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Reflex sympathetic tachycardia during intravenous infusions in chronic spinal cats

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BISHOP, VERNON S., FEDERICO LOMBARDI, ALBERTO MALLIANI, MASSIMO PAGANI, AND GIORGIO RECORDATI. *Reflex sympathetic tachycardia during intravenous infusions in chronic spinal cats.* Am. J. Physiol. 230(1): 25–29. 1976.—The reflex tachycardia elicited by rapid intravenous infusions of a blood substitute was studied in 21 chronic cats with spinal sections at C_8. All animals could breath spontaneously. The day after section the average resting heart rate (HR) and arterial pressure (AP) were 109 beats/min and 98/67 mmHg, respectively. Vagal blockade with atropine (0.5–0.7 mg/kg iv) was performed prior to each infusion, increasing the average HR to 127 beats/min. In 39 infusions in 21 cats the average increase in HR was 10 beats/min (range from −6 to +22 beats/min). A tachycardia was observed in all but five trials, four of which were obtained in two cats that subsequently responded with a tachycardia. In seven animals the neural circuit mediating the response was partially or totally interrupted by section of several thoracic dorsal roots (T_1–T_4 or T_1–T_6) and of the spinal cord at the inferior level of these sections (between T_6 and T_7). The tachycardia response was progressively reduced and finally abolished by these procedures. These experiments indicate that spinal neural mechanisms are likely to contribute to the phenomenon first described by Bainbridge.

Bainbridge reflex; volume loading; heart rate; sympathetic reflexes; atropinized cats; neural control; afferent sympathetic fibers

BAINBRIDGE'S ORIGINAL REPORT IN 1915 (4) describing an increase in heart rate during intravenous infusions of blood or saline has probably generated more controversy than any single neurocirculatory event. Indeed, the expected tachycardia has frequently been elusive in the hands of many investigators and in addition has been often substituted by an unexpected bradycardia (3, 5, 8, 9, 14).

In an attempt to localize the stimulus, balloons have been used to stretch the venous-atrial junctions. This procedure has been reported to produce a consistent reflex tachycardia independent of the initial heart rate (16, 17). However, Edis et al. (10) have shown that either tachycardia or bradycardia can be obtained, depending on the initial heart rate: tachycardia occurred when the initial heart rate was low and bradycardia when the initial rate was high. This latter observation was similar to those previously reported during intravenous infusions in anesthetized animals, in which the type of heart rate response was also influenced by the initial rate (8, 14).

Experimental evidence indicates that during volume loading both an increased sympathetic discharge and a reduced vagal restraint contribute to the reflex tachycardia (13). On the other hand, the afferent neural pathways are still undetermined. Even in the case of a selective stretch of the venous-atrial junctions, the claim that the afferent pathway is restricted to afferent vagal fibers (17) is based on rather indirect experimental procedures.

The anatomical description by Nonidez (22) suggests that the afferent sympathetic fibers are the main sensory innervation of the pulmonary veins. Recently, a variety of cardiovascular sympathetic sensory endings have been identified (1, 2, 7, 12, 21, 28). Stimulation of their afferent cardiac neural fibers can mediate a reflex tachycardia in spinal animals (19) and inhibit the vagal outflow to the heart (27).

In the present study we investigated the possibility of obtaining a reflex tachycardia during intravenous infusions in atropinized, chronic spinal cats, breathing spontaneously. In these animals, in which the cardiocardiac neural control was limited to sympathetic circuits, a consistent tachycardia was observed. Interruption of the afferent limb of the reflex by sectioning the thoracic dorsal roots reduced or abolished the tachycardia.

METHODS

The results were obtained from experiments on 21 cats (3–5 kg). The animals were anesthetized by injection of pentobarbital sodium (35 mg/kg ip). Under aseptic conditions, polyethylene catheters were inserted into a femoral artery and both femoral veins. Through an abdominal incision, a rubber tube (2.5 mm OD) was introduced in the urinary bladder. A spinal section was performed at the level of C_8, after which the animals could breath spontaneously. The wounds were infiltrated with Xylocaine (1%). Antibiotics were administered intramuscularly. Animals then were placed in a thermostatic cage at 38°C. After about 24 h all animals were moving their head in response to clicks and could swallow liquids. Their body temperature was normal. Experimental trials were then started, one every day (range 1–4 days).

