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# The haemodynamic actions of ZENECA ZD7288, a novel sino-atrial node function modulator, in the exercising beagle: a comparison with zatebradine and propranolol

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**1** ZENECA ZD7288 (4-(*N*-ethyl-*N*-phenylamino)-1,2-dimethyl-6-(methylamino) pyrimidinium chloride, formerly ICI D7288) is a novel sino-atrial node function modulator which selectively slows heart rate.

**2** The haemodynamic effects of ZD7288 (0.1, 0.3 and 1.0 mg kg$^{-1}$, i.v.) have been evaluated and compared with those of placebo (physiological saline), zatebradine (ULFS 49, 0.1, 0.3 and 1.0 mg kg$^{-1}$, i.v.) and propanolol (0.03, 0.1, and 0.3 mg kg$^{-1}$, i.v.) in beagles chronically instrumented for measurement of heart rate, aortic pressure, aortic flow and $dP_{LV}/dt_{max}$. The dogs were trained to run at 6.5 k h$^{-1}$ on a level treadmill for 5 min at half hourly intervals over a period of 4 h. Drugs were dosed cumulatively after the second, fourth and sixth exercise periods.

**3** Control experiments demonstrated a degree of accommodation to repeated exercise over a period of 4 h. Resting heart rate decreased by 21 beats min$^{-1}$, but heart rate response to exercise was maintained, whereas $dP_{LV}/dt_{max}$ at rest remained steady while the response to exercise decreased significantly (by 25% after 2 h, $P<0.05$).

**4** ZD7288 and zatebradine both decreased heart rate during exercise in a dose-dependent manner, whilst heart rate at rest did not differ from resting heart rates in saline dosed control animals. In contrast, heart rate at rest and during exercise were lowered equally by the lowest doses of propranolol (approximately by 30 beats min$^{-1}$), and additional doses caused only minor additional decreases. The exercise-induced tachycardia was maintained within 12% of pre-dose levels, presumably by withdrawal of vagal tone.

**5** Cardiac inotropism, as indicated by $dP_{LV}/dt_{max}$, was not affected by ZD7288 or zatebradine at rest, although the inotropic response to exercise decreased in proportion to the decreases in exercise-induced tachycardia. Propranolol caused a marked dose-dependent decrease in the exercise-induced inotropic response (by 85% at 0.3 mg kg$^{-1}$).

**6** Whilst the sino-atrial node modulators increased stroke volume at rest, and augmented increases in response to exercise, propranolol did not affect resting stroke volume and decreased the responses to exercise.

**7** Cardiac output at rest and cardiac output increases during exercise were well maintained in the presence of ZD7288 and zatebradine in contrast to propranolol which induced a significant depression of cardiac output, both at rest and during exercise. Propranolol also caused significant systemic vasoconstriction.

**8** In conclusion, ZD7288 has haemodynamic actions comparable to those of zatebradine despite their chemical dissimilarity. ZD7288 may be of benefit in the treatment of ischaemic heart disease by reducing heart rate without impairing cardiac function.

**Keywords:** Sino-atrial node; selective bradycardic agent; heart rate; exercise; haemodynamics; ZD7288; zatebradine; propranolol

## Introduction

β-Adrenoceptor antagonists, first introduced with the expressed purpose of reducing the increases in myocardial oxygen consumption consequent upon sympathetically mediated reflex responses to the demands of physical exercise or emotional stress (Shanks, 1966) in myocardial ischaemia, can, as a consequence of their mode of action, interfere with inotropic support of compromised myocardium in the instance of myocardial dysfunction. Calcium channel blockers aimed at influencing myocardial blood flow and peripheral resistance in the treatment of ischaemic heart disease, can also influence contractile function in an adverse fashion.

The so-called 'specific bradycardic agents' have been developed in recent years as an alternative approach to combating the effects of myocardial ischaemia. By selectively influencing sino-atrial pacemaker diastolic depolarization rate, these compounds lower heart rate, reducing myocardial oxygen demand whilst improving endocardial blood supply (Gross & Dämmgen, 1987) by prolonging diastolic coronary perfusion interval. They cause little depression of contractile function or interference with sympathetic nervous control (Lillie, 1991).

Recently, the novel sino-atrial node function modulator, ZENECA ZD7288 (Hargreaves *et al.*, 1992), with potential usefulness in the treatment of *angina pectoris*, has been described, along with its actions in a variety of biological preparations (Rouse & Johnson, 1992; Marshall *et al.*, 1993; BoSmith *et al.*, 1993). An account of the haemodynamic effects of ZD7288 in anaesthetized dogs is described in detail in the preceding paper (Rouse & Johnson, 1994) in this issue.

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Raberger *et al.* (1987) and Guth *et al.* (1987) have each modelled exercise-induced regional contractile dysfunction in dogs trained to run on a treadmill, thus mimicking the main features of exercise-induced *angina pectoris* as seen in man. They demonstrated that heart rate reduction by zatebradine was of distinct benefit in their models.

