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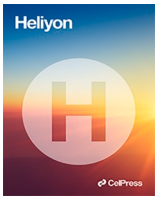

Research article

Effect of the combined use of ivabradine and metoprolol in patients with acute myocardial infarction early after percutaneous coronary intervention: A randomized controlled study

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ABSTRACT

Objective: To investigate the effect and safety of the combined use of ivabradine and metoprolol in patients with acute myocardial infarction (AMI) after percutaneous coronary intervention (PCI).
Methods: Eighty patients with AMI were randomly divided into the ivabradine group and the control group. The ivabradine group was treated with ivabradine combined with metoprolol after PCI, while the control group was treated with metoprolol only. Both groups were treated continuously for 1 year. Echocardiography-derived parameters, heart rate, cardiopulmonary exercise testing (CPET) data, major adverse cardiac events (MACE) and myocardial markers were analyzed. The primary endpoint was the left ventricular ejection fraction (LVEF). The safety outcomes were blood pressure, liver and kidney function.
Results: The LVEF was significantly higher in the ivabradine group than in the control group at 1 week, 3 months and 1 year after PCI. The heart rate of the ivabradine group was significantly lower than that of the control group at 1 week and 1month after PCI. The VO2max, metabolic equivalents, anaerobic threshold heart rate, peak heart rate, and heart rate recovery at 8 min of the ivabradine group were significantly higher than those of the control group at 1 year after PCI. Kaplan-Meier analysis demonstrated the one-year total incidence of MACE in the ivabradine group was significantly lower than that in the control group. The B-type natriuretic peptide of the ivabradine group was significantly lower than that of the control group on Day 2 and Day 3 after PCI. The high-sensitivity cardiac troponin I level of the ivabradine group was significantly lower than that of the control group on Day 5 after PCI.
Conclusion: Early use of ivabradine in patients with AMI after PCI can achieve effective heart rate control, reduce myocardial injury, improve cardiac function and exercise tolerance, and may reduce the incidence of major adverse cardiac events. (Clinical research registration number: ChiCTR2000032731)

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1. Introduction

Acute myocardial infarction (AMI) is a cardiovascular disease that seriously threatens human health and safety and is characterized by rapid disease progression, serious complications and high mortality [1]. Timely and effective revascularization is a critical means of saving the lives of AMI patients, but some patients still have decreased left ventricular systolic function, which leads to heart failure [2]. AMI patients need to optimize drug treatment after percutaneous coronary intervention (PCI) to further improve cardiac function and reduce cardiovascular mortality. Heart rate control is an important measure to improve the long-term prognosis of AMI patients [3]. β-receptor blockers are the most commonly used drugs to control heart rate, which can reduce myocardial infarction area, attenuate myocardial inflammation, and inhibit cardiac remodeling [4]. However, their application is greatly limited by negative conduction and negative inotropic effects. Ivabradine is the first specific inhibitor of If current in the sinoatrial node, which can simply slow heart rate and have no adverse effects on myocardial contractility and cardiac conduction [5]. Previous studies have shown that ivabradine has a good effect in patients with heart failure and stable coronary artery disease [6,7], but few studies have evaluated the effect of ivabradine in AMI patients treated with successful PCI and optimal medical therapy. The aim of this study is to investigate the efficacy of early use of ivabradine in patients with acute myocardial infarction after PCI and to provide new ideas for the treatment of myocardial infarction.

2. Methods

2.1. Population screening

This study is a prospective, single-center, randomized controlled registration study (registration number: ChiCTR2000032731). The study design is shown in Fig. 1. The patients provided their written informed consent to participate in this study. This project adopts the random number method for random grouping. The inclusion criteria were as follows: 1. patients with acute myocardial infarction hospitalized from May 2020 to January 2021; 2. patients with successful emergency PCI, and with TIMI 3 flow after PCI in infarct-related artery; 3. sinus rhythm and heart rate ≥75 beats/min; and 4. age between 18 and 85 years old. The exclusion criteria were as follows: 1. a history of bronchial asthma; 2. a history of bradyarrhythmia; 3. systolic blood pressure≤90 mmHg; and 4. vasoactive drugs were still used for shock 6 h after PCI. The flow chart of population screening is provided in Fig. 2.

2.2. Interventions

All patients received a loading dose of 300 mg aspirin and 180 mg ticagrelor (or 300 mg clopidogrel) before PCI. During the operation, a IIb/IIIa receptor antagonist, low molecular weight heparin, temporary pacemaker implantation, and intra-aortic balloon pump were applied according to the condition. All patients were routinely treated with antiplatelet agents, statins, angiotensin-converting enzyme inhibitors (ACEIs), angiotensin receptor blockers (ARBs) or angiotensin receptor neprilysin inhibitors (ARNIs) after the operation. At 12 h after PCI, the ivabradine group was treated with ivabradine (5 mg twice a day) combined with metoprolol tartrate (12.5 mg twice a day), while the control group was treated with metoprolol tartrate (12.5 mg twice a day) only. On Day 3 after PCI, metoprolol tartrate was replaced with long-acting metoprolol succinate (metoprolol sustained-release tablets), and the dose of β-blockers was titrated according to the 2017 Guidelines for the Diagnosis and Treatment of Acute Myocardial Infarction [8]. At the same time, the drug dose of the two groups was adjusted individually according to the individual's heart rate, and the target heart rate was set at <70 beats/min. If bradycardia (heart rate <50 beats/min) occurred during the treatment, drug administration was stopped, and the trial was terminated.

