

Clonidine Reduces Sympathetic Activity but Maintains Baroreflex Responses in Normotensive Humans

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Clonidine, an α_2 -adrenergic agonist, has been shown to modify the hemodynamic responses to surgery. To examine further the mechanism underlying this action, we evaluated the neurocirculatory effects of oral clonidine and the ability of clonidine to alter the hemodynamic and sympathetic responses to a noxious stimulus (cold pressor test) and to baroreceptor perturbations in nine healthy men (ages 20-29 yr). Heart rate (ECG), blood pressure (radial artery catheter), central venous pressure (jugular vein), and cardiac output (impedance cardiography) were monitored before and after oral clonidine (0.3 mg) or placebo. Plasma norepinephrine was measured with high-performance liquid chromatography. Sympathetic nerve activity (SNA) to skeletal muscle blood vessels was recorded from a Tungsten needle positioned within the peroneal nerve. Baroreceptor testing was carried out by intravenous bolus injections of nitroprusside (100 μ g) followed 60 s later by intravenous phenylephrine (150 μ g). The slope of the linear relationship between the change in R-R interval *versus* the change in mean pressure (cardiac baroslope) or change in SNA *versus* change in diastolic pressure (sympathetic baroslope) was determined at baseline and 75 min after clonidine or placebo. In addition, peak responses to the cold pressor test (60-s hand immersion in ice water) were determined at the same intervals. Clonidine progressively decreased blood pressure and muscle SNA over the 75-min session. Clonidine subtly reduced the sympathoexcitation produced by the cold pressor test but did not alter the gain of the baroreceptor reflex regulating cardiac interval or peripheral SNA; baroslope relationships were simply shifted leftward (to operate at lower pressures). Thus, 0.3 mg clonidine reduced muscle SNA and the sympathetic response to the cold pressor test stress but did not modify the ability of the baroreceptors to respond to blood pressure perturbations. (Key words: Blood pressure; cold pressor; pressoreceptors. Measurement techniques: microneurography. Sympathetic nervous system, α_2 -adrenergic agonists: clonidine.)

CLONIDINE is an α_2 -adrenergic agonist that was introduced as an antihypertensive medication in 1972, but its application has been limited because of undesirable side effects such as xerostomia and sedation. However, these

properties are partially responsible for a new enthusiasm for use of this drug in anesthesia. Clonidine has been given preoperatively to experimental animals and to patients and has reduced intraoperative anesthetic requirements,¹⁻⁷ neuroendocrine responses to stressful stimuli in the perioperative period,^{1,5,6,8} intraoperative blood pressure,^{1,3-6} and blood pressure variability during surgery.^{1,3,4,6,9}

Although the effect of clonidine on blood pressure is thought to be due to a reduction in sympathetic activity, the precise mechanism of this effect is not fully understood. Animal studies have demonstrated that clonidine inhibits central sympathetic outflow, reduces release of norepinephrine from peripheral presynaptic terminals, and may have a vagomimetic action,^{6,10,11} but these effects have not been well documented in humans. In fact, a previous study in hypertensive humans that used direct recordings of efferent muscle sympathetic nerve activity (SNA) failed to document a consistent reduction in sympathetic activity after administration of clonidine.¹² In contrast, numerous studies that used indirect measurements of sympathetic activity have documented significant reductions in sympathetic indices after clonidine administration.^{1,5,6,8,13} Thus, one goal of the current research was to reexamine and to evaluate further the effect of clonidine on blood pressure by using both direct (sympathetic nerve recording) and indirect (plasma norepinephrine) measurements of sympathetic outflow in human volunteers.

This study also sought to determine the mechanism whereby clonidine reduces blood pressure but apparently maintains hemodynamic stability in patients undergoing surgery. We postulated that this effect might be mediated through clonidine's influence on baroreceptor function. Baroreceptor sensors respond quickly to small changes in blood pressure and initiate rapid adjustments of autonomic outflow to the heart and peripheral vasculature to restore equilibrium. Several previous studies used phenylephrine challenges and demonstrated that clonidine augmented the subsequent reflex bradycardia.¹⁴⁻¹⁶ If a similar enhancement of baroreflex restraint on peripheral sympathetic outflow exists, it is conceivable that clonidine's ability to reduce hemodynamic fluctuations during

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surgery might be related to augmented baroreceptor mechanisms. Thus, the second objective of this study was to evaluate the influence of clonidine on baroreflex regulation of sympathetic vasoconstrictor traffic. Microneurography was used to evaluate efferent muscle SNA responses to rapid loading and unloading of baroreceptors.

