

# EFFECT OF TRIMETAZIDINE ON LEFT VENTRICULAR FUNCTION IN HEART FAILURE SECONDARY TO ISCHEMIC HEART DISEASE

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## ABSTRACT

**Background:** Ischemic heart disease is the leading cause of heart failure. This study was conducted to see the effect of Trimetazidine on left ventricular function in heart failure secondary to ischemic heart disease.

**Material & Methods:** This study was conducted at Pharmacology Department, Gomal Medical College, D.I.Khan from 1<sup>st</sup> February 2007 to 1<sup>st</sup> February 2009. Sixty-three patients with heart failure secondary to ischemic heart disease were randomized into two groups; 31 in Trimetazidine group, and 32 in conventional therapy group. All patients underwent assessment for New York Heart Association functional class. Echocardiography was performed to measure the Left ventricular function at start and at 3 months. The primary outcome was improvement in LV function. While the secondary end point was improvement in NYHA functional class.

**Results:** Out of 63 patients, 46(73.02%) were males and 17(26.98%) females. The mean age in Trimetazidine group was  $62.2 \pm 12.9$  and conventional group  $64.4 \pm 6.6$  years. Treatment with Trimetazidine resulted in significant reduction in left ventricular end diastolic dimensions from  $71.7 \pm 4.1$ mm to  $68.1 \pm 6.8$ mm as compared to conventional group with an increase from  $73.3 \pm 3.6$ mm to  $74.8 \pm 6.1$ mm,  $p < 0.001$ . Left ventricular end systolic dimensions reduced significantly in Trimetazidine group from  $58.97 \pm 5.8$ mm to  $54.3 \pm 7.89$ mm as compared to conventional group from  $61 \pm 5.8$ mm to  $62.3 \pm 8.9$ mm,  $p < 0.001$ . There was significant improvement in ejection fraction in Trimetazidine group from  $32.4 \pm 7.2\%$  to  $36.7 \pm 9.1\%$  as compared to conventional group from  $30.7 \pm 9.2\%$  to  $30.9 \pm 10.5\%$ ,  $p = 0.022$ . NYHA functional class reduced significantly in Trimetazidine group from  $2.74 \pm 0.44$  to  $2 \pm 0.52$  and in conventional group from  $2.66 \pm 0.48$  to  $2.81 \pm 0.54$ ,  $p < 0.001$ .

**Conclusion:** Trimetazidine improves left ventricular function with resultant improvement in NYHA functional class in patients with heart failure secondary to ischemic heart disease.

**Key words:** Trimetazidine, Left ventricular function, Ischemic heart disease.

## INTRODUCTION

Heart failure (HF) is a common cause of morbidity and mortality.<sup>1</sup> About 23 million people suffer from HF worldwide. In United States there are estimated 4.7 million people having HF.<sup>2</sup> Ischemic heart disease (IHD) is the leading cause of HF responsible for 60-70% of these cases.<sup>3</sup>

There has been considerable progress in the treatment of HF over the past decade. Treatment modalities that influence cardiac remodeling and neuroendocrine activation exert beneficial effects by decreasing symptoms, improving quality of life, and reducing high mortality. Despite these treatments the prognosis of heart failure remains unfavorable in many patients.<sup>4</sup>

There is emerging evidence that alteration in substrate metabolism has role in the causation of HF.<sup>5</sup> Under aerobic conditions the predominant source of energy in human heart is free fatty acids (FFA's) oxidation, accounting for 60-90% energy generated<sup>6</sup> with carbohydrates contributing only about 10-40% of energy,<sup>7</sup> but FFA's oxidation requires 10-15% more oxygen. This increased FFA's oxidation may have unfavorable effect in the situation of low oxygen supply to the heart.<sup>8</sup> High rate of FFA's oxidation also inhibits glucose oxidation through direct inhibitory action on pyruvate dehydrogenase leading to increased lactate and acid accumulation causing reduction in contractile function.<sup>9,10</sup>

Influencing the energy metabolism of failing heart by stimulating dehydrogenase activity and facilitating glucose oxidation seems attractive from

pathophysiological and metabolic point of view as glucose utilization requires less oxygen and energy.<sup>8</sup> Trimetazidine (TMZ) is a novel anti-ischemic compound which has no significant effect on myocardial oxygen supply to demand ratio.<sup>11</sup> TMZ acts at metabolic level by directly inhibiting mitochondrial long chain 3-ketoacyl Co-enzyme A thiolase,<sup>12</sup> as a result energy substrate is shifted from FFA's to glucose oxidation. This shift in energy substrate improves cardiac energy metabolism in condition of ischemia leading to mechanical efficiency of failing heart.<sup>8,13</sup>

Studies have shown beneficial effect of TMZ in patients with HF in terms of left ventricular (LV) function improvement and symptoms control.<sup>1,13,14</sup>

There is no data available regarding effect of TMZ on LV function and symptoms control in patients with HF secondary to IHD in our part of the country. This study was designed to see the effect of TMZ on LV function and symptoms control of patients with HF secondary to IHD.

