Noradrenaline, infused locally, reduces arrhythmia severity during coronary artery occlusion in anaesthetised dogs

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Abstract

Objective: To contribute to the debate, discussed in an earlier issue, regarding the role of adrenoceptors in the genesis of early, coronary artery occlusion-induced ventricular arrhythmias. Methods: Mongrel dogs anaesthetised with chloralose and urethane were given either noradrenaline (NA, 100 ng kg⁻¹ min⁻¹), phenylephrine (PHE, 200 ng kg⁻¹ min⁻¹) or isoprenaline (ISO 12.5 ng kg⁻¹ min⁻¹) by intracoronary infusion into a side branch of the left anterior descending coronary artery (LAD), commencing 10 min prior to the occlusion and then throughout the 25-min occlusion period. Control dogs were infused for the same period with saline. In another group of dogs noradrenaline was infused intravenously in a dose of 1 and then 2 mg kg⁻¹ min⁻¹ over a period of 60 min, 24 h prior to coronary artery occlusion. Haemodynamic and coronary blood flow changes, as well as changes in the epicardial ST-segment and in the degree of inhomogeneity were continuously recorded. Ventricular arrhythmias were evaluated as ventricular premature beats (VPBs), tachycardiac (VT) episodes and the incidences of VT and ventricular fibrillation (VF) during occlusion and following reperfusion. Results: Compared to the controls, NA markedly reduced the severity of ventricular arrhythmias resulted from coronary artery occlusion and increased survival (to 40%) following reperfusion; there were no survivors in the control group. Noradrenaline released endogenously following guanethidine administration was also protective. Protection was also seen, although to a lesser extent with intracoronary PHE (occlusion VF 20% cp 80% in controls; survival 42%). In contrast, ISO enhanced arrhythmia severity; five out of seven dogs infused with ISO fibrillated within 10 min of the commencement of occlusion and no dog survived reperfusion. Other indices of ischaemia severity (epicardial ST-segment and inhomogeneity) were also reduced by NA and by PHE. NA, infused 24 h prior to occlusion was also protective against ischaemia and reperfusion-induced arrhythmias and ischaemia-induced changes in inhomogeneity. Conclusion: We conclude that exogenously administered NA, or released endogenously by chemical means, reduces the severity of ischaemia and reperfusion-induced ventricular arrhythmias and that this is mediated by α-adrenoceptors, perhaps through presynaptic inhibition of local NA release or by a ‘preconditioning’ effect presumably mediated by PKC. © 2002 Published by Elsevier Science BV.

Keywords: Arrhythmia (mechanisms); Ischemia

1. Introduction

Two papers [1,2] with accompanying editorials [3,4] in a recent issue of the Journal have re-opened the debate about the role of the sympathetic nervous system in the genesis of the early, life-threatening arrhythmias that result from acute coronary artery occlusion. Although one of these editorials [3] concluded that “the importance of sympathetic nervous system activation in arrhythmogenesis remains controversial”, the bulk of the evidence is surely that in the early stages of acute myocardial ischaemia sympathetic activity is an important contributor to arrhythmia severity through β-adrenoceptor activation (reviewed in, for example [5,6]). In neither of the above mentioned editorials was the possibility raised that noradrenaline, the predominant transmitter of cardiac sympathetic nerves, might actually reduce arrhythmia severity. Yet there is earlier experimental evidence that when a coronary artery
is occluded in the presence of exogenous noradrenaline (or adrenaline), either in vivo [7–9] or in isolated perfused hearts [10], there are reductions in all parameters of arrhythmia severity. The protection in vivo does not appear to be due to an increase in perfusion pressure since the protection was apparent in studies when this did not occur [7] or when it was prevented [9].

A protective role of the sympathetic nervous system, mainly through α-adrenoceptor stimulation, has also been evoked to explain the effects of ischaemic preconditioning (reduction in myocardial ischaemic damage; enhanced recovery of contraction after a period of ischaemia and reperfusion). This has been shown in a variety of species, in rats [10–13], in rabbits [14–16] and in some [17] although not all [18], studies in dogs. Further, preconditioning does not limit infarct size in hearts where there are no measurable cardiac noradrenaline levels [11,19,20]. There seems little doubt then that noradrenaline can mimic the infarct limiting effects of preconditioning, most likely through activation of protein kinase C [15,21].

The situation, however, regarding arrhythmias is less clear and has not been examined in large animal models. We now describe, in a well defined canine model, the effects of noradrenaline, and also of the more selective α- and β-adrenoceptor agonists phenylephrine and isoprenaline, infused directly into a side branch of a coronary artery, on those arrhythmias that result from acute coronary artery occlusion and reperfusion. A preliminary account of the initial studies with intracoronary noradrenaline was given in 1994 [22].

