Cardiovascular Drugs and Therapy 1995;9:555–563

Electropharmacology of the Bradycardic Agents Alinidine and Zatebradine (UL-FS 49) in a Conscious Canine Ventricular Arrhythmia Model of Permanent Coronary Artery Occlusion

I. Aidonidis,[1] J. Brachmann,[1] I. Rizos,[1] A. Zacharoulis,[1] I. Stavridis,[2] P. Toutouzas,[1] and W. Kübler[1]

[1]Department of Cardiology at University of Heidelberg, D-69115 Heidelberg, Germany; [2]Departments of Cardiology and Physiology at University of Athens, Athens, Greece

Summary. **Myocardial infarction was produced in 27 anesthetized dogs by ligating the left anterior descending (LAD) coronary artery proximal to the septal branch. Nineteen of these animals survived the operation and were studied by programmed stimulation in a random sequence between the third and seventh days after the infarct. Complete electrophysiologic testing was implemented in each animal prior to and after single doses of either alinidine (1 mg/kg IV) or zatebradine (0.5 mg/kg IV). Alinidine prevented reinduction of sustained ventricular tachycardia (SVT) in only 2 of 9 dogs and zatebradine in 1 of 8 dogs. The SVT cycle length was not significantly changed in all cases in which it was still inducible despite drug administration ($p > 0.05$). Alinidine lengthened the effective refractory period (ERP) in the AV node ($p < 0.01$), whereas zatebradine did not induce a statistically significant prolongation. Conversely, zatebradine increased the left ventricular ERP, while alinidine left it almost unchanged. The rate-corrected QT interval (QTc) did not significantly differ from control values after the administration of either agents. Also, the duration and the ERP of infarct-zone potentials, defined as late potentials, remained unaltered. The results indicate that the bradycardic agents alinidine and zatebradine do not exert antiarrhythmic efficacy against SVT induced during subacute myocardial infarction in conscious dogs. None of these drugs substantially changed ventricular electrophysiology or showed a drug-specific proarrhythmic effect.**

Cardiovasc Drugs Ther 1995;9:555–563

Key Words: **myocardial infarction, conscious dog, programmed stimulation, ventricular arrhythmias, alinidine, zatebradine**

Heart rate acceleration results in excessive myocardial oxygen consumption during acute myocardial infarction, thereby exaggerating myocardial ischemia and promoting arrhythmogenesis [1–6]. Hence, drugs counteracting increases in heart rate in the setting of myocardial infarction may deserve a particular place in the management of symptomatic arrhythmias, especially those exhibiting use-dependent or reverse use-dependent action. In this sense, however, it must be considered that agents producing bradycardia by blocking either the beta-adrenoceptor or the calcium inward current have been shown to exert significant negative inotropic activity in addition to their antitachycardic effect, while calcium antagonism with nifedipine has been found to facilitate the induction of ventricular tachyarrhythmias in conscious dogs with subacute myocardial infarction [7]. Under these circumstances, it is reasonable to search for bradycardic agents that should not affect ventricular electrophysiology via nonspecific ways, thereby avoiding paradoxical proarrhythmic effects.

Alinidine (2-[N-allyl-N-(2,6-dichlorophenyl)-amino]-2-imidazoline) has been suggested to decrease the incidence of ischemic ventricular fibrillation [8] by moderately decreasing positive dp/dt_{max} in dogs [9]. Although the chemical structure of alinidine similar to that of clonidine, its pharmacologic spectrum of action is distinctly different, with minimal, if any, vasodilating activity. Zatebradine (1,3,4,5-tetrahydro-7,8-dimethoxy-3-[3-([2-(3,4-dimethoxyphenyl) ethyl] methylimino) propyl]-2H-3-benzazepin-2-on) is a selective bradycardic agent and congener to AQ-A 39 (falipamil) that has been demonstrated to influence beneficially exercise-induced myocardial contractile dysfunction in dogs without showing negative inotropic effects [10]. This implies another mode of action of zatebradine as compared with alinidine.

We undertook this study in order to investigate the electrophysiologic effects of alinidine and zatebradine

Address for correspondence: Prof. Dr. J. Brachmann, Department of Cardiology, Medical University Hospital of Heidelberg, Bergheimerstr. 58, D-69115 Heidelberg, Germany.

Received 1 November 1994; receipt/review time 41 days; accepted in revised form 3 February 1995

