Delayed sympathetic efferent responses to coronary baroreceptor unloading in anaesthetized dogs

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1. We previously reported that, although stimulation of coronary arterial baroreceptors results in reflex vasodilatation of a magnitude and a time course similar to that seen in response to carotid baroreceptor stimulation, the vasoconstriction that occurs when the stimulus to coronary baroreceptors is removed develops more slowly. We now report the results of experiments designed to investigate the site on the reflex arc that is responsible for the delayed vasoconstriction.

2. In α-chloralose anaesthetized, artificially ventilated dogs, a perfusion circuit allowed independent control of pressures to the aortic root, including the coronary arteries, the aortic arch and the carotid sinuses. Electrophysiological recordings were made of afferent discharge in nerve fibres dissected from the vagus nerve, which responded to changes in coronary pressure, and from renal and lumbar efferent sympathetic nerves. Reflex vascular responses were assessed from changes in perfusion pressure to the systemic circulation, which was perfused at constant flow.

3. The afferent discharge from the coronary baroreceptors responded rapidly to both increases and decreases in coronary perfusion pressure. This indicates that prolonged activation of the coronary receptors cannot be the cause of the delayed vasoconstriction.

4. An increase in pressure to the coronary baroreceptors resulted in an immediate decrease in activity in either renal or lumbar sympathetic nerves. A decrease in coronary pressure, however, was followed by a slow gradual increase in sympathetic discharge. This contrasts with the responses to decreases in carotid or aortic arch pressures, which were followed by rapid increases in efferent discharge, often with an overshoot.

5. We conclude that the slow recovery of efferent sympathetic activity following a reduction in coronary pressure is likely to explain the previously reported slow recovery of vascular resistance.

We have previously reported that an increase in pressure in the aortic root results in reflex vasodilatation and that this response results from distension of coronary arterial mechanoreceptors rather than ventricular receptors *per se* (Al-Timman, Drinkhill & Hainsworth, 1993; Drinkhill, Moore & Hainsworth, 1993). Coronary arterial baroreceptors are attached to myelinated vagal afferent fibres (Drinkhill *et al.* 1993) and are similar to the aortic and carotid baroreceptors in that they show a phasic discharge with the arterial pulse and they induce reflex vasodilatation in response to physiological increases in distending pressure. They differ, however, in that the vasodilatation is not associated with bradycardia (Okinaka *et al.* 1963; Tutt, McGregor & Hainsworth, 1988; Vukasovic, Tutt, Crisp & Hainsworth, 1989; Al-Timman & Hainsworth, 1992). Recently we have reported another interesting difference between the coronary and carotid or aortic baroreceptors, which is that, following a period of elevated coronary baroreceptor pressure, sometimes as short as 15 s, the vasoconstriction following a subsequent decrease in pressure develops much more slowly than that which occurs when either carotid or aortic arch pressure is decreased (McMahon, Drinkhill & Hainsworth, 1996*a*).

There are two possible explanations to account for the slow development of vasoconstriction: (1) coronary baroreceptors may continue to be excited for a period following a decrease in distending pressure; or (2) a prolonged central inhibitory mechanism may result in extended inhibition of sympathetic vasoconstrictor nervous activity. Such a prolonged inhibition of sympathetic efferent activity has indeed been reported in

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several studies following sustained increases in arterial pressure brought about by pressor substances (Undesser, Jing-Yun, Lynn & Bishop, 1985; Kenney, Morgan & Mark, 1990) or following electrical stimulation of the aortic nerve (Kunze, 1986). However, there is no evidence as yet which links this effect specifically to coronary baroreceptors.

This paper is a report of an electrophysiological investigation of the afferent and efferent nervous discharge in the coronary baroreceptor reflex. The study was designed to elucidate which stage of the reflex was responsible for prolonging the vasodilatation.

METHODS

Dogs of either sex, weighing between 13 and 19 kg, were anaesthetized with a 1% solution of α-chloralose I.V. (100 mg kg^{-1}; Vickers Laboratories Ltd, Pudsey, York, UK) in saline. Anaesthesia was subsequently maintained by a continuous I.V. infusion of chloralose (0·5–1·0 mg kg^{-1} min^{-1}). The trachea was cannulated and the animal was artificially ventilated with oxygen-enriched air (approximately 40% O_2) by means of a Starling 'Ideal' pump. The stroke of the respiratory pump was initially 17 ml kg^{-1} at a rate of 17 strokes min^{-1}. An infusion of molar sodium bicarbonate solution was started at a rate of 0·5 mmol min^{-1} to prevent the development of non-respiratory acidosis.

The left side of the chest was opened widely by removing the second to sixth ribs. When the pleural cavity was opened an end-expiratory resistance was applied by placing the expiratory outlet from the pump under 3 cm of water. The descending aorta was mobilized by tying and dividing the upper six pairs of intercostal arteries. The left subclavian artery was dissected free of its surrounding tissues, the pericardium opened and a loose thread passed carefully around the ascending aorta 0·5–1 cm from its origin, just distal to the coronary ostea.

The technique used was similar to that previously described (Drinkhill *et al.* 1993). Initially the dog was connected to an abbreviated circuit which allowed all vascular cannulations to be carried out but which excluded all reservoirs and pumps and did not require heparinization of the animal. This was used during the nerve dissection and greatly reduced blood loss. A curved stainless-steel cannula was inserted into the aortic arch and this linked directly to another cannula inserted into the descending aorta. 'T' connectors, initially clamped, linked this loop to the full perfusion circuit (Fig. 1). Cannulae, which were also initially clamped, were inserted into the left atrium, the central end of the subclavian and the central end of the right common carotid artery, the peripheral end of the subclavian artery, the central end of the left common carotid artery and the peripheral ends of both carotid arteries.

