A Method for Noninvasive Determination of Inspiratory Resistance during Proportional Assist Ventilation

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Currently available noninvasive methods for measuring inspiratory resistance (Ri) are difficult to implement or interpret during assisted mechanical ventilation on account of the confounding effect of respiratory efforts (Pmus). We propose a simple method consisting of brief reductions in airway pressure (Paw) in the early part of the inflation phase (pulse). Paw, flow (V), and volume (V) are measured at the beginning of the pulse (T0), at the trough of the pulse (T1) and at a point 0.1 s before T0 (T-1). Equations of motion of the form \[ P_{mus} + P_{aw} = V \cdot K_1 + V^2 \cdot K_2 + V \cdot E \] are generated for the data at the three time points (E = elastance, K1 and K2 are Rohrer's constants). These three equations can be solved for K1 and K2 if it is arranged that the pulse has appropriate configuration and timing, and if it is assumed that \[ \Delta P_{mus}/\Delta t \] is constant over the brief pulse period. The method was tested in 67 patients ventilated with proportional assist ventilation (PAV). The results were compared with those obtained using the interrupter technique during a period of controlled mechanical ventilation (CMV). Ri, expressed at a standard flow of 1 L \cdot s^{-1}, was slightly higher during PAV (16.4 ± 4.9 versus 15.5 ± 4.5 cm H2O \cdot L^{-1} \cdot s, p < 0.001). The average difference was 0.9 ± 2.0 cm H2O \cdot L^{-1} \cdot s, corresponding to 5.4 ± 12.6% of the average of RCMV and RPAV. The correlation coefficient was 0.92 (p = 8E–28) with a slope (1.01) and intercept (0.8) not significantly different from 1.0 and 0, respectively. We conclude that brief negative pulses applied early during the inflation phase can be used to provide reliable estimates of inspiratory resistance during PAV.

Noninvasive determination of respiratory system resistance (R) in the absence of respiratory muscle output (Pmus), e.g., during controlled mechanical ventilation (CMV), presents little difficulty. Under these conditions the pressure provided by the ventilator is the only applied force and this force is dissipated against resistive and elastic elements which are functions of flow (V) and volume (V), respectively. Because V and V can readily be measured noninvasively, the resistive and elastic properties can readily be determined from two or more points having different values of V and V. Calculation of resistance can be made using either regression analysis (1) or, more commonly, using the interrupter technique (2, 3). These techniques, however, cannot be used in the presence of respiratory muscle effort, such as during assisted ventilation (3), because under these conditions the applied force includes a highly variable component generated by the patient (Pmus). At present, therefore, reliable determination of R requires either the insertion of an esophageal catheter, which adds another invasive intervention to already much instrumented patients, or the abolition of respiratory muscle efforts by paralysis or hyperventilation. The latter procedure is disruptive and labor-intensive.

The work described here was motivated by two considerations:

First, there is every reason to expect that resistance may change spontaneously, and substantially, in the course of mechanical ventilation. Large changes may occur as a result of bronchoconstriction, accumulation of secretions, or slippage of the tip of the endotracheal tube into the right mainstem bronchus. Patients on assisted ventilation often develop episodes of respiratory distress at the same level of support that was adequate previously. An increase in resistance is an obvious potential mechanism for such episodes. The availability of continuous estimates of resistance would make it possible to identify such a mechanism and to take appropriate corrective action. Apart from identifying a possible cause for respiratory distress, the occurrence of large swings in resistance during continuous monitoring of this variable, particularly if secretions and tube slippage can be excluded, would establish the presence of bronchial hyperreactivity and would help guide the use of bronchodilators.

Second, proportional assist ventilation (PAV) (4) has several physiologic advantages (4, 5), including automatic changes in level of support (i.e., airway pressure [Paw]) as ventilatory demands change, lower distending pressures, and better synchrony between patient and ventilator, which should enhance comfort and provide more accurate estimates of changes in patient’s respiratory rate. These physiologic advantages may translate into clinical benefits (less barotrauma, less sedation, faster weaning) with implications for mortality, morbidity, and length of ventilatory support. To date, widespread use of PAV, and hence testing for these potential clinical benefits, has been seriously hampered by lack of simple ways to estimate elastance (E) and R on an ongoing basis; knowledge of E and R is required for proper and trouble-free implementation of PAV. The availability of a simple, noninvasive way to continuously monitor R, along with a correspondingly simple and noninvasive way to monitor E, would greatly facilitate the clinical use of PAV and would also make it possible to apply PAV for extended periods in order to assess its potential clinical benefits, if any. At present, PAV is used only in short-term trials supervised by clinicians with considerable expertise in physiology. Such studies cannot assess the potential of PAV in achieving real clinical benefits (e.g., decreased morbidity and mortality). Availability of online estimates of R would also make it possible to automatically adjust the flow assist component of PAV as R changes.

