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Chloroethylclonidine increases the incidence of lethal arrhythmias during coronary occlusion in anesthetized dogs

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Abstract

We studied the role of α_1-adrenoceptors in the modulation of ventricular tachycardia and fibrillation in chloralose-anesthetized dogs subjected to 30 min left anterior descending coronary artery occlusion. Study groups were control, and those treated with the α_1-adrenoceptor-subtype blockers WB4101 (0.5 mg/kg i.v.) or chloroethylclonidine (1.9 mg/kg i.v.). For the first set of experiments all animals were in sinus rhythm and heart rate was slower in the chloroethylclonidine-pretreated animals than the WB4101-treated group ($P < 0.05$). During occlusion, ventricular tachycardia and ventricular fibrillation incidence did not differ among control, WB4101 or chloroethylclonidine (3 dogs with ventricular fibrillation in each group and 0, 2 and 3 dogs respectively with ventricular tachycardia), but ventricular premature depolarizations were significantly reduced by both interventions, and nonsustained ventricular tachycardia was suppressed by WB4101. In a second set of experiments, animals were atrially paced at a cycle length of 300 ms, and divided into control, WB4101-treated or chloroethylclonidine-treated, as above. Here, 9/10 chloroethylclonidine-treated animals developed ventricular tachycardia and fibrillation during occlusion, whereas only 4/10 controls and 4/10 WB4101-treated animals did so ($P < 0.05$). In conclusion, during sinus rhythm, both types of α_1-adrenoceptor subtype blockade significantly suppressed ventricular premature depolarizations and neither affected ventricular tachycardia and fibrillation. In contrast, when heart rate was held constant, chloroethylclonidine clearly enhanced the occurrence of ventricular fibrillation during occlusion. These results suggest the α_1-adrenoceptor subtype blocked by chloroethylclonidine, but not that blocked by WB4101, is capable of increasing the incidence of lethal arrhythmias that occur at rapid atrial rates during ischemia.

Keywords: Myocardial ischemia; Ventricular arrhythmia; α-Adrenoceptor subtype-selective blocker; Coronary occlusion; Heart rate; Arrhythmia

1. Introduction

Studies of isolated canine Purkinje fibers have permitted us to understand the receptor-effector pathways whereby α-adrenoceptor agonists modulate cardiac rhythm (Del Balzo et al., 1990; Anyukhovsky and Rosen, 1991; Anyukhovsky et al., 1992; Terzic et al., 1993). An α_1-adrenoceptor subtype blocked by chloroethylclonidine (α_{1B}) stimulates the Na^+/K^+ pump (Shah et al., 1988; Zaza et al., 1990) increasing net outward current, thereby increasing automaticity and hyperpolarizing membrane potential. In contrast, a subtype blocked by WB4101 ($\alpha_{1A,C}$) increases automaticity in ischemic Purkinje fibers (Anyukhovsky and Rosen, 1991; Anyukhovsky et al., 1992) apparently by decreasing g_K (Anyukhovsky et al., 1994). During ischemia, incidence of arrhythmias in control fibers was about 20% and this increased to 30–50% in the presence of α-adrenoceptor agonist. In fibers treated with WB4101 the incidence of arrhythmias was reduced to 0% ($P > 0.05$) and in fibers treated with chloroethylclonidine, incidence was 70–100% ($P < 0.05$) (An-

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yukhovsky and Rosen, 1991; Anyukhovsky et al., 1992; Hamra and Rosen, 1988). Hence, one might hypothesize that in the in vivo setting, α_1 contributions to arrhythmogenesis would be enhanced by chloroethylclonidine and be less affected or unaffected by WB4101.

Despite these considerations of α-adrenoceptor effects on isolated tissues, there have been few attempts to test α_1-adrenoceptor subtype specificity of arrhythmias in intact animals (Uprichard et al., 1988; Vanoli et al., 1994). With this in mind the aim of the present study was to investigate the effect of α_1-adrenoceptor subtype-specific blockade using WB4101 and chloroethylclonidine on the incidence of arrhythmias following a two-stage ligation of the canine left anterior descending coronary artery (Harris et al., 1951). In performing these experiments we were cognizant of the likelihood that most lethal arrhythmias would be reentrant (Wit and Janse, 1993), thereby differing in mechanism from those in the isolated tissue studies. However, we were aware, as well, that automatic and/or triggered impulses have been invoked as initiators of reentry during ischemia (Wit and Janse, 1993) thereby relating the mechanisms studied at the cellular level with those that are operative in vivo.

