

The Effect of Stimulus Pattern on the Pressure Response to Electrical Stimulation of the Carotid Sinus Nerve of Cats¹ (37602)

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Electrical stimulation of the carotid sinus nerves (CSN) has been used by several investigators as a means of studying the hemodynamic consequences of baroreceptor reflex activation (1-9). These nerves in the cat have been shown to contain two groups of barosensory fibers, one with a low and one with a high threshold to electrical stimulation. A third group of chemosensory fibers are of intermediate threshold (1, 9). The resultant cardiovascular response to electrical stimulation of the CSN depends on the balance and interactions of these opposing influences on the medullary centers. The normal pattern of impulse traffic along the large barosensory nerves has repeatedly been shown to occur in groups with each systolic discharge, while the impulse traffic in the small barosensory and chemosensory impulses is more continuous (10, 11). Most studies involving electrical stimulation of the CSN have used stimuli which simultaneously stimulate all fiber groups with continuous stimuli separated by a uniform time interval. The pattern of these incoming signals to the medullary centers may play an important role in determining the resultant efferent effects. This study was undertaken to assess that role.

Methods. Eleven cats were used in these experiments. After induction of anesthesia with ether, 50 mg/kg of chloralose was given intravenously. The trachea was cannulated. Blood pressure was measured from the femoral

artery with a Statham strain gage. Heart rate was counted by a cardi tachometer triggered from the ECG or pressure pulse. Breathing rate was recorded from a pneumograph bellows around the thorax. All data were recorded on an Offner dynograph.

Both CSN were carefully dissected free from their juncture with the glossopharyngeal nerve back to the carotid sinus. Both nerves were ligated and cut close to the sinus and drawn into bipolar silver ring electrodes. The electrodes were insulated from the surrounding structures by a pool of mineral oil. The vagal trunks were cut in all experiments. In two cases, studies were conducted before cutting the vagi. An AEL (model 104) electronic stimulator was used for CSN stimulation. Monophasic, rectangular pulses were delivered through an isolation transformer either in trains or in a continuous pattern. The stimulus parameters were monitored on an oscilloscope. In all animals the effects of interrupted and continuous stimuli were compared in two experimental series. In one series the effects of stepwise increases in stimulus duration from 0.005 to 1.0 msec were compared during continuous stimulation at 10 Hz and during interrupted stimulation with 2 stimulus bursts/sec with five stimuli in each burst. The stimulus interval in the bursts was 20 msec while during continuous stimulation this interval was 100 msec. In the other series the responses to increasing stimulus duration at a continuous frequency of 50 Hz were compared to those to 1 burst/sec with five stimuli in each burst. The stimulus interval in this case was the same, 20 msec. Pressure was allowed to stabilize at each duration setting before it was in-

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creased. Each stimulation series lasted about 15 min which was followed by a recovery period of 10–15 min. The continuous and intermittent series were applied in a random order.

During the experiment the animals breathed a 95% O₂–5% CO₂ gas mixture. This prevented the long apneic period that usually follows the hyperventilation which results from stimulation of the CSN. The systemic pressure in animals breathing air often recovers very slowly from the effects of CSN stimulation and in some cases fails to recover back to control level. Breathing the gas mixture prevented the apneic period and hastened recovery of the blood pressure when nerve stimulation ceased. Blood PCO₂, PO₂ and pH were determined at 30 min intervals. These values, with the exception of PO₂, were not greatly different whether the animal was breathing air or 95% O₂–5% CO₂ (PCO₂ 45–50 mm Hg, pH 7.25–7.38). In either case the animals tended to become acidotic. Correction of the blood chemistry to normal values by artificial ventilation with air and infusion of NaHCO₃ did not influence the experimental results in the two animals tested.

Results. Representative blood pressure and respiratory responses to continuous and intermittent stimuli are illustrated in Fig. 1. The continuous stimuli were delivered at a frequency of 50 Hz. The intermittent stimuli were applied—1 burst/sec with 5 stimuli/burst. The interval between stimuli in both cases was 20 msec. Figure 2 presents the average results of the 11 experiments. In the

lower panel the response to continuous (50 Hz) and intermittent (1 burst/sec, 5 stimuli/burst) are compared. The upper panel of Fig. 2 compares the responses to continuous stimulation (10 Hz) with those obtained to intermittent stimulation with 2 bursts of 5 stimuli/sec. In all experiments the stimulus amplitude (1.25–2.0 V) was initially set so that no stimulation of breathing was obvious with a 0.01 msec duration stimulus at a frequency of 50 Hz. It should be noted that this stimulus amplitude did not excite all of the depressor fibers in the CSN even at the 1.0 msec duration setting. Larger depressor responses could be obtained by increasing stimulus voltage with the stimuli of long duration.

