JACC Vol. 8, No. 3
September 1986:661–8

Efficacy of Diltiazem in Two Experimental Feline Models of Sudden Cardiac Death

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The potential role of calcium entry blockers in the prevention of life-threatening arrhythmias associated with acute myocardial ischemia and reperfusion is still controversial. In 98 anesthetized cats, the effect of diltiazem was examined in two experimental models. In protocol I, ventricular tachycardia or fibrillation was consistently induced by the interaction between a 2 minute coronary artery occlusion and a 30 second left stellate ganglion stimulation. After three trials under control conditions, if the same pattern of arrhythmia was induced, the drug under study was administered and three additional trials were performed. In 16 animals the administration of saline solution did not modify the pattern of arrhythmias. In contrast, diltiazem (0.1 mg/kg body weight plus 0.2 mg/kg per h) abolished both ventricular tachycardia and fibrillation that had occurred in 64 and 36%, respectively, of the cats in the control state.

In protocol II, a 20 minute coronary artery occlusion was released in three groups; one served as the control group, one received diltiazem 15 minutes before occlusion and one received diltiazem 3 minutes before reperfusion. The incidence of reperfusion ventricular fibrillation was 62% (16 of 26) in the control group. It was significantly ($p < 0.05$) reduced by diltiazem administered before the occlusion to 25% (4 of 16), whereas it was not affected when diltiazem was administered just before reperfusion (7 [47%] of 15).

These results indicate that diltiazem exerts a striking protective effect against the malignant arrhythmias induced by the combination of acute myocardial ischemia and sympathetic hyperactivity. Diltiazem was also effective in reducing the incidence of life-threatening reperfusion arrhythmias. The potential of this drug for reducing the incidence of malignant arrhythmias in patients with ischemic heart disease warrants careful evaluation.

(J Am Coll Cardiol 1986;8:661–8)

The prevention of sudden death in patients with coronary artery disease requires interventions directed toward some of the most critical events that lead to ventricular fibrillation. Analysis of Holter electrocardiographic recordings in patients who died suddenly has provided evidence suggesting that acute myocardial ischemia precedes the terminal arrhythmia in a large percent of cases (1). Because of the relatively low sensitivity of Holter recordings for revealing changes in ST-T waves, this percent is likely to be underestimated. Signs of sympathetic hyperactivity have been found (2) among patients who develop ventricular fibrillation in the first hour after myocardial infarction, and the critical role of the sympathetic nervous system in the genesis of lethal arrhythmias has been amply documented (3,4). These clinical observations underscore the relevance of the very early ischemic arrhythmias in experimental models, the so-called phase 1A arrhythmias (5).

There is strong experimental evidence (6) that reperfusion of the ischemic myocardium is associated with a very high incidence of ventricular fibrillation. The clinical evidence is not as abundant, but a growing number of reports (7,8) have related the termination of ischemic episodes to the occurrence of malignant arrhythmias in humans.

It would be reassuring if a drug chosen to prevent sudden death in patients with coronary artery disease was effective against both ischemic and reperfusion arrhythmias; however, the latter are resistant to many common antiarrhythmic drugs (9,10). Accordingly, we decided to test potentially useful agents with two protocols. In the first protocol, life-threatening ventricular arrhythmias are induced by the interaction between a brief ischemic episode and sympathetic hyperactivity (11,12); in the second, ventricular arrhythmias are induced by release of a coronary artery occlusion of 20

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Manuscript received November 14, 1985; revised manuscript received February 19, 1986, accepted March 21, 1986.

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0735-1097/86/$3.50

minutes' duration (13). Calcium entry blockers are already widely used in the management of patients with coronary artery disease and, although their antiarrhythmic efficacy is still controversial (14), they represent a logical group of drugs to examine. In this study we evaluated the effects of diltiazem (15,16).

Methods

Experiments were performed on 98 adult cats weighing 2.0 to 3.6 kg. The study was performed in accordance with animal welfare regulation at the authors' institution and with the guiding principles of the American Physiological Society. Details for the two protocols are given separately.

Protocol I: Coronary Artery Occlusion and Sympathetic Stimulation

Surgical preparation. Thirty-three cats were sedated with ketamine (20 mg/kg body weight intramuscularly) and anesthetized with alpha-chloralose (70 mg/kg intravenously). Ventilation with room air was maintained by means of a tracheal cannula connected to a Harvard model 607 respirator. Tidal volume and respiratory rate were adjusted to keep blood gases and pH within physiologic range throughout the experiment. The body temperature was constantly recorded by a rectal thermistor probe (YSI43TA) and maintained in the normal range by means of a heating pad and an infrared lamp.