2. Materials and methods

Mongrel dogs of either sex, weighing 15–20 kg, were anesthetized with ketamine hydrochloride i.m. (Ketalar, 12-15 mg/kg, Parke-Davis, Morris Plains, NJ, USA) followed by i.v. α-chloralose (100 mg/kg, Sigma Chemicals, St. Louis, MO, USA). Additional α-chloralose was given as necessary to maintain anesthesia. Following intubation with a cuffed endotracheal tube, ventilation was maintained with a room-air volume respirator (Harvard respirator, model 607, Harvard Apparatus, Millis, MA, USA), maintaining arterial PO_2, PCO_2 and pH within physiologic limits. Left femoral arterial and venous cannulas were inserted for blood pressure monitoring and drug administration, respectively. Body temperature was maintained with a heating pad and lamp.

The heart was exposed through the left fourth or fifth intercostal space and suspended in a pericardial cradle. For experiments requiring atrial pacing (see Results) pacing was performed throughout the experiment using a bipolar electrode sutured to the right atrium and a constant current pulse generator (Bloom Assoc., Flying Hills, Reading, PA, USA).

To produce myocardial ischemia, the left anterior descending artery was occluded just after its bifurcation from the left main coronary artery proximal to all branches using a silk ligature. A two-stage coronary occlusion was achieved by tightening the ligature and achieving partial occlusion for 5 min, followed by complete occlusion for 30 min (Harris et al., 1951). The occurrence of ischemia was confirmed by the development of ST-T wave changes on the electrocardiogram and bluish discoloration of the antero-septal surface of the heart. Moreover, to ensure comparability of ischemic zone size across groups, at the end of each experiment the occluded artery was perfused with Evans blue dye (Warltier et al., 1981). The right ventricle was cut away and the region of blue discoloration was excised and weighed, as was the remaining left ventricle. Using this method, the ischemic region for experiments reported here was 30–35% of left ventricular mass, with no difference seen in animals that did/did not have lethal arrhythmias.

During the entire protocol standard electrocardiogram limb leads were recorded using an 8-channel recorder (Gould, Cleveland, OH, USA) and the following variables were measured at a paper speed of 25 mm/s: heart rate, number of episodes of nonsustained (< 30 s) and sustained (> 30 s) ventricular tachycardia, and the incidence of ventricular fibrillation. Arterial blood pressure was determined using a pressure transducer (P23-Db, Statham Instruments, Oxnard, CA, USA) that was placed at mid-thoracic level and connected to the catheter in the femoral artery.

In the initial set of experiments, 45 animals were equally divided among three groups: control dogs without drug pretreatment, one group receiving WB4101 and one receiving chloroethylclonidine prior to coronary ligation. Based on the results of the initial experiments, a second set of studies was performed in which 3 groups of dogs (10/group) were paced atrially at a cycle length of 300 ms and then randomized into control, chloroethylclonidine-treated and WB4101-treated, as described above.

2.1. Drugs

WB4101, 0.5 mg/kg, and chloroethylclonidine dihydrochloride (1.9 mg/kg) were given slowly i.v. 10–15 min prior to coronary occlusion. No arrhythmias occurred before coronary occlusion. Both drugs were purchased from Research Biochemicals, Natick, MA, USA.

2.2. Statistics

The data are expressed as mean ± standard errors of the means. Differences in the incidence of ventricular tachycardia and fibrillation were determined by Fisher's exact test (Snedecor and Cochran, 1980). Differences were considered significant at $P < 0.05$.

3. Results

We initially studied 45 dogs in sinus rhythm. WB4101 had no significant effect on heart rate, but chloroethyl-

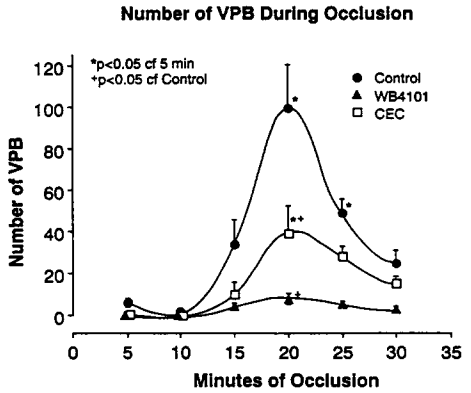

Fig. 1. Number of ventricular premature depolarizations occurring during occlusion for control animals ($n = 12$) and those treated with chloroethylclonidine ($n = 9$) or WB4101 ($n = 10$). The number of ventricular premature depolarizations in each 5-min segment was recorded for all animals that did not develop ventricular tachycardia or fibrillation during the 30-min period of occlusion. The symbols represent the means ± S.E. for the preceding 5 min.

clonidine-treated animals had a significantly slower rate than the WB4101-treated animals (Table 1A). In chloroethylclonidine-treated animals, systolic and diastolic blood pressure were significantly higher than in the control and WB4101-treated groups (Table 1A).

