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ORIGINAL RESEARCH ARTICLE

Potential use of prophylactic intracoronary atropine in reducing reperfusion vagal reflex-related events in ST-elevation myocardial infarction

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Abstract

In this study, we evaluated the potential use of atropine in reducing reperfusion vagal reflex-related events during emergency percutaneous coronary intervention (PCI) for acute inferior ST-elevation myocardial infarction (STEMI). Retrospectively, we included 142 patients with inferior wall STEMI, who were treated between October 2015 and October 2020, in this study. The patients were divided into an experimental group (n = 70) and a control group (n = 72) depending on whether they received prophylactic intracoronary atropine. The experimental group was then subdivided into a low-dose group (0.5 – 1 mg atropine, n = 40) and a high-dose group (2 mg atropine, n = 30). We compared the incidence of reperfusion vagal reflex-related events and the application of temporary pacemakers between these groups. The results showed that the incidence of bradycardia (24.3% vs. 45.8%, P = 0.007), hypotension (18.6% vs. 40.3%, P = 0.005), ventricular tachycardia (4.3% vs. 19.4%, P = 0.005), and ventricular fibrillation (8.6% vs. 20.8%, P = 0.040) as well as the application of temporary pacemakers (14.3% vs. 29.2%, P = 0.032) were all much lower (all P < 0.05) in the experimental group than in the control group. In addition, the incidence of bradycardia (10% vs. 35%, P = 0.016), hypotension (6.7% vs. 27.5%, P = 0.027), ventricular tachycardia (6.7% vs. 25%, P = 0.044), and ventricular fibrillation (0 vs. 15%, P = 0.034) as well as the application of temporary pacemakers (3.3% vs. 22.5%, P = 0.036) were all much lower (all P < 0.05) in the high-dose group than the low-dose group. Our findings demonstrate that atropine pretreatment could prevent reperfusion vagal reflex-related events and reduce the application of temporary pacemakers during emergency PCI for acute inferior STEMI. These effects can be significantly enhanced by high-dose (2 mg) atropine pretreatment.

Keywords: ST-elevation myocardial infarction; Acute inferior myocardial infarction; Emergency percutaneous coronary intervention; Atropine; Vagal reflex; Reperfusion reaction

1. Introduction

Reperfusion vagal reflex-related events, such as bradycardia and hypotension, often occur in acute myocardial infarction, especially in the early stage of inferior or posterior

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wall infarction[1]. Experimental evidence has suggested that this cardiac reflex may result from the activation of inhibitory cardiac receptors with vagal afferents located predominantly in the inferior or posterior wall of the left ventricle[2]. Atropine has been recommended as the treatment of choice for hypotension and/or premature ventricular depolarizations in patients with acute myocardial infarction and bradycardia because atropine can counteract vagal tension[3].

Inferior ST-elevation myocardial infarction (STEMI) is predominantly caused by acute thrombotic occlusion of the right coronary artery or the left circumflex artery. During emergency percutaneous coronary intervention (PCI) for inferior STEMI, severe reperfusion reactions such as bradycardia, hypotension, ventricular tachycardia, nausea, and vomiting often occur[4]. The traditional approach is to provide hypervolemic treatment and drug therapy, such as dopamine, norepinephrine, or atropine, when reperfusion reactions occur, as well as early or immediate temporary pacemaker treatment, which conversely increases the risk of operative complications[5].

Studies have suggested that the use of atropine during PCI for acute inferior myocardial infarction can reduce the risk of reperfusion arrhythmia and hypotension, alleviate myocardial cell injury, improve cardiac function, shorten the treatment time, and reduce the risk of mortality[3,6]. However, evidence concerning the prevalence of reperfusion vagal reflex-related events after atropine preconditioning and the recommended dosage remains elusive. Therefore, the aim of this study was to evaluate the potential of atropine at different doses in reducing reperfusion vagal reflex-related events during emergency PCI for acute STEMI.

