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Therapeutic effect of urapidil on myocardial perfusion in patients with ST-elevation acute coronary syndrome

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Abstract

Objectives: To evaluate the effect of urapidil on myocardial perfusion, and ventricular function in patients with ST-elevation acute coronary syndrome (ACS) treated with primary percutaneous coronary intervention (PCI).
Methods: Fifty-four patients were randomized into urapidil (12.5mg, ic, n=27) or control group. Infarct related artery (IRA) was targeted with PCI following urapidil administration. TIMI blood flow, corrected TIMI frame count (cTFC), myocardial blush grade (MBG), ST resolution (STR) on ECG, creatine kinase MB (CK-MB) and cardiac troponin T (cTnT) were measured before, and after PCI.
Results: cTFC (18.38±3.30 vs. 21.44±4.26, *P*=0.005), in the treatment group was lower than the placebo group, whereas MBG was higher (*P*=0.04). More patients in the urapidil group achieved significant STR following PCI (93% vs. 70%, *P*=0.04). Left ventricular ejection fraction (LVEF), measured with echocardiography, in the urapidil group was higher than the control group 30 days after PCI (0.58±0.06 vs 0.54±0.06, $P = 0.04$). Peak CK-MB and peak cTnT in the urapidil group was lower than the control group ($P<0.01$). Myocardial nitric oxide concentration in the urapidil group was higher than that of the control group ($P<0.01$). Following PCI, the endothlin-1 level did not change in the urapidil group ($P>0.05$) but it was increased in the control group ($P<0.05$).
Conclusions: Urapidil treatment improves coronary flow, myocardial perfusion and left ventricular function following PCI in patients with ST-elevation ACS. These beneficial effects are associated with an enhanced biosynthesis of nitric oxide.
Key words: acute coronary syndrome, percutaneous coronary intervention, urapidil, nitric oxide, endothelins

Introduction

Percutaneous coronary intervention (PCI) has become a major treatment for patients with acute coronary syndrome (ACS) [1, 2]. Successful PCI reduces the incidence of death, myocardial infarction and hospitalisation in patients with ACS [1, 2]. However, slow-flow or no-reflow is present in up to 30% of patients following the successful PCI, and reopening of the infarct-related artery [3, 4]. The "mismatch" between the patency of the artery, and the reperfusion of the myocardium may be due to a number of causes, such as microvascular constriction [5-7]. The primary purpose of this study is to evaluate the effect of urapidil, a selective α_1-adrenoceptor blocker, on the perfusion of myocardium and the left ventricular function following PCI in patients with ACS.

Patients and methods

Patient selection

This study was approved by the Human Research Ethics Committee of Beijing Friendship Hospital. Informed consent in a written form was obtained from all participants. The procedures were in accordance with the ethical standards of the responsible committee on human experimentation.

The selection criteria are: 1) age > 18 years; 2) onset of chest pain less than 12 h; 3) ST-elevation in at least two adjacent ECG leads, or presence of newly developed left bundle branch block. All patients must have an elevation of plasma creatine kinase MB (CK-MB) or cardiac troponin-T (cTnT).

Patients with one or more of the following conditions were excluded from the study: systemic infection, anaemia, renal or hepatic dysfunction, cancer, systemic thromboembolic disease, autoimmune disease or pregnancy, and patients who did not give written consent to participate the study.

Between December 2005 and October 2006, 54 consecutive patients with ST-elevation ACS were recruited into this study.

Patients were randomised , according to their order of hospitalization, into treatment group (urapidil, n=27) and control (normal saline, n=27) group.

Pharmacological management and PCI

Patients from both groups were treated with 300 mg aspirin, and 300 mg clopidogrel before PCI. Clopidogrel 75 mg per day was administered following PCI as a maintenance therapy. Coronary angiography was performed before balloon angioplasty or stent implantation to demonstrate infarct-related artery (IRA). When coronary flow higher than TIMI-1 was present in the IRA, urapidil (12.5 mg in 5 ml normal saline, ALTANA Pharma, Germany), or 5 ml normal saline was injected into the IRA followed by PCI. In patients who were taken blood sample to measure NO and ET-1, nitroglycerin was not used before and during the PCI procedure.