A final objective of this research was to determine whether clonidine modifies sympathetic responses to noxious stimuli. This could contribute to the reduced hemodynamic variability observed in some clonidine-pretreated patients during anesthesia and surgery. We used a cold pressor test (immersion of the hand in ice water) to activate nociceptive and thermal receptors and evaluated subsequent hemodynamic and neural sympathetic responses before and after clonidine administration.

Materials and Methods

Nine healthy, normotensive men (mean age 25 ± 1.5 yr) were studied on three occasions. Each signed consent forms that had been approved previously by the Institution's human research review committee. Research participants were not receiving any medications. Subjects were instrumented and studied while supine. Heart rate was monitored from lead II of the electrocardiogram. A 20-G catheter was inserted into the radial artery for direct determination of arterial blood pressure. An 18-G catheter was inserted into a forearm vein and used for fluid and drug administration. Normal saline was infused at a rate of 100 ml/h. A 20-G, 5-inch catheter was inserted into the jugular vein and used to monitor central venous pressure (CVP). Forearm blood flow was measured by Hg-in-Silastic plethysmography, and forearm vascular resistance was calculated as the ratio of mean arterial pressure (MAP) to forearm blood flow. Cardiac output was estimated noninvasively using impedance cardiography. This consisted of a tetrapolar oscillating current system as previously described.¹⁷ Systemic vascular resistance was calculated as $([MAP - CVP]/CO) \times 80$, where CO = cardiac output.

PERONEAL NERVE RECORDINGS

The right leg was supported and cushioned. The bony prominence at the proximal head of the fibula on the lateral aspect of the leg was identified and marked. Brief electrical impulses (1 Hz, 30–40 V, 150 mA) were delivered below this mark to identify the location of the peroneal nerve. The skin was then cleansed, and two 5- μ m-tipped, epoxy-coated Tungsten needles (TMI Electronics, Iowa City, IA) were inserted. One needle was advanced to an area just outside the peroneal nerve; the second needle was advanced into the peroneal nerve. The location of the nerve was identified by applying brief impulses (1 Hz, 0.3–0.7 V, 150 mA) to the needle. When a muscle

fascicle within the peroneal nerve was entered, a distinct muscle contraction in the distribution of the deep or superficial peroneal nerve was noted. The stimulation was halted, and neural recordings and amplification (100,000 \times) began. Signals common to both needles (*e.g.*, background noise) were cancelled by a common-mode rejection preamplifier. Characteristic bursts of sympathetic efferent activity were sought by fine manipulations of the needle within the muscle fascicle. The identity of these bursts and their distinction from activity occurring in skin sympathetic efferent nerve fibers has been described in detail elsewhere.^{18,19} Muscle SNA was expressed as bursts per minute and as total activity (bursts per 100 cardiac cycles times mean burst amplitude in microvolts).

PROCEDURES

Before peroneal nerve recordings were obtained, subjects underwent a baroreceptor stress test and a trial exposure to the cold pressor test. A 100- μ g bolus of sodium nitroprusside was injected through the intravenous catheter; 60 s later, during peak hypotension (20% below baseline), a 150- μ g bolus of phenylephrine was injected to restore blood pressure and to increase it slightly above baseline ($\sim 10\%$) for 1–2 min. This process resulted in a broad range of blood pressure perturbations to aid in the quantitative analysis of baroreceptor reflex regulation of both cardiac intervals and efferent SNA. The trial cold pressor test was performed by immersing the hand in ice water for 1 min. After hand immersion, subjective assessment of pain was made with a visual analogue scale (1 = no pain, 10 = maximum discomfort).

Once an acceptable sympathetic recording had been obtained, a 10-min quiet rest period was observed, followed by blood sampling for baseline plasma norepinephrine concentration (measured by high-performance liquid chromatography). Then a 5-min sample of control hemodynamic data and muscle SNA was obtained. This was followed by the cold pressor test with the same hemodynamic and muscle SNA monitoring obtained during the last 30 s of the 60-s stress. A 3-min recovery period was observed and was followed by the baroreceptor stress test.

