Original Article

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Trimetazidine improves left ventricular global longitudinal strain value in patients with heart failure with reduced ejection fraction due to ischemic heart disease

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SUMMARY Heart failure with reduced ejection fraction (HFrEF) due to ischemic heart disease (IHD) showed a progressive decline in left ventricular contractile function. However, no previous study has examined the left ventricular global longitudinal strain (LV GLS) parameter that represents LV contractile function. We investigated whether trimetazidine could improve the LV GLS value in patients with HFrEF due to IHD. We performed a double-blind, randomized controlled trial (RCT) including 26 patients with HFrEF due to stable IHD who were given modified-release trimetazidine 35 mg twice per day (n = 13) or placebo (n = 13) for 3 months in addition to standard medication. Left ventricular systolic function including GLS values was assessed at baseline and after 3 months using echocardiography. A total of 25 participants (13 control and 12 trimetazidine groups) were recruited with a baseline average age of 57.1 ± 10 years, and LV ejection fraction (LVEF) value of 34.6% ± 4.4%, and a GLS value of 7.4% ± 2.1%. Baseline clinical characteristics and echocardiogram were similar between the two groups. There was significant GLS improvement in the trimetazidine group (−6.9% ± 2.4% to −8.4% ± 2.6%, p = 0.000), but no significant differences were noted in the control group. The GLS improvement was significantly higher in the trimetazidine group than the control (1.5% + 0.9% *vs.* −0.7% + 1.7%, p = 0.001). No adverse drug reactions from the administration of trimetazidine in this study. Trimetazidine may improve GLS values in patients with HFrEF due to IHD.

Keywords Heart failure with reduced ejection fraction, ischemic heart disease, trimetazidine, global longitudinal strain, LV contractile

1. Introduction

Over the last four decades, the prevalence of heart failure with reduced ejection fraction (HFrEF) related to ischemic heart disease (IHD) has increased by 26% in men and 48% in women (*1*). Despite significant improvements in clinical symptoms and a reduced pace of clinical decline, heart failure progression has remained due to diminished contractile function. Furthermore, it is still the world's greatest cause of morbidity and mortality (*2*). Over the past few years, many studies have established metabolic remodeling as another pathophysiological mechanism of heart failure (HF) that is not widely known (*3,4*). Trimetazidine ([2,3,4-trimethoxybenzyl piperazine dihydrochloride; TMZ) is a metabolic modulator that is useful in treating HF with angina due to IHD. In addition to the treatment of angina, there is growing evidence that TMZ improves cardiac contractile function in heart failure (*5-9*). However, no study has used the global longitudinal strain (GLS) parameter to describe a better left ventricular (LV) contractile function yet. GLS is a strong predictor of mortality and morbidity of HFrEF in various etiologies including IHD and can detect improvement or decrease in contractility function earlier than other conventional echocardiographic parameters (*10-13*). This study aimed to determine whether TMZ administration can increase LV GLS values in patients with HFrEF due to IHD.

2. Materials and Methods

2.1. Research design

This study was an experimental clinical study with a

double-blind, randomized, placebo-controlled trial design conducted at Dr. Kariadi General Hospital Semarang from January to July 2020.

2.2. Research subjects

The subjects were stable patients with HFrEF due to IHD from an outpatient cardiac clinic of Dr. Kariadi General Hospital Semarang who met the inclusion and exclusion criteria and agreed to participate by signing informed consent. The study inclusion criteria were patients with functional class New York Heart Association (NYHA) I–II HFrEF with LV ejection fraction (LVEF) 20-40% of echocardiography, significant IHD evidence from previous coronary angiography examination, and/or a history of the acute coronary syndrome and/or revascularization, who received established standard medical therapy for 4 weeks before randomization. Exclusion criteria were patients who were over 75 years of age; have atrial fibrillation and severe arrhythmias, revascularization history within 60 days, primary heart valve abnormalities, Parkinson's disease, or symptoms, routinely used monoamine oxidase inhibitor drugs, and stage 4 chronic kidney disease (CKD) history; were undergoing dialysis (hemodialysis), and have inadequate echocardiographic image quality (poor echo window). The research protocol has received ethical clearance from the Ethics Commission for Health and Medical Research, Faculty of Medicine, Diponegoro University, and Dr. Kariadi General Hospital Semarang (No. 433/EC/KEPK-RSDK/2020) and a permit to conduct research from the Diklit section of Dr. Kariadi General Hospital Semarang.

