Effects of metabolic modulation by trimetazidine on left ventricular function and phosphocreatine/adenosine triphosphate ratio in patients with heart failure

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Aims The addition of trimetazidine to standard treatment has been shown to improve left ventricular (LV) function in patients with heart failure. The aim of this study is to non-invasively assess, by means of in vivo 31P-magnetic resonance spectroscopy (31P-MRS), the effects of trimetazidine on LV cardiac phosphocreatine and adenosine triphosphate (PCr/ATP) ratio in patients with heart failure.

Methods and results Twelve heart failure patients were randomized in a double-blind, cross-over study to placebo or trimetazidine (20 mg t.i.d.) for two periods of 90 days. At the end of each period, all patients underwent exercise testing, 2D echocardiography, and MRS. New York Heart Association (NYHA) class, ejection fraction (EF), maximal rate-pressure product, and metabolic equivalent system (METS) were evaluated. Relative concentrations of PCr and ATP were determined by cardiac 31P-MRS. On trimetazidine, NYHA class decreased from 3.04 ± 0.26 to 2.45 ± 0.52 (P = 0.005), whereas EF (34 ± 10 vs. 39 ± 10%, P = 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 was increased by 33% to 1.80 ± 0.50 (P = 0.03) with trimetazidine.

Conclusion Trimetazidine improves functional class and LV function in patients with heart failure. These effects are associated with the observed trimetazidine-induced increase in the PCr/ATP ratio, indicating preservation of the myocardial high-energy phosphate levels.

Introduction

Trimetazidine (2,3,4-trimethoxybenzyl-piperazine dihydrochloride) has been reported to exert anti-ischaemic properties without affecting myocardial oxygen consumption and blood supply.1 The beneficial effect of this agent has been attributed to preservation of the phosphocreatine (PCr) and adenosine triphosphate (ATP) intracellular levels2 and reduction of cell acidsis,3,4 calcium overload,4 and free-radical-induced injury caused by ischaemia.5 More importantly, trimetazidine (TMZ) affects myocardial substrate utilization by shifting energy production from free fatty acids (FFAs) to glucose oxidation.6 It has been shown that this effect might be related to a selective block of long-chain 3-ketoacyl CoA thiolase activity, the last enzyme involved in β-oxidation,7,8 even though this issue is still controversial.9 In isolated rat hearts undergoing ischaemia/reperfusion, TMZ delays the occurrence of ischaemic contracture,10 improves recovery of post-ischaemic left ventricular (LV) dysfunction,11 and accelerates the recovery of mitochondrial oxidative phosphorylation and phosphocreatine resynthesis.12 Additional studies have shown that TMZ may also be beneficial in patients with heart failure, in terms of LV function preservation and symptoms' control.13-17

Previous clinical studies using 31P-magnetic resonance spectroscopy (31P-MRS) to measure PCr/ATP ratios in human myocardium have shown that this ratio is reduced in failing human myocardium.18,19 The PCr/ATP ratio is a measure of myocardial energetics and its reduction may depend on imbalance of myocardial oxygen supply and demand,20 and reduction of the total creatine pool, a phenomenon known to occur in heart failure.21

In this report, we measured the relative content of PCr/ATP ratio in heart failure patients undergoing a double-blind, cross-over study with placebo or TMZ for two periods of 90 days. Our hypothesis was that the PCr/ATP ratio was reduced in failing human left ventricle and that TMZ could partly restore this metabolic imbalance.
Methods

