Respiratory responses to selective blockade of carotid sinus baroreceptors in the dog

FRANCIS A. HOPP AND JEANNE L. SEAGARD
Veterans Affairs Medical Center and Department of Anesthesia,
The Medical College of Wisconsin, Milwaukee, Wisconsin 53295

Hopp, Francis A., and Jeanne L. Seagard. Respiratory responses to selective blockade of carotid sinus baroreceptors in the dog. Am. J. Physiol. 275 (Regulatory Integrative Comp. Physiol. 44): R10–R18, 1998.—Activation of carotid sinus (CS) baroreceptors has been shown to increase inspiratory time (TI) and expiratory time (TE) and to have a varied effect on tidal volume. The contribution of two functionally different types of baroreceptors to changes in respiratory function were examined in the current study. The techniques of DC anodal block and bupivacaine anesthetic block were used to selectively block fibers, from largest (type I) to smallest (type II) and smallest to largest, respectively, in the CS nerve (CSN) from an isolated CS in an anesthetized, paralyzed, vagotomized, artificially ventilated dog. Anodal blocking currents from 25 to 60 µA, which blocked primarily large A fibers, produced significant decreases in TI and TE and increased the slope of the average phrenic neurogram (PNG(t)), with no change in peak PNG(t). Further increases in blocking current to levels that also blocked small C fibers did not result in additional changes. Bupivacaine blockade using concentrations that blocked primarily C fibers did not block changes in TI and TE to step CS pressure changes. Increasing bupivacaine concentration to 20 mg/100 ml blocked all CSN conduction, and respiratory responses were eliminated. Therefore respiratory responses arising from CS baroreceptors appear to originate from the larger type I baroreceptors.

METHODS

General. Experiments were performed on 10 mongrel dogs of either sex weighing 15–25 kg. Anesthesia was induced with thiopental sodium (25 mg/kg) and maintained by a continuous infusion at 8–12 mg·h⁻¹·kg⁻¹ iv. The animals were intubated with a cuffed endotracheal tube and ventilated with an air–O₂ mixture using positive-pressure ventilation (Bird Mark 7). PₐCO₂ and pH were maintained in the normal range (PₐCO₂ ~40, pH ~7.4) by adjustments in ventilation and infusion of sodium bicarbonate (1 meq/ml). Esophageal temperature was monitored with a thermistor probe (Yellow Springs YSI-701) and maintained in the range of 37–39°C by use of a servo-controlled heating pad. Aortic BP was measured via a fluid-filled catheter connected to a Gould-Statham P23 ID pressure transducer, and end-tidal CO₂ (ET revive) concentration was continuously measured with an infrared analyzer (Beckman LB-2). After surgery, neuromuscular blockade was initiated and maintained with the administration of pancuronium bromide (0.1 mg/kg iv). Continuous monitoring of respiratory rate and lack of response to nociceptor stimula-
tion were used to ensure that an adequate level of anesthesia was maintained at all times. In addition, in studies utilizing a ganglionic blocker, the infusion of anesthesia was maintained at the same level sufficient to prevent changes in BP and respiration during previous phases of the experiment. After recovery from ganglionic blockade, this level of anesthesia was always found to be adequate.

The area around the left CS was carefully dissected and the CS nerve (CSN) was located and separated from surrounding tissue for later anodal or bipolaricaine block. The nerve was identified by recording the characteristic baroreceptor firing pattern synchronized with pulse pressure. The left CS was vascularly isolated as previously described (30). Briefly, the left common carotid, external carotid, internal carotid, and thyroid arteries as well as any other small vessels in the sinus region were isolated and ligated. CS pressure (CSP) was measured via a cannula placed in the lingual artery and connected to a Gould Statham P23 ID transducer. The left common carotid and external carotid arteries were cannulated to permit a flow-through perfusion of the CS. The left occipital artery was ligated immediately adjacent to the external carotid artery to exclude the carotid body from the perfused segment. Lactated Ringer solution was used as the perfusate, oxygenated with 100% O2 to chemically denervate any chemoreceptors not physically eliminated by the isolation technique. This technique has been found to provide a stable chemoreceptor-free preparation in which isolated sinus pressure can be easily manipulated and baroreceptor activity remains viable for hours. Mean baseline CSP was maintained constant using a servo-controlled roller pump to provide maximal baroreceptor stimulation during bipudicaine and anodal blockades (see below).