2.3. TMZ drug administration

Trizedon modified-release® (MR; PT. Servier Indonesia, Tower of Kadin Indonesia 18th Floor: HR Rasuna Said Road Block X-5 Kav. 2-3, Jakarta 12950, Indonesia) was administered at a dose of 35 mg/12 h for 12 weeks (*14*). It was given with food, swallowed whole, and not chewed (*15*). TMZ adherence rate was defined as the number of doses taken during the study protocol period (12 weeks) of 85% of all TMZ treatment protocols (*16*).

2.4. Echocardiography and GLS examination of the left ventricle

Echocardiography was performed according to the standard procedure of transthoracic echocardiography examination. GLS examination was assessed using the two-dimensional (2D) speckle-tracking method by taking apical views of two, three, and four chambers at a frame rate of 40-90/s and focusing on the left ventricle. The GLS analysis was aggregated into a bull's eye pattern (17 segments), and a mean value was calculated. LV GLS was processed offline using IntelliSpace Cardiovascular version 1.2 B.V with Qlab version 11 (Phillips Medical System, Netherland). GLS was measured twice; at the beginning and end of the study at 12- week intervals, in percentage (%). The change in GLS is obtained by subtracting the final GLS value from the initial GLS value.

2.5. Statistical analysis

Data analysis includes descriptive analysis and hypothesis testing. Descriptive data will be displayed in the form of mean ± standard deviation, frequency, and percentage. The groups were compared using a two-tailed unpaired Student's *t*-test for variables with normal distribution and Wilcoxon test for variables without normal distribution. *P* values < 0.05 were considered statistically significant.

3. Results

Thirty-six subjects met the inclusion criteria. Ten patients were excluded because three had atrial fibrillation, three had CKD stage IV/V, and four underwent a revascularization procedure within 60 days. Twenty-six subjects were randomized using a random sample generator application. Subjects were divided into two groups as follows: the TMZ group with 13 subjects who received standard therapy plus TMZ 35 mg/12 h and the placebo group with 13 subjects who received standard therapy plus placebo. One patient from the TMZ group dropped out 1 week after initial treatment due to stroke, widespread infarction, decreased consciousness, severe lung infection, and sepsis in a private hospital (Figure 1).

3.1. Baseline demographics and clinical characteristics

There were no statistically significant differences in demographic characteristics between the two groups examined by gender, age, and body mass index (BMI). The median age of the participants was 54 (43-68) years old in the TMZ group and about 60 (41-66) years old in the control group ($p = 0.241$). Most subjects from both groups were men, with 11 (91.7%) samples in the TMZ group and 11 (84.6%) samples in the control group ($p = 1.000$). The mean BMIs of the participants were 25.3 ± 4.1 and 23.3 ± 3.5 kg/m^2 in the TMZ and placebo groups, respectively (Table 1).

The clinical characteristics were similar between groups as shown in Table 1. The median serum creatinine levels in the TMZ and control groups were 1.1 (0.5-1.9) and 1.1 (0.7-1.5) mg/dL ($p = 0.324$), respectively, with estimated glomerular filtration rates of 76.2 ± 38.4 and 77.7 ± 30.6 mL/min/1.73 m^2, respectively ($p = 0.914$). Most samples from both groups (76%) had a history of multivessel disease due to coronary angiography, and no substantial difference was found between the two groups. Four respondents (30.8%) in

