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Original Article

Metabolic manipulation in dilated cardiomyopathy: Assessing the role of trimetazidine

Suman Jatain, Aditya Kapoor *, Archana Sinha, Roopali Khanna, Sudeep Kumar, Naveen Garg, Satyendra Tewari, Pravin Goel

Department of Cardiology, Sanjay Gandhi PGIMS, Lucknow 226014, India

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ABSTRACT

Objectives: To study the role of metabolic modulator (trimetazidine: TMZ) in dilated cardiomyopathy (DCM). Optimizing altered substrate metabolism in heart failure (HF) with metabolic modulators allows more efficacious energy production from glucose than from free fatty acids.

Methods: 100 patients of DCM (47.7 years, NYHA class 2.17, LVEF 27.3%) were randomized to TMZ (20 mg tid, $n = 50$) vs conventional therapy ($n = 50$). Functional status, BNP and various echocardiographic parameters were assessed at 3–6 months.

Results: At 3 months, TMZ group had significantly improved NYHA class (2.25 vs 1.85), 6 min walk test (349.7 vs 402 m), LVD-36 score (25.5 vs 21) and BNP (744.7 vs 248.3 pg/ml), all p 0.001. Significant improvement was also seen in LV end-systolic (LVESV, 87.1 ± 27.5 vs 78.5 ± 24.9 ml/m^2, p 0.001), LV end-diastolic volumes (LVEDV, 117.6 ± 29.3 vs 110.9 ± 27.4 ml/m^2, p 0.001), LVEF (27 vs 30.9%, p 0.001) and LV wall stress (90.2 ± 18.9 vs 71.1 ± 13.2 dyn/cm^2, p 0.0001). The % change in LVESV, LVEDV, LVEF and LV wall stress was −9.5%, −5.4%, +8.4% and −21.8%. Other echo parameters also improved after 3 months of TMZ (E/A ratio 1.9 vs 1.2, $p = 0.001$, E/A VTI 2.7 vs 1.6, $p = 0.001$, myocardial performance index, MPI 0.8 vs 0.7, $p = 0.0001$), Tissue Doppler parameters (E/E′ septal (19.7 vs 12.5, $p = 0.001$) and E/E′ lateral (13.3 vs 9.4, $p = 0.0001$)). Patients in control group had no change in NYHA class, LVD-36 scores, LV volumes or LVEF at 3 months although BNP and LV wall stress reduced to a slight extent. Patients on TMZ had further improvement in NYHA class, walk test, BNP levels and echocardiographic parameters at 6 months.

Conclusions: Metabolic modulators (TMZ) may help in improving LV function in DCM. In this study, benefit was noted by 3 months with further improvement at 6 months.

1. Introduction

Chronic heart failure (HF) is a common cause of mortality and morbidity with increasing prevalence both in the developing and the developed world.[1] Despite advances in pharmacological and interventional management of these patients, persistent heart failure with progression of contractile dysfunction and continuing left ventricular (LV) remodeling is common. The growing numbers of such patients with attendant high morbidity and mortality and consequent economic impact on the healthcare systems emphasizes the need to evaluate other therapeutic strategies.

Myocardial dysfunction in HF is due to altered substrate energy metabolism with reduction in mitochondrial oxidative metabolism and down-regulation of glucose and free fatty acid oxidation (FFA).[2] Under resting aerobic conditions, the normal human myocardium derives most of its energy (60–90%) from oxidation of FFA's, while the contribution from carbohydrate metabolism is only about 10–30%.[3,4] Although FFA oxidation yields more ATP than glycolysis, it is less energy efficient because it consumes more oxygen. Apart from this, FFA oxidation also inhibits glucose oxidation through inhibition of pyruvate dehydrogenase leading to lactate and hydrogen ion accumulation within the myocardium with intracellular acidosis and inhibition of contractile function.[5,6] Studies have demonstrated that the failing heart is associated with reduced rates of FFA and increased rates of glucose utilization with

Abbreviations: TMZ, trimetazidine; DCM, dilated cardiomyopathy; HF, heart failure; LV, left ventricular; FFA, free fatty acid; EF, ejection fraction; LVEDD, left ventricular end-diastolic dimension; LVESD, left ventricular end-systolic dimension; LVEDV, left ventricular end-diastolic volume; LVESD, left ventricular end-systolic volume; FS, fractional shortening; SV, stroke volume; LVESS, LV wall end-systolic stress; ACEI, angiotensin-converting enzyme inhibitors; BB, beta-blockers.

