Clinical Trial

Effects of Trimetazidine in Nonischemic Heart Failure: A Randomized Study

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ABSTRACT

Objectives: Heart failure (HF) is associated with changes in myocardial metabolism that lead to impairment of contractile function. Trimetazidine (TMZ) modulates cardiac energetic efficiency and improves outcomes in ischemic heart disease. We evaluated the effects of TMZ on left ventricular ejection fraction (LVEF), cardiac metabolism, exercise capacity, O_2 uptake, and quality of life in patients with nonischemic HF.

Methods and Results: Sixty patients with stable nonischemic HF under optimal medical therapy were included in this randomized double-blind study. Patients were randomized to TMZ (35 mg orally twice a day) or placebo for 6 months. LVEF, 6-minute walk test (6MWT), maximum O_2 uptake in cardiopulmonary exercise test, different markers of metabolism, oxidative stress, and endothelial function, and quality of life were assessed at baseline and after TMZ treatment. Left ventricular peak glucose uptake was evaluated with the use of the maximum standardized uptake value (SUV) by 18-fluorodeoxyglucose positron emission tomography (^{18}FDG-PET). Etiology was idiopathic in 85% and hypertensive in 15%. Both groups were similar in age, functional class, LVEF, and levels of N-terminal pro−B-type natriuretic peptide at baseline. After 6 months of TMZ treatment, no changes were observed in LVEF (31 ± 10% vs 34 ± 8%; $P = .8$), 6MWT (443 ± 25 m vs 506 ± 79 m; $P = .03$), maximum O_2 uptake (19.1 ± 5.0 mL kg^{-1} min^{-1} vs 23.0 ± 7.2 mL kg^{-1} min^{-1}; $P = .11$), functional class (percentages of patients in functional classes I/II/III/IV 10/3753/0 vs 7/40/50/3; $P = .14$), or quality of life (32 ± 26 points vs 24 ± 18 points; $P = .25$) in TMZ versus placebo, respectively. In the subgroup of patients evaluated with ^{18}FDG-PET, no significant differences were observed in SUV between both groups (7.0 ± 3.6 vs 8.2 ± 3.4 respectively; $P = .47$).

Conclusions: In patients with nonischemic HF, the addition of TMZ to optimal medical treatment does not result in significant changes of LVEF, exercise capacity, O_2 uptake, or quality of life. (*J Cardiac Fail 2014;20:149−154*)

Key Words: Trimetazidine, cardiac metabolism, heart failure.

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Heart failure (HF) continues to be a major health problem. Despite advances in the treatment of this condition, its mortality remains high, averaging 50% at 5 years.[1] One of the characteristics of HF progression is the development of alterations in myocardial energy metabolism.[2] In fact, at physiological conditions, most of the adenosine triphosphate (ATP) used by myocardial cells is generated from free fatty acid (FFA) beta-oxidation; a gradual decrease in ATP levels associated with lower FFA utilization has been observed in failing hearts.[2,3] In a compensatory manner, glucose uptake and utilization increase, possibly by activation of fetal gene pathways, in an attempt to maintain the normal myocyte function. In end-stage HF the utilization of both glucose and FFA slowly decreases,[4] reflecting a severe metabolic impairment.

Given the role of metabolic changes in HF development and progression, metabolic modulation therapies have become an interesting field of study for developing new HF treatment options. Trimetazidine (TMZ) is a 3-ketoacyl coenzyme A thiolase inhibitor, which traditionally has been used as an anti ischemic drug but in recent years has also emerged as a novel option for the treatment of advanced HF. Although its mechanism of action is not fully understood, TMZ has been shown to inhibit oxidative phosphorylation, decrease FFA oxidation, and increase glucose utilization and ATP production.[5–9] In addition, TMZ has been linked to other beneficial effects, such as preservation of ATP and phosphocreatine myocardial content,[10,11] reduction of cell acidosis[5,12] and calcium overload,[12] and attenuation of injury caused by reactive oxygen species.[13]

The therapeutic role of TMZ has been evaluated in small randomized trials of patients with ischemic HF with promising results,[5,14–16] including improvement in symptoms, left ventricular ejection fraction (LVEF), and hospitalization rates. In patients with nonischemic HF, however, only a few small experiences have been published.[17–19] We hypothesized that the addition of TMZ to standard treatment in nonischemic HF improves clinical outcomes, laboratory parameters of myocardial contractile function, and systemic markers of metabolism, inflammation, oxidative stress, and endothelial function.

