A Comparison of the Cardiovascular Responses to Stimulation of the Aortic and Carotid Sinus Nerves of the Dog[1] (37601)

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The physiological effects of aortic nerve stimulation have been investigated in cats (1, 2) rabbits (2, 3) and swine (4). Douglas and Schaumann (1) found three fiber groups in the cat based upon their threshold to stimulation. They designated these fibers, based upon their conduction velocity and threshold to stimulation, as A, B and C groups. The A and C fibers mediated depressor and cardiac slowing effects. The B fibers produced pressor responses and increased breathing. In the rabbit and swine the B group was not demonstrated (2–4).

Several investigations have shown that the baroreceptor reflexes arising from the carotid sinus of the dog generally exert a greater influence on systemic blood pressure than those arising from the arch of the aorta. Several possible explanations for this difference in these baroreceptor reflexes have been suggested (5–10). These include differences in the distensibility of the aorta and carotid sinus walls, differences in the discharge characteristics of the baroreceptors (8–10) in the two regions and differences in the neuronal connections made by the barosensory afferents in the medulla (5).

To our knowledge all studies comparing the aortic arch and carotid sinus baroreflexes in the dog have involved pressure changes as a stimulus. No comparison of the cardiovascular and respiratory responses to direct electrical stimulation of the central ends of the carotid sinus (CSN) and aortic (AN) nerves in the same animal appears to have been made. A study of this nature would provide information on the afferent fiber groups in the AN of the dog and would allow an assessment of the relative effectiveness of these reflexes under conditions where the characteristics of baroreceptor discharge is not a factor.

Methods. A total of 16 dogs weighing between 16 and 22 kg were used in these studies. Ten successful experiments were conducted. The dogs were anesthetized with chloralose (100 mg/kg iv) following premedication with morphine sulfate (3 mg/kg sc). Supplementary chloralose was given by iv drip at a rate of 20–25 mg/kg/hr. The trachea was intubated and artificial ventilation was provided by a respirator. The respirator rate was adjusted to maintain arterial blood PCO_2, PO_2 and pH in the normal range. Bicarbonate was administered when necessary to maintain blood pH between 7.30 and 7.40.

Both AN, when identified, were dissected from the vagosympathetic trunk in the manner recently described by Edis and Shepherd (11). This involved separation of the sympathetic trunk and the vagus just caudal to the nodose ganglia. The AN is usually identifiable as a thin nerve lying between the sympathetic trunk and the vagus. Branches of this nerve join the cranial laryngeal or the vagus nerve approximately 1 cm after its separation from the vagal trunk. The left AN was usually more easily identified than the right; however, both nerves have been used in our experiments with identical results. There were six animals in which no nerve was found that fit the above anatomical description or satisfied the physiological tests outlined below. These animals were not included in the study.

To exclude reflex changes from the carotid baroreceptors and chemoreceptors, both CSN

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were isolated and cut. Both vagal trunks were cut below the origin of the AN after these nerves had been identified by physiological tests. This would exclude most of the cardiopulmonary reflexes, aortic reflexes which were not transmitted through the aortic nerve, and also rule out any possibility of direct vagal effects on the heart due to current spread to the vagal trunk during aortic nerve stimulation.

Before cutting the vagi, sodium cyanide (0.1–0.2 mg/kg) was injected into the root of the aorta via a catheter introduced through the carotid artery. Veratridine (1–2 μg/kg) was also introduced into the right atrium through a catheter in the external jugular vein. A transient increase in both respiratory rate and blood pressure was observed in response to sodium cyanide with the AN intact. Following section of the AN little or no change in breathing occurred and the blood pressure rose slightly in some cases but most often fell transiently in response to sodium cyanide. Veratridine caused a decrease in blood pressure of about the same magnitude before and after AN section. These tests, supported by the anatomical criteria, suggested that the nerves in question were the same as those described by Edis and Shepherd (11) as being the AN. After identification was successfully established one of the AN and the CSN on the same side were drawn into silver ring electrodes for stimulation. The area was covered with warm mineral oil to prevent drying of the nerves.

Rectangular pulses from an AEL Mdl. 104 stimulator were delivered to the nerves through an isolation transformer. Pulse duration and voltage were monitored on a cathode ray oscilloscope. Initially the stimulus amplitude, for both nerves, was adjusted to produce a maximum fall in blood pressure with a stimulus duration of 0.1 msec and a frequency of 100 impulses/sec. This voltage (0.75–2 V for the AN, 1–3 V for the CSN) was used throughout any one experiment. Breathing was not increased by this stimulus to either nerve.

