Patients with HFmrEF exhibit an intermediate level of left ventricular dysfunction, making their management and prognosis less well-defined compared to those with heart failure with reduced ejection fraction (HFrEF) or preserved ejection fraction (HFpEF). Coronary artery disease (CAD) is a common underlying cause of HFmrEF and can further exacerbate myocardial dysfunction under stress conditions. In this study, we aimed to evaluate the change in left ventricular ejection fraction with stress in the presence of coronary artery disease in cases of heart failure with mid-range ejection fraction.

Material and Methods: In this retrospective study, we included 507 patients diagnosed with coronary artery disease and an left ventricular ejection fraction (LVEF) of 41-49% measured by echocardiography. All patients underwent a treadmill exercise test using the Bruce protocol, with progressively increasing speed and incline. Myocardial perfusion was assessed using stress gated myocardial perfusion scintigraphy (MPS), and fixed and reversible defects were identified in cases of coronary artery disease. Cardiac scintigraphic images were acquired from the right anterior oblique to the left posterior oblique. We calculated post-stress LVEF and the percentage decrease in LVEF to evaluate cardiac function.

Results: Resting LVEF was measured as 46 (43-50), while post-stress LVEF was 35 (25-47) in all patients. Myocardial perfusion was evaluated using stress gated MPS in all patients, with 200 (39.5%) patients showing both fixed and reversible perfusion defects. The rate of decrease in LVEF due to stress was significantly higher in patients with reversible perfusion defects (15.90 (6-30.43) vs. 28.26 (24-43.18), p: 0.0005). Post-stress LVEF was lower in patients with reversible perfusion defects (40 (31-47) vs. 33 (25-38), p: 0.0005).

Conclusion: In cases of impaired left ventricular perfusion, quantitative calculations of LVEF may vary, and their reliability may decrease as the ejection fraction decreases under stress conditions. Clinicians should consider this variability in the follow-up of patients with heart failure and mid-range ejection fraction.

Keywords: radionuclid imaging, HFmrEF, ejection fraction, myocardial perfusion

INTRODUCTION

Heart failure (HF) is a complex clinical syndrome characterized by impaired ventricular filling or ejection, leading to inadequate tissue perfusion and systemic congestion (1). The severity and management of HF often depend on the LVEF, which categorizes HF into three main subtypes. Preserved EF, defined as LVEF ≥ 50%, typically involves impaired diastolic function and is associated with HF symptoms despite normal systolic function. Reduced EF, with LVEF ≤ 40%, reflects systolic dysfunction and is commonly observed in patients with HF. HFmrEF is diagnosed when LVEF falls between 41% and 49% in the presence of HF.

Following myocardial infarction (MI), the heart undergoes a remodelling process characterized by changes in ventricular wall thickness due to mechanisms such as myocyte hypertrophy and fibrosis (1-3). Myocardial perfusion imaging using cardiac radionuclide imaging techniques allows for the assessment of myocardial perfusion defects, providing valuable insights into the extent and reversibility of myocardial ischemia.

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In this study, we aimed to evaluate the impact of reversible myocardial perfusion defects, as detected by stress gated myocardial perfusion scintigraphy (GMPS), on ventricular function in patients diagnosed with HFmrEF and CAD. By examining changes in ventricular function associated with reversible perfusion defects, we seek to contribute to the existing literature and enhance our understanding of the pathophysiology and clinical implications of myocardial ischemia in patients with HFmrEF.

MATERIAL and METHODs

In our retrospective study, we included 507 patients diagnosed with CAD and an LVEF value of 41-49%, determined by echocardiography (Echo). Each patient underwent both left ventricular echo (Echo-LV) and gated myocardial perfusion scintigraphy (GMPS) evaluations. Echo examinations were conducted within two weeks prior to the GMPS examination. Post-stress LVEF was calculated in all patients using quantitative calculations with MPS following stress induction.

During the GMPS evaluation, all patients exhibited a fixed defect in left ventricular perfusion, with some also presenting a reversible defect. Treadmill exercise testing was performed using the Bruce protocol, with patients reaching at least 85% of their maximum heart rate and exercising for a minimum of 6 minutes before cessation due to fatigue. Patients fasted for a minimum of 3-4 hours prior to testing.

For stress imaging, 9-11 mCi of Tc-99m-sestamibi was administered intravenously, while rest imaging utilized 27-33 mCi of Tc-99m-sestamibi. Wall movements and thickness were evaluated using an automatic analysis program during the MPS examination. SPECT images were acquired from the right anterior oblique to the left posterior oblique using a Siemens-Ecam gamma camera.

Additionally, LVEF was calculated via transthoracic 2D echocardiography. MPS SPECT studies were synchronized with the ECG, allowing determination of end-systolic and end-diastolic volumes. Imaging protocols adhered to established guidelines.