Patients

Among 113 consecutive patients attending our Heart Failure Clinic in the period January–March 2003, we prospectively recruited 12 patients (one female, aged 66 ± 5 years) with heart failure (six post-ischaemic) on conventional therapy, in a randomized double-blind, cross-over study with placebo or TMZ (20 mg t.i.d.) for two periods of 90 days. All recruited patients gave their informed consent and none of them was lost at follow-up. Five patients were randomized to TMZ followed by placebo (group A) and seven patients were randomized to placebo followed by TMZ (group B) according to a computer-generated random list. Considering the short duration of action of the present formulation of TMZ, a wash-out period between study phases was not deemed necessary. All patients were receiving standard treatment with ACE-inhibitors, \( \beta \) blockers, and, where indicated, diuretics, long-acting nitrates, digoxin, and anti-platelet/anticoagulant drugs. Inclusion criteria were: (i) persistent symptoms (dyspnea on exertion, fatigue, orthopnea, paroxysmal nocturnal dyspnoea, or oedema, alone or in combination) despite optimized treatment of heart failure for at least 12 weeks and stabilized doses for the last 4 weeks; (ii) treatment with ACE-inhibitors and \( \beta \) blockers started not less than 6 months before entering the study; (iii) an ejection fraction (EF) \( \geq 45\% \) by M-B-echocardiography. Among the initially screened 113 patients, we excluded those with acute myocardial infarction or unstable angina pectoris within 3 months (15 patients); primary valvular disease (22 patients); history of any alcohol abuse within 6 months (1 patient); previous myocardial infarction localized in the anterior wall (38 patients), which was used as the volume of interest (VOI) for cardiac \( ^{31}\text{P} \)-MR spectroscopy in all subjects; uncompensated congestive heart failure (three patients); high-grade arrhythmias (two patients); significant renal insufficiency (serum creatinine \( \geq 2.2 \text{mg/dL} \)) (five patients); inducible myocardial ischaemia on exercise testing (four patients); presence of coronary lesions suitable for revascularization (four patients); LV aneurysm (six patients); diabetes mellitus (six patients); and known active neoplastic process and any orthopaedic or neurological illness that could limit patients' ability to exercise (five patients).

Experimental protocol

Patients were instructed to consume an isocaloric diet and to abstain from exercise activity for 2 weeks before the study. Patients took all their medications according to the regular schedule. At the end of each study arm period for all patients, the following examinations were obtained by a blinded investigator.

Collection of medical history and physical examination

Symptoms relative to heart failure were classified according to NYHA. Patients also completed the LV dysfunction questionnaire (LV-D-36) to measure the impact of LV dysfunction on daily life and well-being.\(^2\) Finally, overall quality of life (QOL) was evaluated on a visual analogue scale (range 0–100). Additionally, a blood sample for serum brain natriuretic peptide levels (NT-pro BNP, Roche Diagnostics, Basel, Switzerland) was withdrawn in the morning before spectroscopy.

Exercise testing

Treadmill exercise tests were performed in the morning, in the fasting state, according to the Bruce protocol. Heart rate, systolic/diastolic blood pressure, and rate-pressure product (RPP) were measured at rest and at peak exercise. Time to peak exercise was also recorded. To quantify the energy spent during exercise testing, the metabolic equivalent system (METS) was also used. An MET is a unit of energy that approximates the amount of oxygen required under basal conditions at rest and is equivalent to 3.5 mL O\(_2\) kg\(^{-1}\) min\(^{-1}\).

Echocardiography

All studies were performed with an echocardiography equipment (Sonos 5500, Philips Medical Systems, Bothell, WA, USA) with broadband transducers capable of second harmonic imaging (54 with 1.8/3.6 MHz transducer). Left ventricular end-diastolic (EDV) and left ventricular end-systolic (ESV) volumes were obtained from the apical four-chamber view by using the single-plane Simpson’s rule from which LV EF was calculated as \( (\text{EDV} - \text{ESV})/\text{EDV} \). The Tei index, an echocardiographic/Doppler index of combined systolic and diastolic function, calculated as isovolumic relaxation time plus isovolumic contraction time divided by ejection time, was also calculated.\(^2\)

