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SPECIAL REPORT

Sildenafil (Viagra) reduces arrhythmia severity during ischaemia 24 h after oral administration in dogs

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Sildenafil (Viagra) prolongs repolarisation in cardiac muscle, an effect that could lead to ventricular fibrillation (VF). Sildenafil (2 mg kg^{-1}) was given by mouth to 12 mongrel dogs and, 24 h later, these dogs were anaesthetised, thoracotomised and subjected to a 25 min occlusion of the anterior descending coronary artery. Haemodynamic parameters were similar in this and the control group, but there were fewer and less serious ventricular arrhythmias during occlusion in the sildenafil group (VF 17 vs 60%; ventricular premature beats 140 ± 52 vs 437 ± 127% and episodes of ventricular tachycardia 4.0 ± 3.2 vs 19.3 ± 7.7%, all $P < 0.05$). However, reperfusion VF and indices of ischaemia severity (epicardial ST-segment mapping, inhomogeneity) were not modified by the drug. Sildenafil increased the QT interval, especially during ischaemia. Our conclusion is that ischaemia-induced ventricular arrhythmias are reduced by sildenafil, but this protection is less pronounced than that following cardiac pacing or exercise.
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Abbreviations: LAD, left anterior descending; LV, left ventricular; LVEDP, left ventricular end-diastolic pressure; VF, ventricular fibrillation; VPB, ventricular premature beat; VT, ventricular tachycardia

Introduction Sildenafil (Viagra) is a highly selective and potent inhibitor of the breakdown of guanosine 3,5,-cyclic monophosphate (cGMP) by its specific phosphodiesterase isoenzyme (PDE5; Wallis *et al*., 1999), and is used in the treatment of erectile dysfunction (recently reviewed by Gresser & Gleiter, 2002). Questions arose about the safety of the drug in patients with ischaemic heart disease and anecdotal reports of cardiovascular deaths associated with its use generated early concern, although a recent review came to the conclusion that the 'number of deaths potentially associated with sildenafil appears to be extremely small' (Cheitlin *et al*., 1999), even though there were 130 reported cases of cardiac death in the U.S. alone in the initial 6-month period of its use. The fact that sildenafil prolongs cardiac repolarisation by blocking the rapid component of the delayed rectifier current I_k, and the fact that this may lead to triggered ventricular arrhythmias including fibrillation (Priori, 1998), has led to the suggestion that this may be a possible mechanism of the few reported cases of sudden cardiac death that have been associated with sildenafil usage (Geelen *et al*., 2000).

More recently, there have been reports that sildenafil may protect the myocardium by mechanisms similar to those thought to be responsible for the cardioprotective effects of ischaemic preconditioning. Thus, in rabbits, sildenafil given intravenously 1 h, and orally 24 h, prior to acute coronary artery occlusion, reduced the infarct size through a mechanism that involved the opening of mitochondrial K_{ATP} channels, since the protection was blocked by 5-hydroxydecanoate (Ockaili *et al*., 2002). In mice, this protection is mediated by nitric oxide (NO); there was evidence for increases in both eNOS and, later, iNOS and a selective inhibitor of iNOS (1400W) abolished the delayed sildenafil-induced reduction in infarct size (Salloum *et al*., 2003). These mechanisms are reminiscent of NO involvement in mediating the early protection afforded by brief periods of coronary artery occlusion (ischaemic preconditioning; Végh *et al*., 1992a) and the delayed protection by brief periods of ischaemia and by cardiac pacing (Végh *et al*., 1994; Qui *et al*., 1997, Kis *et al*., 1999), both of which are also mediated by NO. The fact that cGMP levels are increased under these conditions is also consistent with the finding that inhibitors of guanylyl cyclase prevent the early (Végh *et al*., 1992b) and late (Kodani *et al*., 2002) effects of ischaemic preconditioning. This led to the suggestion to examine whether selective inhibition of the PDE enzyme responsible for its breakdown is, like preconditioning, a powerful antiarrhythmic procedure (Végh *et al*., 1992b). This suggestion is explored in the present report.

To our knowledge, there have been no studies examining the effects of orally administered sildenafil on the severity of those life-threatening ventricular arrhythmias that arise early after acute coronary occlusion and that are implicated in some cases of sudden cardiac death in the clinical situation. The present study examines the effects of orally administered sildenafil in an established large animal model of ischaemia and reperfusion-induced arrhythmias.

