Control of breathing and volitional respiratory rhythm in humans

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Haouzi P, Bell HJ. Control of breathing and volitional respiratory rhythm in humans. J Appl Physiol 106: 904–910, 2009.—When breathing frequency (f) is imperceptibly increased during a volitionally paced respiratory rhythm imposed by an auditory signal, tidal volume (VT) decreases such that minute ventilation (VE) rises according to f-induced dead-space ventilation changes (18). As a result, significant change in alveolar ventilation and PCO2 are prevented as f varies. The present study was performed to determine what regulatory properties are retained by the respiratory control system, wherein the spontaneous automatic rhythmic activity is replaced by a volitionally paced rhythm. Six volunteers were asked to trigger each breath cycle on hearing a brief auditory signal. The time interval between subsequent auditory signals was imperceptibly changed for 10–15 min, during 1) air breathing (condition 1), 2) the addition of a 300 ml of instrumental dead space (condition 2), 3) an increase in the inspired level of CO2 (condition 3), and 4) light exercise (condition 4). We found that as f was slowly increased the elaborated VT decreased in accordance to the background level of CO2 and metabolic rate. Indeed, for any given breath duration, VT was shifted upward in condition 2 vs. 1, whereas the slope of VT changes according to the volitionally was much steeper in conditions 3 and 4 vs. 1. The resulting changes in VE offset any f-induced changes in dead-space ventilation in all conditions. We conclude that there is an inherent, fundamental mechanism that elaborates VT based on f when imposed by the premotor cortex in humans. The chemoreflex and exercise drive to breath interacts with this cortically mediated rhythm maintaining alveolar rather than VE constant as f changes. The implications of our findings are discussed in the context of our current understanding of the central generation of breathing rhythm.

METHODS

Subjects. Six healthy volunteers were studied after being informed of the general purpose of the study and having provided their written consent to participate. All procedures in this study received prior approval through the research ethics committee of University Hospital of Nancy, Meurthe et Moselle, France, where all of the studies were conducted. The mean age, height, and weight of the volunteers were 35 yr (range 29–50), 1.75 m (range 1.65–1.90), and 72 kg (range 59–92), respectively.

Equipment. The equipment used has been previously described in detail (18). Briefly, the subjects were seated in a condition of relaxed wakefulness, with their eyes closed. Ventilation was recorded using a low dead-space face mask (Hans Rudolph, 7400 Oro-nasal series, small or medium size, Kansas City, KS) connected to a pneumotachograph (MediGraphics Prevent pneumotachograph, Medical Graphies, St. Paul, MN), connected in turn to a two-way valve. The total dead space of the face mask, the pneumotachograph, and the valve was 120–125 ml. Respired gas was continuously sampled for measurement of PCO2 as by a fast responding infra-red analyzer (Datex, Medical Graphics; Datex-Ohmeda Instrumentation, Helsinki, Finland). The respiratory flow and CO2 signals were digitized at 200 Hz (Power Lab system, AD Instruments) and displayed online using a microcomputer. The inspiratory flow signal was integrated to obtain VT separately from expiratory flow, and this was used to determine inspired ventilation, Ttot, f, inspired VE, and end-tidal PCO2 (PetCO2) were all determined on a breath-by-breath basis.

Protocol. Subjects were first familiarized and made comfortable with breathing through the experimental apparatus. After 15 min of

