Trimetazidine Effect on the Cardiac Autonomic Nerve System after Percutaneous Coronary Intervention in Coronary Heart Disease: A Propensity-score Matched Study

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ABSTRACT

Objective: To assess the effects of trimetazidine (TMZ) added to conventional drug therapy on cardiac autonomic nervous CANS in patients with coronary heart disease (CHD) after the percutaneous coronary intervention (PCI).

Study Design: Descriptive study.

Place and Duration of Study: Department of Cardiology, The Second Hospital of Hebei Medical University, Hebei, China, from May 2018 to September 2019.

Methodology: The study included 50 patients with CHD after a successful PCI who received trimetazidine plus conventional therapy were included as cases (exposed group), and 50 matched patients were identified as controls (non-exposed group). Heart rate (HR) and heart rate variability (HRV) parameters including sympathetic activity (SDNN, LF), parasympathetic activity (RMSSD, pNN50, SDSD, HF), and sympathovagal balance (LF/HF ratio) were used to evaluate CANS function.

Results: There were no statistical differences in the HR and HRV parameters before and after PCI ($p>0.05$). In the non-exposed group, conventional therapy significantly improved the HRV parameters (all $p<0.05$), while not affecting HR ($p>0.05$). In the exposed group, all HRV parameters except HR were improved after 4 weeks of treatment. After 4 weeks of treatment, the exposed group had higher parasympathetic-nerve activity, lower sympathetic-nerve activity, and LF/HF ratio compared to the non-exposed group (all $p<0.05$).

Conclusions: The application of TMZ based on conventional therapy effectively improved the CANS in CHD patients who underwent PCI.

Key Words: *Coronary heart disease, Percutaneous coronary intervention, Trimetazidine, Cardiac autonomic nervous system, Heart rate variability.*

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INTRODUCTION

Coronary heart disease (CHD) is the major cause of death worldwide.[1] Epidemiological data reported that the prevalence of CHD across Asia, Europe, and North America ranged from 0.99 to 56.5%, with the overall prevalence of 6.3%.[2] Most patients with CHD had cardiac autonomic nervous system (CANS) dysfunction, which affects the pumping function of the heart and the electrophysiological activity of the myocardium.[3]

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It is known that the sympathetic nervous system (SNS) may participate in atherosclerosis formation by activating platelets, with the subsequent formation of platelet growth factor.[4] In addition, the CANS dysfunction with increased sympathetic nervous activity and decreased parasympathetic-nervous activity usually occurs at an initial stage of CHD, leading to fatal events.[5] In numerous studies, an improvement in CANS balance has proven beneficial for patients with cardiovascular disease,[6] since the CANS is an integral part of the neurohormonal regulation of cardiac function.[7] It comes thus as no surprise that CANS improvement may be critical to reducing cardiovascular events, cardiac failure, and early mortality.[8]

At present, percutaneous coronary intervention (PCI) is the cornerstone of treatment for CHD.[9,10] PCI could minimize the damage to myocardial blood flow reconstruction, thus it is widely adopted in clinical practice.[11] However, previous studies demonstrated that PCI maybe not be the most effective method for improving CANS function in patients with CHD.[12] Moreover, myocardial no-reflow still occurs in some patients after PCI.[13] Thus, any alternative therapy likely to improve the CANS function after PCI would be a valuable asset.

Myocardial energy metabolism therapy is emerging as a new therapeutic regimen for CHD.[14] Trimetazidine (TMZ) is a piperazine derivative, which can increase the blood flow reserve and reduce the frequency of angina pectoris by maintaining the energy of myocardial cells under hypoxia or ischemia conditions.[15] A statistically significant augmentation of heart rate variability (HRV) was observed on CHD patients with TMZ treatment in a randomised controlled trial.[16] Notably, TMZ can be easily combined with conventional pharmacotherapy when traditional drugs are not tolerated.[17] While up to now, no systematic analysis has been reported on the independent effects of TMZ in CHD patients undergoing PCI.

Therefore, the objective of this study was to assess the effects of TMZ on CANS in CHD patients who had a successful PCI.

METHODOLOGY

This descriptive cohort study included patients with CHD after a successful PCI admitted to the Department of Cardiology, The Second Hospital of Hebei Medical University, from May 2018 to September 2019. This study was conducted following the Helsinki Declaration, and approved by the Ethics committee of The Second Hospital of Hebei Medical University (Ethical approval number: 2018-R091). All patients provided written informed consent.