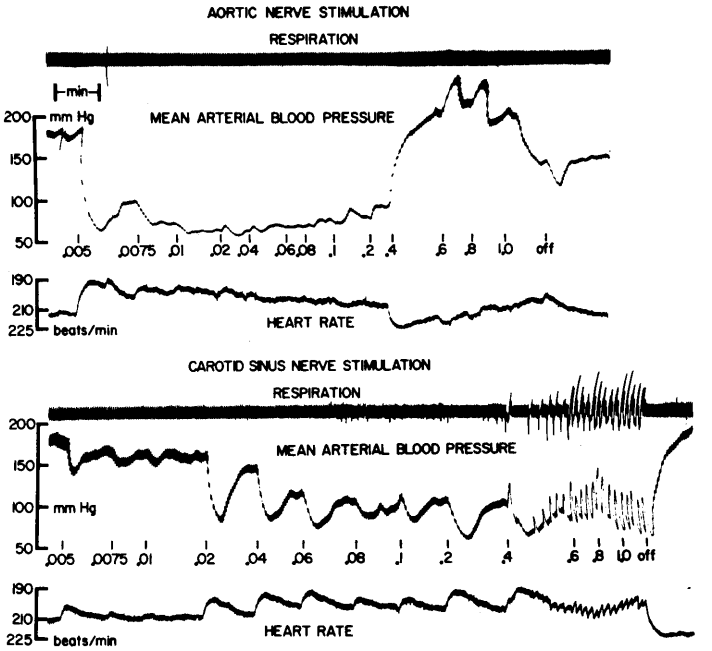

FIG. 1. Mean systemic blood pressure, heart rate and respiratory responses from one experiment to stimulation of the AN and CSN. Stimulus duration was increased stepwise from 0.005 to 1.0 msec. Stimulus amplitude was 2.0 V to the AN and 3.0 V to the CSN. Stimulus frequency was 100 Hz. The animal was artificially ventilated. Spontaneous breathing movements are superimposed on the movements caused by the respirator.

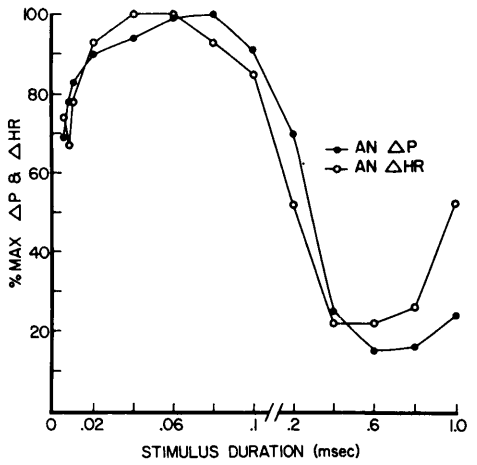

FIG. 2. Average changes ($N = 7$) in blood pressure and heart rate to stimulation of the AN with stimuli of increasing duration. Responses are expressed as a percentage of the maximum response. Stimulus amplitude and frequency (100 Hz) constant.

The cardiovascular and respiratory responses to AN and CSN stimulation were compared in two experimental series. In one series stimulus duration was increased in steps between 0.005 and 1.0 msec. In the other series stepwise increments in frequency (2–100 Hz) were made. Stimulus parameters, other than the one being varied, were kept constant. The responses to a given stimulus setting were allowed to stabilize before changing to the next step. The stabilized values were recorded. Each stimulation series lasted a total of 10–15 min. A 10 min recovery period was allowed after completion of each series.

Systemic arterial blood pressure was measured from a branch of the femoral artery with a Statham P23Gb transducer recording on an Offner dynograph. Heart rate was recorded continuously by a cardiotachometer triggered from the ECG. Breathing movements were measured by a pneumograph around the chest.

The responses to stimulation of the nerves were statistically compared by the paired t test. The 95% confidence level was taken as the level for significant differences between the responses.

