

Response of Ventilator-Dependent Patients to Delayed Opening of Exhalation Valve

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In conventional mechanical ventilation, the inflation cycle often extends into neural expiration (T_{EN}), potentially exacerbating dynamic hyperinflation (DH). We wished to determine the extent to which patients defend against DH when this happens. Such defense may include prolongation of T_{EN} (timing response) and/or expiratory muscle recruitment (neuromuscular response). Fifty patients were ventilated in the Proportional Assist mode, allowing us to infer these responses noninvasively. At random intervals, exhalation of single breaths was delayed by briefly delaying the opening of exhalation valve (occlusion) (T_{occ} = 0.78 ± 0.34 seconds). Timing response was assessed from the change in T_{EN}. Neuromuscular response was assessed from the difference between volume exhaled after release of occlusion and volume exhaled in unoccluded breaths over a similar expiratory flow duration ($\Delta V_{\text{iso-time}}$). There was no evidence of an acute neuromuscular response; $\Delta V_{\text{iso-time}}$ averaged 0.005 ± 0.023 L (NS). Forty-five of 50 patients significantly lengthened T_{EN}. However, the timing response offset only 36 ± 20% of the delay in expiration. Because of absent neuromuscular responses and weak timing responses, DH increased in most patients in postocclusion breaths ($\Delta \text{DH} = 0.10 \pm 0.08 \text{ L}$, $p = 2E-10$). We conclude that acute compensatory responses to delays in opening of exhalation valve are weak in ventilator-dependent patients. As a result, such nonsynchrony tends to exacerbate DH.

Keywords: Hering-Breuer reflex; control of breathing; patient-ventilator interactions; dynamic hyperinflation; ineffective efforts

In pressure support ventilation (PSV) and assisted volume-cycled ventilation, the end of the ventilator's inflation cycle is not synchronized with the end of the patient's inspiratory effort. As a result, inflation may continue into the phase of neural expiration (1, 2). Although there has been no systematic documentation of the frequency and extent of this occurrence, theoretical analysis using realistic ventilator settings and patient characteristics (1), several published records (e.g., references 3–6), and unpublished personal observations on dozens of patients make it clear that this type of dys-synchrony is very common and often quite pronounced; the ventilator is triggered near the end of inspiratory effort, with the inflation cycle falling almost entirely during neural expiration (e.g., Figure 1 in reference 5). When the ventilator cycle extends into neural expiration, the time available for expiratory flow, before the next inspiratory effort, is reduced. If passive functional residual capacity is not reached during the abbreviated expiratory phase, dynamic hyperinflation (DH) results or is aggravated. DH increases the patient's work of breathing and makes it difficult for the patient to trigger the ventilator

(7). The most obvious manifestation of the latter is the occurrence of ineffective efforts (8–11), where a variable number of respiratory efforts fail to trigger the ventilator.

In laboratory animals (12–14), awake normal humans (15–19), and ambulatory patients with chronic obstructive pulmonary disease (COPD) (20), imposed delays in lung emptying during expiration evoke compensatory responses in the form of prolongation of neural expiration (T_{EN}) and, frequently, recruitment of expiratory muscles (21, 22). These responses mitigate the DH that would otherwise result: the former by making more time available for expiratory flow, and the latter through increasing expiratory flow in the available time. There is only very limited information ([23], see DISCUSSION) about whether, or to what extent, mechanically ventilated patients use these responses to defend against DH when the ventilator cycle extends into neural expiration.

In the present communication, we report on the neuromuscular and expiratory timing responses of ventilator-dependent patients after deliberate delays in the opening of the exhalation valve (end-inspiratory occlusions) in the proportional assist ventilation (PAV) mode (24). In this mode, the end of the inflation phase is automatically synchronized with the end of the patient's inspiratory effort. This makes it possible to obtain the desired information noninvasively. Thus, any prolongation in T_{EN} in response to the occlusions is expressed as an increase in the interval between end of inspiratory phase (i.e., beginning of the occlusion) and onset of next inspiratory effort. Furthermore, by comparing expiratory flow after the release of occlusion with expiratory flow after the opening of the exhalation valve in unoccluded breaths, it is possible to make inferences regarding neuromuscular responses that affect expiratory flow. A preliminary report of these findings has been published (25).

METHODS

We studied 50 patients who were intubated for acute respiratory failure. Further details of these methods may be found in the online data supplement.

Apparatus

We used a locally constructed, piston-based, multimode ventilator (Winnipeg Ventilator, Winnipeg, MB, Canada) (26). Flow (\dot{V}) and airway pressure (Paw) were measured. Data were digitized and stored on a computer disk.

Protocol

Preliminary estimates of passive elastance (E) and resistance (R) were made at the bedside using the interrupter technique (27) during a period of controlled ventilation (CMV). The patient was then switched to the PAV mode with volume assist (VA) and flow assist (FA) at 80% of the passive E and R. Subsequently, brief (0.4–1.6 seconds) end-inspiratory occlusions were applied to single breaths at random intervals.

Analysis

CMV data. The stored data were examined to determine passive E and inspiratory resistance (R_{insp}) using the interrupter technique. In addition, we measured expiratory resistance (R_{exp}) at different volumes

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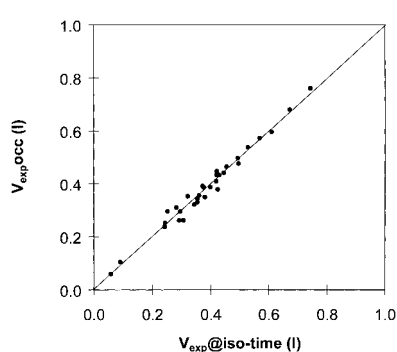


Figure 3. Relation between volume expired after release of occlusion and volume expired during control breaths over the same duration as the duration of flow postocclusion (see Figure 1). The *diagonal line* is the line of identity. Each *dot* is a separate patient. A value above the line of identity signifies an increase in forces that promote expiratory flow in the postocclusion period relative to control breaths.