In the studies of afferent coronary baroreceptor activity the left cervical vagus nerve was dissected free of the carotid artery and covered with warm (37 °C) paraffin oil. A portion of the vagus nerve was laid on a black Bakelite platform. A binocular microscope was used to dissect fine strands from the nerve and afferent activity from single or few-fibre preparations was recorded using bipolar silver electrodes. The output from the electrodes was amplified and filtered (Neurolog system, Digitimer Ltd, Welwyn Garden City, Herts, UK). The action potentials were subsequently displayed on a digital storage oscilloscope (Model OS 1420, Gould Ltd, Hainault, Essex, UK). The signal also passed into a spike processor (Model D130; Digitimer Ltd), which incorporated an audioamplifier and loudspeaker. The conduction velocity of the nerve fibre was measured by applying a single stimulus to electrodes placed on the nerve trunk peripheral to the recording electrodes and measuring the latency of the evoked potential. The distance between the stimulating and recording electrodes was measured post mortem and was always in excess of 45 mm.

In other dogs, an incision was made in the left flank to expose either the renal sympathetic nerves running along the surface of the renal artery or the sympathetic trunk at the level of the 3rd and 4th lumbar sympathetic ganglia. The sympathetic efferent nerves were dissected to obtain single or few-fibre preparations.

Nerve fibres were initially tested before connection of the animal to the full circuit. When a satisfactory unit had been identified, the animal was given heparin (500 i.u. kg^{-1}, I.V.) and the clamps on the tubing between the abbreviated circuit and the full circuit were removed. The circuit (Fig. 1) was initially filled with a mixture of equal parts Ringer solution (g l^{-1}: NaCl, 6·9; KCl, 0·35; $CaCl_2$, 0·28; $MgSO_4$, 0·14; $NaHCO_3$, 2·09; KH_2PO_4, 0·16; glucose, 1) and Dextran in dextrose solution (Dextran, 60 g l^{-1}; glucose, 50 g l^{-1}) (total volume approximately 1·5 l).

The cannula in the aortic arch conveyed aortic flow to a pressurized main reservoir. This reservoir determined coronary perfusion pressure. Blood from this reservoir was pumped at constant flow (604U pump; Watson-Marlow Ltd, Falmouth, UK), through the cannula in the descending aorta to perfuse the systemic circulation. In a few dogs, a hindlimb was vascularly isolated (Challenger, McGregor & Hainsworth, 1987) and perfused at constant flow. The left atrial cannula (7 mm i.d.) drained blood into an open reservoir, from which it was pumped into the main reservoir. The carotid sinuses were perfused at constant pressure and drained via the lingual arteries into the atrial reservoir. The cephalic region of the animal was perfused at constant flow via the peripheral end of the left subclavian artery and the central end of the left common carotid artery. The aortic arch was perfused at constant pressure through the central end of the left subclavian artery and drained from a cannula passed down the central end of the right common carotid artery. This cannula was advanced until its tip reached the aortic arch and was secured by tying the brachiocephalic artery close to its origin. The snare around the ascending aorta was tightened, thereby creating a pouch of the aortic arch around the outside of the cannula.

Nylon catheters attached to strain gauge transducers (Gould-Statham P23Gb) were connected to the right carotid cannula (carotid perfusion pressure), lumen of the aortic cannula (coronary pressure), left subclavian cannula (aortic pouch pressure), peripheral left subclavian cannula (cephalic perfusion pressure) and the right femoral artery (systemic perfusion pressure). These pressures and nerve activity were recorded on a direct-writing electrostatic recorder (Model ES 1000; Gould Electronics, France) and also recorded on magnetic tape (Racal V-Store; Racal Recorders Ltd, Southampton, UK). Data were analysed on-line using a real-time data acquisition unit (Fastdaq; Lectromed, Letchworth, UK).

The temperatures of the animal and the perfusing blood were recorded by thermistor probes (Yellow Springs Instruments Co., Ltd, OH, USA) in the oesophagus and in the circuit blood. These were maintained at 37–39 °C by heat exchangers in the circuit and by heaters under the animal table.

These experiments were carried out in accordance with the current UK legislation, the Animals (Scientific Procedures) Act, 1986. Experiments were terminated by exsanguination of the animal.

Experimental procedures

After connecting the animal to the full perfusion circuit, pressures were allowed to stabilize and blood gases were measured and corrected as necessary to achieve values (means ± S.E.M.) for P_{O_2} of 26·16 ± 2·8 kPa and P_{CO_2} of 5·30 ± 0·15 kPa at pH 7·37 ± 0·03. Haematocrit was 19·4 ± 1%.

Coronary afferent activity. We studied afferent units in the vagus nerve which increased their discharge in response to increases in aortic root pressure. These units were identified before connection of the full circuit. Coronary perfusion pressure was then increased in steps of 4 kPa from 8 kPa until a maximum discharge frequency had been obtained. Activity was recorded at each step for a period of at least 30 s. After attaining the final step, coronary pressure was reduced back to its control value in a single step and the discharge was recorded until it had returned to its previous level.