Polyethylene catheters were inserted in a femoral artery and vein for blood pressure recording and drug administration. The second to fifth ribs were removed on the left side. Through this opening the left stellate ganglion was carefully isolated from the surrounding tissue, without severing its connections, and prepared for electrical stimulation. The right stellate ganglion was removed to decrease cardiac electrical stability (17) and to prevent excessive heart rate changes reflexly mediated, during the stimulation of the left stellate ganglion. A small pericardial incision was performed and the anterior descending branch of the left coronary artery was isolated at its origin; care was taken to avoid damage to surrounding nerves. A thread was gently passed around the vessel and its ends were inserted in a rigid polyethylene tube so that, by pulling them firmly, complete occlusion of the coronary artery could be produced.

A Grass S88 pulse generator connected to two stimulus-isolation units (Grass SIU5) was employed for electrical stimulation of the left stellate ganglion (square wave pulses of 3 ms, 15 to 20 Hz and 15 to 20 V) and for unipolar atrial pacing through a needle inserted in the right atrial appendage. Defibrillation, whenever necessary, was accomplished using a Lifepak 6S defibrillator (5 to 10 J internal shock).

Experimental protocol. Each experiment consisted of six to eight trials. In each trial the left anterior descending coronary artery was occluded for 2 minutes. The left stellate ganglion was stimulated for 30 seconds at the beginning of the last minute of occlusion (Fig. 1). If the combination of ischemia and sympathetic stimulation did not elicit ventricular arrhythmias, the duration of occlusion was increased to a maximum of 3 minutes. If ventricular arrhythmias were not elicited or were not consistent, the cat was excluded from the study (n = 6). If ventricular arrhythmias, similar in quantity and quality, occurred in three consecutive trials, the drug under study was administered and three additional identical trials were performed. In four animals atrial pacing was used to keep the heart rate constant during the postdrug trials. Each trial was followed by a 15 minute interval to allow complete recovery of the preparation. Previous data (11) indicated that if arrhythmias are induced for three consecutive trials, the same type of arrhythmia is reproducibly induced for at least four or five additional trials.

Sixteen cats received an injection of saline solution after the three control trials, whereas diltiazem was administered to the 11 other cats in Protocol I. Therefore, reproducibility of arrhythmias was assessed by the injection of saline so-

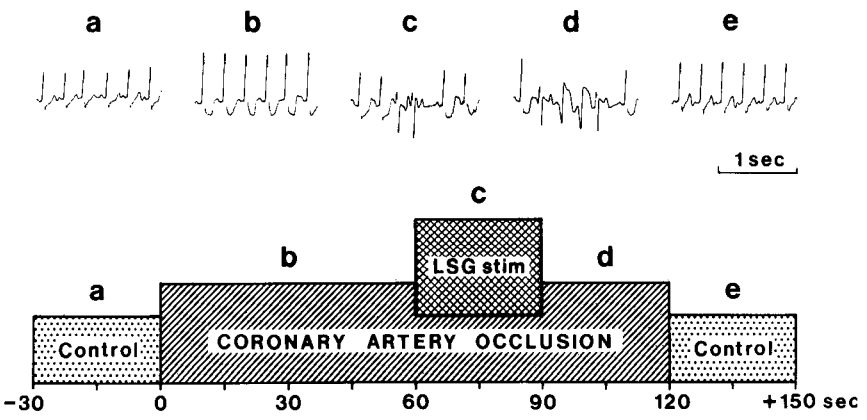

Figure 1. Diagram of the experimental model with an example of the electrocardiographic changes. The letters **a** to **e** indicate the phases of the occlusion/stimulation protocol during which the electrocardiogram was recorded. Ventricular arrhythmias appear during the left stellate ganglion stimulation (LSG stim) and persist during the last part of the occlusion. The electrocardiogram returns to control in a few seconds after the release of the coronary artery occlusion.

lution and the efficacy of diltiazem was tested by means of internal control analysis.

Protocol II: Coronary Artery Occlusion and Reperfusion

Surgical preparation. Sixty-five cats were anesthetized and ventilated as previously described. Polyethylene catheters were inserted in a femoral artery and vein. The fifth rib was removed on the left side. Through this opening a pericardial incision was performed and the left anterior descending coronary artery was isolated at its origin. A suture was gently passed around the vessel and its ends were passed through a polyethylene tube.

Experimental protocol. Coronary artery occlusion was obtained by pulling the two ends of the suture holding the end of the tube against the vessel and securing the snare with a bulldog clamp. The occlusion was maintained for 20 minutes. No attempt was made to resuscitate the animals that developed fibrillation during occlusion (n = 8). In the animals surviving the occlusion, abrupt reperfusion was obtained by releasing the clamp and loosening the suture.

Reperfusion of the previously ischemic myocardium was confirmed by observing the return within seconds of a reddish color of the left ventricular free wall. Arrhythmias occurring within 1 minute after release of the coronary artery occlusion were defined as reperfusion arrhythmias. After reperfusion, data were recorded for an additional 10 minutes.