The response to the 0.01 msec duration stimuli during continuous stimulation with either 10 or 50 Hz was variable. On the average pressure rose slightly to this stimulus but often there was an initial small depressor response. Increasing the stimulus duration in steps from 0.01 msec caused a progressive stimulation of breathing which was maximum at about 0.1 msec. Breathing depth was approximately doubled while less change in rate occurred. The shaded area in Fig. 2 represents the product of breathing rate and depth during stimulation of the CSN at 10 Hz, relative to a control value of 1. The response to 50 Hz stimulation was about the same as that to 10 Hz and is not shown. Similarly the respiratory response to intermittent stimulation was essentially the same as that shown for continuous stimulation. Absolute values of ventilatory volume were

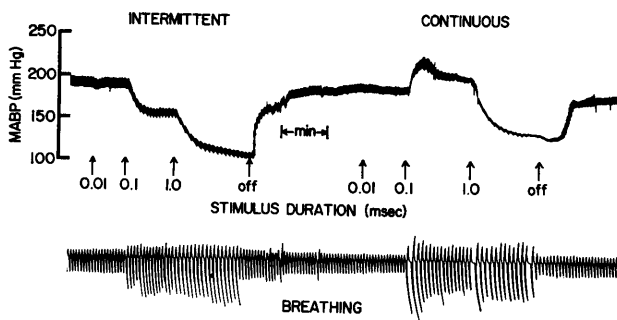


FIG. 1. Blood pressure and breathing responses to stimulation of the CSN. Intermittent stimulation: 1 burst/sec; 5 stimuli/burst; burst length, 100 msec. Continuous stimulation: 50 Hz; stimulus strength, 1.5 V.

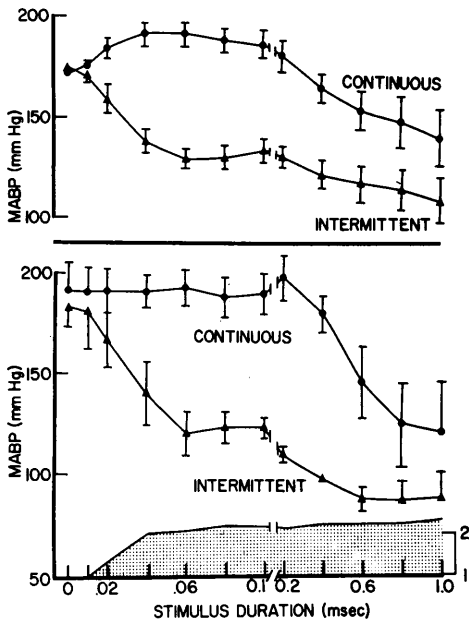


FIG. 2. Average MABP and breathing responses in 11 cats to step increases in stimulus duration during continuous and intermittent stimulation. Upper panel: Continuous stimulation: 10 Hz. Intermittent stimulation: 2 bursts/sec.; 5 stimuli per burst; burst duration, 100 msec. Lower panel: Continuous stimulation: 50 Hz. Intermittent stimulation: 1 burst/sec.; 5 stimuli per burst; burst duration, 100 msec. Vertical bars indicate SEM. Shaded area represents change in respiration relative to a control value of 1. Stimulus strength was constant (1.25–2 V) in all cases.

not obtained. During continuous stimulation with stimuli of 0.1 to 0.2 msec duration, at either frequency, systemic blood pressure rose to a maximum. The respiratory response also reached its maximum over this range. Higher duration stimuli resulted in the predominance of depressor reflexes and a fall in pressure below control level. The pressure responses to intermittent stimulation were significantly greater ($p < 0.05$, paired t test) than those to continuous stimulation at all stimulus durations except 0.01 msec.

In four cats gallamine triethiodide (Flaxedil, 1–2 mg/kg iv) was given to exclude the possibility that differences in the ventilatory responses to the two forms of stimulation were responsible for the greater effectiveness of intermittent stimulation.

These cats were artificially ventilated with air. Flaxedil did not change the relationship between the responses to intermittent and continuous stimulation, although the depressor responses were increased to both forms of stimulation. In two cats the responses to intermittent and continuous stimuli demonstrated the same relationship as described above before and after vagotomy.

