Role of peripheral chemoreceptors in response to smoke-induced apnea vs tracheal occlusion[1]

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Summary. Reflex autonomic changes which occur after cigarette smoke enters the upper airways are partially due to peripheral chemoreceptor stimulation. Chemoreceptor denervation attenuates but does not abolish smoke induced bradycardia. Denervation nearly abolishes bradycardia induced by tracheal occlusion. Hypertension accompanies smoke induced apnea but does not occur during tracheal occlusion.

Key words. Nasal irritant receptors; cigarette smoke; blood pressure; heart rate; rabbits.

When nasal irritant receptors of the rabbit are stimulated with cigarette smoke one observes apnea, bradycardia, increased arterial pressure, widespread vasoconstriction but decreased cardiac contractility[2-4]. The primary sensory input of this autonomic reflex is believed to be the trigeminal nerve with no significant contribution originating from the olfactory nerve[2]. The efferent pathways of the reflex presumably include motor fibers to respiratory muscles[3], vagal efferent nerves which depress heart rate and sympathetic fibers which both depress the heart and excite peripheral vascular constriction[5]. Angell-James and Daly[6] proposed a sequence of events for this reflex beginning with stimulation of nasopharyngeal irritant receptors to produce inhibition of the respiratory center. The resulting apnea leads to a fall in arterial PO_2, a rise in PCO_2 and a reduction in pH which stimulates arterial chemoreceptors. Angell-James and Daly[6] assumed that chemoreceptor stimulation caused the reflex bradycardia and blood pressure rise. McRitchie and White[2] suggested that the arterial baroreceptors contributed to the fall in heart rate while the chemoreceptors were not involved. More recently, Robleto and Peterson[4] have demonstrated substantial bradycardia during upper airway stimulation after total sino-aortic denervation which eliminated both baro and chemoreceptor inputs.

This study's purpose was to determine the influence of intact peripheral chemoreceptors in the nasopharyngeal reflex response to cigarette smoke. This was accomplished by comparing cardiovascular responses produced by smoke to those produced by tracheal occlusion, both before and after sino-aortic denervation.

Materials and methods. Six male albino rabbits (2.8–3.8 kg) were anesthetized using sodium pentobarbital (30–35 mg/kg) i.v. through a marginal ear vein. The femoral vein was cannulated for additional administration of anesthetic. Two tracheal cannulae were inserted through a midcervical incision. The cranial cannula was for delivery of unfiltered cigarette smoke over upper airway receptors. The caudal cannula allowed spontaneous respiration of room air. Respiratory movements were recorded by thermocouple detection of temperature changes between inspired and expired air. Arterial pressure (AP) and mean arterial pressure (MAP) were monitored from a cannulated femoral artery. ECG was recorded with s.c. pin electrodes and heart rate (HR) was obtained from the ECG using a cardiotachometer coupler. All measurements were continuously recorded on a Beckman Instruments eight-channel Dynograph, model R612. For this study experimental cigarettes (code 32, National Cancer Institute) were used. Delivery of smoke occurred by forcing 50 ml of unfiltered smoke from a glass syringe into the cranial cannula, through the upper airways and out of the nares. 10 s of smoke perfusion were immediately followed by perfusion with 50 ml of room air to flush the upper airways. Smoke never entered the lungs. Tracheal occlusion was produced by complete obstruction of the respiratory cannula. In most animals, duration of occlusion simulated the period of apnea observed due to smoke stimulation, although it was always limited to approximately 40 s. Exposure to smoke and tracheal occlusion was repeated 2–4 times in each rabbit with time allowed to return to prestimulus levels between trials. Sino-aortic denervation was then carried out through bilateral surgical section of the aortic nerves and carotid sinus denervation. Each sinus was isolated and all vessels except the common, internal and external carotid arteries ligated and cut.

