J. Pharm. Pharmacol. 1992, 44: 349–354
Received February 25, 1991



# Efficacy of Verapamil against Ventricular Arrhythmias Induced by Programmed Electrical Stimulation in the Late Myocardial Infarction Phase in Dogs

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**Abstract**—The aim of the present study was to investigate the antiarrhythmic potential of verapamil in the late myocardial infarction period in conscious dogs. Verapamil was administered in cumulative doses (0·3 + 0·3 mg $kg^{-1}$). The drug significantly lowered systolic and diastolic blood pressure after both doses. ECG signals showed short-lasting significant decrease in RR and QT intervals together with an increase in QTc interval. The parameters of the atrioventricular conduction system (PQ interval, 2:1 AV-conduction point) were significantly prolonged over the entire observation period. Ventricular effective refractory periods remained unaltered. In contrast to results obtained during acute ischaemia and in the first week thereafter, the present study demonstrates that verapamil moderately increases intraventricular conduction time 14 days after acute myocardial infarction. Verapamil prevented the induction of arrhythmias by programmed electrical stimulation (PES) in only 11% of all induction attempts. The lack of lengthening of refractory periods in the presence of a prolongation of intraventricular conduction time may be responsible for the poor antiarrhythmic efficacy. We conclude that verapamil is only of negligible value for the management of PES-induced ventricular arrhythmias in the late myocardial infarction period.

Since its introduction as a coronary vasodilator (Haas & Härtfelder 1962) verapamil has gained importance in various clinical indications (Baky 1984) such as ischaemic myocardial syndromes, hypertension and certain cardiac arrhythmias. Although it is beyond dispute that verapamil terminates supraventricular tachycardia (Schamroth et al 1972; Heng et al 1975; Rinkenberger et al 1980; Rankin et al 1990) and slows the ventricular response in atrial flutter and fibrillation (Singh et al 1983), the value of verapamil in the management of ventricular arrhythmias is still a matter for discussion. Verapamil has been reported to be effective against several types of ventricular arrhythmias in patients without obvious heart disease (Belhassen et al 1981, 1984; Wu et al 1981; German et al 1983; Lin et al 1983; Sung et al 1983; Sakurai et al 1988). Verapamil may also be useful in the therapy of some arrhythmias associated with acute myocardial infarction (Brooks et al 1980; Bergey et al 1984; Curtis et al 1984; Grenadier et al 1984; Rolli et al 1988). However, there are only a few studies dealing with the antiarrhythmic efficacy of verapamil against ventricular arrhythmias induced by programmed electrical stimulation after myocardial infarction; El-Sherif & Lazzara (1979) demonstrated good antiarrhythmic efficacy in an experimental dog model, whereas in other experimental (Davis et al 1982) and clinical (Mason et al 1983; Sung et al 1983) investigations verapamil has generally been found ineffective against this type of arrhythmia.

We have recently developed a clinically relevant canine model (Krumpl et al 1989a, b, 1990a), where left anterior infarction is induced by 4 h coronary occlusion followed by reperfusion. In the late myocardial infarction phase programmed electrical stimulation (PES) is used to evaluate various antiarrhythmic drugs in conscious dogs. Of all the tested substances lignocaine proved most effective in counteracting PES-induced arrhythmias in this model (Todt et al 1989; Krumpl et al 1990a, b).

This study was undertaken to clarify the antiarrhythmic potential of verapamil in the late myocardial infarction period.

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## Materials and Methods

The animals used in this study were handled in accordance with the animal welfare regulations of the University of Vienna. The method and the experimental protocol were approved by the Animal Subjects Committee of the University of Vienna and by the Austrian Ministry of Science.