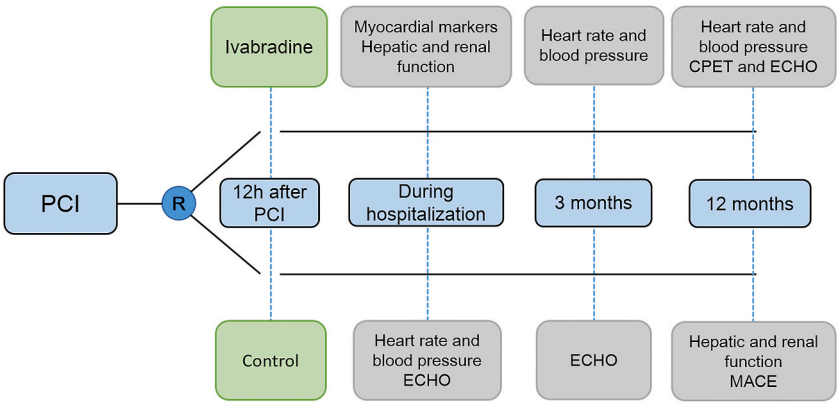

Fig. 1. Flow chart of the study.

2.3. Observation indicators

Echocardiography was performed blinded to treatment allocation. The left ventricular ejection fraction (LVEF), left ventricular end-systolic internal diameter (LVIDs), left ventricular end-diastolic internal diameter (LVIDd), left atrial diameter (LAD), interventricular septal thickness (IVST) and E/e' ratio were recorded at baseline and after treatment (1 week, 3 months, and 1 year after PCI). The modified Simpson method was used to measure LVEF. The heart rate and blood pressure of the two groups were recorded at baseline and after treatment (1 week, 1month,3 months, and 1 year after PCI). The two groups of patients underwent CPET one year after PCI. The maximal oxygen uptake (VO2max), metabolic equivalents (METs), resting heart rate, anaerobic threshold (AT) heart rate, peak heart rate, 8-min heart rate, heart rate recovery at 8 min (HRR8), resting blood pressure, AT blood pressure, and peak blood pressure were recorded. Major adverse cardiac events (MACE), including cardiac death, heart failure readmission, and recurrent myocardial infarction, were recorded at the one-year follow-up. The levels of B-type natriuretic peptide (BNP), high-sensitivity cardiac troponin I (hs-cTnI) and creatine kinase-MB (CK-MB) in the two groups were determined before PCI, 2 h after PCI, and daily for 6 days after PCI. The levels of alanine aminotransferase (ALT), aspartate aminotransferase (AST), creatinine, urea nitrogen and uric acid in the two groups were determined at baseline and 1 year after PCI.

2.4. Sample size estimate

The sample size was determined based on a randomized controlled study [9], which used LVEF as the primary outcome variable. The mean LVEF in the control group was 45.3 %, and the mean LVEF in the treatment group was 50.2 %.The mean difference between the two groups was 4.9 %, with a standard deviation of 7.5 %. According to the sample size estimation formula $n = 2 \times [(Z_{\alpha}+Z_{\beta}) \times \sigma/\delta]^2$, $\alpha = 0.05$ and $\beta = 0.1$ were adopted, we calculated $n = 2 \times [(1.96 + 1.28) \times 7.5/4.9]^{2} = 49.19$, so the overall sample size was at least 50.

2.5. Statistical analysis

SPSS 25.0 statistical software was used for data processing. Measurement data with a normal distribution are expressed as the mean ± standard deviation (±s), and Student's *t*-test was used for comparisons between groups. Measurement data with a nonnormal distribution are expressed as the median (interquartile range, IQR), and the Wilcoxon rank sum test was used for comparisons between groups. Count data are expressed as frequencies (percentages, %), and the chi-square test or Fisher's exact probability method was used for comparisons between groups. Time-to-event data was analyzed by the Kaplan-Meier method with log-rank test. $P < 0.05$ indicated that the difference was statistically significant.