In patients undergoing PCI, target-lesion revascularization was always attempted, and complete revascularization was performed as clinically appropriate. Results of PCI were assessed by visual estimation of the angiograms before, and after the procedure. Success of PCI was defined as less than 50% stenosis in the luminal diameter after balloon angioplasty, and less than 20% stenosis after coronary stent implantation. Other major cardiac drugs following PCI are used listed in Table 2.

Assessment of coronary flow and myocardial perfusion

The cinefilm reviewers were blinded to the treatment group assignment and the clinical outcome of the patient. TIMI flow grade and corrected TIMI frame count (cTFC) was conducted using the methods reported by Gibson et al. [8]. Myocardial reperfusion following PCI was assessed by myocardial blush grade (MBG), using the methods reported by the Zwolle Myocardial Infarction Study Group [9].

A standard 12-lead ECG was recorded before PCI, and at 30min, 60min, 90min, and 120 min following PCI. ECG was also recorded 3h, 4h and 6h following PCI. ST resolution (STR) on the ECGs was measured. The time between completion of PCI, and reaching significant STR was also registered. Significant STR was defined as more than 50% reduction in the elevated ST segment within 90 min following PCI.

Plasma CK-MB and cTnT was measured before PCI, and at 4h, 6h, 10h, 16h, 20h, 24h, 48h, and 72 h following PCI. The peak values of CK-MB, and cTnT were used as the infarct size indices.

Assessment of left ventricular function

The left ventricular systolic function was assessed 24h and again 30 days after PCI, using two-dimensional echocardiography (HP 7500, Philips, Netherlands). The LVEF, left ventricular end-diastolic, and end-systolic diameters were measured.

Measurement of nitric oxide and endothelin-1

In the last five patients of each group, nitric oxide, and endothelin-1 was measured from blood obtained from the root of the aorta and the coronary sinus. The difference in nitric oxide or endothelin-1 levels between the aorta and the coronary sinus was defined as the myocardial levels.

Blood was centrifuged at 1500 rpm for 20 min, and the separated plasma was kept at -80^0C. Nitric oxide was measured by chemiluminescence with a Sievers Nitric Oxide Analyzer, model 280 (Boulder, Colorado, USA). The nitric oxide assay was standardized by a calibration curve using known concentrations of nitrate (0.01 to 100 μmol/L), obtained from

sodium nitrate. For each measurement, a 4-μL sample was placed in a reducing vessel with 5 mL of 0.1 mol/L of vanadium III chloride, 1 mol/L of hydrochloric acid, and 100 μL of antifoaming agent at 90°C. Each standard was analyzed three times, and each plasma sample was analyzed at least five times. The mean value was used for all subsequent analysis.

Plasma endothelin-1 was measured by using an ELISA kits (RapidBio lab, CA, USA). The efficacy of the extraction procedure was 81%; inter-assay variations were 9%, and intra-assay variations were 5%. In this assay, cross-reactivities were less than 5% for endothelin-2, less than 3% for endothelin-3, and less than 37% for proendothelin.

Clinical outcomes

The cardiac events during hospitalization and within 30 days of PCI were monitored. These events included cardiac arrhythmia (excluding reperfusion arrhythmia), recurrent myocardial infarction, post-infarct angina, left ventricular dysfunction, cardiogenic shock or cardiac death.

Statistical analysis

Data were expressed as means ± SD. Student *t* test was used to analyze the differences between the urapidil, and control groups. Comparison of categorical data between the two groups before or after the treatment was performed by Chi-square test, and Fisher exact test. Logistic regression analysis was also performed to asses the predicting factors for cTFC, MBG and STR. $P < 0.05$ was considered to be statistically significant.

