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Postvagal Potentiation of the Chronotropic Effect of Norepinephrine (41951)

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Abstract. Following termination of vagal stimulation, heart rate increases above control (postvagal tachycardia). This phenomenon has been attributed to vagally mediated release of norepinephrine in the sinus node region, although other contributory factors may be important. The possibility that, during the postvagal period, the chronotropic efficacy of norepinephrine is enhanced was investigated. Mongrel dogs ($N = 6$) were pretreated with reserpine in order to minimize postvagal tachycardia and hence allow reliable detection of enhanced responsiveness to norepinephrine. The dogs were then anesthetized with chloralose, autonomically decentralized, and instrumented to record electrocardiogram, aortic blood pressure, and electrograms from right atrium and right ventricle. Thirty-, forty-, or sixty-second infusions of norepinephrine were administered via the sinus node artery. The mean cycle length decrease produced by norepinephrine alone was 95 msec (which corresponds to a heart rate increase of +19.6 bpm). After a 30-sec period of vagal stimulation, norepinephrine infusions produced a cycle length decrease of 139 msec (+32.5 bpm). These results are significant at the $P < 0.05$ level. It is concluded that norepinephrine infusions produce a significantly greater magnitude of tachycardia when administered postvagally. It is proposed that this postvagal potentiation of the chronotropic effect of norepinephrine may contribute to postvagal tachycardia. Indeed, there may be a synergistic relationship between this phenomenon and vagally mediated release of norepinephrine in the mediation of postvagal tachycardia.

Stimulation of the vagus nerve leads to a decrease in sinus node rate while the cessation of stimulation is followed by an increase in sinus rate above the control level (1–3). The latter effect is known as postvagal tachycardia (3). Recently it has been proposed (3, 4) that postvagal tachycardia is mediated by norepinephrine which is liberated from intracardiac chromaffin cells (5, 6) responding to vagally released acetylcholine. However, the presence of such a mechanism does not rule out the coexistence of other mechanisms. For example, it is possible that vagally released acetylcholine might enhance the subsequent responsiveness of cardiac pacemaker cells to norepinephrine. Thus, as an additional mechanism involved in the mediation of postvagal tachycardia, we hypothesized that vagally released acetylcholine, in addition to inducing the release of norepinephrine, might also enhance the effectiveness of this norepinephrine on cardiac pacemaker cells. Hence in our investigation, we sought to determine whether the response of the canine heart to exogenous norepinephrine would be enhanced if the norepinephrine were administered immediately following a short period of vagal stimulation.

Materials and Methods. We used mongrel dogs ($N = 6$) weighing approximately 25 kg. The animals were pretreated with reserpine (0.15–0.20 mg/kg/day) for 2 days prior to the experiment. Prior reserpinization was necessary in order to deplete catecholamine stores, thereby eliminating the vagally mediated release of catecholamines. Such release would obscure the responses to exogenously administered norepinephrine. On the day of the experiment, the animals were premedicated with morphine sulfate (60 mg, im) and anesthetized with α-chloralose (75 mg/kg, iv). Positive pressure ventilation was accomplished using a Harvard respirator via a cuffed endotracheal tube. One femoral vein was catheterized for the maintenance of fluid balance and drug delivery, as was one femoral artery for the measurement of arterial pressure. The contralateral femoral artery was catheterized in order to autologously perfuse the sinus node artery (7). A right thoracotomy was performed at the fourth intercostal space and a pericardial cradle was constructed.

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Bipolar electrograms were recorded from atrial tissue overlying the sinus node and sulcus terminalis, the right atrium and right ventricle. Both vagi were transected in the neck and both stellate ganglia were transected in the thorax.

The sinus node artery was isolated, catheterized, and its distribution verified as previously reported (8). After systemic heparinization, autologous perfusion of this vessel was accomplished using the femoral artery. The adequacy of the reserpinization was confirmed in each animal by the absence of a tachycardic response to two challenges: (1) stimulation of the sympathetic nerves to the heart (ansae subclaviae); and (2) intravenous injection of nitroglycerine in an attempt to provoke a reflex tachycardia in response to systemic hypotension.