## MATERIAL AND METHODS

This study was conducted at Pharmacology Department, Gomal Medical College, Dera Ismail Khan from 1<sup>st</sup> February 2007 to 1<sup>st</sup> February 2009. A total of 63 patients between 25-80 years with history of HF secondary to IHD were divided into two groups. Group one (TMZ group) consisted of 31 patients, received TMZ modified release (MR) 35mg twice daily as add on therapy to the conventional HF therapy for three months while the second group (conventional therapy group) consisted of 32 patients, whom were continued on conventional HF therapy without TMZ during the same period.

All the patients were clinically stable (NYHA functional class 2.7±0.46) and were on stable medical treatment with angiotensin converting enzyme inhibitors (ACEIs) or angiotensin receptor blockers,  $\beta$ -blockers, and, where indicated diuretics, long and short acting nitrates, and digoxin.

Inclusion criteria were patients with documented IHD (either >70% narrowing in at least one artery on coronary angiography or previous history of myocardial infarction (MI), persistent symptoms (dyspnoea on exertion, fatigue, orthopnea, paroxysmal nocturnal dyspnoea or edema, alone or in combination, despite optimized medical treatment for at least 3 months, EF<40% on echocardiography, treatment of ACEIs / ARBs or  $\beta$ -blockers started prior to 6 months before entering the study.

Patients with history of acute myocardial infarction or unstable angina, heart failure due to

primary valvular heart disease, renal insufficiency (serum creatinine >2.0mg/dl), acute heart failure <3 months, and uncontrolled hypertension (B.P>180/110mm Hg), were excluded from the study.

Baseline demographic variables of the study population were noted on the preformed proforma. A thorough physical examination was carried out in all the patients both at start and then at the end of study, especially looking for the pulse, blood pressure, signs of heart failure (i.e. edema feet, raised jugular venous pressure, 3rd heart sound, bi-basal crackles). Chest x-ray was done at study entry and then at the end of study. Symptoms of the HF were classified according to NYHA functional class both at baseline and at the end of study. All the patients underwent echocardiography with left ventricular end diastolic dimension (LVEDD), left ventricular end systolic dimension (LVESD) and ejection fraction (EF) measured both at the start and on completion of study. The primary outcome of the study was improvement in LV function. The secondary end point was change in NYHA functional class at the end of study.

The data was analyzed using Statistical Package for Social Sciences (SPSS) version 10. Categorical variables were expressed as frequencies and percentages while continuous variables were expressed as Mean± SD. Comparative analysis between the two groups regarding LV function, NYHA functional class were done using two tailed student 't' test. P value of <0.05 was taken as significant.

## RESULTS

Out of 63 patients, there were 46 (73.02%) males and 17 (26.98%) females. TMZ group consisted of 23 (75%) males and 8 (25%) females while there were 23 (72%) males and 9 (28%) females in the conventional therapy group. Mean age of the study population was 63.3±10.2 years. The mean age of TMZ group was 62.2±12.9 years while mean age in conventional therapy group was 64.4±6.6 years. (Table 1)

There were 44 (69.8%) patients suffering from diabetes mellitus, 20 (64.5%) in TMZ group and 22 (68.7%) in conventional therapy group, while hypertension was present in 45 (71.42%) patients, 23 (74.2%) in TMZ group and 22 (68.7%) in conventional therapy group. Seven (22.6%) patients in TMZ and 8 (25%) patients in conventional therapy group were suffering from angina pectoris, while 16 (51.6%) patients in TMZ group and 17 (53%) patients in conventional therapy group had previous history of MI.