2. Methods

2.1. Animals and experimental design

Mongrel dogs, of either sex, and with a body weight in excess of 17 kg (mean 27.5±2.0 kg) were anaesthetised with a mixture of chloralose and urethane (60 and 200 mg kg−1 i.v., respectively). They were ventilated with room air using a Harvard respirator at a rate (usually 13 min−1) and volume sufficient to maintain arterial blood gases and pH within normal limits [23]. Body temperature was measured either from the oesophagus or from the rectum and maintained by a heating pad between 36.7 and 37.4 °C. 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 16 December 1991.

A thoracotomy was performed 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. A smaller branch of this artery, proximal to the proposed site of occlusion, was catheterised for the intracoronary infusion of saline, noradrenaline, isoprenaline or phenylephrine. Epicardial ST-segment changes, and the degree of inhomogeneity of activation, were measured from the left ventricular wall distal to the proposed coronary artery occlusion using unipolar electrodes and a composite electrode previously described [23]. This composite electrode gives a summarised recording of R-waves from 30 epicardial measuring points. When the myocardium is adequately perfused and oxygenated all sites are activated almost simultaneously, resulting in a single large spike. Following occlusion, however, widening and fractionation of the summarised R-wave occurs indicating that adjacent fibres are not simultaneously activated because of inhomogeneity of conduction. We express this as the greatest delay in activation (in milliseconds) within the ischaemic area underneath the electrodes.

In some of the experiments blood flow in the left circumflex coronary artery (LCX) was measured with a 2.0-mm electromagnetic flow probe and a Statham SP2202 flow meter. Blood flow was also measured on the (occluded) left anterior descending coronary artery (LAD) by means of a Doppler flow probe (Triton Technology, USA) positioned distal to the proposed occlusion site. These parameters, together with a limb lead electrocardiogram, systemic arterial pressure (S, systolic; D, diastolic; mean, MABP) and left ventricular (LV) systolic (S) and end-diastolic (ED) pressures (Statham P23XL transducers) and LVdP/dt were recorded on an eight-channel Medicor R81 recorder.

2.2. Assessment of ventricular arrhythmias

Ventricular arrhythmias during ischaemia and reperfusion were analysed as outlined previously [23]. This analysis is based on the suggestions made at the ‘Lambeth Conventions’ [24]. No distinction was made between couplets and salvos, which were included as single ventricular ectopic (premature) beats, and we defined ventricular tachycardia (VT) as a run of four or more ectopies at a rate faster than the resting sinus rate.

We also estimated the number of episodes of VT during coronary artery occlusion, and the incidences of VT and ventricular fibrillation (VF) both during occlusion and on reperfusion at the end of a 25-min occlusion period. Survival indicates those dogs which were in sinus rhythm 5 min following reperfusion after a 25-min occlusion period. In some experiments using noradrenaline, where dogs survived the initial occlusion period, the animals were left for a further 1–2 h and the occlusion repeated in the presence of an infusion of normal saline given at the same volume and rate.

At the end of each experiment, the area at risk was assessed by infusing patent blue V dye into the occluded artery at a pressure equivalent to that of mean arterial blood pressure. The area at risk was expressed as a
percentage of the left ventricular wall and septum combined.

2.3. Statistical analysis

Data were analysed statistically as previously described [25], i.e., data are expressed as means±S.E.M. and differences between means were compared by analysis of variance (ANOVA for repeated measures) or the Student’s t-test as appropriate. A one-way ANOVA was undertaken to determine whether or not there were significant haemodynamic differences between the groups. Ventricular premature beats were compared by using the Mann–Whitney rank sum test, and the incidences of VT and VF, and survival from the combined ischaemia and reperfusion insult, were compared using the Fisher exact test. Differences between groups were considered significant when P was less than 0.05.

2.4. Infusions of noradrenaline, phenylephrine, isoprenaline, and normal saline

There were six experimental groups:

(i) Noradrenaline. In 13 dogs noradrenaline was infused in a dose of 100 ng kg⁻¹ min⁻¹ and at a rate of 0.5 ml min⁻¹ into the side branch of the LAD coronary artery commencing 10 min prior to coronary artery occlusion and then throughout the occlusion period.

(ii) Phenylephrine. This was given in a dose of 200 ng kg⁻¹ min⁻¹ by intracoronary infusion and at a rate of 0.5 ml min⁻¹ to a group of 10 dogs, commencing 10 min prior to coronary artery occlusion and then throughout the occlusion period.