Methods

Patients

Sixty patients with dilated cardiomyopathy (DCM) were included in this randomized prospective double-blind study. Patients were eligible if they fulfilled the following criteria: a) clinically stable HF with New York Heart Association (NYHA) functional class II or III; b) left ventricular ejection fraction (LVEF) $<45\%$ as evaluated with radioisotopic ventriculography within 2 weeks before enrollment; c) optimal medical treatment, including beta-blocker therapy at maximal tolerated dose, angiotensin-converting enzyme (ACE) inhibitors or angiotensin II receptor blocker (ARB), spironolactone, and diuretics unless contraindicated; d) clinical stability defined as absence of modifications in therapy in the past 2 months; e) normal coronary angiogram; and f) written informed consent approved by the local Ethics Committee. Exclusion criteria were: a) history of angina or myocardial infarction, or evidence of necrosis in electrocardiogram or surface echocardiography; b) history of coronary artery bypass graft or angioplasty; c) uncontrolled hypertension defined as systolic blood pressure >160 mm Hg or diastolic blood pressure >100 mm Hg; d) systemic illness that could affect the determination of oxidative stress parameters, such as neoplasia, autoimmune disease, renal failure (serum creatinine >2.5 mg/dL), hepatic or lung disease, and acute or chronic inflammatory state.

Patients were enrolled from March 2010 to December 2011 and randomized in a sequential manner to receive TMZ (35 mg twice daily; Vastarel; Laboratoires Servier France, Neuilly-sur-Seine, France) or placebo in addition to standard therapy for a period of 6 months. Patient compliance and adverse effects were evaluated in monthly visits. After the intervention period, clinical and laboratory evaluations were repeated. This study was registered as FONDECYT 1050768 and funded by the Chilean National Commission of Scientific Investigation (http://www.conicyt.cl).

Baseline and 6-Month Assessment

Clinical evaluation included functional capacity and quality of life (Minnesota Living with Heart Failure Questionnaire [MLHF]). Exercise capacity was assessed by 6-minute walk test (6MWT) and cardiopulmonary test with measurement of oxygen maximal consumption (Quinton Qplex). LVEF was evaluated with the use of ^{99}Tc-radioisotopic ventriculography by 2 blinded nuclear medicine physicians.

Laboratory evaluation included plasma levels of pro−B-type natriuretic peptide (proBNP), epinephrine, and norepinephrine (baseline and after exercise) determined by chromatography, glucose, insulin, homeostasis model assessment (HOMA), and plasma FFA (Wako Chemicals). Oxidative stress was assessed by measuring malondialdehyde (MDA; through thiobarbituric acid reactive substances assay), superoxide dismutase (SOD), and endothelial xantine oxidase (eXO; evaluated by the difference between plasma enzymatic activities at baseline and after a heparin bolus). Markers of systemic inflammation were leukocyte blood count, erythrosedimentation rate (ESR), plasma levels of tumor necrosis factor α, and ultrasensitive C-reactive protein (usCRP; enzyme-linked immunosorbent assay; Calbiochem-Novabiochem). Endothelial function was assessed by endothelial-dependent (EDDP) and endothelial-independent (EIDP) dilation percentage of the brachial artery with the use of ultrasound according to current recommendations.[20] To comply with good clinical practice guidelines, adverse events were monitored by an independent safety committee and reported to the local Ethics Committee.