**Table 1: Demographic characteristics of patients in trimetazidine and conventional therapy group.**

Variable	Trimetazidine Group (n=31)	Conventional Therapy Group (n=32)
Age (years) Mean	62.2±12.9	64.4±6.6
Males	23(75%)	23(72%)
Females	8(25%)	9(28%)
Diabetes	20(64.5%)	22(68.7%)
Hypertension	23(74.2%)	22(68.7%)
Smoking	17(58.1%)	19(59.4%)
Angina pectoris	7(22.6%)	8(25%)
MI	16(51.6%)	17(53%)
CABG	3(9.7%)	3(9.4%)
PCI	5(16.1%)	4(12.5%)
<b>Medications:</b>		
ACEIs	23(74.2%)	25(78.13%)
ARBs	8(25.81%)	7(21.8%)
β-blockers	31(100%)	32(100%)
Nitrates	14(45.2%)	16(0.5%)
Diuretics	16 (51.6%)	17 (53.13%)
Digoxin	10 (32.3%)	12 (37.5%)

Abbreviations: ACEIs=angiotensin converting enzyme inhibitor; ARBs=angiotensin receptor blockers, CABG=coronary artery bypass grafting; MI=Myocardial infarction; PCI=Percutaneous coronary intervention.

Table 2 shows the echocardiographic characteristics of patients in two groups at baseline and at the end of study. Treatment with TMZ resulted in significant reduction in left ventricular end diastolic dimension (LVEDD) from 71.7±4.1mm to 68.1±6.8mm as compared to conventional therapy group which had an increase in LVEDD from

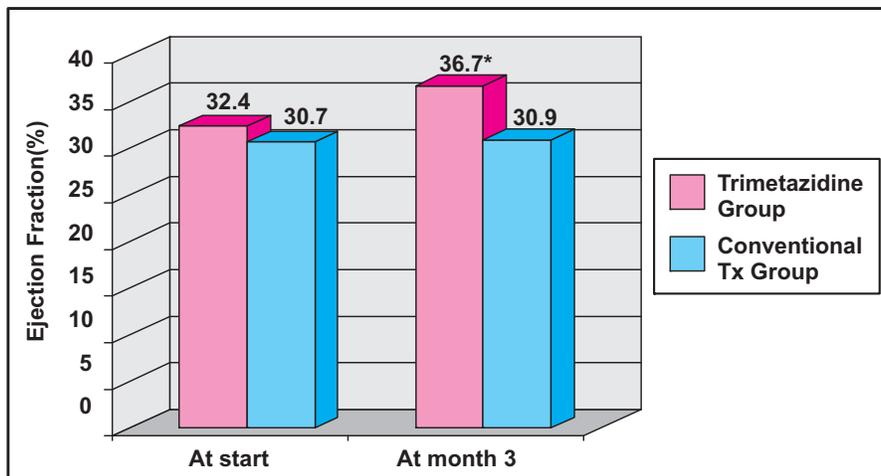
73.3±3.6mm to 74.8±6.1mm, p<0.001. There was also a significant reduction in left ventricular end systolic dimension (LVESD) in TMZ group from 58.97±5.8mm to 54.3±7.89mm as compared to conventional therapy group which showed an increase in LVESD from 61±5.8mm to 62.3±8.9mm, p<0.001.

**Table 2: Echocardiographic characteristics of patients in trimetazidine and conventional therapy group at the start and 3 months of therapy.**

	Trimetazidine Group (n=31)		Conventional Therapy Group (n=32)		p-value*
	Mean at		Mean at		
	Base line	3 <sup>rd</sup> month	Base line	3 <sup>rd</sup> month	
LVEDD (M-mode),mm	71.7±4.1	68.1±6.8	73.3±3.6	74.8±6.1	<0.001
LVESD (M-mode),mm	58.97±5.8	54.3±7.89	61±5.8	62.3±8.9	<0.001
EF (%)	32.4±7.2	36.7±9.1	30.7±9.2	30.9±10.5	0.022

Abbreviation: LVEDD= Left ventricular end diastolic dimension; LVESD= Left ventricular end systolic dimension; EF=Ejection fraction.

\* For percentage change from baseline with Trimetazidine versus Conventional Therapy Group at 3 months.



★ = 0.022 versus Conventional Therapy Group at month 3.

Fig. 1: Ejection fraction of patients in trimetazidine and conventional group.