2. Methods

2.1. Study design

In this retrospective case–control study, anonymized clinical data from October 2015 to October 2020 were collected from Xianyang Central Hospital. This study was conducted according to the principles of the Declaration of Helsinki and approved by the Ethical Committee of Xianyang Central Hospital (Approval No. 20200059). Informed consent was obtained from the patients and their families.

2.2. Study participants

The medical records of consecutive patients receiving emergency PCI for acute inferior STEMI were retrospectively reviewed. The inclusion criteria were patients with acute inferior STEMI who received emergency PCI. STEMI was defined as ST-segment elevation at the J point in at least two adjacent leads of ≥0.25 mV in men below the age of 40 years and/or ≥0.2 mV in men over the age of 40 years, or ≥0.15 mV in women in leads V2 – V3 and/or ≥0.1 mV in other leads (in the absence of left ventricular hypertrophy [LVH] or left bundle branch block [LBBB]). The patients were randomly selected and divided into an experimental group and a control group depending on whether they received atropine preconditioning. The experimental group was further divided into two subgroups: a low-dose group (0.5 – 1 mg atropine) and a high-dose group (2 mg atropine). The exclusion criteria included (1) lack of clinical data; (2) prior implantation of permanent or temporary pacemakers before STEMI; (3) a history of bradycardia, hypotension, ventricular tachycardia, or ventricular fibrillation with a definitive cause (unrelated to the disease under study); (4) prior PCI or coronary artery bypass graft (CABG) for myocardial infarction; and (5) unwillingness to participate in the study.

Atropine preconditioning was defined as the administration of 0.5–2 mg atropine through the coronary artery immediately before the passage of the guidewire. In the low-dose group, 0.5–1 mg atropine was injected into the coronary artery when the guidewire was passed through; in the high-dose group, 2 mg atropine was injected prior to reperfusion. The choice of treatment with atropine and the choice of dose were left to the physician based on the patient's signs and symptoms before administration. The management of the patients was in accordance with the European Society of Cardiology Guidelines for the management of STEMI[6].

2.3. Data collection

The medical records of all the study participants were collected from the electronic medical record system of the hospital and recorded according to a standardized protocol. The patients' age, sex, previous medical history, site of infarction, time of chest pain, door-to-balloon time, and atropine dosage were analyzed.

2.4. Outcomes measures

The primary end point of this study was the difference in prevalence of reperfusion vagal reflex-related events (bradycardia, hypotension, ventricular tachycardia, and ventricular fibrillation) and that of temporary pacemaker application between the experimental group and the control group. The secondary end point of this study was to determine a recommended dosage for patients preconditioned with atropine.

In this study, hypotension was defined as a systolic blood pressure (BP) of <90 mmHg or a 30% decrease from the baseline value[7]; bradycardia was defined as a heart

rate of <60 beats/min (bpm)[8]; and ventricular tachycardia was defined as a series of more than three consecutive premature ventricular complexes at a rate faster than 100 bpm[9].

2.5. Statistical analysis

The Kolmogorov–Smirnov test was used to test the normality of the distribution. Continuous variables were presented as means and standard deviations, and unpaired t-tests and Mann–Whitney tests were used for comparisons between the two groups. Categorical variables were presented as frequencies and percentages and were compared using Chi-squared test. $P < 0.05$ was considered statistically significant for all analyses, which were performed using SPSS 26.0.

3. Results

3.1. Characteristics of the study participants

A flow chart showing the selection and enrollment of patients is presented in Figure 1. Of the 378 patients initially selected, 142 patients were eligible to participate in this study. Of these patients, 70 received atropine preconditioning (40, low-dose atropine; 30, high-dose atropine), while 72 did not.