Results. The responses from one experiment to stepwise increments in stimulus duration are shown in Fig. 1. Stimulus voltage and frequency were constant. Typically, near maximal cardiovascular inhibition was seen to stimulation of the AN with stimuli of 0.005 msec duration. In all cases when stimulus duration exceeded 0.2 msec an increase in blood pressure and heart rate toward the control level occurred. In four experiments blood pressure rose above control level during stimulation with 1.0 msec duration stimuli. Heart rate usually did not surpass the control level. Breathing was either not changed or only slightly increased by AN stimulation.

In contrast to the responses to AN stimulation, CSN stimulation caused smaller depressor responses and less cardiac slowing to the stimuli of short duration (0.005–0.06 msec). Stimuli of longer duration usually resulted in little further decrease in the blood pressure level or heart rate but caused marked stimulation of breathing. The records of spontaneous breathing shown in Fig. 1 are superimposed upon the movements caused by the respirator. Similar changes in breathing were observed, however, in three animals which were breathing spontaneously. Paralysis of the breathing movements in these animals with gallamine triethiodide (Flaxedil, 1–2 mg/kg, iv) did not alter the pressure or heart rate response characteristics to stimulation of either the AN or CSN.

Figures 2 and 3 summarize the relationship between stepwise increments of the stimulus

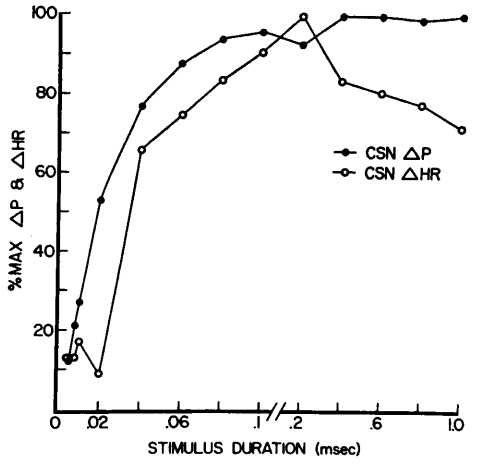

FIG. 3. Blood pressure and heart rate responses to CSN stimulation (same as Fig. 2).

TABLE I. Systemic Pressure and Heart Rate Responses to Stimulation of the Carotid Sinus and Aortic Nerves.

Stimulus duration (msec)	Mean systemic arterial pressure (mm Hg ± SE) AN	CSN	p	Heart rate (beats/min ± SE) AN	CSN	p
A. Progressive increase in stimulus duration $N = 7$						
Control	179 ± 7.3	175 ± 9	NS	216 ± 2.8	213 ± 4.8	NS
0.005	109 ± 6.3	163 ± 7.0	<0.001	196 ± 5.6	209 ± 4.4	<0.05
0.0075	99 ± 7.6	154 ± 7.2	<0.005	198 ± 4.2	209 ± 4.0	<0.05
0.01	94 ± 11.1	149 ± 6.1	<0.01	195 ± 5.4	208 ± 3.4	<0.05
0.02	87 ± 12.5	123 ± 7.5	<0.05	191 ± 6.2	210 ± 3.6	<0.05
0.04	83 ± 11.9	100 ± 9.4	NS	189 ± 8.0	192 ± 3.9	NS
0.06	78 ± 8.3	89 ± 7.3	NS	189 ± 7.0	189 ± 4.1	NS
0.08	77 ± 5.6	83 ± 8.7	NS	191 ± 6.9	186 ± 5.2	NS
0.1	86 ± 8.8	81 ± 8.9	NS	193 ± 6.5	184 ± 5.7	NS
0.2	108 ± 16.5	84 ± 7.0	<0.05	202 ± 5.5	181 ± 7.5	<0.05
0.4	153 ± 23.0	77 ± 6.7	<0.05	210 ± 5.2	186 ± 8.8	<0.05
0.6	164 ± 26.1	77 ± 8.0	<0.05	210 ± 3.7	187 ± 10.7	<0.05
0.8	163 ± 20.4	78 ± 4.0	<0.01	209 ± 2.4	188 ± 10.2	NS
1.0	155 ± 16.4	77 ± 5.7	<0.01	202 ± 5.5	190 ± 8.0	NS
B. Progressive increase in stimulus frequency $N = 10$						
Stimulus frequency (Hz)						
Control	193 ± 7.6	184 ± 7.3	NS	223 ± 5.4	224 ± 6.1	NS
2	186 ± 7.0	153 ± 9.0	<0.05	220 ± 5.1	218 ± 5.6	NS
4	177 ± 7.7	134 ± 9.1	<0.01	220 ± 4.6	213 ± 6.1	NS
6	167 ± 7.0	112 ± 7.6	<0.001	219 ± 5.0	207 ± 6.5	NS
8	160 ± 7.3	89 ± 6.5	<0.001	218 ± 4.5	204 ± 7.4	NS
10	150 ± 8.1	86 ± 6.7	<0.001	216 ± 4.7	200 ± 7.6	NS
20	120 ± 6.2	62 ± 3.8	<0.001	209 ± 6.0	190 ± 7.3	<0.05
40	99 ± 7.9	56 ± 3.3	<0.001	204 ± 6.6	183 ± 6.7	<0.05
60	91 ± 6.7	63 ± 4.7	<0.01	197 ± 6.9	187 ± 7.0	NS
80	91 ± 6.3	66 ± 4.0	<0.05	195 ± 7.3	183 ± 6.6	NS
100	93 ± 6.3	68 ± 4.4	<0.05	196 ± 7.9	179 ± 7.3	NS