The inclusion criteria were age 18-90 years, a clinical diagnosis of CHD and a successful PCI before inclusion. The diagnosis of CHD was made according to the Chinese Society of Cardiology Guidelines for the diagnosis and treatment of chronic stable angina pectoris (2018 edition). Exclusion criteria were patients with non-sinus rhythm, including atrial flutter, atrial fibrillation, severe atrioventricular block, pathological sinoatrial node syndrome, and post-implantation of a permanent artificial cardiac pacemaker; endocrine diseases except for severe cardiac dysfunction (left ventricular ejection fractions<50%) based on angiography examination, hepatic or renal dysfunction, electrolyte disorder or acid-base balance disorder; emergency PCI; patients with the severe 3-vessel disease and left main coronary artery disease that result in the incomplete revascularisation.

Propensity score matching in a ratio of 1:1 was used to minimize the expected significant bias between the two groups. A total of 50 CHD patients after PCI who received trimetazidine plus conventional therapy were included as cases (exposed group), and 50 matched patients were identified as controls (non-exposed group). The score was estimated using logistic regression, which considered age, gender, comorbidities, and medicine combination.

The patients in the non-exposed group were given conventional drugs therapy for 4 weeks. The conventional drugs included antiplatelet agents, anticoagulant agents, statins, angiotensin-converting enzyme inhibitors (ACEI), β-blockers, and nitrates were administrated according to the disease condition. The patients in the exposed group were given conventional drugs combined with TMZ (20 mg three daily oral doses) within 48 hours after surgery.

The data were retrieved from the electronic medical records, collecting the demographic, clinical, and laboratory information for analysis, such as age, gender, comorbidities and drug combination. Heart rate (HR) and the HRV parameters in time and frequency domains were obtained from continuous fifteen-minute short-term electrocardiogram recording performed during spontaneous breathing using a BI 112 (Shenzhen, Boying). Two HRV parameters, the standard deviation of all normal sinus RR intervals (SDNN) and normalised low frequency (norm-LF) were used to evaluate the sympathetic nerve activity. Five HRV parameters, the root mean square of successive heartbeat interval differences (RMSSD), the standard deviation of differences between adjacent RR intervals (SDSD), the percentage of successive normal sinus RR intervals >50 ms (pNN50), and normalised high frequency (norm-HF) were used to evaluate the parasympathetic-nerve activity. LF/HF ratio was calculated to quantify the changing relationship between sympathetic and parasympathetic nerve activities. Evaluations of HRV parameters in all patients were performed within 48 hours of admission, within 48 hours after PCI, and 4 weeks after treatment, respectively. The norm-LF and norm-HF were adopted in this study due to the individual difference of the traditional frequency-domain index. To evaluate the safety, we collected the occurrence of nonfatal myocardial infarction, target vessel complete revascularization, stent thrombosis (ST), and cardiogenic death (CD) within four weeks after PCI.

All statistical analyses were performed by using SPSS version 21.0 (SPSS Institute. IL.USA). The distribution of quantitative data was tested with the Kolmogorov-Smirnov test. The data of age in all groups were considered to be normally distributed and compared with the independent-samples T-test. The data of other parameters were considered to be non-normally distributed in at least one group. Thus, for normally distributed data, the comparison before and after PCI or treatment was performed Wilcoxon signed-rank test, and the comparison between the exposed group and non-exposed group was conducted using the Mann-Whitney test. Normally distributed data were expressed as mean (standard deviation [SD]), while non-normally distributed data were expressed as median (interquartile range [IQR]). Categorical variables were expressed as number (percentage), and compared χ^2 test or Fisher's exact test. Statistical significance was set at $p<0.05$.

RESULTS

As shown in Table I, a total of 100 patients (mean age 59.67±8.88 years, range 39-78 years) who had undergone a successful PCI were retrospectively included in this study. Among them, 64 (64%) patients with hypertension, 31 (31%) patients with diabetes, and 44 (44%) patients with hyperlipemia. Diseased vessels include the anterior descending branch (48 cases), circumflex branch (17 cases), and right coronary artery (35 cases).

Table I: Baseline characteristics.