Efferent sympathetic discharge. After connecting the animal to the full perfusion circuit a series of pressure tests was performed. Pressures perfusing the coronary and aortic baroreceptors were held constant at 8 kPa whilst carotid sinus pressure was increased from 8 kPa to a level which produced maximal vasodilatation. It was held at this level for 30 s and then reduced back in a single step to 8 kPa. Efferent sympathetic activity was recorded during this test and until the initial control level had been regained. The pressures perfusing carotid and aortic baroreceptors were then held constant at 8 kPa whilst coronary perfusion pressure was increased in steps from 8 kPa to a level which produced maximal vasodilatation. It was held at this level for 30 s and then reduced. The efferent activity was recorded until the control level was regained. Following this the carotid baroreceptor test was repeated. Experiments were only accepted if the vascular response exceeded 2 kPa and the perfusion pressure and efferent nerve activity recovered to at least 90% of its initial value following the decrease in baroreceptor pressure.

In some animals the recovery in efferent discharge and systemic perfusion pressure was also examined following loading and unloading of the aortic baroreceptors.

The responses of nerve activity and perfusion pressures were normalized by expressing the responses to the increase in baroreceptor pressure as 100% and calculating the recovery at any time after decreasing the baroreceptor pressure as a percentage of this response.

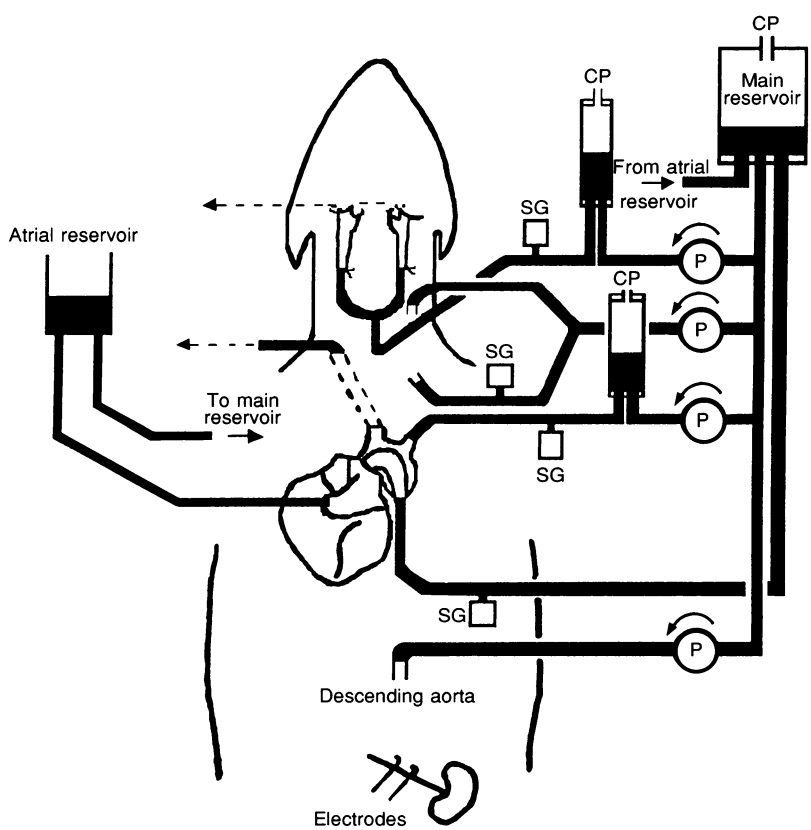

Figure 1. Diagram of experimental preparation

Blood is pumped into a constant pressure reservoir, from which it flows into the isolated carotid sinus regions. Blood is drained through catheters in the lingual arteries into the atrial reservoir. A second constant pressure system perfuses the aortic arch through a cannula in the left subclavian artery; drainage is from a catheter passed through the right carotid artery to the origin of the brachialcephalic artery, at which point it is secured by a tie. A constant flow pump perfuses the cephalic circulation at constant flow through cannulae in the cephalic end of the left subclavian artery and the cardiac end of the left carotid artery. The subdiaphragmatic region is perfused at constant flow through a cannula in the descending aorta. A cannula in the left atrium connected to an open reservoir controls left atrial pressure. Recording electrodes are shown placed on the renal nerves. CP, constant pressure; SG, strain gauge transducer; P, pump.

Data are expressed as means ± S.E.M. and statistical significance was assessed by Student's t test for paired data unless otherwise stated.

RESULTS

Afferent coronary baroreceptor discharge

Six fibres were studied from six dogs. These fibres had regular spontaneous discharges synchronized to the cardiac cycle and all increased their discharge in response to increases in coronary perfusion pressure brought about by increases in aortic root pressure. All had conduction velocities greater than 3·2 m s^{-1} and were therefore considered to be myelinated. The receptive fields associated with these fibres were determined by careful probing and were localized to the bifurcation of the left coronary artery and the proximal parts of the anterior descending and circumflex coronary arteries.

In all six afferent units, discharge frequency increased promptly in response to an increase in coronary pressure. A single step decrease in coronary perfusion pressure from this high level back to the control value of 8 kPa resulted in a prompt decrease in afferent discharge (Fig. 2).

