

Early application of digitalis in patients with acute myocardial infarction complicated with heart failure after PCI.

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Abstract

The purpose of this work was to observe the effects of early application of digitalis on heart function, hemodynamics, and laboratory indexes in patients with Acute Myocardial Infarction (AMI) complicated with heart failure after Percutaneous Coronary Intervention (PCI). We recruited 54 patients with AMI complicated with heart failure after undergoing emergency PCI and randomly divided them into control and experimental groups. The experimental group was treated by digitalis preparation after reperfusion while the control group received saline injection. Left Ventricular End-Diastolic Diameter (LVEDD) increased in both groups, but there were no significant differences between the two groups. Left Ventricular Ejection Fraction (LVEF) was higher in the experimental group than in the control group. Heart Rate (HR), in the experimental group was lower than those in the control group after medication. Stroke Volume (SV) was higher in the experimental group than that in the control group 1 h after medication. The changes in Central Venous Pressure (CVP), Pulmonary Artery Systolic Pressure (PASP), and Cardiac Index (CI) were not significantly different between the two groups. The values of Brain Natriuretic Peptide (BNP), Creatine Kinase isoenzyme MB (CK-MB), and Troponin I (TnI) improved significantly in both groups after surgery. The incidence of ventricular arrhythmia and mortality rate 30 d post-surgery were similar in the two groups. Overall, the heart function and hemodynamic indexes of patients with AMI complicated with heart failure after PCI can be significantly ameliorated after intervention with digitalis drugs without increasing the adverse events.

Keywords: Acute myocardial infarction (AMI), Percutaneous coronary intervention (PCI), Heart failure, Digitalis, Hemodynamics.

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Introduction

Acute Myocardial Infarction (AMI) is a common cardiovascular disease, a key cause of disability and death in patients, and will be the world's leading cause of death by 2020 [1,2]. The common complication of AMI is heart failure. The incidence rate of mild to moderate heart failure in patients with AMI is 48% and the incidence of severe heart failure is around 10% [3]. In recent decades, the prognosis of AMI patients has improved significantly thanks to the experienced gained in the application of β -receptor blockers, antiplatelet agents, statins, angiotensin-converting-enzyme inhibitors, emergency interventional therapy, and early reperfusion therapy [4]. However, the incidence of heart failure after AMI treated by Percutaneous Coronary Intervention (PCI) is still relatively high, mostly in acute left heart failure, which is manifested by cough, dyspnea, irritability, cyanosis, etc. These symptoms are related to hypoxia, ischemia, and necrosis of myocardial cells caused by the interruption of blood flow due to acute coronary

occlusion in AMI patients. Patients with AMI complicated with heart failure after PCI are currently intervened with reperfusion and medication aimed at recovering myocardial blood supply. Although digitalis is a traditional drug in the treatment of heart failure, the value of early application in patients with AMI complicated with heart failure after PCI is still controversial. On the one hand, digitalis is a positive inotropic drug that can increase myocardial oxygen consumption and aggravate left ventricular function damage as well as arrhythmia [5,6]. On the other hand, hemodynamics can be ameliorated by such medications, thereby optimizing blood supply of the endocardium [7]. To investigate the value of early application of digitalis in patients with AMI complicated with heart failure after PCI, we carried out a comparative study in 54 patients treated in our hospital.

Data and Methods

Patient data

We recruited 54 patients with AMI complicated by heart failure after undergoing PCI in emergency of Daqing Longnan Hospital from January 2013 to December 2015.

Inclusion criteria: a) Patients met the criteria in the guide on diagnosis and treatment of acute myocardial infarction, with onset time in emergency less than 24 h [8]; b) Diagnostic criteria of AMI complicated with heart failure after PCI, with Killip Grade II~IV; c) Completed PCI revascularization; d) Patients signed the informed consent form to participate in research.

Exclusion criteria: a) Mechanical complications of myocardial infarction; b) Hypertrophic obstructive or restrictive cardiomyopathy; c) Second-degree atrioventricular block or above; d) Valvular heart disease; e) Severe hepatic and renal insufficiency; f) Received digitalis drugs or other cardiac stimulants before enrollment; g) Allergic to digitalis drugs; h) Gestation and lactation; i) Poor compliance or did not agree to participate in the study. The study was approved by the Ethics Committee of the hospital before we started recruiting patients.

