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Protective Effect of Prenylamine Against Vulnerability to Ventricular Fibrillation in the Normal and Ischemic Canine Myocardium[1] (40489)

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It has long been established that acute coronary artery occlusion may precipitate ventricular fibrillation (VF). In 1935, Tennant and Wiggers (1) demonstrated that VF can also result from reperfusion after removal of the obstructing coronary artery ligature. Numerous other investigators have confirmed the occurrence of VF upon release of coronary artery obstruction after only transient cessation of flow (2, 3). The electrocardiographic changes preceding VF as well as the time course in onset of arrhythmia differ during occlusion and release (4). A difference is also demonstrable in the prophylactic effectiveness of antiarrhythmic drugs. While VF following occlusion can be readily prevented, none of the commonly used antiarrhythmic agents have proved effective in protecting against VF following reperfusion (4, 5).

Antiarrhythmic agents are generally tested during acute myocardial ischemia which follows coronary artery narrowing or obstruction. The prevailing view has been that malignant ventricular arrhythmias result from impaired myocardial perfusion. But there is reason to surmise that in man sudden cardiac death may be related as well to reinstitution of flow following release of coronary artery spasm or upon platelet disaggregation (6, 7). We have therefore studied during both occlusion and release of the left anterior descending coronary artery the antiarrhythmic action of Prenylamine (Fig. 1)—a drug with antianginal, coronary dilating and antiarrhythmic properties (9–12).

Material and methods. General. These investigations involved 14 healthy mongrel dogs of either sex ranging in weight between 13 and 22 kg. Three days prior to the definite testing, a balloon occluder was placed around the left anterior descending coronary artery (4). The inflation tube of the balloon catheter was exteriorized at the nape of the neck. On the day of testing the animals were anesthetized with intravenous α-chloralose (100 mg/kg) and additional doses of 50 mg/kg were administered as needed. Ventilation was maintained with a mixture of room air and oxygen via a cuffed endotracheal tube attached to a Harvard pump. Arterial pH and pO_2 were kept in a range of 7.35–7.45 and 80–120 mmHg, respectively. Right femoral artery and vein were cannulated for blood sampling, arterial pressure monitoring and drug administration. A tripolar catheter unit, as previously described (8), was placed at the right ventricular apex for pacing and for delivering test stimuli.

Cardiac testing. Ventricular pacing maintained heart rate constant at 200 bpm. VF thresholds were determined by delivering a train of stimuli (100 Hz, 2 msec constant current cathodal pulses) as described by Han (13). In our experiments, the train was initiated 80 msec after the pacing spike and spanned the vulnerable period of the cardiac cycle. Two determinations of VF threshold were carried out prior to an experimental intervention. Thresholds were assessed by increasing the intensity of test stimuli by increments of 2 ma from an initial value of 2 ma until VF supervened. The minimal current

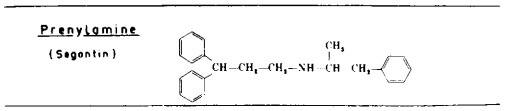

FIG. 1. Molecular structure of Prenylamine (Segontin).

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which induced VF defined the fibrillation threshold. Defibrillation was accomplished usually within 3 sec by a DC—50 to 100 wsec capacitor discharge from a Lown cardioverter. Defibrillation with these low energy levels delivered transthoracically does not significantly affect the stability of the VF threshold (8).

The experimental protocol involved complete occlusion of the left anterior descending artery for 10 min accomplished by inflating the previously implanted balloon catheter. VF threshold was assessed 3 min after inflation, at a time when the threshold is most depressed (8). The balloon was abruptly deflated at 10 min and cardiac testing was immediately repeated to establish the VF threshold during reperfusion.

Two occlusions were carried out in 14 dogs. In 8 animals, the first coronary artery occlusion-release sequence was performed without drug administration. After a rest period of 45 min an intravenous infusion of a 50% aqueous solution of Prenylamine glučonate was instituted at a rate of 100 mcg/kg/min. The infusion was maintained for 10 minutes before the VF threshold was determined. Following a rest period of 10 min, the coronary artery was occluded, and the VF threshold was retested after 3 min of myocardial ischemia and immediately upon reperfusion. The drug was continuously infused during the occlusion-release studies.

In 6 dogs, the sequence of coronary artery occlusion with and without drug was reversed. Namely, after determination of the control VF thresholds, the first occlusion was carried out while infusing Prenylamine. After completing the occlusion-release sequence, the drug was stopped and a period of 120 min elapsed before performing the second occlusion. At this time the VF threshold had returned to the preinfusion level and the effect of occlusion and release could be studied in the absence of drug effect on vulnerability.

Data were analyzed for statistical significance using Student's t test. All data were expressed as mean ± SEM.

Results. I. *Influence of Prenylamine on heart rate, arterial blood pressure, and VF threshold in nonischemic myocardium.* In the nonischemic heart, infusion of Prenylamine did not significantly alter intrinsic heart rate or mean arterial blood pressure (Fig. 2). During administration of the drug the VF threshold increased from 24 ± 2 to 32 ± 3 ma ($p < 0.0015$).

II. *Influence of Prenylamine on VF threshold of ischemic and reperfused myocardium.* After 3 min of coronary artery occlusion the VF threshold decreased from 24 ± 2 to 10 ± 2 ma ($p < 0.0001$). There was an even more striking reduction immediately upon release of coronary artery obstruction. The VF threshold reached a leved of 5 ± 1 ma ($p < 0.0001$). Infusion of Prenylamine significantly diminished reduction in fibrillation thresholds during both coronary artery occlusion and release-reperfusion (Fig. 3). Thus after administration of the drug the VF threshold was 14 ± 2 ma during occlusion and 11 ± 2 ma following release ($p < 0.0015$, when compared to corresponding values obtained without the drug). These effects on VF threshold occurred without any significant changes in heart rate or mean arterial blood pressure.

