Activity patterns of cardiac vagal motoneurons in rat nucleus ambiguus

N. Rentero, A. Cividjian, D. Trevaks, J. M. Pequignot, L. Quintin, and R. M. McAllen. Activity patterns of cardiac vagal motoneurons in rat nucleus ambiguus. Am J Physiol Regul Integr Comp Physiol 283: R1327–R1334, 2002. First published August 22, 2002; 10.1152/ajpregu.00271.2002.—Extracellular recordings were made in the right nucleus ambiguus of urethane-anesthetized rats from 33 neurons that were activated at constant latency from the craniovagal branch. Their calculated conduction velocities were in the B-fiber range (1.6–13.8 m/s, median 4.2), and most (22/33) were silent. Active units were confirmed as cardiac vagal motoneurons (CVM) by the collision test for antidromic activation and by the presence of cardiac rhythmicity in their resting discharge (9/9). Brief arterial pressure rises of 20–50 mmHg increased the activity in five of five CVM by 0.1 spikes/s; they also recruited activity in two of four previously silent cardiac branch-projecting neurons. CVM firing was modulated by the central respiratory cycle, showing peak activity during inspiration (8/8). Rat CVM thus show firing properties similar to those in other species, but their respiratory pattern is distinct. These findings are discussed in relation to mechanisms of respiratory sinus arrhythmia.

The parasympathetic supply to the heart is responsible for beat-to-beat changes in heart rate, also called heart rate variability. Although vagal actions on heart rate variability have been studied extensively at a peripheral level, there is little direct information about the behavior of the neural outflow responsible [cardiac vagal motoneurons (CVM)]. This is especially true of the rat, the animal model most favored for invasive studies on the neural control of autonomic function (e.g., Refs. 2, 10, 28).

The limited direct information on the activity patterns of CVM comes mostly from recordings of their cell bodies in the cat (7, 22, 23) or their efferent fibers in cat (17) and dog (11, 15, 33). The limited availability of such information may be linked to the difficulty (25) in obtaining in vivo single-unit recordings from CVM, as they are scattered in the external formation of the nucleus ambiguus (NA; ventrolateral NA). The first goal of the present study was to address the feasibility of using carbon fiber electrodes (18) to enhance the ability to record such scattered neurons.

Studies of the CVM spontaneous activity in rats have focused only on the subset with unmyelinated C-fibers (13), which originate from the dorsal vagal motor nucleus (13, 31) and are viewed as linked to neurogenic bradycardia. Their actions on the heart, although measurable, are weaker than those of myelinated B-fibers (12, 30). The predominant action of the vagus on heart rate is due to myelinated B-fibers (12, 21, 27, 30), which originate from the NA and are linked to genesis of the respiratory sinus arrhythmia. The present paper thus concentrates on what may be considered the major cardioinhibitory neural pathway in rats. The activity patterns of rat CVM with B-fiber axons are unknown. As a postinspiratory pattern of activity has been observed in cats (7), the second goal was to observe whether the respiratory patterning in rats was similar. Finally, as these neurons presumably provide inhibitory control of heart rate in response to beat-by-beat pressure rises, the third goal was to measure their barosensitivity.

Materials and Methods

Preparation. Experiments were performed in accordance with the American Physiological Society’s “Guiding Principles For The Care And Use Of Animals” and were approved by the Animal Research Ethics Committee of the Howard Florey Institute. Experiments were performed on male Sprague-Dawley rats (300–600 g), which were first anesthetized with methohexitone (80 mg/kg ip; Brietal, Lilly) and given a tracheotomy. They were then mechanically ventilated with 2% isoflurane in oxygen throughout the surgical preparation. Rectal temperature was maintained close to 37°C with a warming blanket. The right femoral artery and vein were catheterized for monitoring blood pressure and injection of anesthetic or drugs, respectively. A slow infusion (<3 ml/h) of normal saline through the arterial catheter was used to prevent clotting and to preserve the animal’s circulatory condition (34). The bladder was cannulated suprapubically and drained. In most animals, an inflatable occlusion

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cuff was introduced through a left lateral thoracotomy and positioned around the lower thoracic aorta; the arterial catheter tip was advanced to lie cranial to this level.