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Fig. 1. Left: the hypothetical condition of a respiratory control system wherein total minute ventilation (V˙E) remains constant (8 l/min) as breathing frequency (f) changes in a “subject” who has, as baseline ventilatory parameters (X), a “constant” dead-space (V˙D) of 0.2 liter, a spontaneous mean f of 10 breaths/min (i.e., TTOT = 0.10 min), and a V˙E of 8 l/min, such that alveolar ventilation (V˙A) is 6 l/min [alveolar P̄CO₂ (P̄A CO₂) = 40 Torr]. Any changes in dead space volume due to changes in tidal ventilation (V˙T) are therefore not represented here (see DISCUSSION). At top left, V˙E (continuous line) is displayed as a function of f. V˙D increases as f rises in a strictly proportional manner (broken lines, V˙D = V˙D· f = 0.2f). As a result, if V˙E remains constant, V˙A will decrease following the relationship V˙A = V˙D + V˙E = −0.2f + 8 (as illustrated by the difference between the continuous and the broken line). Center left illustrates the expected changes in arterial PCO₂ that would result from the lack of change in V˙E when f varies. Bottom left simply shows that, since V˙E remains constant, one can express the TTOT-V˙T relationship as a strictly proportional relation with a slope equal to V˙E (VT = TTOT· V˙E = 8TTOT). Middle: this case illustrates the conditions required to maintain V˙A constant (6 l/min), independent of the variation in f. The “subject” has the same baseline ventilatory parameters as at right (X). This condition would be the “ideal” situation wherein P̄CO₂ is maintained constant despite changes in f. In contrast to the left, V˙E must increase by the same amount as V˙D when f changes. Consequently, the slope of the f-V˙E relationship must have the magnitude of the V˙D (V˙E = V˙D· f = VA), and V˙A is the positive y intercept in that case: V˙E = 0.2f + 6. As can be seen on the bottom panel, V˙T is no longer simply proportional to TTOT, but the TTOT-V˙T relationship has a positive intercept with a magnitude equal to V˙D. Finally, the slope of this linear relationship is no longer V˙E, but V˙A (VT = VA·TTOT + V˙D). Right: the actual response observed in human subjects (18). Ventilation changes according to f, as one would expect from the condition presented in the middle panels, with a slope that has a magnitude corresponding to the value of V˙D. There was a trend for a small decrease in P̄A CO₂ (P̄A CO₂ was estimated from end-tidal P̄CO₂). As a consequence, we found that the TTOT-V˙T relationship displays a positive intercept that averaged −280 ml (and a slope of 6 l/min), consistent with a well regulated respiratory control system that would take into account the increase in V˙D as f varies.

Quiet breathing, their resting f was determined so that a brief auditory signal (few milliseconds) could be generated periodically with an interval of separation that corresponded to their average spontaneous resting f. The subject was then asked to follow this generated signal and initiate each of their breaths on hearing the auditory cue. Other than initiating inspiration when they heard the signal, subjects were asked to allow the rest of the breath cycle to develop as naturally as possible with no voluntary control of the magnitude of inspiration and expiration or their durations. The subjects were able to accomplish this successfully and breathe comfortably during the triggered breathing after one practice session at their own spontaneous respiratory rhythm. Three subjects who had also participated in a previous study did not need to perform this practice session. Once the subjects were familiar with the procedures involved, they participated in the experiments as follows. After 5 min of following the auditory signal at a pace corresponding to their spontaneous, resting f (again determined through monitoring 15 min of resting breathing cycles), the cycle length of the generated signal was shortened by 40 ms in each cycle until the f doubled (which took ~10 min). In other words, the duration of each breath cycle (TTOT) was shortened by 40 ms compared with the previous breath cycle. These gradual changes in TTOT were reported as being impossible to perceive by subjects, who were not made aware of the size or direction of change in imposed f. This was defined as the control condition, or condition 1 (Cond1).

This same protocol was repeated while breathing through a 300-ml instrumental dead space achieved using wide-bore tubing placed distally to the pneumotachograph (condition 2), and the fraction of inspired CO₂ (FICO₂) was increased to 3% (condition 3).

Thus conditions 1, 2, and 3 used a ramp-like increase in imposed f to determine whether V˙T can be effectively regulated in the presence of a cortically mediated f when blood gas homeostasis is altered via an...
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elevated background level of PaCO₂. All subjects completed the ramp increase in cortically triggered f in these three conditions in random order on separate days.

In a fourth condition, we also determined the effect of light intensity exercise on respiratory control during the implementation of a neo-rhythm (condition 4). For these tests, subjects were seated on an electromagnetically braked cycle ergometer (Lode Excalibur) breathing room air through the same equipment as in the aforementioned protocol. Ve and pulmonary gas exchange were also computed as mentioned earlier. The electrocardiogram was monitored from a three-lead configuration during all the procedures. After 3 min of constant work rate exercise (50 W), the spontaneous f was determined and breathing was then paced by an auditory signal at the same frequency as the spontaneous one. The frequency of the imposed f was then changed in a step-like manner for 2-min intervals. These step changes resulted in subjects breathing at six different frequencies imposed in a random order (ranging from 7.5 to 28 min⁻¹, depending on the spontaneous frequency of the subject). This condition differs therefore from conditions 1–3 since the changes in f were not progressive and the range of frequencies that was used included frequencies that were lower than the spontaneous f. In one last experimental condition, each subject also performed this same protocol at rest (f was changed between 6.5 and 25 min⁻¹) and this was used as a control comparison for condition 4. VT, Ttot, and VE were averaged over the last minute of each step change.