Glucose Uptake Distribution by PET

At baseline and after 6 months of therapy, a subgroup of 22 patients underwent cardiac positron emission tomography (PET) with 18-fluorodeoxyglucose (^{18}FDG) for evaluation of glucose uptake distribution on a 64-slice PET/computerized tomography scanner (Siemens, Knoxville, Tennessee). For that purpose, patients received a 75 g oral glucose load. Ninety minutes after glucose loading, 5 mCi ^{18}FDG were injected and 13 dynamic images of the myocardium were obtained during 60 minutes of uptake. Reconstructed PET images formatted in short, long and vertical long axes were obtained to visually analyze myocardial ^{18}FDG distribution with the use of QPS 2008 software package

with PET processing option (Cedars Sinai Medical Center, Los Angeles, California).

Left ventricular (LV) peak glucose uptake was evaluated with the use of the maximum standardized uptake value (SUV) calculated as the ratio between myocardium maximum radioactivity concentration (kBq/g) divided by the injected dose (kBq) and the patient's body weight (g). Polar maps were created with the use of the QGS software package described above to obtain the relative glucose uptake among different segments, and the standard deviation of segmental ^{18}FDG uptake was computed as an index of myocardial metabolic heterogeneity.[21,22]

Sample Size Calculation and Statistical Analysis

The primary outcome of this study was mean LVEF change. Secondary outcomes included exercise capacity, quality of life, endothelial function, and myocardial glucose uptake. Sample size was calculated for an expected mean LVEF change of 5%, based on the mean variation of LVEF in previous clinical studies of ischemic HF.[5,14–16,23–25] To obtain a statistical power of 0.80 and considering a 2-sided alpha error of 0.05, the required number of patients was 20 per group. With an expected 25% follow-up loss, 30 patients per group were included in the design of this study.

Continuous variables were expressed as mean ± SD and categoric variables as percentages (%). The normality of continuous variables was determined by the Kolmogorov-Smirnov test. Comparisons were performed with the use of Student *t* test for normally distributed variables and Mann-Whitney *U* test for nonnormally distributed variables. Changes compared with baseline were assessed in each group with the use of paired *t* test or Wilcoxon signed rank test as needed. Data analysis was performed with the use of the SPSS statistical software v 16.0 (SPSS, Chicago, Illinois).

Results

Baseline Characteristics of Patients

During the study period 60 patients with nonischemic HF were recruited. Mean age was 55 ± 13 years, and 38 (63%) were male. The mean LVEF was 31 ± 10%, and 54% were in NYHA functional class III. All patients had negative serology for Chagas disease.

Both groups had similar baseline characteristics, as presented in Table 1. There were no differences among patients who underwent ^{18}FDG-PET. Patients randomized to TMZ had higher proBNP levels (Table 2). Before admission in this study, medical therapy was titrated to the highest tolerable dose and was kept stable throughout the study period. Compared with control subjects, TMZ-treated patients received higher doses of furosemide (49.6 ± 30 mg daily vs 34 ± 9.4 mg daily; $P = .03$). Beta-blocker, ACE inhibitor, and ARB dosages were similar between groups.