Figure 2 shows the difference between expiratory and inspiratory resistance (i.e., ΔR), plotted against R_{insp} in individual patients. Six patients had ΔR values that were clearly outside the range observed in the others. Of these, the four patients with the highest values also had other features associated with severe COPD, namely an early expiratory flow spike due to dynamic compression of the airway (28, 29) and a very depressed flow rate throughout expiration, beyond the initial spike (see Figure E1 in the online data supplement). These patients will henceforth be termed to have “severe COPD.” In the other two patients in this group, the increase in R_{exp} was limited to low volumes, and there were no other manifestations of COPD. These patients will be referred to as having “possible COPD,” because flow limitation limited to the low volume range need not reflect obstructive disease but may be observed, in the absence of such disease, when FRC is low (e.g., in acute respiratory distress syndrome [30]). In the remaining 44 patients, ΔR averaged 0.9 ± 1.8 cm H₂O/L/second, and none displayed an early expiratory flow spike. The *horizontal dashed lines* in Figure 1 represent our estimate of the range of ΔR values that could be explained by technical errors.* This estimate is based on the fact that R_{exp} cannot, physiologically, be less than R_{insp} . Thus, negative ΔR values represent estimate errors and the most negative value (-4.5 cm H₂O/L/second) provides the outer boundary of negative errors in this group. A corresponding positive error boundary was assumed to exist.

A total of 1,745 occlusions was analyzed in 50 patients (34.9 \pm 14.2 per patient). The average (\pm SD) duration of occlusions was 0.78 ± 0.33 seconds. Average tidal volume in control breaths was 0.49 ± 0.14 L, with a range of 0.21–0.89 in different patients. RR and minute ventilation in control breaths were 24.2 ± 7.1 per minute, and 11.5 ± 3.7 L/minute, respectively. TiN and TeN in control breaths were 1.12 ± 0.26 and 1.61 ± 0.84 seconds, respectively. The inspiratory phase of occluded breaths (i.e., before the occlusions) did not differ from that in preceding “control” breaths in any respect (i.e., V_T , TiN) in any patient. The elastic recoil pressure (including PEEP) during occlusions ranged from 8.4 to 40.2 cm H₂O (19.1 ± 5.9 cm H₂O) in different patients.

The patients displayed a wide range of breath-by-breath variability in breathing pattern. The SD of V_T ranged from 0.02 to 0.17 L (0.08 ± 0.04) in different patients. This resulted

* The subtraction method for estimating ΔR is subject to errors due to: (1) Non-linearities in the P-V relation within the tidal volume range. These can cause small bidirectional errors in estimated alveolar pressure during expiration. (2) Differences between the actual K_2 value (of Rohrer’s equation) of the ET tube and the assumed value of a clean tube used here. This can again cause small bidirectional errors if the flows present during the inspiratory and expiratory measurements are different (see online data supplement for more detail).

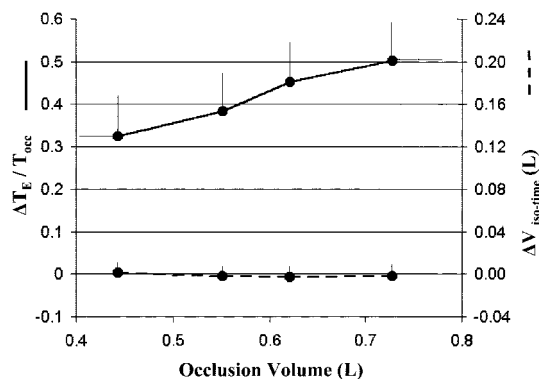


Figure 4. Average responses in 12 patients in whom responses were determined at different occlusion volumes. *Solid line*: timing response, expressed as the ratio of prolongation in TeN to occlusion duration. *Dashed line*: neuromuscular response, expressed as the difference between volume exhaled after occlusion and volume exhaled in control breaths over the same duration ($\Delta V_{\text{iso-time}}$, right axis). Bars are standard errors of the mean.

in coefficients of variation ranging from 0.05 to 0.39 (0.17 ± 0.08). In 12 patients, the SD of V_T was more than 0.1 L, and there were more than 40 observations in total, thereby permitting, after separation into V_T quartiles, analysis of the effect of occlusion V_T on responses in the same patients. None of these patients had evidence of COPD.

Neuromuscular Response to Delaying Mechanical Expiration

The volume exhaled after release of the occlusion before onset of the next inspiratory effort ($V_{\text{exp@occ}}$) averaged (\pm SD) 0.37 ± 0.14 L. The volume exhaled at iso-time in control breaths ($V_{\text{exp@iso-time}}$) was 0.37 ± 0.13 L. There was no significant difference between the two values, indicating that, on average, there was no effective neuromuscular response to increase expiratory flow in the aftermath of the occlusion. Figure 3 is a scatter plot of the two values in individual patients. It can be seen that the data points are scattered very close to the line of identity; the difference between the two values (i.e., $\Delta V_{\text{iso-time}}$) was 0.005 ± 0.023 L.

Figure 4 (*dashed line*) shows $\Delta V_{\text{iso-time}}$ as a function of occlusion volume in the 12 patients in whom this response could be determined over a range of occlusion volumes. $\Delta V_{\text{iso-time}}$ remained very small at all volumes in all patients, with the average response being essentially 0 at all volumes.

Response of TeN to Delaying Mechanical Expiration

The average TeN in occluded breaths (T_{Eocc}) was 1.91 ± 0.91 seconds. The corresponding value for control breaths was 1.61 ± 0.84 seconds. The difference (0.31 ± 0.27 seconds) was significant ($p = 4E - 11$). T_{Eocc} was significantly longer than control TeN in 45 of 50 patients.

The relation between ΔT_{EN} and the duration of occlusion (T_{occ}) is shown in Figure 5A. In general, the more the onset of expiratory flow was delayed (T_{occ}), the more TeN was prolonged (ΔT_{EN}). However, there was considerable scatter, with the ratio of ΔT_{EN} to T_{occ} ranging from -0.12 to 0.93. The average (\pm SD) ratio was 0.36 ± 0.20 , indicating that, on average, TeN prolongation neutralized only a third of the delay in onset of expiratory flow. Figure 6 contrasts the results of two patients, one (Figure 6A) with a strong timing response ($\Delta T_{\text{EN}}/T_{\text{occ}} = 0.8$) and the other with a weak response ($\Delta T_{\text{EN}}/T_{\text{occ}} = 0.08$).