* Corresponding author. Tel.: +91 522 2494220; fax: +91 0522 2668073.
E-mail address: akapoor65@gmail.com (A. Kapoor).

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a shift from FFA oxidation toward carbohydrate oxidation.[7,8] This *metabolic remodeling* probably represents an adaptive cardioprotective mechanism that can help improve contractile function, thus slowing the progression of HF and improving prognosis. Hence metabolic modulators which have the potential to shift myocardial substrate utilization from FFA toward glucose metabolism may have a place in the management of HF patients.

Trimetazidine (1-[2,3,4-trimethoxybenzyl-piperazine dihydrochloride], TMZ) is one such metabolic modulator that can improve myocardial substrate utilization with a shift of energy production from FFAs to the more energy efficient pathway of glucose oxidation, by selectively inhibiting mitochondrial long chain 3-ketoacyl co-enzyme A thiolase, a key enzyme in the B-oxidation pathway.[9] It is known to have anti-ischemic properties without affecting myocardial oxygen consumption or blood flow or exerting any negative inotropic and vasodilator effects.[10,11] By maintaining the intracellular levels of phosphocreatine (PCr) and ATP, TMZ also ameliorates the low PCr/ATP ratio in chronic HF and hence enhances the recovery of mitochondrial oxidative phosphorylation and phosphocreatine resynthesis.[12,13] Reduction in intracellular acidosis, calcium overload, cell apoptosis, ischemia induced free-radical injury and improvement in endothelial function further contribute to the proposed beneficial effects of TMZ in improving myocardial contractile function.[14–16]

The role of TMZ in patients with HF secondary to ischemic cardiomyopathy has been established in previous studies which have demonstrated beneficial effects on symptom status, exercise duration and LV systolic function.[17–21] However only a few studies with limited patient numbers have assessed its role in patients with HF secondary to dilated cardiomyopathy (DCM).[22–24]

We prospectively assessed if addition of TMZ to conventional treatment in patients with heart failure (HF) secondary to DCM would improve functional class, exercise tolerance, LV systolic function and other echocardiographic parameters.

2. Methods

A total of 100 patients with HF and DCM in NYHA in functional class II–IV and with ejection fraction (EF) $\leq$45% (by transthoracic echocardiography) were included in the study. The study conformed to the institutional ethical guidelines and patients were included after obtaining informed consent. All patients had persistent symptoms despite conventional medical therapy for at least 3 months prior to the study. Conventional therapy was defined as optimized up-titration of angiotensin-converting enzyme inhibitors (ACEI) and beta-blockers (BB) with stable doses for the last 4 weeks in all cases, and wherever indicated, long-acting nitrates, digoxin, diuretics, and antiplatelet drugs, as required. Patients were randomized in a 1:1 fashion to receive either TMZ (20 mg three times daily in addition to conventional therapy or conventional therapy alone).

Patients were excluded in case of an acute myocardial infarction or unstable angina pectoris within previous 3 months, previous known coronary artery disease, primary valvular disease, history of any alcohol abuse within 6 months, high-grade arrhythmias, significant renal insufficiency (serum creatinine $\geq$ 2.2 mg/dl), known active neoplastic process, orthopedic or neurological illness that could limit their ability to exercise.

All patients underwent baseline investigations, including complete hemogram, renal and liver function test, blood sugar, serum electrolytes, lipid profile and BNP estimation. Levels of BNP were assessed using fluorescence immunoassay with a commercially available kit (Alere Triage Cardio 3 Panel, Alere, Inc., San Diego, CA, USA). Functional exercise capacity was estimated using the 6 min walk test. The LV dysfunction questionnaire (LVD-36) was used to measure the impact of LV dysfunction on daily life and well-being.[25]