The right cervical vagus and right phrenic nerve were exposed via a lateral incision in the neck. The phrenic nerve was cut distally and desheathed. The cervical vagus was mobilized but left intact. The second right intercostal space was opened and retracted. The cranioventral cardiac branch was identified anatomically by its course from the thoracic vagus, over the trachea toward the heart. This nerve is small and quite variable anatomically. Its identity was confirmed in each case by the bradycardia following stimulation at 20–50 Hz with 2–7 V, 0.2-ms pulses, through a pair of fine stainless steel wires placed against it (21, 29) (Fig. 1A). A small sheet of black polyethylene was inserted beneath the branch to insulate it from the underlying tissue and an implantable electrode was then placed on it. The implanted electrode was made from a pair of Teflon-coated 125-μm silver wires, whose bared tips were wrapped around the cardiac branch. The wires were secured to the trachea with sutures and cyanoacrylate adhesive, while the branch and electrodes were embedded in silicon gel (Wacker). The main thoracic vagus was crushed below the level of the branch. To test that the cardiac branch of the vagus remained functionally intact, it was stimulated again at 20–50 Hz through the implanted electrodes. The cervical vagus was also stimulated at 20–50 Hz with 1–10 V, 0.2-ms pulses. If either failed to give a strong bradycardia, the experiment was discontinued.

The rat was placed in a stereotaxic frame with a clamp fixed to an upper thoracic spine. The head was ventroflexed so that the caudal medulla and upper vertebral base lay in the horizontal plane, under mild tension. The medulla was exposed by opening the dorsal neck muscles and part of the occipital bone. The atlanto-occipital membrane and dura were incised and retracted.

Once surgery was complete, anesthesia was gradually switched from isoflurane to urethane (1–1.5 g/kg iv), over ~30 min. During recordings, the animal was paralyzed with either pancuronium or vecuronium (0.8-mg iv bolus doses). This was done only once a stable plane of anesthesia had been established, sufficient to abolish withdrawal reflexes. Paralysis was allowed to wear off between doses so that the adequacy of anesthesia could be checked each time before repeating the paralysis. If necessary, additional urethane (10–20% of original dose) was given to reestablish deep anesthesia. At the end of the experiments, rats were killed with an overdose of pentobarbital sodium (120 mg/kg iv).

Recordings. The lateral neck incision was held open with sutures, and paired platinum wire hook electrodes were placed under the intact cervical vagus for stimulation and under the central end of the cut phrenic nerve (for recording). Both were positioned clear of the underlying tissues and covered with warmed petroleum jelly. The signal from the phrenic activity was recorded differentially, amplified (×10,000) and filtered (150–3,000 Hz; Neurolog, Digitimer, Welwyn, UK), viewed on an oscilloscope, and recorded on magnetic tape. The signal was fed through a level discriminator that generated digital pulses that were fed into the computer-based analysis system (“1401 Plus” interface and Spike2 analysis program, Cambridge Electronic Design, Cambridge, UK). The signal was also played through a loudspeaker.

The ventilation was adjusted to maintain phrenic activity (~3 ml tidal vol, 60–70 inflations/min), which was usually entrained by the ventilatory cycle, firing in antiphase to lung inflation. The phrenic response to stimulation of the cardiac branch was also used to assess stimulus spread. The cardiac branch electrode was stimulated at 100 Hz at an increasing voltage. When this caused a measurable inhibition of phrenic nerve activity (typically at 6–10 V), the stimulus was considered to have spread to pulmonary stretch afferents in the thoracic vagus. Stimulation of the cardiac branch were thereafter kept below that level.

Carbon fiber electrodes were made by first prepulling a glass capillary tube to form a central isthmus 1 cm long, using a low heating current. A 6-μm-diameter carbon fiber was inserted into the capillary, which was then pulled onto the fiber, using higher heating current. This separated the
two halves and sealed the fiber into the capillary. The protruding fiber was then shortened to 10–15 μm and treated to reduce the background noise (18). Electrical conduction to the fiber was made by filling the shaft of the electrode with 2 M NaCl, from which a silver wire connected it to the preamplifier (Neurolog). On a few occasions, glass micropipettes (2-to 3-μm-tip diameter) filled with 2 M NaCl were used instead.

Unit activity was recorded differentially between the carbon fiber electrode and a reference silver wire on the medullary surface. The signal was amplified (×10,000) and filtered (300–3,000 Hz) before being displayed on an oscilloscope and stored, along with phrenic activity, blood pressure, stimulus, and event markers, on magnetic tape. Spike discrimination was performed either on-line with a time-amplitude window discriminator and/or off-line from the analog signal (digitized at 10 or 20 kHz and stored on computer) by using the spike recognition facility of the Spike2 program. The accuracy of discrimination was extensively checked manually and edited to eliminate mistakes. Only the cases where single-unit discrimination was fully maintained were included in the analysis where discrimination was uncertain or the test was not completed were discarded. Thus, not all neurons were subjected to all tests. The numbers tested and responding are given in each case.

