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Effect of β-blocker atenolol on spatial dispersion of ventricular repolarization of sheep following acute myocardial ischemia

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KEY WORDS heart ventricle; electrocardiography; myocardial ischemia; sheep; atenolol

ABSTRACT

AIM: To investigate the effect of β-blockers on spatial dispersion of ventricular repolarization following acute myocardial ischemia. **METHODS**: Twenty sheep were randomized into control (normal saline, iv) and atenolol (1.5 mg/kg, iv) group. Acute myocardial ischemia was induced by occlusion of the obtuse marginal coronary artery. Unipolar ECG was simultaneously acquired from 64 epicardial sites in both ischemic and non-ischemic regions. Activation-recovery intervals (ARI), an index of ventricular repolarization, was determined from the epicardial ECG. The difference between the longest and shortest ARI was defined as ARI dispersion. **RESULTS**: Ischemic zone in atenolol group was less than that of control group (13 % ± 2 % *vs* 19 % ± 3 %, $P = 0.04$). In the control group, pooled ARI dispersion was increased by (18 ± 21), (27 ± 21), and (16 ± 10) ms at 30, 60, and 90 min of coronary artery occlusion respectively ($P < 0.01$), whereas in the atenolol group, ARI dispersion was only increased by (6 ± 4), (6 ± 7), and (2 ± 7) ms respectively ($P > 0.05$). **CONCLUSION**: These findings indicate that atenolol suppresses ischemia-induced increase in spatial dispersion of ventricular repolarization, which may explain the antiarrhythmic effect of β-blockers.

INTRODUCTION

Early treatment with atenolol, a cardiac selective β-blocker, reduces mortality in patients with acute myocardial infarction[1]. Pretreatment with atenolol also prevents ischemia- and reperfusion-induced ventricular fibrillation in conscious rats[2], and attenuates ventricular fibrillation threshold reduction in sheep with acute myocardial ischemia[3]. Although the antiarrhythmic effect of atenolol has been attributed to its anti-ischemic and/or sympathomilytic action[4], the precise mechanism of action is still poorly understood.

The difference in the duration of ventricular repolarization between different areas of the myocardium, or repolarization dispersion, is an important cause of ventricular arrhythmias, largely because repolarization dispersion facilitates the formation of reentry, a leading mechanism of ventricular tachycardia or fibrillation. Myocardial ischemia aggravates spatial dispersion of ventricular repolarization, which in turn triggers the occurrence of ventricular arrhythmias[5]. Sympathetic activation also increases spatial dispersion of ventricular repolarisation particularly after myocardial ischemia or infarction[6,7]. Increased sympathetic activity in combination with acute myocardial ischemia or infarction is associated with a high incidence of ventricular arrhythmias[8,9]. In patients with a three-month history of myocardial infarction, atenolol appears to decrease QT dispersion[10], the difference between the longest and the shortest QT intervals measured from 12-lead body surface ECG. Depressed QT dispersion following atenolol administration may be responsible for its antiarrhythmic effects. QT interval on body surface ECG, however, is an indirect measurement of ventricular repolarization and it often underestimates the repolarization dispersion in normal myocardium[11]. The purpose of the study is to investigate the effect of atenolol on the spatial dispersion of ventricular repolarization measured directly from an acute ischemic heart.

MATERIALS AND METHODS

Surgical preparation The surgical preparation of this animal model has been previously reported[3]. Briefly, 20 sheep (23 - 32 kg) were randomized into control (normal saline, iv) and atenolol (1.5 mg/kg, iv) group. Under general anesthesia (sodium

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pentobarbital 30 mg/kg, iv), animals were intubated and artificially ventilated with room air at a ventilation rate of 15 – 18 strokes/min. A left thoracotomy was performed from the 4th intercostal space; uhe obtuse marginal branch of left circumflex coronary artery was isolated.