Subjects were randomly assigned to one of three experimental trials in a single-blind design. Each subject participated in all trials on separate days at least 1 week apart, during which they received either 1) placebo, 2) 0.3 mg oral clonidine, or 3) 0.3 mg oral clonidine plus intravenous phenylephrine toward the end of the study session to prevent further decreases in diastolic blood pressure. During baseline conditions and at 18 min, 45 min, and 75 min after the placebo or clonidine administration, a 5-min sample of hemodynamic data and muscle SNA was obtained and blood was obtained for determi-

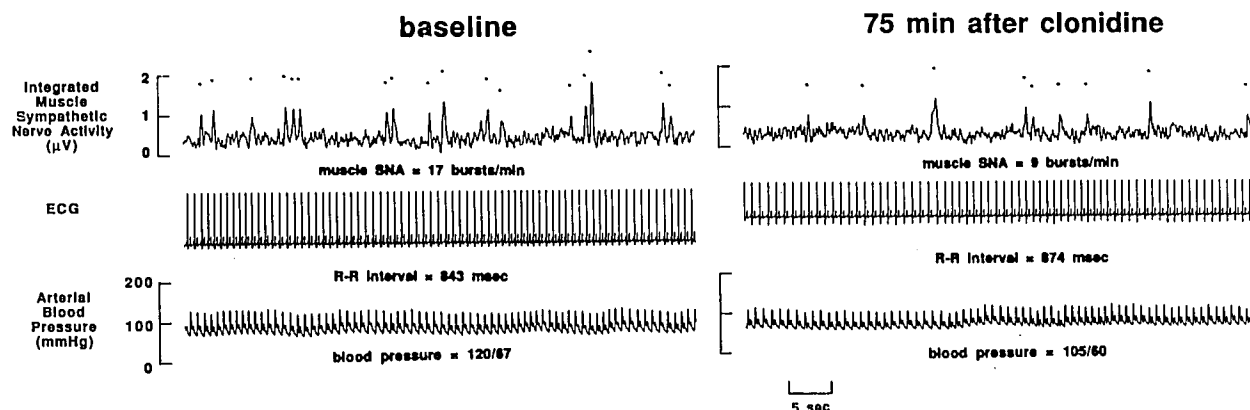


FIG. 1. Representative tracing from one volunteer receiving clonidine. Muscle sympathetic nerve activity (SNA) and blood pressure were significantly reduced after administration of clonidine. Integrated bursts of SNA are marked with a small dot.

nation of norepinephrine concentration. The cold pressor test and the baroreflex stress test were applied at baseline and during the 75th min after clonidine or placebo administration. After the 45-min data acquisition period in the trial of clonidine plus phenylephrine, phenylephrine was titrated to prevent further decreases in diastolic blood pressure between the measurements at 45 and 75 min.

DATA ANALYSIS

Reflex responses to perturbations of arterial pressure were quantitated by applying stepwise least-squares regression analyses to 1) the linear portion of the relationship between MAP and the corresponding R-R interval and 2) the linear portion of the relationship between diastolic pressure and muscle SNA. To reduce variability and improve data selection for regression analysis, R-R interval and muscle SNA were averaged for each 3-mmHg increment of blood pressure, as previously described.¹⁹ Because hemodynamic and neural measurements did not differ between the control recording period and the re-

cording period at 18 min, these data were combined and subsequent differences in measured parameters at 45 and 75 min were assessed using one-way repeated-measures analysis of variance. Tukey's method was used for *post hoc* analysis to discern differences between groups at specific time points. Statistical significance was achieved if *P* was less than 0.05.

Results

A representative tracing from one subject during baseline and 75 min after clonidine administration is provided in figure 1. Clonidine clearly reduced the amount of SNA and reduced blood pressure. Baseline neurocirculatory parameters did not differ among subjects during control periods on separate testing days (figs. 2-4). There were no differences in neurocirculatory parameters during baseline (preclonidine) measurement and measurement at 18 min after administration of clonidine. Therefore, these time points were averaged; statistical analyses and graphic displays of these time periods are collectively

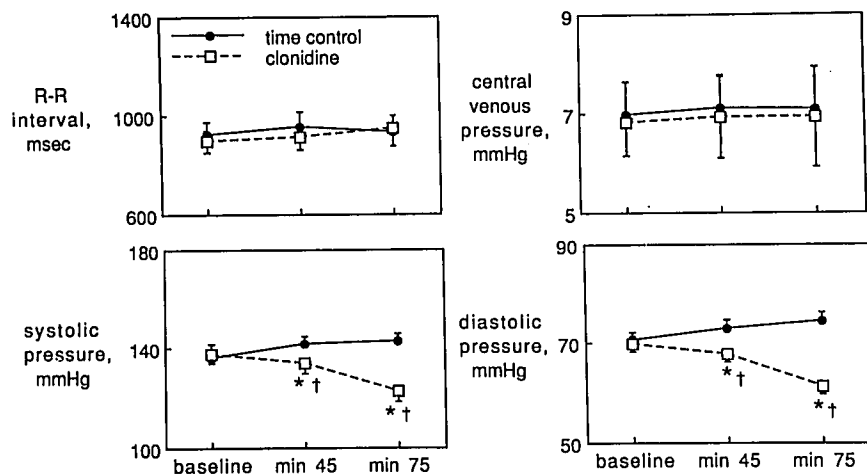


FIG. 2. Steady-state hemodynamic responses during supine rest and at 45 and 75 min after oral administration of placebo (time control) or clonidine (0.3 mg). Values are mean \pm SEM. *Difference between drug conditions. †Value is different from baseline value, *P* < .05.