Echocardiography: All patients underwent detailed echocardiography using a GE Vivid 7 ECHO machine (GE Healthcare, Waukesha, WI). Various 2D Echocardiographic and Doppler indices, including left ventricular end-diastolic dimensions and volumes (LVEDD, LVEDV), left ventricular end-systolic dimensions and volumes (LVESD, LVESV), LV ejection fraction (LVEF), stroke volume (SV) and fractional shortening (FS) were recorded. The LV dimensions were obtained from the parasternal long-axis view while LV volumes were obtained from the apical four- and two-chamber views', using the modified Simpson's rule, from which ejection fraction was automatically calculated as the difference between end-diastolic volume and end-systolic volume normalized to end-diastolic volume. The LV wall stress (LVESS) was calculated as LVWS = [BP $\times$ (LVESD/2)]/{2 $\times$ [(systolic IVS + systolic PW)/2]}, where LVESD is LV end-systolic dimension and IVS is interventricular septum, while Left ventricular (LV) mass (LVM) was calculated by the Devereux formula.[24,26,27]

Transmitral flow velocities (peak early: E wave and late: A wave), their ratio (E/A); velocity time integral (EVTI and A VTI), E deceleration time were also recorded in all patients. The Tei index, an echocardiographic/Doppler index of combined systolic and diastolic function, was calculated as isovolumic relaxation time plus isovolumic contraction time divided by ejection time.[28] All patients underwent repeat assessment at 3 and 6 months of follow up.

2.1. Statistical analysis

Continuous variables are expressed as mean $\pm$ standard deviation (SD), and categorical variables as percent. Student's *t* test and chi-square analysis were carried out for comparison of continuous and categorical variables, respectively and *p* value $\leq$0.05 was considered significant. Paired *t*-test was carried out for comparison of variables before and after RT. All statistical analysis was done using IBM SPSS Statistical Software (IBM SPSS Statistics version 15.0, IBM SPSS, USA).

3. Results

A total of 100 patients (mean age 47.7 $\pm$ 7 years, 77% males) with a mean NYHA class (2.17 $\pm$ 0.5) were included in the study. The mean LVEF was (27.3 $\pm$ 5.3, range of EF $-$11.8 $\pm$ 38.18.) while mean BNP level was 681.5 $\pm$ 733.7 pg/ml (range 5–4240) Overall, 26% had hypertension while 20% had diabetes. All patients were receiving ACEI and BB, while 80 and 84% were receiving diuretics and digoxin respectively. The mean dose of ACEI was 9.2 $\pm$ 4.7 mg, BB 8.25 $\pm$ 4.5 mg and diuretics was 38.0 $\pm$ 12.5 mg respectively (Table 1).

Fifty patients were randomized to receive TMZ in addition to conventional therapy while 50 received conventional therapy alone. The two groups were comparable in age, body mass index, gender distribution, prevalence of hypertension or diabetes, NYHA functional class, 6 min walk time, BNP levels, LVD-36 score and hemodynamic parameters (Table 1).

There was no significant difference in the two groups in terms of baseline LVES and LVED dimensions, indexed volumes and EF (Table 2). Baseline FS (20.9 $\pm$ 4.3 vs 20.7 $\pm$ 3.4, p = 0.25), SV (50.2 $\pm$ 12.3 vs 49.9 $\pm$ 13.3 ml, p = 0.89), SVRI (15.3 $\pm$ 4.4 vs 14.4 $\pm$ 5.4, p = 0.26) and LV wall stress (93.2 $\pm$ 18.9 vs 87.3 $\pm$ 17.9 mmHg, p = 0.22) were also comparable. Baseline diastolic and tissue Doppler echocardiographic parameters were also comparable amongst the two groups.

The drug was well tolerated and none of the patients discontinued the drug due to adverse effects, and the dose did not require to be modified during the study. There was no significant change in any biochemical parameters during follow up including renal function, blood sugar or lipid levels.

Table 1
Baseline demographics of patients.