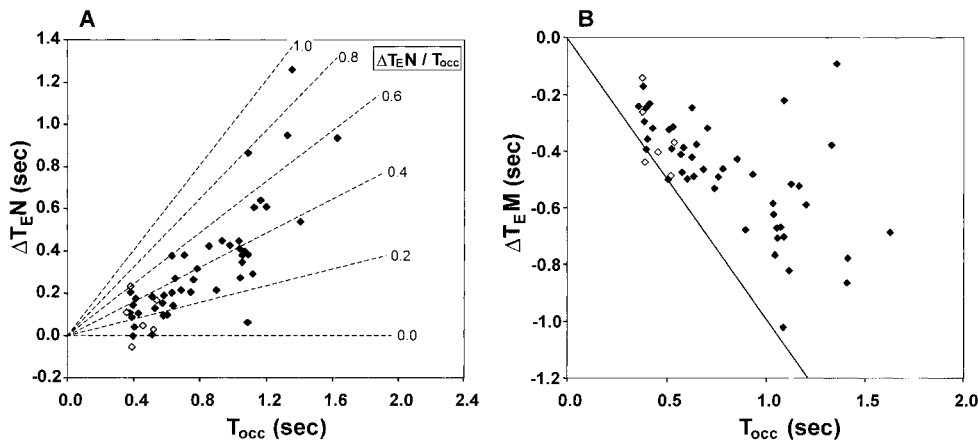


Figure 5. (A) Relation between the duration of occlusion and the extent of prolongation of neural expiratory time in different patients. Isopleths describe different strengths of the T_E response, expressed as the ratio of $\Delta T_{EN}/T_{occ}$. A ratio of 1.0 indicates complete compensation for the occlusion. (B) The magnitude of reduction in the duration of expiration flow as a function of occlusion time in individual patients. The solid line is the line of identity and indicates the response expected in the absence of changes in T_E . Note that all patients sustained a reduction in the duration of expiratory flow, although the magnitude was quite variable among patients. Open symbols ($n = 4$) are patients with severe COPD. Shaded symbols ($n = 2$) are patients with flow limitation at low lung volumes.

The response of the four patients with severe COPD was significantly lower than that of the others ($\Delta T_{EN}/T_{occ} = 0.09 \pm 0.18$ versus 0.38 ± 0.19 , $p = 0.002$) (open symbols, Figure 5). The response of the two patients with possible COPD was not different (shaded symbols, Figure 5).

The 12 patients in whom analysis of the effect of different occlusion volumes was possible showed a wide range of timing responses; $\Delta T_{EN}/T_{occ}$ (computed from all occlusions in the same patient) ranged from -0.01 to 0.93 . Figure 4 (solid line) shows that, on average, the timing response increased progressively with occlusion volume ($p = 0.008$ by analysis of variance for repeated measures). There was also a good correlation between individual responses at low and high occlusion volumes ($r = 0.79$, $p = 0.02$), indicating that patients with weak re-

sponses at low volumes continued to have weak responses at high volumes and vice versa.

Determinants of Strength of the Timing Response

Correlation analysis was performed between $\Delta T_{EN}/T_{occ}$ as the independent variable and the following 10 variables: age, sex, body mass index, V_T , V_E , T_I/T_E ratio of control breaths, the rapid shallow breathing index (RR/V_T), elastance (E_{rs}), ΔR (i.e., $R_{exp} - R_{insp}$), and P_{aw} during the occlusion (after subtracting PEEP), representing the change in elastic recoil pressure associated with the occluded V_T (i.e., P_{occ}). Only RR/V_T , T_I/T_E , P_{occ} , and ΔR showed significant correlations ($p < 0.05$) with $\Delta T_{EN}/T_{occ}$ in univariate analysis. When all 10 variables were entered in stepwise regression analysis, the only variables that were not eliminated were RR/V_T , which showed a negative correlation (coefficient = -0.003 fraction of T_{occ} per unit change in RR/V_T , $p < 0.01$), ΔR , which also showed a negative correlation (coefficient = -0.008 fraction of T_{occ} per unit difference in resistance, $p < 0.02$), and E_{rs} , which was positively correlated (coefficient = 0.005 fraction of T_{occ} per unit elastance, $p < 0.05$). The overall correlation coefficient for the final equation was 0.53 ($r^2 = 0.28$).

Effect of Occlusion on RR

The prolongation of T_{EN} necessarily resulted in a reduction of RR of the occluded breath. Figure 7 is a scatter plot of the change in RR as a function of T_{occ} . Virtually all patients sustained a reduction in RR. ΔRR was quite variable even at

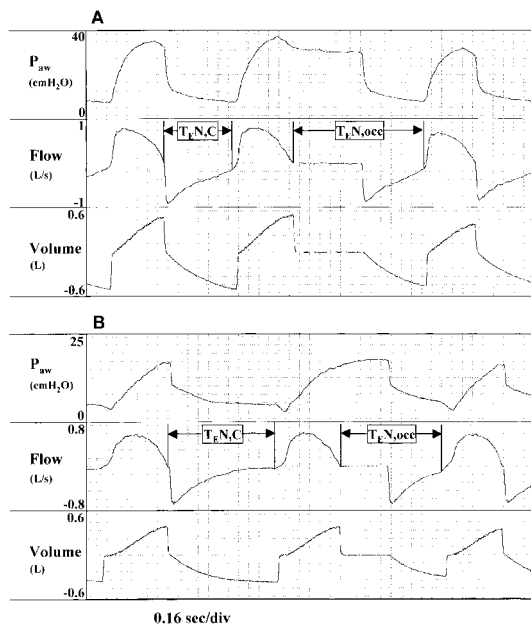


Figure 6. Examples from two patients illustrating very strong (A) and very weak T_{EN} responses. Note that in panel A the duration of expiratory flow was little affected by the long occlusion. The extent of DH (difference between exhaled volume of the occluded and pre-occluded breaths) is fairly small in both cases. In panel A this is because of the substantial prolongation of T_{EN} , which preserved T_{EM} . The minimal change in DH in panel B was because expiratory flow rate in the terminal part of unoccluded breaths was very low, so that reduction in the duration of expiratory flow had little consequence in terms of volume.

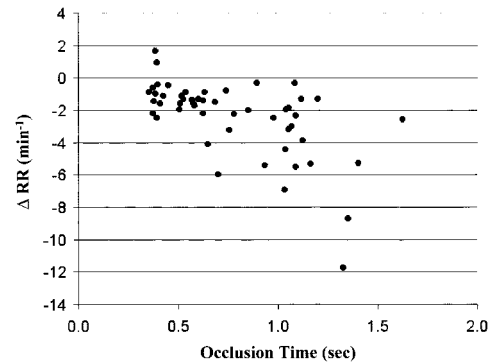


Figure 7. Change in RR (ΔRR) during occluded breaths, relative to control breaths, in individual patients. Results are plotted as a function of occlusion time.