*Surgical preparation and experimental myocardial infarction*

Nine trained mongrel dogs of either sex were fitted with arterial and venous catheters, a hydraulic occluder, which was placed around the left anterior descending coronary artery (LAD), and two pairs of piezoelectric crystals implanted subendocardially in the perfusion areas of the LAD and the circumflex branch of the left coronary artery (LCX). Pairs of stainless steel electrodes were sewn onto the left atrial appendage and the anterior wall of the right ventricle. One pair of electrodes was implanted subcutaneously. One week after surgery, 4 h coronary artery occlusion (CAO) followed by reperfusion was performed in conscious, unsedated dogs. Details of the surgical preparation and the occlusion-reperfusion procedure have been reported (Krumpl et al 1989a).

*Electrophysiological study*

The method of programmed electrical stimulation (Wellens et al 1972; Ehrreich 1986) was used to study the effects of verapamil on electrically-induced arrhythmias in the late myocardial infarction period. The experiments were carried

out in the period between days 13 and 22 after CAO (mean ± s.e.m. = 17 ± 3). No spontaneous arrhythmic activity was observed at that time.

ECG signals from subcutis, left atrium, right ventricle, anterior and posterior left ventricular wall and the arterial blood pressure signal were recorded by a 14-channel videodata tape (TEAC) and continuously monitored on an 8-channel oscilloscope (Knott Elektronik, Germany) using Gould amplifiers. Later on the signals were replayed onto a Gould TA 2000 thermal paper recorder (filter setting: 50 Hz low pass). The QT interval was corrected for heart rate according to the Bazett formula (Bazett 1920):

$$QTc(ms) = QT(ms) \text{ divided by } \sqrt{RR(s)}$$

and to a formula developed in our laboratory for conscious dogs:

$$QT_L(ms) = QT - 0{\cdot}1\ (RR\text{-}1000),$$

QT and RR are measured in ms. This formula assumes a linear relationship between QT and RR and was modelled on the formula of Van de Water et al (1989) for anaesthetized dogs.

Pacing was performed by means of a Medtronic programmable constant-current stimulator (SP 0503 MKIV) with rectangular impulses of 2 ms duration at twice the diastolic threshold.

The following variables were determined. The 2:1 AV-conduction point was defined as the maximal cycle length leading to a stable 2:1 atrioventricular conduction pattern following 30 s continuous atrial stimulation. The effective ventricular refractory periods of one right ventricular site (ERP-RV) and two left ventricular sites (ERP-LCX, ERP-LAD) were determined by premature stimulation with a single extra stimulus after 8 paced beats at two different basic cycle lengths (330 and 250 ms). Intraventricular conduction was assessed during right ventricular stimulation at a cycle length of 250 ms. Conduction time was measured from the stimulus artefact to the maximum negative dV/dt in the LAD lead.

*Ventricular tachyarrhythmia induction*

Induction of ventricular arrhythmias was achieved by ventricular stimulation with up to three extrastimuli. The coupling interval of each extrastimulus was shortened by 5 ms decrements until ventricular tachycardia was induced or ventricular refractoriness was reached. If stimulation via the right ventricular electrodes failed to elicit ventricular tachycardia, the induction was attempted from a left ventricular site (first LCX and finally LAD). If tachycardia was induced from one site no further induction was performed from other locations. All subsequent induction trials during drug testing remained confined to this area. The endpoint of a stimulation cycle was the induction of sustained ventricular tachycardia or ventricular fibrillation or completion of the full pacing protocol.

*Classification of PES-induced arrhythmias*

Non-inducible (NI) was defined as any self-terminating response of less than 6 non-driven beats. Non-sustained ventricular tachycardia (NSVT) was defined as any self-terminating response of at least 6 or more non-driven beats lasting less than 15 s. Sustained ventricular tachycardia (SVT) was defined as a stable arrhythmia with uniform QRS complexes lasting longer than 15 s. Termination was achieved by overdrive stimulation or DC cardioversion. Ventricular fibrillation (VFib) was defined as a fast, pleomorphic tachycardia which lasted longer than 15 s and had to be treated by defibrillation. Antiarrhythmic efficacy was defined as conversion of the respective control tachycardia (SVT or VFib) into NSVT or NI.