Vagal stimuli (30-sec duration, 10 V), with square wave form modulation, at frequencies of 2 to 5 Hz, were delivered to the peripheral end of the right cervical vagus using a bipolar electrode. Frequency of the stimulus was adjusted to produce an approximate doubling of cycle length. Norepinephrine infusions of 30-, 40-, or 60-sec duration, at a flow rate of 2 cc/min, were administered into the sinus node artery. In order to avoid a ceiling effect with regard to tachycardia, concentrations of norepinephrine were titrated to achieve a reproducible but submaximal increase in heart rate. In different animals, norepinephrine concentrations ranged from 0.005 to 0.1 μg/ml, but within each experiment this parameter, as well as all others, was held constant. In addition, titration of norepinephrine concentration was necessary between animals since distribution of the sinus node artery to primary pacemaking cells is variable. Norepinephrine infusions were timed so that the peak tachycardic effect occurred during the 10 sec following the expected peak of postvagal tachycardia, as previously determined in nonreserpinized animals. (This was deemed necessary because a small amount of postvagal tachycardia may persist in animals following reserpinization (3) and it was necessary to preclude the possibility that this remaining postvagal tachycardia would falsely elevate the tachycardic response to postvagally administered norepinephrine.) Therefore, since postvagal tachycardia usually peaks at approximately 18 sec following the termination of vagal stimulation (unpublished observation), norepinephrine infusions were timed so that the peak norepinephrine effect occurred between 18 and 28 sec following vagal stimulation. In animals in which a residual postvagal tachycardia existed which extended into this time window, this magnitude of tachycardia was quantified and subtracted from the norepinephrine induced tachycardia following vagal stimulation.

Results. The mean control cycle length of the animals was 588 ± 13.6 msec (mean ± SEM). The mean decrease in cycle length produced by intrasinus node arterial infusion of norepinephrine alone was 95 ± 28 msec. In contrast, the mean decrease in cycle length produced by equimolar norepinephrine infusions preceded by 30 sec of vagal stimulation was 139 ± 25 msec. These data represent a 47% greater decrease in cycle length in response to norepinephrine following vagal stimulation, compared to control ($P < 0.05$). Expressed in terms of heart rate, the mean control heart rate from these same animals was 102 bpm, the tachycardic response to norepinephrine alone was 19.6 bpm, and the tachycardic response to norepinephrine applied postvagally was 33 bpm. These figures represent a 68.3% increase in the tachycardic response to postvagally applied norepinephrine relative to norepinephrine applied in the control state ($P < 0.05$; control norepinephrine compared to postvagal norepinephrine).

Figure 1 shows a typical tracing of cycle length plotted vs time for vagal stimulation. Note that during the postvagal period there is no decrease in cycle length beyond control thus substantiating that postvagal tachycardia has an adrenergic component which is eliminated in the reserpinized animal. We found in some animals, even with adequate reserpinization, that a trace of postvagal tachycardia persisted which extended into the time period of norepinephrine induced tachycardia. The amount of postvagal tachycardia in these cases was 5 bpm or less, considerably less than the amount typically found in the nonreserpinized animal (i.e., greater than +40 bpm) (2). Furthermore, as stated under the Materials and Methods section, in the cases in which a residual postvagal tachycardia existed, this amount of tachycardia was sub-

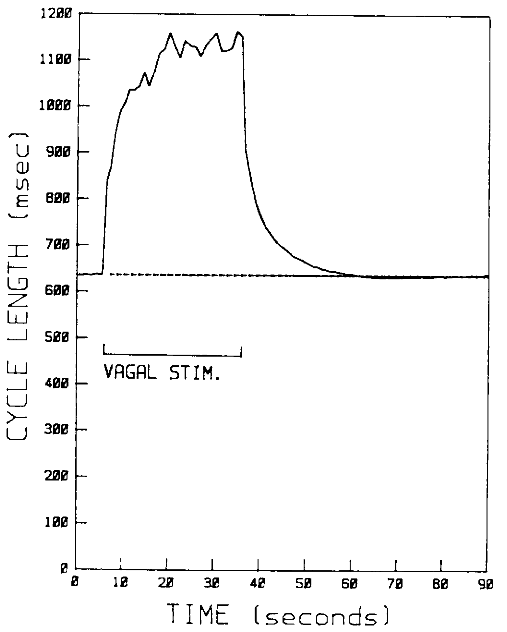

FIG. 1. Cycle length changes induced by stimulation of right cervical vagus nerve after pretreatment with reserpine. Vagal stimulation was applied for 30 sec as indicated.