Discussion. We have found that Prenylamine administration significantly decreases susceptibility to VF in the normal canine heart as well as in the ischemic and reperfused

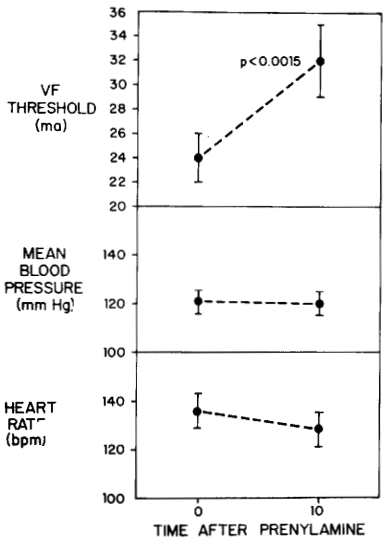

FIG. 2. Effect of intravenous Prenylamine (100 mcg/kg/min) on ventricular fibrillation (VF) threshold, mean arterial blood pressure and heart rate in the nonischemic heart. Within 10 min of Prenylamine infusion VF threshold is substantially increased but heart rate and mean arterial blood pressure remain unaltered. Values are expressed as mean ± SEM.

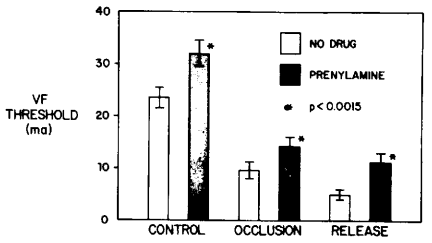

FIG. 3. Influence of Prenylamine on VF threshold during coronary artery occlusion and release-reperfusion. Prenylamine significantly reduced the decrease in threshold during both coronary artery occlusion and release.

myocardium. The beneficial effect of the drug on vulnerability during release-reperfusion is particularly noteworthy since commonly employed antiarrhythmic agents have proved ineffective in preventing VF following sudden reinstitution of coronary flow (4, 5). When Prenylamine is administered intravenously it has been reported to promote slow channel blocking, exert local anesthetic effects and induce coronary artery vasodilatation (9, 10).

Electrophysiologic properties of Prenylamine. The drug's effect on the electrophysiologic properties of the heart have been recently characterized (11, 12). In isolated cardiac tissue, Prenylamine slows the rate of rise of the action potential, prolongs the action potential and refractory period durations, and depresses pacemaker activity (11). Using voltage clamp techniques, Haas and coworkers (12) have shown that in the frog atrial fibers prenylamine ($1.7–2.5 \times 10^{-5} M$) depressed the peak transient sodium conductance and slowed recovery from sodium activation upon repolarization. The drug also depressed the slow inward current carried by calcium and/or sodium ions and the steady-state outward current. Prenylamine is believed to exert local anesthetic effects on isolated nerve tissue (9).

Mechanism of Prenylamine's protective effect on vulnerability in nonischemic myocardium. The present study does not shed light on the precise electrophysiologic mechanisms whereby the drug increases the ventricular fibrillation threshold. Available evidence suggests that the slow channel blocking effect of Prenylamine probably does not account for the increases in VF threshold in nonischemic myocardium because the potent slow channel blocker, verapamil, does not alter fibrillation thresholds in the normal canine heart (14, 15). This is the case irrespective of whether the single stimulus (14) or train of stimuli method (15) is used to assess the influence of verapamil on cardiac vulnerability.

It remains to be established whether or not local anesthetic effect of Prenylamine accounts for the increase in VF threshold observed in the normal heart. This possibility seems worth exploring since drugs with membrane stabilizing action such as lidocaine (16) and quinidine (17) increase fibrillation thresholds in the nonischemic canine myocardium.

Mechanism of Prenylamine's protective effect on vulnerability during myocardial ischemia and reperfusion. The exact mechanism whereby Prenylamine exerts its beneficial action on ventricular vulnerability during coronary artery occlusion and reperfusion is unknown. It is likely, however, that both direct myocardial (11, 12) and indirect coronary vasodilatating (10) effects of the drug may play a role. The latter action would be expected to improve coronary arterial perfusion and decrease the zone of myocardial ischemia. Such coronary dilatation has been implicated as the mechanism for the reduction by nitroglycerin of cardiac vulnerability to VF during acute coronary occlusion (18).

Precipitation of VF during sudden release-reperfusion has been attributed to washout products of cellular ischemia (19). The accumulation of such products would be diminished by the vasodilatory action of Prenylamine through improved perfusion and decreased myocardial ischemia. Consequently, a reduced amount of washout products would be released upon reinstitution of coronary flow and VF would be less likely to occur. This suggestion is supported by the recent observation of Stockman *et al.* (20) that administration of nitroglycerin affords significant protection against VF during reperfusion.

Summary. Obstruction and reestablishment of coronary artery flow both markedly lower the threshold for ventricular fibrillation (VF). This reduction in threshold is partially reversed by infusion of Prenylamine, a drug with slow channel blocking and coronary artery vasodilating properties. Mean blood

pressure and heart rate were unaltered. Prenylamine administration also elevated the VF threshold in the nonischemic myocardium. Its effect on reperfusion VF threshold is unique, since commonly used antiarrhythmic drugs exert no such effect.

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