\( ^{31}\text{P} \)-MR spectroscopy protocol

Cardiac \( ^{31}\text{P} \)-MR spectroscopy was performed at rest and with patients in the supine position with the use of a 1.5 T whole-body scanner (Gyroscan Intera Master 1.5 MR System; Philips Medical Systems, Best, the Netherlands).\(^2\) \( ^{31}\text{P} \) spectra were obtained by means of a 10-cm-diameter surface coil used for transmission and detection of radio frequency (RF) signals at the resonance frequency of \( ^{31}\text{P} \) (at 1.5 T, 25.85 MHz) as described by Lamb et al.\(^4\) A small sample container built in the coil centre, containing an aqueous solution of methyl-phosphonate, served as a geometrical reference. The surface coil was secured in place with a Velcro band around the chest, helping to minimize breathing artefacts in the phase-encoding direction. Electrocardiographically triggered MR imaging was performed to acquire scout images (SURVEY/BTFE). The exact position of the \( ^{31}\text{P} \) surface coil was verified by observing the signal originating from the coil sample. When necessary, the coil was repositioned to place the coil centre just below the mitral valve level of the heart, as observed on the transverse scout images. Localized homogeneity adjustment (shimming) was performed using the body coil and ECG triggering. Shimming was performed with an automatic procedure by optimizing the \( ^{1}\text{H} \)-MR spectroscopy water signal obtained with a volume-selective 90°–180°–180° sequence. Shim volumes were planned on the transverse and sagittal scout images to include the entire left ventricle, while avoiding chest wall muscle and diaphragm muscle as much as possible. The transmitter–receiver was then switched without time delay to the \( ^{31}\text{P} \) frequency. Manual tuning and matching of the \( ^{31}\text{P} \) surface coil were performed to adjust for different coil loading. The RF level was optimized to obtain a good pulse of 40 μs for the reference sample at the centre of the \( ^{31}\text{P} \)-surface coil. The acquisition of \( ^{31}\text{P} \)-MR spectra was triggered to the R-wave of the ECG, with a trigger delay time of 200 ms and a recycle time of 3.6 s. Image Selected in-vivo Spectroscopy (ISIS) volume selection in three dimensions (3D-ISIS) was the employed volume selection. It was based on 192 averaged free induction decays. The coil centre was positioned just below the mitral valve level of the heart, as observed on the transverse scout images, and large part of the signal is collected from the anterior wall of the left ventricle and of the septum. For this reason, anterior myocardial infarction was used as a criterion of exclusion of study subjects. The selection of the VOI for cardiac \( ^{31}\text{P} \)-MR spectroscopy was planned from the transverse and sagittal scout images, and oriented perpendicular to the chest wall, avoiding inclusion of chest wall muscle and diaphragm muscle as much as possible. On the basis of our experience, the volume size was typically 6 × (caudo-cranial) × 7 × 7 cm\(^3\). As the predicted maximal effective depth of the surface coil is \( \sim 9 \) cm below the coil centre, the exact distance in the posterior direction was determined by coil sensitivity. Total acquisition time was 10 min. Adiabatic frequency-modulated hyperbolic secant pulses and adiabatic half-passage detection pulses were used to achieve inversion and excitation over the entire VOI. Total examination time was about 40–45 min. 3D-ISIS was employed after testing.
that using higher spatial resolution (2D-ISIS + 1D SI using a one-dimensional phase encoding bar with 32 rows of 1-cm thickness), the PCr/ATP ratios were in close agreement.

31P-MR spectroscopy analysis
31P-MR spectra were transferred to a remote SUN-SPARC workstation for the analysis. The spectra were quantified automatically by model function analysis in the time domain, using prior spectroscopic knowledge to improve the accuracy of the spectral parameters using Fitmasters. ATP is modelled as doublets (α-ATP and γ-ATP) and a triplet (β-ATP). The spectral fitting routine was based on a non-linear least-squares Gauss–Newton implementation for exponential damping. The ATP level in the 31P-MR spectra was corrected for the ATP contribution from blood in the cardiac chambers based on a previous study in which the 31P-MR spectrum of whole venous blood was quantified. The ratio of ATP to 2,3-diphosphoglycerate (2,3-DPG) was 0.36 and it was used in this work to calculate the contribution of blood ATP to the observed ATP signal in cardiac 31P-MR spectra. Depending on the repetition time (TR), PCr/ATP ratios had to be corrected for partial saturation effects. T1 values obtained from inversion recovery experiments on the human left ventricle (4.43 s for PCr, 2.61 s for α-ATP, 2.51 s for γ-ATP, and 2.67 s for β-ATP) were used. On the basis of these data and a TR of 3.6 s, a saturation correction factor of 1.35 was applied to all 'blood-corrected' myocardial PCr/ATP ratios acquired in this study. Other tissues (liver and diaphragm/ skeletal muscle) were carefully excluded from the VOI and ratios acquired in this study. Other tissues (liver and diaphragm/ skeletal muscle) were carefully excluded from the VOI and ratios acquired in this study.

Free fatty acids (FFA) determination
Blood samples for FFA assessment were collected in pre-chilled tubes containing 0.1% ethylene diamine tetraacetic acid, just before performing spectroscopy. Tubes were immediately placed in ice and plasma was immediately processed by centrifugation at 4°C. Plasma was then frozen and stored at −70°C and FFA determinations were performed as previously described. Coefficient of variation (CV) was 7.9 ± 1.9%.