(iii) Isoprenaline. Isoprenaline (12.5 ng kg⁻¹ min⁻¹) was administered by intracoronary infusion at a rate of 0.5 ml min⁻¹ to a group of seven dogs again commencing 10 min prior to coronary artery occlusion and throughout the occlusion period.

The chosen doses of phenylephrine and isoprenaline were intended to give either similar increases in blood pressure to those resulting from noradrenaline infusion (phenylephrine), or similar increases in positive LVdP/dt to those resulting from noradrenaline infusion (isoprenaline).

(iv) In the controls normal saline, at a rate of 0.5 ml min⁻¹ was infused into a side branch of the coronary artery for a period of 10 min and then throughout the 25-min coronary artery occlusion.

(v) Because of evidence in rats [10] that noradrenaline can induce a delayed protection of the myocardium against early occlusion-induced ventricular arrhythmias, a separate series of experiments was carried out in 13 dogs using intravenous noradrenaline at rates of 1 µg kg⁻¹ min⁻¹ (for 30 min) and then of 2 µg kg⁻¹ min⁻¹ (for a further 30 min). Blood pressure and heart rate were recorded continuously. The following day the dogs were re-anaesthetised and subjected to coronary artery occlusion as outlined above. The mean weight of these dogs was 25.1±1.1 kg.

(vi) In a separate series of experiments and in order to determine whether noradrenaline released endogenously was also protective, a further series of eight dogs (mean weight 23±1.4 kg) was given guanethidine intravenously in a dose of 5 mg kg⁻¹. It is well known [26] that in this dose guanethidine initially releases catecholamines from sympathetic nerve endings and from cromaf®n tissue, a phenomenon sometimes referred to as ‘sympathomimesis’, before eventually depleting tissue catecholamines and exerting an adrenergic neurone blocking effect.

3. Results

3.1. Haemodynamic effects of local intracoronary infusions of noradrenaline and of subsequent coronary artery occlusion

The haemodynamic changes resulting from noradrenaline administration are outlined in Table 1. There were significant increases in arterial blood pressure, in left ventricular systolic pressure and in LV/dP/dt max. Blood flow in the circumflex branch of the coronary artery was significantly increased but there was no change in resistance in this vascular bed (Table 1). Similarly, blood flow was also increased in the vessel (LAD) in which the noradrenaline was infused into a side branch (from 22±1 to 25±2 cm s⁻¹); again there was no change in vascular resistance (from 4.44±0.23 to 4.54±0.27 mmHg cm s⁻¹). There were no significant changes in LVEDP, in epicardial ST-segment elevation or in the inhomogeneity of electrical activation during the infusion.

The haemodynamic effects of subsequent coronary artery occlusion in these dogs are shown in Table 2 and were similar to those obtained in the control saline infused dogs (see below). These changes, which were maximum at 3–5 min, included decreases in arterial blood pressure and in LVdP/dt max, and substantial increases in LVEDP and in left circumflex coronary flow (‘compensatory vasodilatation’).

3.2. Haemodynamic effects of phenylephrine and of subsequent coronary artery occlusion

The results are shown in Tables 1 and 2. The dose of phenylephrine was chosen in order to give approximately similar increases in blood pressure to those already described for noradrenaline (see Table 1). The slight increases in LVdP/dt max were not significant and probably reflect changes in afterload. Phenylephrine, in this dose, did not induce changes in blood flow or resistance in either
the circumflex (Table 1) or the anterior descending (from 24.3±3 to 19±3 cm s−1 and from 3.91±0.59 to 5.53±1.12 mmHg cm s−1) coronary vascular beds. The changes following coronary artery occlusion (Table 2) were similar to those in the control and noradrenaline groups.

3.3. Haemodynamic effects of isoprenaline and of subsequent coronary artery occlusion

These changes are also shown in Tables 1 and 2. The dose of isoprenaline was chosen to induce similar increases in LVdP/dtmax to that obtained with noradrenaline; except in two dogs this was largely achieved. This dose of isoprenaline decreased diastolic arterial blood pressure (by a mean of 19±2 mmHg) and increased heart rate (by a mean of +19±2 beats min−1). It also resulted in a marked increase in coronary blood flow in the vascular bed supplied by the LCX coronary artery (Table 1); flow in the LAD was not measured in these experiments. In most of the dogs given isoprenaline steady-state measurements of cardiovascular haemodynamics after coronary artery occlusion were not possible because of severe ventricular arrhythmias (see below).