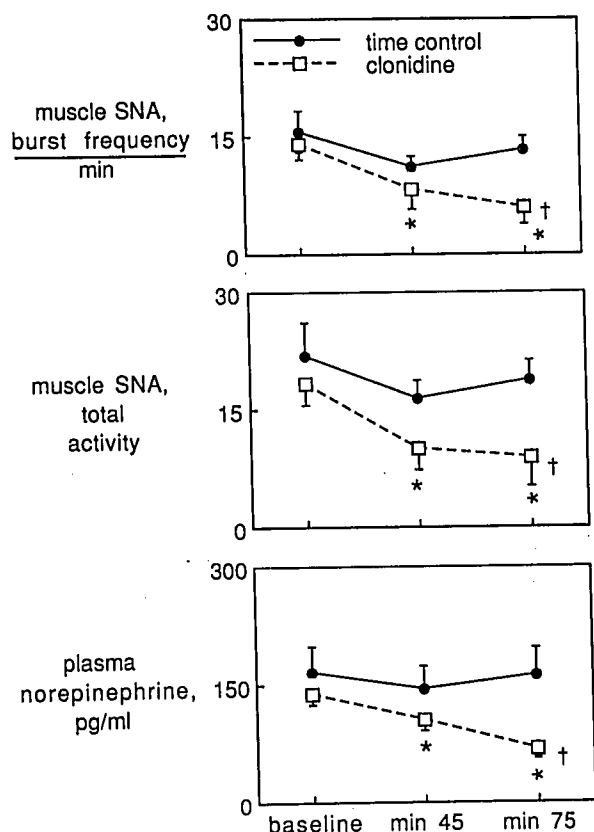


FIG. 3. Direct (muscle sympathetic nerve activity [SNA]) and indirect (plasma norepinephrine) steady-state sympathetic responses during supine rest and at 45 and 75 min after oral administration of placebo (time control) or clonidine (0.3 mg). Values are mean \pm SEM. *Difference between drug conditions. †Value is different from baseline value, $P < .05$.

termed "baseline." Clonidine did not alter R-R interval, CVP, or cardiac output (figs. 2 and 4). However, clonidine did reduce systolic and diastolic arterial blood pressure, muscle SNA, plasma norepinephrine, and forearm and systemic vascular resistances (figs. 2-4). Each parameter was significantly reduced from control at 75 min after administration of clonidine ($P < 0.05$).

In response to the cold pressor test, the visual analogue assessment of pain averaged 5.4 ± 0.8 for the placebo condition and 5.9 ± 0.9 for the clonidine condition during the first exposure to cold. This "quantity" of pain was not changed ($P > 0.05$) during the cold pressor test performed 75 min after placebo (5.7 ± 0.9) or clonidine (5.9 ± 1.0). Blood pressure and SNA responses to the cold pressor test are demonstrated in figure 5. The responses were reasonably reproducible, as seen in the similar neurocirculatory response in the time control study when the cold test was applied on two occasions separated by 75 min. Clonidine tended to reduce the sympathetic response and the MAP response to the cold test. There was a sig-

nificant interaction between the clonidine and placebo effects on total SNA; the response after placebo increased (nonsignificantly), whereas the response after 75 min of clonidine was slightly (nonsignificantly) reduced.

The baroreceptor reflex slopes are shown in figures 6 and 7. Cardiac baroslopes relating R-R intervals to MAP were unchanged in placebo and clonidine-treated subjects.

Relationships were simply shifted leftward (toward lower pressures) in subjects receiving clonidine. The same held true when the sympathetic baroslopes relating muscle SNA to diastolic blood pressure were examined. Slopes were unchanged by clonidine but were reset to lower pressures.

To evaluate better the effects of clonidine on SNA while minimizing the opposing effects of unloading the baroreceptors, phenylephrine was infused to prevent a further reduction of blood pressure between the 45th and 75th min in the trial of clonidine plus phenylephrine (fig. 8). Blood pressure was maintained by a continuous infusion of phenylephrine that was individually titrated to maintain blood pressure at the 45th-min level. This resulted in a slight bradycardia and a significant reduction in muscle SNA ($P < 0.05$).