Data from all six dogs showed that the discharge rate in the 10 s period immediately following reduction of coronary pressure was not significantly different from that in the control period before the increase in coronary pressure. Discharge in the initial control period for these six dogs was 10·5 ± 4·5 impulses s^{-1}, increasing to 22·1 ± 6·4 impulses s^{-1} at a coronary pressure of 28·3 ± 0·2 kPa and, in the 10 s period following the reduction in coronary pressure, decreasing again to 10·5 ± 3·6 impulses s^{-1}.

Efferent sympathetic discharge

Renal nerves. Recordings were made from six units in six dogs. An increase in carotid sinus pressure from 8·2 ± 0·1 to 26·0 ± 0·7 kPa resulted in a decrease in arterial perfusion pressure from 17·9 ± 2·0 to 11·1 ± 1·5 kPa and a decrease in mean renal nerve activity from 12·7 ± 3·7 to 2·2 ± 0·7 impulses s^{-1}. The maximal responses of perfusion pressure and nerve activity were reached in 13·3 ± 1·0 and 1·4 ± 0·2 s, respectively. Carotid pressure was held at the high level for 30 s and then decreased to its former level. Following this, systemic perfusion pressure returned to within 90% of the initial control value in 14·8 ± 2·9 s and renal nerve activity in 2·2 ± 0·5 s. Renal nerve activity then further increased to 212 ± 22·7% of the control value before decreasing again and stabilizing in 21·2 ± 3·1 s.

An increase in coronary perfusion pressure from 8·5 ± 0·2 to 26·1 ± 0·6 kPa resulted in responses of perfusion pressure and renal nerve activity that were not significantly different from the responses to increases in carotid pressure. Perfusion pressure decreased from 18·9 ± 1·9 to 11·4 ± 1·4 kPa and renal nerve activity decreased from 15·0 ± 4·1 to 1·5 ± 0·7 impulses s^{-1}. These responses were maximal in 14·5 ± 1·3 and 1·8 ± 0·2 s, respectively. Coronary pressure was held at this level for 30 s and was then decreased to its initial low level. The time course of the responses of both perfusion pressure and renal nerve activity were completely different from those to decreases in carotid sinus pressure. The return of both pressure and

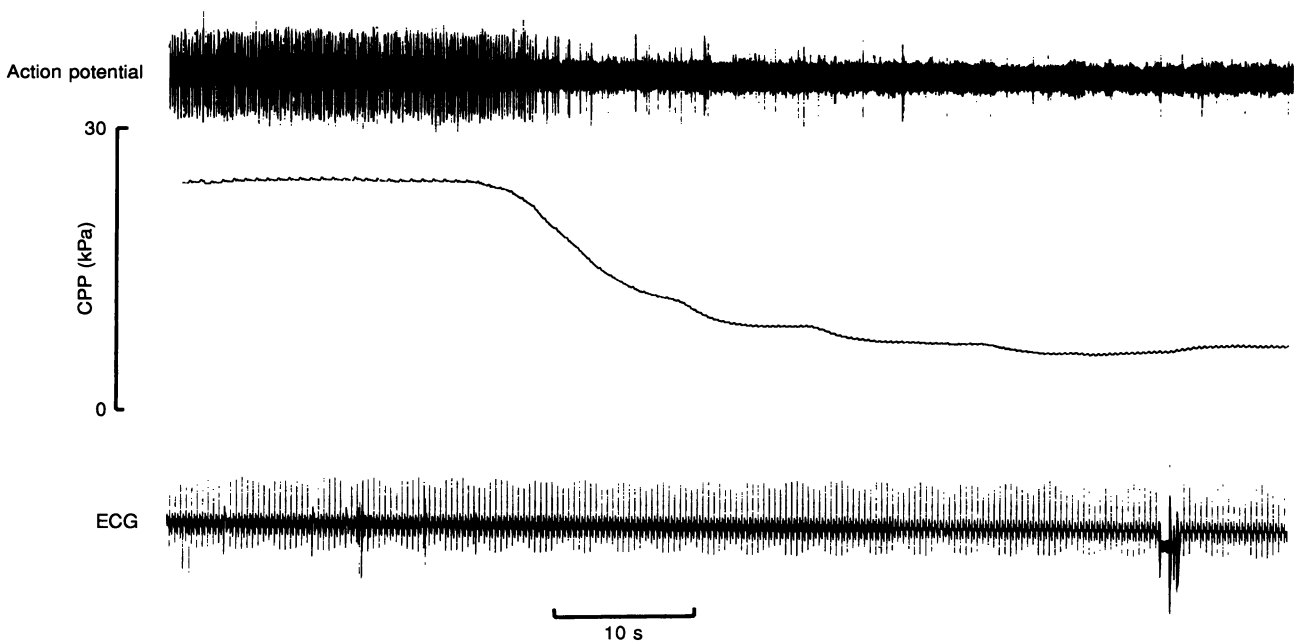

Figure 2. Original trace from 1 dog showing vagal afferent activity, coronary perfusion pressure and electrocardiogram

Vagal afferent activity is shown by the action potential trace, top. Note that the discharge decreases immediately upon a reduction in the coronary perfusion pressure (CPP).

nerve activity to their former levels occurred slowly and there was no overshoot. The times for pressure and neural activity to return to 90% of the initial control values were 110 ± 13 and 76·2 ± 12 s, respectively. Both these times were significantly longer than the recovery times following a decrease in carotid pressure ($P < 0·005$).