3.4. Haemodynamic effects of intracoronary saline and of coronary artery occlusion

There were no haemodynamic effects of saline infused, at a rate of 0.5 ml min−1, by the intracoronary route (Table 1) and the haemodynamic effects of coronary artery occlusion (Table 2) were similar to those obtained previously in several control groups (e.g., Refs. [23,25]) and to

Table 1
Changes in various haemodynamic parameters during intracoronary infusions of either saline (controls), noradrenaline, phenylephrine or isoprenaline

<table>
<thead>
<tr>
<th></th>
<th>Control (n=12)</th>
<th>Noradrenaline (n=13)</th>
<th>Phenylephrine (n=10)</th>
<th>Isoprenaline (n=7)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>Change</td>
<td>Baseline</td>
<td>Change</td>
</tr>
<tr>
<td>SABP (mmHg)</td>
<td>132±7</td>
<td>0</td>
<td>144±6</td>
<td>16±3*</td>
</tr>
<tr>
<td>DABP (mmHg)</td>
<td>97±5</td>
<td>−1±2</td>
<td>97±6</td>
<td>11±2*</td>
</tr>
<tr>
<td>MABP (mmHg)</td>
<td>109±6</td>
<td>−1±2</td>
<td>113±5</td>
<td>11±2*</td>
</tr>
<tr>
<td>HR (beats/min)</td>
<td>155±8</td>
<td>0±1</td>
<td>165±6</td>
<td>−5±2</td>
</tr>
<tr>
<td>LVSP (mmHg)</td>
<td>155±5</td>
<td>1±2</td>
<td>175±9</td>
<td>29±5*</td>
</tr>
<tr>
<td>LVEDP (mmHg)</td>
<td>5.0±0</td>
<td>0</td>
<td>5.6±0.4</td>
<td>0.0</td>
</tr>
<tr>
<td>LVdP/dtmax (+)</td>
<td>2851±379</td>
<td>−45±90</td>
<td>3351±200</td>
<td>966±306*</td>
</tr>
<tr>
<td>LVdP/dtmax (−)</td>
<td>3956±441</td>
<td>−71±128</td>
<td>2971±152</td>
<td>596±161*</td>
</tr>
<tr>
<td>LCX flow diastolic (ml min−1)</td>
<td>102±7</td>
<td>3±2</td>
<td>113±7</td>
<td>12±4*</td>
</tr>
<tr>
<td>LCX resistance diast. (mmHg ml−1 min−1)</td>
<td>0.98±0.06</td>
<td>0.01±0.02</td>
<td>0.88±0.06</td>
<td>0.01±0.02</td>
</tr>
</tbody>
</table>

Values shown are those at baseline (pre-infusion) and the change at the end of 10 min, i.e., immediately prior to coronary artery occlusion. *P<0.05 cp baseline; **P<0.05 cp noradrenaline.

Table 2
Haemodynamic parameters resulting from coronary artery occlusion in control (saline administered) dogs (control) and in dogs administered noradrenaline, phenylephrine or isoprenaline by the intracoronary route