Heart rate responses to CSN stimulation in the vagotomized animals were small. Generally maximum cardiac slowing was about 10% of the control rate. No discernible difference between the response to intermittent or continuous stimulation was observed. This also appeared to be the case in the two animals tested before vagotomy in which a marked transient cardiac slowing was evident.

The responses to continuous stimulation with 20, 30 and 100 Hz and intermittent stimulus bursts (1 burst/sec; 5 stimuli/burst) in which the stimulus interval (50, 33 and 10 msec) was matched to the stimulus interval for each of the above frequencies were compared in four cats. The difference between the responses was similar in all cases to that previously described. Over this range (10 to 50 msec), varying the stimulus interval in the trains had trivial effects on the size of the depressor response.

Discussion. The results presented demonstrate that bursts of electrical stimuli inadequate in strength to excite all the fibers in the CSN of the cat, more effectively reduce blood pressure than continuous stimulation. We have previously shown (9) that the difference between the responses to intermittent and continuous stimulation is small if stimuli of sufficient strength to excite all the depressor fibers are used. In these earlier studies maximal reflex responses to stimulation of the small depressor fibers were observed at stimulus frequencies of 8–10 Hz. The maximum response obtainable to selective stimulation of the large depressor fibers in the CSN was usually not attained at stimulus frequencies below 80 Hz. The large depressor responses obtained at low stimulus frequencies with maximal stimuli precludes assessment of the differences between intermittent and con-

tinuous stimulation. In the present study a stimulus voltage was selected which did not excite all of the small depressor fibers even at the stimulus duration of 1.0 msec. When this stimulus amplitude was used, increasing the duration of the stimulus was expected to first excite the large depressor fibers, then the intermediate sized chemosensory fibers and finally recruit some of the small depressor fibers in the CSN (1). Under these conditions the depressor response was greater to intermittent than to continuous stimulation over most of the duration range from 0.01 to 1.0 msec. The greatest difference was observed in the range of 0.02–0.1 msec. At these stimulus durations we would expect a primary involvement of the large depressor fibers and the chemosensory fibers with minimum excitation of the small depressor fibers.

It is well known that the normal impulse pattern in the large depressor fibers is grouped with each systolic discharge (10, 11). Intermittent activity in these neurons may more effectively inhibit the medullary centers than a continuous stream of impulses. Ead, Green and Neil (12) have shown that pulsatile pressure in the carotid sinus of the cat caused a greater reduction in systemic blood pressure than nonpulsatile pressure at the same mean level. They concluded that stimulus grouping rather than the total number of impulses per second was the critical factor involved. Douglas, Ritchie and Schaubmann (13) challenged this idea and suggested that pulsatile pressure was more effective because of greater receptor recruitment and a consequent greater number of impulses reaching the medullary center per unit time. These workers used electrical stimuli which would appear to be adequate to stimulate all afferent fibers in the CSN. They concluded that grouped stimuli were generally no more effective than continuous stimuli as long as the total number of stimuli per sec was the same. More recently Jonzon *et al.* (14) reached a similar conclusion in studies on the CSN of the dog. Our results support the concept of Ead, Green and Neil (12) that stimulus grouping plays an important role in the reflex response. In our experiments the total number of afferent fibers involved should

have remained the same during both intermittent and continuous stimulation.

The mechanism by which stimulus grouping enhances the depressor effect of CSN stimulation is not clear from these experiments. Richter, Keck and Sellar (8) have suggested that in dogs more adaptation of the medullary centers occurs in response to continuous than to grouped stimuli. They suggest that this difference in central adaptation may explain the greater effectiveness of intermittent stimulation in their experiments. Our results cannot be explained on this basis since little or no recovery in pressure was observed during maintained (5 min) stimulation with either form.

An alternative explanation of our results may be that the pressor reflex, from the chemosensory fibers responds less effectively to the intermittent than to the continuous form of stimulation. If this were the case depressor responses would be unmasked which might account for the larger pressure fall to the stimulus bursts. It should be remembered that the respiratory response was essentially the same in both cases.

Summary. The resultant effect of CSN stimulation, as well as depending on the stimulus strength or duration, also depends upon the pattern of the stimulation. Intermittent stimuli have been shown in these experiments to produce a fall in blood pressure, whereas, stimuli with identical parameters produced a rise in pressure when applied continuously. Similarly, it has been shown that when the stimulus parameters were such that depressor effects were seen to continuous stimulation, grouping the stimuli produced equivalent or greater depressor responses with 10% or less of the total number of stimuli per second. This observation may be of relevance in the design of baropacers for the treatment of certain types of hypertension.

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