Statistics: SPSS-21 software was used for statistical analysis. The number and percentage of cases were given in categorical variables. Continuous variables are expressed as median (minimum-maximum). Mann-Witney U test was used for continuous variables that did not show normal distribution. Chi-square test was used for categorical variables. $p<0.05$ was considered statistically significant.

RESULTs

The median age of the patients included in our study was 63 years (range: 52-78). Among the total 507 patients, 323 (63.7%) were male. The average left ventricular ejection fraction value calculated by echocardiography (Echo-LVEF) was 44 (range: 41-47).

In all patients, both post-stress and rest LVEF values were assessed following myocardial perfusion scintigraphy (MPS) examination. Resting LVEF was determined to be 46 (range: 43-50), while post-stress LVEF was measured at 35 (range: 25-47).

Myocardial perfusion was evaluated using exercise gated MPS in all patients. Among them, 200 (39.5%) exhibited a reversible perfusion defect in addition to a fixed defect.

Patients with a reversible perfusion defect demonstrated a significantly higher rate of decrease in LVEF due to stress compared to those without (15.90 vs. 28.26, p: 0.0005). Furthermore, post-stress LVEF was notably lower in patients with a reversible perfusion defect compared to those without (40 vs. 33, p: 0.0005).

The summarized results are presented in **Table 1-2** and **Figure 1**.

Table 1: Data on left ventricular wall perfusion in cases with Heart Failure with Mid-Range Ejection Fraction

	Patients without Reversible Perfusion Defect (n:307)	Patients with Reversible Perfusion Defect (n:200)	p
Age	63(53-77)	64 (52-78)	0.417
Gender(female/male)	100(32.6%)/207(67.4%)	84(42%)/116(58%)	0.031
EF calculated by echocardiography	44 (41-47)	44 (41-47)	0.859
Radionuclide imaging-rest EF	46 (43-50)	46 (43-50)	0.817
Radionuclide imaging-post-stress EF	40 (31-47)	33 (25-38)	0.0005
Decrease in EF due to stress in radionuclide imaging (rest EF-Stress EF)(%)	15.90 (6-30.43)	28.26 (24- 43.18)	0.0005

Table 2: Significance of gender and percentage reduction in left ventricular ejection fraction in response to effort in patients with Heart Failure with Mid-Range Ejection Fraction

	Confidence Interval	Odds	p
Gender	0.012-0.177	0.46	0.0005
Decrease in EF due to stress in radionuclide imaging (rest EF-Stress EF)(%)	1.683-2.239	1.942	0.0005

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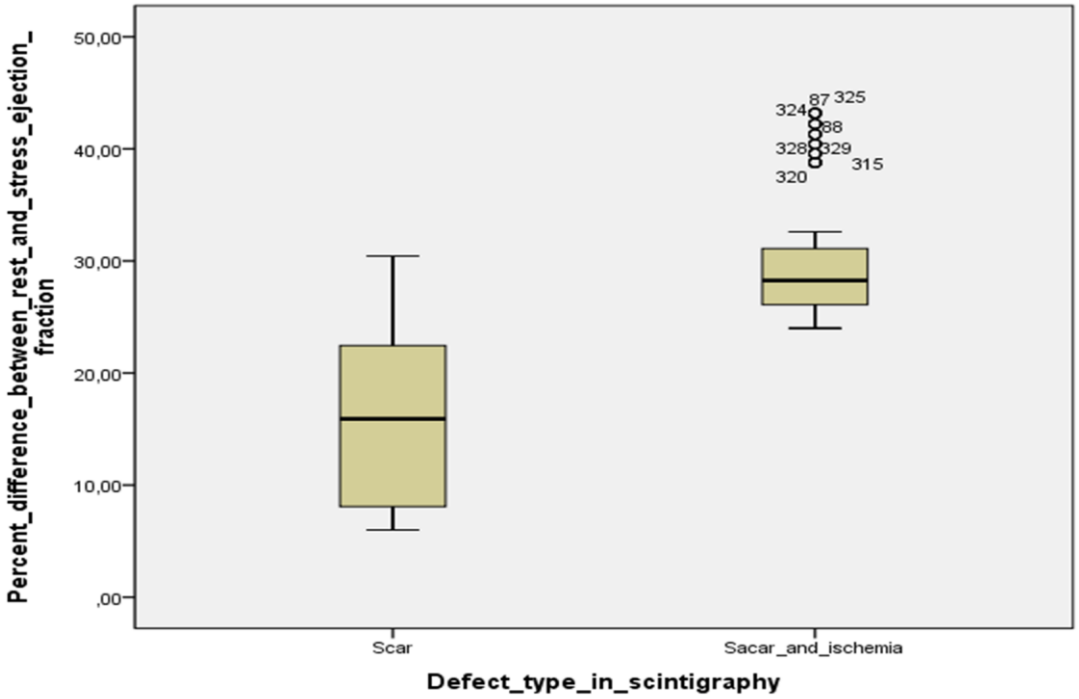
Figure 1: Display of the percentage change in rest and post-stress ejection fraction according to perfusion defect type