	Non-exposed group (n=50)	Exposed group (n=50)	*p*-value
Gender (Male/Female), n (%)	31 (62)/ 19 (38)	37 (74)/ 13 (26)	0.198
Age in years, mean SD	59.48±7.76	59.86±9.94	0.832
Comorbidities, n (%)			
Hypertension	35 (70)	29 (58)	0.211
Diabetes	17 (34)	14 (28)	0.517
Hyperlipidaemia	23 (46)	21 (42)	0.687
Diseased vessels			0.464
LAD	21 (42)	27 (54)	
LCX	10 (20)	7 (14)	
RCA	19 (38)	16 (32)	
Medicine combination, n (%)			
Anti-platelet	50 (100)	50 (100)	--
Statins	48 (96)	49 (98)	>0.999
β-blocker	43 (86)	41 (82)	0.585
ACEI/ARB	38 (76)	35 (70)	0.499
Nitrates	39 (78)	41 (82)	0.617

Normally distributed data were expressed as mean (standard deviation). The comparison between groups were performed using independent-samples T-test. Categorical variable were expressed as number (percentage), and compared with χ^2 test or Fisher's exact test. SD = Standard deviation; LAD = Left anterior descending; LCX=left circumflex artery; RCA = Right coronary artery; ACEI = Aangiotensin-converting enzyme inhibitors; ARB = Angiotensin receptor blockers.

Table II: Effects of percutaneous coronary intervention on cardiac autonomic nervous system in patients.

Parameters, median (IQR)	Before PCI (n=100)	After PCI (n=100)	*p*-value
HR (bpm)	67 (61, 73)	68 (62, 75)	0.348
HRV parameters			
Sympathetic-nerve activity			
SDNN (ms)	36.17 (29.24, 49.48)	36.61 (29.56, 49.39)	0.921
norm-LF (ms^2)	66.85 (52.59, 80.27)	66.36 (49.98, 79.07)	0.986
Parasympathetic-nerve activity			
RMSSD (ms)	17.76 (13.07, 25.35)	19.65 (12.80, 25.31)	0.957
SDSD (ms)	16.97 (13.00, 23.89)	19.36 (12.69, 24.73)	0.708
pNN50 (%)	0.83 (0.21, 3.71)	1.15 (0.29, 3.89)	0.303
norm-HF (ms^2)	25.94 (15.99, 36.83)	22.45 (16.20, 41.54)	0.793
Interaction between sympathetic and parasympathetic-nerve activities			
LF/HF ratio	2.58 (1.61, 4.83)	2.80 (1.34, 4.82)	0.900

Non-normally distributed data were expressed as median (interquartile range) and compared with Wilcoxon signed rank test. IQR = Interquartile range; PCI = Percutaneous coronary intervention; bpm = beats/min; HR = Heart rate; SDNN = Standard deviation of all normal sinus RR intervals; norm-LF = Normalised low frequency; RMSSD = Rroot mean square of successive heartbeat interval differences; SDSD = Standard deviation of differences between adjacent RR intervals; pNN50 = Percentage of successive normal sinus RR intervals >50 ms; norm-HF = Normalised high frequency.

There was no statistical difference in underlying disease (hypertension, diabetes, hyperlipemia), vascular invasion, and therapeutic regimen in both two groups (*p*>0.05). Besides, no patients with peripheral neuropathy were found in both two groups. Taken together, there was no statistical difference concerning baseline characteristics between the non-exposed group and the exposed group (p>0.05).

The effects of PCI surgery on CANS were listed in Table II. No statistical difference in HR was observed before (median 67 bpm; IQR, 61 to 73 bpm) and after PCI surgery (median 68 bpm; IQR, 62 to 75 bpm, p=0.348). With regard to the changes in sympathetic nerve activity, the results showed that PCI had no effects on SDNN (preoperative *vs*. postoperative: 36.17 ms *vs*. 36.61 ms, p=0.921) and norm-LF (66.85 ms^2 *vs*. 66.36 ms^2, p=0.986). Meanwhile, there was no significant difference in parasympathetic-nerve activity before and after PCI surgery, including RMSSD (17.76 *vs*. 19.65 ms, p=0.957), SDSD (16.97 ms *vs*. 19.36 ms, p=0.708), pNN50 (0.83 *vs*. 1.15, *p*=0.303), and norm-HF (25.94 ms^2 *vs*. 22.45 ms^2, p=0.793). Similarly, the changing relationship between sympathetic and parasympathetic nerve activities (LF/HF ratio) did not affect by PCI surgery (2.58 *vs*. 2.80, p=0.900).

In the non-exposed group, HR did not improve after treatment after 4-week treatment with conventional drugs (Before *vs*. After, 68 [IQR, 62-75] *vs*. 64 [IQR, 61-70] bmp, p=0.314). However, the sympathetic nerve activity including SDNN (37.90 *vs*. 42.38, p=0.043) and norm-LF (68.05 *vs*. 63.84, p=0.05) was significantly improved after treatment in the non--exposed group. With regard to parameters reflecting parasympathetic-nerve activity, RMSSD, SDSD, pNN50, and norm-HF were all increased after conventional treatment in the non-exposed group (all p<0.001, Table III). In addition, LF/HF ratio showing sympathovagal balance was significantly decreased after treatment (p<0.001).