The sinus region was then stripped of all other tissue within 5–10

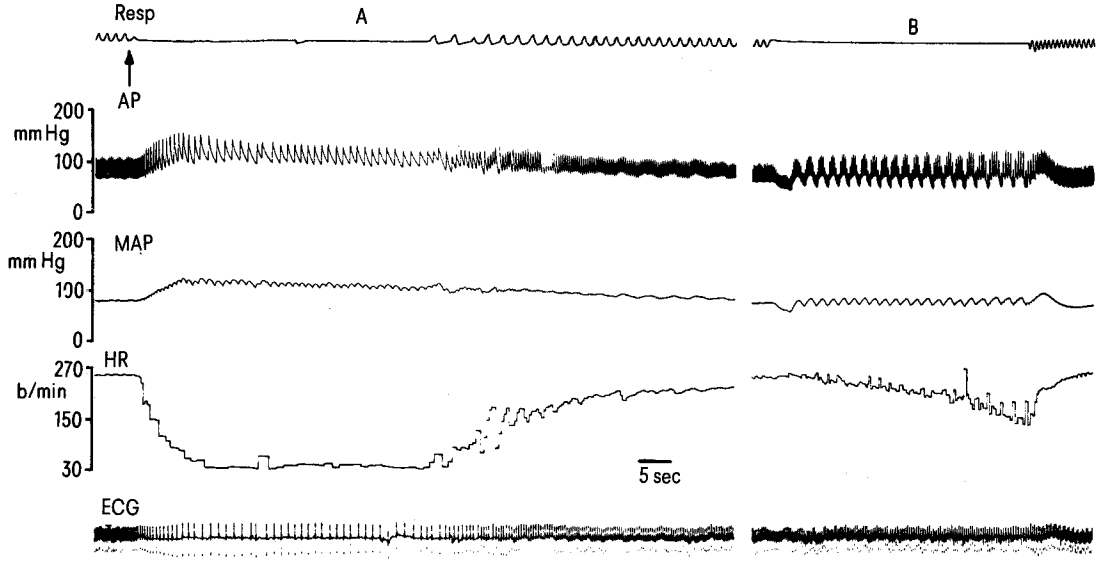

Figure 1. Responses to upper airway perfusion with cigarette smoke (A) compared with responses to tracheal occlusion (B). Duration of occlusion was timed to approximately equal duration of spontaneous apnea. Note the almost immediate exaggeration of respiratory efforts, as indicated on the AP trace, in response to tracheal occlusion. Also note that onset of responses to smoke are rapid but recovery is slow, whereas the opposite is true in response to tracheal occlusion.

mm of the bifurcation. After the denervation was complete and cardiovascular parameters had stabilized, the smoke and tracheal occlusion trials were repeated. Data were taken at 5 s and subsequent 10-s intervals after the initiation of apnea. Statistical analyses performed were paired t-test, one-way analysis of variance and Duncan's multirange test. Differences were considered significant when $p < 0.05$. Values are expressed as means ± SE.

Results. Representative responses to cigarette smoke are illustrated in figure 1, A. Apnea occurred immediately followed by a raid, sustained fall in heart rate and a rise in arterial pressure. Recovery of cardiovascular changes began with the first post-apneic breath was allowed to resume.

Typical responses to tracheal occlusion are represented in figure 1, B. No sustained change was observed in arterial pressure although exaggerated respiratory efforts were visible as increased fluctuations in the blood pressure traces. The HR response to occlusion was characterized by a gradual decline as the duration of apnea progressed. Recovery was rapid as soon as respiration was allowed to resume.

The table indicates resting values for blood pressure as well as average maximum changes under all experimental conditions tested. In response to smoke there was no significant difference in the magnitude of BP rise between pre- and post-denervated trials, and both rose significantly. The occlusion trials did not produce significant changes in BP in either intact or denervated trials. In response to smoke, heart rate fell significantly farther before denervation than after, but under both conditions the change was dramatic (fig. 2). Occlusion produced a large, significant bradycardia which was nearly abolished by denervation (fig. 2). Responses to occlusion were significantly less pronounced than responses to smoke at every point in time when nerves were intact. This too was the case when comparing responses after denervation (fig. 2).