Three groups were studied. Thirty-one cats served as control group; 16 cats received diltiazem 15 minutes before coronary artery occlusion (diltiazem preocclusion group) and 18 cats received diltiazem 3 minutes before reperfusion (diltiazem prereperfusion group).

Drug dosage. Diltiazem (Lirca Synthelabo) was administered in a dose of 0.1 mg/kg as a bolus injection, followed by an infusion at a rate of 0.2 mg/kg per h. This dosage produced an average lengthening of the PR interval of the electrocardiogram by 20 to 40% and a reduction in blood pressure of 10 to 20 mm Hg; these are reliable markers of the biologic effect of the drug (18).

Data recording. Aortic blood pressure (Statham P231D pressure transducer), instantaneous heart rate, surface electrocardiogram and an intracavitary electrogram (for a better distinction between supraventricular and ventricular arrhythmias) were recorded on a Brush recorder (model 260) or a Beckman recorder (model R612) and simultaneously displayed on a Tektronix storage oscilloscope (model 511). The signals were also stored on a Hewlett-Packard 3960A or a Racal Store 7DS magnetic tape recorder for subsequent analysis.

Definitions. For statistical purposes, arrhythmias observed during occlusion and reperfusion were classified into the following categories: ventricular fibrillation; ventricular tachycardia defined as four or more consecutive premature beats at a rate greater than 200 beats/min; and premature ventricular complexes. In the reperfusion experiments ventricular tachycardias were further defined as sustained (duration $\geq$ 30 seconds) or nonsustained ($<$ 30 seconds) because of their different hemodynamic consequences. In these animals we also evaluated the incidence of arrhythmias that occurred during the 20 minutes of ischemia. Arrhythmias were classified as phase 1A if their onset was within the first 10 minutes of coronary artery occlusion and as phase 1B if their onset was in the last 10 minutes of ischemia.

Statistics. Statistical analysis of the hemodynamic values was performed using a paired *t* test in protocol I and one-way analysis of variance plus a modified *t* test in protocol II; arrhythmia incidence was evaluated by the chi-square test with Yates' correction when needed.

Results

Protocol I: Coronary Artery Occlusion and Sympathetic Stimulation

In 6 of the 33 cats, either arrhythmias could not be reproducibly induced or hemodynamic deterioration occurred. These animals were excluded from the study.

Saline solution was tested in 16 animals. In this group during control trials, ventricular fibrillation was induced in six cats (38%), ventricular tachycardia in seven (44%) and premature ventricular complexes in three (18%). The administration of saline solution did not alter the occurrence of arrhythmias (Fig. 2).

Diltiazem was tested in 11 animals. The drug reduced slightly both basal heart rate (from 177 ± 27 to 150 ± 22 beats/min; $p < 0.02$) and blood pressure (from 113 ± 32 to 100 ± 20 mm Hg; $p < 0.01$). The heart rate response to sympathetic stimulation was also blunted by the drug (change in heart rate decreased from 23 ± 17 to 11 ± 15 beats/min; $p < 0.02$) whereas the change in blood pressure was not affected (change in blood pressure increased from 33 ± 17 to 37 ± 26 mm Hg, p = NS). The antiarrhythmic effect of diltiazem in this preparation was striking (Fig. 3). In the control trials, ventricular fibrillation was reproducibly induced in four cats (36%) and ventricular tachycardia in seven (64%). After injection of the drug, there was no instance of ventricular fibrillation or ventricular tachycardia; not even isolated premature ventricular complexes occurred.

In four cats the trials after diltiazem were performed while the heart was paced at a rate comparable with the maximum achieved during the control trials. The effect of the drug was not modified by the higher heart rate. In a fifth cat, pacing the heart after diltiazem administration elicited a 3:2 second degree Mobitz I atrioventricular block; there-

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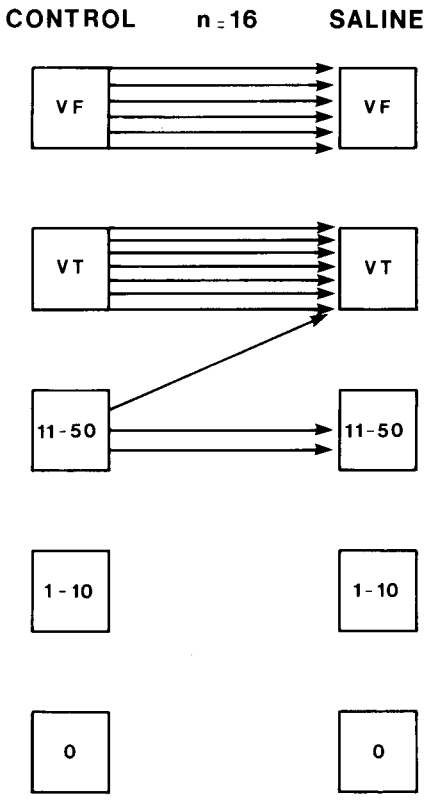


Figure 2. Protocol I. Effects of administration of saline solution. Each **square** represents the result of at least three trials in each cat. Each **arrow** represents one experiment. The **squares** on the **left** show the results observed during the three coronary occlusions plus sympathetic stimulation performed in control conditions, that is, before saline administration. The **squares** on the **right** show the results observed when three additional trials are performed after saline administration. It is evident that the injection of saline solution in 16 cats does not modify the response to coronary occlusion plus sympathetic stimulation. The numbers in the **squares** indicate the number of premature ventricular complexes. VF = ventricular fibrillation; VT = ventricular tachycardia.