In the exposed group, HR decreased obviously after 4-week treatment (Before *vs*. After, 68 [IQR, 63-75] *vs*. 65 [IQR, 61-70] bmp, *p*=0.026). Meanwhile, the sympathetic nerve activity of the SDNN (32.80 *vs*. 47.59) and norm-LF (64.20 *vs*. 59.09) significantly changed after treatment (p<0.001). About parasympathetic-nerve activity, the RMSSD, SDSD, pNN50, and norm-HF were significantly increased after treatment (all p<0.001). LF/HF ratio showing sympathovagal balance was significantly decreased after treatment (p<0.001).

Before the 4-week treatment, no statistical difference among all indicators was detected between the non-exposed group and the exposed group (all p>0.05). There was no statistical difference in HR between the non-exposed group and the exposed group. After 4 weeks treatment, the exposed group had higher parasympathetic-nerve activity (RMSSD [p=0.021], SDSD [p=0.021], pNN50 [p=0.044] and norm-HF [p=0.020]), lower sympathetic nerve activity (SDNN [p=0.037] and norm-LF [p=0.034]) and LF/HF ratio [p=0.017] compared to non-exposed group. Taken together, compared with the non-exposed group, the exposed group can significantly improve the CANS function in patients with CHD.

The number of nonfatal myocardial infarctions and CD were equal between the non-exposed group and the exposed group, and there were no statistical differences between the two groups (p>0.05). The number of complete revascularization and ST in the exposed group was less than that in the non-exposed group with no significant difference (p>0.05).

DISCUSSION

CHD remains a major cause of global death. Most CHD patients have electrophysiological abnormalities of the myocardium, malignant arrhythmia, and heart failure, which are associated with CANS dysfunction and reduction in myocardial perfusion.[18] HRV, the spontaneous fluctuations in the normal sinus rhythm, was commonly used to evaluate the CANS modulation.[3]

Table III: Effects of conventional drug therapy and combination drug therapy in improving CANS function.

Parameters, median (IQR)	Non-exposed group (n=50)			Exposed group (n=50)			*p*-value (Non vs. Exp)	
	Before treatment	After treatment	*p*-value (B vs. A)	Before treatment	After treatment	*p*-value (B vs. A)	Before treatment	After treatment
HR (bpm)	68 (62, 75)	64 (61, 70)	0.314	68 (63, 75)	65 (61, 70)	0.026	0.874	0.912
HRV parameters								
Sympathetic-nerve activity								
SDNN(ms)	37.90 (30.19, 48.32)	42.38 (34.18, 50.26)	0.043	32.80 (25.87, 50.62)	47.59 (38.17, 59.07)	<0.001	0.491	0.037
norm-LF (ms^2)	68.05 (52.01, 79.16)	63.84 (47.69, 73.81)	0.005	64.20 (49.09, 78.98)	59.09 (42.24, 68.18)	<0.001	0.962	0.034
Parasympathetic-nerve activity								
RMSSD (ms)	20.50 (12.38, 25.18)	23.88 (15.69, 33.96)	<0.001	18.89(13.46, 25.53)	26.16 (19.92, 34.28)	<0.001	0.801	0.021
SDSD (ms)	19.65 (12.32, 25.10)	23.82 (15.66, 33.09)	<0.001	18.33 (13.30, 24.73)	26.09 (19.63, 34.19)	<0.001	0.809	0.021
pNN50 (%)	1.25 (0.27, 4.49)	3.47 (0.77, 9.46)	<0.001	0.98 (0.29, 2.83)	4.90 (1.79, 13.29)	<0.001	0.728	0.044
norm-HF (ms^2)	23.02 (14.17, 41.11)	29.92 (21.56, 44.28)	<0.001	22.23 (16.36, 43.25)	35.21 (29.28, 49.84)	<0.001	0.817	0.020
Interaction between sympathetic and parasympathetic-nerve activities								
LF/HF ratio	3.02 (1.38, 4.77)	2.13 (0.95, 3.38)	<0.001	2.47 (1.22, 4.92)	1.56 (0.87, 2.35)	<0.001	0.855	0.017

Non-normally distributed data were expressed as median (interquartile range). The comparison before and after treatment were performed using Wilcoxon signed rank test; and the comparison between groups were performed using Mann-Whitney test. IQR = Interquartile range; CANS = Cardiac autonomic nervous system; PCI = Percutaneous coronary intervention; bpm = beats/min; HR = Heart rate; SDNN=standard deviation of all normal sinus RR intervals; norm-LF = Normalised low frequency; RMSSD = Root mean square of successive heartbeat interval differences; SDSD = Standard deviation of differences between adjacent RR intervals; pNN50 = Percentage of successive normal sinus RR intervals >50 ms; norm-HF = Normalised high frequency; Non = Non-exposed group; Exp = Exposed group.