Procedure. Electrodes were inserted via the dorsal surface of the medulla, 1.5–2.2 mm to the right of the midline near the calamus scriptorius. Penetrations were angled ~20° rostrally to record from the medulla at the rostrocaudal level of the area postrema. The semicompact formation of the right NA was first located by its antidromic field potential in response to low-voltage stimulation (0.5–3 V, 0.1-ms pulses) of laryngeal motor axons in the cervical vagus (Fig. 1B; Ref. 32). The site of the maximum field potential was noted. In the example shown in Fig. 1, A and B, that site was marked by expelling Pontamine blue dye from the pipette and later localized histologically on 50-μm frozen sections of the formalin-fixed medulla, counterstained with Neutral Red (36). Single-unit recordings were then made from the external formation of the NA (9), a region ventral and ventrolateral to that site (the approximate area indicated by the white oval in Fig. 1A). CVM were sought by their antidromic response to stimulation of the craniovagal cardiac branch, using a search stimulus of 1.5–6 V, 0.2 ms delivered at 1.5 Hz.

Analysis. Interspike interval histograms of unit activity were constructed by the Spike2 program, using 20-or 50-ms time bins. Peristimulus histograms of unit or phrenic activity were also constructed, using trigger signals derived from the systolic peak of arterial pressure (cardiac cycle histograms) or from phrenic nerve activity (respiratory histograms). Cardiac cycle histograms used 20-ms bins, extended −300 to +300 ms from the trigger point and were smoothed by three-point averaging before assessment. The arterial pulse wave was averaged with respect to the same trigger pulses over the same period. Cardiac rhythmicity was considered to be present if the histogram showed regular peaks and troughs in spike count consistently linked to the averaged pulse wave over three cardiac cycles. Its magnitude was defined by the peak-to-peak cyclic fluctuation, expressed as a percentage of the mean bin count.

Respiratory histograms used 50-ms time bins and extended from 000 to 1500 ms after the abrupt decline in phrenic activity that defines the end of the central inspiratory phase. They were not smoothed. Background medullary spike activity was used as a substitute on two occasions when the phrenic nerve was not recorded. That background activity was most likely inspiratory because 1) this was normally the case in other experiments when this could be verified directly by a record of phrenic activity; 2) it showed a time profile of activity indistinguishable from the phrenic profile; and 3) it had the same phase relation as phrenic activity to the ventilatory fluctuations in arterial pressure. The significance of respiratory modulation was tested in the grouped data by comparing both the peak and mean activity of each CVM during the central inspiratory phase (first half of histogram) with that during the central expiratory phase (second half of histogram). The data were not normally distributed, so the Wilcoxon signed rank test was used to assess significance.

The barosensitivity of neurons was tested by gently inflating the periaortic balloon with water from an attached 1-ml syringe. The relevant sections of record were analyzed by using the computer to calculate mean arterial pressure and mean unit firing rate (digitally filtered with a 1-s time constant). Mean 1-s values of each were extracted from the relevant sections of the record and plotted against each other. Linear regression was then used to measure pressure-activity relations and test the significance of the relation of firing rate to blood pressure (Microsoft Excel).

RESULTS

Extracellular recordings from NA. The semicompact formation of the NA was first located by the maximum antidromic field potential to stimulating the cervical vagus (MATERIALS AND METHODS; Fig. 1, A and B). From a region ventral and ventrolateral to that locus (circled in Fig. 1A), we then sought single units that responded antidromically to stimulation of the right craniovagal cardiac branch at an appropriate threshold (see MATERIALS AND METHODS). Typically, one or two small, constant-latency potentials were then found during the course of penetrations in the designated region. It was often necessary to track the putative antidromic unit response over several successive penetrations to optimize the signal. An on-line signal averager was helpful for this purpose, and the low intrinsic noise of carbon fiber electrodes was an advantage. Individual units were usually detectable (with or without signal averaging) in penetrations spaced across 200–300 μm. Many respiratory neurons (mostly inspiratory) were also encountered in the region.