The 54 patients were divided into control (n=27) and experimental (n=27) groups according to the random number method. The control group contained 22 males and 5 females, ages 38~76 y old with an average of 59.7 ± 5.7 y old. The average height was 168.4 ± 6.5 cm and the average weight was 67.9 ± 10.5 kg. 17 cases had history of smoking, 2 were complicated with diabetes, 4 with hypertension, and 4 with angina pectoris. Killip grade: 11 cases in Grade II, 3 in Grade III, and 13 in Grade IV. Infarct site: 13 cases of anterior wall infarction, 8 of anterior wall plus lateral wall infarctions, and 6 of anterior wall plus inferior infarctions. Number of diseased vessels: 16 cases in single vessel, 6 in two vessels, and 5 in three vessels. The experimental group had 21 males and 6 females, ages 37~78 y old with an average age of 60.3 ± 6.4 y old. The average height was 169.1 ± 6.1 cm and the average weight was 67.8 ± 10.4 kg. 18 cases had history of smoking, 3 were complicated with diabetes, 3 with hypertension, and 5 with angina pectoris. Killip grade: 12 cases in Grade II, 2 in Grade III, and 13 in Grade IV. Infarct site: 14 cases of anterior wall infarction, 7 of anterior wall plus lateral wall infarctions, and 6 of anterior wall plus inferior infarctions. Number of diseased vessels: 15 cases in single vessel, 7 in two vessels, and 5 in three vessels. The differences in baseline data between the two groups had no statistical significance ($p > 0.05$).

Methods

Patients in both groups were treated by PCI in the Emergency Department. Both groups received anticoagulants (low-molecular-weight heparin), anti-platelet aggregation (clopidogrel and aspirin), serum lipid regulation (statins), diuretics (furosemide), and other routine therapies consistent with the guidelines for treating acute myocardial infarction [9]. The application of milrinone, dopamine, and other positive

inotropic drugs should be avoided. The experimental group received digitalis after reperfusion as 2 ml, 0.4 mg deslanoside injection (Jiangsu Jibeier Pharmaceutical, Batch No: 20021016). Patients received a first dose of 0.2 mg deslanoside plus 20 ml 0.9% sodium chloride injection with a uniform speed within 20 min. They received additional deslanoside injections of 0.1~0.2 mg within 4~12 h. Oral administration of 0.125 mg/d digitalis in 0.25 mg digoxin tablets (Beijing Zizhu Pharmaceutical, Batch No: 20100811) was prescribed as maintenance treatment. The control group was only treated with intravenous drip of 20 ml 0.9% sodium chloride injection with the uniform speed after reperfusion within 20 min for three consecutive days.

Observation indexes

The indexes were examined before medication and 1, 3 and 24 h after receiving medication.

Heart function: Heart function was monitored by IE 33 Color Doppler Ultrasound (Philips, USA). The patients were placed in supine position, and the examination was conducted in a quiet condition with transducer frequency of 2.5~3.5 MHz, monitoring for three consecutive cardiac cycles. We calculated the averages for Left Ventricular End-Diastolic Diameter (LVEDD) and Left Ventricular Ejection Fraction (LVEF).

Hemodynamic parameters: Hemodynamics was monitored with a Swan-Ganz Floating Catheter (Edwards Life sciences, USA). We measured Central Venous Pressure (CVP), Heart Rate (HR), Cardiac Index (CI, $CI = \text{heart stroke} / \text{body surface area}$), Stroke Volume (SV, $SV = \text{heart stroke} / \text{heart rate}$), and Pulmonary Artery Systolic Pressure (PASP).

Laboratory indexes: 5 mL blood was collected from the elbow vein before and after medication. Whole blood was collected with anticoagulants and centrifuged at room temperature for 10 min to separate the plasma. We determined the levels of serum B-type Brain Natriuretic Peptide (BNP), Creatine Kinase isoenzyme MB (CK-MB), and Troponin I (TnI) before medication and 24 h after medication by Enzyme-Linked Immunosorbent Assay (ELISA) (Wuhan Boster Biological Technology).

Postoperative adverse events and mortality rate: The occurrence of arrhythmia (ventricular tachycardia, premature ventricular contraction, ventricular fibrillation, multifocal premature ventricular contraction) 24 h after medication were observed under continuous Electrocardiogram (ECG) monitoring after surgery. The mortality rates within 30 days post-surgery were recorded.