The characteristics of the study participants at the time of enrollment are shown in Tables 1 and 2. No significant differences were found with regard to age, sex, body mass index (BMI), smoking history, hypertension, diabetes mellitus, stroke, left ventricular ejection fraction (LVEF), single branch lesion, right coronary atherosclerosis, chest pain, or door-to-balloon time between the experimental group and the control group (all $P > 0.05$) (Table 1) or between the low-dose group and the high-dose group (all $P > 0.05$) (Table 2).

In the experimental ($n = 70$) and control groups ($n = 72$), bradycardia occurred in 24.3% (17/70) and 45.8% (33/72) of patients, respectively; hypotension occurred in 18.6% (13/70) and 40.3% (29/72) of patients, respectively; ventricular tachycardia occurred in 4.3% (3/70) and 19.40% (14/72) of patients, respectively; ventricular fibrillation occurred in 8.6% (6/70) and 20.8% (15/72) of patients, respectively; and temporary pacemaker was inserted in 14.3% (10/70) and 29.2% (21/72) of patients, respectively. There was no death in either group. The incidence of reperfusion vagal reflex-related events was significantly lower in the experimental group (all $P < 0.05$) (Table 3).

In the experimental group, there were 17 cases of sinus tachycardia with heart rate over 130 bpm and a case of rapid atrial fibrillation. In the control group, there were 15 cases of sinus tachycardia with heart rate over 130 bpm, three cases of frequent premature ventricular contraction, and seven cases of ventricular tachycardia or ventricular fibrillation. There was no significant difference in the incidence of secondary tachyarrhythmia between the experimental group and the control group (25.7% vs. 34.7%, $P > 0.05$). The occurrence of secondary arrhythmia and extracardiac symptoms during and after PCI in the control group and the experimental group is summarized in Table 4.

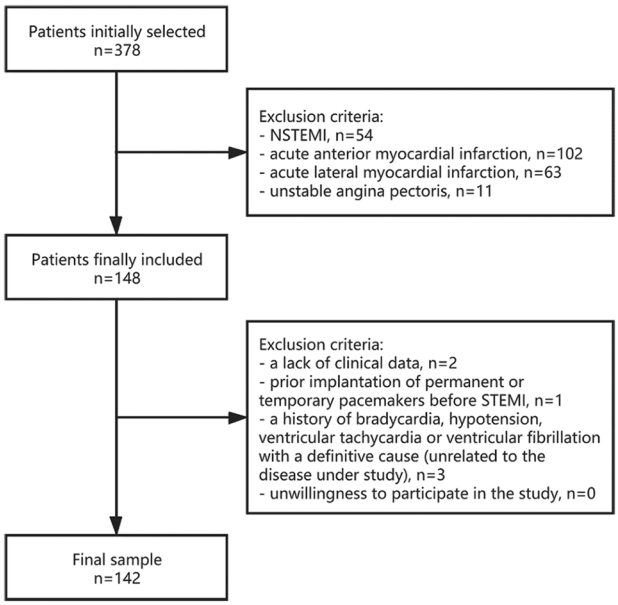

Figure 1. Study protocol.
STEMI: ST-elevation myocardial infarction; NSTEMI: Non-ST-elevation myocardial infarction.

In the subgroup analysis, the inhibition of reperfusion vagal reflex-related events by different doses of atropine indicated that patients who received high-dose (2 mg) atropine had a lower risk of bradycardia (10% vs. 35%), hypotension (6.70% vs. 27.50%), ventricular tachycardia (6.70% vs. 25%), and ventricular fibrillation (0% vs. 15%) than those who received low-dose (0.5–1mg) atropine; moreover, the incidence of temporary pacemaker implantation was also lower in the former group of patients (3.30% vs. 22.50%) (all $P < 0.05$) (Table 5). However, the incidence (46.7% vs. 10.0%, $P < 0.05$) of secondary tachyarrhythmias (sinus tachycardia) with heart rate over 130 bpm was higher in the high-dose group.