Antidromic activation of neurons. Thirty-three single units were activated at constant latency on stimulation of the cardiac branch at an appropriate voltage (see MATERIALS AND METHODS). We refer to these units as presumed CVM. Most (22/33) showed little or no resting activity, so the antidromic nature of their response could not be checked by the collision test. When tested, 15/15 of these inactive neurons showed constant-latency, double-spike responses to paired vagal stimuli, provided these were separated by more than a defined refractory period (range 1.25–9 ms), suggesting antidromic activation.

Antidromic activation from the cardiac branch was confirmed by the collision test in 10/10 presumed CVM with spontaneous activity (Fig. 1D). This, in combination with evidence of barosensitivity (including cardiac rhythmicity), was taken as a full identification of these neurons as CVM. In agreement with previous work (31), the axonal conduction velocities of both presumed
and positively identified CVM were in the B-fiber range (1.6–13.8 m/s; Fig. 2A).

**Patterns of spontaneous activity.** The activity of nine positively identified CVM was studied in detail. Under basal conditions, these neurons fired at rates between 0.4 and 8 spikes/s (median 1.6). Four examples of their interspike interval histogram patterns are shown in Fig. 3, A–D. The fastest firing CVM (Fig. 3A) showed a symmetrical distribution about its modal interval, indicating regular firing. All others showed skewed, Poisson-like distributions, indicating irregular firing. Superimposed on these distributions were subsidiary peaks of variable dominance, corresponding to the cardiac and respiratory cycles (dotted lines) and multiples thereof (indicated by arrows: Fig. 3, B–D).

When peri-event histograms of their activity were triggered by the arterial pulse wave, 9/9 CVM showed histograms with clear peaks and troughs of cardiac periodicity over a span of three cardiac cycles. The time relation of peak CVM activity to the pulse wave was studied in eight cases by measuring its latency from the start of the preceding systolic pressure rise (soon after which baroreceptor afferent activity would have begun). Values from 46 to 109 ms (median 81 ms) were obtained for different CVM. Two CVM recorded from the same animal gave similar values (65 and 70 ms). Figure 2 shows examples of short and longer latency responses (Fig. 2, B and C, respectively). At resting blood pressure, the peak-to-peak cardiac modulation of CVM was 40–120% (median 75%) of their mean activity.

![Fig. 2. Conduction velocity and cardiac cycle-triggered histograms. A: histogram of conduction velocities of confirmed CVM (black) and presumed CVM (open bars). Data from 2 presumed CVM activated by BP rises are hatched. B and C: pulse-triggered histograms of 2 CVM (top traces, data subjected to 3-point digital smoothing) and averaged arterial pressure. Arrows indicate the trigger time. Ordinates indicate spikes per 20-ms bin and BP. B: 1,403 triggers; C: 2,044 triggers.](http://ajpregu.physiology.org/)

In histograms triggered by the phrenic nerve discharge, 6/6 CVM showed evidence of modulation over the respiratory cycle. This was also true for two further CVM whose activity was compared with the background medullary spike activity of presumed inspiratory neurons (when phrenic nerve activity was not recorded). Central respiratory activity was normally locked 1:1 with the ventilator, but on occasions when this was not so, CVM activity followed central respiratory drive. Two examples are shown in Fig. 4: one is taken from an animal where the central respiratory cycle was locked in a 1:2 ratio to the ventilatory cycle (Fig. 4A); the second case was recorded in a different rat from a section of record when the ventilator was turned off (Fig. 4B). In both cases, the CVM activity was clearly modulated by the central respiratory cycle.

By contrast with other species (5, 11, 22), peak activity in these rat CVM occurred in the central inspiratory, rather than the expiratory or postinspiratory phase. This issue was examined critically in peri-event histograms triggered by the rapid decline in phrenic (or background medullary spike) activity at the end of inspiration. These respiratory cycle histograms are shown for all of the eight CVM studied in Fig. 5, A–H (those marked by an * were triggered from background medullary spike activity). The degree of respiratory modulation ranged from a completely cyclic pattern (Fig. 5, A and B) to a mild postinspiratory dip (Fig. 5, G and H). Maximum activity always occurred during the central inspiratory phase and was generally in decline before the phrenic discharge fell. In two cases (Fig. 5, C and F), the inspiratory peak appeared to continue into the early postinspiratory period. For all eight CVM, both mean and peak activities in the inspiratory phase were greater than those in the expiratory phase (P = 0.008 in each case, Wilcoxon signed rank test). The
mean normalized activity of eight CVM is shown in relation to the profile of central inspiratory drive and mean blood pressure in Fig. 5I. There was minimal change in blood pressure over the respiratory cycle in these open-chest, ventilated animals; it was highest during the central expiratory phase.