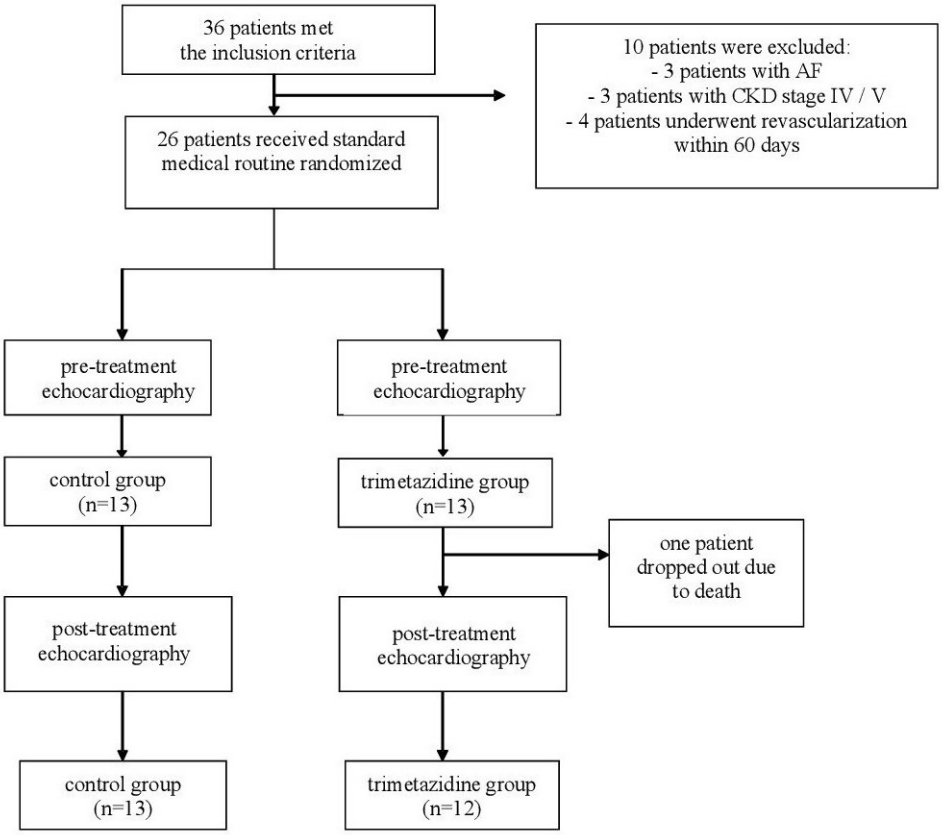

Figure 1. Participant flow. AF, atrial fibrillation; CKD, chronic kidney disease.

the control group and four respondents (33.3%) in the TMZ group underwent a complete revascularization procedure. All patients received angiotensin-converting enzyme inhibitors or angiotensin receptor blockers, beta-blockers, mineralocorticoid receptor antagonists, antiplatelets, and statins as part of the medical treatment. Other medications were calcium channel blockers (4.0%), nitrate (68%), diuretics (20%), and antidiabetic drugs (28%). There was no significant difference in medical treatment between the groups. The TMZ group received standard medical therapy plus TMZ 35 mg/12 h for 88.5 (88-90) days with an adherence rate of 99.3%. The control subjects received standard medical therapy plus a placebo for 89 (87-90) days with an adherence rate of 99.2%.

3.2. Baseline echocardiogram characteristics

Baseline echocardiographic findings were comparable between groups in 2D values and systolic and diastolic functions of the left ventricle. There were no differences in LVEF using the biplane method (LVEF Biplane; 33.3% ± 4.9% *vs.* 35.8% ± 3.5%, $p = 0.150$), GLS (−7.8% ± 1.7% *vs.* −6.9% ± 2.4%, $p = 0.280$), and LV global circumferential strain (GCS) values (−11.9% ± 4.0% *vs.* −14.4% ± 4.5%, $p = 0.150$) between the TMZ and control groups. In LV diastolic function, the E/e′ ratios of the TMZ and control groups were 16 (8.9-29.2) and 13.4 (7.0-10.2, $p = 0.355$), respectively. Left atrial volume index (LAVi) was also comparable between groups (33.7 ± 14.9 *vs.* 35.7 ± 16.1 mL/m^2, respectively; $p = 0.758$; Table 2).

3.3. Comparison of Pre- and Post-echocardiographic findings between groups

There was a significant increase in the parameters of early and late systolic functions in the TMZ group, which included LVEF, GLS, and LV GCS, whereas there was no significant difference in the control group. In the TMZ group, there were significant increases in the LV GLS (from − 6.9% ± 2.4% to − 8.4% ± 2.6%, $p = 0.001$) and GCS values (from −11.6% [−5.9% to −19.4%] to 13.9% [−8.3% to –19.7%], $p = 0.028$). The mean LVEF values increased significantly from the pre-value of 33.3% ± 4.9% to 40.3% ± 5.5% ($p = 0.000$) in the TMZ group but not significantly from a median of 36.7% (29.7%-40.0%) to 37.1% (29.5%-45.2%, $p = 0.542$) in the control group (Table 3).