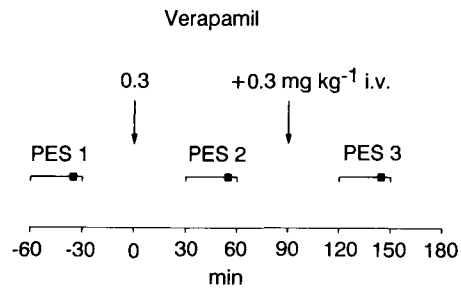


FIG. 1. Time protocol of a single experiment. PES = programmed electrical stimulation; ■ = arrhythmia induction.

*Drug study design*

Experiments carried out with 0·9% NaCl (saline) administration on days before and after the study with verapamil, with a time schedule which was identical to that described below, exhibited an induced arrhythmia which was reproducible a further two times.

The time course of the drug study is shown in Fig. 1. Verapamil (0·3 mg $kg^{-1}$ i.v. over 3 min) was administered twice, with a 90 min interval between the first and second dose. The stimulation procedure commenced 30 min after the first and second administration. According to the protocol the determination of the refractory periods and, immediately thereafter, the attempts to induce ventricular arrhythmias were carried out during a drug-free control phase (min −60 to −30: PES 1) and 30 min after the administration of the respective dosage of verapamil: min 30 to 60: PES 2: 0·3 mg $kg^{-1}$, min 120 to 150: PES 3: +0·3 mg $kg^{-1}$.

*Determination of plasma concentrations of verapamil*

Blood samples were taken 10, 30, 60 and 90 min after the administration of the respective verapamil doses; 20 μL of a 10% EDTA in distilled water solution was used as anticoagulant. Plasma was then frozen until determination of verapamil by HPLC. Internal standard (D 517-HCl) 250 ng/50 μL and 100 μL 2 M NaOH with 1100 μL hexane/iso-amylalcohol (98/2) were added to 500 μL plasma in an Eppendorf 2 mL micro test tube. The mixture was shaken for 3 min and then centrifuged (14000 *g*). One thousand μL of the organic phase was extracted with 400 μL 0·1 M HCl. After 2 min centrifugation (14000 *g*) the organic phase was discarded and 330 μL of the acidic phase was injected. The chemicals used were of analytic grade and obtained from Loba Feinchemie (Austria). The apparatus used included a Merck-Hitachi L-6200 intelligent pump, a Merck-Hitachi 655 A 40 autosampler, a Perkin-Elmer LS 3 fluorescence spectrometer with a 25 μL flow cell, a Merck-Hitachi D 2500 chromato-integrator, and a Supelcosil LC 8 DB 5 μm 50 × 4·6 mm column. The mobile phase consisted of 50 mM $KH_2PO_4$, 25% acetonitrile and

Table 1. Haemodynamic and ECG parameters before and after verapamil.

| | Control | Verapamil (0·3 mg kg$^{-1}$) 5 min | Verapamil (0·3 mg kg$^{-1}$) 30 min | Verapamil (+0·3 mg kg$^{-1}$) 5 min | Verapamil (+0·3 mg kg$^{-1}$) 30 min |
|---|---|---|---|---|---|
| SAP (kPa) | 17·9±0·7 | 16·6±0·7* | 17·8±0·6 | 17·0±0·6** | 17·2±0·5* |
| DAP (kPa) | 11·3±0·3 | 10·3±0·3** | 11·0±0·4 | 10·4±0·3** | 10·5±0·4* |
| PQ (ms) | 91±4 | 121±6*** | 101±5* | 123±8*** | 105±5** |
| QRS (ms) | 60±7 | 62±7 | 62±6 | 57±5 | 58±4 |
| RR (ms) | 521±30 | 393±26** | 510±30 | 413±21** | 488±15 |
| QT (ms) | 196±5 | 186±6* | 196±5 | 184±6* | 196±5 |
| QTc (ms) | 274±10 | 300±11** | 276±8 | 288±7* | 281±8 |
| $QT_L$ (ms) | 244±6 | 247±5 | 245±5 | 245±5 | 247±5 |

Data = mean values ± s.e.m. 5 min: maximum changes, 30 min: start of programmed electrical stimulation. *$P<0·05$, **$P<0·01$, ***$P<0·001$ compared with control. SAP, DAP = systolic and diastolic blood pressure, respectively (1 kPa = 7·5 mm Hg); QTc = QTc interval = heart rate corrected QT interval calculated from the Bazett formula; $QT_L$ = heart rate corrected QT interval calculated from a formula assuming a linear relationship between QT and RR.

