

# Assessing the effect of trimetazidine on NYHA functional class in patients with LV systolic dysfunction in a tertiary care centre

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## Abstract

**Background:** Left ventricular systolic dysfunction (LVSD) is one of the most common causes of heart failure and is an increasingly common disorder. Studies have shown that addition of Trimetazidine(TMZ) to standard treatment improve LV function and NYHA functional class thus symptomatic improvement in patients. Shift of metabolism away from a preference for fatty acid towards more carbohydrate oxidation can improve contractile function, thus slowing progression and improving prognosis. Trimetazidine(TMZ) by altering the substrate preference is a promising agent in this new group of modulator drugs. **Objectives:** To find the effect of addition of Trimetazidine on New York Heart Association (NYHA) functional class, in patients with LV systolic dysfunction receiving optimal medical therapy in comparison with patients receiving only optimal medical therapy. **Materials and Methods:** Study was conducted in Department of Cardiology, Kannur Medical College, Anjarakandy after approval from Institutional Human Ethical Committee and Research Committee. This is a comparative study in patients with LV systolic dysfunction receiving Trimetazidine along with optimal medical therapy and patients receiving only optimal medical therapy. Study period was from November 2014 to August 2015. **Results:** The change in NYHA functional class from 3 months period to 6 months follow up period (p value < 0.001) and from baseline to 6 months follow up period (p value<0.001) were found to be significant. This indicates there is a significant improvement in NYHA functional class in TMZ group. **Conclusion:** The present study showed that shifting the energy substrate preference away from fatty acid metabolism and towards glucose metabolism by TMZ, a specific partial inhibitor of FFA oxidation, added to optimal medical therapy improved NYHA functional class in patient with left ventricular systolic dysfunction. The improvement in left ventricular function is likely the main factor determining the decreased NYHA functional class. However, further investigation through large scale trials is recommended.

**Key Word:** trimetazidine.

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## INTRODUCTION

Left ventricular dysfunction (LVD) refers to impaired left ventricular (LV) function<sup>1</sup>. In general terms, systolic dysfunction is defined as a LVEF less than 45%.<sup>2</sup> The

New York Heart Association (NYHA) classification is the most commonly used system to describe the impact of heart failure on a patient's daily activities<sup>3</sup>. Traditional drugs targeted at improving hemodynamic have not yielded satisfying results. Recent studies have investigated the possibility of increasing cardiac performance without affecting oxygen consumption and hemodynamic by agents aimed at enhancing myocardial energy efficiency. TMZ is a 1-(2,3,4 trimethoxybenzyl) piperazine dihydrochloride salt (C<sub>12</sub>H<sub>22</sub>O<sub>3</sub>N<sub>2</sub>·2HCl) which selectively inhibits activity of long-chain 3-ketoacyl coenzyme A thiolase, the last enzyme involved in  $\beta$ -oxidation. TMZ has been shown to affect myocardial substrate utilization by inhibiting oxidative phosphorylation and by shifting energy production from free fatty acid (FFA) to glucose oxidation.<sup>4,5,6,7</sup> With this

background, this study was done to assess the effect of addition of TMZ on NYHA functional class in patients with left ventricular systolic dysfunction receiving optimal medical therapy compared to patients receiving only optimal medical therapy.

## MATERIAL AND METHODS

The study was conducted in the Department of Cardiology, Kannur Medical College, Anjarakandy. Approval from Institutional Ethical Committee (IEC) was obtained before commencement of the study. This is a comparative study to assess changes in NYHA functional classing patients with LV systolic dysfunction receiving TMZ along with optimal medical therapy versus patients receiving only optimal medical therapy. 46 patients were taken into study from November 2014 to August 2015. All patients who attended Cardiology Outpatient department were screened by echocardiography for LV dysfunction (LVD). Patients with LV systolic dysfunction (LVSD) with an ejection fraction less than or equal to 45% (LVEF ≤ 45%), who fulfilled the inclusion and exclusion criteria were taken into study. The patients were then divided into two groups. The first 46 patients with LV systolic dysfunction (LVEF ≤ 45%) were allocated into group 1 and group 2 respectively. The New York Heart Association (NYHA) classification was used to classify patients into 4 categories (I, II, III, IV), with higher class indicating more severe symptoms, limitation in physical activity, and worse health. Patients in group 1 (Optimal medical therapy group) were given only optimal medical therapy. Patients in group 2 (TMZ group) were given TMZ 35mg BD (twice daily) (FLAVEDON MR) along with optimal medical therapy. Written informed consent was taken from all patients before initiation of study.

All patients were followed up at 3<sup>rd</sup> and 6<sup>th</sup> months for functional assessment of NYHA class.