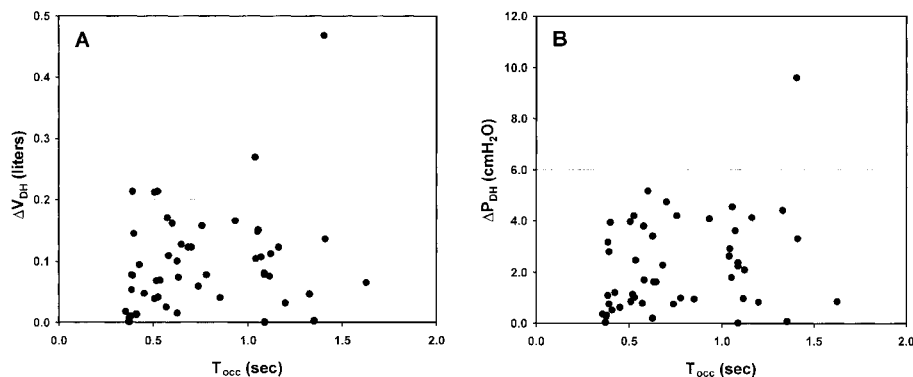


Figure 8. Change in DH as a function of the duration of occlusion. In *panel A* this is expressed in volume units, whereas in *panel B* it is expressed in pressure units. Note the lack of correlation between either variable and T_{occ} .

the same T_{occ} . In 10 patients (20%) it exceeded 6 breaths/minute. On average, ΔRR was -2.4 ± 2.4 /minute ($p < 0.0001$).

Effect of Occlusion on Mechanical Expiratory Time

Because the prolongation in T_{EN} was less than the duration of occlusion, the time available for expiratory flow (T_{EM}) was invariably reduced. Figure 5B shows the magnitude of reduction in T_{EM} in different patients as a function of T_{occ} . The solid line is the line of identity and shows the relation in the absence of prolongation in T_{EN} . In virtually all patients the reduction in T_{EM} was less than T_{occ} , reflecting the prolongation in T_{EN} described earlier (Figure 5A). Although the reduction in T_{EM} was correlated with T_{occ} ($r = 0.62$, $p < 0.0001$), there was much scatter, particularly with long T_{occ} . Thus, with a T_{occ} of approximately 1.4 seconds, the reduction in T_{EM} was as little as 0.09 seconds or as large as 0.9 seconds (Figure 5B). On average, T_{EM} decreased by 0.46 ± 0.20 seconds for an average T_{occ} of 0.77 ± 0.34 seconds.

Expiratory Flow in the Terminal Part of Expiration

The extent to which a given reduction in T_{EM} results in DH depends critically on the magnitude of expiratory flow in the terminal part of expiration ($\dot{V}_{exp,terminal}$). For example, if $\dot{V}_{exp,terminal}$ is close to 0, a 0.5-second reduction in T_{EM} would not appreciably increase DH. Conversely, if $\dot{V}_{exp,terminal}$ is high, small reductions in T_{EM} may result in an important increase in DH. Thus, $\dot{V}_{exp,terminal}$ determines the susceptibility to DH in response to changes in T_{EM} .

Expiratory flow at the onset of inspiratory efforts before occlusion (\dot{V}_0 , Figure 1) ranged from 0 to -0.42 L/second (-0.17 ± 0.12 L/second). Expiratory flow normally decreases in the latter part of expiration (e.g., Figures 1 and 6). To determine the average expiratory flow in that part of expiration corresponding to ΔT_{EM} (i.e., $\dot{V}_{exp,terminal}$), we calculated the slope of expiratory flow in the last 0.5 seconds of expiration[†] in control breaths ($\dot{V}_{exp,slope}$) and estimated $\dot{V}_{exp,terminal}$ from ($\dot{V}_0 - 0.5 [\Delta T_{EM} \times \dot{V}_{exp,slope}]$). The average slope was 0.24 ± 0.18 L/second². $\dot{V}_{exp,terminal}$ ranged from -0.02 to -0.63 (-0.23 ± 0.14) L/second, reflecting a wide range in susceptibility to DH among patients.

Effect of Occlusion on DH

Figure 8 shows the effect of delaying onset of expiratory flow on the magnitude of ΔDH in individual patients. ΔDH is expressed in volume units (ΔV_{DH} , Figure 8A), and in pressure

units (ΔP_{DH} , Figure 8B). End-expiratory lung volume immediately after the occluded breath increased, on average, 0.10 ± 0.08 L (Figure 8A), corresponding to 2.2 ± 1.9 cm H₂O in elastic recoil (Figure 8B). There was no significant correlation between T_{occ} and ΔDH whether the latter was expressed as volume or as pressure.

Effect of Delaying Expiratory Flow on Trigger Delay

The average trigger delay (interval between onset of inspiratory effort and ventilator triggering, T_{delay}) in control breaths was 0.23 ± 0.10 seconds. In 17 patients, some of the inspiratory efforts after the occluded breaths failed to trigger the ventilator. In these patients, the percent of ineffective postocclusion efforts ranged from 3 to 81% ($18 \pm 19\%$). The average percent ineffective postocclusion efforts in the entire group was $6 \pm 13\%$. For all triggered postocclusion efforts the average trigger delay was 0.29 ± 0.12 seconds. This was 0.06 ± 0.05 seconds longer than in control breaths ($p < 0.0001$). Figure 9 is a scatter plot of the magnitude of change in trigger delay (ΔT_{delay}) as a function of T_{occ} .