Both vagi were sectioned to eliminate afferent inputs from aortic baroreceptors, chemoreceptors, and other cardiopulmonary receptors that might produce secondary changes in respiration or BP during anodal or anesthetic block. The contralateral CSN was left intact to provide peripheral chemoreceptor drive to breathing. Hexamethonium bromide (20 mg/kg iv) was administered to block any reflex changes in systemic BP resulting from pressure changes in the isolated sinus, which would have modulated the output of the intact contralateral baroreceptors. Phenylephrine (1 mg/100 ml) was infused intravenously to maintain systemic BP constant at a mean level of ~115 mmHg.

The CS rootlet of the left or right phrenic nerve was isolated from surrounding structures and sectioned caudally. The nerve was placed on small bipolar hook recording electrodes and submersed under warm mineral oil in a tissue pouch. Activity was amplified by an optically isolated wide-band preamplifier (gain = 1,000, 0.01- to 15-kHz bandwidth) followed by an additional filter-amplifier (4th-order filter, -3 db at 100 and 2,000 Hz). The moving time average of the phrenic activity [PNG(t)] was obtained by precision full-wave rectification and low-pass filtering (4th-order Bessel linear averaging filter, averaging interval = 100 ms). The peak height of the PNG(t) (PPNGS) was used as a neural index of tidal volume (11). Timing pulses were generated at the onset and termination of the PNG(t) and used to compute on-line values of Ti and Te using digital timers with digital-to-analog outputs. PNG(t), Ti, Te, BP, CSP, and ET_{CO2} were displayed on a polygraph (Grass model 7), and the raw nerve activity, pressures, and ET_{CO2} were recorded on an FM tape recorder (Vetter model D).

Anodal block. Anodal block has been shown to selectively block nerve conduction in peripheral nerves on the basis of fiber size through the application of polarizing current (18). The largest A fibers are blocked at the lowest current strengths followed by smaller A and C fibers as current strength is increased. To perform anodal block, direct current was applied through a modified wick-type electrode placed on the isolated, desheathed CSN submerged in a pool of warmed mineral oil. The monopolar electrode consisted of a solid felt tip (width ~ 2 mm), notched for nerve placement, that was epoxied into a hollow plastic tube (6.5 mm diam) (18). An insulated silver wire with a bare end was threaded down the tube and into the felt wick to serve as the electrode lead. The electrode was soaked in saline for several hours before its use to ensure complete conduction of the blocking current. The cathodal electrode consisted of an alligator clip that was placed in muscle tissue lateral to the blocking site to provide multiple current paths from the anode, bidirectionally along the nerve, to the cathode. Current density at the nerve-tissue interface was thus reduced by shunting current through multiple pathways, thereby reducing the excitatory effects of depolarization at the cathode.

The selectivity of anodal block was tested in four dogs. In two dogs, a long section of the vagus nerve approximately the same diameter as the CSN was dissected free from the main nerve trunk. Two pairs of wire electrodes were placed ~9 cm apart on the dissected nerve bundle for stimulating and recording, with the wick-type blocking electrode placed between them. Supermaximally evoked A and C fiber potentials were monitored while varying levels of anodal block were applied to the nerve bundle in random order (0–350 µA, Fig. 1). After each blocking current was applied, no additional current was tested until the evoked potentials returned to control levels. As seen in Fig. 1, most A fiber conduction was lost at a blocking current of 60 µA with minimal loss of C fiber conduction at that level. Figure 2 shows a representative plot of the integrated A fiber (conduction velocity > 2.3 m/s; Ref. 27) and C fiber evoked potentials from the animal shown in Fig. 1 as a function of blocking current. As can be seen from Fig. 2, the faster A fiber potentials were reduced to ~23%
of control with currents up to 60 µA, whereas the C fiber potentials maintained a level of 80–90% of control over the same blocking current range. A and C fibers were completely blocked at 60 and 350 µA, respectively. Similarly, in two other dogs, anodal block was applied to the CSN. Because of the blocked at 60 and 350 µA, respectively. Similarly, in two other dogs, anodal block was applied to the CSN. Because of the nerve fibers. In a few cases, as reported by other investigators, the nerve fibers in the reverse order. Respiratory changes due to a precise blocking order of fibers were measured and compared with those obtained from anodal blockade. To perform bupivacaine block, a 2-mm-wide desheathed portion of the CSN was exposed to the anesthetic at concentrations of 5, 10, and 20 mg/100 ml using cotton pledgets. Franz and Perry (14) suggested that a more selective block of small vs. large fibers could be obtained if the application of local anesthetic was restricted to a 2-mm segment. Although some diffusion of the anesthetic was likely, the remaining sheath on the nerve served to restrict the anesthetic spread.