### Inclusion Criteria

Patients included in the study were:

1. Patient who attended Cardiology OPD with an ejection fraction ≤ 45 % by Echocardiography who provided written informed consent

### Exclusion Criteria

Patients with below criteria were excluded from study:

1. Acute MI or unstable angina pectoris within last 3 months
2. Primary valvular disease
3. High grade arrhythmia
4. Renal insufficiency
5. Neurological illness
6. Any active neoplastic diseases
7. Previous cardiac surgery
8. Coronary lesions suitable for revascularization

Optimal medical therapy which includes a combination of the drugs mentioned below-

1. Angiotensin Converting Enzyme Inhibitors (ACEIs) / Angiotensin Receptor Blockers (ARBs)
2. Beta blockers
3. Diuretics - Furosemide, Spironolactone
4. Nitrates
5. Antiplatelets – Aspirin / Clopidogrel, or both
6. Statins – Atorvastatin

The data was entered in an excel sheet and was analysed using SPSS 17.0. Diagrams and graphs depicted by using Microsoft excel 2010. Continuous variables were expressed as mean with standard deviation. Categorical variables summarized in terms of frequency with percentage. Categorical variable (NYHA) was analysed using chi square test. A p value < 0.05 is considered as statistically significant.

## RESULTS

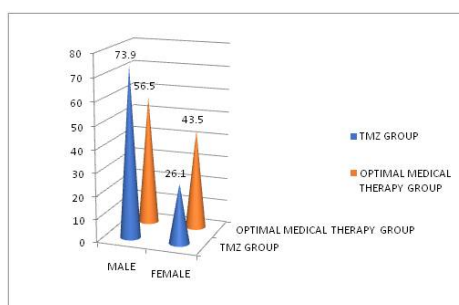
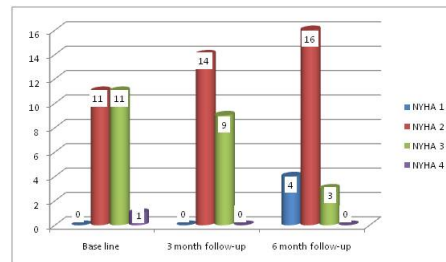


Figure 1: Male –female distribution pattern

TMZ- TMZ This study showed a sex ratio of male 73.9 % and female 26.1 % with a mean age of 65.96±10.40 in TMZ group and ratio of males 56.5% and female 43.5% with a mean age of 61.43±12.58 in optimal medical therapy group.

**Table 1:** Changes in NYHA functional class in TMZ group  
Above table shows improvement in NYHA functional class in TMZ group.

NYHA	TMZ group (n <sub>1</sub> =23)		
	Baseline	3 months follow-up	6 months follow
NYHA 1	0	0	4 (17.4%)
NYHA 2	11 (47.8%)	14 (60.9%)	16 (69.6%)
NYHA 3	11 (47.8%)	9 (39.1%)	3 (13.0%)
NYHA 4	1 (4.3%)	0	0

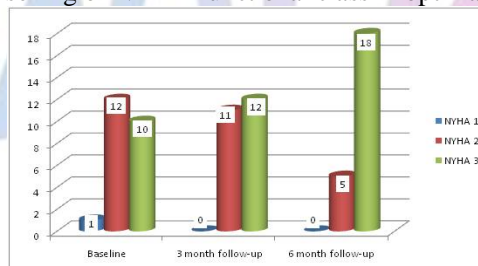


**Figure 2:** Changes in NYHA functional class in TMZ group

**Table 2:** Changes in NYHA functional class in Optimal medical therapy group

NYHA	Optimal medical therapy group		
	Baseline follow-up	3 months follow-up	6 months
NYHA 1	1 (4.3%)	0	0
NYHA 2	12 (52.2%)	11 (47.8%)	5 (21.7%)
NYHA 3	10 (43.5%)	12 (52.2%)	18(78.3%)
NYHA 4	0	0	0

Above table shows worsening of NYHA functional class in optimal medical therapy group.



**Figure 3:** Changes in NYHA functional class in Optimal medical therapy group

**Table 3:** Comparison of NYHA functional class between TMZ group and optimal medical therapy group

Nyha Functional Class	Baseline		3 months		6months	
	TMZ group	Optimal Medical therapy group	TMZ group	Optimal medical Therapy group	TMZ group	Optimal medical therapy group
NYHA 1	0	1(4.3%)	0	0	4(17.4%)	0
NYHA 2	11(47.8%)	12(52.2%)	14(60.9%)	11(47.8%)	16(69.6%)	5(21.7%)
NYHA 3	11(47.8%)	10(43.5%)	9 (39.1%)	12(52.2%)	3(13.0%)	18(78.36%)
NYHA 4	1(4.3%)	0	0	0	0	0
p value		0.555		0.375		<0.001*

**Table 4:** NYHA Functional Classification

Class I	No limitations of physical activities. Ordinary physical activity does not cause undue fatigue, dyspnoea (shortness of breath) or palpitations (asymptomatic LV dysfunction).
Class II	Slight limitation of physical activity. Comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnoea or angina pectoris (mild CHF).
Class III	Marked limitation of physical activity, comfortable at rest. Less than ordinary physical activity leads to fatigue, palpitation and dyspnoea (moderate CHF).
Class IV	Unable to carry on any physical activity without discomfort. Symptoms of heart failure at rest. If any physical activity is undertaken, discomfort increases (severe CHF).