Methods These have been described in detail previously (Végh *et al*., 1992a, c). In brief, 22 adult mongrel dogs (mean weight 25 ± 1 kg) were used for the study, 12 of which had been given, by mouth, 50 mg sildenafil citrate (viagra) 20–25 h previously; this dose (2.0 mg kg^{-1}) is somewhat higher than

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recommended clinical dose (about 1.4 mg kg^{-1}). The dogs were anaesthetised with a mixture of chloralose and urethane (60 and 200 mg kg^{-1} i.v., respectively) and ventilated with room air using a Harvard Respirator. Polyethylene catheters were inserted into the right femoral artery (for monitoring blood pressure) and into the right femoral vein (for further anaesthetic administration as required). Another catheter was introduced into the cavity of the left ventricle, through the left femoral artery, for the measurement of left ventricular systolic (LVSP) and end-diastolic (LVEDP) pressures, as well as changes in positive and negative dP/dt_{max}.

The animals were thoracotomised at the fifth intercostal space and the anterior descending branch of the left coronary artery (LAD) prepared for occlusion just proximal to the first main diagonal branch. Blood flow was measured on the circumflex branch of the left coronary artery (LCX) by means of an electromagnetic flow probe. Epicardial ST-segment changes and, in some dogs, the degree of inhomogeneity of electrical activation were measured from the left ventricular (LV) wall distal to the occlusion site, using a 'composite' electrode (Végh *et al*., 1992c). All parameters, together with a limb lead electrocardiogram, were recorded on an eight-channel Medicor R81 recorder.

Ventricular arrhythmias during coronary artery occlusion and following reperfusion were assessed (Végh *et al*., 1992c). In brief, the total number of ventricular premature beats (VPBs), the incidence and number of episodes of ventricular tachycardia (VT) and the incidence of ventricular fibrillation (VF) were evaluated. The risk area following coronary artery occlusion was assessed in each dog at the end of the experiment, by injecting patent blue V dye into the re-occluded coronary artery, and was expressed as a percentage of the LV wall, together with the septum (Kis *et al*., 1999).

The origin and upkeep of these dogs were in accord with Hungarian law (XXVIII, chapter IV, paragraph 31) regarding large experimental animals, which comply with those of the European Commission, as described in the regulations dated December 16, 1991.

All the data are expressed as means ± s.e.m., and differences between means compared by a Student's *t*-test corrected for multiple comparisons using a two-way ANOVA. VPBs were compared using the Mann–Whitney rank sum test, and the incidences of arrhythmias (such as VT, VF) and survival from the combined ischaemia–reperfusion insult were compared using the Fisher exact test. Differences between groups were considered significant when $P<0.05$.

Results The mean arterial blood pressure was slightly lower in the sildenafil-treated dogs just prior to occlusion (98 ± 3 cp 108 ± 5 mmHg in the controls; n.s.). Diastolic coronary blood flow was also a little lower (103 ± 6 and 115 ± 12 ml min^{-1}, respectively), but coronary vascular resistance was similar (0.87 ± 0.05 and 0.90 ± 0.09 mmHg ml^{-1} min^{-1}). There were also no significant differences between the two groups with respect to the other measured haemodynamic parameters (LVEDP 5.3 ± 0.3 and 4.4 ± 0.4 mmHg; LV dP/dt (+ve) 3627 ± 90 and 3518 ± 269 mmHg s^{-1} and (−ve) 3345 ± 184 and 3584 ± 302 mmHg s^{-1}, heart rate 146 ± 4 and 163 ± 4 beats min^{-1}).

Haemodynamic changes on occlusion were also similar and significant ($P<0.05$), compared to pre-occlusion levels, in both groups. There were decreases in the mean arterial blood pressure of 9 ± 2 and 10 ± 2 mmHg, respectively, in the sildenafil and control dogs, and in LV dP/dt (+ve) of 1102 ± 178 and 828 ± 141 mmHg s^{-1}. There were increases in LVEDP (of 18.0 ± 1.1 and 18.2 ± 1.5 mmHg), heart rate (of 2 ± 2 and 7 ± 1 beats min^{-1}, n.s.) and in the left circumflex coronary blood flow. This was somewhat more pronounced in the sildenafil-treated dogs (31 ± 4 ml min^{-1}) than in the controls (22 ± 3 ml min^{-1}; $P<0.05$).

The major difference between the two groups was in arrhythmia severity during the coronary occlusion. This is illustrated in Figure 1. There were fewer ventricular ectopic beats and fewer episodes of VT in the sildenafil-treated dogs, and lower incidences of both VT and VF during occlusion, although reperfusion-induced VF was unaffected by the drug. The distribution of arrhythmias over the occlusion period is also shown in Figure 1. Those dogs that fibrillated did so during the crucial 15–20 min period, that is, during phase Ib. The QT interval was prolonged by sildenafil (262 ± 11 ms compared to 226 ± 9 ms in the control; $P<0.05$). This was more marked during ischaemia (i.e. 275 ± 8 ms compared to 236 ± 7 ms at 5 min into the occlusion period; $P<0.05$).