Statistical analysis

The SPSS19.0 software (SPSS, Chicago, IL) was used for processing data. Measurement data were expressed as mean \pm SD, and t-test was used for intergroup comparisons. Enumeration data were expressed as percentage and compared by chi-square. Multivariate repeated measures analysis of variance (ANOVA) was utilized for comparisons of data at

different time points between groups. One-way repeated measures ANOVA was used for comparing data at different time points in each group. LSD method was used for pairwise comparison. The data that did not conform to normal distribution were expressed as median ± interquartile range, followed by Wilcoxon rank-sum test. $p < 0.05$ suggested that the difference was statistically significant.

Results

Heart function indexes

LVEF was comparable for the two groups before treatment (Table 1). The values for LVEF increased in both groups after surgery, but the values were significantly higher in the experimental group 1, 3 and 24 h after medication (Table 1). LVEDD was comparable for the two groups before treatment

(Table 1). The values for LVEDD remained statistically similar between the experimental and control groups at all-time points after medication (Table 1).

Hemodynamic indexes

The values for CVP, HR, CI, SV and PASP were comparable between the two groups before the administration of digitalis (Table 2). CVP, CI, and PASP were comparable between the two groups after medication (Table 2). However, the HR was significantly lower in the experimental group 3 and 24 h after medication (Table 2). SV was significantly higher in the experimental group than that in the control group 1 h after medication, but there were no significant differences at 3 and 24 h after treatment (Table 2). The amplitudes of changes of CVP, HR, CI, SV, and PASP among different time points were higher in the experimental group (Table 2).

Table 1. LVEF and LVEDD before and after medication.

Group	Before medication	1 h after medication	3 h after medication	24 h after medication	F	p
LVEF (%)						
Experimental	45.21 ± 5.44	50.41 ± 3.78	54.01 ± 4.22	57.01 ± 3.45	51.224	0.003
Control	46.01 ± 5.89	46.92 ± 3.94	49.21 ± 4.84	52.33 ± 3.24	1.207	0.299
t/F	0.518	3.321	3.884	5.138	F=4.149	
p	0.606	0.001	0	0	0.048	
LVEDD (mm)						
Experimental	50.01 ± 4.33	49.91 ± 4.44	50.88 ± 5.11	50.22 ± 4.74	2.183	0.165
Control	49.98 ± 4.65	48.61 ± 4.36	49.27 ± 4.98	49.96 ± 4.55	1.499	0.245
t/F	0.024	1.085	1.172	0.205	F=0.098	
p	0.98	0.282	0.246	0.837	0.765	

Table 2. Hemodynamic indexes at different time points of medication.

Group	Before medication	1 h after medication	3 h after medication	24 h after medication	F	p
CVP (mmHg)						
Experimental	13.51 ± 4.12	13.21 ± 3.22	11.31 ± 3.14	11.32 ± 2.55	4.388	0.003
Control	12.97 ± 2.38	12.34 ± 2.47	11.89 ± 3.83	12.01 ± 4.32	0.337	0.887
t/F	0.589	1.113	0.608	0.59	F=0.572	
p	0.557	0.27	0.545	0.557	0.619	
HR (b/min)						
Experimental	93.21 ± 9.33	90.41 ± 4.88	87.11 ± 6.51	85.61 ± 7.66	4.376	0.001
Control	92.78 ± 7.45	91.97 ± 6.89	92.24 ± 5.12	91.44 ± 4.78	0.161	0.678
t/F	0.187	0.96	2.779	3.355	F=1.741	
p	0.852	0.341	0.007	0.001	0.132	
CI (L/min.m ²)						
Experimental	2.68 ± 0.66	3.03 ± 0.87	3.23 ± 0.71	3.41 ± 0.71	4.028	0.002

Control	2.67 ± 0.55	2.77 ± 0.28	3.12 ± 0.32	3.20 ± 0.61	4.415	0.002
t/F	0.06	1.478	0.733	1.165	F=0.224	
p	0.952	0.145	0.466	0.249	0.883	
SV (ml)						
Experimental	51.11 ± 12.84	65.44 ± 10.98	61.01 ± 11.89	67.81 ± 16.22	8.372	0.002
Control	52.24 ± 9.87	55.21 ± 7.46	59.31 ± 10.55	60.51 ± 10.46	1.324	0.298
t/F	0.362	4.004	0.555	1.965	F=1.982	
p	0.718	0	0.58	0.054	0.131	
PASP (mmHg)						
Experimental	40.21 ± 11.22	36.31 ± 10.32	32.71 ± 7.66	33.81 ± 7.11	6.549	0.002
Control	39.98 ± 6.78	35.97 ± 3.94	34.98 ± 4.11	34.12 ± 5.21	2.821	0.032
t/F	0.091	0.159	1.356	0.182	F=1.004	
p	0.927	0.873	0.18	0.855	0.398	

Table 3. Hemodynamic indexes at different time points of medication.