duration and the cardiovascular response to AN and CSN stimulation. These results are presented relative to the maximum decrease in blood pressure and heart rate. The absolute values are given in Table I. The maximum decrease in pressure during AN and CSN stimulation averaged 101 and 98 mm Hg, respectively. The average cardiac slowing to AN stimulation was 27 beats/min. CSN stimulation caused an average decrease of 32 beats/min. The difference between the maximal depressor and cardio-inhibitory responses to stimulation of the two nerves is trivial in this experimental series. The inhibition of pressure and heart rate was significantly greater, however, during AN stimulation than during CSN stimulation with stimuli in the duration range of 0.005 and 0.02 msec. The response to the 0.005 msec duration stimuli was about 70% of the maximal response to AN stimulation. The response to CSN stimulation with this stimulus was only 10% of the maximal response. Stimuli in the duration range of 0.2 to 1.0 msec simultaneously excited both depressor and pressor afferents in the nerves. The pressor and cardioaccelerator responses, on the average, largely offset the responses to the depressor reflexes during AN stimulation. The pressor and cardioaccelerator effects of CSN stimulation with

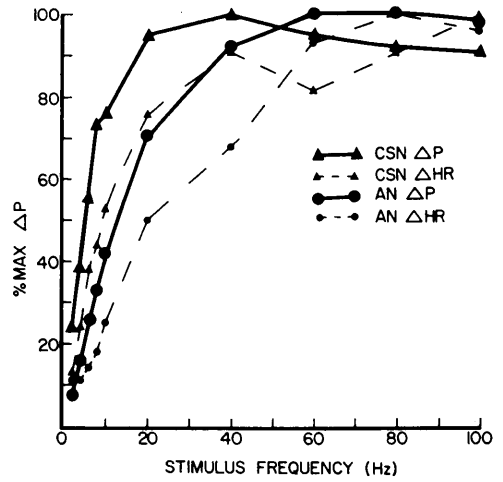

FIG. 4. Comparison of the average changes (N = 10) in blood pressure and heart rate to stimulation of the AN and CSN with stepwise increments in stimulus frequency (2–100 Hz). Stimulus duration is 0.1 msec; voltage constant.

stimuli in this duration range were small, therefore the depressor responses are not offset to any great degree.

The frequency–response (2 to 100 Hz) characteristics of the aortic and carotid sinus reflexes to the 0.1 msec and 1.0 msec duration stimuli are illustrated in Figs. 4 and 5. Stimulus amplitude was adjusted for each nerve to obtain maximum depressor responses to the 0.1 msec stimulus at 100 Hz. There was no discernible increase in breathing with this stimulus. A small increase in stimulus voltage from this setting resulted in either a stimulation of breathing or a rise in pressure or both. It was therefore assumed that this stimulus was subthreshold for most of the chemosensory fibers and excited a majority of the depressor afferents in the nerves.

Under these conditions, CSN stimulation caused large decreases in blood pressure and heart rate at low stimulus frequencies. The depressor response was essentially maximal at 10 to 20 Hz but continued to decline slowly and steadily as frequency was further increased to about 40 Hz. The response to increasing stimulus frequency from 20 to 40 Hz was usually not a definite response. Some failure of the depressor response occurred at still higher stimulation rates in some cases. The heart rate response curve lagged the pressure curve. Heart rate usually continued to decrease over most of the frequency range. Stimulation of the CSN in this experimental series caused a maximum decrease in pressure and heart rate which averaged 128 mm Hg and 45 beat/min, respectively. These responses were greater ($p < 0.05$) than the responses obtained in the series where duration was the variable. With three exceptions both experimental series were conducted on the same animals.