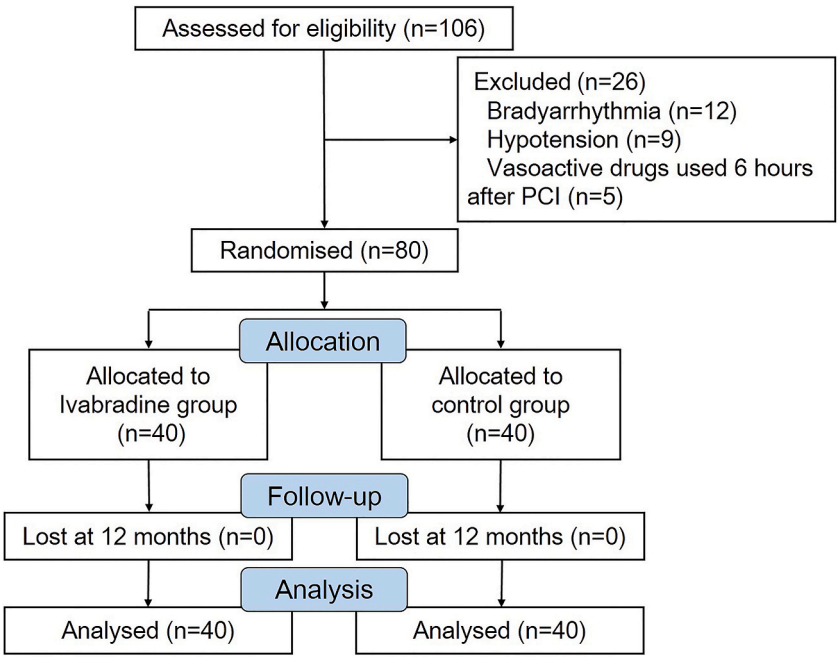

Fig. 2. Flow chart of population screening.

3. Results

3.1. Comparison of baseline data between the two groups

There were no significant differences in the general clinical conditions and coronary artery lesions at baseline between the two groups ($P > 0.05$) (Table 1). All patients received a drug eluting stent (DES), and they received dual antiplatelet therapy (DAPT) for 12 months.

3.2. Comparison of echocardiography-derived parameters between the two groups

There was no significant difference in LVEF between the two groups before treatment ($P > 0.05$). The LVEF of the ivabradine group was significantly higher than that of the control group at 1 week, 3 months and 1 year after PCI ($P < 0.05$). There was no significant difference in LAD between the two groups before treatment ($P > 0.05$). The LAD of the ivabradine group was significantly lower than that of the control group at 1 week after PCI ($P < 0.05$), but there was no significant difference in LAD between the two groups at 3 months and 1 year after PCI ($P > 0.05$). There were no significant differences in LVIDs, LVIDs, IVST and E/e' ratio between the two groups before and after treatment ($P > 0.05$) (Table 2).

3.3. Comparison of heart rate and blood pressure between the two groups

There was no significant difference in heart rate between the two groups before treatment ($P > 0.05$). The heart rate of the ivabradine group was significantly lower than that of the control group at 1 week and 1month after PCI ($P < 0.05$). There was no significant difference in heart rate between the two groups at 3 months and 1 year after PCI ($P > 0.05$). There was no significant

Table 1
Comparison of baseline data between the two groups.

Items	Ivabradine group (40 cases)	Control group (40 cases)	*P* value
Age (Mean ± SD, year)	68.53 ± 10.21	67.4 ± 11.44	0.651
Male [n (%)]	30(75.00)	33(82.50)	0.412
Hypertension [n (%)]	20(50.00)	24(60.00)	0.369
Diabetes mellitus [n (%)]	14(35.00)	10(25.00)	0.329
Hyperlipidemia [n (%)]	15(37.50)	11(27.50)	0.340
STEMI [n (%)]	23(57.50)	28(70.00)	0.245
FMC in STEMI [median (IQR), min)]	240.00(387.50)	240.00(465.00)	0.977
Killip classification [n (%)]			0.661
1	33(82.50)	29(72.50)	
2	4(10.00)	8(20.00)	
3	2(5.00)	2(5.00)	
4	1(2.50)	1(2.50)	
Number of diseased vessels [n (%)]			0.549
1	14(35.00)	10(25.00)	
2	13(32.50)	17(42.50)	
3	13(32.50)	13(32.50)	
IRA			0.314
LAD [n (%)]	24(60.00)	27(67.50)	
LCX [n (%)]	6(15.00)	2(5.00)	
RCA [n (%)]	10(25.00)	11(27.50)	
TIMI 3 flow after PCI [n (%)]	40(100.00)	40(100.00)	1.000
Non-IRA stenosis >70 % [n (%)]	19(47.50)	20(50.00)	0.823
Non-IRA revascularization [n (%)]	15(37.50)	15(37.50)	1.000
ALT [median (IQR), U/L)]	40.00(31.25)	40.00(59.00)	0.722
AST [median (IQR), U/L)]	142.00(181.25)	163.00(296.00)	0.324
Creatinine [median (IQR), μmol/L)]	70.50(24.75)	69.50(23.75)	0.855
Urea nitrogen [median (IQR), mmol/L)]	5.65(3.10)	6.25(3.08)	0.600
Uric acid [median (IQR), μmol/L)]	336.00(129.00)	390.00(154.75)	0.082
Total cholesterol (Mean ± SD, mmol/L)	5.28 ± 1.29	5.21 ± 1.29	0.784
Triglyceride [median (IQR), mmol/L)]	1.35(1.04)	1.26(1.04)	0.324
LDL cholesterol (Mean ± SD, mmol/L)	3.63 ± 0.98	3.63 ± 1.04	0.989
HDL cholesterol (Mean ± SD, mmol/L)	1.16 ± 0.20	1.11 ± 0.26	0.365
GP2b3a inhibitor [n (%)]	33(82.50)	27(67.50)	0.121
ACEI/ARB/ARNI [n (%)]	32(80.00)	31(77.50)	0.785
Beta blocker [n (%)]	40(100.00)	40(100.00)	1.000
Aldosterone receptor antagonist [n (%)]	8(20.00)	6(15.00)	0.556

STEMI ST-segment elevation myocardial infarction, *FMC* first medical contact, *PCI* percutaneous coronary intervention, *IRA* Infarct-related artery, *LAD* left anterior descending artery, *LCX* left circumflex artery, *RCA* right coronary artery, *ALT* alanine aminotransferase, *AST* aspartate aminotransferase, *LDL* low density lipoprotein, *HDL* high density lipoprotein, *ACEI* angiotensin-converting enzyme inhibitor, *ARB* angiotensin receptor blocker, *ARNI* angiotensin receptor neprilysin inhibitor.

