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Short communication

ELECTROPHYSIOLOGIC EFFECTS OF PRAZOSIN DURING ACUTE MYOCARDIAL ISCHEMIA *

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Prazosin, 100 μg/kg, had no effect on baseline refractoriness or intraventricular conduction in anesthetized dogs. During 1 h of coronary artery occlusion followed by reperfusion, prazosin significantly blunted the shortening of the ventricular effective refractory periods within ischemic myocardial region relative to vehicle-treated animals. Prazosin treatment also prevented the delayed conduction of paced ventricular complexes entering and exiting the ischemic zone. These effects may be associated with the blockade of α_1-adrenoceptor activation during the acute phase of myocardial ischemia.

Myocardial ischemia Reperfusion α_1-Adrenoceptor Arrhythmia Prazosin

1. Introduction

The early phase of acute coronary artery occlusion is accompanied by progressive conduction delay and alterations in ventricular refractoriness within the ischemic zone. These evolving abnormalities precede, and critically influence, the subsequent appearance of ventricular fibrillation (VF) (Russell and Oliver, 1978; Fujimoto et al., 1981; Elharrar and Zipes, 1982).

Recent data suggest that α_1-adrenoceptor stimulation of the ischemic myocardium may play an important role in mediating these electrophysiologic events. While the effects of α_1-adrenoceptor stimulation appear to be minor under most physiologic conditions, increases in α_1-adrenoceptor density specific to the ischemic zone have been demonstrated early after coronary occlusion (Corr et al., 1981). Prazosin, a specific α_1-adrenoceptor antagonist, has been reported to have an antifibrillatory effect during coronary artery occlusion and reperfusion in anesthetized cats (Sheridan et al., 1980) and dogs (Benfey et al., 1984). We examined the influence of prazosin on alterations in conduction and refractoriness during acute ischemia and subsequent reperfusion in an anesthetized canine model.

2. Materials and methods

2.1. Surgical preparation

Male mongrel dogs, 12-17 kg, were anesthetized with 0.7 ml/kg of Dial-urethane solution, incubated and ventilated on room air. Left common carotid and left external jugular cannulas were inserted for the monitoring of arterial pressure and the administration of drugs. The heart was exposed, and two diagonal branches of the left

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anterior descending coronary artery were isolated 2-3 mm from their origins. Polyurethane ligatures were placed loosely around each vessel. All visible collaterals to both vessels were ligated. Two sets of quadripolar plunge electrodes (Teflon coated 30 gauge silver wire with distal 1 mm tip exposed, 2 mm separation between each pole) were inserted at a depth of 4-5 mm, one each into the center of the zone to be made ischemic (IZ), and into the normal myocardium (NZ) 3 cm from the IZ. One bipole in each zone was connected to a Grass S88 stimulator through a constant current stimulus isolation unit for the introduction of extrastimuli. Outputs from the second bipole in each zone were filtered at 50-500 Hz and displayed on a storage oscilloscope simultaneously with the lead II surface electrocardiogram. The sinus node was crushed, and atrial pacing was performed at a constant cycle length of 400 ms throughout the study.

2.2. Measurement techniques

Excitation thresholds were determined in each zone by the introduction of extrastimuli (4 ms pulse width) of progressively increasing intensity (0.01 mA increments) every sixth beat at a constant coupling interval of 300 ms. The effective refractory period (to the nearest 1 ms) of each zone was determined by the extrastimulus technique, using a stimulus intensity of twice local diastolic threshold. Brief ventricular pacing at a cycle length of 300 ms from each zone was performed. Conduction time was measured from the stimulus artifact recorded in the paced zone to the first rapid deflection of the bipolar electrogram recorded in the distant zone. Determinations from the 10th to 15th paced beat were averaged and expressed as entrance conduction (time to local activation of IZ from pacing in NZ) and exit conduction time (time to local activation of NZ from pacing in IZ).

2.3. Experimental design

After pretreatment recordings, animals were randomized to receive 100 μg/kg of intravenous (i.v.) prazosin, or an equivalent volume of vehicle. In preliminary experiments, this dose of prazosin produced near maximal inhibition of the pressor response to α_1-adrenoceptor stimuli (10 μg/kg i.v. phenylephrine, and the electrical stimulation of distal thoracic sympathetic chain).

Thirty minutes after treatment, electrophysiologic measurements were repeated. Both diagonal arteries then were occluded for 1 h, followed by 1 h of reperfusion. Serial determinations of excitation thresholds, refractoriness and conduction were made in each zone at 10 min intervals. Ventricular extrastimuli were delivered at twice the excitation threshold determined for the particular time and zone of stimulation. At the end of the experiment both vessels were re-occluded. Four milliliters of fluoroscein dye was injected rapidly into the left atrium, and the heart was fibrillated by high intensity electrical stimulation. The heart was removed and sectioned transversely into 5 mm slices and examined under ultraviolet light. The sharply delineated area of absent fluorescence, corresponding to the hypoperfused zone, was quantitated gravimetrically and expressed as a percentage of the total left ventricular mass.

