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Clonidine Has Comparable Effects on Spontaneous Sympathetic Activity and Afferent A δ - and C-Fiber-mediated Somatosympathetic Reflexes in Dogs

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Background: Clonidine, an α_2 -adrenergic agonist, has been studied as an adjunct or alternative to spinal opioids in the management of moderate to severe pain. This study examined the relative effects of clonidine on efferent spontaneous sympathetic activity and afferent A δ - and C fiber-mediated somatosympathetic responses.

Methods: Spontaneous and evoked sympathetic activity in renal sympathetic nerves, mediated by A δ and C fibers by means of supramaximal electrical stimulation of the radial and tibial nerves, were observed in anesthetized dogs. Incremental doses of clonidine were administered intrathecally or intravenously in each of five preparations followed by intravenous naloxone 2 mg and yohimbine 5 mg.

Results: Both spontaneous sympathetic outflow and afferent A δ - and C fiber-mediated somatosympathetic responses evoked by tibial nerve stimulation were depressed in a similar dose dependent manner by clonidine administered intrathecally or intravenously in a dose ratio of approximately 1:4. Intrathecal clonidine inhibited and eliminated both local spontaneous sympathetic outflow and tibial nerve evoked sympathetic responses but had no significant depressant effect on the radial nerve evoked sympathetic reflexes. When administered intravenously clonidine had a similar depressant effect on both radial and tibial nerve elicited reflexes and spontaneous sympathetic activity.

Conclusions: Clonidine, administered intrathecally or intravenously, has a similar depressant effect on both spontaneous sympathetic outflow and afferent A δ - and C fiber-mediated somatosympathetic reflexes. When administered intrathecally it has little effect on reflexes evoked *via* the descending pathway by radial nerve stimulation. (Key words: Anesthetic techniques: intrathecal; intravenous. Nerves: renal sympathetic; radial; tibial. Sympathetic nervous system, α_2 -adrenergic agonists: clonidine.)

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THE α_2 -adrenoceptor agonists such as clonidine have been used in patients primarily as antihypertensive agents. This effect is generally ascribed to a suppression of sympathetic outflow because of its effect at both supraspinal and spinal level and also probably to enhancement of vagal activity.¹⁻³

In addition an antinociceptive effect of α_2 -adrenoceptor agonists has been demonstrated when they are administered systemically⁴⁻⁶ or spinally.⁷⁻⁹ Electrophysiologic studies have also demonstrated that α_2 -adrenoceptor agonists can cause inhibition of nociceptive reflexes in the spinal cord.¹⁰⁻¹² In humans α_2 -adrenoceptor agonists have been studied as an adjunct or alternative to spinal opioids in the management of moderate to severe pain,¹³⁻¹⁵ but hypotension and bradycardia may occur in response to clonidine whether it is administered spinally or systemically.³

Somatosympathetic reflexes can be regarded as nociceptive reflexes. The somatosympathetic responses evoked by supramaximal electrical stimuli applied to somatic nerves cause two bursts of activity in renal sympathetic nerves in dogs by way of activation of afferent small myelinated group III (A δ) and unmyelinated group IV (C) fibers.^{16,17} By applying electrical stimuli to both radial and tibial nerves when the drug is injected intrathecally in the lumbar region away from the afferent input of the radial nerve, it is also possible to observe the effect of drugs on descending afferent pathways in addition to its effect on spontaneous sympathetic outflow and afferent A δ - and C fiber-mediated somatosympathetic responses.

The purpose of this study was to provide a quantitative comparison of the relative effects of clonidine administered both intrathecally and intravenously on spontaneous renal sympathetic outflow and somatosympathetic reflexes evoked by electrical stimulation of somatic nerves in anesthetized dogs together with its effect on the cardiovascular system.