Since it seems reasonable to suppose that the demonstration of heart rate reduction alone, both at rest and during exercise, even in the absence of myocardial dysfunction, would be indicative of comparable benefits, the actions of ZD7288 on haemodynamics were investigated at rest and during treadmill exercise in conscious beagle dogs without coronary flow restrictions. In this paper, the actions of ZD7288 are compared with those of zatebradine, and the β-adrenoceptor antagonist, propranolol.

## Methods

Beagles of the Alderley Park strain were selected for their ability to run at 6.5 km $h^{-1}$ on a treadmill (Cambridge model XT 1000). After completion of treadmill training, transducers were implanted in selected animals for measurement of haemodynamic responses to exercise.

Premedication consisted of acepromazine maleate 30 μg $kg^{-1}$ with Temgesic 10 μg $kg^{-1}$. Anaesthesia was induced with propofol (Diprivan), 8 to 10 ml (1% w/v) given into a foreleg vein. The trachea was intubated with a cuffed endotracheal tube. The neck region and thorax were clipped and sites of incision were shaved and swabbed liberally with cetrimide in 70% alcohol:water solution. Maintenance anaesthesia was a mixture of 'Fluothane' (halothane) 1.5% approximately, and nitrous oxide (4 l $min^{-1}$) with a supplement of oxygen (3 to 4 l $min^{-1}$). Using full aseptic precautions, the right scalenius muscle was resected rostrally, and a right fourth intercostal thoracotomy was performed. The sensors to be implanted, which had been sterilized by immersion in 10% cetrimide in 70% alcohol:water solution for 1 h, were then inserted into the thoracic cavity *via* a separate small incision behind the scalenius muscle through the second intercostal space, and the pericardium was opened.

The sensors implanted were as follows: a Königsberg P7 pressure transducer inserted into the left ventricular cavity via the apical dimple and secured with a purse string suture, a 'Skalar' electromagnetic flow probe positioned around the aortic root after careful resection of the aortic fat pad and a tripolar silver recording electrode (including 'earth'), over the interventricular sulcus.

During positioning of sensors, it was important that signals were monitored to ensure correct positioning and function of the transducers.

The cut edges of the pericardium were juxtaposed with a single suture, and the thoracotomy was closed by approximating the ribs with three Dacron sutures. The intercostal muscles were carefully sutured together to seal the incision. The scalenus muscle was carefully re-positioned, sealing the exit of the transducer leads. The latter were tunnelled subcutaneously out through a small incision over the right shoulder. The terminating 'neck button' connectors were tunnelled from there to circular, tight fitting exit incisions in the dorsal surface of the neck.

All incisions were closed in layers. Animals were allowed to recover with analgesic and antibiotic cover under the care of qualified veterinarians for at least two weeks, until sinus arrythmia, which is normally observed in healthy dogs at rest, was again in evidence, thereby indicating that alterations in autonomic balance in response to surgery were restored to normal.

Ten days after thoracotomy, under halothane anaesthesia with intravenous propofol induction, two 1mm internal diameter polyethylene catheters were implanted, one via the right jugular vein to the level of the right atrium for drug administration, and the other into the aortic root via the right carotid artery for measurement of blood pressure. These catheters were exteriorized on the dorsal surface of the neck. They were flushed regularly with sterile heparinized physiological saline to prevent blockage.

## Measurements

Dogs were connected to recording equipment by extended leads carried by a counter-balanced arm pivoted on the back of the treadmill, and attached at the free end to an ordinary dog collar worn by the experimental subject, so that the animal had complete freedom of movement within the confines of the treadmill. Aortic pressure was measured with a Statham Spectramed P10EZ transducer attached at shoulder level to the dog collar.

Employing a purpose-built analogue computing system clocked from the ventricular epicardiogram, voltages indicative of heart rate, rate of increase of left ventricular pressure during the isovolumic period of contraction ($dP_{LV}/dt_{max}$), systolic, true mean and diastolic aortic pressure were derived on a beat by beat basis. In addition, aortic flow velocity was integrated with respect to time as an index of