Ejection fraction (EF) improved significantly in TMZ group from  $32.4 \pm 7.2\%$  to  $36.7 \pm 9.1\%$  as compared to conventional therapy group from  $30.7 \pm 9.2\%$  to  $30.9 \pm 10.5\%$ ,  $p=0.022$ . Figure 1

In TMZ group, NYHA functional class improved by two grades in one patient, one grade in 23 patients, while five patients showed no change. There were two patients showing deterioration by one grade. On the other hand, in Conventional therapy group out of 32 patients, 10 patients had worsening of NYHA functional class by one grade, 17 patients showed no change while NYHA functional class improved by one grade in five patients. Statistically significant improvement in NYHA functional Class occurred in TMZ group (from  $2.74 \pm 0.44$  to  $2 \pm 0.52$ ) as compared to Conventional therapy group (from  $2.66 \pm 0.48$  to  $2.81 \pm 0.56$ ),  $p < 0.001$ . (Table 3)

### DISCUSSION

The results of our study show that addition of TMZ to patients with HF secondary to IHD resulted in improvement in LV function and functional class as compared to patients on conventional therapy.

TMZ belongs to a new group of pharmaceutical compounds which exert its anti-ischemic effect by shifting the energy metabolism of failing heart from FFAs to carbohydrate oxidation which require less oxygen to generate same amount of energy.<sup>14</sup> This shift in energy substrate improves cardiac energy metabolism in condition of ischemia leading to mechanical efficiency of failing heart.<sup>8,13</sup>

In our study, at 3 months, there was a significant improvement in LVEDD and LVESD in patients

Table 3: NYHA functional class of patients in Trimetazidine and conventional group at the start and 3 months of therapy.

	Trimetazidine Group (n=31)		Conventional Therapy Group (n=32)		p-value*
	Base line	3 <sup>rd</sup> month	Base line	3 <sup>rd</sup> month	
<b>NYHA Class</b> (Mean $\pm$ SD)	$2.74 \pm 0.44$	$2 \pm 0.52$	$2.66 \pm 0.48$	$2.8 \pm 0.54$	$< 0.0001$
NYHA Class I	0(0%)	4(12.9%)	0(0%)	0(0%)	
NYHA Class II	8(25.8%)	23(74.2%)	11(34.4%)	8(25%)	
NYHA Class III	23(74.2%)	4(12.9%)	21(65.6%)	22(68.8%)	
NYHA Class IV	0	0(0%)	0(0%)	2(6.3%)	

\* For percentage change from baseline with Trimetazidine versus conventional group at 3 months.

receiving TMZ therapy resulting in significant increase in the EF (14%) as compared to the patients receiving conventional therapy. Our results are similar to reported by other studies<sup>1,13,15,16</sup> Tunnanen et al<sup>1</sup> reported 15% improvement in EF (from  $30.9 \pm 8.5\%$  to  $34.8 \pm 12\%$ ) in TMZ from group as compared to placebo which showed a 17% decrease in EF (from  $37.5 \pm 8.4\%$  to  $31.9 \pm 12\%$  in patients with idiopathic dilated cardiomyopathy. Brottier and colleagues<sup>13</sup> demonstrated that EF of patients with ischemic cardiomyopathy treated with trimetazidine for 6 months increased by >9% compared with a placebo group. Fragasso et al<sup>15</sup> reported 18% increase in EF in HF patients treated with TMZ as compared to placebo The study by Belardinelli and Purcaro<sup>16</sup> also reported a significant increase in resting and peak EF with dobutamine infusion in patients treated with TMZ as compared to placebo.

The increase in myocardial contractility during ischemic cardiomyopathy can be explained by the regulation of mitochondrial structure and function, and by the increase in glycolytic adenosine triphosphate (ATP) synthesis.<sup>17</sup> It is possible that hibernated myocardium can be activated by trimetazidine: a favorable effect of trimetazidine on hibernation was demonstrated by Belardinelli and colleagues, who found that trimetazidine improved the contractile response of chronically dysfunctional myocardium to low-dose dobutamine.<sup>16</sup>

Functional class in our patients improved significantly in TMZ group while on the other hand there was worsening of functional class among patients in conventional therapy group. Fragasso et al<sup>15</sup> reported a significant improvement in functional class in TMZ group (from  $3.04 \pm 0.3$  to  $2.45 \pm 0.52$ ) as compared to placebo ( $p < 0.001$ ). Study by Vitale and colleagues<sup>18</sup> reported a significant improvement in NYHA functional class in TMZ group as compared to placebo in elderly patients with left ventricular dysfunction.

Our data have provided support for the therapeutic importance of treatment with trimetazidine in patients with left ventricular dysfunction and ischemic cardiomyopathy.

## CONCLUSION

Trimetazidine reduced left ventricular dimensions with resultant improvement in left ventricular function that lead to improvement in NYHA functional class in patients with heart failure secondary to IHD.

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