Tidal Volume Affects the Response to Inactivation of the Rostral Ventrolateral Medulla

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SUMMARY During preliminary studies of the rostral ventrolateral medulla as a relay site for responses activated from forebrain, loss of the marked depressor effect of lidocaine, microinjected into lateral rostral ventrolateral medulla, was observed when rats were ventilated spontaneously rather than by artificial ventilation. The mechanism of this effect was studied in rats ventilated at a tidal volume of 2.5 ml. Bilateral injection of 4% lidocaine into lateral rostral ventrolateral medulla decreased mean arterial pressure by –47 ± 8 mm Hg and heart rate by –68 ± 21 beats/min. Reduction of tidal volume to 1.5 ml significantly attenuated the fall in mean arterial pressure and heart rate produced by lidocaine to –17 ± 11 mm Hg and –12 ± 8 beats/min. The decrease in tidal volume resulted in decreased arterial Po2 and pH, and increased Pco2. However, the depressor effect of lidocaine was not significantly affected by independently changing Po2 and Pco2. The physical stimuli associated with reduction of tidal volume (i.e., changes in lung inflation and chest wall movement) appeared to mediate the attenuated depressor response to the injection of lidocaine into the lateral rostral ventrolateral medulla. These data suggest that 1) tonic vasomotor activity derived from lateral rostral ventrolateral medulla is strongly influenced by altered mechanics of respiration, and 2) the anatomical location of the putative vasomotor center may not be defined by the lateral rostral ventrolateral medulla under all conditions. (Hypertension 11 [Suppl I]: I-186–I-189, 1988)

KEY WORDS • sympathetic nervous system • vasomotor tone • respiratory system

THE rostral medulla has long been known to be involved in the regulation of arterial pressure. In the late 1800s experiments were performed that examined the role of the central nervous system in the maintenance of arterial pressure. In these experiments, transections were made throughout the neuraxis. None of the transections altered arterial pressure until the rostral medulla was severed from the spinal cord (for review see Reference 1). These experiments demonstrated that the rostral medulla is critically involved in maintaining vasomotor tone. Alexander demonstrated that these transections would significantly reduce sympathetic nerve activity as well as arterial pressure, an additional demonstration that this region is involved in the maintenance of vasomotor tone.

Recent work has further localized the region responsible for maintaining arterial pressure to the ventrolateral aspect of the rostral medulla (RVLM). Bilateral electrolytic lesions of the RVLM result in a fall in arterial pressure to levels comparable to those that occur after spinal cord transection. Application of the inhibitory amino acids glycine and γ-aminobutyric acid to the ventral medullary surface underlying this area has been shown to produce reductions in arterial pressure similar to those that occur after bilateral lesions. Furthermore, the bilateral application of tetrodotoxin also results in a fall in arterial pressure to levels similar to those following spinal transection.

Previous work in our laboratory demonstrated a differential localization of vasomotor pathways in the medulla. Specifically, the renal and mesenteric vasoconstrictor pathways from the hypothalamic paraventricular nucleus were found to project to or through the RVLM; however, the vasodilator pathway to skeletal muscle did not. Thus, the initial purpose of this project was to examine the role of the RVLM as a relay for vasomotor projections from other forebrain sites, with particular emphasis on the possibility that the RVLM is a final common pathway through which all vasoconstrictor information must pass.

The RVLM was examined as a relay for cardiovascular information from several hypothalamic areas. During the course of these experiments an unanticipated effect was seen. As with injections of tetrodotoxin, lidocaine injected into the RVLM from a ventral approach resulted in a profound depressor effect. Yet when lidocaine was injected into the same
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Figure 1. An example of an experiment in which bilateral injections of lidocaine were made while the animal was ventilated at 2.5 and 1.5 ml tidal volumes. Note that the depressor and bradycardic responses are attenuated by the reduced tidal volume. Below is a coronal section illustrating the location of bilateral lidocaine injections into the RVLM made at the level of the posterior pole of the facial nucleus.