tracted for the data analysis. Panel A of Fig. 2 shows an example of data generated during a norepinephrine infusion. The control cycle length was 624 msec, and the norepinephrine infusion reduced the cycle length to 490 msec (−134 msec). Panel B, from the same animal, shows a tracing of the cycle length changes induced by an identical infusion of norepinephrine preceded by 30 sec of vagal stimulation. The control cycle length is 643 msec. The upward deflection of the tracing is the vagally induced bradycardia. It is followed by a norepinephrine induced cycle length decrease to 440 msec (−203 msec). The cycle length decreases in these two panels correspond to heart rate increases of 27.5 bpm for norepinephrine alone, and 43.1 bpm for norepinephrine preceded by vagal stimulation.

Figure 3 depicts summary data from all dogs. The dots at the beginning of the scatterplot diagram represent the decrease in cycle length after norepinephrine infusion, and the dots at the ends of the lines reflect the cycle length change after norepinephrine infusion preceded by vagal stimulation. The

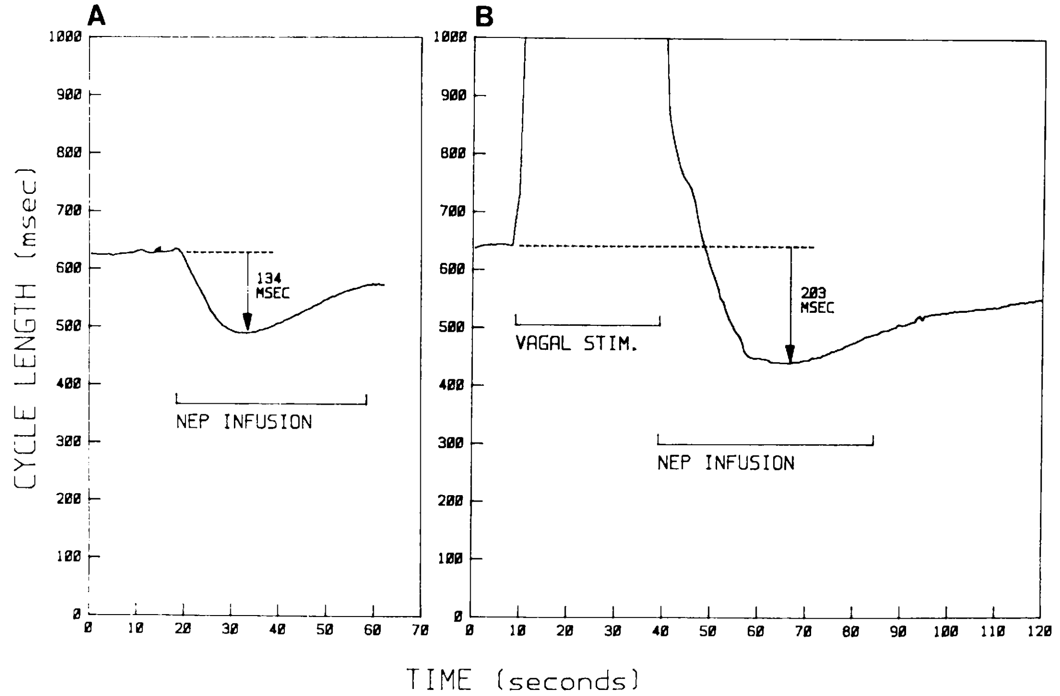

FIG. 2. Cycle length changes induced by norepinephrine infused into canine sinus node artery without (panel A) and with (panel B) prior vagal stimulation. Note that the chronotropic effect of norepinephrine is enhanced by prior vagal stimulation.