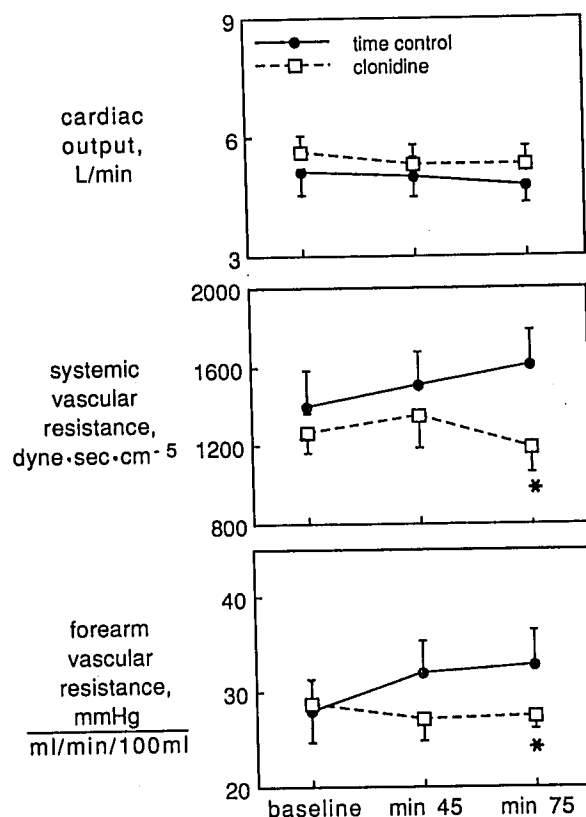


FIG. 4. Steady-state cardiac output and resistance characteristics during supine rest and at 45 and 75 min after oral administration of placebo (time control) or clonidine (0.3 mg). *Difference between drug conditions at the 75th min, $P < .05$.

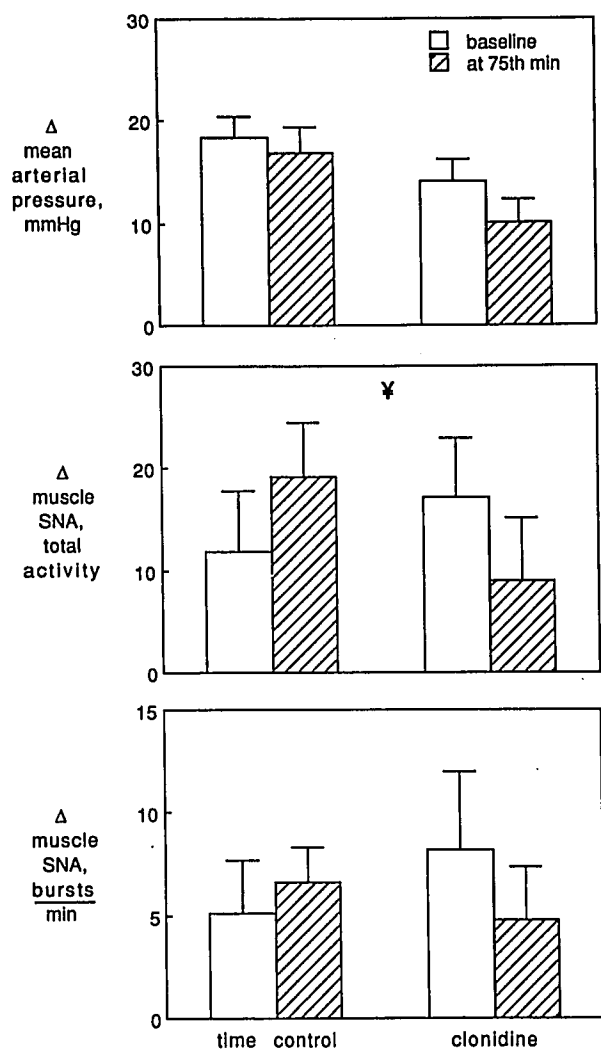


FIG. 5. Average change from control (immediately before cold stress) of mean arterial pressure and muscle sympathetic nerve activity (SNA) during the cold pressor test. Baseline = cold responses before administration of clonidine or time control. \forall Significant interaction between the change in cold response produced by placebo (time control) versus clonidine.