Parameter	Total patients (100)	TMZ (50)	Control (50)	*p* value
Age (years)	47.7 ± 12.0	47.1 ± 12.6	48.31 ± 11.5	0.629
BMI	24.0 ± 4.13	24.6 ± 4.5	23.3 ± 3.5	0.098
Male:female (%)	74:26	73:27	75:25	0.143
Hypertension	26%	29%	21%	0.258
Diabetes	20%	19.2%	20.8%	0.179
Duration of symptoms (months)	14.84 ± 10.36	13.3 ± 8.4	16.5 ± 11.9	0.12
NYHA class	2.17 ± 0.5	2.25 ± 0.5	2.08 ± 0.4	0.092
Heart rate	82.3 ± 8.5	81.9 ± 9.0	88.2 ± 7.9	0.293
Systolic BP	124.8 ± 22.6	126.8 ± 20.9	122.1 ± 12.3	0.07
Diastolic BP	80.4 ± 14.5	81.73 ± 15.5	79.4 ± 8.3	0.358
6 min walk test (m)	347.76 ± 83.83	349.8 ± 89.6	345.6 ± 77.9	0.804
BNP (pg/ml)	741.46 ± 733.7	744.7 ± 834.9	712.9 ± 606.8	0.372
LVD-36 score	24.99 ± 4.6	25.5 ± 4.9	24.4 ± 4.1	0.233
% on diuretics	80	79	81	
% on digoxin	84	83	85	

Table 2
Baseline systolic echocardiographic parameters (TMZ vs control).

Parameter	TMZ (52)	Control (48)	*p* value
LVESD (mm)	4.97 + 0.69	4.98 + 0.62	0.91
LVEDD (mm)	6.2 + 0.6	6.2 + 0.7	0.90
LVESVI (ml/m^2)	87.1 + 27.5	81.9 + 21.7	0.30
LVEDVI (ml/m^2)	117.6 + 29.3	112.9 + 27.8	0.82
LVEF (%)	27.0 ± 6.2	27.6 ± 4.2	0.58
E/A velocity	1.94 ± 1.12	2.08 ± 1.20	0.53
E VTI/A VTI	2.69 ± 1.99	2.77 ± 1.78	0.8
MPI	0.80 ± 0.17	0.75 ± 0.11	0.07
E vel/TDIe′ septal	19.74 ± 9.93	17.95 ± 8.58	0.34
E vel/TDIe′ lateral	13.35 ± 5.17	12.38 ± 5.04	0.34

LVESD, left ventricular end-systolic dimension; LVEDD, left ventricular end-diastolic dimension; LVESVI, left ventricular end-systolic volume indexed to body surface area; LVEDVI, left ventricular end-diastolic volume indexed to body surface area; LVEF, left ventricular ejection fraction; MPI, myocardial performance index.

3.1. Three month follow up (Tables 3 and 4)

There was a significant improvement in mean NYHA Class (2.25 ± 0.5 to 1.85 ± 0.46, $p = 0.001$), 6 min walk distance (349.8 ± 89.6 to 402.1 ± 87.6, $p = 0.001$), LVD-36 score (25.5 ± 4.99 to 21.03 ± 4.6, $p = 0.001$) along with reduction in mean BNP levels (744.7 ± 834.9 to 248.3 ± 278.5, $p = 0.001$) after 3 months of TMZ use. There was no significant change in heart rate, systolic or diastolic BP in patients receiving TMZ.

Amongst those on conventional therapy alone, there was no significant change in mean NYHA class (2.08 ± 0.4 to 2.02 ± 0.32, $p = 0.322$), 6 min walk test (345.6 ± 77.9 to 348.96 ± 63.6, $p = 0.53$) and LVD-36 score (24.4 ± 4.1 to 24.14 ± 3.14, $p = 0.225$), while BNP levels demonstrated a significant fall (712.9 ± 606.8 to 455.44 ± 475.87, $p = 0.001$). However BNP levels at 3 months in this group were still significantly higher than those receiving TMZ (455.44 vs 248.3 pg/ml, p +0.009).

Patients receiving TMZ demonstrated significant reduction in LVES and LVED dimensions and volumes along with improvement in EF (27.0 ± 6.2 to 30.9 ± 6.51, $p = 0.001$) (Table 3). Parameters like SV (50.2 ± 12.3 vs 53.3 ± 13.5 ml, $p = 0.001$), FS (20.9 ± 4.3 to 23.14 ± 4.11, $p = 0.0001$), SVR (15.3 ± 4.4 to 14.42 ± 4.73 $p = 0.05$) and LV wall stress (93.2 ± 18.9 vs 71.1 ± 13.2 mmHg, $p = 0.0001$) also improved significantly.