Fifteen minutes after normal saline or atenolol administration, the obtuse coronary artery was ligated to induce transmural ischemia, which was demonstrated by ST segment elevation on body surface ECG. The left ventricular pressure and surface ECG leads Ⅱ, Ⅲ, and aVF were continuously monitored during the experiments. At the end of each experiment, heart was removed and the obtuse coronary artery was cannulated. A patent blue dye (3 – 4 mL) was injected into the artery and the ischemic area was clearly marked. The size of the ischemic area was expressed a percentage of total left ventricular mass.

Epicardial ECG acquisition and analysis A 64-channel electrode array was attached to the left and right ventricular epicardium covering both ischemic and non-ischemic areas. Sixty-four unipolar ECG were recorded with the same electrodes at 30, 60, and 90 min of coronary artery occlusion. These ECG were also acquired before and after each drug or normal saline administration.

We have previously reported the methodology of activation-recovery intervals (ARI) measurement from epicardial ECG[11]. In brief, the time difference between the most rapid decrease in voltage in the QRS complex (dV/dt_{min}) (activation time) and the most rapid increase (dV/dt_{max}) near the peak of the T wave (repolarization time) was defined as ARI. ARI reflects the action potential duration of myocytes and is generally not affected by heart rate[12,13].

In each animal, the spatial dispersion of ARI was defined as the difference between the maximum and the minimum ARI from 64 epicardial sites.

Statistics Data were expressed as $\bar{x} \pm s$. The average ARI before and after coronary artery occlusion was determined in each animal. ARI and its spatial dispersion in the 10 animals of each group were pooled. Comparisons of heart rate, ventricular pressure, ARI, and ARI dispersion within or between groups were done by an ANOVA test. $P < 0.05$ was considered to be statistically significant.

RESULTS

Transmural ischemia was induced in all animals. No spontaneous, sustained ventricular tachycardia or fibrillation was observed after coronary artery occlusion. Infrequent ventricular ectopics (less than 3 beats/min) occurred in 6 control animals and 4 atenolol-treated animals within 90 min after coronary artery occlusion. Pretreatment with atenolol reduced heart rate and ventricular systolic pressure (Tab 1). The average ischemic zone in the atenolol group 13 % ± 2 % was less than that of the control (19 % ± 4 %, $P = 0.04$).

Effect of atenolol on ARI The pooled ARI from 10 animals of each group was slightly reduced following coronary artery occlusion (Tab 1). The pooled ARI between the control and atenolol group before and after coronary artery occlusion was not statistically significant ($P = 0.13$ and 0.16, respectively).

Effect of atenolol on ARI dispersion There was no significant difference in ARI dispersion between the two groups before coronary artery occlusion [atenolol *vs* control group, (27 ± 9) *vs* (28 ± 10) ms, $P = 0.10$]. ARI dispersion was significantly increased in the control group at 60 and 90 min of coronary artery occlusion (Fig 1, $P < 0.05$). The increase in ARI dispersion was not statistically significant in the atenolol-treated group (Fig 1, $P > 0.05$).

The increase in ARI dispersion in the control group was greater than that of the atenolol group at 30, 60, and 90 min after coronary artery occlusion (Fig 1, $P < 0.01$).

Tab 1. Haemodynamics and ARI in control and atenolol group before and 90 min after coronary occlusion. $n = 10$. $\bar{x} \pm s$. $^bP < 0.05$ *vs* control.

	LVP/mmHg		HR/min^{-1}		ARI/ms	
	Before	After	Before	After	Before	After
Control	106 ± 6	101 ± 11	119 ± 12	123 ± 23	254 ± 22	236 ± 31
Atenolol	104 ± 9	92 ± 5^b	117 ± 16	98 ± 17^b	260 ± 29	246 ± 44

LVP: left ventricular systolic pressure; HR: heart rate.