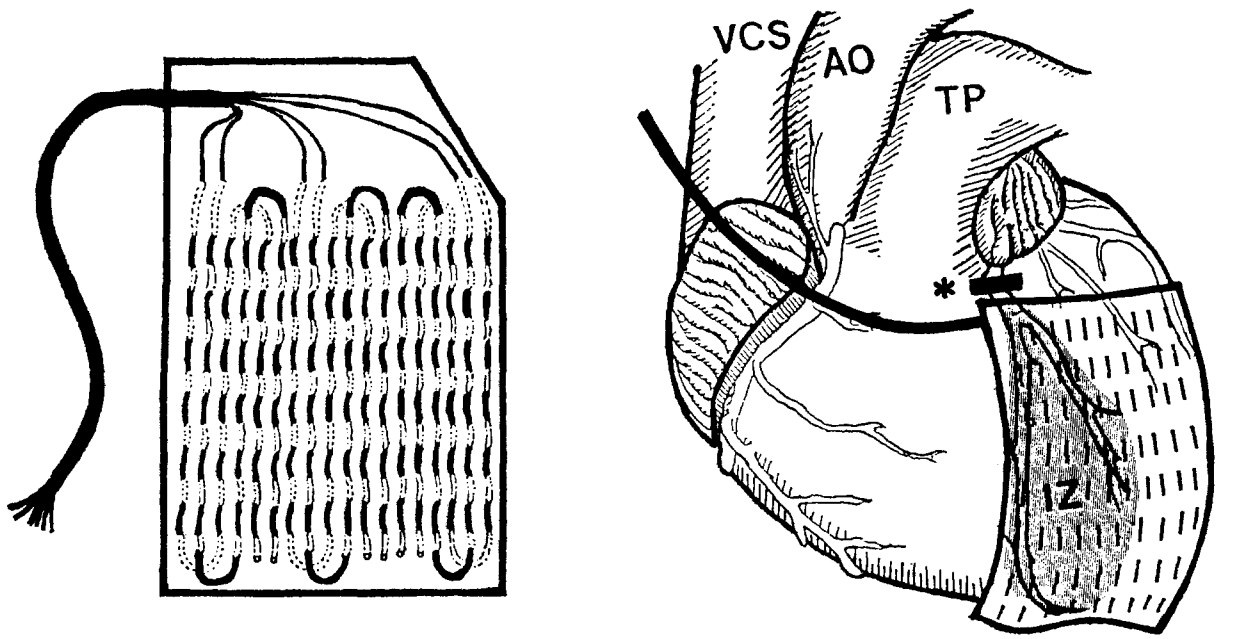

Fig. 1. On the left is shown the epicardial composite electrode, consisting of three bipolar recordings. The wires at the anterior side of the electrode come into direct contact with the free left ventricular wall and thus were not electrically isolated; however only half of the surface of the electrodes (solid lines) came into electrical contact with the myocardium, while the other half of the electrodes did not record electrical activity (dashed lines). On the right is illustrated the placement of the composite electrode on the left ventricle, encompassing the infarction zone (IZ). The asterisk marks the location of the ligature. VCS = vena cava superior; Ao = aorta; TP = truncus pulmonalis.

in conscious, unsedated dogs with subacute myocardial infarction and inducible ventricular tachyarrhythmias. The results should provide information as to whether either of these drugs is proarrhythmic in this stage of myocardial infarction, an action that would limit their use in the ischemic heart.

Materials and Methods

Induction of myocardial infarction and implantation of recording electrodes

Myocardial infarction was produced in 27 healthy adult mongrel dogs of either sex weighing 14–20 kg. Premedication was performed with an intramuscular (IM) injection of 0.64 mg/kg 1-[10-(3-dimethylaminopropyl)-2-phenothiazinyl]-1-propanonphosphate (Combelen). Approximately 20 minutes later, a femoral vein was cannulated for the administration of the anesthetic sodium pentobarbital (Nembutal) in a dose of 30 mg/kg. After induction of deep anesthesia, 1–2 minutes after the administration of the anesthetic, the animals were intubated and ventilated via an Engstroem respirator (ER 312) with a mixture of 1.5 l/min O_2 and 3 l/min N_2O. Electrocardiogram (ECG) lead I was monitored continuously to detect disturbances in cardiac rhythm throughout the experiment. A heating pad maintained the body temperature of each animal between 36.5 and 38°C during the entire operation. Infarcts were created by two-stage ligation of the LAD coronary artery, as has been previously described by Harris in anesthetized dogs [11]. Accordingly, a left-sided thoracotomy was executed through the fourth intercostal space under sterile conditions; after opening the anterior part of the pericardium, a snare was placed around the artery and tightened around a 20-gauge needle, which was then removed to allow 30 minutes of partial occlusion of blood flow. The artery was then completely occluded. This animal model of experimental myocardial infarction has found extensive use by many investigators and by our laboratory as well [7], particularly for studying the mechanisms of arrhythmias and the action of antiarrhythmic compounds.

Prior to ligation, one pair of stainless steel electrodes was positioned in the posterior wall of the left ventricular apex and another in the left atrial appendage for pacing or recording electrical activity (interelectrode distance 2–3 cm). To record local electrical activity from ischemic and contiguous normal myocardium, an epicardial composite electrode [12] was attached on the left ventricular free wall by using a suture in the apical region of the left ventricle and by pressing the pericardium on the electrically isolated surface of the electrode. The composite electrode allowed simultaneous registration of a maximum of three bipolar electrograms. Figure 1 gives a detailed presentation of the composite electrode and its placement on the left ventricular surface.

In addition, two circular silver electrodes were sutured subcutaneously—one on the dorsal and the other on the ventral aspect of the thorax—to record a surface ECG from the awake dog. Arterial blood pressure in the subacute myocardial infarction period was measured by means of a specially modified catheter that was chronically introduced into and stabilized in one of the carotid arteries. The leads from all of the electrodes together with the blood pressure catheter were exteriorized dorsally through the skin and connected to a plug sutured in place at the nape of the neck. The chest was closed without completely apposing the pericardium to reduce the formation of adhesions, and the animals were allowed to recover from surgery. Postoperatively, analgesia was achieved with 0.3 mg IM buprenorphine (Temgesic), and antibiotic prophylaxis with 2 g IV and 2 g IM ampicillin (Binotal) immediately after the operation, and 2 g IM twice daily during the following 3 days. A Reynolds Holter recording system was used to detect arrhythmias arresting the heart during the first 24 hours after coronary artery ligation.

Electrophysiologic testing and definitions

All the surviving animals were studied 3–7 days postinfarction in the conscious state while they were standing in a sling. The bipolar subcutaneous leads, together with one pair of atrial leads and another pair of ventricular leads, as well as three bipolar ECGs of the composite electrode, were led into the input of the amplifiers of a VR-12 Electronics for medicine multichannel oscilloscopic photographic recorder at a paper speed of 50 or 100 mm/sec. The recorder was equipped with a filter setting of 30–500 Hz for registration of atrial and ventricular electrograms and local electrical activity from the composite electrode (100 μV/cm gain, 100 Hz filter). For surface electrograms a 1 mV/cm gain and a 30 Hz filter were employed.