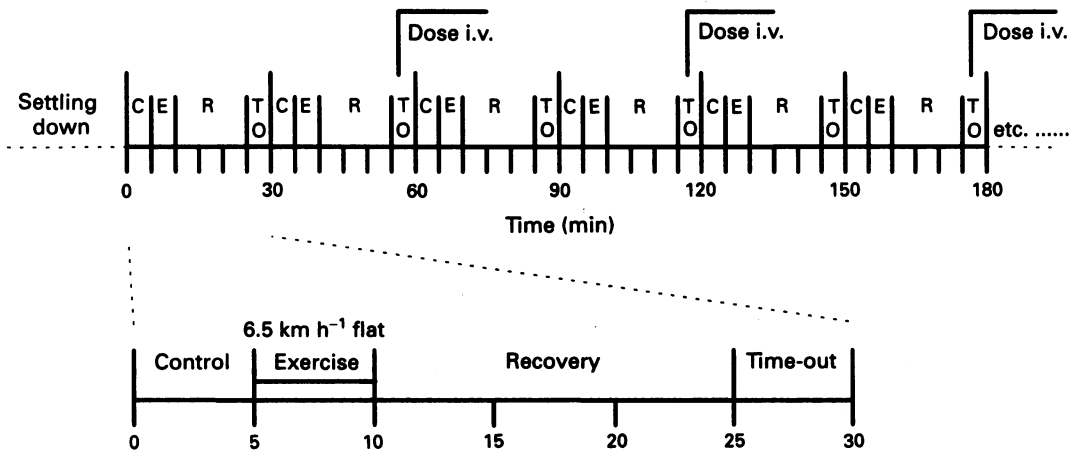


**Figure 1** The upper part of the figure denotes the experimental protocol consisting of eight successive 30 min duration exercise runs following an acclimatization interval during which the dog was allowed to settle down. Each period comprised data collection during 5 min at rest, during 5 min of level running at 6.5 km $h^{-1}$, then during 15 min recovery. A 5 min interval was allowed between runs for catheter flushing, rearrangements of leads and drug administration. Drugs were given after pairs of exercise runs, the results from which were meaned.

stroke volume (ignoring coronary reverse flow). During each cardiac cycle, the integrator operated in two modes, sampling filtered diastolic flow as the initial set-point while developed left ventricular pressure was less than a pre-set level (approximately 50 mmHg), and integrating when left ventricular pressure was in excess of that level. Thus, a voltage indicative of stroke volume with compensation for any drift in input flow level was also derived on a beat-by-beat basis.

The analogue voltages were digitized by a Tandon PC equipped with an 8-channel analogue-to-digital converter board. Using purpose-written software, values sampled each minute (as clocked by the computer) were logged to hard disc as minute-meaned values together with cardiac output and systemic mean vascular resistance calculated from sampled values of stroke volume, heart rate and blood pressure. In addition, sampled data were displayed graphically on-screen to monitor progress of the experiment.

A paper chart recording of analogue aortic and left ventricular pressure, aortic flow velocity and stroke volume, together with beat-by-beat heart rate, was make on a 'Graftek' WR3502 heated stylus recorder equipped with alpha-numeric printers. Using the latter, minute-mean values of variables, including calculated cardiac output and systemic vascular resistance, were printed to the recording chart by the computer each minute.

Lotus 'Symphony' spreadsheet software was used subsequently for data manipulation and analysis.

### *Protocol*

Drug effects were studied under the protocol illustrated by Figure 1. Each 30 min exercise period consisted of a 5 min control interval at rest followed by 5 min running at 6.5 km $h^{-1}$ with a 20 min recovery interval. A between-exercise