For a method that estimates resistance to be accurate and suitable for widespread clinical use in the intensive care unit (ICU) environment, it should satisfy certain practical requirements: (1) It should measure inspiratory resistance (Ri) because it is Ri that is relevant to the work of breathing. Resistance during expiration (Re) may greatly overestimate Ri in patients with expiratory flow limitation. In addition, in the latter patients changes in Ri need not be reflected in Re. (2) It

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should be independent of changes in Pmus that occur over the interval of the inspiratory phase during which the measurements are made. (3) Because resistance in intubated patients is flow-dependent (2), the method should ideally define the relation between R and V. (4) The method should not include interventions that evoke behavioral responses or, if it does, all relevant measurements must be obtained within the latency of such responses. (5) Any interventions that may be required to obtain the measurements should be well tolerated by patients. (6) It should be possible to obtain measurements at frequent intervals. (7) It should be possible to automate the interventions and measurements. Otherwise, obtaining the information may entail an unacceptable increase in time and expertise of clinical staff. (8) The technical requirements of the pressure and flow measuring systems (i.e., frequency response, phase relation between Paw and V signals) should not be so stringent as to require placement of the flow meter and pressure outlets near the patient, far away from the ventilator. To have to do so substantially complicates patient management. (9) The method should ideally be noninvasive.

In this communication, we describe a method that, we believe, meets all of these requirements. To put this approach in context, it is necessary to first review other noninvasive approaches that are potentially suitable during assisted ventilation. Only a very brief review is provided here. A more detailed account of these methods and their limitations is given in Section A of the online data supplement.

A number of approaches have been proposed to estimate R in patients with spontaneous inspiratory efforts (6, 7). The use of Re as a surrogate for Rt has several limitations, chief among which are possible corruption of the measurement by phasic expiratory muscle activity and the fact that Rt may greatly exceed Rt in patients with expiratory flow limitation.

The forced oscillation technique (FOT) of Dubois and coworkers (8) has been used extensively to measure resistance in spontaneously breathing nonintubated patients. Application of this method to mechanically ventilated patients poses substantial technical and interpretative challenges (see Section A of the online data supplement). Although these difficulties are currently being addressed by several investigators, and progress is being made (9–13), much additional work remains to be done before FOT can be accepted as a clinical tool.

The interrupter technique, introduced by Neergaard and Wirz (14), has also been extensively used to measure Rt in spontaneously breathing, nonintubated patients. It entails very brief occlusions applied during inspiration. To provide reliable results in mechanically ventilated patients, the occluder must be placed very close to the endotracheal (ET) tube and Paw and V must also be measured at that location (see Section A of the online data supplement). This is cumbersome and further complicates ventilator and patient management by clinical staff.

The approach we propose entails a transient reduction in V during the early part of inspiration. It is not necessary to reduce V (at the airway) to zero. Nor is it necessary to reach the new flow level instantly or to maintain it constant at the low level. These features make it possible to apply the technique using the ventilator’s valve. The change in Pmus between the points of high and low V is taken into account through appropriate utilization of the equation of motion. These same manipulations of the equation of motion make it possible to minimize the impact of the change in V between the two points such that precise knowledge of passive elastance is not necessary.

Theory

During assisted ventilation applied pressure is made up of two components, one provided by the ventilator (Paw) and one provided by the patient (Pmus). According to the equation of motion (15), applied pressure is dissipated against elastic, resistive, and inertial forces. Thus, during assisted ventilation:

\[ \text{Paw} + \text{Pmus} = V \cdot E + V \cdot R + V \cdot I \]  

where V is instantaneous volume relative to passive FRC, E is elastance, V is instantaneous flow, R is resistance, V is flow acceleration (in L · s⁻²), and I is inertance.

To the extent that Pmus at a given instant is not known, accurate elastance values may not be available, and V, relative to passive FRC, is also not known (in view of possible dynamic hyperinflation or active reduction in volume below FRC by expiratory muscles), it is not possible to solve Equation 1 for the resistive terms using a set of measurements made at one point during the inflation phase. For this reason, any approach to measure resistance during inflation in such patients must involve measurements at more than one point, having different flow values.