There were significant differences between the initial and final diastolic function parameters in the TMZ group (E/e' ratio and LAVi), whereas there was no significant difference in the control group. The mean E/e' ratio decreased significantly in the TMZ group from 16.8 ± 6.1 to 13.5 ± 6.6 ($p = 0.046$), whereas it also decreased but not significantly in the control group from a median of

Table 1. Baseline demographic and clinical characteristics

Variables	Groups		*p*-value
	Trimetazidine (*n* = 12)	Control (*n* = 13)	
Age (years)*	54 (43-68)	60 (41–66)	0.241[a]
Sex**			
Male	11 (91.7%)	11 (84.6%)	1.000[b]
Female	1 (8.3%)	2 (15.4%)	
Body Mass Index (kg/m^2)*	25.3 ± 4.1	23.3 ± 3.5	0.195[a]
Systolic Blood Pressure (mmHg)	111.5 ± 13.5	119.4 ± 16.4	0.197[a]
Heart Rate (times/min)	71.5 ± 1.5	73.9 ± 10.8	0.634[a]
QRS complex duration (ms)	111 (96–177)	115.5 (91–140)	0.703[a]
History of Disease**			
DM	4 (33.3%)	5 (38.5%)	1.000[b]
Hypertension	5 (41.7%)	7 (53.8%)	0.551[c]
Obesity	2 (16.7%)	0 (00.0%)	0.220[b]
Acute Coronary Syndrome	7 (41.7%)	5 (38.5%)	1.000[b]
Multivessel Disease	9 (75.0%)	10 (76.9%)	1.000[b]
CTO lession	1 (8.3%)	3 (23.1%)	0.593[b]
Complete Revascularization	4 (33.3%)	4 (30.8%)	1.000[b]
Medical treatment**			
Diuretic	3 (25.0%)	2 (15.4%)	0.645[b]
ACEi/ARB	12 (100%)	13 (100%)	0.842[c]
Beta blocker	12 (100%)	13 (100%)	0.842[c]
MRA	12 (100%)	13 (100%)	0.842[c]
Nitrate	9 (75.0%)	8 (61.5%)	0.673[b]
CCB	0 (0.0%)	1 (7.7%)	1.000[b]
Ivabradine	0 (0.0%)	1 (7.7%)	1.000[b]
Digoxin	1 (8.3%)	0 (0.0%)	0.480[b]
Antiplatelet	12 (100%)	13 (100%)	0.842[c]
Statin	12 (100%)	13 (100%)	0.842[c]
Diabetes Mellitus Drugs	4 (33.3%)	3 (23.1%)	0.576[c]
Renal Function*			
Creatinine (mg/dL)	1.1 (0.5–1.9)	1.1 (0.7–1.5)	0.324[a]
eGFR (mL/min/1.73 m^2)	76.2 ± 38.4	77.7 ± 30.6	0.914[a]

*Described as mean ± standard deviation and median (min-max). **Described in *n* (%). The value is significant if $p < 0.05$. [a]Unpaired *t*-test with the alternative Mann–Whitney *U* test. [b]Fischer exact test. [c]Chi-square test. DM, diabetes mellitus; CTO, chronic total occlusion; ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; MRA, mineralocorticoid receptor antagonist; eGFR, estimated glomerular filtration rate; CCB, calcium channel blocker.

Table 2. Baseline echocardiogram characteristics

Variables	Groups		*p*-value
	Trimetazidine (*n* = 12)	Control (*n* = 13)	
Echocardiographic measurements Left ventricle dimension*			
EDV (mL)	177.0 ± 42.6	149.5 ± 37.7	0.100[a]
ESV (mL)	118.9 ± 34.2	96.9 ± 29.3	0.096[a]
EDVi (mL/m^2)	102.8 ± 26.3	95.3 ± 27.8	0.456[a]
ESVi (mL/m^2)	69.1 ± 21.0	61.8 ± 18.1	0.359[a]
Left Ventricular Systolic Function*			
LVEF (%)	33.3 ± 4.9	35.8 ± 3.5	0.150[a]
GLS (%)	– 6.9 ± 2.4	–7.8 ± 1.7	0.280[a]
GCS (%)	–11.9 ± 4.0	–14.4 ± 4.5	0.150[a]
Left Ventricular Diastolic Function*			
E/A	1.2 (0.5–3.2)	0.8 (0.6–3.6)	0.742[a]
E/e'	16 (8.9–29.2)	13.4 (7.0–10.2)	0.355[a]
LAVi (mL/m^2)	33.7 ± 14.9	35.7 ± 16.1	0.758[a]
Diastolic Dysfunction**			
Grade I	4 (33.3%)	8 (61.5%)	0.347[b]
Grade II	5 (41.7%)	2 (15.4%)	
Grade III	3 (25.0%)	3 (23.1%)	

*Described as mean ± standard deviation (intersection of deviation) and median (min-max). **Described as *n* (%). The value is significant if $p < 0.05$. [a]Unpaired *t*-test with the alternative Mann-Whitney *U* test. [b]Chi-square test. EDV, End-Diastolic Volume; ESV, End-Systolic Volume; EDVi, End-Diastolic Volume index; ESVi, End-Systolic Volume index; GLS, Global Longitudinal Strain; GCS, Global Circumferential Strain; LAVi, Left Atrial Volume index.