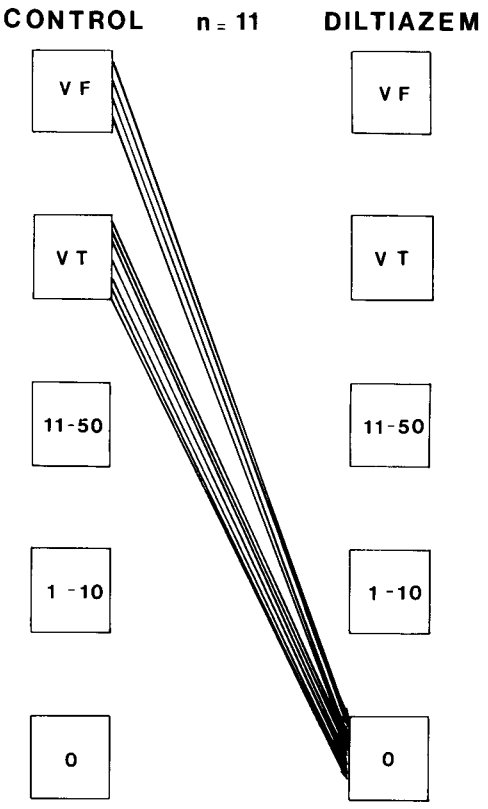


Figure 3. Protocol I. Effect of diltiazem in 11 cats. Format and abbreviations as in Figure 2.

fore the occlusion and sympathetic stimulation trial was performed without pacing.

Protocol II: Coronary Artery Occlusion and Reperfusion

Hemodynamic data (Table 1). All three groups of these 65 animals had homogenous baseline values for heart rate and blood pressure as assessed by analysis of variance. Diltiazem injected either before or after occlusion transiently decreased both blood pressure and heart rate ($p < 0.01$). However, heart rate and blood pressure values at the moment of reperfusion, although slightly lower in the diltiazem-treated group, were not significantly different from those in the control group.

Ischemic arrhythmias (Table 2). During the 20 minutes of ischemia preceding reperfusion, ventricular fibrillation occurred in 5 (16%) of the 31 cats in the control group, whereas it was never observed in the 16 cats in the diltiazem preocclusion group and it occurred in 3 (17%) of the 18 cats in the diltiazem prereperfusion group. Moreover, in the animals pretreated with diltiazem before occlusion there was also a significantly lower incidence of ventricular tachycardia and premature ventricular complexes. The drug afforded protection against both phase 1A and 1B arrhythmias.

Reperfusion arrhythmias (Table 3). Ventricular fibrillation occurred in 16 (62%) of 26 cats in the control group, and in 7 (47%) of 15 when diltiazem was given before reperfusion but was significantly reduced by diltiazem injected before ischemia (4 [25%] of 16) ($p < 0.05$). Also, the mode of onset of ventricular fibrillation was apparently affected by diltiazem. In 12 (75%) of 16 control animals, ventricular fibrillation occurred as a degeneration of a preceding ventricular tachycardia. This was never the case among those cats that received diltiazem before occlusion and that had ventricular fibrillation. In this group the onset of ventricular fibrillation was always sudden (Fig. 4). When sustained ventricular tachycardia is taken into account, the protective effect of diltiazem injected before coronary artery occlusion becomes even more striking.

The combined incidence of ventricular fibrillation and sustained ventricular tachycardia was 93% in the control group, 74% in the diltiazem prereperfusion group and 38% in the diltiazem preocclusion group. This difference with

Table 1. Heart Rate and Blood Pressure in the Three Groups of Cats in Protocol II

	Heart Rate (beats/min)			Blood Pressure (mm Hg)		
	Basal Value	Before Coronary Artery Occlusion	Before Reperfusion	Basal Value	Before Coronary Artery Occlusion	Before Reperfusion
Control group (n = 31)	214 ± 33	212 ± 24	206 ± 42	135 ± 39	130 ± 27	115 ± 37
Diltiazem groups	207 ± 27	185 ± 21*	185 ± 27*	125 ± 35	108 ± 20†	99 ± 29†
Preocclusion (n = 16)						
Prereperfusion (n = 18)	215 ± 29	214 ± 30	187 ± 27*	140 ± 32	135 ± 28	110 ± 30†

*$p < 0.01$ versus basal values; †$p < 0.05$ versus basal values. Diltiazem groups: Preocclusion = group of cats receiving diltiazem before coronary artery occlusion; Prereperfusion = group of cats receiving diltiazem before reperfusion.

respect to the preocclusion group is highly significant ($p < 0.002$ versus control group) (Fig. 5).