4. Discussion

The majority of inferior STEMI cases are caused by right coronary occlusion, with a small proportion being attributed to left circumflex artery occlusion. Both the right coronary artery and the left circumflex artery supply blood to the sinoatrial node, atrioventricular node, and atrium.

Table 1. Baseline characteristics of the treatment group and the control group.

Variables	Experimental group (n=70)	Control group (n=72)	*P*-value
Age (years)	61.62±12.90	62.68±9.66	0.589
Male, *n* (%)	57 (81.4)	60 (83.3)	0.766
BMI (kg/m^2)	24.0±3.1	23.6±2.9	0.805
Smoker, *n* (%)	48 (68.6)	43 (59.7)	0.272
Hypertension, *n* (%)	31 (44.3)	22 (30.6)	0.075
Diabetes mellitus, *n* (%)	18 (25.7)	14 (19.4)	0.371
Stoke, *n* (%)	1 (1.4)	5 (6.9)	0.209
LVEF (%)	58±6	57±7	0.912
Single branch lesion, *n* (%)	23 (32.9)	22 (30.6)	0.768
Right coronary atherosclerosis, *n* (%)	63 (90.0)	63 (87.5)	0.638
Proximal	8 (11.4)	12 (16.7)	0.370
Mid	17 (24.3)	30 (42.9)	0.069
Distal	11 (15.7)	12 (17.1)	0.878
Chest pain (min)	300 (180.00, 600.00)	300 (195.00, 433.50)	0.641
Door-to-balloon (min)	83.5 (52.75, 99.75)	70.5 (52.75, 101.75)	0.239
Occluded coronary artery, *n* (%)			
Right coronary	63 (90%)	63 (87.5)	0.638
Left circumflex	7 (10%)	9 (12.5)	0.638
Potassium (mmol/L)	3.9±0.4	4.0±0.4	0.875
Creatinine (μmol/L)	67.3±16.0	68.4±17.1	0.712
QT interval (ms)	395.7±43.0	397.9±42.5	0.757
PR interval (ms)	169.6±22.9	170.3±21.5	0.847
ST elevation (mm)	1.9±1.2	1.8±1.4	0.812
β-blockers, *n* (%)	18 (25.7)	20 (27.8)	0.781

BMI: Body mass index; LVEF: Left ventricular ejection fraction

This may, in part, explain why the vagal reflex is evident in acute inferior myocardial infarction reperfusion[1,10,11].

Atropine is an anticholinergic drug with potent and nonspecific anticholinergic activity. The common side effects of atropine are parasympathetic stimulation, including dry mouth and eyes, decreased sweating, hyperthermia, headache, blurred vision, constipation, urinary retention, tachycardia, palpitation, and anxiety[12]. Atropine has a rapid onset of action and short half-life. It is commonly used in the emergency treatment of cardiac arrhythmias, acute bronchospasm, and anticholinesterase overdose or intoxication; prevention of vagal reflexes; and reduction of secretions during anesthesia; currently, it is also used in the treatment of myopia[13]. Atropine antagonizes the central nervous system and muscarinic symptoms caused by stimulation of the postsynaptic membrane through competitive inhibition of postsynaptic acetylcholine receptors and direct vagolytic effects[14]. In this study, prophylactic intracoronary atropine significantly reduced the incidence of reperfusion vagal reflex-related events, such as bradycardia, hypotension, ventricular tachycardia, and ventricular fibrillation, during emergency PCI for inferior wall STEMI and improved the safety of this procedure. High-dose (2 mg) atropine administration has more advantage in terms of safety and effectiveness than low-dose (0.5–1 mg) atropine treatment.

When the guidewire and balloon pass through the right coronary artery or the circumflex branch during emergency PCI, tissue cells are reperfused, and excessive calcium excites the cardiac ganglion plexus, causing the quantum release of acetylcholine accumulated in a number of vesicles[15]. During this process, numerous muscarinic potassium (K_{Ach}) channels are activated with potential for negative inotropic, negative frequency, and negative conduction effects on the heart[16]. This causes vagal nerve excitation, as evidenced by a slow heart rate and atrioventricular block.