The distribution of NYHA functional class favours the TMZ group as the severity decline in this group compared to optimal medical therapy group. The change in NYHA functional class from 3 months period to 6 months follow up period (p value < 0.001) and from baseline to 6 months follow up period (p value<0.001) were found to be significant. This indicates there is a significant improvement in NYHA functional class in TMZ group.

## DISCUSSION

Chronic limitation of exercise aerobic response is a central clinical feature of heart failure syndrome, occurring because of decreased cardiac reserve and altered peripheral responses, and is an important determinant of survival. Current measures of disease severity related to exercise tolerance are often heavily reliant on subjective measurements made by both the clinician and the patient. These include use of the New York Heart Association (NYHA) classification to grade the severity of functional limitation and patient estimates of how far they are able to walk before they become breathless. The NYHA classification is a useful way of categorizing the severity of heart failure in individual patients and this categorization also has prognostic utility<sup>3</sup> The New York Heart Association (NYHA) classification is the most commonly used system to describe the impact of heart failure on a patient's daily activities. The classification was originally developed in 1928 and subsequently revised. It classifies patients with heart failure into 4 categories (I, II, III, IV), with higher class indicating more severe symptoms, limitation in physical activity, and worse health. Clinicians assign NYHA class on the basis of their indirect interpretation of reported patient's symptoms, medical history, and results from clinical tests on cardiac structure and function. Physician-assigned NYHA class has been shown to be predictive of outcomes in heart failure including hospitalization and mortality.

Parameters include:

1. Limitations on physical activity
2. symptoms (undue fatigue palpitations dyspnoea and/or angina pain) with ordinary physical activity
3. Status at rest

The table below describes the most commonly used classification system, the New York Heart Association (NYHA) Functional Classification. It places patients in one of four categories based on how much they are limited during physical activity. NYHA functional classification is often used to grade disability.<sup>3</sup>

The standard of care has been influenced by three decades of randomised trials extolling the benefits of lifestyle modification, pharmacological therapies, implantable

devices and in a minority of cases, surgery. Although this resulted in a decline in mortality rates of heart failure, the persisting human and financial cost attributable to HF mandates the identification of novel pathways and strategies for its treatment. LVD refers to altered LV function. LVD can be divided into systolic and diastolic dysfunction. Metabolic modulation with shifting the energy substrate preference away from FFA metabolism and toward glucose metabolism has been shown to be an effective adjunctive treatment in patients with LVD.<sup>8</sup> TMZ, a partial free fatty acid oxidation inhibitor, selectively inhibits activity of long-chain 3-ketoacyl coenzyme A thiolase, the last enzyme involved in  $\beta$ -oxidation. TMZ thus affects myocardial substrate utilization by inhibiting oxidative phosphorylation and shifts energy production from FFA to glucose oxidation. The effect of TMZ is obtained at the cellular level, by shifting the energy substrate reference from fatty acid oxidation to glucose oxidation, which is more efficient in terms of ATP production per mole of oxygen used.<sup>8</sup> The change in NYHA functional class in TMZ group from 3 months period to 6 months follow up period (p value < 0.001) and from baseline to 6 months follow up period (p value<0.001) were found to be significant. This indicates there is a significant improvement in NYHA functional class in TMZ group. None of the patients in TMZ group showed worsening of NYHA class. However, in optimal therapy group, the NYHA class either remained same or worsened except for one patient. This finding is in accordance with studies by C. Vitale, Napoli and Fragasso<sup>8,9,10</sup> which showed an improvement in functional class in TMZ group whereas it worsened or remained same in optimal therapy group. The improvement in left ventricular function is likely the main factor determining the observed improvement of NYHA functional class.

## CONCLUSION

The present study showed that shifting the energy substrate preference away from fatty acid metabolism and towards glucose metabolism by TMZ, a specific partial inhibitor of FFA oxidation, added to optimal medical therapy improved NYHA functional class in patient with left ventricular systolic dysfunction. The improvement in left ventricular function is likely the main factor determining the decreased NYHA functional class.

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