Discussion

This study demonstrates that the calcium entry blocker diltiazem is quite effective in preventing life-threatening arrhythmias induced by either acute myocardial ischemia or reperfusion. The different protocols used require separate comments.

Diltiazem and ischemic arrhythmias. The effect of diltiazem in the prevention of arrhythmias related to acute myocardial ischemia has been examined in a few studies. Patterson et al. (19) found no effect of diltiazem on ventricular fibrillation threshold under either normal or ischemic conditions, whereas Anastasiou-Nana et al. (20) had different results. They observed after diltiazem administration an increase in ventricular fibrillation threshold in the absence of ischemia, and less change in ventricular fibrillation threshold induced by ischemia. This discrepancy may partly depend on the use in both studies of a "train of pulses" to measure ventricular fibrillation threshold. This technique is controversial and may produce inconsistent results (21). Patterson et al. (19) also found no protection with diltiazem for arrhythmias induced by programmed electrical stimulation; however, there is still uncertainty as to the exact relation between ischemia-induced and electrically induced arrhythmias.

Clusin et al. (18) found that diltiazem delays from 138 to 295 seconds the time to onset of ventricular fibrillation after occlusion of both the left anterior descending and the left circumflex coronary artery. The model of global ischemia is questionable in terms of its relevance to clinical sudden death, and the significance of postponing ventricular fibrillation for a few minutes might be limited. Nonetheless, this latter study can be viewed as suggesting some protective effect of diltiazem. The model used in these experiments has the limitation common to such acute studies, namely, the use of anesthesia in an open chest preparation. In addition, the removal of the right stellate ganglion has been used to increase cardiac electrical instability (17,22); this helps to overcome the anesthesia-induced depression of sympathetic reflexes.

In our experiments the striking antiarrhythmic efficacy of diltiazem probably depended on a combination of actions that can antagonize the arrhythmogenic effects of neural activation on an ischemic myocardium. In our model, the enhancement of arrhythmias by the alteration of sympathetic input may depend on one or more of the following mechanisms: 1) an extension of the ischemic area as a result of left stellate ganglion stimulation (23); 2) direct electrophysiologic effects of neural stimulation to further lower the threshold for ventricular fibrillation (24) or to facilitate the occurrence of focal mechanisms on the border zone, or

Table 2. Incidence of Arrhythmias During the 20 Minutes of Ischemia in the Three Groups of Cats in Protocol II

	Phase 1A Arrhythmias (%)	Phase 1B Arrhythmias (%)	Total Arrhythmias (%)
Control group	51	45	67
Diltiazem groups	19*	19*	31*
Preocclusion			
Prereperfusion	61	61	89

*$p < 0.05$. Abbreviations as in Table 1.

Table 3. Incidence of Reperfusion Arrhythmias in the Three Groups of Cats in Protocol II

	VF (%)	VTs (%)	VTns (%)	PVCs (%)	No Arrhythmias (%)
Control group (n = 26)	62	31	7	0	0
Diltiazem groups	25*	12.5	31	19	12.5
Preocclusion (n = 16)					
Prereperfusion (n = 15)	47	27	26	0	0

*$p < 0.05$ versus control animals. The number of animals in each group differs from that in Table 2 because ventricular fibrillation occurred during ischemia in five animals in the control group and three animals in the group treated before reperfusion. PVCs = premature ventricular complexes; VF = ventricular fibrillation; VTns = nonsustained ventricular tachycardia; VTs = sustained ventricular tachycardia (> 30 seconds); other abbreviations as in Table 1.