Table 1. Baseline Characteristics

	Trimetazidine (n = 30)	Placebo (n = 30)	*P* Value
Gender, male, n (%)	20 (66%)	21 (70%)	.91
Age, y	53 ± 13	57 ± 13	.27
Etiology n (%)			.17
Idiopathic	26 (88%)	23 (76%)	
Hypertensive	2 (7%)	7 (23%)	
Other	1 (3%)	0 (0%)	
NYHA functional class n (%)			.55
II	14 (46%)	14 (46%)	
III	16 (54%)	16 (54%)	
BMI, kg/m^2	27 ± 4	27 ± 3	.86
Hypertension n (%)	16 (53%)	18 (60%)	.55
Diabetes n (%)	4 (13%)	1 (3%)	.33
Smoking history n (%)	2 (6%)	3 (10%)	.57
Dislipidemia n (%)	6 (20%)	7 (23%)	.87
Chronic kidney disease n (%)	2 (6%)	1 (3%)	.59
Sinus rhythm n (%)	26 (86%)	26 (86%)	.76
Atrial fibrillation n (%)	4 (14%)	4 (14%)	.76
LBBB, n (%)	12 (40%)	13 (44%)	.81
LVEF, %	30 ± 10	33 ± 10	.26
Hematocryt, %	40.2 ± 4.5	42.6 ± 4.1	.05
Creatinine, mg/dL	1.02 ± 0.37	0.96 ± 0.28	.49
Sodium, mEq/L	139.4 ± 2.1	140.2 ± 2.6	.95
Glucose, mg/dL	90.4 ± 14.7	100.8 ± 47.2	.28
HOMA	2.6 ± 2.0	3.4 ± 4.8	.44
Treatment, n (%)			
ACEI/ARB	27 (90%)	26 (86%)	.81
β-Blocker	27 (90%)	29 (96%)	.59
Spironolactone	25 (83%)	26 (86%)	.76
Diuretics	26 (86%)	22 (76%)	.07
ASA	14 (46%)	14 (46%)	.99
Statins	12 (40%)	13 (43%)	.81

NYHA, New York Heart Association; BMI, body mass index; LBBB, left bundle branch block; LVEF, left ventricle ejection fraction; HOMA, homeostasis model assessment (insulin resistance); ACEI/ARB, angiotensin-converting enzyme inhibitors/angiotensin receptor blockers; ASA, acetylsalicylic acid (aspirin).

Effects of TMZ Treatment on Ejection Fraction, proBNP Levels, Exercise Capacity, and Quality of Life

After a period of 6 months, LVEF did not differ between patients treated with TMZ or placebo (31 ± 10% vs 34 ± 8% respectively; $P = .8$); nor were differences observed in LVEF after treatment compared with baseline (paired *t* test: $P = .89$ and $P = .54$, respectively). There were no significant reductions in proBNP levels during follow-up or compared with baseline values (paired *t* test: $P = .66$ in TMZ, $P = .18$ in placebo). As Table 2 presents, functional class and quality of life assessed with the Minnesota Questionnaire did not improve in the TMZ group compared with the placebo group. Likewise, exercise capacity measured with 6MWT and O_2 maximal consumption were similar in both treatment arms (Table 2).

Effects of TMZ Treatment on Glucose, FFA, Insulin Resistance, and Myocardial Uptake of ^{18}FDG

There were no baseline differences in plasma levels of glucose, FFA or HOMA between both groups (Table 3). Thirteen percent of patients in the TMZ group and 3% in the placebo group had a history of diabetes ($P = .33$). Insulin resistance (defined as HOMA ≥2.6) was present in 36% of patients in the TMZ group and 30% in the placebo group ($P = .55$). After a 6-month period we found no differences in plasma glucose or HOMA between groups (Table 3). In the same manner, there were no significant differences in plasma levels of FFA at baseline or after the treatment period (Table 3).

Maximal myocardial ^{18}FDG uptake was evaluated by PET. SUV values between TMZ and placebo groups

Table 2. Effects of Trimetazidine on Exercise Capacity, Ventricular Function, and Quality of Life at 6-Month Evaluation

	Trimetazidine (n = 30)	Placebo (n = 30)	*P* Value
NYHA functional class n (%)			.14
I	3 (10%)	2 (7%)	
II	11 (37%)	12 (40%)	
III	16 (53%)	15 (50%)	
IV	0 (0%)	1 (3%)	
LVEF (%)			
Baseline	30 ± 10	33 ± 10	.26
6 mo	31 ± 10	34 ± 8	.80
proBNP (pg/mL)			
Baseline	2,607 ± 3,302	1,118 ± 991	.03
6 mo	2,402 ± 3,653	1,158 ± 1,381	.12
MLHF score (points)			
Baseline	44 ± 26	37 ± 22	.34
6 mo	32 ± 26	24 ± 18	.25
6MWT distance (m)			
Baseline	451 ± 96	467 ± 64	.47
6 mo	443 ± 25	506 ± 79	.03
Peak VO_2 (mL kg^{-1} min^{-1})			
Baseline	18.1 ± 4.0	20.0 ± 7.0	.36
6 mo	19.1 ± 5.0	23.0 ± 7.2	.11