At the beginning of each trial one venous catheter

was positioned near the right atrium and the other venous catheter was placed into the right atrium. Right atrial pressure, arterial pressure, electrocardiogram (ECG), and heart rate were registered on a Grass P7 polygraph and simultaneously fed into a tape recorder (Hewlett-Packard 3907C) as previously described (18, 21, 27). Vagal efferent blockade was performed with atropine (0.5–0.7 mg/kg iv). This procedure was used since surgical vagotomy seriously impairs the respiratory function of chronic spinal animals. Isotonic solution of NaCl or 5% solution of xylitol (Solutran X, Pierrel) heated to 37.5°C was infused through the catheter positioned near the right atrium. Infusions (50–150 ml) were given over a period of 2–5 min until the heart rate had reached a maximum level, which was not exceeded despite further rises in right atrial pressure. The rate of the infusion was adjusted to ensure a steady rise in right atrial pressure (13). Values for right atrial pressure and arterial pressure were determined when the heart rate had reached a maximum level.

After the first infusion, two animals were lightly anesthetized with pentobarbital sodium intravenously. The dorsal roots from T_1 to T_4 were exposed and cut.

In a separate group of five animals the dorsal roots (T_1–T_4 in one cat, T_1–T_6 in four cats) were exposed but not cut; these five animals are referred to as sham preparations as the first infusion was performed with the dorsal roots intact. Subsequently, under light pentobarbital anesthesia, the exposed roots of the same animals were cut. In three of the four cats in which dorsal roots T_1–T_6 were cut, the spinal cord was also simultaneously sectioned between T_6 and T_7. Infusions after each of these procedures began at least 24 h after each surgical intervention.

Data were averaged for each cat under a given experimental condition. The average response for all animals was based on the individual averages of the trials in each cat (see Tables 1 and 2).

No animals showed signs of infection. Cats were usually drowsy during the first 12 h after surgery and became progressively more and more alert. Repeated measurements of P_{O_2}, P_{CO_2}, and pH before and after infusion were always in the physiological range (see RESULTS). After four trials had been performed or as soon as an animal started showing signs of discomfort (restlessness, continuous mewing) or deterioration (systolic arterial blood pressure below 90 mmHg) they were sacrificed by intravenous injection of pentobarbital sodium. The completeness of the spinal and dorsal root sections was then verified.

RESULTS

Right atrial pressure (RAP) and arterial pressure (AP) after spinal section were similar to the normal values reported for cats (11), but the heart rate (HR) was markedly lower (Table 1, before atropine). Vagal blockade with atropine increased the HR (Table 1, after atropine). However, the maximum HR obtained during vagal blockade was much lower than that reported for intact atropinized cats (11). These differences in HR can be attributed to the lower sympathetic activity resulting from the spinal section. Vagal blockade with atropine also stabilized the HR, reducing the spontaneous oscillations to less than 3 beats/min.

During the infusion that followed atropinization the mean HR increased to 136.3 beats/min at a RAP of 12.6 cmH_2O. This corresponded to a mean increase of 9.6 beats/min (Table 1, infusion). In 39 infusions performed in 21 cats a tachycardia was observed in all but five trials (Fig. 1). In three trials a slight bradycardia was present. In two of these the bradycardia (−6, −5 beats/min) was obtained during the 1st and 2nd day postoperative from an animal that responded with a tachycardia (+8 beats/min) on the 3rd day. The third negative response (−2 beats/min) was recorded in an animal that deteriorated quickly and was sacrificed on the 2nd day. Finally, the two trials in which the HR did not change were obtained from an animal that on the final trial had a tachycardia of +7 beats/min.

The data shown in Fig. 1 indicate that peak HR response was not correlated with the initial HR. This was also supported by observations in individual animals in which initial HR was not indicative of the response.

Figure 2*A* shows an analogue recording of HR, RAP, AP, and ECG during an infusion. A parallel increase in HR and RAP is well evident. When the maximum increase in HR was reached it remained constant despite further elevations in pressure. A similar relationship between RAP and HR was present during the descending part of the curves. Arterial pressure and pulse pressure were only slightly increased during infusions (Ta-

TABLE 1. *Effects of atropine and intravenous infusions in chronic spinal cats*

	Heart Rate, beats/min	Right Atrial Pressure, cmH_2O	Arterial Blood Pressure, mmHg
Before atropine	109.0 ± 3.7	−0.3 ± 0.2	98/67 ± 3/2
After atropine	126.7* ± 4.4	0.2 ± 0.3	104/71 ± 3/3
Infusion	136.3* ± 4.4	12.6* ± 0.7	108/72 ± 3/2

All values are means ± SE of average responses of 21 cats. Values before and after atropine and values after atropine and during infusion were compared and statistical significance was determined by Student *t* test. * $P < 0.001$.