The mean transmitral E/A velocity ratio, E/A VTI, MPI, TDI E/E′ (septal) and TDI E/E′ (lateral) all improved significantly in the TMZ group (Table 3). The % improvement in MPI, TDI E/E′ (septal) and TDI E/E′ (lateral) was 10%, 36% and 29.2% respectively.

In the control group, there was no significant change in LV dimensions and volumes. LVEF (27.6 ± 4.2 to 27.80 ± 4.78, $p = 0.42$), SV (49.9 ± 13.3 to 50.4 ± 13.4 ml, $p = 0.08$), FS (20.7 ± 3.4 to 20.83 ± 3.49, $p = 0.66$) and SVR (14.4 ± 5.4 to 14.89 ± 5.43, $p = 0.41$) also did not demonstrate any significant change at 3 months. Only LV wall stress exhibited a reduction (87.3 ± 17.9 to 76.47 ± 17.43 mmHg, $p = 0.03$) albeit to a lesser extent than in the TMZ group. None of the parameters of diastolic function including transmitral E/A velocity ratio, E/A VTI or tissue Doppler parameters (TDI E/E′ (septal) and TDI E/E′ (lateral) or MPI showed any significant change in those not receiving TMZ, Table 4).

3.2. Six month follow up

Patients on TMZ had further improvement in NYHA Class (from 1.85 ± 0.46 to 1.28 ± 0.49, $p = 0.001$) and LVD-36 score (21.03 ± 4.6 to 16.14 ± 5.15, $p = 0.001$). The 6 min walk test and BNP levels also showed a sustained improvement at 6 months (Fig. 1a and b).

Table 3
Comparison of echo parameters at baseline, 3 and 6 months in TMZ group.

Parameter	Baseline (52)	3-Month (52)	*p* value	6-Month (50)	*p* value*
LVESD (mm)	4.97 + 0.69	4.78 ± 0.69	0.0001	4.51 ± 0.71	0.001
LVEDD (mm)	6.2 + 0.6	6.20 ± 0.65	0.0001	6.00 ± 0.65	0.001
LVESVI (ml/m^2)	87.1 + 27.5	78.5 ± 24.9	0.0001	68.48 ± 23.11	0.001
LVEDVI (ml/m^2)	117.6 + 29.3	110.9 ± 27.4	0.0001	103.02 ± 25.22	0.001
LVEF (%)	27.0 ± 6.2	30.9 ± 6.51	0.0001	34.84 ± 8.10	0.001
E/A velocity	1.94 ± 1.12	1.19 ± 0.6	0.001	1.01 ± 0.43	0.001
E VTI/A VTI	2.7 ± 1.9	1.6 ± 0.7	0.001	1.38 ± 0.54	0.001
MPI	0.80 ± 0.2	0.72 ± 0.10	0.001	0.64 ± 0.08	0.001
E vel/TDIe′ septal	19.7 ± 9.9	12.5 ± 5.8	0.001	10.26 ± 5.10	0.001
E vel/TDIe′ lateral	13.3 ± 5.2	9.4 ± 3.7	0.001	8.03 ± 3.06	0.001

All abbreviations as in Table 2.
The first p value represents comparison between baseline and 3 months.
The second p value (*) represents comparison between 3 and 6 months.

Table 4
Comparison of echo parameters at baseline, 3 and 6 months in control group.

Parameter	Baseline	3-Month	*p* value	6-Month	*p* value*
LVESD (mm)	4.98 + 0.62	5.00 ± 0.06	0.184	5.03 ± 0.62	0.53
LVEDD (mm)	6.28 + 0.68	6.31 ± 0.65	0.017	6.36 ± 0.66	0.113
LVESVI (ml/m^2)	81.9 + 21.7	82.31 ± 21.54	0.532	84.21 ± 24.31	0.210
LVEDVI (ml/m^2)	112.9 + 27.8	113.65 ± 27.41	0.228	115.73 ± 29.74	0.173
LVEF (%)	27.6 ± 4.2	27.80 ± 4.78	0.42	27.69 ± 5.56	0.893
E/A velocity	2.08 ± 1.20	1.94 ± 0.97	0.48	1.91 ± 0.93	0.830
E VTI/A VTI	2.77 ± 1.78	3.12 ± 5.28	0.640	3.28 ± 5.93	0.940
MPI	0.75 ± 0.11	0.73 ± 0.14	0.948	0.74 ± 0.25	0.863
E vel/TDIe′ septal	17.95 ± 8.58	17.13 ± 7.19	0.108	17.34 ± 6.87	0.631
E vel/TDIe′ lateral	12.38 ± 5.04	12.04 ± 4.32	0.329	12.42 ± 3.99	0.826

All abbreviations as in Table 3.
The first *p* value represents comparison between baseline and 3 months.
The second *p* value (*) represents comparison between 3 and 6 months.