Group	BNP (pg/ml)		TnI (ng/ml)			CK-MB (ng/ml)		
	Before medication	24 h after medication	Before medication	24 h after medication	24 h after medication	Before medication	24 h after medication	24 h after medication
Experimental	706 ± 881	460 ± 396*	24 ± 20	16 ± 14*	16 ± 14*	61 ± 66	40 ± 39*	40 ± 39*
Control	470 ± 593	380 ± 412*	19 ± 22	15 ± 18*	15 ± 18*	52 ± 56	37 ± 35*	37 ± 35*
H	1.152	0.726	0.749	4.217	4.217	0.516	3.795	3.795
p	0.254	0.47	0.457	0.01	0.01	0.607	0.029	0.029

Note: Compared with that before medication in each group, *p<0.05.

Laboratory indexes

The laboratory indexes before and after medication in the two groups that did not conform to normal distribution was expressed as median ± interquartile range. The values for BNP, TnI, and CK-MB in serum before medication were comparable between the two groups (Table 3). The laboratory indexes 24 h after medication decreased significantly in both groups (Table 3). The differences in the values of TnI and CK-MB between the experimental group and the control group were statistically significant 24 h after medication, but the values of BNP were not statistically different between the two groups (Table 3).

Incidence rate of ventricular arrhythmia and mortality rate 30 d post-surgery

The incidence rate of premature ventricular contraction, multifocal premature ventricular contraction, ventricular tachycardia, and ventricular fibrillation were similar in the two groups (Table 4). The mortality rate 30 d postoperative was slightly lower in the experimental group than that in the control group, but the difference had no statistical significance (Table 4).

Table 4. Incidence of ventricular arrhythmia and mortality rate within postoperative 30 d.

Group	n	Arrhythmia (n (%))				Mortality rate within 30 d (n (%))
		Premature ventricular contraction	Multifocal premature ventricular contraction	Ventricular tachycardia	Ventricular fibrillation	
Experimental	27	13 (48.15)	4 (14.81)	4 (14.81)	2 (7.41)	2 (7.41)
Control	27	12 (44.44)	3 (11.11)	5 (18.52)	1 (3.70)	5 (18.52)

χ^2	0.074	0.164	0.133	0.352	1.477
p	0.784	0.685	0.715	0.552	0.224

Discussion

Heart failure is the leading cause of disability and death due to cardiovascular disease. The incidence rate of AMI complicated with heart failure reaches 32.4% and the mortality rate is 21.6% [10]. Coronary heart disease is the main cause leading to heart failure at present. Normally, acute heart failure is characterized by acute onset, critical illness, and rapid deterioration. More patients show more severe symptoms and signs of heart failure, which has a higher fatality rate. Particularly, AMI complicated with heart failure is very serious, showing a higher risk of death than simple heart failure [11].

Obvious changes of body hemodynamics, namely decompensation, can be found when the myocardial infarction area exceeds 20% in AMI patients, and cardiogenic shock may occur when it exceeds 40% [12]. Therefore, early reperfusion intervention can not only decrease infarction area but also reduce the rate of cardiogenic shock [13]. However, the incidence rate of heart failure after AMI treated by reperfusion is relatively high, which is related to excessively large myocardial infarction area, much loss of myocardial cells, reperfusion injury, and the relatively long time from onset to reperfusion therapy. Normal heart function cannot be maintained by rapid revascularization in patients with a large area of myocardial infarction. Additionally, the necrotic myocardial cells cannot be saved by revascularization due to the long time from onset time to reperfusion therapy [14]. Currently, early diagnosis and treatment are considered as treatment principles of AMI complicated with heart failure after PCI in the emergency room. Immediate and rapid emergency treatment should be utilized in case of heart failure in AMI patients to correct hemodynamic disorders, ameliorate symptoms and signs, and reduce mortality rate.