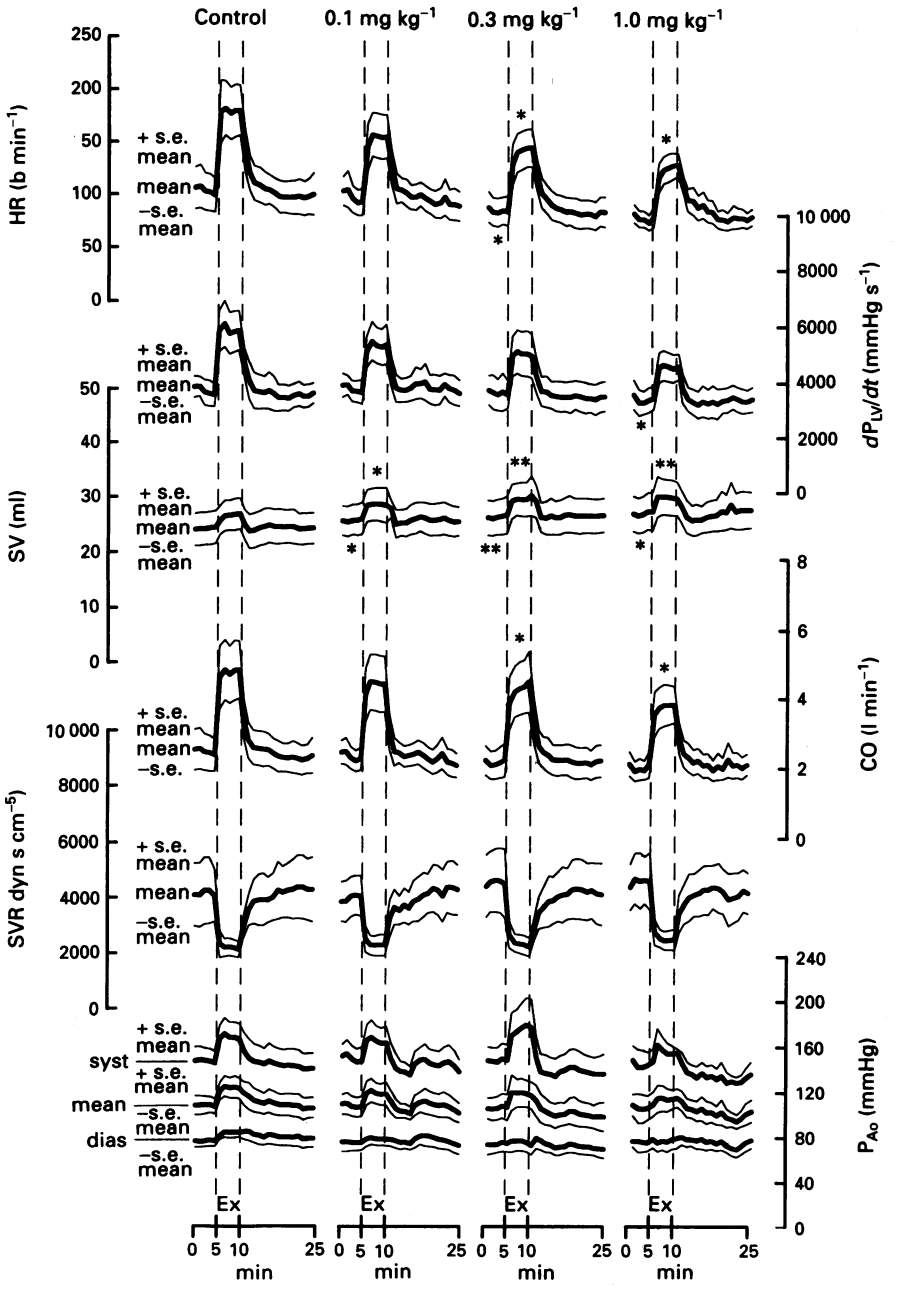


**Figure 2** Effects of cumulative doses of ZD7288 on haemodynamic responses to treadmill exercise in dogs (n = 4). Mean changes in heart rate, contractile function ($dP_{LV}/dt_{max}$), stroke volume (SV), cardiac output (CO), calculated systemic vascular resistance (SVR) and aortic blood pressure (PAo) from four dogs, together with s.e.means are shown. Each response is the mean of paired successive periods of exercise on the level at 6.5 km $h^{-1}$. ZD7288 caused a decrease of exercise heart rate with concomitant decrease of cardiac output. Stroke volume increased both at rest and during exercise (Ex). (Differences from respective pre-dose control values: $^{*}P<0.05$, $^{**}P<0.01$ by Student's paired $t$ test).

interval of 5 min, during which recording was suspended, was allowed for flushing of catheters, repositioning of recording leads if required, and for drug administration, when due.

An experiment consisted of 8 exercise runs over a period of 4 h. The drug under study was administered intravenously between each pair of exercise runs, so that three cumulative doses of drug were studied in each experiment. Results from pairs of exercise runs between drug doses were meaned.

### *Doses*

Cumulative doses were dissolved in sterile physiological saline solution and given intravenously as follows: ZD7288 and zatebradine, 0.1, 0.3 and 1.0 mg $kg^{-1}$; and propranolol, 0.03, 0.1 and 0.3 mg $kg^{-1}$. In control experiments, sterile physiological saline was given as placebo at the appropriate intervals.

Ideally, all experiments would have been performed in the same four animal. However, this study involved six animals (mean weight 14.5 kg, range 13.3–16 kg), since the results described here were taken from a wider study involving other drugs, the results of which will not be described here.

### *Statistics*

Statistical comparisons were made with Student's two-tailed paired $t$ tests on absolute measurements in all instances.

## Results

Control experiments demonstrated a degree of accommodation to repeated exercise over four hours, and heart rate, $dP_{LV}/dt_{max}$ and cardiac output tended to decrease with time, although only changes in $dP_{LV}/dt_{max}$ during exercise were statistically significant. Aortic pressure, cardiac output and calculated systemic vascular resistance, both at rest and during exercise, did not show any significant changes with time. It was considered that the response to repeated exercise was sufficiently reproducible to allow the study of the effects of drugs on the haemodynamic changes induced by exercise in this model.

Table 1 summarises the mean absolute values of results from all experiments, whilst Figure 2 illustrates the results obtained with ZD7288.

ZD7288 in the dose range 0.1 to 1.0 mg $kg^{-1}$ caused a dose-related reduction of heart rate during exercise. The effects were statistically significant at the two higher doses. There was also a trend for heart rate at rest to be reduced, significant ($P<0.05$) only at 0.3 mg $kg^{-1}$, but similar in magnitude to that seen in the placebo experiments. The inotropic response during exercise was essentially unaffected by ZD7288 at any dose level, though resting $dP_{LV}/dt_{max}$ before the top dose was significantly reduced ($P<0.05$). Effects were comparable to those seen in the placebo experiments. Stroke volume (SV), both at rest and during exercise, was

**Table 1** Comparison of the haemodynamic effects of ZD7288, zatebradine and propranolol in beagles at rest and during level exercise at 6.5 km $h^{-1}$; responses during control experiments with the same time course are also shown