Table 2
Comparison of echocardiography-derived parameters between the two groups.

Items				Changes from baseline		
	Ivabradine group	Control group	*P* value	Ivabradine group	Control group	*P* value
LVEF (%)						
Baseline level	52.05 ± 7.42	50.08 ± 9.05	0.623			
7 days later	57.00 ± 7.87	50.70 ± 10.79	0.042	5.20 ± 5.96	0.35 ± 5.36	0.010
3 months later	56.57 ± 9.99	50.97 ± 10.30	0.023	4.29 ± 8.86	0.70 ± 8.26	0.107
12 months later	59.32 ± 8.11	51.94 ± 11.75	0.006	6.87 ± 8.14	1.35 ± 10.35	0.022
LVIDs (mm)						
Baseline level	33.88 ± 5.60	34.15 ± 5.86	0.493			
7 days later	32.20 ± 5.49	34.85 ± 5.91	0.101	−2.90 ± 8.04	0.45 ± 4.63	0.158
3 months later	32.93 ± 6.39	35.42 ± 6.56	0.070	−0.82 ± 3.85	1.15 ± 5.06	0.062
12 months later	33.74 ± 6.63	36.38 ± 7.81	0.149	−0.23 ± 6.17	2.29 ± 6.36	0.101
LVIDd (mm)						
Baseline level	47.35 ± 5.10	48.43 ± 5.67	0.375			
7 days later	48.20 ± 5.60	50.60 ± 5.37	0.175	0.95 ± 7.38	2.00 ± 4.94	0.600
3 months later	48.82 ± 7.18	49.76 ± 5.04	0.357	1.21 ± 5.50	1.06 ± 5.53	0.914
12 months later	49.39 ± 5.91	50.76 ± 6.42	0.373	1.94 ± 5.79	2.59 ± 5.17	0.633
LAD (mm)						
Baseline level	37.90 ± 3.78	38.00 ± 3.40	0.739			
7 days later	37.30 ± 3.13	39.50 ± 2.78	0.024	0.15 ± 3.35	1.30 ± 2.74	0.241
3 months later	36.96 ± 4.69	38.06 ± 5.04	0.385	−1.39 ± 4.49	−0.21 ± 4.42	0.306
12 months later	37.55 ± 3.02	37.97 ± 3.93	0.721	−0.23 ± 3.65	0.15 ± 4.21	0.705
IVST (mm)						
Baseline level	10.72 ± 1.19	10.77 ± 1.21	0.911			
7 days later	10.40 ± 1.39	10.95 ± 1.28	0.098	−0.05 ± 1.27	0.35 ± 1.14	0.077
3 months later	9.82 ± 1.36	10.42 ± 1.42	0.080	−0.67 ± 1.66	−0.30 ± 1.47	0.313
12 months later	10.00 ± 1.34	10.18 ± 2.11	0.721	−0.83 ± 1.98	−0.59 ± 1.86	0.594
E/e'						
Baseline level	11.80 ± 4.26	11.17 ± 3.00	0.832			
7 days later	10.86 ± 3.03	12.42 ± 3.18	0.124	0.06 ± 4.78	0.50 ± 3.41	0.769
3 months later	11.01 ± 5.13	10.26 ± 3.39	0.592	−0.87 ± 7.37	−1.09 ± 3.63	0.985
12 months later	10.32 ± 2.32	10.06 ± 2.72	0.441	−1.66 ± 5.21	−1.22 ± 3.02	0.774

LVEF left ventricular ejection fraction, *LVIDs* left ventricular end-systolic internal diameter, *LVIDd* left ventricular end-diastolic internal diameter, *LAD* left atrial diameter, *IVST* interventricular septal thickness.

difference in blood pressure between the two groups before and after treatment ($P > 0.05$) (Table 3).

3.4. Comparison of CPET data between the two groups

The VO2max, METs, AT heart rate, peak heart rate and HRR8 in the ivabradine group were significantly higher than those in the control group at 1 year after PCI ($P < 0.05$). There were no significant differences in resting heart rate, 8-min heart rate, resting blood pressure, AT blood pressure or peak blood pressure between the two groups ($P > 0.05$) (Table 4).

Table 3
Comparison of heart rate and blood pressure between the two groups.