Conclusions. We have confirmed previous observations that stimulation of nasopharnygeal irritant receptors with smoke produces profound bradycardia, apnea, and a rise in blood pressure[8]. This study has also demonstrated that the heart rate changes observed during smoke induced apnea are influenced in part by peripheral chemoreceptor stimulation whereas blood pressure changes are not. Tracheal occlusion caused slowly developing bradycardia but did not produce significant blood pressure change. Hence, sympathetic vasoconstriction producing the BP rise must be a direct result of airway receptor stimulation and unrelated to peripheral chemoreceptor stimulation[2]. Previous studies have demonstrated that vagal afferents do not contribute to the blood pressure rise[4]. The bradycardia produced by tracheal occlusion was nearly abolished by sino-aortic denervation indicating direct chemoreceptor involvement. In contrast, during smoke induced apnea, bradycardia after sino-aortic denervation was still profound even though it was significantly less than when all peripheral chemoreceptors were intact. Our results are similar to those observed when comparing the diving response to tracheal occlusion in the seal[9]. Daly et al.[9] concluded that bradycardia due the tracheal occlusion is reflex in origin due to stimulation of carotid body chemoreceptors but that the early bradycardia (before 45 s) associated with diving in the seal was unrelated to chemoreceptor stimulation. In our experiments bradycardia was near maximal within 10 s after onset in the smoke response whereas during tracheal occlusion the heart rate change was more gradual, continuing to fall for at least 40 s (fig. 2). As suggested by others[2], it is possible that the increasing chemoreceptor drive was responsible for interruption of apnea in our experiments.

Daly and Taton[7] indicated that simultaneous stimulation of the upper airways with smoke and carotid chemoreceptor stimulation with cyanide potentiated the bradycardia that originated at the chemoreceptors when pulse interval was the measured variable. Under our experimental conditions, measuring heart rate directly, there did not appear to be potentiation between the two influences. Chemoreceptor stimulation alone (due to tracheal occlusion) plus nasopharyngeal stimulation alone (smoke after sino-aortic denervation) produced heart rate changes which approximately totaled or exceeded the combined effect of the two (smoke stimulation with intact chemoreceptors) (fig. 2). When, however, pulse interval changes were calculated, the combined effect (1446 ms increase) far exceeded the sum of the two stimuli alone (319 ms increase, occlusion; 243 ms increase, smoke). Hence, whether or not there is potentiation between the two sensory inputs appears to depend upon which method of data analysis is employed. Measuring heart rate change directly argues against potentiation, measuring pulse interval suggests more than a two-fold increase in response due to potentiation. Our results do not completely rule out a possible baroreflex component to the observed bradycardia. Since sinoaortic denervation would eliminate peripheral baroreceptors, the observed rise in blood pressure might have contributed to the heart rate fall before denervation. The blood pressure rise seems to be an especially likely contributor to the early, rapid fall in heart rate due to smoke since tracheal occlusion had very little early influence on heart rate (fig. 1).

Maximum changes in MAP in response to either upper airway perfusion with smoke or tracheal occlusion

Mean arterial pressure		Resting	Response	Change	n
Smoke	Intact	75 ± 5	96 ± 5	21 ± 4**	16
	Denervated	93 ± 8	113 ± 6	20 ± 7*	13
Tracheal occlusion	Intact	79 ± 4	79 ± 4	0 ± 1	22
	Denervated	95 ± 8	99 ± 6	4 ± 2	14

n = number of trials. Significance of changes are: *$p < 0.05$; **$p < 0.001$

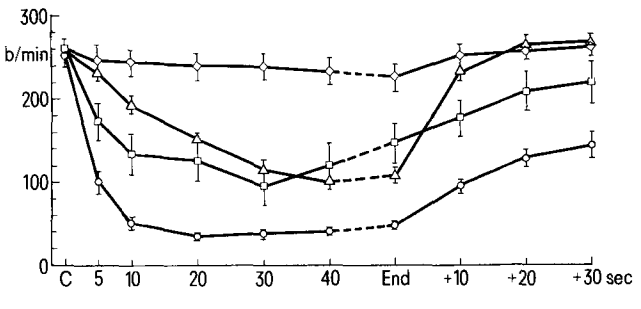

Figure 2. Heart rate responses as a function of time. Responses to smoke before (circles) and after (squares) sino-aortic denervations as well as responses to tracheal occlusion before (triangles) and after (diamonds) denervation. C, prestimulus heart rate. End, end of spontaneous apnea, or release of occlusion.

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