The occurrence of arrhythmias is detailed in Table 2. During occlusion there was no significant difference in the incidence of ventricular tachycardia or fibrillation across groups. Ventricular premature depolarizations were seen most frequently in control animals. These were suppressed by both pharmacologic interventions. The temporal occurrence of ventricular premature depolarizations during the 30 min occlusion period is detailed in Fig. 1. Note that the greatest number was seen at 15–20 min in all groups, and that pharmacological suppression of the ectopic impulses (seen more markedly with WB4101) occurred throughout the 30-min period. Nonsustained ventricular tachycardia was not seen in WB4101-treated animals (Table

Table 1
Hemodynamic variables before coronary occlusion

	n	Cycle length (ms)	Systolic blood pressure (mm Hg)	Diastolic blood pressure (mm Hg)
A. Sinus rhythm				
Control	15	377 ± 21	148 ± 5	98 ± 3
WB4101	15	302 ± 15	136 ± 5	82 ± 4 [a]
Chloroethylclonidine	15	423 ± 25 [b]	169 ± 6 [a,b]	115 ± 2 [a,b]
B. Atrial pacing				
Control	10	300	156 ± 9	97 ± 5
WB4101	10	300	126 ± 4 [a]	79 ± 3 [a]
Chloroethylclonidine	10	300	157 ± 7	107 ± 5

[a] $P < 0.05$ cf. control; [b] $P < 0.05$ cf. WB4101.

Table 2
Numbers of ventricular premature depolarizations and incidence of tachyarrhythmias during coronary occlusion (sinus rhythm)

	Sinus cycle length (ms)	VPD [d]	Non-sustained ventricular tachycardia	Ventricular tachycardia	Ventricular fibrillation
Control	377 ± 21	213 ± 32	9/12	0/15	3/15
WB4101	302 ± 15	22 ± 4 [b]	0/10 [a]	2/15	3/15
Chloroethylclonidine	423 ± 25 [c]	93 ± 16 [b]	7/ 9	3/15	3/15

[a] $P < 0.05$ cf. control; [b] $P < 0.05$ cf. control; [c] $P < 0.05$ cf. WB4101. [d] Reported for those animals surviving 30 min without ventricular tachycardia or ventricular fibrillation.

Table 3
Incidence of tachyarrhythmias during coronary occlusion (atrial pacing)

	Cycle length (ms)	n	Non-sustained ventricular tachycardia	Ventricular tachycardia	Ventricular fibrillation	Total ventricular tachycardia and ventricular fibrillation
Control	300	10	1	0	4	4
WB4101	300	10	1	0	4	4
Chloroethylclonidine	300	10	1	2	7	9 [a]

[a] $P < 0.05$ cf. WB4101 and control.

2) and occurred to an equivalent degree in the other groups.

We reasoned that these experiments might have been confounded, in part, by the variations in sinus rate, i.e., sinus cycle length was 423 ± 25 ms in the chloroethylclonidine group and 302 ± 15 ms in the WB4101 group, $P < 0.05$. In fact, the slowing of heart rate alone in the chloroethylclonidine-treated group might well have been antiarrhythmic. For this reason, we studied 30 additional animals: 10 treated with chloroethylclonidine, 10 with WB4101 and 10 controls. All were atrially paced at cycle length = 300 ms, approximating the heart rate that had occurred during WB4101 treatment of animals in sinus rhythm. Arterial pressures (Table 1B) were equivalent in the chloroethylclonidine and control groups, and lower in the WB4101 group. As shown in Table 3, this protocol resulted in a significantly greater incidence of occlusion-induced ventricular tachycardia and fibrillation following chloroethylclonidine treatment than was seen following WB4101 treatment or control. Because of the high mortality rate in the atrial pacing protocol and the resultant variability of duration of each experient (limited by onset of ventricular tachycardia and fibrillation), it was impossible to compare accurately the incidence of ventricular premature depolarizations in these animals.