Data analysis. For the ramp-like change in Ttot, a linear regression analysis was applied to the breath-by-breath Ttot vs. VT and f vs. VE data plots for each subject. The rationale for using this analysis methodology has been described in a previous report (18) and will be addressed further in the discussion section. All breaths that occurred during the change in Ttot were included in the regression analysis (i.e., no filtering was applied to these data). A nonparametric test (Friedman or Wilcoxon) was used to compare conditions 1–3 and the changes in the f–VE and f–VT relationships increased by 2.51 l/min (R² = 0.52 ± 0.11). As a result, PETCO₂ did not significantly affect (6.12 ± 0.24 Torr; P = 0.05). As a result of this relationship, increased from 532 ± 105 ml (Δ = +238 ± 73 ml; P < 0.05), whereas the slope remained unaffected (Δ = 0.468 ± 0.678 l/min; P = not significant). As a result the f–VE regression line had a much steeper slope than control (0.55 ± 0.107 liter; P < 0.01), whereas the intercept was not significantly affected (6.123 ± 2.16 l/min). The increased f–VE slope (or Ttot–VT intercept) prevented any significant changes in alveolar PCO₂ when f was changed. As a result, the changes in PETCO₂ as a function of f averaged 0.10 ± 0.22 Torr per unit of f (Fig. 4).

Effect of additional dead space (condition 2). Baseline PETCO₂ in condition 2 was higher than in condition 1 (44.9 ± 5.38 vs. 41.8 ± 3.85 Torr; Δ = +3.13 ± 2.36 Torr; P < 0.05). The addition of a 300-ml dead space shifted the Ttot–VT relationship upward in all subjects. The positive y intercept of this relationship increased to 532 ± 105 ml (Δ = +238 ± 73 ml; P < 0.05), whereas the slope remained unaffected (Δ = 0.468 ± 0.678 l/min; P = not significant). As a result the f–VE regression line had a much steeper slope than control (0.55 ± 0.107 liter; P < 0.01), whereas the intercept was not significantly affected (6.123 ± 2.16 l/min). The increased f–VE slope (or Ttot–VT intercept) prevented any significant changes in alveolar PCO₂ when f was changed. As a result, the changes in PETCO₂ as a function of f averaged 0.10 ± 0.22 Torr per unit of f (Fig. 4).

Effect of 3% FiCO₂ (condition 3). During CO₂ inhalation, baseline PETCO₂ was significantly higher compared with the control condition, condition 1 (46.76 ± 4.17 vs. 41.8 ± 3.85 Torr; Δ = +4.9 ± 2.56 Torr; P < 0.05), but was not different from condition 2 where an increased dead space was applied. However, the characteristics of the ventilatory response in condition 3 was different from the response produced condition 2 in that the slope of the f–total ventilation relationship did not change (0.45 ± 0.24 liter) but the value of the positive y intercept almost doubled (9.03 ± 4.67 l/min; P < 0.05). This change in ventilation could be accounted for by the fact that, although VT remained strongly correlated to Ttot, it was the slope of this relationship that doubled (9.34 ± 5.12 l/min) and was significantly different from the control tests (Δ = +3.51 ± 3.01 l/min; P < 0.05) (Figs. 2 and 3). The slope of the change in PETCO₂ as a function of f was similar to the control tests (−0.20 ± 0.16 Torr per unit of f; Fig. 4).

Effect of increasing metabolic rate (condition 4). Exercise increased the level of CO₂ production by 3.2 ± 1.5 times (from 230 ± 11 to 791 ± 71 ml/min), whereas total ventilation doubled (from 11.17 ± 4.21 to 23.56 ± 4.19 l/min). Subject-by-subject analysis shows that the slope of the Ttot–VT relationship increased by ~3.4 ± 0.3 times (17.70 ± 5.63 vs. 5.73 ± 1.36 l/min; P < 0.01), while the intercept was not significantly affected (0.41 ± 0.33 vs. 0.279 ± 0.65; P = not significant). Since metabolic load was similar across subjects, VT was a function of the Ttot, whereas f was volitionally paced by the subjects, and therefore the data of all subjects fit along the same regression line illustrated in Fig. 5. The changes in PETCO₂ averaged −0.19 ± 0.12 Torr per unit of f. The average changes in PETCO₂ are shown in Table 1 for all conditions.