13.4 (7.1-30.2) to 12.6 (5.4-21.9, $p = 0.301$). There was a significant decrease in the mean LAVi value in the TMZ group from 33.7 ± 14.9 to 25.5 ± 12.2 mL/m^2 ($p = 0.049$), whereas there was no significant difference in the control group from 35.7 ± 16.1 to 36.3 ± 13.1 mL/m^2 ($p = 0.889$). There was no significant difference between the mean E/A ratio's initial and final values in the two groups (Table 3). There were significant differences between the initial and final diastolic function parameters in the TMZ group (E/e' ratio and LAVi), whereas there was no significant difference in the control group. The mean E/e' ratio decreased significantly in the TMZ group from 16.8 ± 6.1 to 13.5 ± 6.6 ($p = 0.046$), whereas it also decreased but not significantly in the control group from a median of 13.4 (7.1-30.2) to 12.6 (5.4-21.9, $p = 0.301$). There was a significant decrease in the mean LAVi value in the TMZ group from 33.7 ± 14.9 to 25.5 ± 12.2 mL/m^2 ($p = 0.049$), whereas there was no significant difference in the control group from 35.7 ± 16.1 to 36.3 ± 13.1 mL/m^2 ($p = 0.889$). There was no significant difference between the mean E/A ratio′s initial and final values in the two groups (Table 3).

3.4. Δ Changes in LV GLS and others chocardiographic parameters between TMZ and Control Group

After 3 months intervention, there were no differences in LV GLS (−8.4% ± 2.6% *vs.* −7.1% ± 1.8%, $p = 0.170$), and LV GCS (−13.8% ± 3.9% *vs.* −13.3% ± 5.5%, $p = 0.828$) and LVEF using the biplane method (40.3% ± 5.5% *vs.* 37.0% ± 5.5%, $p = 0.142$), between the TMZ and control groups as shown in Table 3.

A significant difference was noted in the change (Δ) in GLS values between the TMZ and control groups (1.5% + 0.9% *vs.* −0.7% + 1.7%, $p = 0.001$). TMZ also increased the mean LV GCS by 1.9% ($p = 0.024$) and there was a significant difference (Δ) in the mean GCS value between the TMZ and control groups (Δ 1.9 *vs.* −1.1, respectively; $p = 0.005$). Using the biplane method, significant increases were noted in the mean LVEF values of the TMZ (7.0%, $p = 0.000$) and there was a significant difference in the increase (Δ) of the mean LVEF value between the TMZ and control groups (Δ 7.0 *vs.* 1.1, respectively; $p = 0.001$) (Table 3).

There was no significant difference between TMZ and control groups in the change (Δ) of diastolic function,

Table 3. Pre-Post Echocardiographic and Δ Changes between Trimetazidine and Control groups