4. Discussion

Four α_1-adrenoceptor subtypes have been identified (for review see Terzic et al., 1993). Chloroethylclonidine is an antagonist at the α_{1B} subtype, via irreversible blockade secondary to alkylation: WB4101, initially considered to be a competitive α_{1A} subtype blocker, was subsequently recognized to block α_{1C}-adrenoceptors, as well (Schwinn et al., 1990). More recent data have suggested the α_{1A}- and α_{1C}-adrenoceptors to be the same (Hieble et al., 1995).

Microelectrode studies of α_1 subtype blockade in canine Purkinje fibers rendered 'ischemic' with superfusates having pH = 6.8, $[K^+]_o = 10$ mM and $pO_2 < 20$ mm Hg, have shown these fibers develop abnormal automaticity in the presence of α-adrenoceptor agonists (Anyukhovsky and Rosen, 1991). This abnormal rhythm is enhanced in the presence of chloroethylclonidine and blocked by WB4101 (Anyukhovsky et al., 1992). The receptor-effector coupling pathway blocked by chloroethylclonidine incorporates signal transduction via a pertussis toxin-sensitive G protein (Del Balzo et al., 1990; Anyukhovsky and Rosen, 1991), and stimulation of the Na^+/K^+ pump (Shah et al., 1988; Zaza et al., 1990), resulting in a net outward current that hyperpolarizes the membrane and would tend to reduce automaticity. WB4101 blocks a pathway that incorporates a pertussis toxin-sensitive G protein (Del Balzo et al., 1990; Anyukhovsky and Rosen, 1991) linked to an increase in membrane resistance (Anyukhovsky et al., 1994), which is assumed to be secondary to a decrease in g_K, thereby increasing automaticity. Hence, via its inhibition of α_1 stimulation of the Na^+/K^+ pump, chloroethylclonidine would prevent the α-adrenoceptor agonist from hyperpolarizing the membrane and would promote an unopposed action of the agonist to decrease K^+ conductance and be arrhythmogenic. In contrast, by blocking the α_1 effect on K^+ conductance and by facilitating the agonist effect on the Na^+/K^+ pump, WB4101 would tend to be antiarrhythmic. These arguments have been used to explain the in vitro results concerning α-adrenergic effects on ischemic Purkinje fibers (Anyukhovsky and Rosen, 1991; Anyukhovsky et al., 1992).

In isolated Purkinje fibers studied in the absence of α-adrenoceptor agonist in a simulated ischemic environment, automatic arrhythmias occur in about 20% of preparations (Anyukhovsky and Rosen, 1991; Anyukhovsky et al., 1992, 1994; Hamra and Rosen, 1988). This incidence increases to 30–50% in the presence of α-adrenoceptor agonist. That WB4101 consistently reduces the incidence to 0 is *not* statistically significant. That chloroethylclonidine increases the incidence to 70–100% is significant ($P < 0.05$).

It is difficult to extrapolate these cellular electrophysiologic findings to our study of the ischemic heart in vivo, where the mechanisms for arrhythmogenesis are more varied and complex than in isolated tissues. That more than one mechanism may be involved is suggested by the fact that ventricular ectopic beats were suppressed by both chloroethylclonidine and WB4101 during sinus rhythm and ischemia, whereas the incidence of ventricular tachycardia/fibrillation was unaffected by WB4101 and significantly increased by chloroethylclonidine during rapid atrial pacing. Reentry is presumed to be the major cause of arrhythmias during the first 30 min after coronary ligation in vivo, although automaticity and/or triggered activity are capable of initiating sustained and/or lethal arrhythmias (see Wit and Janse, 1993, for review). Regardless of mechanism, our study indicates that when heart rate is removed as a variable (by pacing at CL = 300 ms), chloroethylclonidine has a strong arrhythmogenic potential. That WB4101 had no significant effect on pacing-induced ventricular tachycardia/fibrillation during ischemia may reflect a lack of involvement of its receptor subtype(s) in initiation of tachyarrhythmias during rapid pacing or may reflect a limitation in study design itself.

α_1-Adrenoceptor subtype actions were not systematically investigated in other studies of α-adrenoceptor blockade and it may be for this reason that mixed results have occurred. For example, Corr et al. (1981)

and Sheridan and Culling (1985) found that in the cat, α_1- and α_2-adrenoceptor blockade with phentolamine or α_1-adrenoceptor blockade with prazosin reduced lethal arrhythmias during ischemia. Using [^{3}H]prazosin as a ligand, they also found that after 30 min of ischemia there was a 2-fold increase in α-adrenoceptor number. This increase in α-adrenoceptor number has been confirmed by others in various species, including dogs (Dillon et al., 1988; Maisel et al., 1987).