Statistical analysis
Data are presented as a mean ± SD. Analyses were performed using the SSPS (version 10.0; SPSS Inc., Chicago, IL, USA). An estimate of the signal-to-noise ratio (SNR) of each spectra was obtained from the Cramer–Rao standard deviation (CRSD) calculated for the PCr/ATP, which is an indicator of the accuracy of the spectral quantification. The CRSD is based on the statistical theory of maximum likelihood estimation, leading to lower bounds on the statistical errors in the parameter estimates and is related to noise measurement. Determination of the CRSD is an important feature of the applied time domain fitting routine. For each 31P-MR spectrum, the CRSD of PCr/ATP was divided by the PCr/ ATP ratio yielding a relative CRSD (rCRSD), which is inversely related to the SNR. Cardiac 31P-MR spectra with an rCRSD exceeding 20% were excluded. To assess accuracy and reproducibility of the PCr/ATP ratio, we selected 18 individuals (43 ± 20% were excluded. To assess accuracy and reproducibility of the PCr/ATP ratio, we selected 18 individuals (43 ± 20% were excluded. To assess accuracy and reproducibility of the PCr/ATP ratio, we selected 18 individuals (43 ± 20% were excluded. To assess accuracy and reproducibility of the PCr/ATP ratio, we selected 18 individuals (43 ± 20% were excluded. To assess accuracy and reproducibility of the PCr/ATP ratio, we selected 18 individuals. A sample size of 12 patients achieves 80% power to detect a difference of at least 30% in PCr/ATP ratio, with an estimated SD of the PCr/ATP ratio difference between TMZ and placebo of 0.45.

Results
All 12 recruited patients completed the study. None of them complained of significant side effects. Table 1 shows the baseline clinical characteristics of the study patients. During the study period, none of the patients discontinued or changed dosage of previously stabilized therapy with ACE-inhibitors, angiotensin receptor blockers, β-blockers, nitrates, and digoxin. On TMZ, NYHA class did not change in five patients and decreased of at least one class in the remaining seven patients. Overall, NYHA class decreased from 3.04 ± 0.26 to 2.49 ± 0.52 (P = 0.005). Accordingly, LVD-36 score decreased from 30 ± 18 to 23 ± 15 (P = 0.04), whereas QOL score was not significantly different (from 65 ± 13 to 79 ± 15, P = 0.05). Serum BNP and FFA levels were not significantly different between placebo and TMZ (from 694 ± 489 to 449 ± 209 pg/mL, P = 0.05; and 0.57 ± 0.32 vs. 0.57 ± 0.27 mmol/L, P = 0.48, respectively).

Table 1 Baseline clinical characteristics of study patients

| Age (years) | 66 ± 5 |
| Male/female | 11/1 |
| Drug treatment (patients/total, %) | | |
| ACE-inhibitors | 12/12, 100% |
| Angiotensin receptor blockers | 3/12, 25% |
| β-Blockers | 12/12, 100% |
| Digoxin | 5/12, 42% |
| Diuretics | 10/12, 83% |
| Nitrates | 4/12, 33% |
| Resting heart rate (bpm) | 71 ± 9 |
| Resting systolic blood pressure (mmHg) | 118 ± 11 |
| Resting diastolic blood pressure (mmHg) | 71 ± 8 |
| Exercise time (s) | 312 ± 131 |
| EDV diameter (mm) | 70 ± 9 |
| ESV diameter (mm) | 59 ± 11 |
| ESV volume (ml) | 185 ± 51 |
| EDV volume (ml) | 130 ± 42 |
| EF (%) | 33 ± 7 |
| Tei index | 0.68 ± 0.25 |

The distribution of ergonomic and echocardiographic variables was tested for normality by means of the Shapiro–Wilk statistic. The possibility of a period effect was tested by a two-sample t-test or Mann–Whitney test as appropriate comparing the mean difference (placebo-TMZ) in group A vs. the mean difference (TMZ-placebo) with the opposite sign in group B. To investigate the possibility of a treatment–period interaction, a two-sample t-test was performed comparing patients average response to the two treatments in group A vs. group B. The change was calculated as the difference between the variable levels at the end of the placebo and those at the end of TMZ treatment. To compare the changes between the two treatments, paired t-test or Wilcoxon test was used as appropriate. Baseline values between groups are compared by two-sample t-test or Mann–Whitney test. The McNemar test of symmetry was performed to investigate the change of NYHA class from one treatment to the other. Pearson correlation coefficient was calculated to investigate the correlation between EF and PCr/ATP. The significance level was set at P < 0.05.
Ergometric results