Items				Changes from baseline		
	Ivabradine group	Control group	*P* value	Ivabradine group	Control group	*P* value
Heart rate (bpm)						
Baseline level	90.00 ± 8.80	87.95 ± 9.66	0.212			
7 days later	73.20 ± 4.54	76.95 ± 5.87	0.010	−16.80 ± 8.23	−10.93 ± 5.78	0.001
1 month later	67.10 ± 2.75	68.93 ± 2.33	0.002	−22.90 ± 7.01	−17.83 ± 8.49	0.003
3 months later	65.38 ± 4.06	66.83 ± 4.40	0.142	−24.63 ± 6.61	−21.23 ± 8.99	0.025
12 months later	65.50 ± 3.34	65.83 ± 3.18	0.657	−24.50 ± 7.12	−20.93 ± 8.98	0.022
SBP (mmHg)						
Baseline level	135.23 ± 22.05	128.43 ± 19.55	0.148			
7 days later	130.23 ± 12.98	124.83 ± 13.18	0.069	−5.00 ± 9.70	−3.60 ± 7.03	0.404
3 months later	130.20 ± 8.32	126.45 ± 9.54	0.065	−5.03 ± 15.22	−1.63 ± 4.44	0.110
12 months later	130.50 ± 11.63	127.35 ± 17.43	0.450	−6.21 ± 20.63	−1.10 ± 15.83	0.200
DBP (mmHg)						
Baseline level	77.65 ± 12.56	75.20 ± 9.00	0.319			
7 days later	76.00 ± 7.85	73.03 ± 6.56	0.070	−1.65 ± 5.56	−2.18 ± 2.93	0.599
3 months later	75.55 ± 5.55	74.23 ± 4.90	0.261	−2.10 ± 7.83	−0.98 ± 4.92	0.444
12 months later	75.71 ± 8.71	74.77 ± 10.22	0.722	−1.67 ± 15.78	−0.58 ± 12.96	0.780

SBP systolic blood pressure, *DBP* diastolic blood pressure.

Table 4
Comparison of the CPET data between the two groups at one-year follow-up.

Items	Ivabradine group	Control group	*P* value
VO_2max [ml/(min·kg)]	22.41 ± 4.74	20.19 ± 4.54	0.048
METs	6.41 ± 1.36	5.76 ± 1.30	0.022
Resting heart rate (bpm)	77.78 ± 10.06	74.08 ± 8.95	0.086
AT heart rate (bpm)	107.90 ± 14.51	101.70 ± 11.22	0.036
Peak heart rate (bpm)	135.03 ± 18.30	124.88 ± 16.33	0.011
8-min heart rate (bpm)	79.40 ± 9.53	83.10 ± 7.79	0.061
HRR8 (bpm)	55.63 ± 15.99	41.78 ± 15.19	0.000
Resting systolic pressure (mmHg)	119.15 ± 16.74	123.13 ± 16.31	0.285
Resting diastolic pressure (mmHg)	79.53 ± 13.58	77.93 ± 9.52	0.544
AT systolic pressure (mmHg)	139.55 ± 22.60	139.20 ± 20.59	0.942
AT diastolic pressure (mmHg)	77.28 ± 13.82	76.13 ± 10.41	0.675
Peak systolic pressure (mmHg)	158.10 ± 23.43	157.25 ± 22.73	0.870
Peak diastolic pressure (mmHg)	81.23 ± 15.25	75.73 ± 11.26	0.070

CPET cardiopulmonary exercise testing, *VO_2max* maximum oxygen uptake, *METs* metabolic equivalents.
AT anaerobic threshold.

3.5. Comparison of the incidence of MACE between the two groups

All patients were followed up for 1 year. The total incidence of cardiac death, heart failure readmission, and recurrent myocardial infarction was 2.5 % in the ivabradine group, which was lower than the 20.0 % in the control group ($P < 0.05$) (Table 5). Kaplan-Meier analysis demonstrated the one-year total incidence of MACE in the ivabradine group was significantly lower than that in the control group (Fig. 3).

3.6. Comparison of myocardial markers between the two groups

The BNP of the ivabradine group was significantly lower than that of the control group on Day 2 and Day 3 after PCI ($P < 0.05$) (Fig. 4a). The hs-cTnI of the ivabradine group was significantly lower than that of the control group on Day 5 after PCI ($P < 0.05$) (Fig. 4b). There was no significant difference in CK-MB between the two groups ($P > 0.05$) (Fig. 4c).

3.7. Comparison of medication between the two groups

There were no significant differences in ACEI/ARB/ARNI, β-blocker, aldosterone receptor antagonist, loop diuretic, and dual antiplatelet medications between the two groups at baseline and at the one-year follow-up ($P > 0.05$) (Table 6).

3.8. Comparison of liver and kidney function between the two groups

There were no significant differences in liver and kidney function between the two groups at the one-year follow-up ($P > 0.05$) (Table 7).

4. Discussion

Acute myocardial infarction is mostly caused by acute vascular occlusion due to coronary atherosclerotic plaque rupture and secondary thrombosis, inducing myocardial ischemia, hypoxia and necrosis, which can lead to serious complications, including malignant arrhythmia, heart failure, cardiogenic shock and sudden cardiac death [10]. At present, emergency PCI can quickly open the occluded vessels and restore myocardial blood flow perfusion, but the mortality of myocardial infarction in China has not been decreased to an ideal level [11]. An accelerated heart rate is significantly associated with AMI mortality. The possible mechanisms are as follows [12–14]: increased heart rate can shorten the ventricular diastole and lead to coronary artery hypoperfusion, affecting myocardial blood supply; increased heart rate leads to excessive myocardial oxygen consumption and imbalance of oxygen supply and consumption, which further aggravates myocardial ischemia. At the same time, increased heart rate is often accompanied by excessive

Table 5
Comparison of the incidence of MACE between the two groups.