In the proposed approach Paw (and hence flow) is transiently reduced (pulse) during the inflation phase in the PAV mode (Figure 1) and primary measurements of Paw, V, and V are made immediately before Paw and flow begin declining (T₀, Figure 1), at the trough of pressure during the negative pulse (T₁, Figure 1), and at a point between T₀ and ventilator triggering (T₋₁, Figure 1). To facilitate the description of how these measured values are used to derive R, we shall initially

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**Figure 1.** Tracings illustrating an example of a negative pulse (second breath) and the relevant measurements. The arrows in the Paw tracing denote the three times at which pressure, V, and V were measured. P₂ is the highest pressure reached beyond the negative pulse. The external pulse channel illustrates the shape of the negative voltage applied to result in the negative pulse. Pmus is the estimated pressure generated by the respiratory muscles and was calculated from the pressure, V, and V channels using the equation of motion. Small arrows in Pmus channel denote calculation artifacts when flow is decreasing rapidly, both during the pulse and at the end of the breath. These artifacts are because we ignored inertial forces in the application of the equation of motion.
treat $R$ as a constant and consider the case where the pulse is designed such that the interval between $T_0$ and $T_1$ (i.e., $\Delta T_{-1}$) and the interval between $T_0$ and $T_1$ (i.e., $\Delta T_1$) are equal and the average flow rates in these two intervals are also equal.

Equation 1 can be written for points $T_{-1}$, $T_0$, and $T_1$ as follows:

$$V_{-1} \cdot R = P_{aw-1} + P_{mus-1} - V_{-1} \cdot E - \tilde{V}_{-1} \cdot I \quad (2)$$

$$V_0 \cdot R = P_{aw0} + P_{mus0} - V_0 \cdot E - \tilde{V}_0 \cdot I \quad (3)$$

$$V_1 \cdot R = P_{aw1} + P_{mus1} - V_1 \cdot E - \tilde{V}_1 \cdot I \quad (4)$$

Subtracting Equation 2 from Equation 3, and Equation 4 from Equation 5, assigning $\Delta X_1$ to the difference $(X_0 - X_{-1})$ and $\Delta X_2$ to the difference $(X_0 - X_1)$ yields the following two first difference equations:

$$\Delta V_{-1} \cdot R = \Delta P_{aw} + \Delta P_{mus-1} - \Delta V\cdot E - \Delta \tilde{V}_{-1} \cdot I \quad (5)$$

$$\Delta \tilde{V}_1 \cdot R = \Delta P_{aw} + \Delta P_{mus} - \Delta \tilde{V}_1 \cdot E - \Delta \tilde{V}_1 \cdot I \quad (6)$$

Adding Equations 5 and 6 yields:

$$(\Delta \tilde{V}_1 + \Delta \tilde{V}_{-1})R = (\Delta \tilde{P}_{aw} + \Delta \tilde{P}_{mus})$$

$$(7)$$

$$+ \Delta P_{mus} - \Delta \tilde{V}_1 \cdot E - \Delta \tilde{V}_{-1} \cdot I$$

In the PAV mode $\tilde{V}$ rarely exceeds 5 L $\cdot$ s$^{-2}$, even during the early rising phase of flow, and $\tilde{V}$ at $T_0$ and $T_1$ are, by design, near zero. As a result, the maximum that $\Delta \tilde{V}_{-1}$ can be is 5 L $\cdot$ s$^{-2}$, and $\Delta \tilde{V}_1$ is zero. The bracketed $V$ term cannot, therefore, exceed 5 L $\cdot$ s$^{-2}$. Inertial pressure losses at these levels of acceleration are negligible (16). Accordingly, the inertial term in Equation 7 can be ignored.

Because volume is rising continuously during the pulse (Figure 1), $\Delta \tilde{V}_1$ and $\Delta V_{-1}$ have opposite signs and tend to cancel out. If the pulse is designed so that the two terms are equal, the entire volume term is reduced to zero and knowledge of $E$ is not essential. Thus, if the value of $E$ is not known, a default value (representing, for example, average $E$ in mechanically ventilated patients) can be used with little risk of important errors.