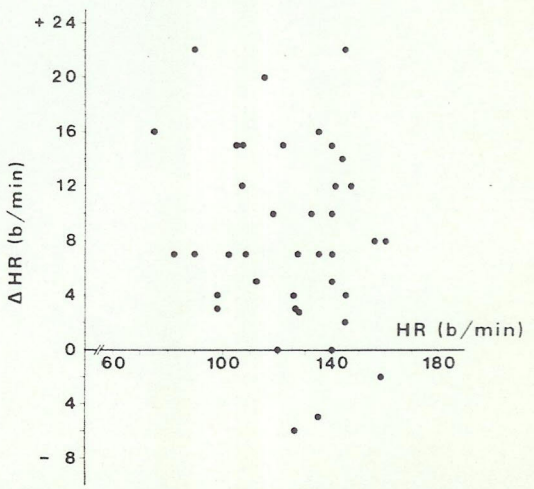

FIG. 1. Changes in heart rate (Δ HR) versus initial rate (HR) in beats/min in 39 infusions in 21 cats.

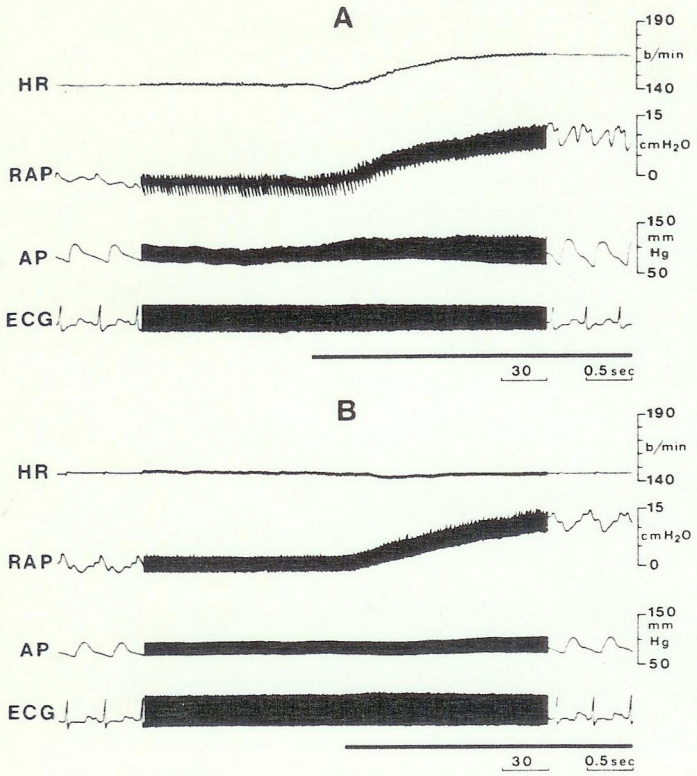

FIG. 2. Analogue recording of heart rate (HR), right atrial pressure (RAP), arterial pressure (AP), and electrocardiogram (ECG) in chronic spinal cat in control conditions and during intravenous infusions. *A*, sham preparation (dorsal roots T_1–T_6 isolated but not cut); *B*, after section of dorsal roots T_1–T_6 and of spinal cord between T_6 and T_7. Recordings in *B* were obtained 36 h after those shown in *A*. Infusions indicated by bars.

ble 1). In the 16 infusions during which a tachycardia of 10 beats/min or more (Fig. 1) was obtained, the threshold (ΔRAP) for the beginning of the response corresponded to an increase of 2.3 ± 0.2 (SE) cmH_2O.

The depth and rate of respiration were not clearly affected by the infusion and thus no relationship between respiration and HR was discerned. Previous studies have demonstrated that stimulation of afferent cardiac sympathetic fibers produces tachycardia independent of changes in respiration (19).

The Po_2, Pco_2, and pH in four animals averaged 93 mmHg (range 92–94), 33 mmHg (range 30–36), and 7.42 (range 7.39–7.44), respectively, in the control resting state. Immediately after the infusion the Po_2, Pco_2, and pH were 92 mmHg (range 90–94), 32 mmHg (range 30–34), and 7.38 (range 7.35–7.40), respectively, suggesting that the acute volume loading did not alter appreciably the respiratory state of the animal.

Reflex nature of response. The afferent limb of the neural circuit mediating the HR response was interrupted in seven animals by various interventions (five of these animals were those described as sham preparations in METHODS).

In three of these cats the dorsal roots were cut from T_1 to T_4. The tachycardia response was decreased, respectively, from a control of 20 beats/min to 6, 0, and 6 beats/min (3 trials); from a control of 15 beats/min to 5 beats/min; and from a control of 15 beats/min to 4 beats/min. In one animal the dorsal roots were cut from T_1 to T_6 and the tachycardia response was reduced from a control of 16 beats/min to 2 beats/min.

Since sympathetic sensory fibers with cardiovascular receptors are also likely to project to spinal segments lower than T_6 (1), in the three remaining animals the section of the dorsal roots T_1–T_6 was associated with an additional interruption of the spinal cord between T_6 and T_7. In these animals the tachycardia responses (Δ HR 22, 15, and 14) were abolished (five trials).