Figure 3 shows original records from one experiment and contrasts the rapid recovery of pressures and nerve activity following a decrease in carotid pressure (Fig. 3*A*) with the much slower responses following a decrease in coronary pressure (Fig. 3*B*). Figure 4 shows data expressed as percentages of the responses to the increases in baroreceptor pressure. Values are shown at 5 s intervals from tests of a decrease in carotid pressure (Fig. 4*A*), followed by a decrease in coronary pressure (Fig. 4*B*), and a subsequent carotid test (Fig. 4*C*). This emphasizes the slower responses to the coronary test. The mean data from all six dogs are shown in Fig. 5*A* and *B* and this again emphasizes the much slower responses and the absence of overshoot of both efferent sympathetic activity and arterial perfusion pressure.

In three of the dogs the responses were determined to changes in aortic arch pressure. An increase in aortic pressure from 7·9 ± 0·1 to 27·6 ± 0·2 kPa decreased efferent renal nerve activity from 37·4 ± 17·6 to 18·0 ± 8·7 impulses s^{-1}. After 30 s a decrease in aortic pressure to its original level resulted in the efferent discharge returning to within 90% of its initial value in 2·7 ± 0·67 s.

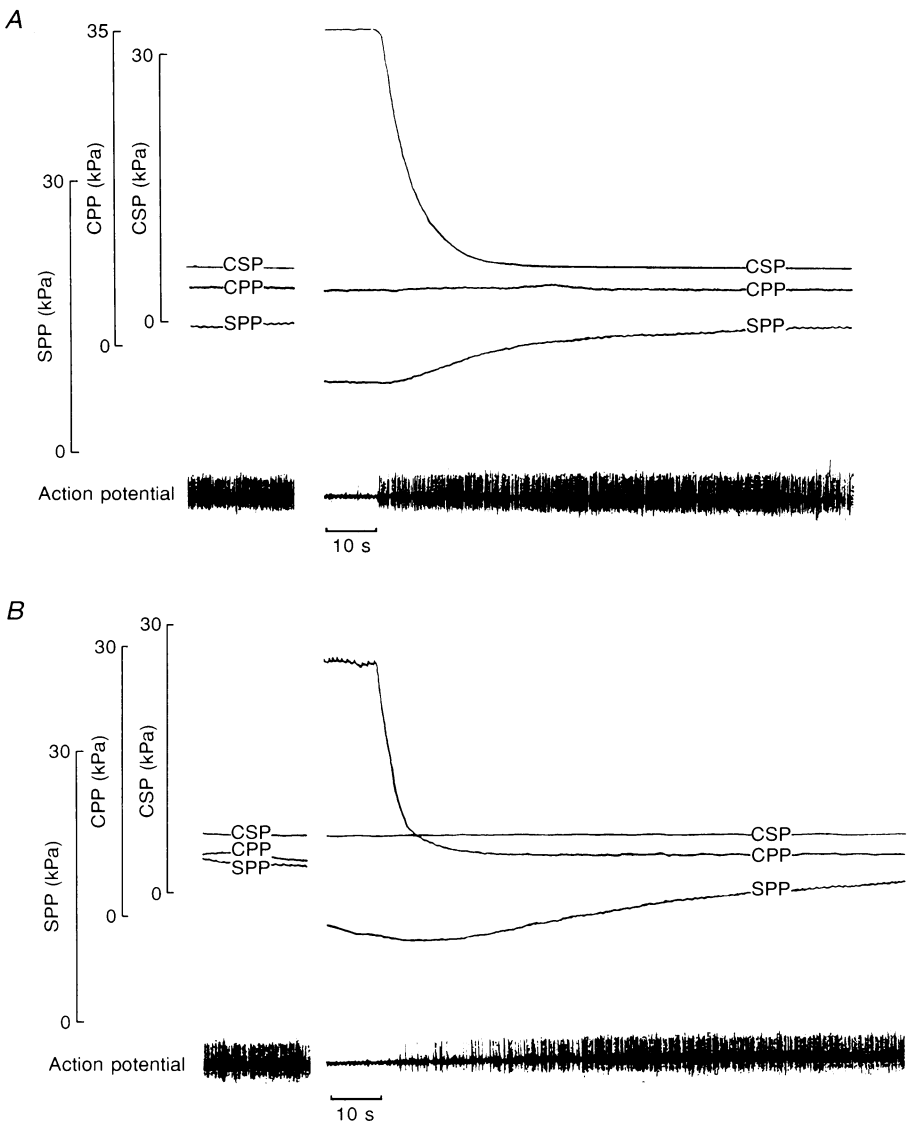

Figure 3. Electrical activity recorded from a strand of the renal nerve showing the responses to decreases in pressure to carotid (*A*) and coronary baroreceptors (*B*)

These traces contrast the rapid increases in nerve activity and systemic perfusion pressure following a decrease in carotid pressure (*A*) with the slower responses to the decrease in coronary pressure (*B*). Original records from 1 dog. CSP, carotid sinus pressure; CPP, coronary perfusion pressure; SPP, systemic perfusion pressure.

Lumbar efferent sympathetic nerves. In six dogs, six efferent lumbar sympathetic nerves were examined. In these dogs, increasing carotid sinus pressure from 8·2 ± 0·1 to 27·8 ± 0·7 kPa resulted in decreases in systemic perfusion pressure from 19·3 ± 1·6 to 10·6 ± 0·4 kPa and in mean lumbar efferent nerve activity from 11·0 ± 2·8 to 2·8 ± 1·1 impulses s^{-1}. These responses were maximal in 11·6 ± 0·8 and 1·5 ± 0·2 s, respectively. Following a decrease in carotid perfusion pressure back to the initial low level, systemic perfusion pressure and lumbar efferent discharge recovered to within 90% of the initial values in 18 ± 7·2 and 1·8 ± 0·6 s, respectively.