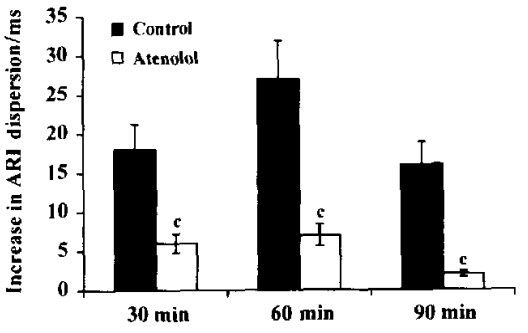

Fig 1. Effect of atenolol on increase in ARI dispersion at 30, 60, and 90 min of coronary artery occlusion. $n=10$. $\bar{x}\pm s$. $^cP<0.01$ *vs* control.

DISCUSSION

This study demonstrates that acute myocardial ischemia increases spatial dispersion of ventricular repolarization. It also shows that atenolol, when administered 15 min before coronary artery occlusion, suppresses the increase in repolarization dispersion between the ischemic and non-ischemic regions. The evaluation of spatial dispersion of ventricular recovery time, or the duration of ventricular repolarization, has been a challenge methodologically. The prerequisite of measuring spatial dispersion of ventricular repolarization is a simultaneous recording of unipolar or bipolar ECG from multiple ventricular sites of ischemic and non-ischemic regions, which is difficult to achieve with conventional ECG acquisition techniques. The mean ventricular fibrillation intervals, which can be assessed with multiple electrodes attached to the epicardium, have been used for such a purpose in non-ischemic myocardium[14]. However, the validity of such a method in evaluating ventricular repolarization and its spatial dispersion in ischemic myocardium remains to be seen. Although QT dispersion from 12-lead body surface ECG, a relatively non-invasive and more convenient method, has been widely used in animal and human studies[15], its value in estimating actual ventricular repolarization dispersion is uncertain. Indeed, QT dispersion on body surface ECG often underestimates the actual repolarization heterogeneity or dispersion in non-ischemic myocardium or during enhanced intracoronary perfusion in sheep[11].

In this study, 64-channel ECG were simultaneously acquired with the same electrodes from the sheep epicardium before and after coronary artery occlusion. ARI on these ECG was used as an index of ventricular recovery time, or repolarization, because ARI from the epicardial ECG has been shown to have an excellent correlation with action potential duration of individual myocytes of both normal and ischemic myocardium[12,13]. Thus, ARI is a preferred parameter to other methods in assessing the effect of acute myocardial ischemia or antiarrhythmic drugs on repolarization dispersion.

The limitation of the study is that although atenolol reduces ischemia-induced increase in ARI dispersion, it is not clear whether this beneficial electrophysiologic action of atenolol is associated with any antiarrhythmic effect. Occlusion of the obtuse branch of left circumflex coronary artery creates a small-sized ischemic area at the lateral part of left ventricular wall, and is associated with only occasional ventricular ectopic beats even without pharmacological intervention. Because the incidence of ventricular arrhythmias is closely related to the extent of myocardial ischemia, a larger coronary artery, such as the proximal part of left circumflex or left descending artery, may need to be occluded to induce ventricular tachycardia or fibrillation in order to evaluate the actions of atenolol on ischemic or reperfusion arrhythmias.

In conclusion, our study has demonstrated that acute myocardial ischemia increases spatial dispersion of ventricular repolarization, a well-known mechanism of ventricular arrhythmias. Pretreatment with a cardiac-selective β-blocker atenolol significantly diminishes the ischemia-induced increase in ventricular repolarization dispersion, which is accompanied by a reduction in the extent of ischemic damages to the myocardium following coronary artery occlusion. These novel findings may explain, at least in part, the antiarrhythmic actions of atenolol observed in the previous experimental studies and clinical trials.

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β阻滞剂阿替洛尔对绵羊急性心肌缺血后心室复极化离散度的影响

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关键词 心室；心电描记术；心肌缺血；绵羊；阿替洛尔

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