Variables	Mean ± SD; Median (min–max)		*p*-value
	Trimetazidine (*n* = 12)	Control (*n* = 13)	
Left Ventricular Dimension			
EDV (mL) Pre	177.0 ± 42.6	149.5 ± 37.7	0.100[d]
EDV (mL) Post	159.8 + 41.6	151.1 ± 39.2	0.594[d]
P	0.075[c]	0.824[c]	
Δ EDV	–17.2 ± 30.2	1.6 ± 26.1	0.108[d]
ESV (mL) Pre	118.9 ± 34.2	96.9 ± 29.3	0.096[d]
ESV (mL) Post	96.5 ± 30.8	96.8 ± 32.2	0.983[d]
P	0.005[c]	0.991[c]	
Δ ESV	–22.4 ± 22.4	–0.1 ± 18.2	0.012[d]
EDVi (mL/m^2) Pre	102.8 ± 26.3	95.3 ± 27.8 89 (68–142)	0.456[d]
EDVi (mL/m^2) Post	91.7 ± 21.4	97.1 ± 26.6 89 (62–143)	0.586[d]
P	0.056[c]	0,946[b]	
Δ EDVi	–11.0 ± 17.9	1.8 ± 17.9	0.008[d]
ESVi (mL/m^2) Pre	69.1 ± 21.0	61.8 ± 18.1	0.359[d]
ESVi (mL/m^2) Post	55.3 ± 16.4	62.2 ± 21.3	0.379[d]
P	0.005[c]	0.901[c]	
Δ ESVi	–13.8 ± 13.6	–0.4 ± 12.2	0.012[d]
Left Ventricular Systolic Function*			
LVEF (%) Pre	33.3 ± 4.9	35.8 ± 3.5 36.7 (29.7–40)	0.150[d]
LVEF (%) Post	40.3 ± 5.5	37.0 ± 5.5 37.1 (29.5–45.2)	0.142[d]
P	0.000[c]	0.542[b]	
Δ LVEF	7.0 ± 4.5	1.1 ± 3.1	0.001[d]
GLS (%) Pre	–6.9 ± 2.4	–7.8 ± 1.7	0.280[d]
GLS (%) Post	–8.4 ± 2.6	–7.1 ± 1.8	0.170[d]
P	0.000[c]	0.162[c]	
Δ GLS	1.5 ± 0.9	–0.7 ± 1.7	0.001[d]
GCS (%) Pre	–11.9 ± 4.0 11.6 (5.9–19.4)	–14.4 ± 4.5 13.9 (9.8–22.1)	0.150[a]
GCS (%) Post	–13.8 ± 3.9 13.9 (8.3–19.7)	–13.3 ± 5.5 10.3 (7.9–20.2)	0.828[a]
P	0.024[b]	0.175[b]	
Δ GCS	1.9 ± 2.6	–1.1 ± 2.1	0.005[a]
Left Ventricular Diastolic Function*			
E/A Pre	1.4 ± 0.9 1.2 (0.5–3.2)	1.5 ± 1.0 0.8 (0.6–3.6)	0.742[a]
E/A Post	1.4 ± 1.1	1.2 ± 0.7	0.935[d]
P	0.760[c]	0.877[c]	
Δ E/A	0.04 ± 0.5 0.1 (–0.9 to 1.0)	–0.3 ± 0.7 –0.1 (0.7 to–2.1)	0.299[a]
E/e' Pre	16.8 ± 6.1 16.1 (8.9–29.2)	14.8 ± 6.6 13.4 (7.1–30.2)	0.355[a]
E/e' Post	13.5 ± 6.6 10.0 (7.1–26.0)	13.2 ± 5.1 12.6 (5.4–21.9)	0.907[a]
P	0.046[b]	0.301[c]	
Δ E/e'	–3.3 ± 5.0 –2.2 (–13.8 to 5.6)	–1.6 ± 5.8 –1.7 (–17.6 to 7.8)	0.264[a]
LAVi (mL/m^2) Pre	33.7 ± 14.9 32.3 (9.4–56.4)	35.7 ± 16.1 33.9 (12.7–67.3)	0.758[a]
LAVi (mL/m^2) Post	25.5 ± 12.2 24.8 (12.5–50.9)	36.3 ± 13.1 33.9 (19.4–68.2)	0.041[a]
P	0.049[b]	0.889[b]	
Δ LAVi	–8.2 ± 12.9	0.6 ± 16.0	0.144[d]

Statistical analysis was performed using the [a]Mann–Whitney *U* test, [b]Wilcoxon test, [c]paired *t*-test and [d]unpaired *t*-tests. The value is significant if $p < 0.05$. SD, standard deviation; EDV, End-Diastolic Volume; ESV, End-Systolic Volume; EDVi, End-Diastolic Volume index; ESVi, End-Systolic Volume index; GLS, Global Longitudinal Strain; GCS, Global Circumferential Strain; LAVi, Left Atrial Volume index.

although in the TMZ group there were improvements in E/e' and LAVi parameters as shown in Table 3.

3.5. Intrarater and Interrater variability

Intrarater and interrater reliability of the GLS examination were analyzed by calculating the intraclass and interclass correlation coefficients. Intraclass and interclass correlation coefficients and 95% CI were

calculated using MedCalc Statistical Software version 19.1 based on the mean-rating (k = 2), absolute-agreement, and two-way mixed-effect model. Intraclass correlation coefficient = 0.991 with 95% CI = 0.978-0.997 for interrater reliability and interclass correlation coefficient = 0.982 with 95% CI = 0.954-0.993 for interrater reliability were obtained. Thus, it can be said that the interrater and interrater reliability of the GLS examination in this study is excellent.