DISCUSSION

The main findings are that when, in ventilator-dependent patients, the onset of expiratory flow is delayed relative to the onset of neural expiration, (1) there is no effective neuromuscular response to speed up expiratory flow in the abbreviated time available for expiration; (2) there is compensatory prolongation in T_{EN} , but the response is generally weak offsetting, on average only 36% of the initial delay in onset of expiratory

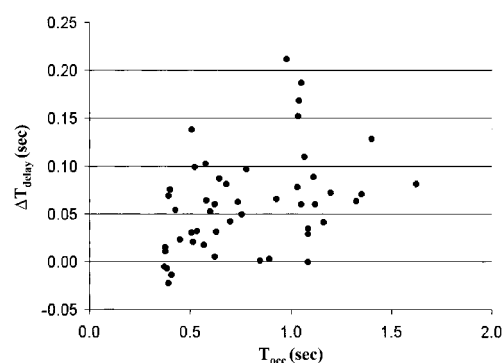


Figure 9. Change in trigger delay (ΔT_{delay}) following occluded breaths, relative to control breaths, in individual patients. Results are plotted as a function of occlusion time. Trigger delay is the interval between onset of inspiratory effort (T_0 , Figure 1) and ventilator triggering and includes the time required to reduce expiratory flow to 0 in the presence of DH.

[†] The slope of expiratory flow in the last 0.5 seconds of T_{EN} was estimated from: $\dot{V}_{exp,slope} = 2(\dot{V}_0 - \dot{V}_{-0.5})$, where $\dot{V}_{-0.5}$ is flow 0.5 seconds before T_0 .

flow; (3) as a result of weak responses, most patients sustain an increase in DH and trigger delay; and (4) the timing and DH responses are highly variable among patients.

Technical Considerations

The extent of muscular response to the expiratory occlusion was assessed from the difference between volume exhaled after release of occlusion and volume exhaled over a corresponding duration, beginning with the onset of T_{EM} , in unoccluded breaths. The two durations occurred at different times within T_{EN} (late T_{EN} in occluded breaths and early T_{EN} in control breaths, Figure 1), and volume history was different in the two cases. Because muscular pressure (P_{mus}) may normally change in the course of neural expiration,[‡] and viscoelastic behavior may have resulted in different elastic recoil pressure (P_{el}) at the onset of expiratory flow, it can be argued that the index we used may have missed an important increase in expiratory muscle pressure in response to the occlusion. We believe this is extremely unlikely because the two responses (change in P_{mus} and in passive recoil) tend to cancel each other in the course of occlusion. Thus, the decrease in inspiratory P_{mus} should, at the same volume, cause a progressive increase in P_{alv} , whereas viscoelastic behavior should result in a lower P_{alv} . In a separate analysis of the same data (32), we calculated the time course of change in alveolar pressure (P_{alv}) in the course of these occlusions. The change in P_{alv} during occlusion represents the net effect of changes in P_{mus} and P_{el} . We found that at high levels of assist, such as those used here ($\sim 80\%$), the two changes cancel out; the change in P_{alv} beyond the first 0.05 seconds of occlusion was 0.0 ± 1.05 cm H₂O (e.g., see P_{aw} in Figures 1 and 6). It follows that there should have been no systematic difference in the driving pressure at the onset of expiratory flow (i.e., P_{alv}) in occluded and unoccluded breaths, and any differences that may have existed in individual patients were small and bidirectional.

In the presence of flow limitation (FL), recruitment of expiratory muscles will not result in an increase in expiratory flow. It may be argued, therefore, that expiratory recruitment could have been missed because of the presence of expiratory FL. We believe that this is very unlikely for the following reasons: (1) The difference between $V_{exp,occ}$ and $V_{exp}@iso-time$ was minimal in all patients (Figure 3). For expiratory FL to explain this finding, all patients must have had FL, a possibility that is extremely unlikely in a general medical intensive care unit (ICU) and which was discounted by the ΔR results (Figure 2), or expiratory recruitment occurred exclusively in patients with FL. There is no functional or known neurophysiologic reason to expect this selectivity in response. (2) The indexes used ($V_{exp,occ}$ and $V_{exp}@iso-time$) represent the integration of flow over a substantial period (T_{EM} of occluded breaths), beginning with the onset of expiratory flow where lung volume is highest and FL is least likely. For there to be no difference, despite expiratory recruitment, FL must have been present throughout expiration. This occurs only in patients with very severe COPD. Only four patients (8%) could

be placed in this category. Although we cannot exclude expiratory recruitment in these patients, it would be extremely unlikely that such recruitment would occur exclusively in patients with very severe COPD. In fact, given that these patients demonstrated a smaller timing response, one would not expect them to display a stronger neuromuscular response; at least in laboratory animals, timing and neuromuscular responses appear to be linked (22).

It is difficult to envision a situation, in the absence of FL, where an important increase (e.g., > 2 cm H₂O) in expiratory muscle pressure related to the occlusion could have been missed. In the patient who had the largest difference between $V_{exp,occ}$ and $V_{exp}@iso-time$ (0.049 L, Figure 3), the increase in mean expiratory flow in the postocclusion period over the corresponding duration in control breaths was 0.08 L/second. Given this patient's resistance (8.0 cm H₂O/L/second, including tubing), the increase in mean V_{exp} could be accounted for by a difference in net forces of no more than 1 cm H₂O. Given that the differences between $V_{exp,occ}$ and $V_{exp}@iso-time$ were smaller in all patients (mean \pm SD = 0.005 ± 0.023 L), we believe we are justified in concluding that the patients did not mount a functionally important expiratory muscle response.

The aforementioned conclusion does not entirely rule out an increase in the electrical activity of expiratory muscles. Although demonstration of such a response, if any, may be of interest from a neurophysiologic perspective, it would not be interpretable in functional terms without the demonstration of a change in expiratory muscle pressure; the units by which electrical activity of respiratory muscles is measured (volts) are, *per se*, meaningless in terms of mechanical action. We elected to proceed directly to a mechanical index because we were primarily interested in functionally important responses.

Neural timing was also estimated indirectly from mechanical variables. The end of neural expiration was identified as the point at which expiratory flow and P_{aw} deviated, in an inspiratory direction, from their earlier trajectories. According to the equation of motion ($P_{mus} = \dot{V} \cdot R + V \cdot E - P_{aw}$) such a change could only occur if P_{mus} changed in an inspiratory direction (see section B in the online data supplement). Although this could occur either because of an increase in inspiratory P_{mus} or, in the presence of phasic expiratory activity, decline in expiratory P_{mus} , in practice either event defines the end of neural expiration.