<table>
<thead>
<tr>
<th></th>
<th>Preocclusion</th>
<th>Max change</th>
<th>Preocclusion</th>
<th>Max change</th>
<th>Preocclusion</th>
<th>Max change</th>
<th>Preocclusion</th>
<th>Max change</th>
</tr>
</thead>
<tbody>
<tr>
<td>SABP (mmHg)</td>
<td>132±6</td>
<td>−11±3*</td>
<td>160±6</td>
<td>−11±3*</td>
<td>145±9</td>
<td>−16±5*</td>
<td>120±11</td>
<td>−13±5*</td>
</tr>
<tr>
<td>DABP (mmHg)</td>
<td>97±5</td>
<td>−5±2*</td>
<td>108±5</td>
<td>−8±2*</td>
<td>95±7</td>
<td>−13±5*</td>
<td>66±6</td>
<td>−6±2*</td>
</tr>
<tr>
<td>MABP (mmHg)</td>
<td>108±5</td>
<td>−7±3*</td>
<td>124±5</td>
<td>−8±2*</td>
<td>112±7</td>
<td>−14±5*</td>
<td>81±6</td>
<td>−6±2*</td>
</tr>
<tr>
<td>HR (beats/min)</td>
<td>104±7</td>
<td>21±4*</td>
<td>161±3</td>
<td>42±2*</td>
<td>164±4</td>
<td>9±3**</td>
<td>154±8</td>
<td>−8±3**</td>
</tr>
<tr>
<td>LVSP (mmHg)</td>
<td>116±5</td>
<td>−9±2*</td>
<td>203±7</td>
<td>−26±5*</td>
<td>151±10</td>
<td>−16±4*</td>
<td>115±9</td>
<td>−9±4</td>
</tr>
<tr>
<td>LVEDP (mmHg)</td>
<td>5.0±0</td>
<td>18.2±2.5*</td>
<td>5.7±0.4</td>
<td>17.4±1.9*</td>
<td>6.0±0.7</td>
<td>13.5±0.8*</td>
<td>9.7±1.9</td>
<td>7.1±2.1*</td>
</tr>
<tr>
<td>LVdP/dtmax (+)</td>
<td>2806±361</td>
<td>258±170</td>
<td>4316±315</td>
<td>−987±311*</td>
<td>3290±310</td>
<td>−545±292*</td>
<td>4978±631</td>
<td>−1519±386* **</td>
</tr>
<tr>
<td>LVdP/dtmax (−)</td>
<td>3885±417</td>
<td>−267±161</td>
<td>3588±287</td>
<td>−632±182*</td>
<td>2992±235</td>
<td>−340±75*</td>
<td>2965±388</td>
<td>−672±230*</td>
</tr>
<tr>
<td>LCX flow diastolic (ml min−1)</td>
<td>104±8</td>
<td>24±3*</td>
<td>126±6</td>
<td>13±4**</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LCX resistance diast. (mmHg ml−1 min−1)</td>
<td>0.95±0.66</td>
<td>−0.21±0.04*</td>
<td>0.90±0.06</td>
<td>−0.13±0.03*</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*P<0.05 cp preocclusion value; **P<0.05 cp controls.
those following noradrenaline or phenylephrine infusions (see above). In summary, there were slight (5–11 mmHg) decreases in arterial blood pressure and in positive LVEDP/\(dr_{max}\) (of \(-258\pm170\) mmHg s\(^{-1}\)) and significant increases in LVEDP (from 5.0 to 23.2±2.5 mmHg) and in blood flow to the essentially normal region of the left ventricular wall, i.e., that supplied by the circumflex coronary artery (of 24±3 ml min\(^{-1}\)).

3.5. Haemodynamic effects of intravenous noradrenaline given 24 h prior to coronary artery occlusion

These included marked increases in arterial blood pressure (of 99±7 mmHg systolic and 40±5 mmHg diastolic from pre-infusion levels of 155±6 and 126±5 mmHg, respectively) which were maximal after 5 min. Heart rate responses were variable; in some dogs there were marked decreases in heart rate (by as much as 50 beats min\(^{-1}\)) whilst in others there were slight increases (of up to 30 beats min\(^{-1}\)). The mean change was insignificant (+6±11 beats min\(^{-1}\)). When the infusion was switched off at the end of 1 h there was a substantial post-infusion hypotension to levels, after 5 min, of 115±8 mmHg (systolic) and 87±7 mmHg (diastolic).

3.6. Effects of noradrenaline, phenylephrine and isoprenaline on arrhythmias resulting from coronary artery occlusion and reperfusion

3.6.1. Effects of intracoronary noradrenaline

During the 10-min pre-occlusion period intracoronary noradrenaline infusions resulted in ventricular ectopic activity in 10 out of the 13 dogs and ranging from four to 129 ectopic beats (mean 23±6). The results of infusing noradrenaline on occlusion and reperfusion-induced arrhythmias are illustrated in Fig. 1. There was a substantial reduction in all parameters of arrhythmia severity. Particularly marked were the reductions in the incidences of VT during occlusion and in VF during occlusion and reperfusion. In four of the five dogs that survived reperfusion at the end of the occlusion period, saline was substituted for noradrenaline and infused for a period of 1 h before the coronary artery was re-occluded. There were more arrhythmias in these dogs during the second (saline) infusion than during the first (noradrenaline) infusion. For example there were only 0, 4, 4 and 61 ectopic beats in these four dogs during the noradrenaline infusion (mean 17±6) but 151, 135, 308 and VF, respectively, during the subsequent saline infusion (mean 198±116; \(P<0.05\)). These results are illustrated in Fig. 2.

3.6.2. Effects of intracoronary phenylephrine

There were only occasional ventricular ectopic beats during the 10-min infusion of phenylephrine prior to the occlusion. However, there was substantial ventricular ectopic activity during the occlusion period in these dogs; this was not significantly different to that in the control, saline infused group (total number of VPBs during the 25-min occlusion period of 291±91 cp 430±72 in the controls; ns). Although most (80%) of the dogs had periods of VT only two of the 10 dogs fibrillated during occlusion and four survived the combined ischaemia–reperfusion insult. These results are also summarised in Fig. 1.