Materials and Methods

Subjects and Surgical Procedures

The experiments were carried out on ten greyhound dogs weighing 18.9–24.4 kg. The study was approved by the Home Office (license PPL 70/016540). Anesthesia was induced with methohexital 15 mg/kg intravenously and maintained with 1% α -chloralose initially as a bolus dose of 30 mg/kg intravenously followed by an infusion at a rate of 17–20 mg \cdot kg⁻¹ \cdot h⁻¹. The animals were paralyzed with succinylcholine hydrochloride 10 mg intravenously every 20–30 min. The depth of anesthesia was assessed by immobility, floppy ears and absent response to glabellar tap stimulation after the effect of each dose of succinylcholine had decreased and before administration of the next dose. After tracheal intubation, the lungs were mechanically ventilated (Harvard, Dover, MA) with oxygen-enriched air (fraction of inspired oxygen 0.4–0.6). A femoral artery and vein were cannulated. Esophageal temperature was measured with a thermistor (Yellow Springs Instruments, OH) and maintained at 37–39°C using heaters, when required, in the operating table. Arterial blood gas tensions and *p*H_a were measured with a blood gas analyzer (Radiometer ABL2, Copenhagen), and values were maintained within a limited range throughout: *p*H_a 7.30–7.40, arterial carbon dioxide tension 34–42 mmHg and arterial oxygen tension 170–210 mmHg. For intrathecal injections a cannula (22-G Y-can, Wallace, Essex, UK) was inserted into the subarachnoid space *via* dura exposed by laminectomy at L2–L3. A lateral superficial branch of the radial nerve in the left foreleg and the tibial nerve in the right hindleg were exposed. Single fascicles of the renal sympathetic nerves were exposed retroperitoneally close to the renal artery. All the nerves were desheathed, cut distally and placed across silver–silver chloride electrodes in warm mineral oil for stimulation or recording.

Nerve Stimulation

Supramaximal electrical stimuli were applied to the radial and tibial nerves by a stimulator (S88, Grass, Quincy, MA) with matching isolation units (478A, Grass). For A δ - and C fiber-mediated responses in renal sympathetic nerves, the stimulation frequency was 0.33 Hz, intensity 30 V and pulse duration 0.5 ms. For pressor responses, 10-s trains of stimuli with a frequency of 30 Hz of the same intensity and pulse duration were applied to the radial or tibial nerves. The pressor response reached its maximal value within 10 s.

Efferent Sympathetic Activity

The electrical activity recorded in renal sympathetic nerves was amplified (Tektronix 122, Beaverton, OR) and displayed on an oscilloscope (Tektronix 565). For spontaneous renal sympathetic discharges, the signal was subjected to full-wave rectification and then integrated with a time constant of 100 ms (Neurolog NL90, Welwyn Garden, UK). Both amplified and integrated signals were displayed on an oscilloscope (Gould 1602, Essex, UK) and plotted with a pen recorder. For evoked responses in renal sympathetic nerves due to repeated single stimulation (0.33 Hz, 30 V, and 0.5 ms) of the radial and tibial nerves, the amplified signals were averaged (16 responses), rectified and integrated (Neurolog NL90). Both rectified and integrated signals were displayed on a pen recorder (Devices MX2, Welwyn Garden, UK), and the integrated signals were also displayed on the oscilloscope. The total electrical activity in the integrated signals of the evoked sympathetic reflexes and the spontaneous sympathetic outflow during 20-s periods was measured in arbitrary units using the oscilloscope and expressed as a percentage of control values. Data were based on the average of three measurements at each point in each preparation. The responses evoked by high-frequency train stimulation (30 Hz, 30 V, and 0.5 ms) could not be quantified as the repeated stimulus artifact distorted and added to the sympathetic signals.

Blood Pressure and Heart Rate

Mean arterial blood pressure (MAP) was measured using calibrated Satham strain gauges (Oxnard, CA) and displayed continuously together with beat-by-beat heart rate (HR) using a heated stylus recording system (Devices M19, Welwyn Garden, UK). The responses in MAP and HR due to low-frequency repeated single (0.33 Hz) and high-frequency train (30 Hz) stimulation of same intensity (30 V) and pulse duration (0.5 ms) were recorded and measured as the peak responses. To allow these responses to reach maximal levels, stimulation was sustained to 1 min for repeated single stimuli and to 10 s for train stimuli. The MAP and HR were then allowed to return to the prestimulus level.

