

## Central Summation of Barosensory Impulses over both Carotid Sinus Nerves in the Dog<sup>1</sup> (38763)

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Barosensory signals to the medullary neurons involved in the regulation of systemic blood pressure originate from several sources and probably arrive centrally in asynchronous bursts. The resultant reflex effect may be influenced by both the total number of impulses arriving per unit time, the incoming impulse pattern, and the manner in which the impulse bursts coming from different barosensory regions sum together. The relative role played by each of these factors is not clear.

One major source of barosensory information arises from the carotid sinus baroreceptors. In the physiological pressure range these receptors have been shown to reach maximal activity during systole and show minimal activity during diastole (1-3). The importance of the incoming pattern of signals on their central interpretation and the resultant reflex response is not clear. However, many studies suggest that the total number of impulses/sec arriving centrally is the major factor that determines the magnitude of the carotid sinus reflex response (3-6). The effect that the temporal relationship between the incoming impulse volleys, from the two carotid sinuses, may have on the reflex response does not appear to have been studied.

In the present study we have evaluated the relative importance of impulse frequency, impulse pattern, and the temporal summation of the impulse bursts from the two carotid sinuses on the baroreflex response from these regions. Our results confirm those of others (3-6) that have shown the total number of impulses/sec to be the major determinant of the carotid sinus reflex response in anesthetized dogs.

*Methods.* Two series of experiments were conducted on a total of 16 dogs (14-20 kg).

All animals were anesthetized with chloralose (100 mg/kg iv) 30 min following premedication with morphine sulfate (3 mg/kg sc). The trachea was intubated and both cervical vagus nerves were cut in all cases. The animals were artificially ventilated with either room air or in a few cases 100% O<sub>2</sub>. Ventilatory rate was adjusted to keep blood pCO<sub>2</sub>, pO<sub>2</sub> and pH in the normal range. Systemic blood pressure was measured from a branch of the femoral artery. Heart rate was recorded by a cardiachometer which was triggered from the ECG. These data were recorded on an Offner polygraph for later analysis.

*Carotid sinus nerve (CSN) stimulation.* In nine dogs both CSN were carefully isolated from their juncture with the glassopharyngeal nerve back to their origin in the carotid sinus. The nerves were cut close to the sinuses and their peripheral ends were drawn into silver ring electrodes. Each nerve was separately stimulated with a Grass SD9 stimulator. The output from each SD9 stimulator was triggered from one channel of a dual channel Grass S88 stimulator. With this system trains of stimuli were generated by each SD9 stimulator. Train duration and train frequency were set at 50 msec and 2 Hz in all cases. The number of stimuli in each train was varied between 1 and 10. This corresponds to a total number of stimuli to both CSN between 4 and 40/sec. The delay between the SD9 stimulator outputs was varied between 0 and 250 msec. (0° and 180°). The individual stimuli in each train were 0.1 msec in duration and from 0.5 to 1.3 V in amplitude. The stimulus parameters were monitored on a CRO.

A fall in systemic pressure of about 30 mmHg occurred in response to stimulation of each CSN separately with two trains/sec and 10 impulses per train. Simultaneous stimulation of both CSN caused a fall in pressure of about 60 mmHg. This depressor

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response was about 0.5 of the response that could be obtained with maximal stimulation and therefore in the linear portion of the stimulus-response curve.

The reflex responses to intermittent and continuous stimulation of both CSN were obtained. The intermittent bursts were applied synchronously to both nerves or with a 250 msec delay between bursts. During continuous stimulation trains with one stimulus per train were synchronously applied to each sinus nerve. The train frequency was increased from 2 to 20/sec in steps so that the total number of stimuli/sec corresponded to that used during intermittent stimulation. Statistical comparison of the responses to continuous and intermittent stimulation was made at each frequency setting by the paired *t* test. The 95% level of significance was selected. Steady state levels of blood pressure and heart rate were attained at each setting. Each stimulation series required about 20 min to complete and at least 10 min was allowed between series.