Amongst those not on TMZ, while mean NYHA class improved slightly (2.02 ± 0.32 to 1.85 ± 0.5, $p = 0.04$) there was a non-significant trend toward reduction in BNP levels (455.44 ± 475.87 to 382.96 ± 400.7, $p = 0.07$). The 6 min walk test and LVD-36 score did not show any further improvement at 6 months (Fig. 1a and b).

Patients on TMZ had a sustained improvement in all echocardiographic parameters at 6 months with the LVEF improving from 30.9 ± 6.51% at 3 months to 34.84 ± 8.1% at 6 months, SV (53.3 ± 13.5 to 56.8 ± 13.6 ml, $p = 0.001$), FS (23.14 ± 4.11 to 25.18 ± 5.01, $p = 0.001$) and LV wall stress (71.1 ± 13.2 to 56.4 ± 14.9 mmHg, $p = 0.001$). Amongst those on conventional therapy, there was no further improvement in any echocardiographic parameter at 6 months (Tables 3 and 4).

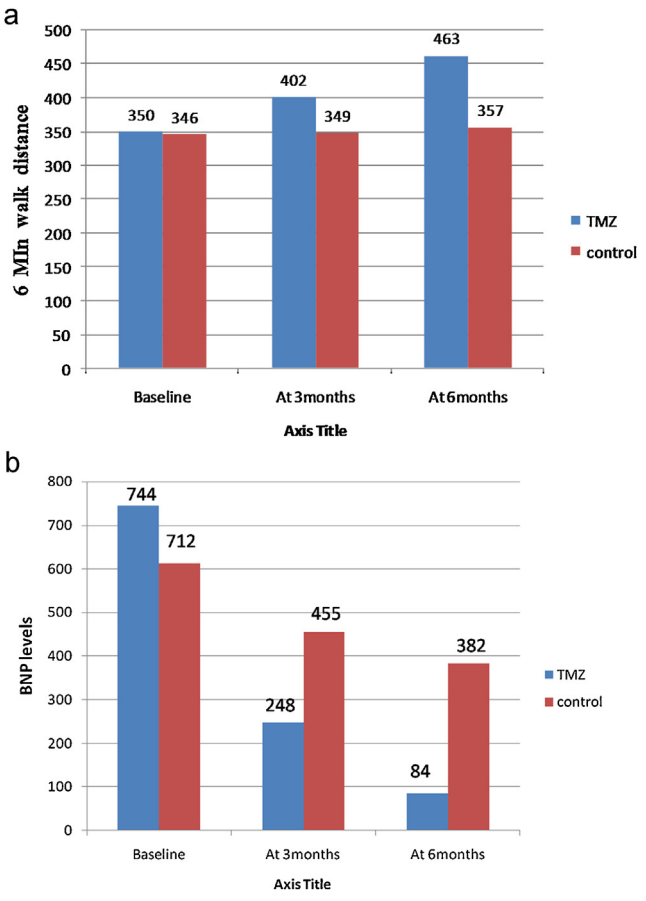

Fig. 1. (a) Change in 6 min walk test in TMZ and controls. (b) Change in BNP levels in TMZ and controls.

3.3. Changes in use of CV drugs

At 3 months amongst those receiving TMZ, rates of usage of diuretics and digoxin was 61.5 and 63.5% respectively, while in those on conventional therapy, the corresponding rate was 73% (p = ns for diuretics) and 79.2% ($p = 0.05$ for digoxin). Those on TMZ also required significantly lesser doses of bb (5.9 ± 1.4 vs 10.8 ± 5.3 mg, $p = 0.0001$) and diuretics (32.21 ± 11.4 vs 44.27 ± 10.6 mg, $p = 0.0001$).