Drug Administration

The following drugs were used: α -chloralose (Sigma, UK), clonidine hydrochloride (Boehringer Ingelheim, UK), methohexital sodium (Eli Lilly, UK), naloxone hydrochloride (Sigma), succinylcholine hydrochloride (Wellcome, UK) and yohimbine (Sigma).

In five preparations, clonidine (clinical formulation 150 $\mu\text{g}/\text{ml}$) was administered intrathecally in incremental doses of 50 μg , 100 μg and 150 μg , when necessary diluted with 0.9% saline, in volumes of 0.5, 1.0 and 1.0 ml respectively at intervals of 15 min. In another five preparations it was injected intravenously in incremental doses of 50 μg , 100 μg , 150 μg and 300 μg at intervals of 15 min. Naloxone 2 mg was administered intravenously 15 min after the last dose of clonidine. 15 min later yohimbine (5 mg) was administered intravenously. The recordings were started 5 min after each drug administration.

Statistics

Statistical analysis was performed by analysis of variance followed, where this indicated significance ($P < 0.05$), by paired t tests.

Results

Somatosympathetic Reflexes

Results are shown in figures 1–3.

Clonidine administered intrathecally. The tibial nerve evoked somatosympathetic reflexes mediated by the A δ and C fibers were slightly depressed after clonidine 50 μg and abolished after a total dose of 150

μg . There was no significant difference ($P > 0.05$) in its relative effects on A δ and C reflexes.

The radial nerve evoked reflexes mediated by the A δ and C fibers did not change significantly ($P > 0.05$) after clonidine 150 μg and 300 μg .

Clonidine administered intravenously. The radial and tibial nerves evoked somatosympathetic reflexes mediated by the A δ and C fibers were depressed by clonidine intravenously in a similar dose dependent manner. The A δ and C reflexes were significantly depressed ($P < 0.05$) after total doses of 150 μg and were completely or almost abolished after total doses of 600 μg ; in other words, the C reflexes were completely abolished in all five preparations, whereas the A δ responses were greatly depressed and completely eliminated in only two of five preparations.

Spontaneous Renal Sympathetic Activity

Clonidine Administered Intrathecally. The spontaneous sympathetic activity was reduced to a mean of 18.8% of control values at the dose of clonidine, total dose 150 μg , which abolished the somatosympathetic reflexes to tibial nerve stimulation. When the total dose of clonidine was increased to 300 μg , the mean spontaneous sympathetic activity was decreased to only 4.7% of control values and was completely eliminated in three of five preparations (figs. 1 and 3).