2.4. Statistical analysis

Data are expressed as means $\pm$ S.E. Changes in each electrophysiologic variable were examined using a factorial analysis of variance incorporating treatment, zone of measurement, and time from onset of occlusion. To minimize the influence of baseline variability between animals, baseline determinations were included in the analysis as a covariate (ANCOVA).

3. Results

Pretreatment excitation thresholds, refractory periods and conduction times were similar in animals treated with prazosin, 100 μg/kg ($n = 5$) and those treated with vehicle ($n = 5$). No significant changes in these variables were observed after treatment with either prazosin or vehicle before coronary artery occlusion.

In vehicle-treated animals, the IZ refractory period shortened by 30% within the first 30 min of coronary artery occlusion, followed by a slight

prolongation, despite persisting ischemia (fig. 1A). After reperfusion, there was a progressive lengthening of the IZ refractory period (from 130 to 226 ms), to values that exceeded baseline determinations. In contrast, pretreatment with prazosin blunted the initial post occlusion shortening of the IZ refractory period (mean 9% decrease), and attenuated the overshoot prolongation of refractoriness during reperfusion (fig. 1B). In both treatment groups, NZ refractory periods did not vary from the baseline values during the periods of occlusion and reperfusion. The influence of treatment on alterations in ischemic zone refractoriness over time was highly significant ($P < 0.0001$, ANCOVA). Excitation thresholds in the ischemic zone of vehicle-treated animals tended to increase over time during both occlusion and reperfusion, but the observed change was not statistically significant ($P = 0.37$, ANCOVA).

Both entrance and exit conduction times of paced ventricular complexes lengthened after coronary artery occlusion (fig. 2). Significantly greater conduction delay in both directions developed in vehicle-treated animals compared to those treated with prazosin ($P = 0.02$, ANCOVA). Conduction velocity tended to improve toward baseline values after reperfusion.

There was a slight decline in the mean arterial pressure after treatment with prazosin (from 108 $\pm$ 4 to 101 $\pm$ 6 mm Hg), but there were no significant differences between the two treatment groups at any point during the study. Two vehicle-treated animals developed VF during the study, at 35 min

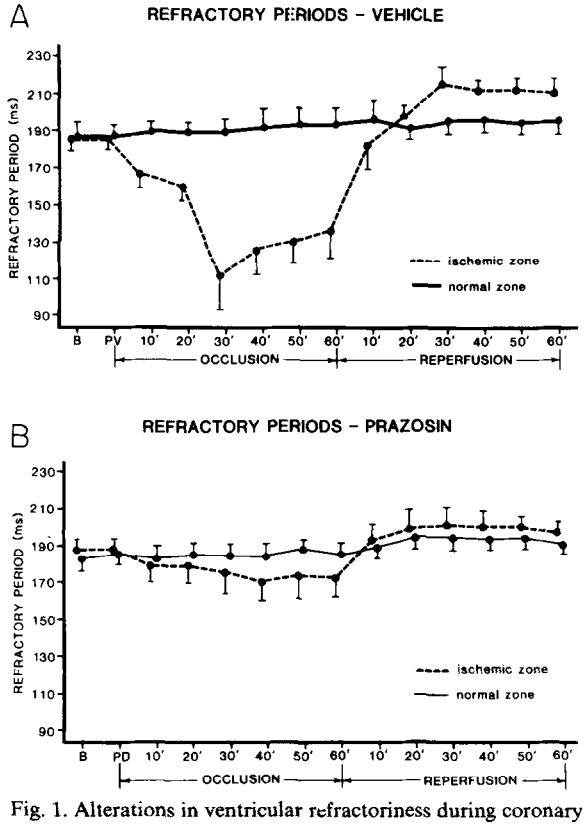

Fig. 1. Alterations in ventricular refractoriness during coronary artery occlusion and reperfusion in vehicle-treated (A), and prazosin-treated (B) anesthetized dogs. The effective refractory period in ms is represented on the abscissa. For this and the following figure, numbers on the ordinate represent time in min post occlusion and reperfusion respectively. B, baseline; PV, 30 min post vehicle administration; PD, 30 min post prazosin administration.

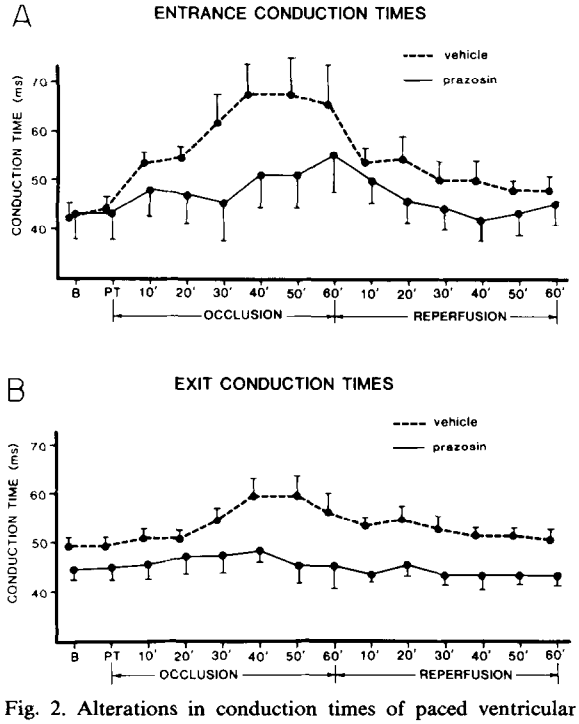

Fig. 2. Alterations in conduction times of paced ventricular complexes entering (A) and exiting (B) the ischemic zone during coronary artery occlusion and reperfusion. Conduction time in ms is represented on the abscissa. PT, 30 min post treatment.