6MWT, 6-minute walk test; VO_2, oxygen consumption; MLHF, Minnesota Living with Heart Failure Questionnaire; other abbreviations as in Table 1.

showed no differences at baseline evaluation (9.4 ± 4.4 vs 7.9 ± 4.2, respectively; $P = .27$) or after the treatment period (7.0 ± 3.6 vs 8.2 ± 3.4, respectively; $P = .47$). Paired *t* test showed no differences in both groups compared with baseline ($P = .12$ in TMZ, $P = .66$ in placebo). The results of the evaluation of myocardial glucose uptake are shown in Figure 1. The evaluation of glucose uptake heterogeneity showed the lack of differences in glucose uptake SD between the TMZ and placebo groups at baseline (39 ± 9 vs 36 ± 7, respectively; $P = .29$) and after 6 months of treatment (40 ± 11 vs 39 ± 4, respectively; $P = .75$).

Effects of TMZ Treatment on Plasma Catecholamines and Oxidative Stress Levels

Markers of systemic inflammation, such as leukocyte blood count, ESR, and usCRP were similar at baseline and after the treatment period in both groups. Plasma levels of catecholamines at rest and after exercise did not show any differences between the TMZ and placebo groups.

The evaluation of oxidative stress revealed no differences in levels of MDA, SOD, and eXO at baseline and after treatment between both study arms (Table 3).

Effects of TMZ Treatment on Endothelial Function

Baseline EDDP was similar between the TMZ and placebo groups (7.3 ± 3.6% vs 8.3 ± 5.2%, respectively; $P = .48$) and no significant differences were observed after 6 months of treatment (6.9 ± 3.6% vs 10.1 ± 6.4%, respectively; $P = .11$). EIDP showed similar results, without differences between TMZ and placebo at baseline (18.3 ± 5.4% vs 16.9 ± 6.2%; $P = .45$) or after treatment (17.1 ± 5.4% vs 19.5 ± 4.8%, respectively; $P = .22$).

Table 3. Effects of Trimetazidine on Inflammation, Catecholamines, Metabolism, and Oxidative Stress at Baseline and After 6 Months Treatment

	Trimetazidine (n = 30)	Placebo (n = 30)	*P* Value
Leukocytes ($\times 10^3/mm^3$)			
Baseline	6,859 ± 1,514	7,264 ± 1,856	.39
6 mo	6,786 ± 1,176	7,279 ± 1,846	.29
Erythrosedimentation velocity (mm/h)			
Baseline	10.4 ± 6.6	9.8 ± 7.0	.76
6 mo	11.5 ± 9.0	10.8 ± 7.8	.77
usCRP (mg/L)			
Baseline	2.6 ± 2.1	2.3 ± 1.4	.66
6 mo	4.2 ± 8.0	3.7 ± 4.4	.79
Adrenaline (pg/mL)			
Baseline	27 ± 14	45 ± 28	.07
6 mo	34 ± 22	23 ± 5	.11
Adrenaline (after exercise, pg/mL)			
Baseline	42 ± 27	149 ± 254	.68
6 mo	57 ± 43	50 ± 30	.18
Noradrenaline (pg/mL)			
Baseline	568 ± 301	509 ± 351	.67
6 mo	510 ± 263	370 ± 179	.16
Noradrenaline (after exercise, pg/mL)			
Baseline	1,274 ± 435	970 ± 409	.10
6 mo	1,082 ± 537	842 ± 361	.24
Glucose (mg/dL)			
Baseline	90 ± 15	101 ± 47	.28
6 mo	90 ± 15	94 ± 34	.62
HOMA			
Baseline	2.6 ± 2.0	3.4 ± 4.8	.44
6 mo	2.7 ± 1.4	2.8 ± 2.7	.85
FFA (μmol/L)			
Baseline	0.5 ± 0.2	0.5 ± 0.1	.78
6 mo	0.5 ± 0.2	0.8 ± 0.3	.21
eSOD (AUC)			
Baseline	200 ± 170	298.73 ± 190.07	.36
6 mo	302 ± 92	475.45 ± 182.83	.17
MDA (mmol/L)			
Baseline	0.57 ± 0.33	0.51 ± 0.23	.66
6 mo	0.63 ± 0.29	0.43 ± 0.17	.17