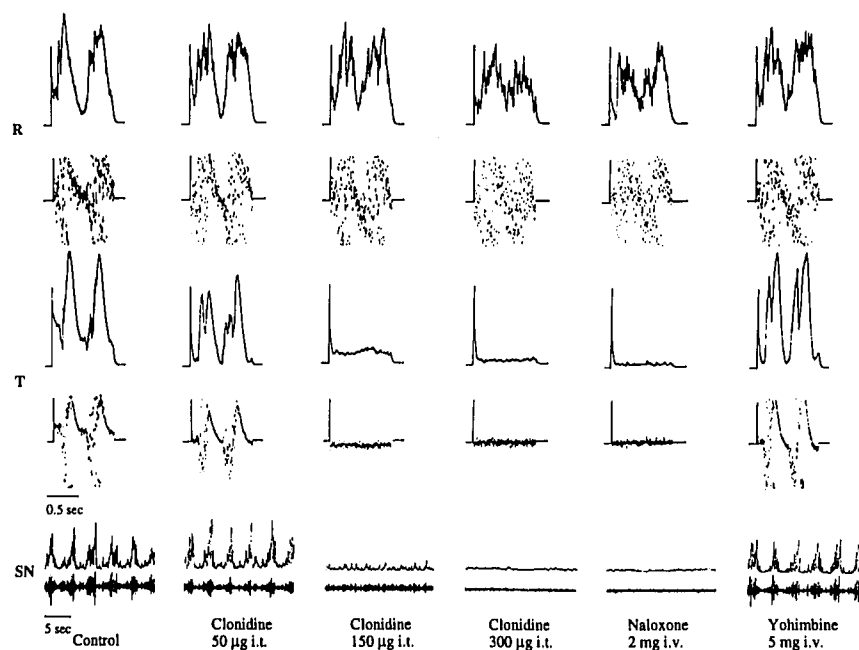
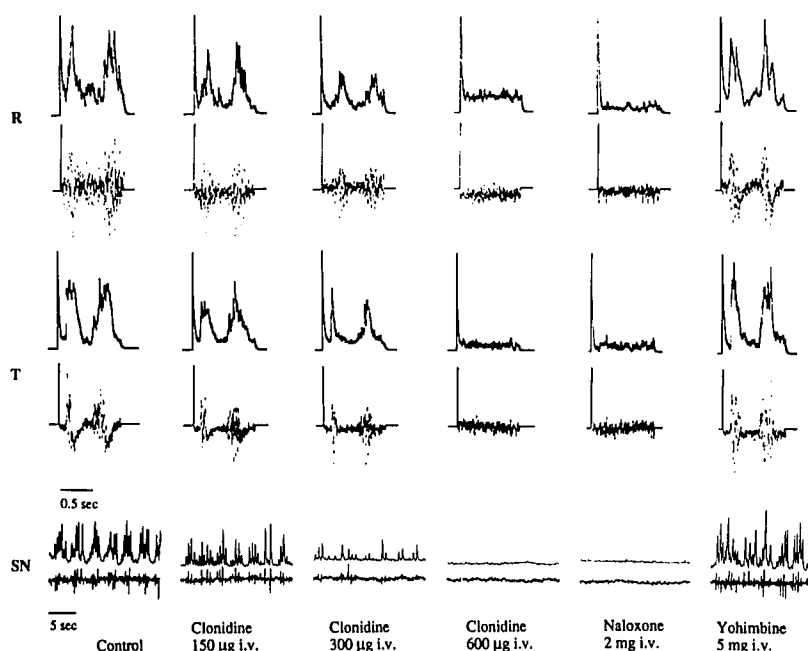


Fig. 1. Effects of clonidine injected intrathecally followed by intravenously administered naloxone and yohimbine on somatosympathetic reflexes mediated by afferent A δ (early responses) and C (late responses) fiber pathways, by supramaximal electrical stimulation (0.33 Hz, 30 V, and 0.5 ms) of the radial (R) (top) and tibial (T) (middle) nerves, in a renal sympathetic nerve from a representative preparation. Lower traces = the averaged transient of 16 responses; upper traces = the rectified integral of the averaged signals. (Bottom) Effects on spontaneous renal sympathetic nerve activity (SN). Lower traces = transient amplified signals; upper traces = integrated signals.

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Fig. 2. Effects of clonidine followed by naloxone and yohimbine administered intravenously on somatosympathetic reflexes mediated by A δ (early responses) and C (late responses) fiber pathways in a renal sympathetic nerve evoked by supramaximal electrical stimulation (0.33 Hz, 30 V, and 0.5 ms) of the radial (R) (*top*) and tibial (T) (*middle*) nerves from a representative preparation. Lower traces = the averaged transient of 16 responses; upper traces = the rectified integral of the averaged signals. (*Bottom*) Effects on spontaneous renal sympathetic nerve activity (SN). Lower traces = transient amplified signals; upper traces = integrated signals.