| *Dose* (mg $kg^{-1}$, i.v.) | | *HR* ($min^{-1}$) | $dP_{LV}/dt$ (mmHg $s^{-1}$) | $P_{Ao}$ *mean* (mmHg) | *SV* (ml) | *CO* (l $min^{-1}$) | *SVR* (dyn s cm-5) |
|---|---|---|---|---|---|---|---|
| *Controls* (saline) | | | | | | | |
| hour 1 | Rest | 103.8 ± 7.7 | 3453 ± 433 | 99.2 ± 3.9 | 22.6 ± 4.8 | 2.39 ± 0.57 | 3802 ± 800 |
| | **Exercise** | **204.7 ± 9.3** | **6743 ± 873** | **118.7 ± 3.3** | **24.0 ± 5.1** | **4.89 ± 1.18** | **2202 ± 482** |
| hour 2 | Rest | 89.9 ± 8.9 | 3147 ± 337 | 101.4 ± 7.6 | 23.1 ± 5.2 | 2.20 ± 0.67 | 4342 ± 776 |
| | **Exercise** | **195.9 ± 12.2** | **6046 ± 902** | **119.4 ± 3.0** | **24.3 ± 5.0** | **4.88 ± 1.23** | **2196 ± 431** |
| hour 3 | Rest | 87.6 ± 10.5 | 3146 ± 371 | 92.8 ± 3.4 | 23.7 ± 5.4 | 2.24 ± 0.73 | 4172 ± 963 |
| | **Exercise** | **191.3 ± 13.4** | **5831 ± 885[1]** | **113.7 ± 3.1** | **24.3 ± 5.1** | **4.82 ± 1.27** | **2145 ± 432** |
| hour 4 | Rest | 82.1 ± 5.8 | 3139 ± 330 | 93.4 ± 2.6 | 23.6 ± 5.2 | 2.06 ± 0.51 | 4201 ± 822 |
| | **Exercise** | **187.4 ± 12.1** | **5605 ± 691[1]** | **112.4 ± 2.9** | **24.3 ± 5.2** | **4.74 ± 1.24** | **2127 ± 398** |
| *ZD7288* | | | | | | | |
| Control | Rest | 103.6 ± 18.1 | 3702 ± 405 | 109.7 ± 7.6 | 24.0 ± 3.0 | 2.49 ± 0.54 | 4161 ± 1142 |
| | **Exercise** | **179.7 ± 24.5** | **5888 ± 739** | **125.3 ± 9.2** | **26.5 ± 2.8** | **4.82 ± 0.85** | **2177 ± 303** |
| 0.1 | Rest | 97.5 ± 13.5 | 3758 ± 399 | 109.3 ± 8.7 | 25.5 ± 2.8[1] | 2.35 ± 0.33 | 3984 ± 727 |
| | **Exercise** | **155.4 ± 21.1** | **5359 ± 666** | **120.4 ± 9.9** | **28.3 ± 3.0[1]** | **4.48 ± 0.81** | **2274 ± 357** |
| 0.3 | Rest | 84.3 ± 13.3[1] | 3623 ± 586 | 107.4 ± 10.3 | 26.1 ± 3.3[2] | 2.17 ± 0.43 | 4554 ± 1155 |
| | **Exercise** | **142.3 ± 18.4[1]** | **5034 ± 789** | **120.0 ± 12.3** | **29.4 ± 3.2[2]** | **4.63 ± 0.79** | **2301 ± 326[1]** |
| 1 | Rest | 77.1 ± 8.1 | 3366 ± 458[1] | 108.3 ± 11.0 | 26.7 ± 3.3[1] | 2.02 ± 0.32 | 4589 ± 917 |
| | **Exercise** | **125.4 ± 12.5[1]** | **4557 ± 504** | **115.4 ± 9.4** | **29.6 ± 3.2[2]** | **3.83 ± 0.58** | **2480 ± 338[1]** |
| *Zatebradine* | | | | | | | |
| Control | Rest | 94.5 ± 12.2 | 3578 ± 484 | 98.0 ± 5.8 | 22.8 ± 3.9 | 2.25 ± 0.62 | 4228 ± 1108 |
| | **Exercise** | **178.6 ± 18.9** | **5747 ± 862** | **117.5 ± 6.2** | **25.0 ± 3.7** | **4.51 ± 0.96** | **2200 ± 441** |
| 0.1 | Rest | 91.3 ± 13.3 | 3690 ± 576 | 97.8 ± 5.9 | 23.5 ± 3.8 | 2.21 ± 0.59 | 4419 ± 1184 |
| | **Exercise** | **164.6 ± 16.9[2]** | **5431 ± 1005** | **115.4 ± 4.4** | **26.0 ± 3.6** | **24.3 ± 0.89** | **2280 ± 468** |
| 0.3 | Rest | 78.4 ± 12.1[1] | 3533 ± 551 | 84.9 ± 1.4 | 24.6 ± 4.0 | 2.02 ± 0.65 | 5366 ± 2362 |
| | **Exercise** | **141.8 ± 12.8[1]** | **4989 ± 761** | **102.5 ± 4.6** | **27.4 ± 3.8** | **4.04 ± 0.89** | **2302 ± 650** |
| 1 | Rest | 67.2 ± 1.8 | 3616 ± 435 | 81.7 ± 3.2 | 25.9 ± 4.2[1] | 1.66 ± 0.35 | 4913 ± 1594 |
| | **Exercise** | **120.1 ± 6.4[1]** | **4701 ± 604** | **94.1 ± 5.6** | **28.2 ± 3.9[1]** | **3.44 ± 0.61** | **2367 ± 604** |
| *Propanolol* | | | | | | | |
| Control | Rest | 92.6 ± 8.0 | 3830 ± 654 | 98.4 ± 5.6 | 25.4 ± 4.4 | 2.40 ± 0.48 | 3635 ± 769 |
| | **Exercise** | **167.3 ± 13.8** | **5950 ± 843** | **113.6 ± 5.1** | **28.1 ± 3.9** | **4.88 ± 0.85** | **1886 ± 297** |
| 0.03 | Rest | 68.8 ± 6.4 | 3334 ± 429 | 96.5 ± 6.3 | 26.3 ± 3.9 | 1.93 ± 0.46 | 4631 ± 981 |
| | **Exercise** | **142.7 ± 13.6[1]** | **4185 ± 549[1]** | **117.3 ± 6.1** | **27.8 ± 3.8** | **4.18 ± 0.74[1]** | **2307 ± 330[2]** |
| 0.1 | Rest | 64.0 ± 4.0[2] | 3093 ± 409 | 98.4 ± 4.6 | 25.4 ± 3.9 | 1.69 ± 0.35[1] | 5271 ± 1197 |
| | **Exercise** | **134.5 ± 10.0[1]** | **3536 ± 438[1]** | **117.0 ± 3.6** | **26.6 ± 3.8** | **3.77 ± 0.66[1]** | **2567 ± 407[2]** |
| 0.3 | Rest | 60.3 ± 1.9[1] | 2958 ± 405 | 97.3 ± 4.0 | 25.4 ± 3.8 | 1.56 ± 0.28[1] | 5377 ± 960[1] |
| | **Exercise** | **126.7 ± 11.2[1]** | **3273 ± 347[1]** | **111.7 ± 6.9** | **26.7 ± 3.7** | **3.59 ± 0.64[2]** | **2538 ± 361[2]** |