DISCUSSION

Respiratory motor outflow is patterned by the medullary respiratory centers to generate total ventilation (Ve) through

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alterations in the depth and rate of breathing, i.e., through changes in VT and f. However, it is V̇A and not V̇E that is the determinant of PCO₂ in the lung. Due to the existence of a pulmonary dead space (VD) in series with the regions of the lungs where gas exchange occurs (i.e., the alveolar space), the level of total ventilation (V̇E) produced by the respiratory centers can maintain a constant level of V̇A, or arterial PCO₂, only if V̇E changes offset the changes in the ventila-

![Graph](image)

**Fig. 2.** Online display of the breath-by-breath response of one subject to changes in the frequency of the auditory signal triggering breathing. *Left:* condition 1 (Cond1), air breathing; *middle:* condition 2 (Cond2), with an added 300 ml dead space; *right:* condition 3 (Cond3), while breathing 3% CO₂. FETCO₂: end-tidal CO₂ fraction; TTOTS, period of the auditory signal (s). Note that as f increases, VT decreases. The decrease in VT does not offset the rise in f so that ventilation increases without noticeable increase in FETCO₂. When breathing through an additional 300-ml dead space, VT is increased by the same amount at any given f (or TTOT). In contrast, during CO₂ breathing, the rise in VT becomes a function of TTOT resulting in a higher slope of the VT-TTOT relationship (see also Fig. 3). Note that, in this example, despite a higher FETCO₂ during the hypercapnic challenge than in control condition, there is, if anything, a slight, progressive decrease in FETCO₂ during the test as ventilation increases.

![Graph](image)

**Fig. 3.** Relationship between TTOT and VT for all breaths. Data were exported from the traces shown in Fig. 2. In control condition, VT was strongly correlated to TTOT. Note the positive intercept of the VT-TTOT linear regression line, which in this subject is ~300 ml. The positive intercept increased when a 300-ml experimental dead space was added, whereas the slope was primarily affected during CO₂ breathing.
tion of the dead space ($V_D = V_D \cdot f$) as $f$ is altered. In other words, as shown in Fig. 1, the slope of the $f-V_E$ relationship must have the magnitude of dead space if $P_{CO_2}$ is to be kept constant when $f$ varies. In this approach, we have considered the actual reduction in dead space resulting for the decrease in $V_T$ to be negligible since the increase in $V_D$ when $f$ rises is out of proportion of such a reduction. Assuming that dead space changes on average by 20 ml/l of $V_T$ (13), a decrease in $V_T$ of 0.5 liter would result in a reduction by 10 ml in $V_D$, which would be negligible in offsetting the effects of the change in $f$. In other words, a change in $f$ of 10 breaths/min is going to increase $V_D$ by 2–2.5 l/min, whereas the concomitant decrease in $V_T$ may offset this rise by at best 0.1 l/min. Finally, there is clear evidence in the literature that $CO_2$ per se has no significant effect on $V_D$ except from stretching the intrathoratic airways as $V_T$ increases in hypcapnia (20).

This simple prerequisite for $P_{ACO_2}$ homeostasis (Fig. 1) requires that either information related to changes in $V_D$ are made available for the respiratory control system so that $V_T$ can be adjusted to $f$ or that the $f-V_E$ relationship is mediated by intrinsic properties of the structures generating breathing. In this paper, we have described the breath-by-breath responses to changes in $f$ by plotting $V_E$ as a function of $f$ and $V_T$ as a function of $TTOT$. The latter expression has a direct physiological meaning in terms of control, since when $f$ is imposed on the respiratory control system by volitional control, this leaves only $V_T$ to be regulated by the automatic control system (18).

As in our previous report, we have observed in all subjects tested that when $f$ and therefore $TTOT$ was imposed volitionally, $V_T$ decreased and behaved as would be predicted in a situation of “ideal” regulation (see Fig. 1). $V_T$ was strongly correlated to $TTOT$ (and $V_E$ to $f$). The slope of this relationship averaged 5.8 l/min, close to expected values for $V_A$, whereas $V_E$ was 8.03 ± 0.9 l/min. Furthermore, we observed a positive

Table 1. $P_{ETCO_2}$ during the first and last minute of the ramp increase in breathing frequency

<table>
<thead>
<tr>
<th>$P_{ETCO_2}$, Torr</th>
<th>First Minute</th>
<th>Last Minute</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>41.8±3.8</td>
<td>39.2±4.7</td>
</tr>
<tr>
<td>Dead space</td>
<td>44.9±5.3</td>
<td>45.2±4.3</td>
</tr>
<tr>
<td>3% $CO_2$</td>
<td>46.7±4.1</td>
<td>44.1±4.6</td>
</tr>
<tr>
<td>Exercise*</td>
<td>43.4±5.4</td>
<td>41.1±6.4</td>
</tr>
</tbody>
</table>