The point at which inspiratory flow ended was used to define the onset of T_{EN} . In PAV, this point invariably occurs during the declining phase of inspiratory P_{mus} (24, 32). The validity of this approach depends on how one defines T_{iN} and T_{EN} . If, as is customary, the transition from T_{iN} to T_{EN} is defined from the point at which inspiratory activity begins declining rapidly (33), then our reported absolute values of T_{iN} slightly overestimate T_{iN} , and the reported T_{EN} slightly underestimates T_{EN} . Such discrepancies between reported and actual absolute values of T_{iN} and T_{EN} should, however, have no impact on the variable of interest (namely, change in T_{EN} in response to occlusion). Because the occlusion began at the end of inspiratory flow, and there was no intervention before this point, any difference between reported and actual absolute T_{EN} was the same for "control" and occluded breaths. Thus, any real change in T_{EN} in occluded breaths was faithfully expressed in our reported ΔT_{EN} .

Neuromuscular Response

In anesthetized animals, occlusion during expiration is associated with expiratory muscle activation (21, 22). Such recruitment may, therefore, have been expected in the current study. The lack of a functionally important increase in expiratory

[‡] During PAV, flow reversal (onset of T_{EM}) occurs, as it does normally (31), during the declining phase of inspiratory P_{mus} (24). There is, therefore, some residual inspiratory P_{mus} at the beginning of T_{EM} , which causes some braking of V_{exp} . This inspiratory P_{mus} dissipates over a fraction of a second (32). To the extent that this early braking influence disappears later, the effect would be to cause V_{exp} to be higher after the occlusion, even in the absence of occlusion-related expiratory muscle recruitment. The presence of phasic expiratory P_{mus} , unrelated to the occlusion, would also favor a higher V_{exp} in the postocclusion breaths, relative to control breaths, because phasic expiratory activity, if present, is higher later in T_{EN} (33).

pressure is probably related to the fact that the increase in activity observed in animals is strictly related to the vagally mediated prolongation of T_{EN} , which permits the ramping phasic expiratory activity to progress to a higher level (22). In our patients, the prolongation of T_{EN} was modest. Furthermore, inflation during expiration actually delays the onset of phasic expiratory activity when the latter is present in unobstructed breaths (22). Thus, there are two opposing responses to lung inflation during expiration, one (delayed onset) that tends to decrease expiratory activity at comparable times during T_{EN} , and another that tends to increase it through T_{EN} prolongation. The likely explanation for our finding is that the two responses canceled each other out. Our findings do not preclude recruitment of expiratory muscles in the steady state. Delaying onset of expiratory flow results in respiratory slowing (Figure 7) and, unless V_T is concomitantly increased, reduction in \dot{V}_E . Expiratory muscles may be recruited later as a result of the increase in chemical drive. Our results indicate that if delayed expiration, when sustained breath after breath, is associated with expiratory muscle recruitment, the recruitment is chemically, and not reflexly, mediated.

The absence of a functionally important neuromuscular response was evident in all patients, even though in many patients elastic recoil pressure during the occlusion was more than 20 cm H_2O , and in some it was greater than 30 cm H_2O (Paw during occlusion was 19.1 ± 5.9 cm H_2O). These pressures are associated with volumes near the patient's pathophysiological total lung capacity. That a response was absent in all these patients, and at the largest volumes in 12 patients (Figure 4), indicates that the negative results were not due to failure to reach a high threshold for recruitment of expiratory muscles.

Timing Responses

In the absence of significant expiratory muscle recruitment, compensation for the delayed onset of mechanical expiration is entirely dependent on prolongation of T_{EN} . Although statistically significant prolongation occurred in 45 of 50 patients, the response was incomplete, and fairly weak in most patients (Figure 5A). On average T_{EN} prolongation countered less than 40% of the initial delay. As a result, the duration of mechanical expiration decreased in nearly all patients (Figure 5B).

To our knowledge, there has been only one study that assessed the response of T_{EN} to changes in timing of ventilator cycling off, relative to end of neural T_I , in mechanically ventilated patients. Kondili and coworkers measured the change in T_{EN} when V_T was increased at constant flow (i.e., mechanical T_I was increased [23]). They found that the increase in T_{EN} was, on average, equal to the increase in delay between ventilator cycling off and end of neural T_I . On the basis of their findings, one may conclude that the timing response is powerful and results in complete compensation. This is clearly different from what was seen here ($\Delta T_{EN}/T_{occ} = 0.36 \pm 0.2$). Several factors can account for this difference. First, they only studied patients with acute respiratory distress syndrome. We studied a larger population with assorted clinical disorders, representative of the general ICU population. Second, the range of delays examined by Kondili and coworkers (23) was very limited. With the longest delay, the interval between end of ventilator T_I and end of neural T_I (defined as onset of decline in inspiratory P_{mus}) was only 0.44 seconds. In our study, delays ranged from 0.4 to 1.6 seconds, measured from zero flow crossing. When it is considered that flow crossing in PAV occurs on the declining phase of P_{mus} , sometime beyond the onset of decline in inspiratory P_{mus} (32), the range of delays examined here is well beyond that examined in their study.

Third, baseline T_{EN} , with which the T_{EN} of the delayed breaths was compared, was associated with a smaller V_T . It is, therefore, not possible to ascertain how much of the increase in T_{EN} was related to increased delay and how much to the increased V_T , relative to baseline; an increase in V_T , even without lengthening ventilator T_I , also lengthens T_{EN} (19, 34, 35).

The timing response was highly variable among patients. Correlation analysis with many potentially relevant variables revealed a significant effect for only three: elastance, ΔR , and the rapid shallow breathing index. Collectively, however, these variables accounted for only 28% of the scatter. It follows that the strength of this compensatory response is largely unpredictable.

The correlation with the rapid shallow breathing index (RR/V_T) was negative. Thus, patients with rapid shallow breathing are, all else being the same, less equipped to deal with delays in onset of expiratory flow. The multiple regression coefficient was -0.003 . Quantitatively, this translates into an average difference in $\Delta T_{EN}/T_{occ}$ of 0.3 across the range of RR/V_T observed (RR/V_T averaged 55 ± 30 per minute per liter). Thus, whereas in an average patient with RR/V_T of 55, ΔT_{EN} is 36% of T_{occ} , a patient with RR/V_T of 125 would have, on average, a ΔT_{EN} of only 15% of T_{occ} . The mechanism of this association between RR/V_T and $\Delta T_{EN}/T_{occ}$ is not clear.