3.6.3. Effects of intracoronary isoprenaline

Ventricular ectopic activity occurred in each of the seven dogs during the isoprenaline infusion prior to occlusion (mean of 22±7 ventricular ectopic beats) and two of these had brief periods of VT. Five of the seven dogs infused with isoprenaline fibrillated within 10 min of the commencement of occlusion (mean time to VF 5.4±1.3 min) and the remaining two fibrillated during reperfusion. These
two dogs had marked ectopic activity during the occlusion period (Fig. 1).

3.7. Effects of noradrenaline and phenylephrine on epicardial ST-segment elevation and on changes in inhomogeneity of electrical activation within the ischaemic area

3.7.1. Effects of intracoronary noradrenaline

The mean results for all 13 dogs on epicardial ST-segment changes are illustrated in Fig. 3. In the four dogs that were re-occluded and in which saline was substituted for noradrenaline, the ST-segment elevation was more pronounced during the initial occlusion in the presence of noradrenaline (e.g., 22.3±2.3 cp 14.9±4.3 mV at 5 min; P<0.05).

Changes in the inhomogeneity of electrical activation are also illustrated in Fig. 3. As with the epicardial ST-segment changes, these were less marked when the coronary artery was occluded in the presence of noradrenaline. In the four dogs in which the artery was re-occluded, and when saline was given in place of noradrenaline, changes in inhomogeneity were again more marked during the second occlusion (Fig. 4; e.g., an increase of 183±20 cp 68±20 ms; P<0.05 at 5 min).

3.7.2. Effect of intracoronary phenylephrine and of isoprenaline

The results for phenylephrine are also given in Fig. 3. As with noradrenaline, ischaemic changes were less pronounced when phenylephrine was infused during the occlusion compared to controls. Because most of the dogs infused with isoprenaline fibrillated within 5 min of the occlusion, and because even prior to this there was substantial ventricular ectopic activity, no calculations were possible in these dogs of changes in the epicardial ST-segment, or in the degree of inhomogeneity.

3.8. Area at risk in controls, and in dogs infused with noradrenaline, phenylephrine and isoprenaline

There were no significant differences between the groups either in body weight (26.4±1.2 kg in the controls, 27.5±2.0 kg in the noradrenaline group, 26.0±1.8 kg in the phenylephrine group and 27.9±1.8 kg in the isoprenaline group) or in the risk area (36.5±1.4% in the controls; 39.3±1.6% in the noradrenaline group; 42.2±2.6% for phenylephrine and 36.8±2.1% for isoprenaline).

3.9. Delayed cardioprotection by noradrenaline infused intravenously 24 h previously

The maximum changes in blood pressure and heart rate that occurred during the intravenous infusion of noradrenaline (1 and then 2.0 μg kg⁻¹ min⁻¹) have been given above. There were ventricular extrasystoles during the infusions and, occasionally, brief periods of VT. These usually reverted to sinus rhythm during the infusion period. One dog died during administration of the higher

Fig. 3. Changes in ST-segment elevation (mV), recorded from epicardial electrodes, and in the inhomogeneity of activation (ms), as recorded from a composite electrode over the ischaemic area, during a 25-min occlusion of the LAD coronary artery in control dogs (filled circles) and in dogs infused, by the intracoronary route, with either noradrenaline (filled squares) or phenylephrine (filled triangles). Both noradrenaline and phenylephrine reduce these two indices of ischaemia severity. The differences at each measured time point between controls and dogs given either noradrenaline or phenylephrine are significant at a level of $P<0.05$.

dose of noradrenaline and two further dogs died overnight.
Next day the remaining 10 dogs were subjected to coronary artery occlusion as outlined above; one of these was later omitted from the series because the area at risk exceeded 50%. The area at risk in the remaining nine dogs was $42.7\pm1.9\%$.

Although arrhythmias in the noradrenaline-treated dogs tended to be less than those in the controls (Fig. 5), the only significant changes were reductions in the number of ectopic beats, in the incidence of VF during coronary artery occlusion, in epicardial ST-segment elevation and in the degree of inhomogeneity during ischaemia (Fig. 6). Although the control group was not strictly comparable, our previous studies have shown that catheterisation and re-anaesthesia have no effect on arrhythmias, or on ischaemia severity as recorded from the composite electrode, when the coronary artery is occluded 24 h later [27,28].