Higher stimulus frequencies (av 60 Hz) were required to obtain maximal responses during AN stimulation than during CSN stimulation, In most experiments definite responses were obtained to increasing the stimulus frequency from 60 to 80 Hz and in some cases a definite response was seen when the frequency was changed from 80 to 100 Hz. The heart rate response curve was displaced to the right of the pressure curve as was the case during CSN stimulation. The pressure response to CSN stimulation was greater at all stimulus frequencies than the response to AN stimulation (see Table I).

The relationship between the stimulus frequency and the reflex response to AN stimulation with 0.005 msec duration stimuli was determined in three dogs. The pressure response curve obtained closely resembled that shown in Fig. 4 to the 0.1 msec duration stimuli. The maximum depressor response

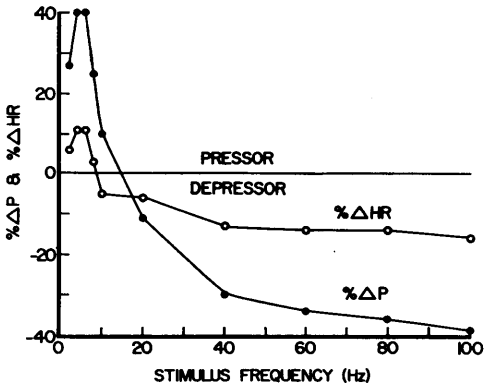

FIG. 5. Average changes (N = 4) in blood pressure to AN stimulation with 1.0 msec duration stimuli. Stimulus frequency varied; voltage constant. Responses are expressed as a percentage change from control.

(av 95 mm Hg) was obtained at 80 Hz in all three cases. It was presumed that only the large depressor fibers were stimulated in these experiments. Stimuli of 0.1 msec duration should excite both the large and small depressor fibers.

Stimulation of the AN or CSN with stimuli of 1.0 msec duration essentially activated all the afferent fibers in these nerves. Increasing the stimulus duration (or voltage) further had little or no additional effect. Figure 5 illustrates the frequency–response characteristics to AN stimulation with 1.0 msec duration stimuli. The four experiments represented in Fig. 5 were selected on the basis that pressor responses greater than 25 mm Hg were obtained in response to stimulation at 2 Hz. Pressor effects and cardioacceleration predominated over the lower frequency range (2–10 Hz). Frequencies above this range caused slowing of the heart and depressor responses. Stimulation of the CSN with stimuli of 1.0 msec duration caused cardiac slowing, decreased pressure and increased breathing at all stimulus frequencies (2–100 Hz). These results are not shown.

In the vagotomized animals maximal heart rate slowing averaged 20% during CSN stimulation and 13% during AN stimulation. In 7 dogs a comparison of the cardiac responses was made before cutting the vagal trunk on the side opposite from the CSN and AN being stimulated. The vagal trunk on the same side was cut or cooled. The sustained heart rate response to AN and CSN stimulation differed ($p < 0.05$) significantly with vagal efferents intact. The decrease in heart rate during AN stimulation (av 44%) was always greater than the sustained slowing during CSN stimulation (av 11%).

Discussion. Assuming that the threshold to stimulation of a nerve fiber is directly related to its diameter, our results indicate that the AN of the dog consists of two and probably three distinguishable fiber groups. In order of decreasing excitability these groups are the large and small depressor fibers and a third group of still smaller fibers which have pressor effects. The large diameter fibers appear to be the major depressor group in this nerve. The present experiments and those we previously reported (12) indicate that the major depressor fibers in the CSN are the smaller fibers. Both groups of depressor fibers reflexly decrease heart rate and blood pressure. The observation that the AN is more effective than the CSN in decreasing heart rate through the vagal reflexes suggests, that the large depressor afferents may play a greater role in the regulation of heart rate than the small depressor fibers. Winder (13) has reported that the aortic reflexes are more effective than the carotid sinus reflexes in cardiac control.