In five of the nine dogs the delay between the stimulus bursts to each CSN was progressively increased from 0 to 200 msec. The response obtained at each delay setting was compared to that obtained to synchronous bursts of stimuli.

*Carotid sinus perfusion.* In a separate group of seven, vagotomized dogs both carotid sinuses were vascularly isolated and separately perfused at a constant rate of flow (75 ml/min) and at a pump rate of 120/min with a Sigmamotor pump. Blood from canulas in the peripheral common carotid arteries was pumped through a centrally directed cannula in each of the carotid arteries just below the sinus. The sinus outflow was taken from cannulas in the external carotid arteries and returned through a common outflow tube to a jugular vein. Clamps on the outflow tubing from each sinus were used to adjust the mean pressure level in each carotid sinus. By placing the two independent perfusion circuits on the same side of the pumping fingers, pulsatile pressure rose simultaneously in both carotid sinuses. When the perfusion circuits were placed on opposite sides of the pump head the pressure rose 180 degrees out of phase in the two carotid sinuses. Flow in each perfu-

sion circuit was the same regardless of position. An air chamber in each perfusion circuit provided an independent adjustment of the pulsatile pressure in each carotid sinus. During pulsatile perfusion pressure fluctuations were kept constant (avg.  $40 \pm 2$  mmHg) over the range of mean pressures. Non-pulsatile ( $0 \pm 2$  mmHg) perfusion was achieved by the complete incorporation of the air chambers in the perfusion circuits.

The pressure and heart rate responses to raising mean pressure in the carotid sinuses in 20 mmHg steps were compared during pulsatile (in phase and out of phase) and non-pulsatile perfusion. Mean carotid sinus perfusion pressure was limited to 160 mmHg because in some cases systemic pressure fell to levels inadequate to maintain inflow to the perfusion circuit. Each experimental series required 15–20 min to complete. A recovery period of 10 min was allowed between each series.

*Results.* The systemic pressure responses to stimulation of both CSN with continuous and intermittent stimuli are compared in Table I. In each comparison the total number of stimuli/sec applied to both CSN was the same. The difference between the responses to continuous and intermittent stimulation was not significant ( $P > 0.05$ ) in any case. A delay of 250 msec between the impulse volleys applied to the right and left CSN did not significantly change the response from that observed to simultaneous volleys applied to both nerves. Heart rate responses were small (max. about 10%) and variable in these vagotomized animals and are not presented. There was, however, no discernible difference between the heart rate response to intermittent and continuous stimulation. This also appeared to be the case in two animals before vagotomy.

Varying the delay from 0 to 200 msec between the stimulus bursts delivered to the two CSN caused no significant change in the reflex response. Table II summarizes this data and compares the responses to combined stimulation of both CSN with the sum of those obtained to separate stimulation of these nerves. The responses to combined stimulation were not significantly different from the sum of the separate responses in any case. This suggests that the baroreceptor

TABLE I. SYSTEMIC PRESSURE RESPONSES TO CONTINUOUS AND INTERMITTENT STIMULATION OF BOTH CSN.  $N = 9$ .

Total No. imp/sec	Continuous			Intermittent stimulation					
	MABP (mmHg)	$\Delta P$ (mmHg)	% of Control	0 msec delay between volleys to Rt.-Lt. CSN			250 msec delay between volleys to Rt.-Lt. CSN		
				MABP (mmHg)	$\Delta P$ (mmHg)	% of Control	MABP (mmHg)	$\Delta P$ (mmHg)	% of Control
0	167 $\pm$ 7*	0	100	179 $\pm$ 10	0	100	179 $\pm$ 8	0	100
4	147 $\pm$ 7	20	88 $\pm$ 1	158 $\pm$ 9	21	89 $\pm$ 1	164 $\pm$ 10	15	90 $\pm$ 2
8	133 $\pm$ 8	34	80 $\pm$ 3	147 $\pm$ 11	32	82 $\pm$ 3	147 $\pm$ 11	32	81 $\pm$ 3
12	127 $\pm$ 9	40	76 $\pm$ 3	136 $\pm$ 12	43	75 $\pm$ 1	130 $\pm$ 11	49	72 $\pm$ 3
20	115 $\pm$ 9	52	69 $\pm$ 4	127 $\pm$ 11	52	71 $\pm$ 4	123 $\pm$ 10	56	68 $\pm$ 4
40	100 $\pm$ 11	67	59 $\pm$ 5	112 $\pm$ 10	67	63 $\pm$ 4	105 $\pm$ 9	74	58 $\pm$ 4