Either the left atrium or the left ventricle of the awake dog was driven by means of a Medtronic SP 0503 programmable stimulator at cycle lengths of 300, or 330 and 250 msec, respectively. The stimuli were rectangular pulses 4 msec in duration that were two times the diastolic voltage threshold and were separately determined in each experiment prior to and after administration of either agents.

Ventricular pacing thresholds usually were found to be elevated in our experiments, probably because the electrodes for ventricular stimulation were implanted near the infarcted region. After every seven regularly driven impulses, a single premature stimulus was applied to the atrium or the ventricle to determine the effective refractory period (ERP) of the AV node (AV-ERP) or the left ventricular muscle, respectively. Major problems that in some cases limited the measurement of AV-ERP were (a) transient block within the AV conduction system during atrial pacing, which was predominantly attributable to large infarcts seemingly encompassing this region, and (b) ventricular arrhythmias that were sometimes elicited during atrial stimulation. This latter limitation was also validated by determination of the ventricular ERP, especially at coupling intervals bordering the ERP.

To determine the ERP of the AV node of the left ventricular myocardium, the interval between the last drive stimulus and the premature stimulus was gradually shortened by steps of 5 msec until no propagated ventricular response was inducible. Then the coupling interval was lengthened stepwise at 1 msec intervals until a ventricular response was observed. ERP was defined as the shortest coupling interval at which a ventricular response was still inducible.

Either double and triple premature extrastimuli or high-rate ventricular burst pacing at constant coupling intervals were additionally used to elicit sustained ventricular tachycardia (SVT). Each type of arrhythmia, except ventricular fibrillation (VF), was reproducibly induced by utilizing a complete stimulation protocol prior to and after drug administration. In dogs developing VF in the control period, the electrophysiologic protocol was undertaken 15 minutes after successful external defibrillation. The indication for electrical defibrillation was the presence of VF in the surface ECG according to the criteria of the Lambeth Conventions [13], particularly when the ECG changes were accompanied by hemodynamic collapse and loss of consciousness for approximately 1–2 minutes. At this point it is interesting to note that during the time between the second to third minutes after initiation of VF there is a period in which cardiac sympathetic tone and postganglionic nervous activity remain maximally elevated (plateau phase), so that relative low-energy electrical discharges are frequently successful in restoring sinus rhythm [14].

Ventricular late potentials were defined as low-amplitude depolarizations observed immediately after the end of the QRS complex in ECGs, from the composite electrode. The end of the QRS complex was determined by the point at which its terminal part met the isoelectric line or by superimposing the end of the QRS complex of surface leads on that of composite ECGs. Changes in the duration of late potentials have been suggested to reflect alterations of the depressed conduction in ischemic myocardium. This can indirectly be confirmed by the fact that drugs decreasing the slope of phase 0 of the action potential (sodium channel blockers) increased the duration of late potentials, whereas agents that mainly block the outward potassium current (compounds prolonging refractoriness) did not alter the duration of late potentials [15].

The stability and reproducibility of such potentials during constant atrial pacing as well as during SVT (defined as continuous or diastolic electrical activity) support their reliability in estimating local conduction derangements within the ischemic region. A more precise determination of local conduction alterations and detection of reentrant circuits is attainable by us-

ing isochronal mapping studies. The ERP of the infarction zone was determined by measuring the ventricular extrastimulus coupling interval at which late potentials were maximally extended into the ST segment of the respective composite electrogram [7].

Each ventricular tachycardia consisting of at least 100 nonstimulated QRS complexes of regular morphology and rate that required adaptive or nonadaptive overdrive ventricular pacing for its termination was defined as SVT. Ventricular tachycardias consisting of at least five uniform or nonuniform QRS complexes that terminated spontaneously were called *nonsustained ventricular tachycardia* (NSVT). Drug-related deterioration of an inducible arrhythmia or elicitation of an arrhythmia not inducible during control stimulation was termed the *proarrhythmic action* of the respective agent.

Drug administration

Both agents were administered in the conscious dog via a catheter chronically implanted into the jugular vein. Alinidine (1 mg/kg) or zatebradine (0.5 mg/kg) was given as a bolus injection over 5 minutes. When the heart rate had stabilized, approximately 15 minutes after application of the bolus injection, programmed stimulation was repeated and all determinations were carried out again.

Statistical analysis

All data are expressed as the mean ± SD. Changes in electrophysiologic parameters prior to and after alinidine or zatebradine were analyzed by Student's paired t test. A p value <0.05 was considered significant.

Results

Of the 27 dogs entered into the study, 3 died of incessant VF during the first 30 minutes following LAD ligation despite repeated attempts at electrical defibrillation. Four other animals succumbed to VF, and one animal died of progressive bradycardia, as detected by Holter monitoring during the 24 hours after infarction. The results that follow are based on data from 19 dogs that completed the study.

Arrhythmias

Nineteen dogs were investigated in the conscious state by programmed stimulation before and after acute administration of single doses of either 1 mg/kg alinidine or 0.5 mg/kg zatebradine. Neither of these agents significantly protected against any of the arrhythmias elicited during control stimulation (Figures 2 and 3). In detail, alinidine prevented SVT inducibility in 2 out of 9 animals (22%), while the cycle length of reinducible reentrant tachycardia (SVT-CL; n = 7 dogs) remained almost unchanged after acute alinidine administration (Table 1; Figure 4). Conversion of

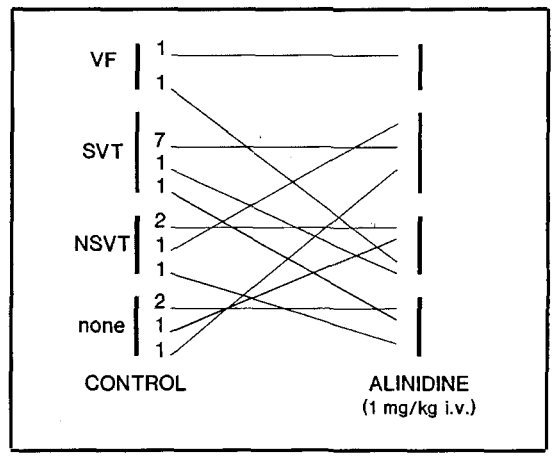

Fig. 2. *Ventricular arrhythmias elicited by programmed stimulation in the conscious dog with subacute myocardial infarction. Numerals indicate the number of animals with inducible arrhythmias prior to and after alinidine administration. See the text for additional comments.*