Materials and Methods

Male Sprague-Dawley rats (375–475 g; Biolab, St. Paul, MN, USA) were anesthetized with urethane (1.2 mg/kg i.p.) and placed on a heating pad to ensure proper body temperature (American Medical Systems, Cincinnati, OH, USA). The femoral artery and vein were catheterized for arterial pressure measurement (Century Technology, Inglewood, CA, USA) and drug infusion, respectively. The trachea was intubated to ensure a patent airway. Two 26-gauge guide cannulas were stereotaxically placed such that a 32-gauge injector could be lowered bilaterally into the lateral aspect of the RVLM.

Figure 1 illustrates a typical injection site. Two hundred nanoliters of a 4% solution of the local anesthetic lidocaine was bilaterally injected into the lateral RVLM at the level of the posterior pole of the facial nucleus. This region is 2 mm lateral to the midline and 1 mm dorsal to the ventral surface of the brain. All injection sites were verified histologically. The effective spread of 500 nl of a 4% solution of lidocaine has been determined physiologically to have a radius of approximately 0.5 mm.

The neuromuscular blocking agent pancuronium (0.48 mg/kg initially, with 0.24 mg/kg given hourly) was injected intravenously, and the animals were ventilated using a rodent respirator (Harvard Apparatus, South Natick, MA, USA). Normal tidal volumes were assessed by mimicking the respiratory rate (75/min) of the anesthetized animals and altering the tidal volume to give equivalent values for partial pressure of oxygen (PO2). This tidal volume was determined to be 2.5 ml. Reduced tidal volume was defined as 60% of the control value (1.5 ml). Animals were ventilated with air unless otherwise noted.

For measuring blood gas values, 0.6 ml of blood was removed from the femoral artery and replaced with an equal volume of blood from a donor animal. All blood samples were placed on ice immediately after removal, and PO2, partial pressure of carbon dioxide (PCO2), and pH values were determined.

Experiments showing the initial differential responses and baseline blood gas values were analyzed by paired t test. Experiments in which blood gas values were altered by changing the inspired gas were tested by analysis of variance with a Dunnett’s post hoc test.

Results

Figure 1 illustrates the response to bilateral injection of 200 nl of 4% lidocaine under conditions of normal and reduced tidal volumes. Injection of lidocaine resulted in a profound fall in mean arterial pressure (MAP) and heart rate (HR) when the animal was ventilated at the 2.5 ml tidal volume; however, the response was greatly attenuated when the animal was ventilated at the 1.5 ml tidal volume. Injections of lidocaine were made 15 minutes after the change in tidal volume. These effects are summarized in Figure 2. It should be noted that the change in tidal volume did not significantly alter baseline MAP and HR, as shown in the top panel. The depressor and...
bradycardic responses to injection of lidocaine into the lateral RVLM were significantly attenuated when the animal was ventilated at the reduced tidal volume ($n = 5$).

Three physiological parameters that would be altered by the decreased tidal volume are $P_o_2$, $P_c_o_2$, and pH. Figure 3 illustrates the alterations in each of these values after the reduction of tidal volume to 1.5 ml. The columns on the left summarize the control responses obtained when the animals were ventilated at the 2.5 ml tidal volume. It should be noted that the $P_o_2$ values include animals ventilated with room air ($90 \pm 4$ torr, $n = 5$), and those ventilated with 100% $O_2$ ($391 \pm 61$ torr, $n = 2$). Reduction of tidal volume to 1.5 ml resulted in a reduction in $P_o_2$, increase in $P_c_o_2$, and fall in pH. Thus, any one of these three physiological parameters could be the signal that mediates the attenuated depressor response to injection of lidocaine into the lateral RVLM.