Means and s.e.mean: $n = 4$ for all groups: [1]$P<0.05$, [2]$P<0.01$ by Student's paired $t$ test versus respective initial control.

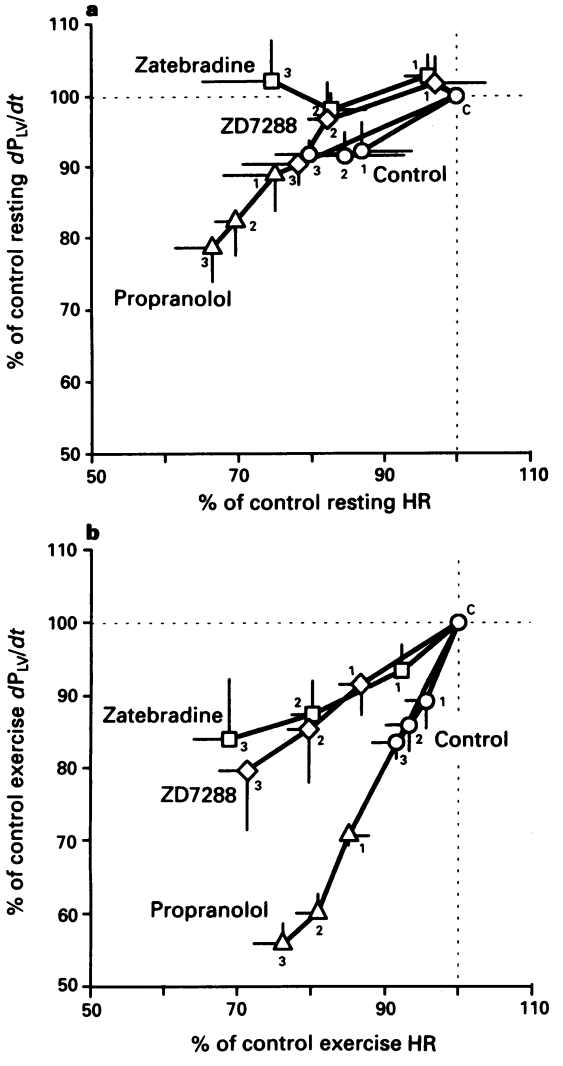


**Figure 3** (a) The relationship between heart rate (HR) and contractile function ($dP_{LV}/dt_{max}$) at rest, each normalized with respect to initial control values, was similar whether animals were treated with saline in control experiments (○), or cumulative doses of ZD7288 (◇), zatebradine (□), each at 0.1, 0.3 and 1.0 mg kg$^{-1}$ i.v., or propranolol (△) 0.03, 0.1 and 0.3 mg kg$^{-1}$i.v. (n = 4, means and s.e.mean at each dose). The effects of saline may be taken to represent changes with the progress of time common to all experiments both in this figure and in Figure 4. Points on trend lines are labelled in ascending dose order; C represents pre-drug controls. (b) During level treadmill exercise level at 6.5 km h$^{-1}$, the relationship between heart rate and contractile function normalized with respect to initial control exercise values clearly differentiate between the effects of propranolol, which prevents sympathetically mediated inotropic support of the myocardium, and sino-atrial node function modulators ZD7288 and zatebradine, which selectively reduce heart rate.