Clonidine Administered Intravenously. The mean sympathetic activity was reduced significantly, to 83.3% of control ($P < 0.05$) after clonidine 50 μg and abolished after total doses of 600 μg . The A δ and C reflexes evoked by both tibial and radial nerve stimulation were reduced in similar measure to the depression of spontaneous sympathetic activity by the same dose of clonidine (figs. 2 and 3).

Resting Mean Arterial Blood Pressure and Heart Rate

Clonidine Administered Intrathecally. The mean resting HR was reduced significantly, to 100 and 90 beats/min from a mean control value of 138 beats/min ($P < 0.05$) after total doses of 150 μg and 300 μg , respectively (fig. 4). MAP did not change significantly ($P > 0.05$).

Clonidine Administered Intravenously. Mean HR was also reduced to 90, 77, and 62 beats/min from the control value of 132 beats/min after doses of 150, 300, and 600 μg of clonidine ($P < 0.05$). MAP did not show any significant reduction ($P > 0.05$).

Evoked Responses in Mean Arterial Blood Pressure and Heart Rate

Clonidine Administered Intrathecally. The tibial nerve evoked reflex increases in MAP and HR by low-

frequency repeated single stimulation (0.33 Hz, 30 V, 0.5 ms) were also eliminated after total doses of 150 μg , which just abolished the evoked responses in renal sympathetic nerves (fig. 5). However, the tibial nerve evoked responses in MAP and HR due to high-frequency train stimulation (30 Hz, 30 V, 0.5 ms) were similar to control, even when the total doses were increased to 300 μg .

The radial nerve evoked reflex responses in MAP and HR to both repeated single and train stimulation did not change significantly from control values ($P > 0.05$).

Clonidine Administered Intravenously. Both the tibial and radial nerves evoked reflex increases in MAP and HR to low-frequency stimulation were also almost eliminated after total doses of clonidine 600 μg (fig. 5), the dose that almost abolished both the A δ - and C fiber-mediated somatosympathetic responses. However the tibial and radial nerve evoked reflex responses in MAP and HR to high-frequency train stimulation remained similar to control (difference not significant).

Naloxone

Naloxone (2 mg intravenously) did not reverse the effects of intrathecal or intravenous clonidine on A δ - and C fiber-mediated somatosympathetic reflexes, spontaneous renal sympathetic activity, MAP and HR. This was also true when 5 mg was administered intravenously to one preparation.