Benfey et al. (1984) found that prazosin decreased the incidence of ischemia-induced ventricular premature depolarizations and ventricular fibrillation in the dog, but not the pig, and Wilber et al. (1987) using a conscious canine model of subacute infarction and acute ischemia demonstrated a protective effect of prazosin against ventricular fibrillation as well. In contrast, Bolli et al. (1984) reported that phentolamine but not prazosin reduced the incidence of ventricular premature depolarizations in ischemic canine heart, and neither intervention modified the occurrence of ventricular tachycardia and ventricular fibrillation. Hence, depending on species and protocol, it is apparent that the effect of α_1-adrenoceptor blockade to modify arrhythmias varies.

Studies of ischemic arrhythmias have been performed with abanoquil, a putative α_{1A}-adrenoceptor subtype blocker whose α_{1A}/α_{1B}-adrenoceptor selectivity is about 90:1 (the α_{1A}/α_{1B}-adrenoceptor selectivity of WB4101 is reportedly 180:1) (Greengrass et al., 1991). An α_{1C}-adrenoceptor blocking action of abanoquil has not, to our knowledge, been described. Uprichard et al. (1988) noted abanoquil decreased ventricular ectopic beats during the first 30 min after coronary stricture in halothane-anesthetized dogs. No mention is made of the occurrence of ventricular fibrillation in these animals, but it must be emphasized that the left anterior descending artery was not completely occluded (in contrast to the present study, where occlusion was complete). In a conscious canine model of chronic anterior wall myocardial infarction and lethal arrhythmia during exercise and acute circumflex ischemia, neither prazosin nor abanoquil protected against ventricular fibrillation (Vanoli et al., 1994), whereas propranolol was protective.

In contrast to the above-mentioned studies, the present report permits a direct comparison of the actions of two different α_1-adrenoceptor subtype-selective blockers. During sinus rhythm α_1-adrenoceptor subtype blockade with WB4101 was protective against nonlethal arrhythmias (i.e., ventricular premature depolarizations and nonsustained ventricular tachycardias). That chloroethylclonidine also had a salutary effect appears contradictory to the idea that different receptor subtypes might have opposite actions, until one notes that in the setting of chloroethylclonidine there were both a significant elevation of blood pressure and a significant slowing of sinus rate. It should be noted that a major heart rate reduction in its own right or modulated by an α-adrenoceptor-induced vagotonia would be protective against arrhythmias triggered by delayed afterdepolarizations and would also modify the propensity of reentrant arrhythmias that might occur at a more rapid heart rate (Wit and Janse, 1993). Hence, the antiarrhythmic effect of chloroethylclonidine might simply be attributed to a combination of slowed heart rate and vagotonia induced by the blood pressure elevation. An alternative explanation of the blood pressure elevation might be a partial agonist effect of chloroethylclonidine, which has been suggested, but not definitively tested (LeClerc et al., 1980). The actions of WB4101 are explicable based on its cellular effect, i.e., suppression of α-adrenoceptor-induced triggered and automatic arrhythmias (Molina-Viamonte et al., 1991; Anyukhovsky and Rosen, 1991). With respect to lethal arrhythmias supervening during sinus rhythm, there were no significant effects of either antagonist.

A very different result emerged when all groups were atrially paced at a cycle length of 300 ms (approximating the sinus cycle length in the WB4101 group). Here, a significantly higher incidence of ventricular tachycardia and fibrillation was seen in the chloroethylclonidine than the WB4101 or control groups. The extent to which Na^+/K^+ pump inhibition and/or facilitation of the other α-adrenoceptor subtype effector pathways contributed here is uncertain.

Hence, it appears that in the setting of anesthesia and acute coronary ligation, blockade of an α_1-adrenoceptor subtype by chloroethylclonidine is associated with a significantly greater incidence of lethal arrhythmias than in control or in the presence of WB4101. The fact that the difference in arrhythmogenic potential of the α_1-adrenoceptor subtype blockade blocked by chloroethylclonidine could only be demonstrated when heart rate was controlled emphasizes the previously held perception that the causes of arrhythmias due to occlusion are multifactorial and that the α_1-adrenoceptor contribution is a modulator rather than a prime determinant of the arrhythmias that occur.

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