Experimental protocol. Two different protocols were used to study the effects of anodal blockade of the CSN on respiration. The first protocol involved the random application of anodal blocking currents to the CSN from 0 µA up to a maximal blocking current of 350 µA, which has been shown to block all fibers. Ti, Te, PNG, PNG(t) slope calculated in 200-ms intervals, CSP, and BP were analyzed for a 1-min control period followed by 1 min of blocking and an end control period. Runs were separated by 3–5 min to allow variables to return to control values. The second protocol involved increasing the blocking current in steps from 0 to the maximal blocking current for 1-min intervals without returning to control until the completion of a run. Because it required less time to complete a run, it was easier to maintain a constant background respiratory drive using the second protocol. Results were not different between the two protocols, and therefore the combined data are presented. Responses were normalized as a percentage of control ± SE, and stimulus-response curves were generated for each variable by plotting the appropriate response vs. blocking current. Mean systemic and mean CSP values ± SE were maintained at 115.7 ± 5.0 and 171.46 ± 7.9 mmHg, respectively. Systemic pressure was selected such that a step decrease in CSP or a complete block of the CSN resulted in a near maximal respiratory response. CSP was selected to provide a maximal pressure stimulus to both type I and II baroreceptors as previously described by Seagard et al. (32).

The effect of the bupivacaine block of the CSN on respiration was assessed by applying bupivacaine in increasing concentrations of 5, 10, and 20 mg/100 ml to the CSN and measuring the effects on respiration 3 min postapplication. Because the degree of block is a function of both concentration and time, changes in Ti and Te in response to a precisely controlled, 1-min step decrease in CSP was used as a test. The pressure step was applied by varying the speed of a servo-controlled roller pump (developed in this laboratory) in a stepwise manner at the appropriate times after the onset of the block. Mean baseline CSP ± SE was maintained at 155.76 ± 1.6 mmHg to provide a maximal baroreceptor stimulus (32), and a step decrease in CSP to 47.57 ± 0.13 mmHg was used as a test stimulus.

Data analysis. Data were played back from the Vetter tape recorder for computer analysis. Systemic BP, CSP, average PNG(t), and a voltage pulse used to mark changes in blocking current were sampled at 20 Hz/channel using a Hewlett-Packard model 310 computer equipped with a Newport Digital Turbo-25 accelerator card and an Infotek AD200, 16-channel analog-to-digital converter.

Data were analyzed using a computer program developed in this laboratory. For the anodal block, 6–12 min of data...
were sampled and stored in computer memory and in a floppy disk file. The time sequence of each file included a 1- to 2-min control period followed by a blocking run and an appropriate recovery period. The computer was used to plot data vs. time, and a cursor was used to divide the plotted data into control and blocking periods so that data from the various blocking currents could be analyzed, averaged, and compared with that of the control period. For each period, the average phrenic neurogram was analyzed on a breath-by-breath basis to determine 1) the upstroke, corresponding to the onset of the inspiratory phase for a particular breath, 2) the rapid fall from the peak value, corresponding to the onset of the expiratory phase for that breath, 3) PPNG, which is proportional to VT for that breath, and 4) the slope of the PNG(t), calculated in 200-ms increments for each breath. In addition, mean systemic BP and mean CSP were calculated for each respiratory phase (i.e., twice/breath) to obtain a more accurate representation of BP changes. From these data, Ti, Te, PPNG, PNG(t) slope, mean BP, and mean CSP were calculated for each breath and averaged over control periods and for each blocking current. The reduced data were stored in a second summary disk file so that, for each animal, one summary data file that could be pooled with similar files from different animals for later statistical analysis was generated. In some cases, it took several breaths to reach a steady state, and therefore the first two to three breaths after initiation, change, or cessation of the blocking current were not included in the analysis.