Increasing coronary pressure from 8·4 ± 0·2 to 25·9 ± 0·9 kPa decreased systemic perfusion pressure from 19·4 ± 1·5 to 12·6 ± 1·5 kPa and mean lumbar efferent nerve activity from 15·7 ± 6·9 to 4·1 ± 1·8 impulses s^{-1}; maximal responses were obtained in 11·5 ± 0·7 and 2·0 ± 0·5 s, respectively. Following a decrease in coronary pressure to its initial level, the times for recovery were significantly longer than the responses to carotid baroreceptor unloading: 74·8 ± 17·4 s ($P < 0·005$) for systemic perfusion pressure and 30·7 ± 2·1 s ($P < 0·005$) for lumbar efferent nerve activity; no overshoot of either response was seen. The recovery of both systemic perfusion pressure and lumbar efferent nerve activity for these six dogs is shown in Fig. 5*C* and *D*.

There was no significant difference in the times for recovery between renal and lumbar sympathetic nerve discharge after

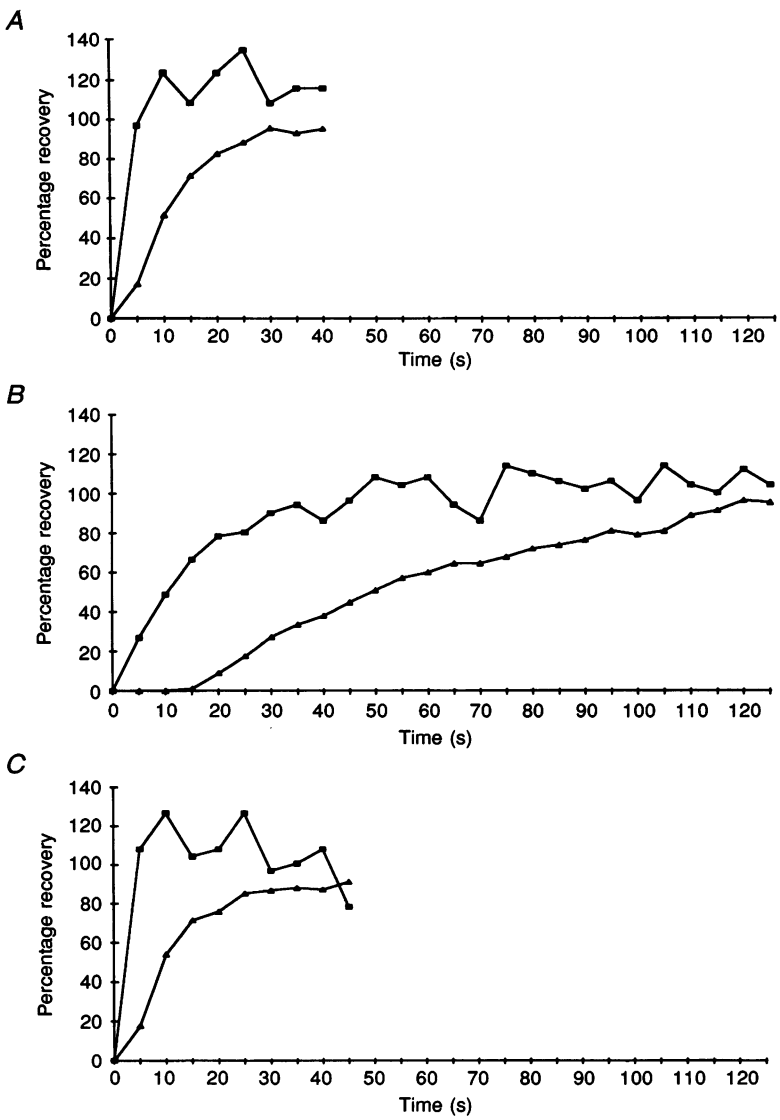

Figure 4. Results from 1 dog contrasting the time course of the increases in renal efferent nerve activity and arterial perfusion pressure following a decrease in carotid pressure (*A* and *C*) and coronary pressure (*B*)

Pressures to each baroreceptor region were maintained at saturation levels for 30 s before decreasing. The coronary test was bracketed by two carotid tests. ■, renal efferent nerve activity; ▲, systemic perfusion pressure.

a decrease in carotid sinus stimulation (2·2 ± 0·7 and 1·8 ± 0·6 s, respectively). However, the time for recovery of renal sympathetic efferent discharge following coronary baroreceptor stimulation was significantly longer than the recovery time of lumbar sympathetic efferent discharge (76·2 ± 12 and 30·7 ± 2·1 s, respectively, $P < 0·05$, Student's unpaired t test).

Hindlimb vascular responses

In five dogs, in addition to recording systemic perfusion pressure, a hindlimb was vascularly isolated and perfused at constant flow (Challenger *et al.* 1987). The time for recovery in this isolated vascular bed following a decrease in carotid sinus stimulation was 16·6 ± 2·7 s and following a reduction in the coronary baroreceptor stimulation it was significantly ($P < 0·05$) longer at 90·0 ± 25·2 s. These times were not significantly different from those observed in the remainder of the systemic circulation.