There were two deaths in both study groups while 5 patients required hospitalization (1 in the TMZ group and 4 in the control group).

4. Discussion

The results of the present study indicate that trimetazidine, a partial inhibitor of FFA oxidation, when added to conventional therapy in patients with DCM and HF, improved NYHA functional class, 6 min walk test, quality of life and diverse parameters of LV systolic and diastolic function within 3 months of initiation of therapy. In those receiving conventional therapy alone, there was no significant change in mean NYHA class, 6 min walk test, LVD-36 score and echocardiographic parameters.

Amongst those taking TMZ, the mean NYHA functional class improved by 1–2 grades in 37% while none of these patients had any deterioration in NYHA class. In contrast, in those receiving conventional therapy, NYHA class deteriorated by grade 1–2 in 11.5%, improved in 7.5% and remained stable in 80%. By 3 months of follow up, patients on TMZ had a significant reduction in LVES and LVED dimensions and volumes and LV wall stress along with improvement in FS. The % change in LVESV, LVEDV, FS and LV wall stress was −9.5%, −5.4%, +8.4% and −21.8% respectively. A greater absolute % fall in LVES volume (−9.5%) as compared to LVED volume (−5.4%) resulted in a significant improvement in LVEF (+9.4%). This improvement in LVEF is in keeping with what has been reported previously in patients with both ischemic and non-ischemic HF (9%,[17] 7%,[22] 18%,[23] 15%,[24] 14%[29]).

Patients receiving TMZ had further improvement in NYHA Class, LVD-36 score, 6 min walk test and BNP levels at 6 months. This group also had a sustained improvement in all echocardiographic parameters at 6 months (change in LVESVI of −12.4%, LVEDVI of −7.8%, EF +10.9%, LV wall stress of −18.3% and MPI −9.6%). Amongst those on conventional therapy, there was no further improvement in any echocardiographic parameter at 6 months.

Since therapeutic interventions which potentiate shift of myocardial substrate utilization toward glucose metabolism are expected to protect the ischemic myocardium, the effects of TMZ have previously been assessed mainly in patients with ischemic HF.[17–21,29] Reported benefits include positive outcomes on symptom status, exercise parameters and LV systolic function. Although a few studies have assessed the role of TMZ role in

patients with HF secondary to non-ischemic DCM, most of these included patients with both ischemic and non-ischemic HF. In 55 HF patients (ischemic $n = 35$, non-ischemic $n = 30$). Fragasso et al. reported that while quality of life and LVD-36 improved only in ischemic patients, TMZ significantly improved EF regardless of the etiology of HF, with a trend toward improvement in exercise parameters as well.[22] Use of TMZ in 12 HF patients (6 non-ischemic) improved NYHA class, LVEF and PCr/ATP ratio which is an indirect measure of myocardial energy utilization indicating preservation of the myocardial high-energy phosphate levels.[23] Since TMZ is only a partial and not total inhibitor of FFA oxidation, the metabolic switch from FFA to glucose oxidation is not complete, and hence this may not be the predominant mechanism of action of TMZ. In support of this, in a small study of 19 patients with DCM, Tuunanen et al. reported that although TMZ significantly improved EF in non-ischemic HF, myocardial FFA oxidation was only modestly decreased; TMZ was postulated to have other extra-cardiac metabolic effects like enhanced insulin sensitivity and resultant increased glucose oxidation.[24] Other studies have also reported improved whole-body insulin sensitivity and glucose control with TMZ in insulin-resistant idiopathic DCM as well as diabetic patients with ischemic HF.[19,30]

Diastolic function: An important finding of the present study is the improvement in parameters of diastolic function as well, after 3–6 months of TMZ. Chronic LV dysfunction alters diastolic function and can progressively impair ventricular compliance, further aggravating LV filling and forward flow. Data on amelioration of diastolic function in chronic HF after TMZ therapy are limited.[20,31] No other study has previously reported benefit with TMZ on diverse parameters like E/A ratio, E/A VTI, global myocardial performance index (MPI) as well as tissue Doppler parameters (E/E′ septal and E/E′ lateral) in chronic HF secondary to DCM.