Results

General findings

Between the two groups, there was no significant difference in age, sex, medical history, left ventricular function, time from onset of the symptoms to PCI, or pharmacological therapies (Table 1, 2).

Intracoronary administration of urapidil had no significant effect on systolic blood pressure (BP 131±11 vs 134±12 mmHg, $P>0.05$), or heart rate (HR 92±5 vs 90±7 bpm, $P>0.05$). The blood pressure (BP 128±15 vs 129±14 mmHg, $P>0.05$), and heart rate (HR 93 ±10 vs 94 ±8, $P>0.05$) of the control group also remained unchanged.

In the urapidil group we found 12 cases of reperfusional arrhythmia (including 8 cases of accelerated idioventricular rhythm and 4 sinus bradycardia), compared to 13 cases of reperfusional arrhythmia (including 9 cases of accelerated idioventricular rhythm , 3 sinus bradycardia and 1 atrioventricular block in the control group) ($P>0.05$).

During the 30-day follow up, there was no cardiac death, recurrent infarction or re-hospitalization in either group of the patients.

Coronary angiography

There was no significant difference in the coronary angiography between the two groups prior to urapidil administration and PCI. TIMI flow, cTFC, MBG and, the diameter of IRA or the reference coronary artery was similar between the two groups ($P>0.05$, Table 3).

After urapidil administration, there was no significant difference between the two groups in TIMI flow grades (Table 3, $P>0.05$). However, a lower cTFC ($P<0.01$), and a higher MBG ($P<0.05$), was observed in the urapidil group (Table 4, $P<0.01$).

Logistic regression analysis showed that administration of urapidil, the duration of chest pain, sex, and cTFC before PCI are the factors were associated with post-PCI cTFC (Table 5). Administration of urapadil (OR, 0.126; 95% CI, 0.019-0.847; P=0.033), and the duration of chest pain (OR, 1.384; 95%CI, 1.059-1.808; P=0.017) are the independent predictors of MBG.

ST resolution, myocardial biomarkers and left ventricular function

In the urapidil group, more patients achieved ST resolution within 90 min of PCI (Table 6, P<0.01). Logistic regression analysis showed that urapidil is the independent predictor of improved ST resolution (OR, 0.148; 95%CI, 0.025-0.8767; *P*=0.035).

The peak values of CK-MB and cTnT was lower in the urapidil group (Table 6, P<0.01). There was no significant difference in hypersensitive C reactive protein between the two groups (Table 6, P>0.05).

LVEF was higher in the urapidil group 24h, and 30 days after PCI (Table 6, P<0.01).

Levels of nitric oxide and endothelin-1

Prior to PCI, there was no significant difference in the levels of nitric oxide or endothelin-1 in the plasma obtained from the aorta or coronary sinus between the two groups (Table 7 and 8, P>0.05). After PCI, the nitric oxide levels in the coronary sinus were elevated in the two groups (P<0.01, Table 7). It was also elevated in the aorta in the urapidil group (P<0.01, Table 7). The nitric oxide levels in the urapidil group were higher than the control group (P<0.01, Table 7).

After PCI, the endothlin-1 levels were increased in the control group (P<0.05), whereas they remained unchanged in the urapidil group (*P*>0.05, Table 8).

Discussion

The major findings of the study are: 1) In patients with ST-elevation ACS, intracoronary injection of urapidil prior to PCI improves coronary flow and myocardial perfusion following primary PCI; 2) Urapidil treatment enhances ST resolution on ECG and diminishes the peak values of CK-MB and cTnT; 3) The left ventricular function in the urapidil group was greater than the control group following PCI; and 4) Urapidil treatment is associated with an increased cardiac biosynthesis of nitric oxide and reduced production of endothelin-1.