DISCUSSION

The existence of receptors influenced by changes in coronary pressure had been suspected for a number of years (Abraham, 1962; Szentivanyi & Nagy, 1962; Okinaka *et al.* 1963; Coleridge, Coleridge & Kidd, 1964; Brown, 1965). Coronary arterial baroreceptors, distinct from ventricular receptors, were demonstrated by use of combined electrophysiological and perfusion techniques, which separated the stimulus to the coronary artery from that to the ventricle (Al-Timman *et al.* 1993; Drinkhill *et al.* 1993). Although these coronary receptors were shown to be similar to the 'classical' carotid and aortic baroreceptors in that stimulation leads to reflex vasodilatation (McMahon *et al.* 1996*a*; McMahon, Drinkhill & Hainsworth, 1996*b*), they differ in that there is no consistent effect on the heart rate (Okinaka *et al.* 1963; Challenger *et al.* 1987; Tutt *et al.* 1988; Vukasovic *et al.* 1989; Al-Timman & Hainsworth, 1992). This reflex vasodilatation was shown to be abolished by cooling of the cervical vagi (Challenger *et al.* 1987).

Recently we compared the responses to localized pressure stimuli applied to the individual baroreceptor regions of the carotid sinus, aortic arch and coronary circulation (McMahon *et al.* 1996*a*). These findings demonstrated that, although the magnitudes of the reflex vasodilatation from the carotid and coronary baroreceptors were similar, recovery (i.e. vasoconstriction) following coronary baroreceptor unloading occurred much more slowly. The purpose of the

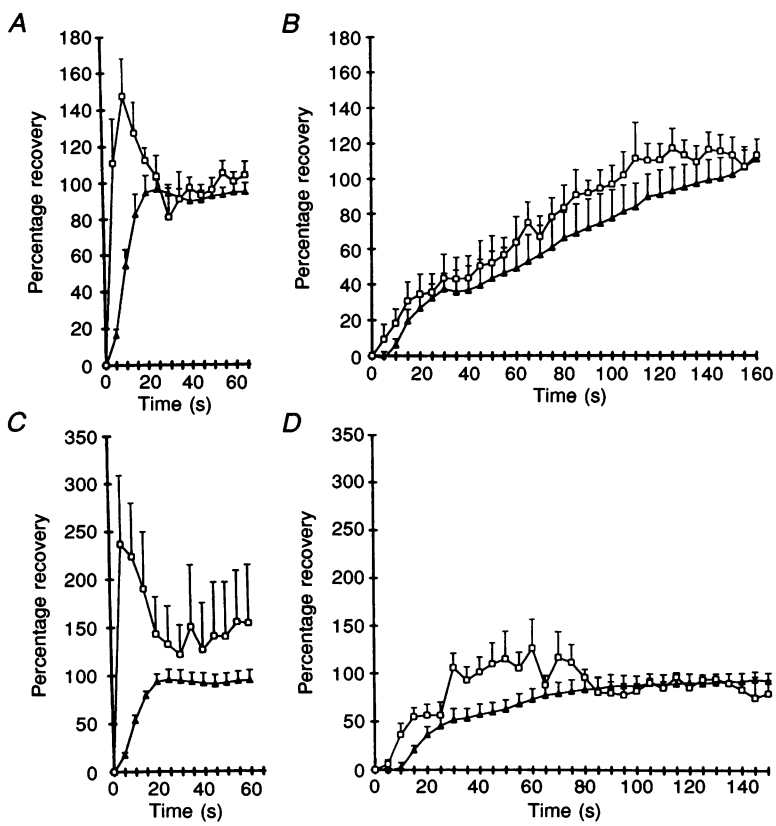

Figure 5. Comparison of renal (*A* and *B*) or lumbar (*C* and *D*) efferent nerve activity recovery, following a decrease in carotid (*A* and *C*) or coronary (*B* and *D*) pressures

A and *B* show responses of renal nerve activity (□) and systemic perfusion pressure (▲) following a decrease in carotid pressure (*A*) and in coronary pressure (*B*). *C* and *D* show responses of lumbar nerve activity (□) and systemic perfusion pressure (▲) following a decrease in carotid pressure (*C*) and in coronary pressure (*D*). Results show means ± S.E.M. from 6 dogs for each group. Note the rapid increases in nerve activities (with overshoots) and perfusion pressures following the carotid but not the coronary tests.

present investigation was to determine, by means of an electrophysiological study, which stage of the reflex arc was responsible for this delay. We investigated this by combining electrophysiological techniques with similar perfusion techniques to those we had used previously to study the reflex responses.

One possible explanation for the delayed recovery from hypotension following stimulation of coronary baroreceptors is that it might have been due to the increased afferent activity from the coronary baroreceptors persisting for some time after removal of the stimulus. To assess this possibility, we recorded activity from six myelinated vagal afferent fibres which responded with an increase in discharge to an increase in the coronary perfusion pressure and which had receptive fields localized to the coronary arteries. These afferent fibres showed an instantaneous increase in their discharge following an increase in coronary pressure and all showed an immediate decrease in their discharge when coronary perfusion pressure decreased. These experiments, therefore, confirmed that the delay in recovery from hypotension following unloading of the coronary baroreceptors could not have been due to persistent activation of the coronary receptors.