\*  $\pm$ SEM.TABLE II. CHANGES IN SYSTEMIC PRESSURE TO COMBINED STIMULATION OF BOTH CSN WITH BURSTS OF STIMULI SEPARATED IN TIME.  $N = 5$ .

Delay between volleys to Rt. and Lt. CSN (msec)											
0		20		50		100		150		200	
$\Delta P$ mmHg	% of Lt + Rt	$\Delta P$ mmHg	% of Lt + Rt	$\Delta P$ mmHg	% of Lt + Rt	$\Delta P$ mmHg	% of Lt + Rt	$\Delta P$ mmHg	% of Lt + Rt	$\Delta P$ mmHg	% of Lt + Rt
50	92	53	92	61	105	57	98	53	100	60	93
$\pm 5^*$	$\pm 19$	$\pm 7$	$\pm 14$	$\pm 5$	$\pm 14$	$\pm 2$	$\pm 15$	$\pm 2$	$\pm 17$	$\pm 5$	$\pm 14$

\*  $\pm$  SEM.

afferents in each CSN project centrally to independent neuronal pools.

Figure 1 illustrates the greater efficacy of pulsatile pressure over nonpulsatile pressure in initiating the baroreflexes from the carotid sinuses. The pressure response during pulsatile perfusion was significantly greater ( $P < 0.05$ ) than that to nonpulsatile pressure at all mean pressure levels except 0 and 150 mmHg. The heart rate responses to nonpulsatile pressure tended to be greater, particularly at the higher carotid sinus pressures, than those to pulsatile pressure. However, this difference was not significant ( $P > 0.05$ ). Changing the relationship between the pressure pulses so that they were 180 degrees out of phase did not result in blood pressure or heart rate responses which were significantly different from those obtained during inphase perfusion of the carotid sinuses.

*Discussion.* Pulsatile perfusion of the carotid sinuses elicited the baroreceptor reflexes more effectively than nonpulsatile pressure at

the same mean level over most of the range from 0 to 150 mmHg pressure in the carotid sinuses. These results illustrate the greater efficacy of pulsatile pressure in the dog as demonstrated by Ead *et al.* (2) in the cat. Three possible explanations for the greater efficacy of pulsatile pressure in eliciting the baroreceptor reflexes were explored in these studies: (1) The effect of temporal separation of impulses from the two carotid sinuses. (2) The effect of impulse pattern and (3) The effect of the total number of impulses per unit time. The results suggest that the most important factor in the operation of the carotid sinus reflex is the total number of impulses per unit time.

The temporal relationship of the incoming signals from the two sinuses did not appear to be an important factor in determining the magnitude of the reflex response. This is suggested both by the experiments in which the pulsatile pressure in the sinuses was out of phase by 180° and by the experiments in

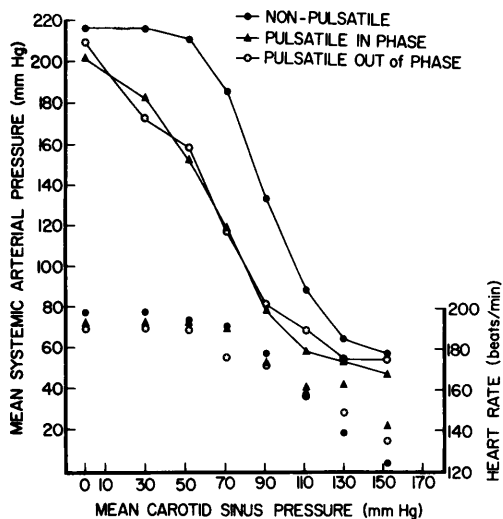


FIG. 1. Average systemic pressure and heart rate responses to increasing mean carotid sinus pressure during pulsatile and nonpulsatile perfusion of both carotid sinuses.  $N = 7$ .

which a delay was introduced between the intermittent stimulus bursts applied to both CSN. The failure to demonstrate any effect on the reflex response related to the synchronicity of the impulses in the two CSN suggests that the barosensory afferents from each side project to essentially independent neuronal pools. Thus the simple addition of the reflex effects from the two sinuses, as was reported by Sagawa and Watanabe (7), is confirmed by a different experimental method.