Effect of urapidil on myocardial reperfusion

α-adrenergic activities impact on the ischemic myocardium from two perspectives. First, ischemia and hypoxia often leads to a 2-3 fold increase in α_1-adrenoceptors in ventricular myocytes [10]. The alterations in the α_1-adrenergic receptor system may contribute significantly to arrhythmogenesis in the ischemic heart [10]. For these reasons there have been calls to include α_1-adrenoceptor blockers in the management approaches to reduce the incidence of sudden cardiac death in patients with ACS [10].

Second, α-adrenergic activities contribute significantly to the vasoconstriction of the coronary circulation during myocardial ischemia [11]. The vasoconstriction after coronary angioplasty, and the left ventricular dysfunction secondary to the vasoconstriction, are the direct results of enhanced α -adrenergic activities [12, 13].

The present study has demonstrated that urapidil, a selective α_1-receptor blocker, is associated with further improvement of coronary flow and myocardial perfusion following successful PCI. The indices that we have chosen to reflect coronary flow or myocardial perfusion (cTFC, MBG and ST resolution rate) are commonly used in clinical trials of similar nature [14-16]. They are relatively reliable in demonstrating the alterations in coronary flow or myocardial perfusion in ACS patients [14-16]. There was a significant improvement in all three indices in the urapidil group. These beneficial effects are likely due to the antagonism of α_1-adrenoceptors in the coronary circulation and the resultant dilation of coronary arteries or microcirculation.

A recent study found that in patients with intermediate coronary stenosis, urapidil induced a significant but small decrease in fractional flow reserve, an indicator of the fraction

of hyperaemic myocardial flow that is preserved despite the presence of epicardial coronary stenosis [17]. The authors of the study concluded that α_1-adrenoceptor blockers unmask a small, clinically irrelevant degree of microvascular tone in patients with intermediate coronary stenoses. Our study was centred on a different patient population who had AMI and underwent PCI. Urapidil administration before PCI resulted in a significant increase in coronary flow and myocardial perfusion after successful PCI.

It is important to note that urapidil treatment in the present study was not associated with a significant improvement of TIMI flow in the IRA. Previous studies have shown that in healthy subjects, and in patients with stable angina, selective α_1-adrenoceptor blockers reduce the coronary resistance [18, 19]. Intracoroanry injection of phentolamine, another α-adrenoceptor blocker, diminishes the increase of coronary resistance following coronary angioplasty [13]. These results indicate that although the TIMI flow was not significantly increased after urapidil therapy, the microcirculation may have been improved with a reduction in coronary resistance, leading to improved coronary flow and myocardial perfusion.

Effect of urapidil on left ventricular function

Ventricular dysfunction following myocardial ischemia is the result of the interplay of a number of factors, including the reflex activation of sympathetic nerve system, through stimulation of the receptors in the ventricular myocardium and coronary smooth muscle cells [11]. Following coronary angioplasty or stenting, a transient reduction in left ventricular function was observed in the IRA-dependent, and non-IRA-dependent myocardium [20]. The transient reduction in ventricular function following PCI was diminished by pre-treatment with α-receptor blockers, such as phentolamine or urapidil [20].

The current study has clearly shown that urapidil treatment is associated with reduced peak values of plasma CK-MB and cTnT, indicating a reduction in myocardial ischemia. The left ventricular function in the urapidil-treated patients was also better than the placebo group following PCI. These results indicate that in addition to the anti-adrenergic activities, urapidil also improves ventricular function by limiting the infarct size.

Effect of urapidil on the biosynthesis of nitric oxide and endothelin-1

Balloon angioplasty, and stenting are effective in re-opening the occluded coronary arteries. However, the revascularization following PCI is not always associated with the full restoration of myocardial perfusion [20]. As shown in our study, α-antagonism reduced cTFC, and improved MBG following PCI, suggesting significant improvement in coronary flow and myocardial perfusion.

To explore other potential contributors to the improved coronary flow or myocardial perfusion following urapidil treatment, we measured the levels of nitric oxide, and endothelin-1 following urapidil administration in five patients. Compared with the control group, the myocardial levels of nitric oxide in the urapidil group were clearly elevated, whereas the biosynthesis of detrimental endothelin-1 was suppressed.