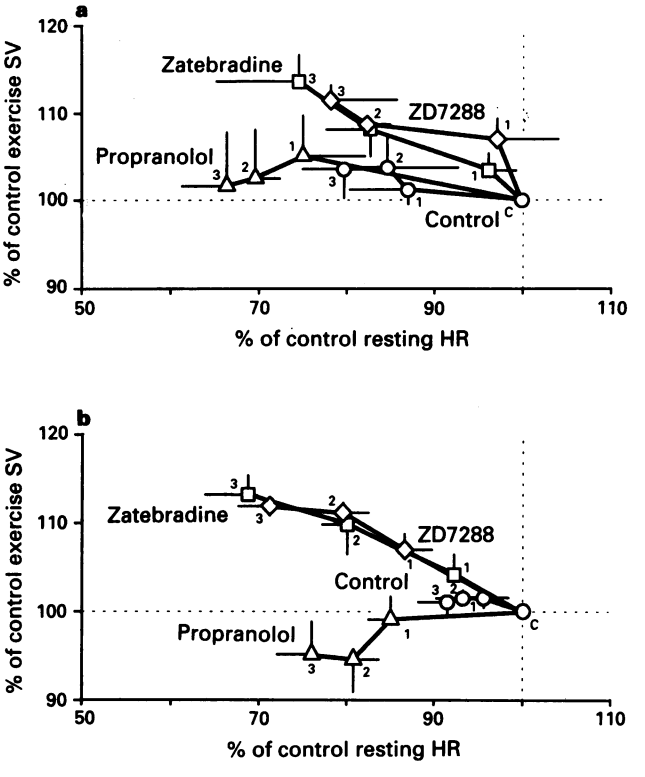


**Figure 4** (a) The relationship between heart rate (HR) and stroke volume (SV) at rest (normalized with respect to initial resting levels) in control (○) and propranolol-dosed (△) animals shows little change of stroke volume as heart rate declines, but under the influence of ZD7288 (◇) or zatebradine (□), the relationship shows a more marked increase in stroke volume with less slowing of rate. (b) Propranolol decreased stroke volume response during exercise as heart rate decreased, whereas ZD7288 and zatebradine allowed stroke volume to increase as heart rate during exercise was lowered. (Cumulative drug doses as in Figure 3)

significantly increased (see Table 1) after all doses of ZD7288. As a consequence of this increase in stroke volume, even though there was a tendency for cardiac output to decrease, the latter was well maintained, despite the decrease in heart rate during exercise. Systemic vascular resistance at rest was unaffected by ZD7288, but the vasodilation during exercise was less at the two higher dose levels.

Zatebradine caused effects essentially similar to those seen after ZD7288: resting and exercise heart rates were reduced with no significant effects on contractile function: stroke volume increased dose-dependently both at rest and during exercise, though these changes only attained statistical significance after 1.0 mg kg$^{-1}$ zatebradine. Cardiac output was well maintained and aortic blood pressure and systemic vascular resistance were not significantly affected.

In contrast, β-adrenoceptor antagonism by propranolol produced a different pattern of changes. Heart rate both at rest and during exercise were significantly reduced to a similar degree, so that the incremental responses to exercise remained relatively unchanged. Contractile function during exercise and the inotropic response to exercise, however, were grossly and significantly impaired at all doses studied (see Table 1). Stroke volume at rest did not change, but tended to decrease during exercise. Cardiac output was significantly reduced both at rest and during exercise. Aortic blood pressure was maintained, ostensibly as a consequence of increased systemic vascular resistance, but the dilator response to exercise increased (significantly after 0.3 mg kg$^{-1}$, $P<0.01$).

Because of the limited dose-response data obtained in these experiments, it is not possible to compare results directly on a dose for dose basis. However, the relative effects of the compounds studied may be illustrated as in Figures 3 and 4, which relate heart rates, normalized with respect to pre-drug control values, to corresponding contractile function and stroke volume, both at rest and during exercise. These figures clearly differentiate between the effects of blockade of sympathetic drive and the effects of ZD7288 or zatebradine.

## Discussion

ZD7288 has been described as a sino-atrial node modulating agent which affects heart rate through a direct action on sino-atrial pacemaker cells (Briggs & Heapy, 1992; Marshall *et al.*, 1993; BoSmith *et al.*, 1993). A previous study in the

anaesthetized dog (Rouse & Johnson, 1992) has shown the drug to have a direct effect principally on intrinsic heart rate. Other observed haemodynamic changes (such as increases in stroke volume and systemic vascular resistance, fall in cardiac output and myocardial contractile function) were secondary and proportional to the reduction in heart rate, since they were reversed during atrial pacing. There was also dose-dependent prolongation of atrio-ventricular conduction during pacing at 180 beats per minute (an effect also seen after zatebradine and atenolol administration). The present studies have examined the effects of ZD7288 on the cardiovascular system in the conscious dog, and its effects on the haemodynamic response during exercise.