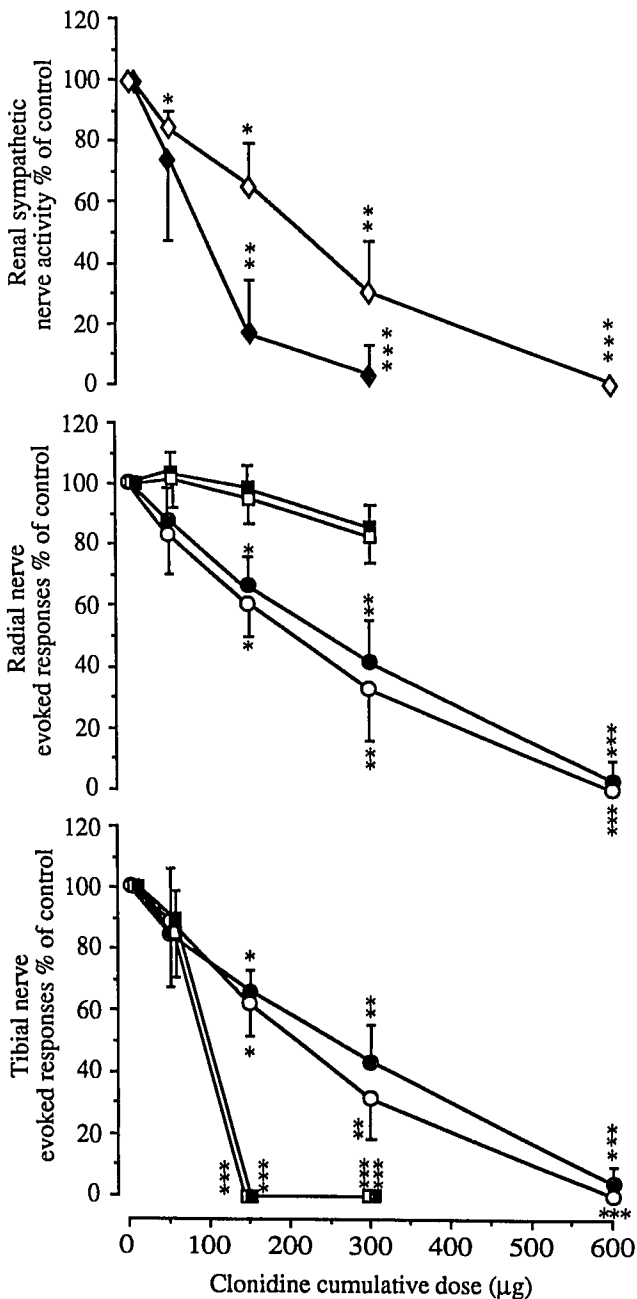


Fig. 3. Dose-response curves (mean, SD; $n = 5$) for depression of A δ - and C fiber-mediated somatosympathetic responses due to stimulation of the radial and tibial nerves, and spontaneous sympathetic nerve activity (SN) caused by clonidine administered intrathecally (open squares = C-fiber responses; filled squares = A δ -fiber responses; filled diamonds = SN) and intravenously (open circles = C-fiber responses; filled circles = A δ -fiber responses; open diamonds = SN). Comparison with control: * $P < 0.05$; ** $P < 0.01$; *** $P < 0.001$.

Yohimbine

Yohimbine (5 mg intravenously) completely reversed the effects of clonidine, whether it was administered intrathecally or intravenously, so that A δ - and C fiber-mediated reflexes (figs. 1 and 2), spontaneous sympathetic activity, MAP and HR all returned to control values.

Discussion

This study clearly demonstrates that evoked nociceptive reflexes and spontaneous sympathetic activity are depressed in a similar dose dependent manner, and also that the A δ - and C fiber-mediated somatosympathetic reflexes are depressed equally by clonidine, whether administered intrathecally in the case of tibial nerve evoked reflexes or intravenously for both radial and tibial reflexes. When the spontaneous sympathetic outflow and tibial nerve evoked reflexes in renal sympathetic nerves are abolished by clonidine administered intrathecally in the lumbar region, the radial nerve evoked responses remain unchanged, indicating that it has no effect on the descending efferent pathway. This observation has not been reported previously. Clonidine acts *via* an α_2 -adrenergic system and not an opioid mechanism, as confirmed by the reversal of its effect by yohimbine and not by naloxone.

In the present study, the spontaneous sympathetic outflow was depressed and eventually abolished by

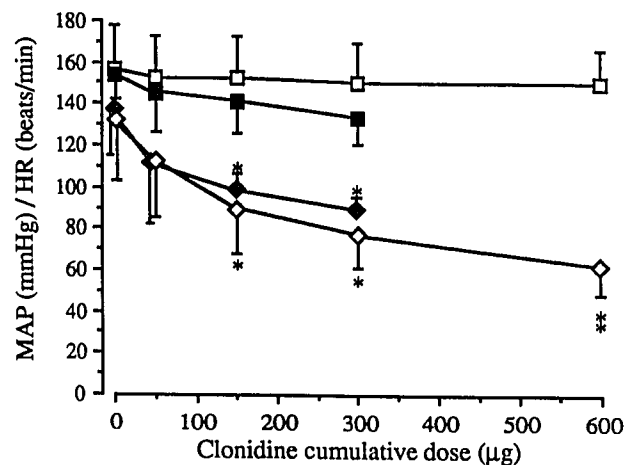


Fig. 4. Effect of clonidine administered intravenously (open symbols) or intrathecally (filled symbols) on mean arterial pressure (MAP, squares) and heart rate (HR, diamonds). Results are mean (SD; $n = 5$). * Comparison with control: * $P < 0.05$; ** $P < 0.01$.