Items	Ivabradine group	Control group	*P* value
Cardiogenic death [n (%)]	0(0.00)	0(0.00)	1.000
Heart failure readmission [n (%)]	0(0.00)	7(17.50)	0.018
Reinfarction [n (%)]	1(2.50)	1(2.50)	1.000
MACE [n (%)]	1(2.50)	8(20.00)	0.034

MACE major adverse cardiac events.

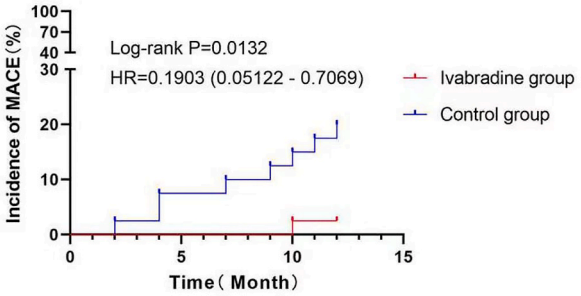

Fig. 3. Kaplan-Meier analysis of MACE at one year between the two groups.

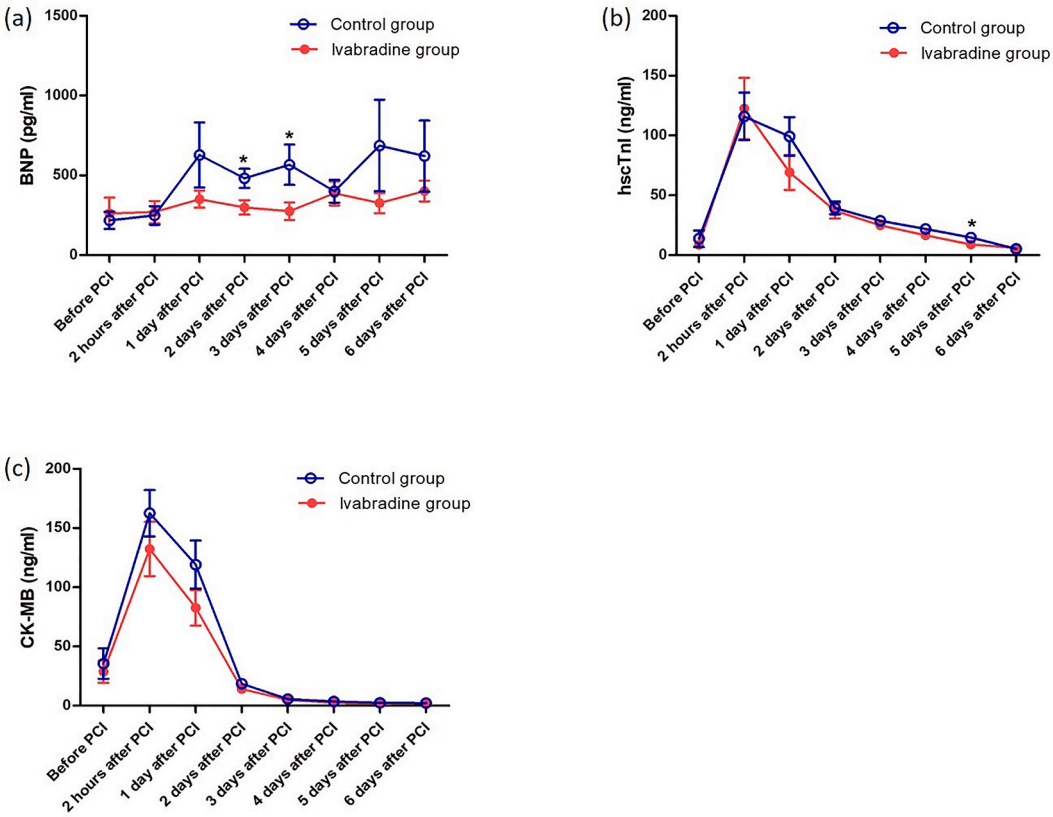

Fig. 4. Comparison of myocardial markers between the two groups. (a) Comparison of BNP between the two groups. (b) Comparison of hs-cTnI between the two groups. (c) Comparison of CK-MB between the two groups.

activation of sympathetic nerves and elevated catecholamine levels, which can directly induce vascular endothelial injury and myocardial remodeling. Therefore, heart rate should be strictly controlled after PCI to improve the prognosis of patients with myocardial infarction.

Metoprolol is the most commonly used β-blocker in clinical practice and can slow heart rate, reduce myocardial oxygen consumption, decrease catecholamine levels, and inhibit myocardial remodeling. However, long-term and massive use may produce side effects such as negative inotropy, negative conduction, asthma and hypotension [15]. Ivabradine is a highly selective If current inhibitor that can inhibit the sinus node rhythm and thus slow the heart rate. Moreover, the drug can reduce the heart rate without affecting the atrioventricular conduction time and myocardial contractility [16].

In this study, cardiac function was evaluated by echocardiography. It was found that LVEF was significantly higher in the ivabradine group than in the control group at different time points. Gerbaud et al. [17] used cardiac magnetic resonance to evaluate cardiac remodeling, and they found that ivabradine added to basic drug therapy could significantly improve LVEF at 3 months after PCI. Barilla et al. [18] found that ivabradine could improve LVEF in patients with cardiogenic shock complicating STEMI. Xu et al. [19] found that LVEF, left ventricular end systolic volume (LVESV) and left ventricular end diastolic volume (LVEDV) in the ivabradine

Table 6
Comparison of medication between the two groups.