Data for the bupivacaine block were analyzed in a similar manner, with blocking runs being divided into control (constant CSP), a 1-min step decrease in CSP, and end control for each concentration of bupivacaine. Because the purpose of the bupivacaine block was to verify the anodal blocking data using a second method that blocks in the reverse order, data were analyzed only for changes in Ti, Te, and systemic BP.

Statistical methods. ANOVA was used to determine the statistical significance of changes in Ti, Te, PPNG, the rate of rise of PNG(t), BP, and CSP for each level of blocking current at the P ≤ 0.05 level. Further post hoc tests were used to determine statistical significance between levels of blocking. For this purpose, a Newman-Keuls post hoc test was used to determine within-group differences at the P ≤ 0.05 level.

RESULTS

Examples of the changes in PNG(t) in response to an increase and a decrease in CSP are shown in Fig. 3, A and B, respectively. An increase in pressure resulted in an increase in Ti and Te, whereas a decrease in pressure caused a decrease in Ti and Te. Neither maneuver had a significant effect on neural VT over the group of animals, although in some specific animals there was a inverse trend as indicated by a small change in PPNG. Systemic BP was controlled by the hexamethonium blockade and phenylephrine administration and therefore did not change in response to changes in CSP. In preliminary experiments, when BP was not controlled, the initial PNG(t) responses were similar to those above. However, as systemic BP began to change in response to changes in CSP, discharges of nondenervated receptors including the contralateral CS baroreceptors and chemoreceptors were altered and produced antagonism of the responses, which at first blunted and then returned the responses, toward control values.

Figure 4 shows an example of the effect of increasing the level of anodal blocking current on PNG(t) with systemic BP and CSP held constant. There was a graded increase in respiratory frequency due to a decrease in both Ti and Te, with no change in neural VT, as indicated by PPNG. Further increases in blocking current beyond 75 µA, a current sufficient to block most A fibers, caused no additional decrease in Ti or Te.
For all animals, the mean TI ± SE ranged from 4.35 ± 0.56 s with no blocking current to 3.36 ± 0.39 s with complete CSN block. Similarly, TE ranged from 7.99 ± 0.84 to 3.85 ± 0.36 s. When systemic BP was allowed to change in response to anodal blockade of the CSN, the respiratory responses were variable. Data presented in this study are only for experiments in which BP was controlled.

A summary of changes in TI, TE, and systemic BP in response to increasing anodal block of the CSN with BP controlled is shown in Fig. 5. CSP (mean 100 ± 0.16%) and PPNG (mean 105 ± 1.6%) are not shown, since these parameters were not significantly changed from control during block. Both TI and TE were decreased as blocking current was increased from 0 to 50–60 µA, eliminating input from the larger, primarily type I, Aδ fiber baroreceptors. These current-dependent responses plateaued, with no additional significant change seen in TI or TE as blocking current was increased up to 125 µA, at which most small Aδ fibers and a significant number of C fibers (primarily type II baroreceptors) were blocked. In a few animals, blocking current was increased up to 350 µA, and no further change in TI or TE was observed. As blocking currents were increased from 0 µA, a small increase in systemic BP was seen at a few points, indicating that hexamethonium blockade was not 100% effective in blocking baroreflex-induced BP changes. These changes were considered acceptable if they were <10% of control BP. Any effect on TI or TE arising from the contralateral sinus would tend to antagonize the direct responses.

Changes in respiratory drive can result in proportional changes in the peak PNG(t) (PPNG) with increases in anodal block of left CSN. Mean CSP and systemic BP were maintained constant. Blocking currents were held constant between marker pulses (trace at top).