0·015% triethylamine; to achieve pH 3·0, concentrated HCl was added. The excitation wavelength was 230 nm and the emission wavelength 320 nm. Standards were prepared of D 517-HCl and verapamil hydrochloride, which were supplied by Knoll AG (Ludwigshafen, Germany). Linear calibration curves with verapamil concentrations of up to 150 ng mL$^{-1}$ were obtained by addition of 50 μL standard solution to 500 μL blank dog plasma.

*Statistical analysis*

Results are expressed as mean values ± s.e.m. unless otherwise stated. Student's *t*-test for paired data was used for statistical evaluation. A *P*-value of 0·05 was considered the limit of statistical significance.

## Results

*Haemodynamic and ECG parameters*

Maximum changes in haemodynamic and ECG parameters were observed 5 min after administration of the respective doses of verapamil (Table 1).

Table 2. Electrophysiological parameters before and after verapamil.

| | Control | Verapamil (0·3 mg kg$^{-1}$) | Verapamil (+0·3 mg kg$^{-1}$) |
|---|---|---|---|
| 2:1 (ms) | 154±7 | 183±8** | 191±7*** |
| Th-LAD (mA) | 1·6±0·5 | 1·6±0·5 | 1·6±0·5 |
| ERP-LAD330 (ms) | 121±5 | 121±5 | 123±5 |
| ERP-LAD250 (ms) | 118±5 | 118±5 | 119±5 |
| Th-LCX (mA) | 1·3±0·2 | 1·4±0·3 | 1·3±0·2 |
| ERP-LCX330 (ms) | 122±3 | 125±4 | 126±4 |
| ERP-LCX250 (ms) | 117±3 | 121±4 | 121±3 |
| Th-RV (mA) | 3·0±0·3 | 3·0±0·3 | 3·0±0·3 |
| ERP-RV330 (ms) | 128±5 | 129±3 | 133±4 |
| ERP-RV250 (ms) | 124±4 | 127±3 | 128±3 |
| Conduction time (ms) | 65±3 | 67±4* | 69±3* |

Data = mean values ± s.e.m. *$P<0·05$, **$P<0·01$, ***$P<0·001$ compared with control. 2:1 = 2:1 AV-conduction point, the maximal cycle length leading to a stable 2:1 atrioventricular conduction pattern following continuous atrial stimulation of 30 s duration; Th-LAD, LCX, RV = threshold of the LAD, LCX and right ventricular area; ERP-LAD, LCX, RV 330 and 250 = effective refractory period of the LAD, LCX and right ventricular area as assessed by the extrastimulus technique. Basic rhythm: 8 beats with a coupling interval of 330 or 250 ms; conduction time = intraventricular conduction time from the right ventricular area to the LAD area.

The first dose of verapamil induced a transient decrease in both systolic and diastolic blood pressure, which lasted for 20 min. After the second dose, systolic and diastolic blood pressure remained decreased for the rest of the observation period.

A prolongation of the PQ interval by 33% appeared 5 min after administration of the first dose. Twenty-five min later, at the beginning of PES 2, the increase in PQ interval had declined to 10%. The maximum increase in PQ interval after the second dose was again 33%; at the beginning of PES 3 an increase of 15% was still present. Verapamil did not significantly alter QRS duration. After each dose the shortening of RR and QT intervals was transient, reaching statistical significance only for the first ten min after drug administration. A significant increase of the QTc interval was registered 5 min after the respective doses of verapamil, whereas $QT_L$ remained unaltered.