Items	Ivabradine group	Control group	*P* value
Medication at baseline			
ACEI/ARB/ARNI [n (%)]	32(80.00)	31(77.50)	0.785
Maximum tolerable/standard dose [n (%)]	26(65.00)	28(70.00)	0.633
Beta blocker [n (%)]	40(100.00)	40(100.00)	1.000
Maximum tolerable/standard dose [n (%)]	25(62.50)	20(50.00)	0.260
Dose [median (IQR), mg]	23.75(0.00)	23.75(23.75)	0.876
Aldosterone receptor antagonist [n (%)]	8(20.00)	6(15.00)	0.556
Loop diuretic [n (%)]	8(20.00)	5(12.50)	0.363
Dual antiplatelet therapy [n (%)]	40(100.00)	40(100.00)	1.000
Medication at 12 months			
ACEI/ARB/ARNI [n (%)]	34(85.00)	33(82.50)	0.617
Maximum tolerable/standard dose [n (%)]	28(70.00)	29(72.50)	0.805
Beta blocker [n (%)]	40(100.00)	40(100.00)	1.000
Maximum tolerable/standard dose [n (%)]	29(72.50)	34(85.00)	0.172
Dose [median (IQR), mg]	47.5(23.75)	47.5(23.75)	0.495
Aldosterone receptor antagonist [n (%)]	3(7.50)	2(5.00)	1.000
Loop diuretic [n (%)]	1(2.50)	4(10.00)	0.356
Dual antiplatelet therapy [n (%)]	40(100.00)	39(97.50)	1.000

ACEI angiotensin-converting enzyme inhibitor, *ARB* angiotensin receptor blocker, *ARNI* angiotensin receptor neprilysin inhibitor.

Table 7
Comparison of hepatic and renal function between the two groups at one-year follow-up.

Items	Ivabradine group	Control group	*P* value
ALT [median (IQR), U/L)]	18.00(8.00)	20.50(24.00)	0.380
AST [median (IQR), U/L)]	20.00(6.00)	20.50(11.50)	0.890
Creatinine [median (IQR), μmol/L)]	80.50(52.50)	81.00(27.50)	0.607
Urea nitrogen [median (IQR), mmol/L)]	6.20(3.15)	7.10(4.20)	0.161
Uric acid [median (IQR), mmol/L)]	377.00(142.25)	357.00(187.00)	0.477

ALT alanine aminotransferase, *AST* aspartate aminotransferase.

group were significantly higher than in the control group at 3 months after PCI, but there were no significant differences at 6 months after PCI. They therefore concluded that the effect of ivabradine on cardiac remodeling was not sustained. However, our study indicated that the LVEF difference between the two groups was sustainable at different follow-up times. In addition, the changes of LVIDs in the ivabradine group was lower than that in the control group, but the difference was not statistically significant. Similar results were found in a meta-analysis included six RCTs [20], it showed that ivabradine was associated with greater improvement of LVEF and LVESV, but not LVEDV, which demonstrated that ivabradine could improve left ventricular systolic function and cardiac remodeling.

It was found that the heart rate of the ivabradine group was significantly lower than that of the control group at 1 week and 1 month after PCI, suggesting that early use of ivabradine can control the heart rate faster and better. However, the heart rate of the two groups further decreased and tended to be consistent at 3 months and 1 year after PCI. Throughout the trial, both groups were gradually titrated to the maximum tolerable dose of the drug to reach the target heart rate, which might result in little difference in heart rate between the two groups at longer follow-up times. Therefore, the changes in heart rate were further analyzed. Compared with the control group, the changes in heart rate were significantly higher at 1 week, 1 month, 3 months and 1 year after PCI in the ivabradine group. Rezq et al. [21] found that the use of ivabradine in addition to bisoprolol was associated with better control of resting heart rate, and was further associated with a lower risk of hospitalization for unstable angina or heart failure. The early control of heart rate in the ivabradine group may be the fundamental reason for reducing cardiac load and improving myocardial remodeling, which is in line with the findings of several large multicenter clinical trials. The BEAUTIFUL study [22] demonstrated that reducing resting heart rate can decrease overall mortality, particularly among patients with myocardial infarction and heart failure with reduced ejection fraction (HFrEF). In a subgroup analysis where the heart rate was >70 beats per minute, ivabradine reduced the hospitalization for fatal and nonfatal myocardial infarction and need for coronary revascularization. The SHIFT study [23] subgroup analysis showed that ivabradine not only lowered heart rate but also reversed left ventricular remodeling in patients with HFrEF, thereby improving cardiac function and long-term prognosis.