Table 2 shows the detailed results. As there was neither period effect (P > 0.05 for all variables) nor treatment–period interaction (P > 0.05 for all variables), a simple comparison between the two groups of treatment is shown. Resting heart rate was higher when on TMZ compared with placebo (77 ± 14 vs. 69 ± 9 bpm, P = 0.03). TMZ treatment, compared with placebo, significantly increased peak METS (8.78 ± 2.72 vs. 7.44 ± 1.84, P = 0.03), whereas total exercise time (334 ± 148 s vs. 323 ± 148 s, P = 0.36) and peak RPP (1889 ± 4893 vs. 17462 ± 3601 mmHg bpm, P = 0.09) were not significantly different between treatments.

Echocardiographic results

Table 3 shows the detailed results. As there was neither period effect (P > 0.05 for all variables) nor treatment–period interaction (P > 0.05 for all variables), a simple comparison between the two groups of treatment is shown. Treatment with TMZ significantly increased EF (from 33 ± 9 to 39 ± 9%, P = 0.03). In eight patients, EF increased, whereas in the remaining four patients EF slightly decreased (from 36 ± 7 to 33 ± 8%) (Figure 1A and B). The Tei index (from 0.64 ± 0.27 to 0.59 ± 0.36, P = 0.24) was not significantly different between placebo and TMZ.

Cardiac PCr/ATP ratio

Both period effect (P = 0.11) and treatment–period interaction (P = 0.34) were not statistically significant. The mean cardiac PCr/ATP ratio was 1.35 ± 0.33 with placebo but was increased by 33% to 1.80 ± 0.50 (P = 0.03) with TMZ (Figure 2A and B). On TMZ, the PCr/ATP ratio increased in nine patients and decreased in three patients who evidenced a decrease in EF (from 1.64 ± 0.40 to 1.26 ± 0.49). However, no significant correlation between EF and PCr/ATP ratio was found (r = 0.13). Figure 3 shows an example of the MRS on placebo and after TMZ (from PCr/ATP = 1034 to PCr/ATP = 1810).

Discussion

The results of this study show that, in patients with heart failure on full standard medical therapy, the addition of TMZ may consistently improve functional class and LV function. The observed TMZ-induced improvement of PCr/ATP ratio, as a measure of myocardial energetics, supports the hypothesis that these beneficial clinical effects are probably due to preservation of the myocardial high-energy phosphate intracellular levels. These results appear particularly interesting, especially in view of previous evidence indicating the PCr/ATP ratio as a significant predictor of mortality.28

The observation of higher resting and peak exercise heart rate during TMZ treatment, despite stable doses of...
β-blockers, is difficult to explain. In fact, all previous clinical studies have confirmed that this agent does not exert any significant effect on heart rate and blood pressure. However, considering that both resting and peak exercise RPP were not different between treatments, we surmise that the observed increment in heart rate was unrelated to a direct pharmacological action of TMZ. Despite we did not find any significant improvement in exercise capacity with TMZ compared with placebo, a previous study employing cardiopulmonary exercise testing has shown an association between improvements in LV function and peak VO₂ in patients with LV dysfunction, treated with TMZ. These different findings are probably due to better accuracy of cardiopulmonary exercise testing compared with the simple evaluation of treadmill exercise time.