The five sham preparations proved that the disappearance of the tachycardia was not due to the surgical trauma since these animals responded to the infusion with tachycardia (Δ HR 22, 16, 15, 15, 14) that was reduced or abolished after deafferentation (Δ HR 0, 2, 5, 0, 0; $P < 0.001$).

One of these latter experiments is shown in Fig. 2. In spite of similar changes in RAP and AP, the heart rate response was abolished after the surgical intervention (compare Fig. 2*A*, sham preparation, with Fig. 2*B*, same animal after section of the dorsal roots T_1–T_6 and of the spinal cord between T_6 and T_7).

Table 2 summarizes the effects of the various interventions designed to reduce or abolish the reflex response in the seven animals.

DISCUSSION

The present experiments with the use of changes in preload as a stimulus add physiological significance to those in which reflex tachycardia was obtained by electrical stimulation of afferent cardiac sympathetic fibers (19). In both studies the maximum and mean increases in heart rate were similar and comparable with the tachycardia reported by Jones (14) during acute volume loading in intact anesthetized cats.

The disappearance of the heart rate response after selective interruption of the afferent neural pathway establishes its reflex nature and in addition suggests that afferents from the heart may be involved (15). This intervention did not alter the efferent discharge to the heart as illustrated by the basal heart rate before and after deafferentation (Fig. 2 and Table 2).

The fact that tachycardia was not completely abolished by a restricted deafferentation (T_1–T_4) is not surprising. This type of surgical intervention probably did not eliminate all central connections of afferent cardiac sympathetic fibers (15). In addition, the reflex response might well be partially initiated by vascular receptors

TABLE 2. *Effects of intravenous infusions in chronic spinal cats before and after deafferentation*

	Heart Rate, beats/min		Right Atrial Pressure, cmH_2O		Arterial Blood Pressure, mmHg	
	Before	After	Before	After	Before	After
Before atropine	113.6 ±4.5	124.8 ±4.6	−0.5 ±0.4	1.4 ±0.4	101/68 ±3/3	101/66 ±3/3
After atropine	129.4* ±5.9	136.1* ±4.2	−0.6 ±0.4	1.4 ±0.4	107/74 ±4/3	102/67 ±2/2
Infusion	146.1* ±6.1	138.0 ±3.9	13.3* ±1.4	15* ±0.6	107/71 ±5/5	102/66 ±5/3

All values are means ± SE of average responses of 7 cats before and after various procedures of deafferentation (see METHODS and RESULTS). Statistical evaluation of results as in Table 1. * $P < 0.001$.

projecting to other segments of the spinal cord (1, 18). For instance, distension of the thoracic aorta caused tachycardia (18), initiated by sensory receptors that probably have their nerve fibers running through dorsal roots lower than T_4. It seems unlikely that direct stretch of the sinoatrial node contributed to the observed heart rate response in our experimental conditions, which were substantially different from those used by others (6, 25).

Since the magnitude of response was not dependent on the initial heart rate, other factors such as the spinal section, recovery from surgery, and anesthesia undoubtedly affected the response. In addition, it is important to recall that, although spinal sympathetic reflexes appear to be mainly excitatory when measured in terms of target-organ function (18–20, 26), both excitation and inhibition can be detected by electrophysiological techniques (23).

We have shown in the present study that when the innervation to the heart is limited to spinal circuits, tachycardia can be initiated by stimulating stretch receptors located in or near the cardiopulmonary region. The importance of this neural circuit in the control of heart rate in the intact animal is unknown. A previous study has shown that electrical excitation of afferent cardiac sympathetic fibers leads to an increase in the impulse discharge of cardiac sympathetic efferent fibers and a reduction in the discharge of cardiac vagal efferent fibers. Electrical stimulation of vagal afferent fibers produces the opposite effects (27).

Thus, in intact animals, stimuli exciting the various types of vagal (24) and sympathetic (7, 12, 21, 28) cardiac mechanoreceptors may reflexly modify the heart rate through sympathosympathetic, sympathovagal, vagosympathetic, and vagovagal circuits. Since most of the vagal and sympathetic cardiac receptors appear to increase their impulse activity during intravenous infusions, it seems likely that an augmented preload activates all of the above circuits. Furthermore, each of these circuits has to be considered as a complex entity with multiple effects at the central level. This complexity is easily illustrated by the effects of anesthesia on the reflex. Different anesthesias may change the reflex tachycardia from a consistent response in unanesthetized animals (13) to one that may yield either tachycardia or bradycardia depending on initial heart rate (8, 14).

In conclusion, although our present understanding of the neural control of heart rate makes it impossible to predict the relative contribution of each circuit to the reflex tachycardia described by Bainbridge (4), the danger of overlooking afferent sympathetic paths is clearly evident.

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