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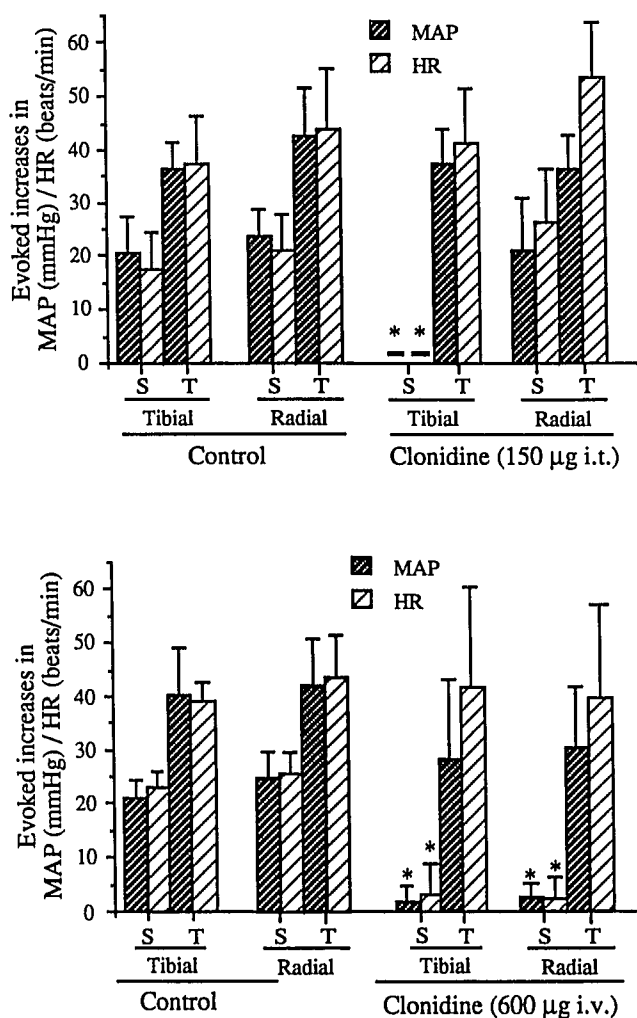


Fig. 5. Effects of clonidine administered intrathecally (*top*) and intravenously (*bottom*) on evoked increases (mean, SD; $n = 5$) in mean arterial pressure (MAP) and heart rate (HR) from nonstimulation control levels by repeated single (S) (0.33 Hz, 30 V, and 0.5 ms) and high-frequency train (T) stimulation (30 Hz, 30 V, and 0.5 ms) applied to the tibial and radial nerves. The doses of clonidine just or almost abolished the A δ - and C fiber-mediated somatosympathetic reflexes to repeated single stimuli. Whereas 150 μ g clonidine administered intrathecally (*top*) abolished the cardiovascular responses to low-frequency tibial stimulation, it had no statistically significant effect on high-frequency train stimulation of the tibial nerve or on lower- or higher-frequency stimulation of the radial nerve. In contrast, 600 μ g clonidine administered intravenously almost completely abolished the cardiovascular effects of low-frequency stimulation of the tibial and radial nerves but had no significant effect on high-frequency stimulation ($P > 0.05$). * $P < 0.05$ compared with control.

clonidine administered intrathecally or intravenously, and the ratio of the effective doses was approximately 1:3, suggesting that clonidine has a direct spinal action on spontaneous sympathetic activity. However, the inhibition of sympathetic outflow also may involve supraspinal pathways¹⁻³; the involvement of such pathways is suggested in this study by the major relative reduction in HR, compared with MAP, when sympathetic activity became severely depressed.