Effects of TMZ on cardiac metabolism

There is ample experimental and clinical evidence that myocardial high-energy phosphate metabolism is substantially deranged in chronic heart failure. Depletion of the PCr and free creatine levels has been described as a uniform phenomenon occurring in animal models of heart failure of various origins. Total creatine content/creatine kinase activity is also reduced in human dilated cardiomyopathy and the decrease has been shown to correlate with the degree of LV dysfunction. On this ground, attempts to improve PCr/ATP ratios in heart failure using 31P-MR spectroscopy have been pursued. In rats after myocardial infarction, the decrease of total creatine content was prevented by ACE-inhibition and β-blockade. Thus, the beneficial effects of these established therapies on mortality seen in clinical trials could be, at least in part, related to changes in improved cardiac efficiency in energy transfer. Interestingly enough, recent studies have shown that, like TMZ, one of the main effects of β-blockers and ACE-inhibitors in patients with heart failure is the reduction of FFA utilization. When circulating FFA concentrations are high, for instance, in heart failure, the oxidation of glucose and pyruvate is decreased. As a result of this, pyruvate is redirected towards lactate production and released from the heart. This produces protons, which the heart must also clear, a process that requires energy, and results in redirecting ATP away from contractile function, which can decrease cardiac efficiency. Conversely, decreasing plasma FFA concentrations, or directly inhibiting their oxidation, increases pyruvate oxidation and cardiac efficiency. In fact, a

![Figure 2: Individual data (A) and mean ± SD (B) of PCr/ATP ratio on placebo (plac) and on TMZ.](https://academic.oup.com/eurheartj/article-abstract/27/8/942/438951)

![Figure 3: Representative cardiac-phosphorus spectra of a patients while taking placebo (left panel) or TMZ (right panel). The 31P spectrum shows resonance peaks of PCr, ATP, phosphodiesters (PDE), and the combined signals of 2,3-DPG originating from blood and inorganic phosphate (Pi).](https://academic.oup.com/eurheartj/article-abstract/27/8/942/438951)
major factor in the development and progression of heart failure is already a reduced availability of ATP, determining a metabolic state that has been defined as 'energy starvation'.

Previous studies have suggested that TMZ could inhibit the utilization of fatty acid substrates and shift metabolism from fatty acid to glucose oxidation, by selectively blocking the activity of 3-ketoacyl CoA thiolase, the last enzyme of the oxidative chain, even though this issue is still controversial. By inhibiting fatty acid oxidation, TMZ stimulates total glucose utilization, including both glycolysis and glucose oxidation. Because utilization of fatty acid oxidation is less efficient than glucose oxidation, it may be possible to improve myocardial contractile function by reducing FFA oxidation and increasing the flux through pyruvate dehydrogenase. This could be the mechanism by which TMZ improved symptoms and LV function in our patients, as supported by the observed improvement in the PCr/ATP ratio, indicating preservation of the myocardial high-energy phosphate intracellular levels. Additionally, the fact that serum FFA levels were similar between placebo and TMZ supports the notion that the agent interferes with FFA utilization rather than availability.

In this context, a recent study has evidenced that energy deficiency in heart failure might result from increased uncoupling proteins (i.e. less efficient ATP synthesis) and depleted glucose transporter protein (i.e. reduced glucose uptake). On this ground, the adoption of drug therapies (such as TMZ and ranolazine) aimed at interrupting the metabolic vicious circle in heart failure has been advocated.

Study limitations
One limitation of this study was the small sample size. Patients recruitment was limited by the fact that this was a pilot, not sponsored study. However, the study population was very well characterized and homogeneous and this partly reduces the limiting effect of a small study sample. Additionally, the aim of this study is to evaluate the myocardial high-energy phosphate intracellular levels and to correlate them to functional outcome, which had already been shown to be beneficial in previous studies performed in populations of similar size.

The large VOI used in this work represents a limitation of the study because of the low spatial resolution. However, based on the facts that (i) in preliminary studies using higher spatial resolution (but longer acquisition times) the PCr/ATP ratios were in close agreement and (ii) the aim of the study is to assess the metabolic alterations involving the entire LV and not to detect local abnormalities within small amount of tissue, we consider as appropriate the use of 3D-ISIS.

Conclusions
The results of our study support the concept that the administration of a metabolic modulator such as TMZ may represent an effective adjunctive treatment in patients with heart failure. In fact, TMZ improves functional class, exercise performance, and LV function in patients with heart failure. These beneficial effects are associated to the observed TMZ-induced increase in the PCr/ATP ratio, indicating preservation of the myocardial high-energy phosphate intracellular levels.

Although the hypothesis that metabolic modulation could represent a new therapeutic complement in heart failure is highly suggestive, the question whether the observed beneficial effects could translate into decreased morbidity and mortality needs further investigation. The results of this study warrant large-scale trials to investigate the long-term effects in terms of morbidity/mortality of metabolic modulation in patients with heart failure.

Conflict of interest: G.F. has given remunerated lectures on behalf of Servier International, the manufacturer of TMZ.

References
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