Discussion

This study documents in healthy human volunteers the well-described decrease in blood pressure that occurs after administration of clonidine. In addition, there are several new findings. First, clonidine-mediated hypotension is due in part to a reduction in sympathetic vasoconstrictor nerve traffic to blood vessels supplying skeletal muscles. It appears that in normal volunteers, decreases in heart rate and cardiac output do not contribute to this hypotension. Second, oral clonidine subtly changed the sympathoexcitatory and hemodynamic response to the stress of local cold exposure. Third, the gain of the baroreceptor reflex regulation of heart rate and peripheral SNA was not

changed by clonidine. Baroreflex function relationships were simply reset to operate at lower pressures.

The peak blood-pressure-reducing effect of clonidine has been reported to occur approximately 90 min after oral administration.²⁰ However, we were unable to maintain a relaxed experimental environment and sustain stable nerve recordings much beyond 75 min because subjects became uncomfortable and anxious while supine and completely immobile. In fact, in subjects receiving placebo, a gradual increase in blood pressure and vascular resistance occurred over time. There were no significant differences in the hemodynamic and neural measurements during the initial supine predrug control period and measurements taken 18 min after the ingestion of clonidine (or placebo). This is due to gastrointestinal absorption time and clonidine's pharmacokinetic profile. Therefore, data from these two time points were averaged and used as a baseline from which to compare subsequent responses.

Our demonstration of clonidine's ability to decrease blood pressure is consistent with many earlier reports in both experimental animal⁷ and human investigations.^{6,10,11,21,22} In addition, clonidine appears reliably to reduce plasma norepinephrine concentrations.^{1,5,6,8,22} However, the interpretation of plasma norepinephrine concentrations is complicated by the fact that they reflect the difference between the total quantity of norepinephrine released into the circulation and that removed by uptake and clearance mechanisms.²³ Although it is well-established that clonidine reduces sympathetic outflow, a previous study in humans that used direct recordings of efferent SNA directed to skeletal muscle blood vessels provided data suggesting that the blood-pressure-reducing effect of clonidine is not due to reductions in muscle SNA.¹² The report raised several questions that were addressed in the current study. First, does clonidine result in selective inhibition of efferent SNA? Clonidine-induced reductions in plasma norepinephrine without an effect on muscle SNA could be due to selective inhibition of SNA to other vascular beds, such as the cardiac, renal, skin, or splanchnic beds. Second, could the initial response to clonidine lead to a global reduction in SNA, but the subsequent unchanged levels of muscle SNA be due to baroreflex-mediated augmentations in nerve traffic specifically directed to this vascular bed? Our study provides answers to these questions. We demonstrate that clonidine reduces muscle SNA, and, in addition, that clonidine decreases forearm and systemic vascular resistances and lowers circulating plasma norepinephrine concentrations in humans. These effects, in combination, support the possibility that clonidine produces a generalized (nonselective) reduction in efferent SNA.

The failure to observe reductions in heart rate and cardiac output despite reductions in both direct and indirect indices of sympathetic outflow probably is due, in