Responses to baroreceptor stimulation. Recordings from five CVM were successfully held, while arterial pressure was raised 20–50 mmHg by constricting the aorta with a pneumatic cuff. In all cases, this increased CVM activity (e.g., Fig. 6, A and B). Linear regression analysis was used to measure the relation of firing rate to blood pressure (Fig. 6B), which was highly significant in all cases ($P < 0.001$). The mean increase was $0.1 \pm 0.02$ spikes$^{-1} \cdot \text{mmHg}^{-1}$ from a resting level of $3.8 \pm 1.2$ spikes/s at a mean blood pressure of $97 \pm 1.5$ mmHg ($n = 5$). The regression lines for the blood pressure-firing rate relations of the five CVM satisfactorily tested are shown in Fig. 6C. The dotted line estimates their “population mean” activity. Four presumed CVM without resting activity were also tested, and two of these were activated by the cuff-induced rise in blood pressure (data not shown).

Fig. 4. CVM activity follows central respiratory drive (CRD). Respiratory cycle histograms taken from situations when CRD was not entrained 1:1 to the ventilator. A: background medullary spike activity, an index of CRD, was locked 1:2 with the ventilator (whose period length is shown). B: taken from a different animal while the ventilator was disconnected. Histograms were triggered by the rapid decline in phrenic (B) or central respiratory neuron (A) activity at the end of inspiration. Top traces: CVM spike activity (counts per 50-ms time bin); averaged BP; CRD, counts per 50-ms time bin of multunit central respiratory neuron activity or phrenic nerve discharge. Numbers of triggers: A, 246; B, 47.

Fig. 5. Respiratory cycle-triggered histograms. A-H: respiratory cycle histograms of 8 CVM, triggered (at vertical dotted line) by the rapid decline in phrenic (Phr; B-F, H) or central respiratory activity (A, G, *). Histograms cover 0.5 s before and after the trigger, in 50-ms time bins. I: grouped data, showing (from above) mean BP ($n = 7$), normalized mean bin counts of CVM taken from histograms A-H (CVM, $n = 8$), mean normalized phrenic or central respiratory activity (Phr, $n = 8$), both plotted in arbitrary units (A.U.) but with the baseline set at zero activity. In all cases, the dotted line indicates the trigger time, error bars give SE, and zero levels are set at the baseline. Numbers of triggers: A, 680; B, 807; C, 19; D, 294; E, 875; F, 401; G, 221; and H, 213.
Efferent B-fibers mediate the major component of vagal cardioinhibitory actions in rats (12, 30) and in other mammalian species (11, 27). They originate from cells in the external formation of the NA and a few scattered cells dorsomedial to that region (9, 29, 31).

The animals received continuous volume infusion via the arterial line to prevent circulatory deterioration and metabolic acidosis over time (34). End-tidal CO$_2$ was monitored to avoid any respiratory acidosis. We did not check blood gases in these experiments. We have done so in other experimental series using equivalent preparations and conditions (37, 38). We infer that the condition of the present animals was stable and such that they generated a normal pattern of central respiratory drive.

This study is the first to describe the ongoing activity patterns of antidromically identified CVM in the rat NA. These neurons were identified by the same methods as used in previous studies on the cat: antidromic activation with appropriate threshold and latency from the cardiac branch, plus evidence of barosensitivity (23). These criteria eliminate both interneurons and other types of vagal motoneuron (e.g., bronchomotor or esophageal) that might have been recorded, so there is little doubt about their identity. Two previous studies on the activity of neurons in the NA of rats considered that recording site and barosensitivity were sufficient criteria to identify neurons as CVM (1, 24). Although we cannot exclude this possibility, our own and others’ experience suggests that CVM are sparsely distributed, and we believe that they would rarely have been isolated by random sampling of neurons in the area. The alternative possibility is that those cells were barosensitive interneurons; their firing pattern in relation to the respiratory cycle was not studied. The one previous investigation of antidromically identified CVM in the rat NA reported on their location and conduction velocity, but not their ongoing activity (31). The present findings confirm and extend that work. The CVM identified in the present study were on the right side of the medulla and projected down the right vagus; their primary function was most likely to have been to regulate sinus rate rather than atrioventricular conduction (20).