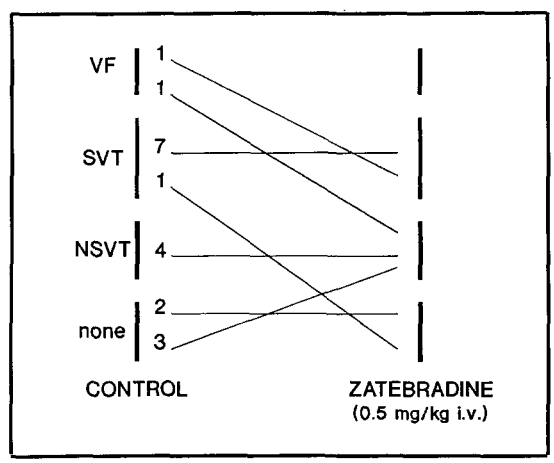

Fig. 3. *The effect of zatebradine on inducible ventricular tachyarrhythmias during programmed stimulation in dogs succumbing to 3- to 7-day-old myocardial infarctions.*

NSVT or SVT in one animal and elicitation of SVT in another animal exhibiting no arrhythmias in the control were taken as proarrhythmic effects of alinidine (2 out of 19 dogs, 10%; Figure 2). Zatebradine showed effects similar to alinidine in abolishing SVT (1 out of 8 animals, 12%), without statistically significant changes on the cycle length of tachycardia (n = 7 dogs). Proarrhythmic effects were observed in 3 out of 19 animals (15.8%); thus zatebradine facilitated the inducibility of NSVT in those animals that developed no arrhythmias during control stimulation (Figure 3). Most tachycardias were terminated by overdrive ventricular burst pacing; however, due to hemodynamic compromise, protracted tachycardias with rates ex-

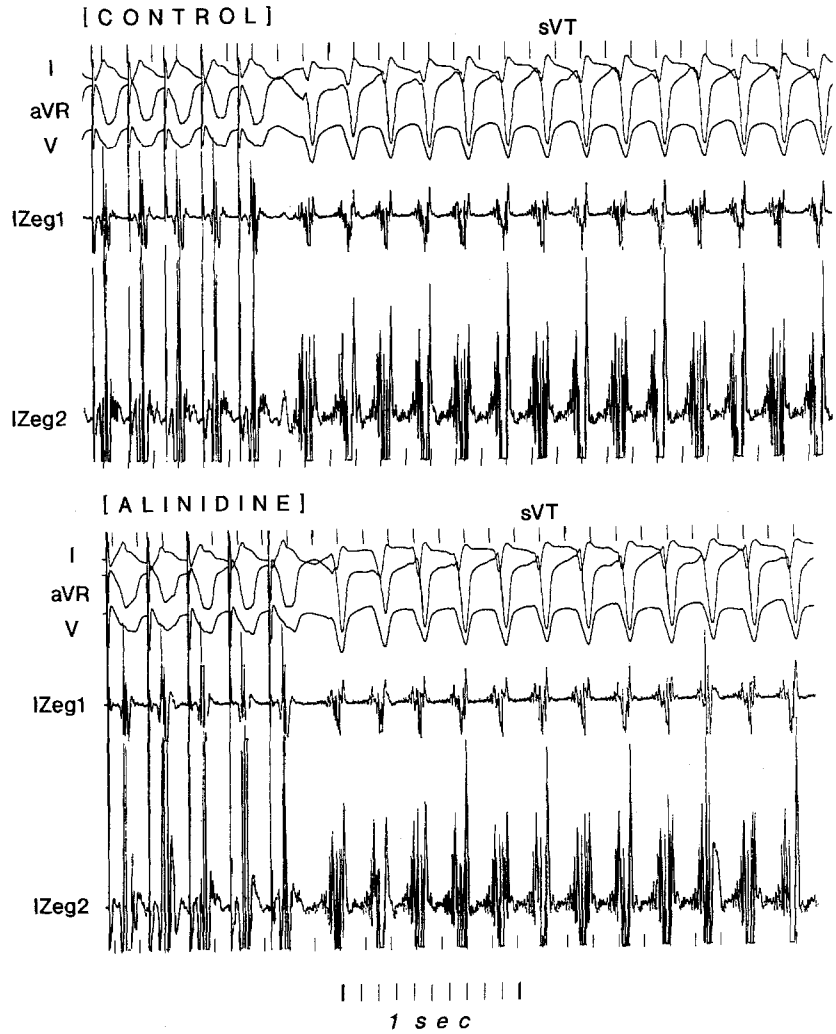

Fig. 4. *Inefficacy of 1 mg/kg IV alinidine on the inducibility and development of a monomorphic sustained ventricular tachycardia (SVT) in a conscious animal with 5-day-old left anterior descending (LAD) coronary artery ligation.*

Table 1. *Effects of alinidine and zatebradine on refractory periods and SVT rate in conscious dogs with subacute myocardial infarction*

	AV-ERP (n = 16)	2:1 AV-block (n = 16)	LVERP-NZ (n = 18) 330 ms	LVERP-NZ (n = 18) 250 ms	LVERP-IZ (n = 9) 250 ms	SVT-CL (n = 7)
CON	161 ± 30	154 ± 20	131 ± 16	126 ± 15	177 ± 11	139 ± 41
ALI	181 ± 32[b]	160 ± 24[b]	133 ± 18	127 ± 17	180 ± 10	140 ± 44
	(n = 15)	(n = 15)	(n = 18)		(n = 8)	(n = 7)
CON	171 ± 25	186 ± 32	127 ± 16	121 ± 14	170 ± 14	126 ± 18
ZAT	180 ± 32	201 ± 28	131 ± 14[a]	129 ± 12[b]	171 ± 11	137 ± 43

Values are given in msec means ± SD ERP = effective refractory period; SVT-CL = cycle length of sustained ventricular tachycardia; n = number of animals evaluated; LV = left ventricle; ALI = alinidine; ZAT = zatebradine; CON = control; SVT = sustained ventricular tachycardia.