The other possibility that we considered was that delayed development of vasoconstriction following a period of stimulation of coronary arterial baroreceptors might have been due to persistent central inhibition and a consequent delay in the onset of vasoconstrictor nerve activity. The efferent pathway of the vasodilatation to coronary baroreceptor stimulation, like that of the carotid baroreceptor reflex, is known to involve the sympathetic nerves (Challenger *et al.* 1987). However, it is not known whether coronary baroreceptor stimulation affects the same or a different population of sympathetic nerves or whether it induces different discharge patterns in the same nerves. To evaluate these possibilities we recorded sympathetic efferent activity from strands of the renal or lumbar nerves. These studies showed that all the sympathetic efferent fibres that were tested responded to stimulation of both carotid and coronary baroreceptors and, in those that were examined, also to aortic baroreceptors. This proves that the delayed recovery in vascular resistance following coronary baroreceptor stimulation could not have been due to reflex activation of a different population of efferent sympathetic fibres.

Although the same sympathetic efferent fibres responded to stimulation of all three groups of baroreceptors, the pattern of discharge following unloading of the coronary baroreceptors was quite different from that occurring in response to unloading of the other baroreceptors. Decreasing either carotid sinus or aortic arch pressure from saturation to threshold value resulted in very rapid increases in efferent discharge; often in the first few seconds the discharge reached a level greater than that seen in the preceding control period, and this was associated with a correspondingly rapid rise in systemic perfusion pressure, sometimes also with an overshoot. In contrast, reducing coronary perfusion pressure over its sensitivity range resulted in only a slow gradual increase in efferent sympathetic discharge and a correspondingly slower increase in systemic perfusion pressure with no overshoot in either response. In most of these experiments we were relating the time courses of the nervous responses with that of the overall response of systemic vascular resistance, whereas the actual vascular beds supplied by these sympathetic nerves would be the kidney and the hindlimbs. In some experiments, therefore, we related the responses of lumbar nerves to those of perfusion pressure to a hindlimb on the side opposite to the lumbar nerves being studied. In these experiments we found vascular responses to be similar to those in the remainder of the circulation, with the time course of the vascular responses showing a pattern of recovery similar to that of the efferent activity in the lumbar nerves.

Interestingly, following unloading of the coronary baroreceptors, activity in the renal sympathetic nerves took even longer to recover (76·2 ± 12 s) than activity in the lumbar sympathetic nerves (30·7 ± 2·1 s). Since the renal nerves influence the release of renin and thereby angiotensin, this may have an implication with regard to the longer-term control of blood pressure. In this connection it should be noted that, in the present study, the baroreceptors were stimulated for only 30 s duration. In our previous study (McMahon *et al.* 1996*a*) we found that stimulation of the coronary baroreceptors for periods of 8 min was associated with a further lengthening of the recovery period of the perfusion pressure and this raises the possibility that humoral effects may become particularly important when coronary baroreceptors are stimulated for longer periods.

The findings of this study indicate that the delay in the recovery of systemic perfusion pressure following unloading of the coronary baroreceptors can be explained by delayed activation of the sympathetic nerves and the absence of an overshoot. Another possibility is that the different efferent nerve discharge patterns may release different neurotransmitters. The sympathetic nervous system is known to have the ability to release different cotransmitters according to discharge frequency (Lundberg, Rudehill, Sollevi, Theodorsson-Norheim & Hamberger, 1986; Burnstock & Milner, 1992; Shepherd & Hainsworth, 1993). It is therefore possible that the initial transient very high discharge frequency following decreases in the stimulation of carotid baroreceptors may promote the release of a transmitter which causes a more rapid constriction in the vascular bed. However, there is no evidence as yet for the contribution of any cotransmitters to our findings.

Our findings of prolonged inhibition of sympathetic efferent nervous activity following a localized stimulus to the coronary baroreceptors could explain previous observations of persistent sympathetic inhibition following sustained increases in arterial pressure induced by pressor substances (Undesser *et al.* 1985; Kenney *et al.* 1990). Indeed, Undesser *et al.* (1985) reported that efferent sympathetic nerve

activity recovered more rapidly after a period of hypertension following vagotomy and aortic nerve section, which would have removed the effect of coronary baroreceptors. However, Kunze (1986) reported that electrical stimulation of the aortic nerve in the rabbit also resulted in prolonged inhibition of efferent sympathetic activity. Our results were different, however, in that we found that specific physiological stimulation of aortic baroreceptors did not result in a prolonged inhibition of sympathetic activity. The difference between our findings and those of Kunze (1986) may be ascribed to the difference between the effects of stimulating a mixed nerve and of applying a more physiological stimulation to a reflexogenic area.

The mechanism behind the prolonged inhibition of the sympathetic nervous system that occurs following cessation of a stimulation to coronary baroreceptors is not known. The central neuronal pathways that process information from the carotid baroreceptors are currently the subject of extensive investigation, with anatomical connections, chemical character and direction of pathways being examined (Spyer, 1994). How the coronary baroreceptors integrate within this system is at present not known.

To conclude, we have demonstrated that the prolonged vasodilatation following stimulation of coronary baroreceptors is not due to persistent discharge from sensory receptors but is due to a prolonged central inhibition of efferent sympathetic activity. The baroreceptors of the carotid sinus and aortic arch respond rapidly to both increasing and decreasing blood pressure but they are not thought to be of importance for its long-term control. The different time course of the responses to unloading the coronary baroreceptors raises the possibility that they may be of greater relevance to the longer-term control of blood pressure.

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