Urapidil is a peripheral α_1-adrenoceptor antagonist and central 5-HT_{1A} agonist. We are not aware of any direct association between α_1-antagonism and nitric oxide biosynthesis. Therefore, the increased myocardial level of nitric oxide following urapidil therapy is likely due to improvement in coronary circulation or endothelial function.

Peripheral α_1-adrenoceptor antagonists do not appear to have a significant effect on circulating endothelins in healthy humans [21]. There is no suggestion in the literature of any relationship between central serotoninergic stimulation and peripheral endothelin peptides. Therefore, it is reasonable to assume that in our patients with ST-elevation ACS, the

improvement in coronary circulation, and myocardial reperfusion, which were initiated by urapidil, were responsible for the unchanged circulating endothelin-1 levels.

Limitations of the study

This was a prospective study in a relatively small number of patients. There were clear and significant evidence to show the beneficial effect of urapidil on the coronary flow, myocardial perfusion and left ventricular function. However, there was no significant change in the major adverse cardiac events in either group. Therefore, no conclusion can be drawn on the impact of urapidil on the prognosis of ST-elevation ACS. Furthermore, although the dosage of urapidil used in the present study was effective, and in agreement with a previous study [19], it remains to be seen if a higher dose may elicit a greater improvement in myocardial perfusion and left ventricular function.

Conclusions

In patients with ST-elevation ACS, PCI may salvage impaired myocardium. However, ischemia-induced activation of α-adrenergic nerve system and the resultant vasoconstriction may offset some of the perfusion benefits from successful PCI. Pre-treatment with α_1-adrenoceptor antagonists will improve the coronary flow, myocardial perfusion and left ventricular function following PCI. These hemodynamic and clinical benefits are associated with improved levels of nitric oxide, and suppressed biosynthesis of deleterious endothelin-1. The impact of α_1-adrenoceptor antagonists on the major cardiac events following PCI remains unclear, and further studies are warranted.

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Table 1. Baseline patient characteristics

	Urapidil□n□27□	Control (n□27□	*P*
Age (years)	61.2±6.0	60.6±7.3	0.12
Male (%)	15 (56)	18 (67)	0.78
Diabetes (%)	12 (44)	11 (39)	0.27
Hypertension (%)	18 (67)	16 (58)	0.79
Dyslipidemia (%)	11 (39)	9 (33)	0.84
Smoking history (%)	9 (33)	11 (39)	0.84
History of MI (%)	3 (11)	6 (22)	0.93
Onset of symptom to PCI (h)	4.1±1.8	3.9±1.9	0.26
Left ventricular function (Killip) (%)			0.49
I	16 (61)	15 (56)	
II	9 (33)	9 (33)	
III	1 (4)	2 (8)	
IV	0 (0)	0 (0)	

Table 2. Medical treatment following PCI

	Urapidil (n□27)	Control (n□27)	*P*
Aspirin	27 (100%)	27 (100%)	1.00
β-blockers	18 (67%)	16 (58%)	0.76
ACEI	23 (84%)	24 (89%)	0.24
ARB	3 (11%)	3 (11%)	1.00
Clopidogrel	27 (100%)	27 (100%)	1.00
LMWH	27 (100%)	27 (100%)	1.00
GP IIb/IIIa receptor	15 (56%)	14 (52%)	0.36
blockers	23 (84%)	24 (89%)	0.24
Statins			

ACEI: angiotensin-converting enzyme inhibitor, ARB: angiotensin receptor blocker, LMWH: low molecular weight heparin.