The present studies failed to demonstrate a significant effect of impulse pattern on the carotid sinus reflex response. Stimulation of the CSN with impulses grouped into 50 msec trains was no more effective in lowering systemic pressure or heart rate than continuous stimulation with the same total number of impulses/sec. Jonzon *et al.* (6) reached a similar conclusion in anesthetized dogs. However, in a later report they (8) found that stimulus bursts to the intact CSN of unanesthetized dogs were more effective than continuous stimulation. In these experiments the stimulus bursts were synchronized to the ECG and thus arrived centrally in a temporal relationship with incoming impulses which arose normally from the carotid sinus and aortic arch baroreceptors. Their results,

therefore may not demonstrate an ability of the medullary centers to discriminate the impulse pattern but may be the result of temporal summation of the impulses which arose normally from barosensory regions with those which arose from the stimuli. Warzel and Brattström (9) have demonstrated that the timing of CSN stimulation during the cardiac cycle affects the reflex response to bursts of stimuli. They suggest that the greatest reflex response to the stimulus trains is obtained when they coincide with endogenous impulse activity. Douglas, Ritchie and Schaumann (5) observed no difference in the reflex response to stimulation of the aortic nerve of the rabbit with continuous and intermittent stimuli. They concluded that the greater effectiveness of pulsatile pressure was due to baroreceptor recruitment rather than impulse pattern. These results are at variance with those we obtained from cats (10). In the cat stimulus volleys more effectively activated the barosensory reflexes than continuous stimulation of the CSN. However, the majority of barosensory fibers in the CSN of the cat are smaller than the chemosensory fibers. Therefore, electrical stimulation of the barosensory fibers necessarily involves simultaneous excitation of chemosensory fibers. The larger depressor response to the impulse volleys, in this case, may have been due to a decreased pressor effect of the chemosensory afferents. In the dog, however, the majority of the barosensory fibers in the CSN have a lower threshold to electrical excitation than the chemosensory fibers (11). Therefore, in the present study stimulus parameters were selected which primarily activated the larger barosensory fibers and caused minimal excitation of the chemosensory fibers in this nerve. Richter *et al.* (12) demonstrated a greater sustained lowering of blood pressure in anesthetized dogs during intermittent than during continuous stimulation of the CSN. Their stimulus parameters were such that they may have been activating a significant number of chemoreceptor as well as the baroreceptor afferents.

The results of the present experiments suggest that the barosensory afferents from the carotid sinuses influence separate neuronal pools in the medulla. Thus, they inter-

act in a simple additive manner in the physiological range of blood pressure. The central interpretation of carotid sinus baroreceptor activity is largely dependent upon the total number of impulses reaching the medullary centers per unit time. This however does not preclude significant central interactions between the signals from the carotid sinuses and baroreceptor signals from other sources.

*Summary.* Stimulation of both CSN in dogs with continuous stimuli decreased blood pressure and heart rate as effectively as intermittent bursts of stimuli. The temporal separation between the stimulus bursts to the two CSN was without effect on the reflex response. Similarly perfusion of both carotid sinuses with pressure pulses which were in phase was no more effective in eliciting the reflex than perfusion with pressure pulses 180° out of phase. These results suggest that the barosensory fibers project centrally to independent neuronal pools. Pulsatile perfusion of the carotid sinuses lowered systemic pressure more than nonpulsatile pressure at the same mean level. The greater efficacy of pulsatile pressure appears to result from baroreceptor recruitment and not from the impulse pattern.

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