decreasing pressure stimulus

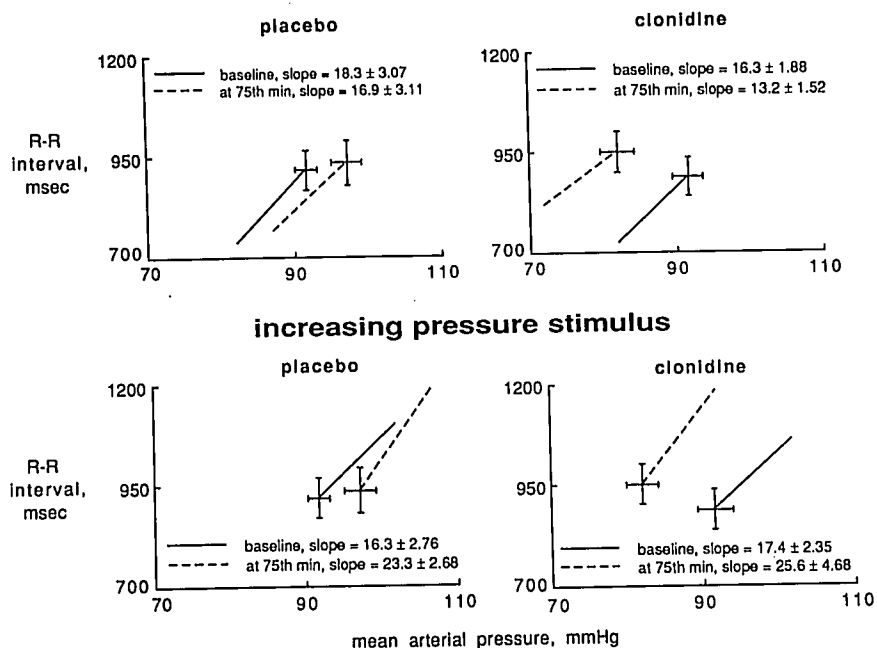


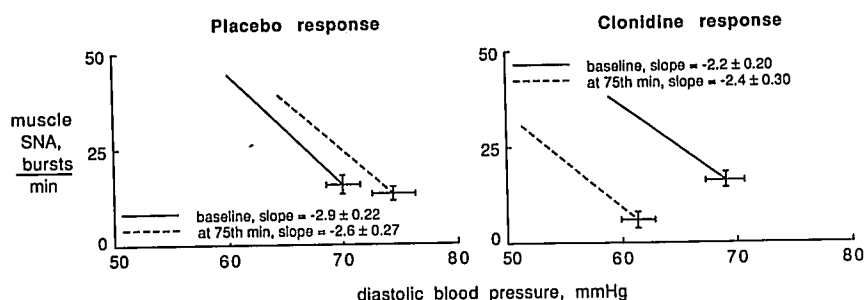
FIG. 6. Cardiac baroreceptor reflex relationships during hypotensive (sodium nitroprusside) and hypertensive (phenylephrine) stresses. The corresponding slope of the relationship between mean blood pressure and the cardiac interval as determined by the linear regression is shown. These slopes were unchanged by clonidine administration ($P > .05$).

part, to the relatively low sympathetic drive to the hearts of supine resting research volunteers. Moreover, the overriding influence of intrinsic cardiac mechanisms responding to reduced afterload probably contribute importantly to the stable cardiac output during reductions in sympathetic outflow. Animal studies have shown that the hypotensive action of clonidine in low doses is mediated primarily by a reduction in systemic vascular resistance with little change in cardiac output.¹¹ Similarly, in cardiac surgery patients, clinical doses of clonidine (0.2–0.4 mg) have had negligible effects on cardiac function.¹

CVP showed little change in subjects receiving clonidine despite reductions in all indices of SNA. One might expect reductions in CVP due to sympathetic withdrawal to venous smooth muscle; however, basal levels of sympathetic tone to the venous vasculature are minimal in supine humans.²⁴ Moreover, if small degrees of venodilation occurred in supine hydrated volunteers, it may not be reflected in CVP recordings.

Clonidine has been increasingly prescribed by anesthesiologists as a preoperative medication, partly because of its perceived ability to attenuate the hypertension and tachycardia associated with stressful stimuli such as laryngoscopy, tracheal intubation, and surgery. Numerous investigators have speculated that this attenuating effect of clonidine is related to its ability to inhibit sympathetic mechanisms at spinal or supraspinal sites. Such an effect would be similar to that observed in a previous investigation in this laboratory using intravenous lidocaine.²⁵ Clonidine also has intrinsic analgesic effects^{26,27} that might contribute to the reduction of sympathetic responses to painful stimuli such as the cold pressor test. In the current study, clonidine reduced the sympathoexcitation but not the pressor response to stimulation of nociceptive and thermal receptors with ice water. This attenuation of the sympathetic response was not due to a decreased perception of pain, because the visual analogue assessment of pain during the cold test was not reduced by clonidine.

FIG. 7. Sympathetic baroreceptor reflex relationships. The slope of the relationship between diastolic pressure and muscle sympathetic nerve activity (SNA) are displayed. There were no differences in these relationships between drug conditions ($P > .05$).



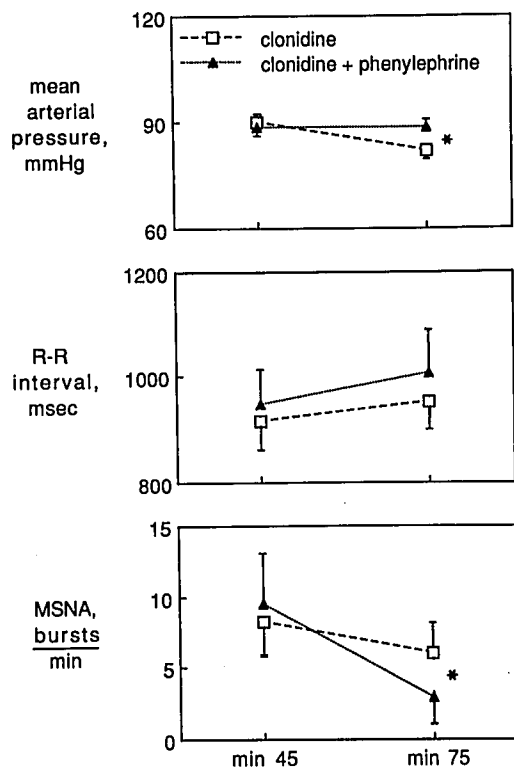


FIG. 8. Steady-state hemodynamic and neural responses at 45 and 75 min after oral administration of clonidine (0.3 mg) or clonidine plus phenylephrine. Values are mean \pm SEM. *Difference between conditions.