3.6. TMZ safety

Two subjects from the control group experienced gastrointestinal side effects, including nausea, stomach pain, and vomiting. The subjects who experienced digestive system disorders had the same complaints before they participated in the study; thus, these complaints could not be ascertained to be related to the intervention conducted in this study. The patients well-tolerated this indigestion complaint. Meanwhile, in the TMZ group, no subjects complained of any side effects. There were no subjects who stopped treatment because of the complaints they felt.

4. Discussion

4.1. Effect of TMZ on the LV GLS values

The results of this study showed that administration of TMZ MR 35 mg/12 h for 3 months can improve LV contractile function with an LV GLS value parameter of 1.5% ± 0.9% (p = 0.001), followed by an increase in other contractility function parameters, including LV GCS (1.9% ± 2.6%, p = 0.005) and LVEF values (7.0 ± 4.5, p = 0.000).

Improvement of LVEF with the addition of TMZ to the standard medical procedure has been shown by previous studies. For instance, the meta-analysis of Gao *et al*. (*2*) (17 randomized clinical trials [RCTs]/n = 955) that reported that the addition of TMZ can increase weighted mean difference LVEF + 7.37% ($p < 0.01$) on IHD-induced HFrEF and the meta-analysis of Zhang *et al.* (*17*) (16 RCTs/n = 884) showed that TMZ could increase LVEF + 6.46% ($p < 0.01$).

Most studies used the LVEF parameter to represent the LV contractility function. This technique has limitations, including the determination of suboptimal endocardial margins and extensive wall motion abnormalities. Other technical challenges include geometric assumptions related to using two axes to assess LV function globally, optimal apical display alignment without foreshortening, arrhythmias, and loading-dependent factor influence on the ventricular function assessment (*10*). Given the limitations of this routine parameter, the complexity of LV's contractile function is unlikely to be comprehensively represented by the LVEF assessment method alone. GLS with 2D-speckle-tracking echocardiography is a new noninvasive method of ultrasound imaging with quantitative and objective capabilities to assess the global and regional functions of the cardiac myocardium. This modality is semi-automatic and capable of analyzing a complex cardiac mechanical system and a reproducible, angle-independent examination with no geometric assumptions and less load-dependent and of detecting early changes in myocardial contractile function and predictors of mortality and morbidity of HFrEF due to IHD (*18-20*).

Inhibition of metabolic remodeling, which includes mitochondrial dysfunction, energetic disturbances, oxidative stress, and EC coupling disorders in the myocardium, is the mechanism underlying the increase in GLS values in TMZ administration. The four components of metabolic remodeling are interrelated with structural remodeling, which underlie decreased contractility function in HFrEF. Administration of TMZ induces partial β-FA (β-ox) oxidation inhibition, increases pyruvate dehydrogenase and glucose oxidation, which is energetically beneficial in IHD (*21*), limits the accumulation of sodium, Ca^{2+}, and intracellular acidosis, reduces induced cell damage reactive oxygen species (ROS), inhibits cardiac fibrosis and inflammation through the ROS/connective tissue growth factor pathway, prevents cell apoptosis through the mitogen-activated protein kinase/ATK pathway, reduces uncoupling protein, and increases the creatinine phosphate (PCr)/adenosine triphosphate (ATP) ratio. ATP and its final effects are decreased cellular damage and repair of HF (*2*).

The TMZ mechanism improves contractility using GLS through improved mitochondrial and energetic functions. In Fragasso *et al*. study (*22*), which involved 12 patients with HFrEF due to IHD, TMZ increased the functional grade and LV function in patients with HF and increased the PCr/ATP ratio, indicating preservation of levels of noninvasive myocardial high-energy phosphate, as viewed using *in vivo* 31P magnetic resonance spectroscopy. On TMZ, the NYHA grade decreased from 3.04 ± 0.26 to 2.45 ± 0.52 ($p < 0.005$), whereas EF (34 ± 10 *vs.* 39% ± 10%, $p \leq 0.03$) and METS (from 7.44 ± 1.84 to 8.78 ± 2.72, $p < 0.03$) increased. The mean cardiac PCr/ATP ratio was 1.35 ± 0.33 with placebo but increased 33% to 1.80 ± 0.50 ($p < 0.03$) with TMZ.