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Changes in respiratory drive can result in proportional changes in the peak PNG(t) (PPNG) with increases in anodal block of left CSN. Mean CSP and systemic BP were maintained constant. Blocking currents were held constant between marker pulses (trace at top).
An example of the changes in PNG in response to a step decrease in CSP during control and bupivacaine blockade of 5, 10, and 20 mg/100 ml is shown in Fig. 7. The lower concentrations of bupivacaine (5 and 10 mg/100 ml) primarily block C fibers and have little effect on the increase in PNG rate to decreasing CSP. At 20 mg/100 ml, a concentration sufficient to block both A and C fibers, the increase in PNG frequency is eliminated. Summary data from one animal showing the mean changes in TI and TE under different anesthetic blocking conditions are presented in Fig. 8 (top) for the step pressure response and in Fig. 8 (bottom) for changes in baseline values. These data demonstrate that there are no baseline changes in TI or TE until a bupivacaine block of 20 mg/100 ml is applied to the CSN. Similarly, the responses to a step decrease in CSP are not eliminated until 20 mg/100 ml is reached, at which point A fibers are blocked. Therefore data from both blocking methods indicate that the respiratory responses to changes in CS baroreceptor input arise primarily from A fibers, which correspond primarily to type I baroreceptors.

**DISCUSSION**

Other investigators have used changes in BP to investigate the role of CS baroreceptors in the control of respiration. Dove and Katona (10) and Maass-Moreno and Katona (23) used pressure pulses and pressure steps in the isolated CS of spontaneously breathing, vagotomized dogs to stimulate CS baroreceptors during either the inspiratory or expiratory phase. Stimuli during inspiration or expiration lengthened the respective phase, but neither stimulus had a significant effect on VT. A similar study in the cat (23) showed a marked species difference, with stimuli given during inspiration shortening Ti and decreasing VT or PPNG. The present study used the technique of anodal block to tonically decrease rather than increase baroreceptor activity, but the results are consistent with the studies cited above in the dog. Removal of baroreceptor activity resulted in a decrease in Ti and TE with no change in PPNG (VT). The use of transient stimuli, such as pressure pulses and steps in the earlier studies, prevented changes in systemic BP while allowing measurements of the affects of baroreceptors on Ti, TE, and VT. The present study used hexamethonium blockade and phenylephrine infusion to prevent changes in systemic BP and found similar results with prolonged baroreceptor blockade, indicating that the central pathways for this reflex were still active in the presence of these drugs.

Brunner et al. (2) used tonic step pressure changes in the isolated CS of spontaneously breathing, vagotomized dogs to look at steady-state changes in ventilatory parameters. Step increases in CSP lengthened Ti and TE and increased VT, whereas step decreases shortened Ti and TE and decreased VT. When systemic BP was held constant, the magnitude of the changes in respiratory frequency were increased, and changes in VT were smaller but still significant. Because these animals were breathing spontaneously, blood gases changed slightly with total ventilation and may have contributed to the differences seen in the VT response between this study and the present study. In addition, present study used the technique of anodal block to tonically decrease rather than increase baroreceptor activity, but the results are consistent with the studies cited above in the dog. Removal of baroreceptor activity resulted in a decrease in Ti and TE with no change in PPNG (VT). The use of transient stimuli, such as pressure pulses and steps in the earlier studies, prevented changes in systemic BP while allowing measurements of the affects of baroreceptors on Ti, TE, and VT. The present study used hexamethonium blockade and phenylephrine infusion to prevent changes in systemic BP and found similar results with prolonged baroreceptor blockade, indicating that the central pathways for this reflex were still active in the presence of these drugs.

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respiratory responses arising from changes in CS baroreceptor activity could be attributed to either of two functionally different types of baroreceptors. Type I baroreceptors have been found to have primarily larger myelinated A\(\delta\) fiber afferents and respond with a hyperbolic discharge pattern to a ramp CSP increase (32). Type II baroreceptors have primarily smaller A\(\delta\) fiber and unmyelinated C fiber axons and show a sigmoidal increase in response to CS ramp pressure increases (32). Type I but not type II baroreceptors acutely reset to sustained changes in CSP (29) and have been shown to be primarily involved in buffering dynamic changes in BP, whereas type II baroreceptors are primarily involved in regulating the tonic level of BP (31). The fact that larger type I baroreceptors reset to changes in CSP does not mean that they are incapable of producing the responses observed in this study. Type I baroreceptors discharge with an ongoing pulsatile pattern at the baseline CSP used in these studies and have been shown to reset \(\sim 10-15\%\) within 20 min after a change in CSP (29). Therefore, in the case of anodal block in which CSP is not changed, resetting effects are not an issue with respect to the data. For the bupivacaine protocol, the step change in pressure lasts only 1 min, and there will therefore be little resetting during this time period. Even if resetting occurs to the same degree as stated above, 85–90% of the change in type I activity due to a step change in CSP will be maintained and thus could easily mediate the respiratory responses observed in this study.