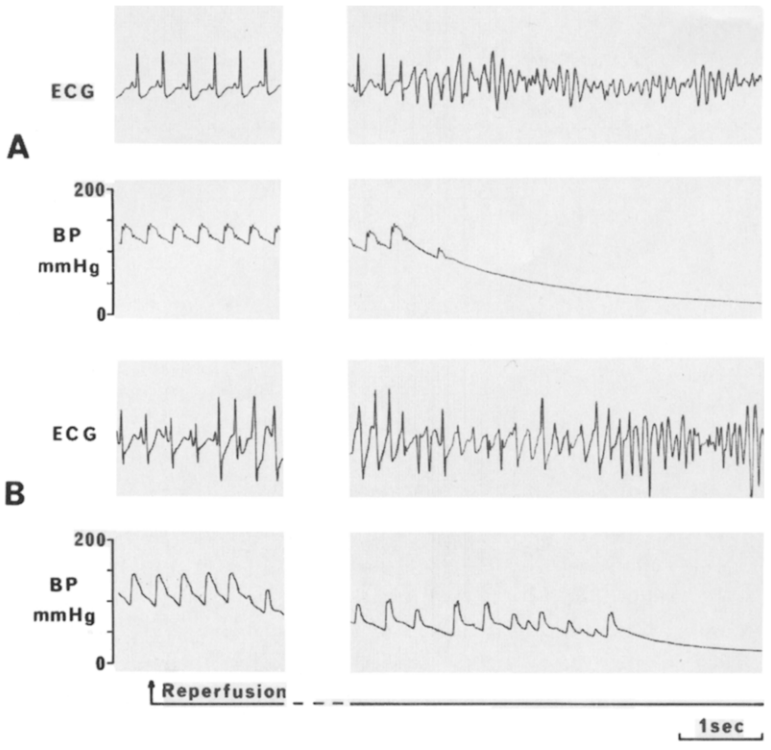
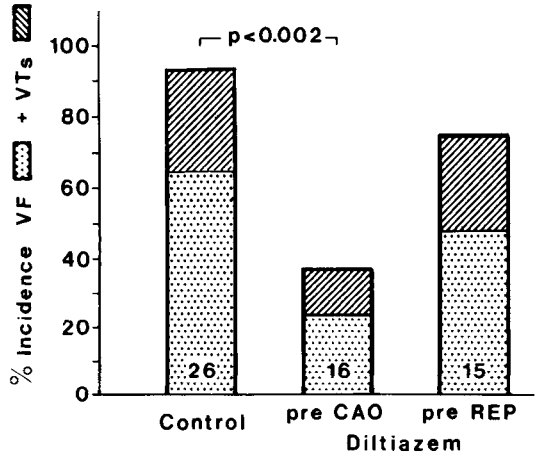


Figure 4. Protocol II. Examples of reperfusion ventricular fibrillation with a sudden onset (**A**) or preceded by ventricular tachycardia (**B**). The second tracing in **A** and **B** follows reperfusion by 11 and 10 seconds, respectively. Note the sudden decrease in blood pressure (BP) in **A** coincident with the onset of ventricular fibrillation, whereas in **B** blood pressure decreases mildly during ventricular tachycardia and falls abruptly only when ventricular fibrillation begins. ECG = electrocardiogram.

both (25); and 3) facilitation of the increase in intracellular calcium concentration which in turn may enhance arrhythmias related to abnormal automaticity-triggered firing or so-called slow responses. Diltiazem is certainly able to deeply interfere with the effect of sympathetic activation on the ischemic myocardium, particularly with the first (26) and the third (18) of these mechanisms. These properties might also explain the effectiveness of diltiazem on the ischemic arrhythmias of the 20 minute occlusion without sympathetic stimulation, in which a spontaneous release of catecholamines by reflex activation could occur (27). However, we cannot rule out other potential protective activities; for example, diltiazem has been shown to reduce conduction delay (28), an effect usually viewed as antiarrhythmic. It is unlikely that the diltiazem-induced reductions in heart rate and blood pressure played a major role because 1) pacing the heart to the highest rate observed during sympathetic stimulation did not modify the protective effect of diltiazem, and 2) the blood pressure responses to sympathetic stimulation were unaffected by diltiazem. Although the mechanisms involved have not yet been elucidated, it is important for both theoretical and practical reasons to appreciate that, against the same type of arrhythmias, class I antiarrhythmic drugs have been totally ineffective, alpha- and beta-adrenergic blocking agents have conferred good but incomplete protection and total prevention of ventricular tachycardia and ventricular fibrillation has been obtained only by amiodarone and the other well known calcium channel blocker, verapamil (12).

Figure 5. Protocol II. Effect of diltiazem on reperfusion arrhythmias in the three groups, showing the incidence of ventricular fibrillation (VF) (**dotted columns**) and sustained ventricular tachycardia (VTs) (**hatched columns**). The administration of diltiazem before coronary artery occlusion (pre CAO) significantly reduced the incidence of malignant ventricular arrhythmias. No protective effect was observed when the drug was administered before reperfusion (pre REP).



Diltiazem and reperfusion arrhythmias. Diltiazem proved to be of considerable, although not complete, efficacy in the prevention of reperfusion arrhythmias. The reduction of the incidence of ventricular fibrillation from 62 to 25% and the major reduction of the combined incidence

of ventricular fibrillation and sustained ventricular tachycardia from 93 to 38% is significant because reperfusion arrhythmias are difficult to prevent; that is, they are resistant to both Class I antiarrhythmic drugs and beta-adrenergic blocking agents (6).