First, hypoxia was examined as a stimulus for the differential response to the bilateral injection of lidocaine into the lateral RVLM. The third series of columns in Figure 3 illustrates the effects of ventilating the animals at the reduced tidal volume when the inspired gas is 100% $O_2$. Thus, all physiological parameters remained the same except that the previous reduction in $P_o_2$ was prevented. Under these conditions, the depressor response to lidocaine remained attenuated even though the $P_o_2$ values were not reduced. Thus, hypoxia does not appear to mediate the differential depressor response to injection of lidocaine into the lateral RVLM.

The next physiological parameter tested was $P_c_o_2$. The $P_c_o_2$ was elevated under the 2.5 ml tidal volume by raising the $C_o_2$ content of the inspired gas to 5%. This increase gave blood levels comparable to those seen with the 1.5 ml tidal volume. The fourth series of columns in Figure 3 illustrates the levels of $P_c_o_2$ versus

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**Figure 2.** Summary of the effects of injection of lidocaine into the lateral aspect of the RVLM. The top two panels illustrate the baseline values for MAP and HR at the two tidal volumes (TV). The bottom panels illustrate the attenuated responses of MAP and HR to injection of lidocaine when the animal was ventilated at the reduced tidal volume ($n = 5$).

**Figure 3.** Shown are the differences in arterial $P_c_o_2$, $P_o_2$, baseline MAP, and percent change in MAP after injection of lidocaine under the different respiratory states (TV = tidal volume). Note that none of the blood values is correlated with the attenuated depressor response to the injection of lidocaine into the lateral RVLM. Asterisks indicate significant differences ($^*p < 0.05$) from control responses.
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the fall in MAP after the injection of lidocaine. Despite increased Pco₂, MAP fell similarly under these conditions as compared to control values. The pH values, a function of the arterial Pco₂ values, are also not correlated with the attenuated response to lidocaine. Thus, hypercapnia is not the determining factor that mediates the differential response to injection of lidocaine into the lateral RVLM.

The role of the sympathetic nervous system in maintaining arterial pressure under conditions of reduced tidal volume was next evaluated. In animals resired at normal tidal volumes, injection of lidocaine resulted in a -51 ± 2% change in MAP (from 113 ± 9 to 57 ± 5 mm Hg, n = 6). Reduction of tidal volume attenuated this response to -31 ± 4% change (from 131 ± 10 to 88 ± 5 mm Hg). Subsequent ganglionic blockade with trimethaphan (3.3 mg/kg) resulted in MAP falling to equivalent levels (37 ± 2 mm Hg at 2.5 ml tidal volume; 42 ± 4 mm Hg at 1.5 ml tidal volume).

Discussion

These experiments were designed to test the hypothesis that the respiratory system is integrally involved in regulating the role of the lateral aspect of the RVLM in the maintenance of arterial pressure. Figures 2 and 3 clearly illustrate that reducing tidal volume can significantly attenuate the depressor response to inactivation of this region. Figure 3 further shows that reduction of tidal volume is accompanied by changes in blood gas values. Systematic examination of hypoxia and hypercapnia as the afferent signals regulating the differential response revealed neither to be involved. Similarly, pH was not responsible for the attenuated response to inactivation of the lateral RVLM. Other candidates that may be involved in sensing the reduced tidal volume are pulmonary stretch receptors and chest wall proprioceptors.11

These data suggest that the lateral RVLM is not the only site capable of maintaining vasomotor tone. First, ganglionic blockade does decrease arterial pressure to similar levels regardless of tidal volume.12 Second, we have also shown that renal sympathetic nerve activity is as high or higher in animals that are ventilated at the reduced tidal volume.11 Together, these data demonstrate that sympathetic vasomotor tone remains high in animals ventilated at normal and reduced tidal volumes. Since sympathetic vasomotor tone originates in the central nervous system and we show that this region of the lateral RVLM is less responsible for the maintenance of vasomotor tone under reduced tidal volume, we can conclude that another site in the central nervous system must be activated to maintain sympathetic vasomotor tone at a normal or slightly elevated level. Thus, these data demonstrate that the systems that regulate vasomotor tone are dynamic and are capable of responding to challenges to the homeostatic balance of the organism.

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