Initiating inspiration outside the medulla does produce eupneic breathing

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ARTERIAL PaCO2 IS DICTATED by the ratio between the level of pulmonary gas exchange and alveolar ventilation (VA), not minute ventilation. If so, how could isocapnia be maintained if only the magnitude (tidal volume, VT) and duration (T1 and TTOT) of the neural output produced by the central pattern generator of breathing (CPG) can be altered? In other words, what is the strategy used by the respiratory control system to match its output to the level of pulmonary gas exchange to keep arterial blood gas homeostasis if this neural output contributes to dead space ventilation?

In this Viewpoint, we will show that when the spontaneous breathing is replaced by a cortically triggered breathing pattern at various breathing frequencies (we will name this new rhythm an “ecto-rhythm”), the relationship between TTOT and VT has a positive intercept that averages the pulmonary dead space. As a result, the coupling between ventilation and the pulmonary gas exchange becomes possible (17). We will present the idea that whenever isocapnia is maintained during spontaneous or automatic breathing, the magnitude and duration of breath cycles must display the same relationship as during an ecto-rhythm (15). Conversely, we will discuss the implications of the observation that breathing can display the same essential regulatory properties whether generated outside or within the pontomedullary CPG area (7).

**Ecto-rhythm, breathing pattern, and gas exchange: the relationship between tidal volume and breath duration as a prerequisite for PaCO2 homeostasis.** Figure 1 illustrates the breathing pattern adopted by one subject during volitional changes in frequency breathing. The inspiration of each respiratory cycle is initiated voluntarily following a brief auditory signal in which frequency is changed insidiously with a step or ramp-like pattern (ecto-rhythm). Although the subject does not volitionally control his tidal volume and inspiratory time, they both change linearly with the imposed TTOT, but in a non-proportional manner. Indeed, the TTOT-VT relationship has a positive intercept that takes the value of pulmonary dead space (VD). As a result, the TTOT-VT relationship has a slope that approximates the level of alveolar ventilation (VA). A strict proportionality between TTOT and VT, leading to a constant minute ventilation, would have been unable to maintain alveolar ventilation constant as f varies (see Ref. 17 for further explanation). One can therefore describe the relationship between the duration and the amplitude of all the breaths triggered volitionally as VT = VA × TTOT + VD. Such a relationship illustrates the strategy through which neural inputs to the respiratory motoneurons are coupled to the pulmonary gas exchange. Interestingly, neither the slope nor the intercept of the TTOT-VT relationship are affected by hyperoxia (17), suggesting that the fundamental characteristics of this relationship does not rely on CO2 chemosensitivity. Conversely, peripheral signals of chemical nature—as during exposure to 5% CO2 or when adding an experimental dead space—increase the slope and intercept of the TTOT-VT relationship and limit the rise in PaCO2 (15).

As discussed in the next paragraph, it is very likely that the structures controlling breathing during volitional and spontaneous breathing are different, nevertheless they both lead to the same outcome: maintaining blood gas homeostasis. It is therefore not surprising that that VT values during spontaneous breathing fall into the relationship established during an ecto-rhythm (Fig. 1). Indeed, during spontaneous ventilation, the relationship between the duration and amplitude of the respiratory output must follow, as a prerequisite for isocapnia, a linear relationship with a positive intercept and a slope averaging VD and VA, respectively. This should also remain true during various types of entrainment (1, 19, 24) if isocapnia is to be maintained regardless of the nature of the rhythm imposed by peripheral inputs. Any breath can thus be represented as one element of a “family” of breaths, which “share” the same PaCO2 as long as they all are on the same TTOT-VT relationship (isocapnic line). The level at which such a relation is elaborated is not known; this may include the pontomedullary CPG itself (for spontaneous resting breathing), the network of spinal and bulbar motoneurons (for volitional and spontaneous breathing), and must involve the integration of peripheral somatic chemical or vagal feedbacks (9) as suggested by the effects of hypercapnia or light exercise during an ecto-rhythm (15).

**Spontaneous and volitional inspiration: evidence for degeneracy in respiratory control.** The above observations nevertheless pose a conceptual challenge: as VT and T1 are generated following a rhythm imposed by the cortex, how could breathing be regulated, and more importantly how could the characteristics of the TTOT-VT relationship be modified by peripheral or central feedback such as hypercapnia and exercise (14). The structures implicated in an ecto-rhythm in humans are likely to be similar to those involved during the volitional contractions of the respiratory muscles (4, 12, 20, 21) following the corticospinal tract (6, 18, 25), whereas the medullary CPG “utilizes” the reticulo-spinal pathway.

A simple explanation would be to consider that the volitional initiation of inspiration is the result of cortical inputs relaying into some of the fundamental medullary structures initiating breathing (2, 3, 10, 11, 13, 26), the rest of the cycle including the production of T1 and VT may develop according to non-

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“mal” mechanisms producing spontaneous breathing. This explanation could, however, be challenged on several grounds. First, there is no evidence that the volitional act of triggering a breath relays in the structures initiating automatic breathing (5, 14). Although cortical inputs do affect various populations of medullary neurons in anesthetized cats (29), during behavioral response in unanesthetized cats (27), or in humans during voluntary inspiration (22), the nature and the effects of the medullary structures involved remain unknown (14, 16, 30).

Second, acute destruction of the reticulo-spinal pathway in the cervical cord in human abolishes spontaneous breathing but maintains the ability to mobilize lung volumes voluntarily (see Ref. 30 for review), although the respiratory efforts are somehow reduced. This observation has long been viewed as a proof that for a large part voluntary breathing does bypass the structures in the pontomedullary CPG elaborating automatic breathing, to make more direct synaptic connections with the spinal motoneurons. It seems therefore that it is the timing at which the respiratory motoneurons are activated to sustain rhythmic breathing activity rather than the structures imposing the frequency of breathing on the overall respiratory premotor and motoneurons that might be essential for establishing the empirical relationship between TTOT and VT.

The mechanisms controlling TTOT and VT and their relationship are therefore not all embedded into the medullary structures generating the automatic breathing rhythm. A profound
DISCLOSURES

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REFERENCES