[a]$p < 0.05$; [b]$p < 0.01$, control versus drug.

ceeding 400–500 beats/min were terminated by DC cardioversion.

Refractory periods

Alinidine lengthened the AV-ERP, increasing from 161 ± 30 msec to 181 ± 32 msec ($p < 0.01$), compared with zatebradine, which did not increase AV-ERP significantly. Determination of the AV-ERP was obtained by premature atrial stimulation at a drive cycle length of 300 msec. High-rate atrial pacing (atrial frequency series) induced a 2:1 AV conduction block by a 154 ± 20 msec constant pacing cycle length prior to alinidine, and by 160 ± 24 msec after alinidine ($p < 0.01$). Zatebradine induced a 2:1 AV conduction block with a 201 ± 28 msec compared with a 186 ± 32 msec, basic drive cycle length during control atrial stimulation ($p > 0.05$).

The mean left ventricular ERP of the normal zone (LVERP-NZ) during control ventricular extrastimulation did not significantly differ from values measured after alinidine administration, whereas zatebradine increased LVERP-NZ from 127 ± 16 msec to 131 ± 14 msec ($p < 0.05$) at a drive cycle length of 330 msec, and from 121 ± 14 msec to 129 ± 12 msec ($p < 0.01$) at a drive cycle length of 250 msec. Refractoriness of the infarction zone (LVERP-IZ), determined at a drive cycle length of 250 msec to avoid transient capture of early premature depolarizations during constant drive stimulation, remained almost unaltered after alinidine or zatebradine. This was indicated by the lack of changes in ventricular late potentials prior to and after drug administration. Atrial and ventricular pacing thresholds did not change after alinidine or zatebradine, and ranged from 2 to 5 mA with atrial stimulation and from 7 to 12 mA with left ventricular stimulation.

ECG variables and blood pressure

Both alinidine and zatebradine significantly increased sinus cycle length ($p < 0.01$; Figure 5). Neither of these drugs notably altered QRS, QTc, or late potential duration. The QTc was calculated using the formula $QTc = QT/RR^{1/2}$ [16]. The PQ interval measured during sinus rhythm increased with zatebradine from 100 ± 15 msec to 108 ± 17 msec ($p < 0.01$), in comparison with alinidine, which did not change this parameter significantly. The systolic aortic blood pressure decreased after alinidine from 140 ± 21 mmHg to 132 ± 16 mmHg ($p < 0.01$), while the diastolic pressure showed insignificant alterations. Conversely, zatebradine reduced the diastolic blood pressure from 96 ± 21 mmHg to 89 ± 18 mmHg ($p < 0.05$), but it left the systolic pressure almost unchanged (138 ± 24 mmHg pre- vs. 136 ± 18 mmHg post-zatebradine).

Discussion

These findings show that alinidine and zatebradine significantly decrease spontaneous heart rate without notably affecting either conduction in normal and ischemic ventricular myocardium or ventricular repolarization. In addition, alinidine markedly prolonged AV-ERP, whereas zatebradine did not. Conversely, while zatebradine lengthened LVERP-NZ in a use-

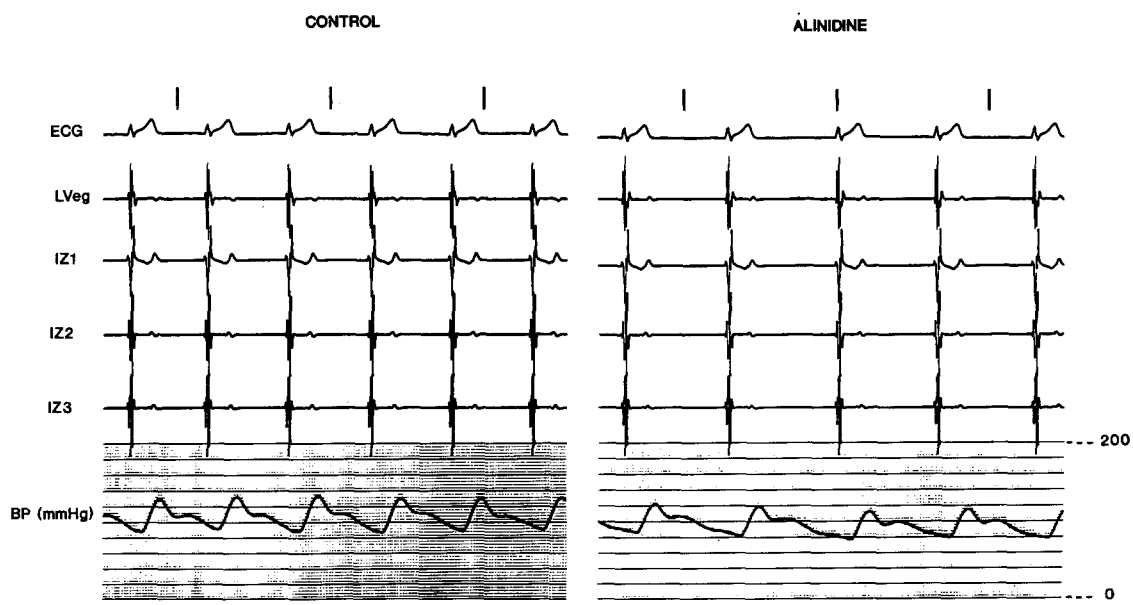

Fig. 5. Demonstration of the bradycardic effect of alinidine. Note small changes in aortic blood pressure (BP), endocardial left ventricular electrogram (LVeg), and composite electrograms (IZ_{1-3}). The solid vertical lines shown at the top of the figure indicate time intervals of 1 second.