Table 3. Results of coronary angiography

	Urapidil (n□27)	Control (n□27)	*P*
Target vessel (%)			
LAD	15 (56)	13 (49)	0.83
LCX	3 (11)	3 (11)	1.00
RCA	9 (33)	11 (39)	0.86
Number of stents used (%)	26 (96)	25 (93)	0.23
Before PCI			
RD□mm□	2.62±0.48	2.81±0.49	0.76
MLD□mm□	0.44±0.32	0.45±0.31	0.89
DS□□□	83.7±13.3	82.1±15.7	0.91
After PCI			
RD□mm□	3.22±0.33	3.10±0.30	0.84
MLD□mm□	2.46±0.46	2.52±0.54	0.78
DS□□□	13.2±0.20	12.8±0.24	0.73
TIMI flow (%) before PCI			0.45
Grade 0/1	22 (81)	22 (81)	
Grade 2	2 (7)	1 (4)	
Grade 3	3 (11)	4 (15)	
TIMI flow (%) after PCI			0.37
Grade 0/1	0 (0)	0 (0)	
Grade 2	1 (4)	0 (0)	
Grade 3	26 (96)	27 (100)	

LAD: left anterior descending, LCX: left circumflex, RCA: right coronary artery, RD: reference artery diameter, MLD: minimum luminal diameter, DS: diameter stenosis.

Table 4. Reperfusion after PCI and urapidil administration

	Urapadil (n□27)	Control (n□27)	*P*
cTFC before PCI	85.0±32.1	85.6±31.0	0.95
cTFC after PCI	18.4±3.3	21.4±4.3	0.01
MBG (%) before PCI			
Grade 0/1	24 (89)	23 (85)	
Grade 2	2 (7)	2 (7)	
Grade 3	1 (4)	2 (7)	
MBG (%) after PCI			0.04
Grade 0/1	1 (4)	2 (7)	
Grade 2	3 (11)	9 (33)	
Grade 3	23 (85)	16 (59)	

cT

FC: corrected TIMI frame count, MBG: myocardial blush grade

Table 5. Logistic regression analysis of factors associated with post-PCI cTFc

	Regression coefficient	P
Urapidil	0.360	0.001
cTFC before PCI	0.353	0.002
Duration of chest pain (hours)	0.318	0.004
Sex	0.256	0.018

Table 6. ST resolution, left ventricular function and myocardial biomarkers

	Uradipil (n□27)	Control (n□27)	P
STR > 50% in 90 min (%)	25 (93)	19 (70)	0.038
Peak CK-MB (U/L)	1269.9±515.8	1895.3±1239.0	0.021
Peak cTnT (ng/mL)	3.64±2.35	5.81±5.27	0.050
CRP (mg/L)	3.47±3.53	4.10±3.28	0.498
24h LVEF	0.55±0.05	0.52±0.06	0.021
30d LVEF	0.58±0.06	0.54±0.06	0.041

CRP: C reactive protein.

Table 7. Changes in nitric oxide (μmmol/L) after PCI.

	Urapidil (n□5□	Control (n□5)	P
Before PCI			
Aorta	40.66±5.78	41.99±7.38	0.759
Coronary sinus	135.57±6.89	136.91±15.16	0.864
After PCI			
Aorta	55.74±10.78	42.83±9.79	0.083
Coronary sinus	241.13±21.99	188.47±14.14	0.003
Differences before and after PCI			
Aorta	15.08±7.32*	1.16±1.01	0.001
Coronary sinus	105.56±16.65*	51.56±14.43*	0.001

*, *P*=0.001 compared with the pre-PCI level within the same group.

Table 8. Changes in endothelin-1 (pg/mL) after PCI

	Urapidil (n□5□	Control (n□5)	P
Before PCI			
Aorta	82.48±2.08	83.58±7.71	0.766
Coronary sinus	158.36±8.70	157.56±6.38	0.872
After PCI			
Aorta	81.14±5.54	81.42±9.12	0.955
Coronary sinus	164.98±7.11	183.48±7.41	0.004
Differences before and after PCI			
Aorta	1.34±0.76	2.16±0.98	0.131
Coronary sinus	6.62±2.17	25.92±4.36*	0.001

*, *P*=0.001 compared with the pre-PCI level within the same group.