Although type I and II baroreceptors have been characterized on the basis of functional differences, the fact that they can be grouped to a large extent on anatomical fiber size allows the use of anodal or anesthetic blockade to separate the primary contributions of these two groups to respiratory control. The respiratory responses to increasing levels of anodal blocking currents plateau in the range of 50–80 \(\mu\)A, which corresponds to a blockade of mostly A fiber afferents (Fig. 2). No further changes in respiratory parameters were seen as blocking current was increased to include smaller A\(\delta\) and unmyelinated C fibers, which include primarily type II baroreceptors. These data were confirmed by the bupivacaine block as shown in Figs. 7 and 8. It therefore appears that type I and II baroreceptors not only have functionally different roles in BP regulation but also in the regulation of respiration.

Although much is known about the central projections of CS baroreceptors, differences in the sites of central input for A vs. C fiber baroreceptors have not been clearly established. Studies utilizing anterograde transport of horseradish peroxidase in the CSN of the cat (4, 19, 24) and rat (3) have shown labeling in the nucleus tractus solitarius (NTS) and various other areas of the medulla depending on the study. All studies have shown that CS afferents project to various subnuclei of the NTS, primarily the dorsomedial, medial, lateral, and commissural subnuclei. However, the extent of convergence for A vs. C fiber afferent inputs to neurons in these various subnuclei is not clear. Using an antidromic mapping technique, Donoghue et al. (8) could find no differences in the patterns of projection and termination of A vs. C fiber CS baroreceptors within the NTS of the cat. On the other hand, in studies recording central neural activity in the NTS, Donoghue et al. (9) have shown limited convergence between myelinated and nonmyelinated aortic nerve afferents. Two recent studies from this laboratory utilizing neuronal expression of c-fos in neurons activated by step changes in CSP in the dog suggest that there may be...
differences in the distribution of A vs. C fiber baroceptors in the dog. Maximal activation of baroceptors using large steps in CSP resulted in activation of neurons in the ipsilateral commissural and medial subnuclei of the caudal NTS and the dorsolateral, dorsomedial, and medial subnuclei in the intermedial and rostral levels of the NTS (6). Elimination of A fiber input using anodal block of the CSN during the pressure step decreased the number of neurons expressing c-fos in the dorsomedial subnucleus of the rostral NTS (7). These results suggest that although there is widespread distribution of smaller A and C fiber baroceptor input to the NTS, there is a predominant distribution of large A fiber baroceptor input to the dorsomedial subnucleus. Therefore, although the potential for convergence of projections of carotid A and C fiber baroceptors exists, some data exist to suggest potentially different sites of input for type I and II baroceptors that could contribute to different functional roles for type I and II CS baroceptors in the control of respiration.

The projections of baroceptor afferents onto central respiratory neurons are not well described. There is little evidence to suggest that baroceptors project directly to respiratory neurons in the NTS. Gabriel and Seller (15) showed an increase in respiratory cycle time and in the total number of spikes per respiratory cycle due to an increase in CSP while recording from expiratory neurons near the nucleus ambiguus of the cat. Due to the relatively greater increase in respiratory cycle time, the mean firing rate in these neurons was decreased slightly. In a later study of the retroambigual region of the cat, Richter and Seller (25) showed that baroceptor-activated depolarizing changes in the membrane potentials of expiratory neurons were probably indirect effects gated by connections from inspiratory neurons, possibly from the nucleus para-ambigualis (12). Inspiratory neurons recorded from the retroambigual area, however, were inhibited by both CSP increases and electrical stimulation of the aortic nerve independent of the respiratory phase. The exact roles of retroambigual neurons in the generation of the central respiratory pattern are unknown. However, many neurons in this area are bulbospinal neurons and may project to inspiratory and expiratory muscles with little effect on the generation of central respiratory rhythm. Data from the present study suggest that, in the dog, removal of baroceptor afferent input primarily affects the central respiratory timer, with little effect on respiratory drive as measured from PPNG. These data are similar to the effects of aortic chemoreceptor stimulation in the dog (17). Although the abovementioned studies demonstrate baroceptor-mediated effects on central respiratory neural activity and central respiratory timing, the pathways involved and sites of neural integration resulting in the reflex changes in respiration due to baroceptor activation are largely unknown, and further study is needed in this area.