It is known that both descending pathways and neurons located in the spinal cord can independently modulate nociceptive transmission. The spinal analgesic effect of α_2 -adrenoceptor agonists is believed to be partially mediated at least in part in the dorsal horn of the spinal cord at the postsynaptic terminals of descending inhibitory systems,^{18,19} and they may also exert a presynaptic action in the primary afferent pathway to modulate spinal antinociceptive processing.²⁰ Sympathetic preganglionic neurons located in the intermediolateral cell column of the spinal cord represent a final location for the central integration of efferent sympathetic nerve activity. Both they and their adjacent antecedent interneurons receive a variety of inputs descending from supraspinal sites and from somatic and visceral afferent pathways.²¹ The α_2 -adrenergic receptors are highly concentrated on a cluster of sympathetic preganglionic neurons in the intermediolateral cell column. Microiontophoretic studies also suggest that a descending noradrenergic pathway to the intermediolateral cell column inhibits sympathetic preganglionic neurons *via* an α_2 -adrenergic system.²¹ The results of this study clearly show that the reduction of spontaneous sympathetic outflow is similar to the depression of tibial nerve evoked somatosympathetic responses when clonidine was administered both intravenously or intrathecally, indicating that the effects of clonidine on spontaneous sympathetic outflow and local nociceptive reflexes are closely linked.

Although clonidine administered intrathecally depressed and abolished the spontaneous and tibial nerve evoked sympathetic activity, the radial nerve evoked somatosympathetic reflexes, acting entirely through descending and efferent pathways, were hardly changed. This indicates that intrathecal clonidine does not significantly affect the descending efferent pathway. It also implies that the spinal effect of clonidine is attributable to a direct effect on the intrinsic neurons in the spinal cord without a marked effect on the descending pathway *per se*. In preliminary observations, we also found that after the spontaneous renal sym-

pathetic activity has been abolished by clonidine administered intrathecally, it could still be reactivated or increased by reducing the arterial blood pressure with sodium nitroprusside administered intravenously. This could indicate that the descending baroreflex pathway routed to sympathetic preganglionic neurons in the spinal cord was not blocked.

It is known that activation of afferent pathways by a variety of noxious stimuli causes reflex responses in the autonomic nervous system, which are manifested, for example, by changes in blood pressure. In this study we found that clonidine, administered intrathecally or intravenously in doses that completely or almost completely blocked the A δ - and C fiber-mediated somatosympathetic reflexes and reflex increases in MAP and HR to low-frequency repeated single stimulation (0.33 Hz), had little or no effect on the reflex increases in MAP and HR to high-frequency train stimulation (30 Hz) of the same intensity and pulse duration. Fentanyl and alfentanil have a similar frequency-dependent antinociceptive effect, unlike that of local anesthetic blocking agents.²² It is uncertain if this is one of the reasons for inadequate pain relief by clonidine in some conditions; for instance, in a double-blind placebo-controlled study reported by Gordh, epidural clonidine in a dose of 3 μ g/kg failed to show any analgesic effect in postthoracotomy pain.²³

Clonidine is an antihypertensive agent causing baroreflex sensitization, direct inhibition of sympathetic outflow and enhanced vagal activity.¹⁻³ In the present study whether administered intrathecally or intravenously it produced only a small reduction of MAP even when the recorded spontaneous sympathetic outflow was almost eliminated. This probably is a result of a direct stimulating effect on peripheral α_2 -adrenergic receptors causing vasoconstriction. However, HR was markedly decreased by intrathecal or intravenous clonidine, a result consistent with the work of Gordh *et al.*, who showed that when administered epidurally in anesthetized pigs it caused a significant decrease in HR without hypotension.²⁴ Eisenach and coworkers also reported that clonidine administered epidurally, in a total dose comparable to that used clinically (50–750 μ g), did not cause a decrease in MAP or HR in conscious sheep.²⁵ Previous clinical observations have also found that in postoperative patients clonidine administered epidurally causes only small decreases in MAP and HR.²⁶

In conclusion, clonidine administered either intrathecally or intravenously has comparable effects on spontaneous efferent sympathetic activity and A δ - and

C fiber-mediated nociceptive somatosympathetic responses. When injected intrathecally it has little effect on the descending efferent pathway.

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