*Electrophysiological parameters*

Table 2 presents the electrophysiological data as assessed by programmed electrical stimulation. The 2:1 AV-conduction point was increased by 19% after the first and by 24% after the second dose of verapamil. Ventricular effective refractory periods of the right ventricular site and of the two left ventricular sites showed no significant changes after either dose. A slight, but significant prolongation of intraventric-

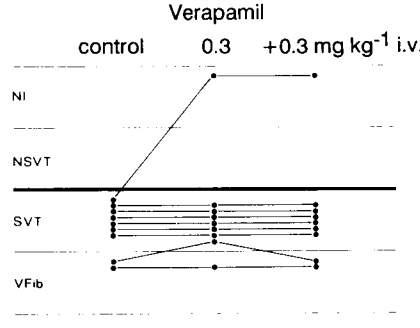


FIG. 2. Antiarrhythmic efficacy as assessed by programmed electrical stimulation. NI = non-inducible; NSVT = non-sustained ventricular tachycardia; SVT = sustained ventricular tachycardia; VFib = ventricular fibrillation.

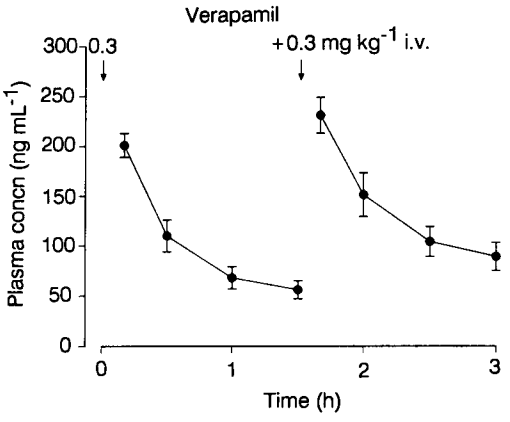


FIG. 3. Plasma levels of verapamil. Data = mean values ± s.e.m. shown by vertical bars.

ular conduction time was observed after both doses of verapamil.

*Arrhythmia induction*

In the drug-free control PES all animals were inducible (Fig. 2). Two dogs developed ventricular fibrillation and 7 dogs showed sustained ventricular tachycardia in response to PES. The first dose of verapamil rendered one dog non-inducible, one dog exhibited SVT instead of ventricular fibrillation, but in 7 dogs inducibility remained unaltered. The second dose prevented the induction of SVT again only in one case, whereas no antiarrhythmic efficacy was observed in the remaining eight animals. In summary verapamil was effective in only 11% of all induction attempts (n = 18). A non-significant increase in mean cycle length of induced tachycardias was observed after both doses of verapamil. The values amounted to 113·5 ± 4·7 ms during control, 119·4 ± 6·1 after the first and 116·8 ± 5·9 ms after the second dose of verapamil. Plasma levels of verapamil (Fig. 3) were in the range of 68 to 110 ng mL$^{-1}$ during PES 2 and 104 to 151 ng mL$^{-1}$ during PES 3. The antiarrythmic effect observed in the solitary responder was not associated with higher plasma levels; haemodynamic, ECG and electrophysiological parameters were also comparable with those measured in the non-responders.

## Discussion

We have recently presented a canine model (Krumpl et al 1989a, b, 1990a) in which programmed electrical stimulation was used to evaluate the antiarrhythmic efficacy of various antiarrhythmic drugs in the late myocardial infarction phase after coronary occlusion. The inducibility of ventricular arrhythmias remains stable over the course of at least one month (Krumpl et al 1990a). All experiments were carried out in the conscious state to avoid the influence of anaesthesia on arrhythmic outcome (Echt et al 1983; Hunt & Ross 1988), thus mimicking closely the clinical situation.