The TMZ mechanism to improve LV contractility through inhibition of oxidative stress was demonstrated in the study of Belardinelli *et al.* (23). The research involved 51 patients (mean age 51.4 ± 6 years) with cardiac HF secondary to ischemic cardiomyopathy (EF 32.5% ± 4.5%), decreased plasma malondialdehyde levels (from 3.98 ± 0.69 to 2.15 ± 0.59 mmol/L), and decreased lipid hydroperoxides (from 3.72 ± 0.9 to 2.06 ± 0.6 mmol/L) versus the placebo group ($p < 0.01$), demonstrating the antioxidant properties of TMZ after 4 weeks of treatment with oral TMZ (20 mg TID). Similarly, the study of Di Napoli *et al.* (*6*), involving 61 patients with dilated ischemic cardiomyopathy, showed

that the 18-month administration of TMZ increased the mean C-reactive protein of the control group than the TMZ group ($p < 0.001$) and showed an increase in LVEF + 11% ($p < 0.001$), an improvement in NYHA, and a decrease in mean LVESV and LVEDV ($p < 0.001$) in the TMZ group ($p < 0.001$).

Another mechanism for enhancing LV contractility with TMZ was also shown in the study of Belardinelli *et al.* (*14*), which included 49 patients with ischemic cardiomyopathy and multivessel disease who received TMZ with standard HF therapy for 2 months. The sample was tested for low-dose contractile response to dobutamine, with an improvement in mean LVEF + 5.6%. This improvement is also consistent with this study in which TMZ administration of 35 mg/12 h for 3 months significantly increased GLS values in HFrF by 1.5% ± 0.9% ($p = 0.001$) due to IHD for 3 months.

Another finding of this study, besides the improvement in LV systolic function, is the increase in diastolic function after 3 months of TMZ administration. IHD and severe LV dysfunction altered the diastolic function and progressively decreased LV compliance and increased left atrial pressure and LV filling pressure at the diastolic as assessed by the parameters recommended by the 2016 American Society of Echocardiography guidelines for diastolic dysfunction assessment (*24*). This effect on TMZ's LV diastolic function may also be related to TMZ's metabolic anti-ischemic effect in the myocardium undergoing chronic hypoperfusion. Improvements in diastolic function due to the addition of TMZ in ischemic cardiomyopathy have been shown in the study of Vitale *et al.* (*25*), which showed that adding TMZ to standard therapy for 6 months improved diastolic function as assessed by mitral flow doppler analysis with echocardiography, in addition to improving LVEF.

The clinical importance of GLS improvement after TMZ administration to HFrEF was demonstrated in the study of Sengeløv *et al*. (*13*), which involved 1,065 HFrEF patients and showed that GLS remains an independent predictor of all-cause mortality in a multivariable model after adjusting for age, sex, BMI, total cholesterol, mean arterial pressure, heart rate, ischemic cardiomyopathy, percutaneous transluminal coronary angioplasty, Cardiac bypass surgery, noninsulin-dependent diabetes mellitus, and conventional echocardiographic parameters (hazard ratio [HR]: 1.15; 95% CI 1.04-1.27, $p = 0.008$ per 1% decrease). No other echocardiographic parameters remained independent predictors after adjusting for these variables. This study is the first double-blind RCT that evaluated the effect of TMZ on LV contractile function with the GLS value parameter in patients with HFrEF due to IHD. The results of this study indicate that TMZ can improve LV systolic function as assessed by the LV GLS value and is clinically significant because each reduction in GLS value is 1% (HR: 1.15; 95% CI 1.04-1.27, $p = 0.008$).

4.2. Adherence to drugs and side effects of TMZ

In this study, TMZ was relatively safe and well-tolerated in patients with HFrEF, which can be seen from the compliance level, with 99.3% TMZ at a median of 88.5 (88-90) days of taking medication. During the study period, no allergies or serious side effects were reported by the TMZ administration. None of the patients discontinued the TMZ drug. This safety is relevant to various previous studies, which also stated that TMZ is safe enough to be given to HFrEF sufferers due to IHD even for a longer period (*2,26-27*).

4.3. Research limitations

This study assessed the short-term effect (3 months) of TMZ on echocardiographic parameters alone and did not assess other clinical outcome parameters such as exercise capacity, major cardiovascular events, and HF hospitalization incidence. Additionally, most standard HF treatments of the subjects could not achieve the maximum recommended daily dose target guidelines for HF.

5. Conclusion

TMZ may improve the LV contractile function in patients with HFrEF due to IHD using the LV GLS value.

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