Brooks et al. (29) observed a protective effect of verapamil in preventing a reperfusion-induced decrease in ventricular fibrillation threshold; Ribeiro et al. (30) and Naito et al. (10) observed, respectively, the efficacy and failure of verapamil in preventing reperfusion arrhythmias. Sheehan and Epstein (31), using a 30 minute coronary artery occlusion, reported lack of efficacy of both diltiazem and nifedipine in preventing reperfusion ventricular fibrillation in dogs. Because few studies have been performed, the inconsistency of results does not allow definitive conclusions. However, the fact that species and duration of occlusion (6) were not homogeneous among the studies may at least partially account for the different results.

In our study, diltiazem was effective only when it was administered before coronary artery occlusion. This indicates that the presence of the drug in the area that is going to become ischemic is essential to prevent the arrhythmias produced by reperfusion. Diltiazem is likely to quantitatively reduce the ischemic injury produced during coronary artery occlusion; indeed, this drug has been shown to greatly attenuate the decrease in adenosine triphosphate (ATP) (32), diminish the inhibition of anaerobic glycolysis and lower the cardiac levels of lactic and free fatty acids, thus minimizing the metabolic consequences of acute myocardial ischemia. This anti-ischemic activity could reduce the electrical inhomogeneity that seems to play such a critical role in the development of reperfusion arrhythmias. In addition, a direct effect in preventing the massive intracellular calcium overload that occurs during reperfusion (33) should be considered. This latter phenomenon can be prevented only if a calcium channel blocker is administered before coronary artery occlusion (34).

Clinical implications. If one considers that the very early phase of acute myocardial ischemia is quite often associated with reflexly augmented sympathetic activity, the ability of diltiazem to prevent malignant arrhythmias induced by the combination of these two factors should not be overlooked. On the other hand, the protective effect of diltiazem on reperfusion arrhythmias has, in addition to its theoretical implications, some practical significance because the calcium channel blockers are widely used in the management of patients with variant angina, a patient group at great risk for reperfusion arrhythmias. Even with the caution necessary in extrapolating experimental results to the clinical setting, the combined results of our study on the effects of diltiazem on ischemia and reperfusion arrhythmias provide a rationale for a thorough evaluation of diltiazem in patients with coronary artery disease at high risk for sudden death.

We express our gratitude to Ralph Lazzara, MD for reviewing the manuscript and for helpful criticism. We are also grateful to Luciana Lucchini for typing the manuscript and Carla Zanchetti for assistance in preparing the figures.

References

1. Roelandt J, Klootwijk P, Lubsen J, Janse MJ. Sudden death during long term ambulatory monitoring. Eur Heart J 1984;5:7–13.
2. Adgey AAJ, Delvin JE, Webb SW, Mulholland HC. Initiation of ventricular fibrillation outside hospital in patients with acute ischaemic heart disease. Br Heart J 1982;47:55–64.
3. Schwartz PJ, Stone HL. The role of the autonomic nervous system in sudden coronary death. Ann NY Acad Sci 1982;382:162–80.
4. Zaza A, Schwartz PJ. The role of the autonomic nervous system in the genesis of early ischemic arrhythmias. J Cardiovasc Pharmacol 1985;7:S8–S12.
5. Russell DC, Lawrie JS, Riemersma RA, Oliver MF. Mechanisms of phase 1a and 1b: early ventricular arrhythmias during acute myocardial ischemia in the dog. Am J Cardiol 1984;53:307–12.
6. Manning AS, Hearse DJ. Reperfusion-induced arrhythmias: mechanisms and prevention. J Mol Cell Cardiol 1984;16:497–518.
7. Tzivoni D, Keren A, Granot H, Gottlieb S, Benhorin J, Stern S. Ventricular fibrillation caused by myocardial reperfusion in Prinzmetal's angina. Am Heart J 1983;105:323–5.
8. Salerno JA, Previtali M, Chimienti M, Klersy C, Bobba P. Vasospasm and ventricular arrhythmias.Ann NY Acad Sci 1984;427:222–33.
9. Verrier RL, Hagestad E. Mechanisms of reperfusion arrhythmias. Eur Heart J 1986;7(Suppl A):13–22.
10. Naito M, Michelson EL, Kmetzo JJ, Kaplinsky E, Dreifus LS. Failure of antiarrhythmic drugs to prevent experimental reperfusion ventricular fibrillation. Circulation 1981;63:70–9.
11. Schwartz PJ, Vanoli E. Cardiac arrhythmias elicited by interaction between acute myocardial ischemia and sympathetic hyperactivity: a new experimental model for the study of antiarrhythmic drugs. J Cardiovasc Pharmacol 1981;3:1251–6.
12. Schwartz PJ, Vanoli E, Zaza A, Zuanetti G. The effect of antiarrhythmic drugs on life-threatening arrhythmias induced by the interaction between acute myocardial ischemia and sympathetic hyperactivity. Am Heart J 1985;109:937–48.
13. Zuanetti G, Vanoli E, Zaza A, Priori S, Stramba-Badiale M, Schwartz PJ. Lack of correlation between occlusion and reperfusion arrhythmias in the cat. Am Heart J 1985;109:932–6.
14. Stone PH, Antman EM, eds. Calcium Channel Blocking Agents in the Treatment of Cardiovascular Disorders. Mount Kisco, NY: Futura, 1983.
15. Priori S, Vanoli E, Zaza A, Zuanetti G, Schwartz PJ. Diltiazem and life-threatening arrhythmias due to acute myocardial ischemia and sympathetic hyperactivity (abstr). Proceedings of Cardiovascular Pharmacotherapy International Symposium 1985, Geneva, Switzerland. 1985: abstr. no. 326.
16. Priori S, Zaza A, Zuanetti G, Vanoli E, Schwartz PJ. Effect of diltiazem in the prevention of reperfusion arrhythmias (abstr). Eur Heart J 1985;6:127.
17. Schwartz PJ, Snebold NG, Brown AM. Effects of unilateral cardiac sympathetic denervation on the ventricular fibrillation threshold. Am J Cardiol 1976;37:1034–40.
18. Clusin WT, Bristow MR, Baim DS, et al. The effects of diltiazem and reduced serum ionized calcium on ischemic ventricular fibrillation in the dog. Circ Res 1982;50:518–26.
19. Patterson E, Eller BT, Lucchesi BR. Effects of diltiazem upon experimental ventricular dysrhythmias. J Pharmacol Exp Ther 1983; 225:224–33.