The value of verapamil in the management of ventricular arrhythmias is still controversial. Verapamil has proved effective only against special types of ventricular arrhythmias such as ventricular tachycardia in acute myocardial infarction (Brooks et al 1980; Bergey et al 1984; Curtis et al 1984; Grenadier et al 1984; Rolli et al 1988), idiopathic ventricular tachycardia with a morphological pattern of right bundle branch block and left axis deviation (Belhassen et al 1981, 1984; German et al 1983; Lin et al 1983; Sakurai et al 1988) and exercise-triggered ventricular tachycardia with a morphological pattern of left bundle branch block and right axis deviation (Wu et al 1981). The current study was undertaken to investigate the influence of verapamil on PES-induced ventricular arrhythmias in the late myocardial infarction period. There have been only a few studies which have tested the efficacy of verapamil in this type of arrhythmia. Sung et al (1983) found verapamil ineffective in 10 patients with inducible ventricular tachycardia; in another clinical study verapamil prevented induction of ventricular tachycardia in only 3 of 16 patients (Mason et al 1983). Two experimental studies gave conflicting results. Davis et al (1982) showed that verapamil 0·2 and 0·4 mg kg$^{-1}$ did not exert any antiarrhythmic effect in dogs with reperfused hearts. However, El-Sherif & Lazzara (1979) reported that verapamil 0·5 mg kg$^{-1}$ was able to prevent electrically-induced arrhythmias in a dog model 3 to 7 days after permanent coronary occlusion.

In our model only one animal responded to verapamil. Whereas El-Sherif & Lazzara observed improvement of conduction in the re-entrant pathway and attributed the efficacy of verapamil to this phenomenon, conduction time in our experiments showed, in fact, a slight increase. El-Sherif & Lazzara (1979) postulated that the observed improvement of conduction may be due to improvement of the depressed $Na^+$ channels by sparing of endogenous energy resources and that slow-response action potentials play no significant role in the genesis of the ischaemia-related re-entrant ventricular arrhythmias. Several studies have been performed to elucidate the mechanisms which are responsible for the effects of verapamil on ischaemia-induced conduction changes (Nakaya et al 1981; Nakaya & Kanno 1982; Fleet et al 1986): a decrease in the rate and inhomogeneity of extracellular $[K^+]$ accumulation and a prevention of fall in pH may mediate the effect of verapamil on conduction during ischaemia (Fleet et al 1986). In contrast to the above studies the present investigations were performed at a later phase, i.e. 17 ± 3 days after the occlusion-reperfusion procedure. Although slow conduction is still present at that time, infarct structure and cellular electrophysiology of infarcts are different during the healing phase, which encompasses the first two weeks after coronary occlusion, and the healed phase thereafter (Janse & Wit 1989). Anatomical and histological studies revealed that especially in reperfused infarcts during the healed phase surviving myocardial fibres are separated from each other by large amounts of connective tissue, which lead to a high coupling resistance and, thus, to slowing of conduction. This means that conduction slowdown during the first two weeks after coronary occlusion is mainly due to changes in transmembrane potentials and changes in $K^+$ distribution and pH, whereas during the healed phase the high coupling resistance accounts for depression of conduction. There is a lack of data concerning the influence of verapamil on conduction time during the healed phase. It is likely that verapamil does not influence coupling resistance; on the contrary, verapamil further depresses conduction because of its potential to reduce the

safety factor of conduction by elevating the threshold potential and by reducing both the amplitude and steepness of the upstroke in Purkinje cells and in slow response potentials (Cranefield 1975).

Consistent with the increase in intraventricular conduction time, we observed a slight, but not significant, trend towards longer cycle lengths of induced ventricular tachycardia. Ventricular refractory periods did not exhibit a significant change after verapamil. The underlying mechanism of arrhythmias induced by programmed electrical stimulation is re-entry (Michelson et al 1980). Prolongation of conduction time without sufficient lengthening of ventricular refractory periods may thus result in a shortening of the area of refractoriness and favour initiation of ventricular tachycardia rather than prevent it (Sakurai et al 1988).