3.10. Effect of guanethidine

The administration of guanethidine resulted in marked sympathomimetic effects which were prolonged, in some dogs persisting for up to the time when the coronary artery was occluded 1 h later. The maximum responses occurred within 5–10 min and were characterised by substantial increases in blood pressure (of $116\pm18$ and $64\pm9$ mmHg from preinjection levels of $141\pm3$ mmHg systolic and $96\pm4$ diastolic; $P<0.01$), in heart rate (an increase of $91\pm11$ beats min$^{-1}$ from a basal level of $140\pm6$ beats min$^{-1}$) and in LVEDP (of $6.0\pm0.9$ mmHg from $5.0\pm0$ mmHg). There was also, in each dog, ventricular ectopic
activity following the injection (of from three to 282 ventricular premature beats; mean 61 ± 34); in one of these dogs there were several episodes of VT and in another sudden VF occurred 10 min after the administration; just prior to this the arterial pressure in this dog was 290/190 mmHg and the heart rate 230 beats min⁻¹.

When the coronary artery was occluded there were fewer VPBs (181 ± 47, i.e., less than 8 VPBs/min) during the 25-min ischaemic period than in the controls and only one of the seven dogs (14%; P < 0.05) fibrillated during the occlusion period. Further, other ischaemic changes were less than in the control group (e.g., degree of inhomogeneity at 5 min 117 ± 10 ms compared to 210 ± 10 ms in the controls; P < 0.05). Survival from reperfusion was also higher than in the controls (50 vs. 0%; P < 0.05) despite the fact that the area at risk (43.6 ± 1.6%) was rather greater than in the controls (36.5 ± 1.4%). In two of the dogs that survived reperfusion at the end of the 25-min occlusion period, the same coronary artery was re-occluded, again for 25 min, 2 h later, i.e., at a time when neither the sympathomimetic effects of guanethidine, nor the preconditioning effects of infused noradrenaline, were no longer apparent. These dogs had fewer VPBs (35 and 76, respectively) during the second occlusion and both of these dogs survived reperfusion at the end of the ischaemic period.

4. Discussion

These results show that the local intracoronary administration of noradrenaline to the canine heart reduces the severity of arrhythmias that result from coronary artery occlusion; this protection fades within 1 h. Protection is also seen, albeit to a lesser extent, with intracoronary phenylephrine; isoprenaline, in contrast, enhances arrhythmia severity. Other indices of ischaemia severity such as changes in the degree of inhomogeneity of activation and ST-segment changes, recorded from epicardial electrodes, were also reduced by noradrenaline and by phenylephrine but not by isoprenaline.

In previous studies implicating α-adrenoceptor stimulation as a mechanism in reducing myocardial ischaemic damage and stunning [10,11,13–17], and in enhancing the recovery of contractile force following reperfusion, use was made of a variety of drugs that block the effects of noradrenaline on these receptors. The facts that several such drugs (prazosin, chloroethyldionine, phenotolamine and phenoxybenzamine) antagonised the beneficial effects of noradrenaline in these models [11,13,15,29–31], and that protection was also observed with the rather more selective α-adrenoceptor agonist phenylephrine [11,13,15,16] argue strongly for a role of α-adrenoceptor stimulation in mediating these particular protective effects. We could not use the first of these approaches because these drugs, especially prazosin, are themselves powerfully antiarrhythmic [9,32,33]. In the present study, and in a dose that resulted in a similar pressor effect, phenylephrine was less effective than noradrenaline in reducing the incidence of VT and the number of ventricular ectopic beats, although VF during occlusion was similarly reduced and survival from the combined occlusion–reperfusion insult was increased. Our conclusion is that it is α-adrenoceptor stimulation that is responsible for this suppression.
of those life-threatening ventricular arrhythmias that normally result in the first few minutes following coronary artery occlusion. This is supported by the failure, as expected, of isoprenaline to beneficially modify these arrhythmias; it could thus hardly be the β-adrenoceptor stimulant property of noradrenaline that is responsible for its ability to protect.

It was of interest that, in the present study, protection was also seen following the administration of guanethidine. Initially this leads to substantial noradrenaline release with resultant, very marked, sympathomimetic effects. We suggest that this endogenous release of catecholamines from stores throughout the body also preconditions the heart against the consequences of a subsequent coronary artery occlusion. Presumably, this is also mediated through an α-adrenoceptor mechanism.