Values are means ± SD. End-tidal $Pco_2$ ($P_{ETCO_2}$) is during the first minute [where imposed frequency was similar to spontaneous breathing frequency (f)] and the last minute (when f was highest) of the ramp increase in f in control condition, with an added dead space, and while breathing 3% CO2. *During exercise, data were obtained at a frequency equal to the spontaneous frequency (first minute) and during the last minute of a step change in imposed f with the highest f (last minute).
intercept in the T_{TOT}-VT relationship for each subject that averaged 290 ml, a figure that has the approximate magnitude of expected pulmonary dead space. The novel finding is that the relationship between a cortically mediated rhythm and VT was greatly influenced by the background level of p_{ACO2} and the level of metabolic rate, following a very predictable relationship that again allows VE to compensate for the changes in VD. As a result, the changes in VT and VE according to f clearly prevented significant changes in alveolar CO2 when f increased. To which extent blood gas homeostasis was perfectly maintained during all conditions can be disputed here. Indeed, we found that PETCO2 had a tendency to decrease in most subjects as f increases, whereas in few cases an increase in PETCO2 by few Torr was observed. These observations question, therefore, the validity of the view that isocapnia is being strictly maintained in all conditions. To do so would require total ventilation to increase by the exact same amount as VD when f varies. The methodological approach we used in the present study (PETCO2, measurement in awake human subjects) will certainly make such a property impossible to establish with sufficient accuracy. For instance, the small reduction in end-tidal CO2 that we observed is consistent with a truncation of the plateau as f increases rather than a real hypocapnia. Nevertheless, what the present study reveals is that significant changes in p_{ACO2} do not occur as f varies through an adjustment of VT that “takes into account” f-induced VD changes.

Influence of the level of metabolic rate and hypercapnia on the T_{TOT}-VT relationship. When we added a 300-ml external dead space to increase PETCO2, the respiratory control system seemed to “view” this intervention as an increase in pulmonary dead space and therefore altered VT appropriately. This alteration involved increasing the positive intercept of the linear function of the T_{TOT}-VT plot (i.e., an upward shift in the relationship), without any appreciable change in the slope of the line describing this function, as if the additional dead space was taken into account when elaborating the new T_{TOT}-VT relationship. In other words, the respiratory control system responds to an increase in dead space by simply maintaining the same increase in VT regardless of what T_{TOT} might be. This is consistent with the response to breathing through an increased dead space during spontaneous breathing as observed in most human subjects (12) and animals (3, 9, 10, 22), i.e., an increase in VT.

Adding CO2 to the inspired air also causes an increase in the PETCO2. However, this represents a condition quite different from the above condition of added dead space (7, 12). When PETCO2 was increased by adding CO2 to the inspired gas, all but one subject displayed an increase in the slope of the T_{TOT}-VT relationship. This result was never observed in any subject in the condition of added dead space, where it was the y intercept of the T_{TOT}-VT relationship that was affected. Since p_{ACO2} = PETCO2 + k·CO2/VE·VD, keeping p_{ACO2} constant when f is increased would require VT to change differently as a function of f or T_{TOT}, depending on whether it is VD or PETCO2 that is affected. We find it intriguing that the ventilatory responses to increases in p_{ACO2} represent an optimal approach to prevent additional changes in p_{ACO2} when f increases; when PETCO2 rises, the slope of the T_{TOT}-VT relationship increases, and, when an instrumental dead space is added, the y intercept of the relationship is increased.

Sensory feedback control mechanisms are likely responsible for the disparity in the response to hypercapnia when elicited via increased inspired CO2 or increased dead space, since both conditions result in a change respiratory chemoreflex feedback via the peripheral and/or central chemoreceptors. Since intrabreath CO2 oscillations in the arterial blood are larger with an experimental dead space compared with CO2 inhalation (7), the frequency response of the arterial chemoreceptors may be put forward as an explanation to account for the difference in ventilatory response to high inspired CO2 vs. increased dead space according to f changes.