A higher stimulus frequency is necessary to produce maximal inhibition of blood pressure and heart rate during AN stimulation than is required during CSN stimulation. This difference appears to be related to the proportion of large and small depressor fibers in the two nerves. The major depressor effects to AN stimulation are mediated by the large depressor fibers. The small depressor fibers appear to constitute the major depressor component of the CSN. The frequency–response characteristics of these fiber groups in the CSN and AN of the cat (1–3, 14), and the AN of the rabbit (2, 3) and swine (4) are similar to our findings in the dog. The higher stimulus frequency required for the large fibers to produce their maximal effects suggests that these fibers may have fewer terminations on the medullary neurons than the small depressor fibers.

Donald and Edis (6) constructed pressure–reflex response curves for the aortic and carotid sinus baroreflexes in the dog. The response curves they obtained to raising the pressure in these regions closely resemble those we obtained to step increases in stimulus frequency (see Fig. 4). The pressure response curve to the aortic reflexes is displaced to the right of that obtained to stimulation of the carotid sinus response curve in both cases. This relationship suggests that increasing the frequency of baroreceptor discharge is of greater importance than baroreceptor recruitment in response to raising pressure in the aortic arch. The limited frequency range over which the carotid sinus reflexes operate suggests that the rate of baroreceptor discharge frequency may be less

important than recruitment for this reflex.

Comroe (15) observed that in dogs the carotid bodies produce the larger part of the hyperpnea to anoxia and the aortic chemoreceptors account for most of the hypertension. More recent reports from Daly's group (16–18) have suggested that the difference in the vasoconstrictor response elicited by stimulation of the carotid and aortic bodies are secondary to the increased pulmonary ventilation and the consequent involvement of the lung-inflation vasodilator reflex and a reduction of blood PCO_2. In our experiments both vagal trunks were severed which should have largely excluded reflexes from the lungs. In addition, in three experiments, respiratory paralysis by Flaxedil did not change the responses to aortic or carotid sinus nerve stimulation. In all experiments we found that increasing the stimulus duration to the AN above 0.1 msec caused the pressure and heart rate to recover toward and in some cases surpass the control levels. Minor changes in breathing occurred in response to these stimuli. On the other hand, stimulation of the CSN with the longer duration stimuli always increased respiration but caused small changes in the level of blood pressure and heart rate. The results suggest that chemosensory fibers are activated by the stimuli of longer duration. The pressor reflexes mediated by these fibers in the AN can offset the depressor reflexes from this region. The chemosensory reflexes from the carotid bodies had a weaker effect on pressure but caused marked hyperpnea.

Several reports (5–10) suggest that the depressor response to raising pressure in the isolated carotid sinus is greater than the response obtained to raising the pressure in the isolated aortic arch by an equivalent amount. Pelletier, Clement and Shepherd (10) recorded baroreceptor activity in the AN and the CSN of the dog. They concluded that the difference in effectiveness between the two reflexes was due to a difference in the rate of impulse formation from the baroreceptors. Our results support this view. We have observed that both reflexes are equally effective in reducing pressure when the depressor afferents are maximally excited. Therefore, it seems that the baroreceptor discharge characteristics are largely responsible for the greater effectiveness that has been reported for the carotid sinus reflex.

Summary. The maximum decrease in blood pressure and heart rate in response to electrical stimulation of the aortic (AN) and carotid sinus nerves (CSN) of the dog was essentially the same in both cases. Thus, reported difference in the effectiveness of the reflexes served by these nerves must be due to the baroreceptor discharge characteristics in response to a rise in pressure in the respective regions. Both nerves consist of at least two groups of depressor afferents and one fiber group which appears to arise from chemoreceptors. These fiber groups are distinguishable by their threshold to electrical stimulation. The major group of depressor fibers in the AN have a low threshold to stimulation while the major group of depressor fibers in the CSN are of higher threshold and presumably smaller in diameter. Maximal depressor effects to stimulation of the CSN are attained at lower stimulus frequencies (10–20 Hz) than is the case during AN stimulation (60–80 Hz). The chemosensory fibers in both nerves have a higher threshold than either group of depressor fibers. Stimulation of these fibers in the AN causes a rise in pressure and cardiac acceleration which nearly offsets the effects of stimulating the depressor fibers. However, little increase in breathing is observed. Stimulation of the chemosensory fibers in the CSN causes a marked hyperventilation but has relatively little effect on blood pressure and heart rate.

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