The attenuated sympathoexcitation following clonidine was not profound and was insufficient to reduce significantly the pressor response to the cold stress. Recent data have suggested that clonidine decreases blood pressure but does not modify the pressor response to the stimulus of laryngoscopy and tracheal intubation.²⁸ This observation, however, is at variance with several reports demonstrating attenuated stress responses after clonidine administration.¹⁻⁵

Acute perturbations in blood pressure are buffered by rapid responses mediated through the baroreceptor reflex. Previous investigations, using clonidine as a premedication prior to major surgery, have suggested that clonidine reduces blood pressure fluctuations during the perioperative period.^{1-5,9} One potential mechanism mediating this stabilizing effect might be related to an enhanced baroreceptor reflex function. Previous studies in both animals and humans have documented that baroreflex slowing of the heart rate is enhanced after administration of clonidine.^{14,15} It is conceivable that this effect and a similar enhancing effect on the reflex regulation of peripheral sympathetic outflow could account for the observed greater intraoperative hemodynamic stability when clonidine is used as a premedication. However, our data

demonstrate that clonidine did not augment the gain of the baroreflex regulation of either muscle SNA or heart rate. The slope (or sensitivity) of the relationship between blood pressure and either heart rate or muscle SNA was not changed by clonidine. However, relationships were reset to a lower operating point, *i.e.*, to a lower blood pressure. Our data also demonstrate that clonidine would have slowed heart rate and reduced resting SNA to a greater extent if baroreceptors had not been unloaded by the decreased blood pressure after administration of clonidine. This is shown in subjects who received phenylephrine to support blood pressure at a time when clonidine had its peak effect (fig. 8). This resulted in a bradycardia and a further reduction in SNA. These findings suggest that baroreceptors remain active after clonidine administration and contribute to some degree to maintain heart rate and to lessen the decrease in SNA.

The lack of a change in the baroreflex gain observed in this study is inconsistent with a previous human investigation¹⁴ that reported an increased gain of the baroreflex control of heart rate. However, this earlier study used intravenous doses of clonidine given to patients with hypertension and coronary artery disease. These patients have impaired baroreceptor function that is due in part to underlying vascular disease and reduced vascular compliance at baroreceptor sites. The administration of clonidine and subsequent withdrawal of SNA directed to the vasculature containing the baroreceptors could improve vascular compliance and thereby might improve reflex function in atherosclerotic patients.

LIMITATIONS

First, this study was not designed to determine dose-response relationships with clonidine. Moreover, only healthy young individuals were included in this research. We cannot be certain that similar doses of clonidine given to patients with underlying cardiac or vascular disease result in different responses. Because of the complexity of this experimental protocol, it was unrealistic to pursue these other issues in a timely manner. Second, we have recorded sympathetic activity directed to one vascular bed, the skeletal muscle vasculature. We cannot be certain that sympathetic activity to other sites such as heart, splanchnic circulation, or kidneys were similarly affected, although a previous publication has documented that clonidine reduces renal SNA in rabbits.²¹ Finally, we have not identified the site or mechanism whereby clonidine reduces sympathetic outflow and resets baroreceptor function curves.

In summary, we document that oral clonidine reduces sympathetic vasoconstrictor nerve traffic to blood vessels supplying skeletal muscles and subtly attenuates the sympathoexcitatory response to nociceptive and thermore-

ceptor input. However, clonidine does not alter the gain of the baroreceptor reflex regulation of heart period or peripheral muscle SNA in healthy humans. Baroreflex function curves were significantly reset to operate at lower pressures. These observations provide new information concerning the mechanism whereby clonidine might influence perioperative blood pressure lability: adrenergic responses to noxious stimuli may be attenuated by clonidine, and blood pressure perturbations appear to be efficiently buffered by the baroreceptor reflex. These combined effects may lessen blood pressure "swings" in the perioperative period. This effect may be enhanced if clonidine-pretreated patients receive lower concentrations of inhalational agents, since the potent inhaled agents are known to reduce baroreflex function.²⁹

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