When metabolic rate increases during exercise under physiological conditions, even by several fold, arterial pCO2 is maintained at a near-constant level by an appropriate increase in VA. The present results show that across each of the six subjects there was an increase in the slope of T_{TOT}-VT relationship during an increase in metabolism. This means that the respiratory system adjusted the magnitude of VT at any given imposed f according to the background status of CO2 production. Although the nature of the afferent signal(s) that encodes for changes in metabolic rate remains debated (16), our present observations show that a fundamental coupling between ventilation and metabolism is preserved even when f is imposed by volitional control and cannot be regulated by the automatic centers located in the medulla. Indeed, regardless of the precise nature of the feedback or feedforward mechanisms involved, they continue to operate even when breath cycle length (or f) is under volitional control. A volitionally paced respiration can therefore interact with chemical and nonchemical afferent feedback information to match ventilation to lung gas exchange.

Implications for respiratory control and respiratory rhythm generation. When f is voluntarily imposed, each breath cycle is most likely initiated by cortical regions of the brain known to be involved in the voluntary control of inspiration (5, 11, 29). How this voluntary activation of inspiration overrides the “automatic” pacing of breathing via the medulla remains a fascinating but unanswered question (15, 17). Pathways involved in the automatic control over the respiratory musculature follow the reticulo-spinal track and are thought to be anatomically dissociated from pathways involved in volitional control over the respiratory muscles, which follow the pyramidal tract (1, 23, 28, 30). For instance, the ability to generate volitional respiratory movements remains intact when the reticulo-spinal pathway, and thus motor outflow from the automatic breathing centers, is abolished (23). In addition, magnetic stimulation of the primary motor cortex where the respiratory muscles are represented provokes respiratory movements with little or no effect of the background rhythmicity of automatic breathing activity (6).

Various cortical structures, although different from the motor cortex, do interact with medullary respiratory neurons (25–27). However, whether the rhythmogenic components of the medullary respiratory control centres are involved in this interaction has never been shown (4, 15), the implications of our observations remain, however, unchanged. Any respiratory central pattern generator-related neuronal network(s) downstream of the volitional centers lose their governance over the determination of breath cycle length and yet the system retains fundamental regulatory properties minimizing changes in p_{ACO2} when f varies.

Although the neuro-anatomical structure(s), which may be involved in this regulatory process, have yet to be determined, our present data suggest that brain stem and cortical rhythm...
generators may feed into a common pool of neurons that are
within or part of the so-called central pattern generator to

determine VT according to f. Chemoreceptors (both central
and peripheral) and exercise stimuli might also feed into this pool
of neurons and thereby elicit a VT to maintain blood gases
irrespective of changes in Pco2 and metabolic rate. The iden-
tification of such structures remains essential if we are to
understand how breathing is regulated in physiologically rele-
vant situations. Structures with integrative respiratory func-
tions, such as those recently proposed for the retrotetropezoid
nucleus (RTN) (19, 24), which receives inputs from the pe-

deripheral chemoreceptors (31) and probably from supra-medul-

lar structures (14), may prove essential in awake humans
where the generation of breath cycles depends on a mix of
cortical and medullary influences, enabling PaCO2 homeostasis as
f varies.

Although the primary function of the human motor cortex is
not to generate respiratory motor activity aimed at maintaining
blood pH homeostasis, we found that a cortically imposed
breathing rhythm is influenced by regulatory feedback signals,
which ultimately result in a control over VA rather than total
ventilation. Our findings might be interpreted to mean that a
“nonrespiratory” structure (in this case the cortex), which as a
result of evolution is well developed and operational in human
beings, can be involved in a complex regulatory vegetative
processes such as respiratory control, in a manner where “mim-
ics” functions normally associated with medullary brain stem
structures. Such a scenario can be described as “degeneracy”
(8) by analogy to observations made in other biological sys-
tems (8) including breathing (2, 21).

In summary, when an increase in f is volitionally imposed
on the respiratory control system, VT decreases in such a way that
VA is kept constant. This regulation of VA points to the
existence of a fundamental mechanism that may well be an
innate property of the respiratory system. This mechanism,
which regulates VT as f changes, is influenced by the back-
ground level of PaCO2, and the level of metabolic rate, and
changes in these conditions cause predictable effects on the f
Ttot-VT relationship. The coupling between VT and f when
breathing pace is controlled volitionally allows VT to compensate
for changes in VD in a manner appropriate to the background CO2
status and metabolic rate. Finally, the observation that nonmed-
ullary respiratory structures capable of initiating breathing can
control respiration demonstrates the presence of profound degen-
eracy, i.e., distinct control structures yielding the same output.

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