Biomarker and exercise tolerance: Clinical and echocardiographic improvement in our patients on TMZ was accompanied by a significant fall in BNP from 744.7 ± 834.9 to 248.3 ± 278.5 pg/ml, reflecting a % reduction of −56.8% at 3 months. Although patients on conventional therapy also exhibited a fall in BNP (712.9 ± 606.8 to 455.44 ± 475.87 pg/ml, fall of −25.6%), the quantum of change was lesser and BNP levels at follow up were higher than in patients on TMZ. Improvement in plasma markers of HF severity with TMZ has been reported previously and reflects the favorable effect of the drug on neurohormonal pathways in chronic HF and amelioration of LV remodeling.[22,32]

Although we observed a significant improvement in the 6 min walk test at 3 months, previous studies assessing changes in functional capacity have reported conflicting results. While Fragasso et al.[23] failed to demonstrate significant improvement in total exercise duration with TMZ, others have reported increased peak METS, improvement in peak exercise VO_2 and better exercise tolerance in patients with HF treated with TMZ.[18,22,32] These contrasting results reflect differences in patient populations and types of exercise protocols use in the various studies.

Since all patients in our study were receiving bb and ACEI, the improvement in functional status, 6 min walk test and all echocardiographic variables in the TMZ group, indicates that TMZ can improve cardiac function even when added on the background of current standard therapies. It has been reported that a greater benefit of TMZ was evident in patients of HF with a higher degree of b-blockade (as estimated by a b1-adrenoceptor occupancy), suggesting an additive effect of TMZ and bb in patients with HF and DCM.[24]

Drug tolerance and change in medications: The drug was well tolerated and none of the patients required discontinuation of the study medication. Absence of systemic hemodynamic effects with no significant change in systolic or diastolic BP or heart rate, were in keeping with the known pharmacological actions of TMZ.[10,11] Use of TMZ resulted in significantly lesser use of digoxin (63.5% vs 79.2%, $p = 0.04$) and a trend toward lesser use of diuretics (61.5% vs 72.9%) at 3 months; the mean dose of bb and diuretics was also significantly lesser in those randomized to receive TMZ.

Mortality benefit: Given the improvement in LVEF with TMZ, it is important to know if these benefits translate into improved prognosis and survival. In a meta-analysis of randomized trials of TMZ in HF, Zhang et al. concluded that although there was no mortality benefit, improvement in symptoms, LVEF and hospitalization rates for cardiac causes was demonstarble.[33] In contrast, Gao et al. in their meta-analysis reported that TMZ therapy was associated with improved all-cause mortality and reduction in cardiovascular events and hospitalizations.[34] Reduction in mortality and better event-free survival in patients with CHF with TMZ has also been reported in a recent international multicentre retrospective cohort study.[35]

We did not find any significant differences in death (1 in each group). Overall 4 patients required hospitalization for recurrent HF in the conventional therapy group as compared to only 1 in the TMZ group. The low event rate along with a follow up of only 3–6 months in our study precluded us from making any meaningful conclusions on the effect of TMZ in improving survival or reducing mortality.

5. Limitations

Our study included 100 patients (50 in each group) and the small sample size represents an important limitation. More studies need to be performed with larger patient numbers to further clarify the role of TMZ in HF secondary to DCM. The effects of TMZ were observed at 3–6 months of follow up. Longer follow up with a larger sample size will also help determine the effect of TMZ of reduction of all cause/cardiac mortality in patients with non-ischemic HF.

6. Conclusion

Trimetazidine, a specific partial inhibitor of FFA oxidation, added to usual treatment improved NYHA functional class, exercise tolerance, quality of life, and various echocardiographic parameters of left ventricular function in patients with HF secondary to non-ischemic DCM. The drug was well tolerated and beneficial effects were observed within 3 months of initiation of therapy with sustained and consistent improvement noticed till 6 months of follow up.

What is already known?

- Myocardial dysfunction in HF is due to altered substrate energy metabolism with reduction in mitochondrial oxidative metabolism and down-regulation of glucose and free fatty acid oxidation.

What this study adds?

- This study adds to the existing evidence that metabolic modulation with trimetazidine (a partial inhibitor of free fatty oxidation), improves NYHA functional class, exercise tolerance and diverse echocardiographic parameters of left ventricular function in patients with heart failure.

Conflicts of interest

The authors have none to declare.

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