In the Alderley Park beagle, 5 min of mild exercise on a treadmill induced the expected increases of heart rate, cardiac output and left ventricular $dP_{LV}/dt_{max}$, whilst systemic vascular resistance was reduced overall (see Table 1). However, changes in stroke volume in response to exercise were marginal at this exercise level, increases in cardiac output being achieved predominantly as a consequence of increased heart rate. Responses to exercise were consistent over a period of 4 h, although there was a tendency for the resting haemodynamic variables to change in directions indicative of decreasing sympathetic-drive, as the animals presumably became more relaxed during the experimental procedure. This notion is consistent with Figures 3 and 4, in which control relationships tend to follow the trends occurring during removal of sympathetic drive by β-adrenoceptor antagonism. Although heart rate response to exercise, together with cardiac output and systemic vascular resistance during exercise remained constant, $dP_{LV}/dt_{max}$ response to exercise declined.

The principal effect of ZD7288 on such exercise-induced responses was to reduce heart rate during exercise, which resulted in a further increase of stroke volume (see Figure 4). These effects mirrored those reported in the anaesthetized dog (Rouse & Johnson, 1994). As the tachycardic response to exercise was further reduced (by over 30%), so the increases of cardiac output and the vasodilator responses (falls in systemic vascular resistance) were blunted. Myocardial contractile function ($dP_{LV}/dt_{max}$) was only significantly reduced following the highest dose, and then only at rest. As the effect was similar to that seen in control (placebo) experiments, this result is also likely to be a consequence of the animals becoming more relaxed, rather than being due to any negative inotropic effects of ZD7288. It is probable that the blunted cardiac output response and the increase of systemic vascular resistance seen following ZD7288 administration were secondary to the large reduction of exercise tachycardia following the higher doses of ZD7288. These effects, again, were not seen in the anaesthetized dog when the heart rate was held constant during atrial pacing (Rouse & Johnson, 1994).

Our results are similar to those reported by Krumpl *et al.* (1988), in their study on zatebradine. This agent has also been shown to attenuate the heart rate response to exercise in the dog, a change which was accompanied by an increase in stroke volume. Both drugs were of a similar potency in the present studies, as has been described in studies of their electrophysiological actions on isolated sino-atrial node cells (Briggs & Heapy, 1993). ZD7288, therefore, could be described as a 'selective bradycardic agent', despite being chemically dissimilar from previously described drugs of this class (Hargreaves *et al.*, 1992).

In contrast to the haemodynamic effects of ZD7288 and zatebradine, when contractile function was well maintained during exercise, β-adrenoceptor antagonism following administration of propranolol prevented the positive inotropic effects mediated by the sympathetic nervous system in response to exercise, causing an apparent marked negative inotropic effect in the exercising dog (see Figure 3). It was noticeable, in our strain of beagles, that although resting heart rate and heart rate during exercise were each significantly reduced by propranolol, the tachycardic response to exercise was diminished by only 11%: this can be adequately accounted for by withdrawal during exercise of vagally-mediated slowing of resting heart rate (sinus arrhythmia). The reduction of heart rate produced by propranolol was not associated with an increase of stroke volume, as was the case after treatment with ZD7288 (see Figure 4: relationships shown in this figure echo results from conscious pig experiments described by van Woerkens *et al.*, 1992, where 'propranolol and (zatebradine) had opposite effects on stroke volume', as shown in Figure 3 of their paper). In addition, propranolol significantly impaired the vasodilator response to exercise.

β-Adrenoceptor antagonists were originally developed for the treatment of ischaemic heart disease, based upon their ability to attenuate the increase of myocardial oxygen demand resulting from sympathetic nerve activity (Shanks, 1966). Their efficacy as anti-ischaemic agents is well proven (Vedin & Wilhelmsson, 1985), but the concomitant antagonism of increases in inotropic activity limits their use in patients with left ventricular dysfunction. An alternative approach to the treatment of ischaemic heart disease is provided by the vasodilator actions of calcium channel blockers. These agents reduce cardiac afterload, thereby reducing cardiac work, as well as affording varying degrees of coronary vasodilatation (Warltier *et al.*, 1981). However, the use of such drugs can be offset by the incidence of side-effects which are consequent upon their peripheral vasodilator activity (Julian, 1985). Recently, a new class of potential anti-ischaemic drugs, the 'specific bradycardic agents', has been described (Kobinger & Lillie, 1987). These agents attenuate heart rate increases through a selective action on the sino-atrial node (Seidl *et al.*, 1991) and, particularly the most recent agent, zatebradine, are essentially devoid of negative inotropic and vasodilator activity (Riley *et al*, 1987). Zatebradine has shown anti-anginal efficacy in a small number of clinical trials (Baiker *et al.*, 1991) and may represent the prototype of a new class of anti-anginal agents suitable for clinical use.

In summary, ZD7288 has been shown to possess a direct effect only on heart rate in the exercising dog. Other haemodynamic effects associated with the drug were considered to be secondary to the reduced heart rate. Thus, the drug shares a cardiovascular profile of activity similar to the selective bradycardic agent, zatebradine. Both drugs show significant differences in their activity from β-adrenoceptor antagonists. Being devoid of direct negative inotropic effects, ZD7288 would be expected to be of use for the treatment of ischaemic heart diseas, especially in those patients in whom β-adrenoceptor antagonists might be contra-indicated.

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