One of the main complications following emergency PCI for acute thrombotic occlusion of the right coronary

Table 2. Baseline characteristics of the low-dose group and the high-dose group

Variables	Low-dose group (n = 40)	High-dose group (n = 30)	*P*-value
Age (years)	60.50 ± 11.59	63.17 ± 14.53	0.396
Male, *n* (%)	30 (75.0)	27 (90.0)	0.110
BMI (kg/m^2)	24.0 ± 3.2	24.8 ± 3.5	0.857
Smoker, *n* (%)	28 (70.0)	25 (83.3)	0.198
Hypertension, *n* (%)	14 (35.0)	7 (23.3)	0.292
Diabetes mellitus, *n* (%)	11 (27.5)	7 (23.3)	0.693
Stoke, *n* (%)	1 (2.5)	0	1
EF (%)	57.82 ± 7.21	60.67 ± 3.06	0.200
Single branch lesion, *n* (%)	16 (40.0)	7 (23.3)	0.142
Right coronary atherosclerosis, *n* (%)	35 (85.0)	29 (96.7)	0.107
Proximal	5 (12.5)	3 (10.0)	1
Mid	9 (22.5)	10 (33.3)	0.313
Distal	5 (12.5)	6 (20.0)	0.394
Chest pain (min)	300 (180.00, 519.00)	300 (216.00, 720.00)	0.494
Door-to-balloon (min)	80 (52.75, 99.75)	97 (70.50, 114.25)	0.054

BMI: Body mass index; LVEF: Left ventricular ejection fraction

Table 3. Reperfusion vagal reflex-related events in the experimental group and the control group

Variables	Experimental group (*n*=70)	Control group (*n*=72)	*P*-value
Bradycardia, *n* (%)	17 (24.3)	33 (45.8)	0.007
Hypotension, *n* (%)	13 (18.6)	29 (40.3)	0.005
Ventricular tachycardia, *n* (%)	3 (4.3)	14 (19.4)	0.005
Ventricular fibrillation, *n* (%)	6 (8.6)	15 (20.8)	0.040
Temporary pacemaker, *n* (%)	10 (14.3)	21 (29.2)	0.032

Table 4. Secondary arrhythmia and extracardiac symptoms during and after percutaneous coronary intervention

Variables	Experimental group (*n* = 70)	Control group (*n* = 72)	*P*-value
Arrhythmia, *n* (%)	18 (25.7)	25 (34.7)	0.243
Sinus tachycardia, *n* (%)	17 (24.3)	15 (25.8)	0.623
Frequent PVC, *n* (%)	0 (0)	3 (4.2)	0.245
VT/VF, *n* (%)	0 (0)	7 (9.7)	0.013
AF, *n* (%)	1 (1.4)	0 (0)	0.049
Nausea and vomiting, *n* (%)	3 (4.3)	4 (5.6)	1.000
Urinary retention, *n* (%)	3 (4.3)	1 (1.4)	0.363

AF: Atrial fibrillation; PVC: Premature ventricular contraction; VF: Ventricular fibrillation; VT: Ventricular tachycardia

artery is reperfusion vagal reflex. When hypotension, bradycardia, and other reperfusion reactions occur,

Table 5. Reperfusion vagal reflex-related events in the low-dose group and the high-dose group