The most obvious mechanism to explain T_{EN} prolongation is the Hering-Breuer (HB) reflex (36). In awake (37), sleeping (37), and anesthetized (22) animals, maintaining the lung inflated, even at very modest volumes, throughout expiration invariably causes a vagally mediated prolongation, often marked, of T_{EN} . When inflations are maintained for only a fraction of T_{EN} , and withdrawn before the onset of the next inspiration (as in the present study), there is still (in animals) a prolongation of T_{EN} , evidencing residual after effect (memory) from the earlier inflation (14, 38). The main difficulty with advocating this mechanism is that, unlike sleeping animals (37), in sleeping humans the lungs must be maintained inflated at volumes in excess of half inspiratory capacity for any T_{EN} prolongation to be observed (39, 40). Evidently, then, this expiratory prolonging HB reflex has a high volume threshold in humans. Because the HB reflex is mediated by pulmonary stretch receptors that respond to transpulmonary pressure (41), and in view of the increased lung stiffness in most of our patients, it is possible that the threshold was reached even though V_T (0.49 ± 0.14 L) was considerably less than one-half of a normal inspiratory capacity. The strength of the timing response correlated positively with elastance and negatively with ΔR , an index of dynamic collapse of the airways during expiration, and by extension, of loss of elastic support of airways. These observations are in keeping with a contribution from airway stretch receptors to the response. However, the variability in response could only be explained to a small extent by these variables. Two explanations may be entertained: (1) There is considerable variability in the strength of this reflex even among healthy animals (42). Thus, innate variability may have contributed to the considerable variability in response among patients (Figure 5A). (2) In conscious normal humans, delaying lung emptying using an expiratory resistance is associated with considerable prolongation of T_{EN} (15–17). Likewise, in mechanically ventilated awake normal subjects, introduction of a pause at the end of inflation markedly lengthens cycle duration (18). These responses are to be contrasted with the absence of timing responses to complete expiratory obstructions at moderate tidal volumes in sleeping normal humans (39, 40). The different responses in awake and sleeping humans cannot be explained by a sleep effect on HB expiratory prolonging reflex; this response remains very strong

during sleep (37), and even under deep anesthesia (22), in animals. It is, therefore, likely that other mechanisms exist that cause expiratory lengthening when expiratory flow is retarded and that are operative only in the conscious state. These mechanisms, whose nature is unclear, may have been operative in our patients, many of whom were conscious.

On average, ΔT_{EN} in the current study was considerably less than the prolongation observed in awake normal subjects. For example, in the study of Laghi and colleagues (18) in mechanically ventilated awake normal subjects, the addition of a 2-second pause lengthened cycle duration by 1.7 seconds, or 85% of pause duration. By contrast, in the current study, prolongation of cycle duration, as expressed in ΔT_{EN} , was only 36% of occlusion (pause) duration. The weaker response in the patients may reflect their generally less alert state, when the mechanism involved is sensitive to level of consciousness (LOC). We did not formally document LOC. However, because patients were not selected on the basis of LOC, we expect that LOC covered the usual range encountered in a general ICU (alert to comatose). Whether this accounts for the variability in response remains to be determined.

We do not believe the T_{EN} prolongation was a nonautomatic behavioral response to the occlusion. In a separate report on the same patients (32), we carefully looked for evidence of new respiratory muscle action in the course of these occlusions. Less than 1% of occlusions displayed motor acts that could possibly be considered nonautomatic (32). These rare occlusions were not considered in the present study. It would be extremely unlikely for T_{EN} prolongation to represent a nonautomatic behavioral response after the occlusion when there were no nonautomatic motor responses during the occlusion.

Patients with severe COPD had a significantly depressed timing response. In a recent study on ambulatory stable patients with COPD connected to a ventilator via a mouthpiece, Laghi and colleagues found that delaying the opening of the exhalation valve by 2 seconds was associated with a 1.34-second (i.e., 67% of pause duration) increase in cycle time (20). Although somewhat less than the response observed in normal subjects under similar conditions (85%, [18]), it was still a substantial response in comparison with our patients (9% of occlusion time). The differences may reflect differences in LOC (the patients in Laghi and coworkers' study were fully alert). Alternatively, the patients in Laghi and coworkers' study (20) may not have been as severely affected as our four patients. Regardless of the reason, patients with severe COPD on mechanical ventilation in the ICU are very poorly equipped to deal with delays in onset of expiration.

The increase in timing response with occlusion volume in the same patients (Figure 4) is to be expected, given that these expiratory timing responses are well known to be volume dependent both in animals (14, 22, 37, 38) and humans (39, 40). It is noteworthy that even in the highest volume range, the response remained rather weak ($\Delta T_{EN}/T_{occ} = 0.5$), and highly variable ($SD \pm 0.28$). In fact, there were four patients with V_T greater than 0.8 L in this subset (0.83, 0.89, 0.92, and 1.04 L). Their timing ratios were 0.51, 0.38, 0.15, and 0.86, respectively. Thus, the main conclusion regarding the timing response, namely that it is variable but generally weak, is not related to a generally lower (than used in practice with other modes) V_T with PAV (43).

In the volume-cycled and pressure support modes, volume usually increases in the interval between end of inspiratory effort and end of ventilator cycle. In the current study, volume was kept constant in this interval. It may be argued that the responses may be different if volume increases during the period

of delay in ventilator cycling off. This possibility is difficult to address in practice, as well as being very unlikely given the totality of our results. The practical difficulty of addressing this issue stems from the fact that, in practice, there is a wide variety of patterns and rates of increase in volume during the period of delay.[§] It would be impractical to design experiments to address all these patterns and also not to cause concurrent changes in ventilator output during inspiration, which would greatly confound interpretation. In the current study, we examined the responses when volume was kept constant at a low value (0.44 ± 0.17 L) during the delay and when volume was higher by, on average, 0.3 L at the same delay (Figure 4). These two conditions essentially cover the extremes of possible changes in volume, encountered in practice, during the delay. That the same range of responses was seen in the high and low volume ranges, as well as the fact that patients who had weak responses at low volumes continued to have weak responses at the high volume (and vice versa), strongly suggest that our current conclusions apply equally to situations in which volume increases during the delay. The timing response may be expected to be somewhat higher if volume increased during the delay, simply because volume at the end of the delay would be higher than otherwise. However, there is little reason to believe that the act of volume increasing specifically *during* the delay will convert a weak responder to a strong responder, or vice versa.