Table 2. *Effects of alinidine and zatebradine on electrocardiogram variables and systolic/diastolic blood pressure in dogs*

	SCL (ms) (n = 19)	QRS (ms) (n = 19)	QTc (ms) (n = 19)	LPD-AP (ms) (n = 9)	BP [mmHg] (S)/(D) (n = 19)	
CON	484 ± 77	58 ± 10	276 ± 33	45 ± 8	140 ± 21	99 ± 15
ALI	548 ± 79[b]	59 ± 11	273 ± 33	46 ± 8	132 ± 16[b]	95 ± 12
	(n = 19)	(n = 19)	(n = 19)	(n = 9)	(n = 19)	
CON	542 ± 75	61 ± 11	274 ± 30	38 ± 6	126 ± 15	96 ± 21
ZAT	655 ± 118[b]	63 ± 14	265 ± 24	38 ± 6	127 ± 17	89 ± 18[a]

Values are means ± SD.
SCL = sinus cycle length; QRS = QRS duration; QTc = corrected QT interval; ALI = alinidine; ZAT = zatebradine; CON = control; S = systolic; D = diastolic; BP = blood pressure; LPD-AP = late potential duration during atrial pacing; n = number of dogs studied.
[a]$p < 0.05$; [b]$p < 0.01$, control versus drug.

dependent manner, alinidine scarcely influenced this parameter.

Agents antagonizing heart rate acceleration, especially in ischemically injured myocardium, may indirectly enhance coronary circulation via increases in diastolic intervals, thereby acting as antianginal substances with undoubtedly beneficial effects on arrhythmogenesis. Accordingly, earlier and more recent investigations suggested a close relationship between spontaneous heart rate and ventricular ectopic rhythms in dogs during acute myocardial ischemia [4–6]. Increased supernormal periods [6] in association with larger amplitudes of delayed afterdepolarizations during phases of accelerated heart rate are possible mechanisms generating ventricular ectopic rhythms in ischemic heart. Besides triggered activity, enhanced abnormal automaticity and desynchronization of cellular activation during states of elevated heart rate [17] are additional causes that may initiate a reentrant arrhythmia under certain conditions.

Alinidine and zatebradine have been found to reduce the amount of the hyperpolarization-activated pacemaker current i_f (phase 4 of action potential), which is an inward sodium current [18,19]. Activation of this current mainly appears during the late phase of diastolic depolarization, while earlier phases of diastolic depolarization are controlled by i_{Ca}. In addition, Satoh and Hashimoto demonstrated in voltage clamp experiments that alinidine suppressed the slow inward current and the outward current in rabbit sinoatrial node cells [20]. The present findings do not support such an effect, at least at the ventricular level, and are in good correlation with in vitro investigations demonstrating a slight effect of alinidine on action potentials of normal ventricular muscle [21]. Contrasting results of different research groups are predominantly attributed to differences in dosing of alinidine and experimental design. The doses used for alinidine (1 mg/kg) and zatebradine (0.5 mg/kg) in our study were high enough to obtain a sufficient reduction in heart rate. Thus, alinidine diminished the mean heart rate from 124 to 109 beats/min (13%), while zatebradine slowed it from 111 to 91 beats/min (18%). Comparable or higher doses of alinidine were given by other investigators [22–24]; however, higher doses were administered to attain an antiarrhythmic effect. This study has not primarily been designed to investigate an antiarrhythmic action of either agent but to preclude possible proarrhythmic effects at doses substantially decreasing heart rate. Zatebradine at a dose of 0.5 mg/kg has been shown to reduce heart rate significantly in the anesthetized dog [25].

Although the extent of myocardial depression with alinidine still remains controversial [26,27], König et al. recently demonstrated a clinically irrelevant negative inotropic effect in patients with chronic congestive heart failure [28]. On the other hand, the ability of alinidine to delay the release of calcium from the intracellular membranous system [29] has been suggested as one mechanism by which this drug can change myocardial performance. Traunecker and Walland found that alinidine at a dose of 1.5 mg/kg did not result in a significant reduction of systolic left ventricular blood pressure in anesthetized dogs [30]. However, we observed in conscious unsedated dogs with subacute myocardial infarction that 1 mg/kg alinidine significantly reduced the aortic systolic blood pressure without showing subsequent reflex tachycardia. The moderate hypotensive effect of alinidine is presumably explained by its negative effect on myocardial contractility accompanied by an increase in total peripheral vascular resistance [30]. Verdouw et al. demonstrated in pigs that alinidine at doses exceeding 0.4 mg/kg had a pronounced negative inotropic action, which, in combination with its bradycardic effect, substantially decreased cardiac output [24]. Nonetheless, this negative inotropic effect can be counterbalanced by an increase in endocardial blood flow and the endo/epi ratio, together with an improvement of the performance of the ischemic myocardial segment [23].

In comparison to alinidine, zatebradine has been reported to exert a marked bradycardic effect without affecting positive dp/dt_{max} [10]. Other investigators showed that zatebradine exerted either a positive ino-

tropic effect [9,25] or no effect on the inotropic state of the heart [31], depending on the experimental design. Rouse and Johnson found an approximately 30% reduction in heart rate after 0.2 mg/kg zatebradine in the anesthetized pig [25], while we found an 18% reduction after 0.5 mg/kg in the conscious dog. These differences are at least partially attributed to another activation state of the autonomic nervous system in the anesthetized versus conscious animal. In this respect, the animals in the experiments of Rouse and Johnson revealed higher predrug heart rates than our animals, which is perhaps an effect of prevailing cardiac sympathetic tone due to anesthesia.