We assessed the severity of ischaemia during the occlusion period by mapping epicardial ST-segment changes and measuring the degree of inhomogeneity. There was no significant difference between the two groups with regard to the severity of ischaemia assessed by these methods. There was also no difference in the area at risk of infarction (35.1 ± 1.5 and 34.3 ± 0.9% in the sildenafil and control dogs, respectively).

Discussion The purpose of the present study was to determine whether sildenafil administration influenced

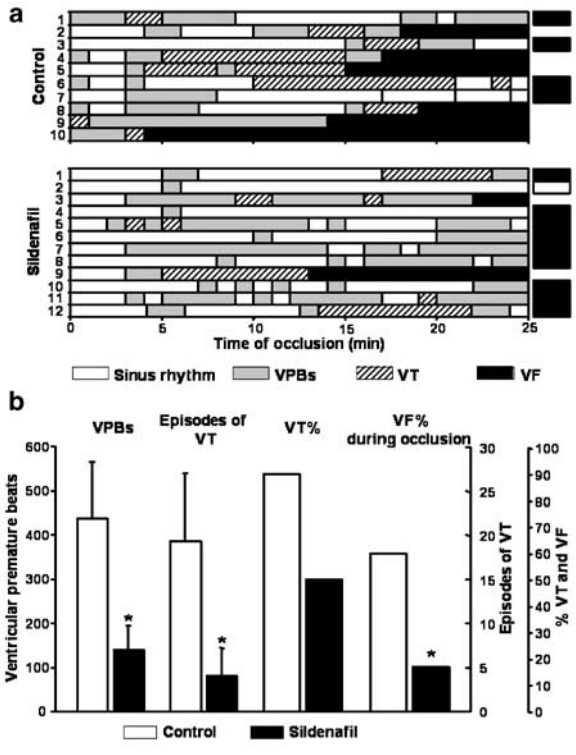

Figure 1 (a) The distribution of ventricular arrhythmias during a 25-min coronary artery occlusion and (b) the total number of VPBs, the incidence and the number of episodes of VT, and the incidence of VF in control dogs and in dogs treated with sildenafil. Values are means ± s.e.m. *$P<0.05$ compared with controls. The severity of arrhythmias is less marked in the sildenafil-treated dogs.

arrhythmia severity 24 h after administration. This time was chosen because this drug has been shown, like delayed ischaemic preconditioning induced by brief periods of coronary artery occlusion, by cardiac pacing or by exercise, to protect the myocardium against the consequences of ischaemia by upregulating iNOS. Kukreja's group (Ockaili *et al*., 2002; Salloum *et al*., 2003) have shown that a delayed protection, as assessed by a reduction in infarct size, is evident at this time and that it is mediated by NO. The delayed antiarrhythmic effect of sildenafil could also involve NO, as with cardiac pacing (Kis *et al*., 1999) and exercise (Babai *et al*., 2002). The moderate prolongation of QT duration could also contribute, since drugs that prolong cardiac repolarisation, like sildenafil (Geelen *et al*., 2000), can also be protective against ischaemia-induced arrhythmias. There was certainly no evidence in this experimental model that sildenafil worsens these arrhythmias or that VF (and sudden cardiac death) is more likely under these conditions. We have not examined whether such protection against arrhythmias is also present soon after administration, especially if the hearts are paced to levels one might expect during sexual activity. Certainly, there was no evidence in the Ockaili *et al*. (2002) study that coronary artery occlusion soon (30 min) after (intravenous) administration increased myocardial ischaemic damage; indeed, protection was just as marked when a coronary artery was occluded early after sildenafil administration, as it was when the occlusion was delayed for 24 h. As in the study of Przyklenk & Kloner (2001), we could find no evidence that the severity of ischaemia was modified by the drug.

The mechanism by which PDE5 inhibition leads to NOS upregulation and increased NO production is unclear, since cardiac myocytes do not contain the enzyme (Wallis *et al*., 1999). Salloum *et al*. (2003) did not study its distribution, and it could be that the increase in cyclic GMP occurs within the coronary vasculature. This would make the protection similar, in mechanism, to ischaemic preconditioning, where it has been proposed (Parratt & Végh, 1997) that the genesis of the protection is at the level of the endothelial cell. Various stimuli, by activating endothelial receptors, would activate NO production by the cNOS enzyme and this NO, diffusing to the myocyte, triggers the cascade leading, *via* the opening of mitochondrial K_{ATP} channels, to protection against the consequences of ischaemia. The early generation of NO would also trigger further formation *via* the iNOS enzyme. The key role of endothelial cells would explain why preconditioning is a general phenomenon and not restricted to the heart.

In conclusion, we show that sildenafil leads to a delayed protection against those ventricular arrhythmias that occur early after acute coronary artery occlusion. This antiarrhythmic effect is not as marked as that resulting from cardiac pacing or exercise.

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