DH and Trigger Delay

The changes in end-expiratory lung volume (ΔV_{DH}) and elastic recoil pressure (ΔP_{DH}) in response to delaying expiration were highly variable (Figure 8). Delays of as little as 0.4 seconds could result in an increase in end-expiratory volume (EEV) greater than 0.2 L and in end-expiratory pressure (i.e., $PEEP_i$) greater than 4.0 cm H₂O. Conversely, the changes in these variables with much longer delays (e.g., > 1.0 seconds) could be considerably less (Figure 8). There are two major factors that account for this variable response to a given T_{occ} . First, the actual reduction in the duration of expiratory flow (T_{EM}), at a given T_{occ} , was quite variable depending on the strength of the T_{EN} response (Figure 5). Second, for a given reduction in T_{EM} , the extent of increase in EEV is very dependent on the magnitude of expiratory flow rate in the terminal part of expiration ($\dot{V}_{exp,terminal}$), and this was highly variable among patients (-0.23 ± 0.14 L/second). Thus, if expiratory flow in the interval before the onset of T_i , and corresponding to ΔT_{EM} , is close to zero (e.g., Figure 6B), the reduction in T_{EM} will have little consequence on EEV and, hence, $PEEP_i$. Conversely, if $\dot{V}_{exp,terminal}$ is high, even a small reduction in T_{EM} can result in a large increase in EEV. The importance of these two variables (i.e., strength of T_{EN} response [$\Delta T_{EN}/T_{occ}$] and $\dot{V}_{exp,terminal}$) is emphasized by the fact that, for a given T_{occ} , ΔV_{DH} can be precisely predicted from the equation: $pred. \Delta V_{DH} = T_{occ}(1 - \Delta T_{EN}/T_{occ}) \cdot \dot{V}_{exp,terminal}$. This prediction equation had a correlation coefficient (with actual

[§] In some ventilators, the last part of the inflation cycle may have no volume increase, or volume may increase initially during the delay but remain constant later on (e.g., Evita ventilator with the autoflow function switched off). Alternatively, with square-flow patterns, volume will increase at the same rate that applied throughout inflation, and this rate varies considerably from patient to patient. In the decelerating flow pattern of volume-cycled ventilation, volume increases at a progressively decreasing rate and this deceleration pattern varies among ventilators. Finally, in the PSV mode, volume also increases at a decelerating rate with the deceleration pattern being extremely variable depending on respiratory mechanics and pattern of inspiratory muscle pressure beyond the end of inspiratory effort.

ΔV_{DH}) of 0.96 with a slope of 0.98 and intercept of 0. This agreement further emphasizes the lack of any significant other responses to defend against DH.

As may be expected (as a consequence of the increase in PEEP), trigger delay was lengthened in nearly all patients (Figure 9). The magnitude of this response was quite variable, reflecting the wide range of ΔP_{DH} (Figure 8B) and the expected wide range in $\Delta P_{mus}/\Delta t$ in the early phase of inspiratory effort.

On average, 6% of postocclusion inspiratory efforts failed to trigger the ventilator. Leung and associates reported that approximately 28% of efforts are ineffective in patients placed in the PSV or volume-cycled modes at a V_T of 10 ml/kg (9). This much higher incidence during routine ventilator care suggests that the degree of nonsynchrony between the end of the ventilator's and the patient's inspiratory cycles under these conditions is considerably more pronounced than was deliberately induced here (average $T_{occ} = 0.78 \pm 0.34$ seconds). In other words, we believe that the delays imposed in the present study are likely to be well within the range of delays that occur during routine ventilator care.

Clinical Implications

The current study shows that, all else being the same, delays in onset of mechanical expiration relative to neural expiration will tend to: (1) Increase DH with, consequently, an increase in trigger delay and in frequency of ineffective efforts. This is primarily due to lack of a reflex (i.e., immediate) neuromuscular response to effectively expedite expiratory flow in the abbreviated T_{EM} , and secondarily, to incomplete timing response in most patients. (2) Decrease ventilation. This is in part due to slowing of the patient's RR and in part to promotion of ineffective efforts.

In practice, these primary effects of delayed cycling-off may be enhanced or mitigated by other ventilator settings that affect overall level of ventilation and respiratory timing via chemical and other neural mechanisms (*see* reference 44 for review). Nonetheless, this study shows that delayed cycling off, *per se*, has adverse consequences that, if not offset by other ventilator settings, will inevitably lead to an increase in chemical drive and respiratory efforts.

In the current study, the delay in onset of expiration was applied for only one breath. The results, therefore, need not reflect what might happen in the steady state. The latter, it may be argued, is what is clinically relevant. Although steady state responses need to be documented, we believe that identifying the immediate responses is valuable in that these responses point out the primary changes that will challenge the respiratory control system. In fact, interpretation of steady state changes may be difficult without knowledge of the immediate responses. For example, an immediate response that causes a reduction in \dot{V}_E will, in due time, evoke secondary responses (e.g., via chemical feedback) that may restore \dot{V}_E toward the pre-intervention value. Without knowledge of the immediate responses, an unchanged steady state \dot{V}_E may lead to the false impression that the intervention is inconsequential. With knowledge of the immediate responses, it will be realized that the maintenance of \dot{V}_E was at the expense of increased respiratory drive and efforts.

Patients vary considerably in their susceptibility to DH in response to cycling delays. This susceptibility can, to a considerable extent, be assessed at the bedside by noting the magnitude of expiratory flow just before the onset of inspiratory effort (defined here as the point at which flow and Paw deviate, in an inspiratory direction, from the trajectory established earlier in expiration, Figure 1). The higher this terminal flow value, the more susceptible the patient is, and the more care-

ful one needs to be to avoid cycling delays. Given the relatively weak timing responses observed here ($\Delta T_E/T_{occ} = 0.37 \pm 0.2$) and the resulting magnitude of DH (Equation 1), the increase in DH as a result of delays is, on average, two-thirds (i.e., $1.00 - 0.37$) of the value of terminal flow per second of delay. As a corollary, a patient with a terminal expiratory flow of, for example, 0.4 L/second is likely to benefit substantially (in terms of reduced DH and, by extension, reduced inspiratory effort) from measures that would reduce or eliminate the cycling delay, whereas in a patient with a near zero terminal flow such measures would have little consequence in terms of DH.

Patients with severe COPD are notably lacking in timing responses. In them, mechanical T_E decreases on a nearly 1:1 basis with increases in delay. This, and their need for a long exhalation time, makes them particularly vulnerable to developing more DH in the presence of delays.

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