Previous studies revealed that HRV has important value in the occurrence of malignant arrhythmia and sudden cardiac death after acute myocardial infarction.[19] Thus, the improvement of HRV has the potential to benefit for the prognosis and reduce the incidence of adverse cardiovascular events in patients with CHD.

Currently, the effect of PCI on the improvement of CANS function is controversial. In some studies, it is demonstrated that PCI could improve the HRV *via* eliminating sympathetic hyperactivity and improving the stability of CANS function in patients with CHD.[20] However, opposite conclusions still exist, which showed that the HRV reduction is not exclusively related to PCI, even is not significant after PCI.[21]

Similar to this opinion, the results of the present study supported that PCI has no effects on the improvement of HRV. Nonetheless, the finding was preliminary due to the short follow-up time.

The most important finding of the present study is that TMZ improved the CANS function, manifesting as the improvement of parasympathetic-nerve and sympathetic nerve activity. TMZ has been widely used for patients with cardiovascular and cerebrovascular diseases attribute to effectively restore myocardial function, improve mitochondrial energy metabolism, and the long-term survival in patients with CHD.[22] In the present study, the results showed that all HRV parameters were significantly improved after 4-week TMZ-based therapy. In particular, SDNN, and all parameters related to the parasympathetic-nerve activity (including RMSSD, SDSD, pNN50, and norm-HF) after TMZ exposure were significantly improved when compared with the non-exposed group, which was in line with the data from a previously published study.[23] As Zhang *et al*. reported, TMZ treatment led to the increase of SDNN, SDANN, RMSSD, pNN50, and HF, which further improved HRV and reduced the incidence of cardiovascular adverse events in elderly patients with the acute coronary syndrome.[23] The beat-to-beat HRV was regulated by CANS predominantly through cardiac parasympathetic (vagal) innervation of the sinus node. Thus, the more obvious improvement of HRV by TMZ treatment reflected the correction of CANS function. Similarly, another research also reported the beneficial effects of short-term preoperative preconditioning with TMZ on myocardial injury, endothelial function and CANS function during the perioperative period of PCI in patients with coronary artery disease,[24] further supporting this finding. LF/HF ratio is often used to determine sympathovagal balance. In this study, the most obvious change is LF/HF ratio among all HRV indices. Thus, LF/HF should be noticed when other HRV indices are insensitive. With regard to the incidence of major adverse cardiovascular events, there was no statistical significance between the two therapeutic regimens, indicating that TMZ would not increase the risk of adverse cardiovascular events on the basis of conventional therapy. Collectively, TMZ has the potential to be an effective and safety method for CANS improvement.

The small sample size and short follow-up time are the potential criticisms for this respective study, which may lead to bias in these results. Even so, by sample size calculation, 45 patients in each group would provide 90% power. Therefore, the sample size of 50 in each group is sufficient to ensure statistical validity. Additionally, this study had its inherent limitations of the non-randomised and retrospective design. Thus, a long-term, prospective study is in progress.

CONCLUSION

The present pilot study demonstrated that the application of TMZ based on conventional therapy effectively improved the HRV in CHD patients who underwent PCI, suggesting that TMZ has the potential to be used in the improvement of CANS function. However, a wide investigation is still needed to verify our findings

ETHICAL APPROVAL:
This study was conducted in accordance with the Helsinki Declaration, and approved by the Ethics committee of The Second Hospital of Hebei Medical University (Ethical Approval No. 2018-R091).

PATIENTS' CONSENT:
Informed consent was obtained from all individual participants included in the study.

COMPETING INTEREST:
The authors declared no conflicts of interest.

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AUTHORS' CONTRIBUTION:
BX, PY, YJ: Conception or design of the work, analysis or interpretation of data for the work.
XY, PY, FL, JL, XY: Drafting the work or revising it critically for important intellectual content.
XY: Final approval of the version to be published.
All authors agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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