Alinidine has been found to interact with the autonomic nervous system by inducing a gradual decrease in the rate of spontaneous preganglionic sympathetic discharges at a dose of 2.5 mg/kg in anesthetized cats [32]. Moreover, Boucher et al. observed a fall in sympathetic tone after 2 mg/kg alinidine in the conscious dog; they attributed this effect to stimulation of presynaptic or central alpha$_2$-adrenoceptors [33].

In the meantime, it has been recognized that some antiarrhythmic drugs exhibit use-dependent (class I agents) or reverse use-dependent (class III agents) activity during periods of increased heart rate, and that this activity can potentiate or attenuate their antiarrhythmic efficacy, respectively [34]. A number of these drugs, especially those exerting reflex tachycardia or not sufficiently hampering heart rate acceleration, could be combined favorably with specific bradycardic agents. The antiadrenergic effects of alinidine can also beneficially influence reduced heart rate variability after myocardial infarction, which has been found to be associated with low vagal activity and a higher risk for malignant arrhythmias [35]. Other possible indications for specific bradycardic agents may be reperfusion arrhythmias [5,36] and chronic ischemic left ventricular dysfunction [37], whereby heart rate acceleration is thought to facilitate the occurrence of life-threatening ventricular arrhythmias.

In our infarct model of inducible reentrant ventricular tachycardia, neither alinidine nor zatebradine convincingly affected their course or inducibility. The electrophysiologic variables principally governing the recurrence and aggressiveness of such arrhythmias, namely, refractoriness, repolarization, and conduction velocity in the infarction zone [38,39], were not decisively changed by either agent. A recently demonstrated prolongation of ventricular repolarization (predominantly phase 2 of the action potential) with zatebradine, probably via inhibition of potassium delayed rectifier current (I_k) [40], could not be confirmed by our experiments in the conscious dog. It is thus possible that zatebradine blocks, at least partially, the inward calcium current under in vivo conditions, thereby counterbalancing the prolonging effect of I_k inhibition.

In conclusion, the fact that alinidine and zatebradine did not apparently influence ventricular electrophysiology after subacute myocardial infarction principally excludes drug-specific proarrhythmic effects. Finally, lengthening the AV nodal ERP with alinidine suggests a preventive effect on a variety of supraventricular arrhythmias, including AV nodal reentry tachycardia.

Acknowledgments

This study was supported by the SFB 320 Herzfunktion und ihre Regulation of the German Research Foundation. The excellent technical help of Dr. G. Krumpl and Ms. Patricia Kraft in the surgical and electrophysiological parts of the study is greatly appreciated. The authors also wish to thank Ms. Cecilia Ibacache for her contribution to the presentation of the results and for careful secretarial assistance.

References

1. Hope RR, Williams DO, El-Sherif N, Lazzara R, Scherlag BJ. The efficacy of antiarrhythmic agents during acute myocardial ischemia and the role of heart rate. *Circulation* 1974; 50:507–514.
2. Norris RM, Mercer CJ, Yeates SE. Sinus rate in acute myocardial infarction. *Br Heart J* 1972;34:901–908.
3. Kent KM, Smith ER, Redwood DR, Epstein SE. Electrical stability of acutely ischemic myocardium: Influences of heart rate and vagal stimulation. *Circulation* 1973;47:291–298.
4. Chadda KD, Banka VS, Helfant RH. Rate dependent ventricular ectopia following acute coronary occlusion: The concept of an optimal antiarrhythmic heart rate. *Circulation* 1974;49:654–658.
5. Lederman SN, Wenger TL, Harrell FE, Strauss HC. Effects of different paced heart rates on canine coronary occlusion and reperfusion arrhythmias. *Am Heart J* 1987;113: 1365–1369.
6. Spear JF, Moore EN. The effect of changes in rate and rhythm on supernormal excitability in the isolated Purkinje system of the dog. *Circulation* 1974;50:1144–1149.
7. Brachmann J, Aidonidis I, Dembowsky K, Seller H, Kübler W. Bepridil versus nifedipine for ventricular tachycardia induced in the late postinfarction phase in conscious dogs. *Cardiology* 1989;76:211–221.
8. Uprichard AC, Chi LG, Lynch JJ, Driscoll EM, Frye JW, Lucchesi BR. Alinidine reduces the incidence of ischemic ventricular fibrillation in a conscious canine model, a protective effect antagonized by overdrive atrial pacing. *J Cardiovasc Pharmacol* 1989;14:475–482.
9. Raberger G, Krumpl G, Schneider W, Mayer N. Effects of specific bradycardic agents on exercise-induced regional myocardial dysfunction in dogs. *Eur Heart J* 1987;8 (Suppl L):53–59.
10. Krumpl G, Schneider W, Raberger G. Can exercise-induced regional contractile dysfunction be prevented by selective bradycardic agents? *Naunyn Schmiedebergs Arch Pharmacol* 1986;334:540–543.
11. Harris AS. Delayed development of ventricular ectopic rhythms following experimental coronary occlusion. *Circulation* 1950;1:1318–1328.
12. El-Sherif N, Scherlag BJ, Lazzara R, Hope RR. Re-entrant ventricular arrhythmias in the late myocardial infarction period: I. Conduction characteristics in the infarction zone. *Circulation* 1977;55:686–702.