Variables	Low-dose group (*n* = 40)	High-dose group (*n* = 30)	*P*-value
Bradycardia, *n* (%)	14 (35.0)	3 (10.0)	0.016
Hypotension, *n* (%)	11 (27.5)	2 (6.7)	0.027
Ventricular tachycardia, *n* (%)	10 (25.0)	2 (6.7)	0.044
Ventricular fibrillation, *n* (%)	6 (15.0)	0 (0)	0.034
Temporary pacemaker, *n* (%)	9 (22.5)	1 (3.3)	0.036

most of these events can be corrected within 30 min after corresponding treatment is given; however, the risk and difficulty of the procedure as well as the cost of hospitalization could increase. Compared with that in the normal heart, the insertion of a temporary pacemaker during emergency PCI for inferior STEMI is associated with higher risks, which include pericardial tamponade caused by intraoperative perforation of the right ventricle and ventricular arrhythmias caused by catheter activation or the differences in the refractory periods between Purkinje fibers and myocardial cells[17].

In this study, atropine preconditioning alleviated the vagal reflex; prevented hypotension, bradycardia, nausea, and vomiting; decreased the incidence of ventricular tachycardia or fibrillation; and improved the safety of the procedure. The previous studies have indicated that low doses of atropine (0.5 – 1 mg) can temporarily slow down

the heart rate in some patients[3], without changes in blood pressure or cardiac output. The mechanism by which atropine slows the heart rate is by blocking the negative-feedback inhibition of parasympathetic postganglionic fibers. High doses of atropine (2 mg) can block nerve receptors and remove the inhibitory effect of the vagus nerve on the heart, leading to an increased heart rate[18]. In this study, high-dose atropine had greater advantage in inhibiting the reperfusion response than low-dose atropine and significantly reduced the incidence of reperfusion arrhythmia. In the low-dose atropine preconditioning group, mild bradycardia and hypotension still occurred in some patients during reperfusion, with the majority of them requiring a full dose of atropine. In addition, the use of atropine before reperfusion can reduce the incidence of ventricular fibrillation. Ventricular fibrillation did not occur in any of the patients in the high-dose atropine group. The use of atropine significantly reduced the occurrence of ventricular arrhythmias, while correcting bradycardia and hypotension. These findings further strengthen the evidence that atropine has significant therapeutic value in patients with acute inferior STEMI.

However, it has been reported that prophylactic atropine may cause severe ventricular fibrillation after ameliorating bradycardia, but the exact mechanism responsible for the induction of ventricular irritability after atropine administration is not entirely clear. The increase in myocardial oxygen demand brought about by the increased heart rate appears to be the most important factor, and it may be akin to that of ventricular irritability that occasionally occurs during atrial pacing or exercise in patients with ischemic heart disease[19,20]. Moreover, the egress of potassium from myocardial cells, which is associated with tachycardia, may play an important role in promoting ventricular irritability. Atropine can lower the threshold of ventricular fibrillation and increase the disparity of refractory periods during ischemia[21]. However, in this study, the apparent provocation of ventricular arrhythmias by atropine was not observed. Hence, we conclude that atropine may be beneficial in certain circumstances for preventing reperfusion vagal reflex-related events in acute myocardial infarction[22].

We acknowledge certain limitations of our work. First, given the retrospective nature of this study, we were unable to gather clinical information on every prognostic factor in the cohort despite our extensive exploration of the clinical data. Second, this was a single-center retrospective study with a small sample size. Third, the discrepancies in the dose and duration of atropine administration due to differing experiences or skills among clinicians as well as the resulting differences in the potential of atropine to act may lead to biases.

5. Conclusion

Prophylactic intracoronary atropine could significantly reduce the risk of reperfusion vagal reflex-related events during emergency PCI for acute inferior STEMI and improve the safety of this procedure. These effects can be significantly enhanced by high-dose (2 mg) atropine pretreatment.

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Conflict of interest

The authors declare no conflicts of interest.

Author contributions

Conceptualization: Lingping Xu
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Ethics approval and consent to participate

This study was approved by the Ethical Committee of Xianyang Central Hospital (Approval No. 20200059), and informed consent was obtained from the patients and their families.

Consent for publication

Informed consent was obtained from the patients and their families.

Availability of data

Data can be obtained from the corresponding author following request.

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