The therapies for patients with AMI complicated with heart failure after PCI in emergency are similar with those used for acute heart failure: diuretics and vasodilator drugs followed by opioids and blood pressure regulating drugs as supplements. However, the corrective effects of these drugs on the symptoms of patients with heart failure are limited [15]. Positive inotropic drugs are commonly used in the treatment of heart failure, including digitalis and non-digitalis drugs. Non-digitalis positive inotropic drugs can be improved the clinical symptoms of heart failure in the short term, but may also increase myocardial cell energy consumption, aggravate neuroendocrine disorders, and raise the risk of arrhythmia [16]. However, the value of digitalis in the treatment of cardiovascular diseases is still controversial. Digitalis was firstly used in the treatment of edema owing to its diuretic effect, which is found in a later phase than its positive inotropic effect and strong heart function. However, the positive inotropic effect of digitalis preparations on AMI patients was relatively weak and changes

of heart function were not found in 120 patients after intravenous administration with digitalis drugs (e.g. digoxin) [17]. The effects of early application of digitalis preparations in patients with AMI were not obvious, but the signs of heart failure in patients basically disappeared after the continuous application [18]. Another study confirmed that the cardiac indexes of patients with AMI complicated by heart failure who received digoxin were significantly increased [19]. In our study, the heart function and hemodynamic indexes in patients treated with digitalis improved significantly compared to the control group, which was consistent with the conclusion reported by Wu et al. [20].

Digitalis can increase peripheral vascular tension and promote contraction of the coronary arteries and smooth muscle. Currently, digitalis intervention not only improves heart function of patients with heart failure but also reduces peripheral vascular tension and ameliorates vasoconstriction [21,22]. Additionally, the neuroendocrine state can be regulated by digitalis, which impacts reperfusion for AMI patients. Generally, heart failure is often complicated with neuroendocrine abnormalities that are closely associated with prognosis. Nevertheless, digitalis drugs can improve symptoms and signs of heart failure, regulate neuroendocrine, and improve prognosis of heart failure through positive inotropic effect [23]. Here we showed that HR was significantly reduced in patients treated with digitalis, which agrees with the effects of digitalis described in the literature. Additionally, the reperfusion of patients with AMI complicated with heart failure can be rapidly restored by early application of digitalis, thereby improving heart function, restoring peripheral myocardial oxygen supply of infarction in a short period of time, and ameliorating the hemodynamics of ischemic myocardium of infarction area, which plays a key role in the recovery of left ventricular function. Moreover, early reperfusion is conducive to the recanalization of occluded vessels, restoring myocardial oxygen supply rapidly. Of note, digitalis can enhance velocity of contraction of myocardial fiber and increase myocardial oxygen consumption in patients with no heart failure, and decrease left ventricular end-diastolic volume and reduce myocardial oxygen consumption in patients complicated with heart failure. The increased oxygen consumption resulted from left ventricular systolic velocity caused by digitalis can balance the oxygen consumption decreased by the reduction of ventricular wall tension myocardial contraction [24]. Here, we showed that digitalis combined with reperfusion promoted the recovery of myocardial blood supply, amelioration of hemodynamic indexes, and improvement of TnI and CK-MB, demonstrating the safety of digitalis therapy.

Arrhythmias, poisoning, and other adverse events induced by digitalis are related to its total applied dosage. The risk of digitalis-induced arrhythmias increases in patients also

presenting hypotension, renal insufficiency, hypoxemia, or acidosis [25]. The mortality rate of patients with heart failure can be effectively reduced by low dose digitalis (mass concentration of digitalis in plasma at less than 1 ng/ml) [26]. In our study, we found no differences in the incidence of arrhythmia and mortality between the two groups, indicating that digitalis did not cause adverse effects in our cohort. The infarction area can be expanded by the enhanced ventricular wall tension and increased myocardial oxygen consumption caused by digitalis, thereby elevating the mortality rate of patients [27]. However, such side effects mostly occur in older patients with poor heart function. On the contrary, digitalis can improve cardiac dysfunction in patients with coronary heart disease caused by exercise or low potassium levels, decrease oxygen consumption, and reduce the risk of left heart failure [28].

In conclusion, heart function and related blood indexes of patients with AMI complicated with heart failure after PCI can be significantly ameliorated after intervention with digitalis drugs, which is conducive to improving prognosis. We also found no increase in adverse events in the digitalis-treated group, which shows a higher safety.

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