With the exception of respiratory patterning, the properties of rat CVM found here agree well with those described for the homologous neurons in cats (21–23).
as well as data from fiber recordings in cats and dogs (7, 14, 15, 17, 33). Only a minority of CVM appeared to show tonic activity under experimental conditions; ~30% in the present sample compared with 22% in cats (23). This low percentage may be due to the effects of general anesthesia and surgical trauma. When present, activity was generally slow (<10 Hz; Ref. 15). CVM are excited by baroreceptors, whose rhythmic input links their firing to the cardiac cycle. In response to a rise in blood pressure, CVM population activity is increased both by active cells firing faster and by recruitment of previously silent neurons (this paper and Ref. 17). The present data have been used to reconstruct the pressure-activity relations for this outflow.

As in other species, rat CVM activity is linked to the central respiratory cycle. But in contrast to the cat, dog, and (by inference) human (5, 11, 22), we found that rat CVM activity is greatest during inspiration. Why this should be so is not clear. It might be linked to the “reversed” (compared with other species) respiratory pattern of sympathetic nerve activity to skeletal muscle, which is inspiratory in cats but expiratory in rats (8). Interesting new findings that may throw light on the basis of the respiratory pattern of rat CVM activity have been made by Mendelowitz and colleagues (10, 25, 26). They showed by anatomic methods, including tracing with pseudorabies virus, that rat CVM are innervated by axon collateral branches of superior laryngeal motoneurons (10). Work from the same laboratory showed that CVM (prelabeled with a fluorescent retrograde tracer and recorded in a slice preparation) were directly excited by cricothyroid motoneurons (also prelabeled) (26). On the basis of the in vivo respiratory patterns of CVM in other species, Mendelowitz (25) suggested that the excitatory input would be exerted in the postinspiratory phase of respiration. Cricothyroid motoneurons, however, act synergistically with posterior cricoarytenoid motoneurons to dilate the larynx (16) and are most active during inspiration (39). These findings thus provide a neat explanation for why rat CVM are most active during the central inspiratory phase. Future experiments will be needed to assess the importance of this mechanism for the overall activity of CVM.

In cats, by comparison, the dominant feature that sets the respiratory firing pattern of CVM appears to be synaptic inhibition (7), which may be muscarinic cholinergic because locally applied atropine appears to remove the inhibitory inhibition of their discharge (7). In line with this idea, low systemic doses of muscarinic antagonists enhance mean CVM activity in dogs (14) or its effects on heart rate in humans (35). But in this case, the effect is to enhance respiratory fluctuations (35) rather than cause the reduction that would be expected from the mechanism described by Gilbey and colleagues (7) in cats. Clearly, further work will be necessary before the neuronal basis of respiratory sinus arrhythmia is understood.

Heart rate in rats shows very little fluctuation with the respiratory cycle, presumably reflecting the high resting heart rate and short respiratory cycle. The neuroeffector delay between the arrival of CVM action potentials and their effect on heart rate (~200–400 ms in cats; Ref. 3) also occupies a greater proportion of the respiratory cycle in rats than in larger animals. An inspiratory maximum in CVM firing rate could thus easily have its main bradycardic action in the expiratory period, effectively “normalizing” the respiratory pattern of heart rate variation to that of other animals. Any resultant heart rate effects would be very small, however, and unlikely either to give a clear guide to the underlying pattern of rat CVM activity or to have great consequences for cardiovascular function. In larger mammals such as cats, dogs, and humans, respiratory sinus arrhythmia is often prominent and is entirely due to fluctuations in CVM activity [sympathetic actions are too slow to influence heart rate over the respiratory cycle (35, 41)]. It has been suggested that rapid changes in CVM activity help to buffer the circulation in the face of rapid perturbations such as the respiratory fluctuation in filling pressure (4). Such actions do not appear to be functionally important in rats.

Perspectives

There is growing clinical interest in the factors that determine parasympathetic activity or shift “sympathovagal balance” in the neural control of the heart. Indexes of these neural drives are important prognostic indicators for the outcome in heart failure or myocardial infarction (6, 19). Moreover, measures of increased parasympathetic activity per se predict a more favorable outcome independently of sympathetic activity. An animal study has confirmed the beneficial action of vagal efferent fibers in lowering the incidence of fatal arrhythmias after myocardial ischemia (40). Therapeutic measures to increase parasympathetic activity are therefore being sought, but these are normally assessed by indirect measures such as heart rate and heart rate variability.

The present paper establishes direct methods whereby factors determining CVM activity in vivo may be studied in the animal used most frequently for invasive neural/cardiovascular studies. The effects of physiological or pharmacological manipulations of parasympathetic activity may also be readily tested in this model, in a quantitative manner, giving scope to define their sites and modes of action.

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