usPCR, ultrasensitive C-reactive protein; HOMA, homeostasis model assessment (insulin resistance); FFA, free fatty acids; eSOD, endothelial superoxide dismutase; MDA, malondialdehyde; AUC, area under the curve.

End Points and Safety

After a period of 6 months, 2 patients retired from the protocol (1 in each study arm). One patient died from heart failure in the TMZ group 2 months after randomization. Five patients required hospitalization for worsening HF, 3 of which were receiving TMZ ($P = .63$). The most commonly reported adverse effects were: headache (1 patient in each group), nausea (2 patients in each group), heartburn (1 patient receiving TMZ), and dizziness (4 patients in TMZ group), with no significant differences between groups ($P = .15$).

Discussion

In this study, the addition of TMZ to standard medical therapy in stable nonischemic HF patients did not result in

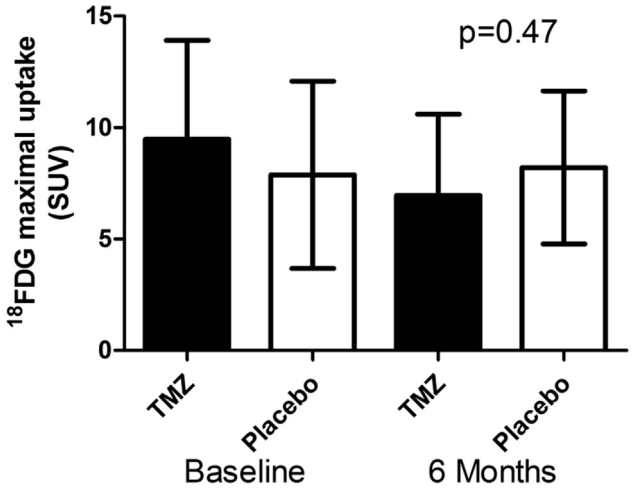

Fig. 1. ^{18}F-Fluorodeoxyglucose (^{18}FDG) maximal uptake evaluated with the use of positron-emission tomography at baseline and after 6 months of trimetazidine (TMZ) treatment in TMZ (*solid bars*) and placebo (*open bars*) groups. Results are shown as mean ± SD.

improvement of ventricular function, exercise capacity or quality of life. Also TMZ did not lead to significant changes in ^{18}FDG uptake, systemic inflammation, blood catecholamine levels, oxidative stress, or endothelial function.

TMZ has consistently demonstrated an improvement in symptoms and LVEF in individuals with HF secondary to coronary disease,[5,14,15] and part of this effect could be explained by its antianginal action. Two recent meta-analyses of studies conducted in patients with HF, most of them of ischemic etiology, revealed a significant improvement of LVEF (∼7%) with a reduction in LV end-diastolic diameter. TMZ was also associated with improvements in functional status and reductions in hospitalization from cardiac causes and mortality.[26,27]

In nonischemic HF, however, the experience with TMZ is scarce. Fragasso et al studied 55 HF patients with LVEF < 45% and functional class II−IV, only 8 of them with ischemic DCM.[17] In that retrospective study, TMZ for a period of 13 months was associated with improvements in functional class, BNP levels, LVEF, and end-systolic volume regardless of the etiology of HF.[17] Gunes et al found improvements in LVEF and tissue Doppler velocities in 87 patients with HF and LVEF ≤40% after 3 months of TMZ treatment in both ischemic (69% of patients) and nonischemic HF[17]; patients with both ischemic HF and diabetes showed the greater improvement in LVEF.[18] Only nonischemic HF patients were included in a small experience described by Tuunanen et al.[19] In that study, TMZ in doses of 70 mg/d significantly increased LVEF.