post occlusion and at 21 min of reperfusion, respectively. These animals were defibrillated immediately. None of the prazosin-treated animals developed VF. Appropriate positioning of all electrodes was confirmed at postmortem examination. Hypoperfused zone size was similar between vehicle-treated ($9.5 \pm 0.8\%$ left ventricular mass) and prazosin-treated ($10.6 \pm 1.0\%$ left ventricular mass) animals.

4. Discussion

In this study, coronary artery occlusion in untreated animals was followed by a shortening of the effective refractory period in the ischemic myocardium and a progressive delay in the conduction time of paced ventricular complexes entering and exiting the ischemic zone. These observations agree with those of previous investigators using similar techniques (Russell and Oliver, 1978; Fujimoto et al., 1981; Elharrar and Zipes, 1982). Pretreatment with prazosin significantly blunted these evolving electrophysiologic changes during acute ischemia and, in addition, abolished the excessive prolongation in the ischemic zone refractoriness upon reperfusion. The effects of prazosin were specific for the ischemic myocardium. Refractoriness in normal myocardium as well as the conduction time of paced ventricular complexes were not influenced by prazosin.

In normal superfused rabbit Purkinje fiber and papillary muscle preparations, α_1-adrenoceptor stimulation has been shown to prolong the action potential duration (Dukes and Vaughan Williams, 1984a). In similar preparations, prazosin also prolongs the action potential duration and, in addition, depresses maximal upstroke velocity in a dose-dependent manner (Dukes and Vaughan Williams, 1984b). These observations challenge the role of α_1-adrenoceptor stimulation in producing the electrophysiologic abnormalities accompanying acute ischemia, and suggest that the protective effect of prazosin may be mediated by direct electrophysiologic actions.

However, it is uncertain that observations in isolated superfused non-ischemic tissues pertain to conditions during myocardial ischemia. In guinea-pig isolated hearts depleted of catecholamines, there was a blunting of the shortening of the action potential duration and effective refractory period during global myocardial ischemia, and a reduced incidence of VF during both coronary occlusion and reperfusion (Sheridan and Culling, 1985). These effects were mimicked by both the non-specific α-receptor antagonist, phentolamine, and the α_1-adrenoceptor antagonist, indoramin. The addition of phentolamine to catecholamine-depleted hearts had no further influence on the action potential duration or refractoriness. The addition of the α_1-adrenoceptor agonist, methoxamine, to catecholamine-depleted hearts reversed the protective effects of catecholamine depletion. These findings suggest that ischemia-related shortening of ventricular refractoriness is mediated at least in part by α_1-adrenoceptor activation, and that the attenuation of the electrophysiologic consequences of ischemia by the α_1-adrenoceptor antagonist is mediated via adrenergic rather than direct myocardial electrophysiologic effects. As in the present study, the addition of α_1-adrenoceptor antagonists to non-ischemic, non-catecholamine-depleted preparations resulted in relatively slight electrophysiologic changes (Sheridan and Culling, 1985). The apparent conflict in the results regarding the direct electrophysiologic actions of prazosin between the in vitro assessments of Dukes and Vaughan Williams (1984b) and the present in vivo study may be due to many factors. Empirically, assessment of the electrophysiologic actions of prazosin in isolated tissue preparations provides the most controlled determination of direct drug action, while the in vivo assessment in the present report constitutes a determination of direct drug action as well as the influence of potential reflex actions. Alternatively, the results of Sheridan and Culling (1985) and those of the present studies may reflect the ability of prazosin to attenuate electrophysiologic changes that evolve during acute ischemic injury in the heart at concentrations below that required to produce direct electrophysiologic actions in non-ischemic tissue.

During the early phases of acute myocardial ischemia, tissue catecholamine release with intense adrenergic stimulation of ischemic myocardium

has been proposed to play an important role in the genesis of abnormal cellular electrical activity and ultimately arrhythmias (Riemersma, 1982). The present in vivo findings, in conjunction with the in vitro data of Sheridan and Culling (1985) indicate that the emergence of serious conduction delays and alterations in refractoriness within acutely ischemic myocardium are mediated, at least in part, by α_1-adrenoceptor activation. An attenuation of such electrophysiologic aberrations by α_1-adrenoceptor antagonists such as prazosin may be responsible for the observed antifibrillatory effects of this class of drugs during coronary artery occlusion and reperfusion.

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