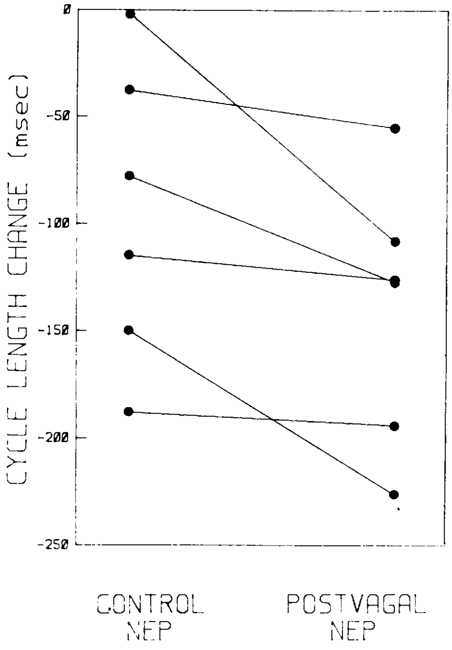

FIG. 3. Scatterplot diagram of cycle length changes induced by norepinephrine infusions without (left) and with (right) prior vagal stimulation. The enhancement of cycle length after vagal stimulation was statistically significant ($P < 0.05$).

lines connect the data points from each dog. In all dogs, norepinephrine produced a greater decrease in cycle length when preceded by vagal stimulation ($P < 0.05$).

Discussion. We conclude from these results that immediately following a short vagal stimulation, there is an increase in the positive chronotropic effectiveness of norepinephrine infused into the sinus node artery of the canine heart. Prior to vagal stimulation, norepinephrine infusion resulted in a mean cycle length decrease of 94.7 msec; however, following vagal stimulation, equimolar norepinephrine infusions resulted in a mean cycle length decrease of 139 msec ($P < 0.05$).

Many investigators have reported that following trains of vagal stimulation, sinus rate increases above the control. Numerous mechanisms have been proposed to explain postvagal tachycardia. For example, it has been suggested that vagally released acetylcholine, acting on a nicotinic receptor, induces the release of catecholamines from intracardiac chromaffin cells (3, 4). However, other mechanisms have also been suggested to account for postvagal tachycardia. It has been proposed that vagally released acetylcholine induces the release of norepinephrine from sympathetic nerve terminals in the sinus node region (9). Others have suggested that stimulation of the vagus nerve concomitantly results in stimulation of sympathetic nerve fibers which run in the vagal nerve ("vagosympathetic") trunk (10). However, the proposal most germane to the present experiments supports the notion that vagally released acetylcholine acts on local chromaffin cells causing release of norepinephrine which in turn acts upon β-adrenergic receptors on cardiac pacemaker cells to induce a tachycardia after termination of vagal stimulation (3, 4). In view of the complex nature of autonomic interactions in the heart (11), the existence of ancillary or synergistic mechanisms must also be considered. One possibility is the modulation of the response to one neurotransmitter by another neurotransmitter. A somewhat similar sort of interaction between two neurotransmitters has been demonstrated elsewhere in the autonomic nervous system. Libet and co-workers (12), working with the superior cervical ganglion of the rabbit, have shown that the administration of dopamine leads to a prolonged change in the responsiveness of postganglionic cells to acetylcholine. These authors suggested that this modulation may consist of long lasting metabolic and/or structural changes induced in the postsynaptic neurons by dopamine (12). Furthermore, they have provided evidence which suggests that cAMP is the intracellular mediator which produces the dopamine enhancing action (13).

Parallel to the data of Libet *et al.*, the present data also suggest that one neurotransmitter is having a persistent modulatory effect on the efficacy of another. Thus, norepinephrine's effect on cardiac cycle length is significantly greater if preceded by a short period of vagal stimulation. Whether the mechanism of the modulation in the sinus node is similar to that in the superior cervical ganglion is open to speculation. Whatever the mechanism, however, postvagal potentiation of the chronotropic effect of norepinephrine represents another of the complex interactions which exist in the autonomic nervous system to mediate its regulatory functions on the organism. Postvagal potentiation may serve as a synergistic adjunct to any of the mechanisms which have been proposed to explain postvagal tachycardia. Although the precise physiologic significance of postvagal tachycardia can only be speculated upon, Vassalle has pointed out that because the consequences of even brief cessation of circulation can be devastating to the organism, it is of paramount importance that sinus node discharge be restored promptly. Indeed, a temporary acceleration of sinus rate would facilitate the quick recovery of the normal circulatory status in an animal whose cardiovascular function has been temporarily compromised (14).

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