The biggest retrospective analysis of TMZ in HF compared 362 HF patients with TMZ added to optimal therapy with 307 matched control subjects. TMZ was associated with reduced mortality and lower cardiovascular hospitalization rates.[28] In that study ∼20% of the subjects had a nonischemic etiology. In 2 recently published meta-analyses, the small subgroup of patients with nonischemic HF also showed improvements in LVEF and clinical outcomes, but in the experience described by Zhang et al[27] the benefits of TMZ were restricted to LVEF with no benefits in ventricular diameters or functional class. In the present work, TMZ was not associated with changes in LVEF, and clinical outcomes were not different between groups.

Even though the postulated mechanism of action of TMZ is linked to the inhibition of FFA oxidation, it is still a matter of controversy. In HF patients, an attempt to evaluate FFA oxidation with the use of PET after TMZ therapy revealed unchanged myocardial uptake of FFA and only 10% decrease in beta-oxidation rate constant without changes in oxidative metabolism, implying increased levels of glucose oxidation. In addition, laboratory evaluation showed that patients had decreased insulin resistance and raised high-density lipoprotein levels. These results suggest that TMZ exerts its action in myocardial tissue but also has extracardiac effects that could explain its benefits.[19] Similar results were reported by Fragasso et al[15] in patients with diabetes and ischemic HF, where TMZ significantly lowered fasting plasma glucose levels. In another clinical experience from the same group,[29] TMZ improved clinical outcomes in 44 HF patients, predominantly with ischemic etiology, and decreased resting energy expenditure evaluated by continuous indirect calorimetry showing again that TMZ action is not exclusively exerted in myocardial tissue. However, in our study, we were unable to demonstrate a significant change in HOMA after TMZ treatment.

Our data also show no differences in endothelial function as evaluated by ultrasound on brachial artery in patients treated with TMZ. These results differ from the experience described by Park et al,[30] in which patients who received TMZ after transradial coronary angiography showed significant improvements in flow-mediated dilation of radial artery after treatment; a different mechanism of endothelial dysfunction in those patients could account for the observed differences.

The lack of effect of TMZ in this cohort could be explained by multiple causes. Shifting from FFA to glucose utilization as the primary myocardial energetic substrate could be more important in subjects where oxygen supply is impaired, as is the case of coronary disease. Furthermore, TMZ has been shown to be more effective in patients with metabolic disturbances that are associated with increased FFA oxidation, such as diabetic and obese individuals.[18,31] In our cohort, the prevalence of diabetes was low (8%) and our patients' body mass index was discretely over normal limits, which could partially explain the lack of response to TMZ treatment in this group. However, even after these consideration, and despite its apparent safety in nonischemic HF subjects, the lack of clinical benefit does not support the use of TMZ in this group of patients.

Study Limitations

Even when our patients were in NYHA functional class II−III, their performance in the 6MWT was unexpectedly

good. However, their high proBNP levels despite optimal therapy are concordant with advanced HF. On the other hand, ^{18}FDG-PET evaluates only glucose uptake and does not reflect glucose metabolism. These limitations should be acknowledged when interpreting the results.

Conclusion

The addition of TMZ to standard medical therapy in patients with nonischemic HF was not associated with significant changes in LVEF, functional class, or exercise capacity. TMZ did not show any improvements in proBNP levels, systemic inflammation, systemic glucose metabolism or myocardial glucose uptake, catecholamines, oxidative stress, or endothelial dysfunction. It seems likely that interventions that block FFA oxidation, promoting glucose metabolism, are more relevant in patients with an ischemic etiology and in the subgroup of patients with diabetes or obesity; in nonischemic HF patients, who have preserved oxygen supply, interventions that increase global metabolism (glucose and beta-oxidation) could be an interesting option to be evaluated in future studies.

Disclosures

None.

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