DISCUSSION

In 10-24% of heart failure patients, left ventricular ejection fraction falls within the range of 41-49%, leading to the classification of mid-range ejection fraction (mrEF) (2-5). Approximately half of the remaining patients exhibit LVEF ≤ 40%. Decreased LVEF serves as an adverse prognostic indicator in HF patients. However, it's important to note that LVEF calculated by echocardiography (Echo-LVEF) may not always reflect contractility accurately, and patients with similar LVEF values may have different underlying pathophysiology, resulting in varying prognoses (6).

While LVEF is commonly regarded as a measure of cardiac function, structural changes also significantly impact function. In hearts unaffected by structural changes from CAD, stroke volume experiences minimal alterations in response to changes in afterload. However, in cases of CAD, such as those included in our study, the decrease in LVEF during exertion is more pronounced, especially in the presence of reversible perfusion defects. Our findings suggest that in patients with heart failure and mid-range ejection fraction, the presence of reversible perfusion defects exacerbates the decline in cardiac function during exertion.

This decline in function during exertion may stem from the heart reaching its maximum capacity to increase contraction in response to increased stretch. Factors such as decreased calcium affinity for Troponin C and reduced calcium availability in myocardial cells may contribute to this phenomenon (7). Structural changes following myocardial infarction, including stretched and infarcted tissue, lead to increased left ventricular volume, hypertrophy in non-infarcted areas, and alterations in heart shape from elliptical to spherical, negatively impacting heart function (9-11).

Cardiac remodelling, characterized by adaptive and maladaptive processes, further influences heart function. Adaptive remodelling initially maintains heart function in response to acute cardiac damage, while progressive remodelling is associated with a poor prognosis (12). The transition from adaptive to maladaptive remodelling remains poorly understood, but it contributes to the progression of HF (13). Post-MI cellular changes, such as myocyte hypertrophy, loss, and fibrosis, along with mechanical tension on myocytes, trigger signalling pathways and lead to increased wall stress and thickness, further exacerbating energy imbalance and ischemia (14-16).

Collagen synthesis and degradation, influenced by hemodynamic and neuro-hormonal factors, play critical roles in HF due to cardiac remodelling (17, 18). Additionally, inflammatory cytokines contribute to pathological remodelling and HF pathophysiology (21). Angiotensin-II and ACE inhibitors may modulate this process, while inflammatory cytokines potentially exacerbate heart dysfunction (20,21).

CONCLUSION

In conclusion, our study highlights the impact of impaired left ventricular perfusion on ejection fraction in patients with heart failure, particularly those with mid-range ejection fraction. We observed that as the ejection fraction decreases, especially in the presence of reversible perfusion defects, quantitative calculations may become variable, leading to decreased reliability in assessing cardiac function.

These findings underscore the importance of careful consideration and monitoring in the follow-up of patients with impaired left ventricular perfusion.

Healthcare professionals should be aware of the potential variability in quantitative measurements and exercise caution when interpreting these results in clinical practice. Additionally, further research is warranted to elucidate the underlying mechanisms contributing to this variability and to develop more accurate methods for assessing cardiac function in these patients. Such efforts will ultimately improve patient care and outcomes in the management of heart failure with impaired left ventricular perfusion.

Study Limitations:

The weakness of our study is that it is retrospective.

Abbreviations:

HFmrEF: Heart Failure with Mid-Range Ejection Fraction
MPS: myocardial perfusion scintigraphy
ME: Myocardial Enfarction
SPECT: single photon emission computerized tomography
BP: Bruce protocol
LVEF: left ventricular ejection fraction
EDV: end-diastolic volume
ESV: end-systolic volume
CAD: coronary artery disease
Echo: echocardiography

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Author Contributions: SC: Designed and directed the study, Literature search, Data collection, Statistics **SC:** Article writing, Final revisions. All authors reviewed the results and approved the final version of the manuscript.

Ethical approval: The present study was conducted in strict accordance with the principles outlined in the Declaration of Helsinki. Ethical approval for the study was obtained from the appropriate ethics committee. Informed consent was obtained from all participants of this study. Our retrospective study was approved by Gaziosmanpaşa Training and Research Hospital Ethics Committee with 70 numbers on 08.06.2022.

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