13. Walker MJA, Curtis MJ, Hearse DJ, et al. The Lambeth Conventions: Guidelines for the study of arrhythmias in ischemia, infarction, and reperfusion. *Cardiovasc Res* 1988; 22:447–455.
14. Aidonidis I, Brachmann J, Seller H, Dembowsky K, Czachurski J, Kübler W. Cardiac sympathetic nervous activity during myocardial ischemia, reperfusion, and ventricular fibrillation in the dog: Effects of intravenous lidocaine. *Cardiology* 1992;80:196–204.
15. Aidonidis I, Egel E, Hilbel T, Kübler W, Brachmann J. Effects of prenylamine and AQ-A 39 on reentrant ventricular arrhythmias induced during the late myocardial infarction period in conscious dogs. *J Cardiovasc Pharmacol* 1993;22:401–407.
16. Bazett HC. An analysis of the time-relations of electrocardiograms. *Heart* 1920;7:353–370.
17. Janse MJ, Kleber AG, Downar E, Durrer D. Changements electrophysiologiques pendant l'ischemie myocardique et mecanisme possible des troubles du rythme ventriculaire. *Ann Cardiol Angeiol Paris* 1977;26:551–554.
18. van-Bogaert PP, Goethals M. Pharmacological influence of specific bradycardic agents on the pacemaker current of sheep cardiac Purkinje fibres: A comparison between three different molecules. *Eur Heart J* 1987;8(Suppl L):35–42.
19. van-Ginneken AC, Bouman LN, Jongsma HJ, Duivenvoorden JJ, Opthof T, Giles WR. Alinidine as a model of the mode of action of specific bradycardiac agents on SA node activity. *Eur Heart J* 1987;8(Suppl L):25–33.
20. Satoh H, Hashimoto K. Electrophysiological study of alinidine in voltage clamped rabbit sino-atrial node cells. *Eur J Pharmacol* 1986;121:211–219.
21. Tritthart HA, Windisch H, Heuberger S. The effects of the bradycardia-producing compound alinidine on action potentials and tension development in cardiac fibres. *Naunyn Schmiedebergs Arch Pharmacol* 1981;316:172–177.
22. Harron DWG, Allen JD, Wilson R, Shanks RG. Effect of alinidine on experimental cardiac arrhythmias. *J Cardiovasc Pharmacol* 1982;4:221–225.
23. Schamhardt HC, Verdouw PD, Saxena PR. Improvement of perfusion and function of ischaemic porcine myocardium after reduction of heart rate by alinidine. *J Cardiovasc Pharmacol* 1981;3:728–738.
24. Verdouw PD, Saxena PR, Schamhardt HC, Van der Hoek TM, Rutteman AM. The effects of alinidine, an N-allyl derivative of clonidine, on regional myocardial perfusion and performance in the pig with or without atrial pacing. *Eur J Pharmacol* 1980;64:209–220.
25. Rouse W, Johnson IR. Haemodynamic actions of a novel sino-atrial node function modulator, ZENECA ZD7288, in the anesthetized dog: A comparison with zatebradine, atenolol and nitrendipine. *Br J Pharmacol* 1994;113:1064–1070.
26. Wiegand V, Kreuzer H. Acute haemodynamic effects of a specific bradycardic agent in patients with coronary heart disease and impaired left ventricular function. *Eur Heart J* 1987;8(Suppl 8):105–108.
27. Jaski BE, Serruys PW. Anion-channel blockade with alinidine: A specific bradycardic drug for coronary heart disease without negative inotropic activity? *Am J Cardiol* 1985;56: 270–275.
28. König W, Stauch M, Sund M, Wanjura D, Henze E. Hemodynamic effects of alinidine (ST 567) at rest and during exercise in patients with chronic congestive heart failure. *Am Heart J* 1990;119:1348–1354.
29. Brutsaert DL, De Clerck NM, Stanlas US. Activation stabilization: Further support for a new class of cardioactive substances. *J Cardiovasc Pharmacol* 1982;4:808–811.
30. Traunecker W, Walland A. Haemodynamic and electrophysiologic actions of alinidine in the dog. *Arch Int Pharmacodyn* 1980;244:58–72.
31. Van Woerkens LJ, Van der Giessen WJ, Verdouw PD. The selective bradycardic effects of zatebradine (UL-FS 49) do not adversely affect left ventricular function in conscious pigs with chronic coronary artery occlusion. *Cardiovasc Drugs Ther* 1992;6:59–65.
32. Pichler L. Effect of alinidine (St 567) on sympathetic and vagal activities. *Arch Int Pharmacodyn* 1982;255:162–167.
33. Boucher M, Chapuy E, Lefebvre MA, Mignot A, Duchene-Marullaz P. Mechanisms of chronotropic cardiac effects of alinidine and plasma concentration-response relationships in the conscious dog with chronic atrioventricular block. *Naunyn Schmiedebergs Arch Pharmacol* 1989;339:630–637.
34. Hondeghem LM, Snyders DJ. Class III antiarrhythmic agents have a lot of potential but a long way to go: Reduced effectiveness and dangers of reverse use dependence. *Circulation* 1990;81:686–690.
35. Algra A, Tijssen JGP, Roelandt JRTC, Pool J, Lubsen J. Heart rate variability from 24-hour electrocardiography and the 2-year risk for sudden death. *Circulation* 1993;88: 180–185.
36. Bolli R, Patel B. Factors that determine the occurrence of reperfusion arrhythmias. *Am Heart J* 1988;115:20–29.
37. Pouleur H. Calcium antagonists or beta-blockers in chronic ischaemic left ventricular dysfunction? *Eur Heart J* 1993; 14(Suppl F):26–28.
38. El-Sherif N, Hope RR, Scherlag BJ, Lazzara R. Re-entrant ventricular arrhythmias in the late myocardial infarction period. 2. Patterns of initiation and termination of re-entry. *Circulation* 1977;55;702–717.
39. Garan H, Fallon JT, Ruskin JN. Sustained ventricular tachycardia in recent canine myocardial infarction. *Circulation* 1980;62:980–987.
40. Thollon C, Cambarrat C, Vian J, Prost JF, Peglion JL, Vilaine JP. Electrophysiological effects of S 16257, a novel sino-atrial node modulator, on rabbit and guinea-pig preparations: Comparison with UL-FS 49. *Br J Pharmacol* 1994; 112:37–42.