Type I baroceptors exhibit adaptation, whereas type II baroceptors show little tendency to adapt. Central recordings from putative second-order neurons in the dog NTS show a wide variety of responses to slow ramp increases in CSP (28). Some neurons adapt to the CSP stimulus; however, most neurons do not adapt. There is some evidence suggesting that adapting neurons receive input from type I baroceptors and non-adapting neurons receive input from type II baroceptors. If this were the case, however, one might wonder if an adapting input is capable of maintaining a tonic change in respiratory frequency. Seagard et al. in the dog (28) have shown that adapting neuronal firing patterns remain elevated to an increased CSP after the adaptation and could therefore easily relay the baroceptor information to the central respiratory timer. These data are consistent with data of Lipski et al. for the cat (22) but do not show the same degree of adaptation or extinction as seen by Rogers et al. in the rabbit (26). Whether this is due to species or methodological differences is unknown. It should be noted, however, that the same conclusions with regard to respiratory control by type I vs. II baroceptors was reached with the withdrawal of type I input using anodal block of activity from a tonic pulsatile pressure in the isolated CS and from bupivacaine block of input from a dynamic pulsatile pressure change.

In summary, the present study has demonstrated that selectively blocking larger myelinated CS baroceptors (mostly type I) in a vagotomized dog, while holding systemic BP constant, resulted in a decrease in Ti and TE with no change in PPNG. Further increases in blocking current to include smaller A and C fiber baroceptor afferents (mostly type II) resulted in no further changes in respiratory parameters. Blocking mostly C fibers with bupivacaine produced no effect on the Ti or TE response to a step decrease in CSP; however, blocking both A and C fibers eliminated the responses. Similarly, baseline values of Ti and TE did not change until both A and C fibers were blocked. Type I and II baroceptors have been shown to have differential effects on the baroreflex control of BP. This study expands the previous findings to suggest that there is also differential baroreceptor control of respiration.

Perspectives

Many studies have shown that most baroceptors have their first synapse in various subnuclei of the NTS, with subsequent projections to the caudal ventrolateral medulla and rostral ventrolateral medulla. These sites appear to be in close conjunction with areas associated with the dorsal and ventral respiratory groups, and inspiratory neurons in the retroambigual area in the cat have been shown to be inhibited by CS baroceptor activation. Baroceptors have significant effects on both respiratory and cardiovascular control, and these systems must work together to provide for homeostasis with respect to tissue O2 delivery and CO2 removal. A system that can provide differential control of sympathetic outflows can adjust heart rate and peripheral resistance to regulate blood flow to specific tissues. The addition of respiratory control provides a means to optimize O2 delivery and may provide a means of minimizing the work involved in maintaining homeostasis. In the present study, CS baroceptors affected respiratory timing but not depth. Many of the
mechanisms for the transmission of afferent information to the areas controlling respiratory timing and respiratory depth are at present unknown. The latest theory for the location of the central respiratory timer puts it in the pre-Bötzinger complex of the rostral ventral respiratory group. However, it is not known at this time where or how (pacemaker or neural network) respiratory timing is generated, and it is therefore difficult to speculate on how the baroreceptor information acts on the timing mechanism. The magnitude of baroreceptor input required and the time constants involved in mediating the respiratory responses are not necessarily the same as those mediating the well-known cardiovascular responses. Most work in this area has attempted to define the cardiovascular pathways of the baroreflex, and further studies will be required to clarify the respiratory pathways of the baroreflex.

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Address for reprint requests: F. A. Hopp, Jr., Zablocki VA Medical Center and Dept. of Anesthesia, The Medical College of Wisconsin, Research Service 151, 5000 W. National Ave. Milwaukee, WI 53295.

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