20. Anastasiou-Nana M, Nanas J, Menlove RL, Anderson JL. Experimental antifibrillatory effects of calcium channel blockade with diltiazem: comparison with beta-blockade and nitroglycerin. J Cardiovasc Pharmacol 1984;6:780–7.

21. Verrier RL, Brooks WW, Lown B. Protective zone and the determination of vulnerability to ventricular fibrillation. Am J Physiol 1978;234:H592–6.

22. Schwartz PJ. Sympathetic imbalance and cardiac arrhythmias. In: Randall WC, ed. Nervous Control of Cardiovascular Function. New York: Oxford University Press, 1984:225–51.

23. Janse MJ, Schwartz PJ, Wilms-Schopman F, Peters R, Durrer D. Effects of unilateral stellate ganglion stimulation and ablation on electrophysiological changes induced by acute myocardial ischemia in dogs. Circulation 1985;72:585–95.

24. Kliks BR, Burgess MJ, Abildskov JA. Influence of sympathetic tone on ventricular fibrillation threshold during experimental coronary occlusion. Am J Cardiol 1975;36:45–53.

25. Janse MJ, Van Capelle FJL, Morsink H, et al. Flow of "injury" current and patterns of excitation during early ventricular arrhythmias in acute regional myocardial ischemia in isolated porcine and canine hearts. Circ Res 1980;47:151–65.

26. Hossack KF, Brown BG, Stewart DK, Dodge HT. Diltiazem-induced blockade of sympathetically mediated constriction on normal and diseased coronary arteries: lack of epicardial coronary dilatory effect in humans. Circulation 1984;70:465–71.

27. Malliani A, Schwartz PJ, Zanchetti A. A sympathetic reflex elicited by experimental coronary occlusion. Am J Physiol 1969;217:703–9.

28. Peter T, Fujimoto T, Hamamoto H, Mandel WJ. Comparative study of the effect of slow channel inhibiting agents on ischemia-induced conduction delay as relevant to the genesis of ventricular fibrillation. Am Heart J 1983;106:1023–8.

29. Brooks WW, Verrier RL, Lown B. Protective effort of verapamil on vulnerability to ventricular fibrillation during myocardial ischaemia and reperfusion. Cardiovasc Res 1980;14:295–302.

30. Ribeiro LGT, Brandon TA, Debauch TL, Maroko PR, Miller RR. Antiarrhythmic and hemodynamic effects of calcium channel blocking agents during coronary arterial reperfusion. Am J Cardiol 1981;48:69–75.

31. Sheehan FH, Epstein SE. Effects of calcium channel blocking agents on reperfusion arrhythmias. Am Heart J 1982;103:973–8.

32. Weishaar R, Ashikawa K, Bing RJ. Effect of diltiazem, a calcium antagonist, on myocardial ischemia. Am J Cardiol 1979;43:1137–43.

33. Corr PB, Sharma AD. Alpha adrenergic-mediated effects on myocardial calcium. In: Opie LH, ed. Calcium Antagonists and Cardiovascular Disease. New York: Raven Press, 1984:193–204.

34. Nayler WC, Ferrari R, Williams A. Protective effect of pretreatment with verapamil, nifedipine and propranolol on mitochondrial function in the ischemic and reperfused myocardium. Am J Cardiol 1980; 46:242–8.