Whereas the plasma levels of verapamil were not determined in the two experimental studies (El-Sherif & Lazzara 1979; Davis et al 1982), a mean plasma concentration of 126 ng $mL^{-1}$ was reported in the clinical study by Sung et al (1983). In the present study plasma level determination showed values in the range of 68 to 110 ng $mL^{-1}$ during PES 2 and 104 to 151 ng $mL^{-1}$ during PES 3.

A value of 120 ng $mL^{-1}$ has been recommended for the termination of supraventricular tachycardia (Benet & Williams 1990). The different efficacy of verapamil in supraventricular as opposed to ventricular arrhythmias can easily be explained by the fact that verapamil is generally more effective in the slow channel-dependent tissues of the sinoatrial and atrioventricular nodes. Although it is useful to study the actions on these structures in-vitro or in anaesthetized animals, investigations in conscious dogs with an intact autonomic nervous system are necessary to determine the net effect of verapamil since it has been shown that the depressant effects of calcium antagonists on atrial structures may be variably modified by reflex sympathetic activation secondary to the hypotensive effect (Kawai et al 1981; Nakaya et al 1983).

In the present study verapamil induced a transient increase in sinus rate in response to the blood pressure reduction. This is in agreement with data derived from other experimental investigations in conscious animals (Nakaya et al 1983; Schneider et al 1988) and clinical studies (Kawai et al 1981) and contrasts with the slowing of sinus rate observed in isolated tissues (Yamaguchi et al 1978). As for the atrioventricular conduction system, we found an increase in the 2:1 AV-conduction point, a parameter which has been shown to correlate well with the refractoriness of the AV-node (Bissett et al 1975); the PQ interval, reflecting atrioventricular conduction time, was prolonged by up to 33%. There are several possibilities to explain the fact that the direct negative chronotropic effect, but not the negative chronotropic effect, of verapamil is counteracted by reflex factors: the atrioventricular node is more sensitive to verapamil than the sinus node (Mangiardi et al 1978); the sinus and atrioventricular nodes have a different sensitivity to the reflex release of sympathetic transmitters (Kawai et al 1981); the increase in AV-conduction time may be caused not only by a direct depressant effect on the slow channels within the AV-node, but also by additional cholinergic stimulation (Angus et al 1976).

Neither dose of verapamil altered QRS duration significantly, but a significant decrease in QT interval was registered 5 min after each dose of verapamil. This change in QT interval may be due to the observed increase in heart rate. In principle, one might expect that after verapamil, which does not influence ventricular repolarization time, the rate-corrected QT interval would remain unchanged. Nevertheless, in the present study verapamil induced a significant increase in QTc interval 5 min after drug administration. In our opinion this observation provides further support for the concept that after sudden steep increases in heart rate the Bazett formula is unsuitable for the determination of the rate-corrected QT interval (Ahnve & Vallin 1982). The $QT_L$ formula, which was developed in our laboratory for conscious dogs with reference to the Van de Water formula for anaesthetized dogs (Van de Water et al 1989) did not exhibit any significant change after verapamil. Further investigations will be necessary to examine whether this formula is also of value in the clinical setting and whether it is superior to the Bazett formula.

In summary, although verapamil has been shown to improve intraventricular conduction during ischaemia or in the first days after acute myocardial infarction, the present study illustrates that verapamil moderately depresses intraventricular conduction fourteen days after the induction of myocardial infarction. In conclusion, verapamil is of only negligible value for the management of PES-induced ventricular arrhythmias in a conscious dog model, in which both lignocaine (Todt et al 1989; Krumpl et al 1990a) as well as labetalol (Krumpl et al 1990b) exhibited good antiarrhythmic efficacy.

*Acknowledgements*

This work was supported by the Jubiläumsfond der Österreichischen Nationalbank. Dr Krejcy and Dr Todt were supported by a grant of the Fonds zur Förderung der wissenschaftlichen Forschung. The authors wish to thank P. Krivanek for determination of the verapamil plasma levels and A. Karel for expert technical assistance.

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