CPET is an important noninvasive method to evaluate cardiopulmonary function and aerobic exercise capacity. Peak oxygen uptake is a strong predictor of exercise capacity in patients with cardiac insufficiency and is closely related to the prognosis of patients [24]. Studies have shown that every 1 ml/(min•kg) increase in peak oxygen uptake can reduce all-cause mortality by approximately 10 % [25]. This study found that VO2max, METs, AT heart rate, and peak heart rate were significantly higher in the ivabradine group than in the control group at 1 year after PCI, suggesting that ivabradine can significantly improve the cardiopulmonary function and exercise tolerance of patients. Heart rate recovery (HRR) after an exercise test is affected by the cardiac sympathetic nerve and vagus nerve, which can reflect the regulatory ability of the cardiac autonomic nerve. Delayed or abnormal heart rate recovery is an

independent risk factor for predicting cardiovascular disease mortality and can predict the prognosis of patients with ischemic heart disease [26,27]. The HRR value of the ivabradine group was significantly higher than that of the control group, which may be related to the significant inhibition of sinoatrial node autonomic rhythm by ivabradine. In this study, patients in both groups were followed up for 1 year, and no cardiac death occurred. The proportion of heart failure readmission in the ivabradine group was lower than that in the control group, which was consistent with the results of the SHIFT study [28]. Meanwhile, the total incidence of MACE at 1 year after PCI in the ivabradine group was significantly lower than that in the control group, which was because ivabradine combined with β-blockers can more significantly reduce the heart rate, increase the coronary flow reserve, and improve vascular endothelial function, thereby reducing the incidence of myocardial ischemia and heart failure and improving the long-term prognosis of patients.

BNP is a reliable indicator for predicting the prognosis of myocardial infarction and is positively correlated with the onset of heart failure in AMI patients [29,30]. This study found that the BNP of the ivabradine group after PCI was lower than that of the control group, and the difference was statistically significant on Days 2 and 3 after PCI, suggesting that ivabradine can reduce the occurrence of early heart failure after myocardial infarction, probably because it can slow the heart rate earlier and improve cardiac function. This study found that the hs-cTnI of the ivabradine group was lower than that of the control group from Day 1 to Day 5 after PCI, and there was a statistically significant difference between the two groups on Day 5 after PCI, suggesting that ivabradine can significantly reduce the degree of myocardial injury in patients, which may be related to its ability to reduce heart rate, myocardial oxygen consumption and myocardial infarction area. High levels of troponin after myocardial infarction often indicate poor prognosis. Strict heart rate control can alleviate myocardial ischemia, reduce troponin release, and improve the long-term prognosis of patients. After adjusting for confounding factors such as diabetes, hypertension, the number of diseased coronary arteries and previous myocardial infarction, Haroon et al. [31] found that heart rate in AMI patients was independently and positively correlated with the increase of troponin and the decrease of ejection fraction. Studies have shown that ivabradine can improve myocardial blood supply by increasing coronary artery reserve and thus reduce myocardial infarction area, and this effect is independent of its effect on heart rate reduction [32]. In addition, ivabradine can inhibit oxidative stress, reduce cardiomyocyte inflammation and protect cardiomyocyte viability [33]. It can thicken the ventricular wall of the infarcted area, inhibit infarct expansion, and protect the contractile function and synchrony of the distal viable myocardium [34].

5. Limitations

This study is a prospective, single-center randomized controlled study with a small sample size, which may lead to bias in the results. The lack of placebo and blinding may also have affected the objectivity of the results. This study did not distinguish the type of myocardial infarction, such as STEMI or NSTEMI, anterior or inferior MI. The mean LVEF at baseline was more than 50 %, and the majority of the Killip classification was in class 1 and 2. Some issues have yet to be clarified, such as whether the effect of ivabradine is identical in patients with different types of MI or different cardiac function classification. It still needs to be further verified by multicenter and large-sample studies.

6. Conclusion

Early use of ivabradine in patients with acute myocardial infarction after PCI can better control heart rate, reduce myocardial injury, improve cardiac function and exercise tolerance of patients, and may reduce the incidence of major adverse cardiac events, and is worthy of further promotion in clinical practice.

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Ethic statement

This study was approved by Ethics Committee of Shanghai Putuo District Central Hospital (Putuo Hospital Affiliated to Shanghai University of Traditional Chinese Medicine) (Approval number: PTEC-A-2019-36-1). The study was conducted according to established ethical guidelines and informed consent obtained from the participants.

Data availability statement

Data will be available upon reasonable request.

CRediT authorship contribution statement

Ruiqing He: Writing – original draft, Methodology. **Lingyan Li:** Writing – original draft, Methodology. **Chao Han:** Investigation.

Wen An: Investigation. **Zongjun Liu:** Data curation. **Junqing Gao:** Conceptualization.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

Junqing Gao reports financial support was provided by The Shanghai Medical Innovation Research Project of Scientific and Technological Innovation Action Plan. Zongjun Liu reports financial support was provided by The Shanghai Medical Innovation Research Project of Scientific and Technological Innovation Action Plan. Zongjun Liu reports financial support was provided by Clinical Advantage Discipline of Health System of Putuo District in Shanghai. Junqing Gao reports financial support was provided by Scientific Research Hundred Personnel Plan of Shanghai Putuo District Central Hospital. Ruiqing He reports financial support was provided by Shanghai Municipal Health and Health Commission Health Industry Clinical Research Project. Lingyan Li reports financial support was provided by Budget Project of Shanghai University of Traditional Chinese Medicine. Lingyan Li reports financial support was provided by Shanghai Putuo District Health System Science and Technology Innovation Project. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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