There are several possible mechanisms involved in α-adrenoceptor mediated cardioprotection:

(1) The antiarrhythmic effect may result from a reduction in the severity of ischaemia, as suggested by the less marked changes in epicardial ST-segment elevation and in the inhomogeneity of conduction. The fact that other studies have demonstrated a reduction in ultrastructural ischaemic damage [14–16] and an enhanced recovery of contractile function following reperfusion [11,13], would suggest that this is certainly a factor in suppressing ventricular ectopic activity during ischaemia. That the reduction in the severity of ischaemia is the result, rather than the cause, of the less pronounced ectopic activity seems less likely, despite the fact that coronary blood flow to the ischaemic region is compromised during such activity, as shown by the marked decrease in peripheral pressure especially during periods of VT [34]. However, one might expect the severity of ischaemia to be increased, rather than decreased, by noradrenaline administration since myocardial contractility, at least as assessed by alterations in LVDP/dt,max, is increased and the coronary blood flow elevation seems too small to solely explain the marked changes in epicardial ST-segment elevation or in conduction delay.

(2) Some authors [29,35] have suggested that α-adrenoceptor-mediated noradrenaline protection involves adenosine receptor activation. The evidence for this is that PD 115,199, which antagonises the effects of adenosine on most adenosine receptors, also abolishes the protection that results from the administration of tyramine, which induces noradrenaline release from cardiac sympathetic nerves. Adenosine involvement is not now thought to be critical [15], although it could contribute to the antiarrhythmic effects of noradrenaline shown in the present studies since in this, and other, species exogenous adenosine powerfully suppresses coronary artery occlusion induced arrhythmias [36].

(3) In the original study of Regan et al. [7], in which noradrenaline was infused intravenously 15 min after the onset of myocardial ischaemia induced by thrombus formation in the LAD, the reduction in arrhythmias that occurred over the next hour of ischaemia was associated with a reversal of the potassium loss that normally occurs during ischaemia, and this despite the persistent production of lactate.

(4) The antiarrhythmic effect of exogenous noradrenaline might be due to modulation of neuronal noradrenaline release by an action on presynaptic α-adrenoceptors situated on the terminal endings of cardiac sympathetic nerves. Inhibition of neuronal noradrenaline release probably explains the cardioprotective effects of dopamine receptor agonists such as Z1046 [25], and of adrenergic neuron blocking drugs such as guanethidine, several hours after administration (see Section 3.10). Such a presynaptic effect of exogenous noradrenaline could explain why, whereas this can
mimic ischaemic preconditioning, sympathetic nerve stimulation, for example via the stellate ganglion, is ineffective in this respect. The explanations offered that ‘insufficient noradrenaline is released to trigger the protection’ or that ‘dogs differ fundamentally from rabbits’ [15] seem improbable. We know of no in vivo studies designed to explore the possibility that α-adrenoceptor agonists given exogenously inhibit the release of endogenous noradrenaline from cardiac nerve endings, by loading these neurones, for example, with [3H]noradrenaline. We did take up a suggestion to examine the role of presynaptic α2-adrenoceptors in the cardioprotective effects of exogenous noradrenaline by attempting to selectively block these receptors with yohimbine using a dose (0.03 mg kg−1) that has been used to study the role of these receptors in the release of cardiac noradrenaline during exercise [37]. However, in this study [37] even in the resting state yohimbine itself resulted in a 3-fold elevation of noradrenaline in the coronary sinus and, perhaps as a result of this, yohimbine in our hands itself reduced arrhythmia severity. It was thus not possible to examine whether yohimbine could modify the effects of locally infused noradrenaline in this model. However, it should be borne in mind, that many agents that mimic preconditioning, and which incidentally are also antiarrhythmic, such as nitric oxide donors, adenosine and prostacyclin, also have the ability to inhibit neuronal noradrenaline release.

(5) Stimulation of α-adrenoceptors is one of the principal activating pathways for protein kinase C [38] and this pathway also plays a major role in mediating some of the manifestations of ischaemic preconditioning, such as the reduction in infarct size (reviewed in Ref. [39] and see Section 1) It is as yet unclear what role, if any, PKC activation plays in the acute antiarrhythmic effects of preconditioning. However, it is certainly possible that the delayed preconditioning effect of noradrenaline might also result from protein kinase C activation since this can lead to the expression of induced nitric oxide synthase [40]. There is some evidence that the arrhythmia suppression, seen 24 h after a preconditioning (cardiac pacing) stimulus [27] or after exercise [41,42], involves nitric oxide since this protection is abolished by drugs that inhibit nitric oxide synthase by the iNOS enzyme [43].

Whatever the mechanisms, the antiarrhythmic effect of noradrenaline given locally to the heart is clearly short-lived; when saline was substituted for noradrenaline 1 h later much of the protection was lost (Fig. 2). However, as with ischaemic preconditioning, there is a much delayed component as shown by the protection observed 24 h after the intravenous administration of noradrenaline. This delayed protection has been observed before; in studies when the main left coronary artery was occluded in anaesthet-