Derivation of resistance. From each applied pulse an equation of the following form results:

$$K_1 \cdot X + K_2 \cdot Y = Z \quad (9)$$

where $X$ is the flow term (first bracketed term in Equation 8), $Y$ is the $V^2$ term (second bracketed term in Equation 8), and $Z$ is the resistive pressure (Pres) term (right side of Equation 8). To obtain $Z$ a known value of $E$ is used or, in the absence of this information, a default value of 28 cm H$_2$O $\cdot$ L$^{-1}$, representing average $E$ in mechanically ventilated patients (personal observations), may be used. Resistance can be obtained from Equation 9 in one of two ways: (1) If a range of $V$ and $V^2$ terms is obtained in successive pulses, either spontaneously or by design (e.g., initiating the pulse at different $V$ or reducing $V$ by different amounts), $K_1$ and $K_2$ can be obtained by regression analysis. (2) In the absence of reliable, directly determined $K_1$ and $K_2$ values, in accordance with approach number 1, $K_1$ can be assumed to equal $K$ of the ET tube and Equation 9 is solved for $K_1$. Thus, $K_1 = (Z - (Y - K_2 \cdot ET))/X$. The $K_2$ values of clean ET tubes of different sizes are widely available. Resistance can be reported as $K_1 + K_2 \cdot ET$, reflecting resistance at a standard flow of 1.0 L $\cdot$ s$^{-1}$. The resistance so reported may differ from actual resistance at 1 L $\cdot$ s$^{-1}$ to the extent that actual $K_2$ may differ from the assumed $K_2$ of a clean tube and the flow at which $R$ estimates are made is different from 1.0 L $\cdot$ s$^{-1}$. The error in estimated resistance (at 1 L $\cdot$ s$^{-1}$) if actual $K_2$ (K2 actual) is different from assumed $K_2$ is given by:

$$R_{error} = (K_2 \text{ actual} - K_2 \text{ assumed}) (1 - Y/X) \quad (10)$$

It can be seen that the error in estimating $R$ at 1 L $\cdot$ s$^{-1}$ using an assumed $K_2$ is a fraction of the difference between the actual and assumed $K_2$ values. The magnitude of this potential error will be assessed experimentally.

What resistance is being measured? Observations of the response to flow interruption during CMV at constant flow have led to the concept that total respiratory system resistance is made up of a strictly flow-related component, produced primarily by airway resistance, and a time-dependent component related to viscoelastic behavior of the lung and, to a smaller extent, the chest wall (2, 17). The flow-related component is expressed by the rapid drop in Paw at the onset of flow interruption. Resis-
tance calculated from this initial ΔP is referred to as $R_{\text{max}}$. The time-dependent component is expressed by the subsequent gradual decline in Paw, at constant volume, over the following few seconds and is referred to as ΔR. The sum of the two components is referred to as $R_{\text{max}}$. Because the time interval between peak flow and trough flow (i.e., $\Delta T_1$) in the proposed technique (0.1 to 0.15 s) is small relative to the time required for viscoelastic behavior to be fully expressed (usually several seconds), it would seem reasonable to suggest that Rpulse will be much closer to $R_{\text{max}}$ than to $R_{\text{min}}$. This was confirmed by model analysis provided in Section C of the online data supplement.

Potential sources of error. These are discussed briefly here. More details are provided in Section D of the online data supplement:

1. Measurement noise: In mechanically ventilated patients the Paw and V signals are subject to noise from many sources. These can be reduced by a variety of approaches: (a) ensuring that the change in flow produced by the intervention (i.e., $\Delta V_t$) is large relative to the amplitude of the noise; (b) elimination of sources of noise to the extent possible; (c) critical filtering of the Paw and V signals; (d) pulse should not begin when a specified flow is reached; (e) averaging the resistance results obtained from a number of pulses.

2. Difference in response characteristics of Paw and V measuring systems: Difference in response characteristics of the measuring systems would cause the peak and trough of the measured pressure to occur at different times relative to the flow signal even if the peaks and troughs of the two signals were, in reality, simultaneous. If $T_0$ is taken at the time of peak Paw, flow at $T_0$ will underestimate real flow, and vice versa. To minimize the impact of these differences, the phase lag between the Paw and flow measuring systems should be as short as possible. In addition, the pulse should be designed so that flow is fairly flat over a 30- to 40-ms interval in the vicinity of $T_0$ and $T_1$.

3. Errors related to extrapolation of the Pmus trajectory: These are potentially the most serious, particularly when respiratory drive and, hence, rate of rise of Pmus (i.e., $\Delta P_{\text{mus}}/\Delta t$), are high. Our approach involves the assumption that $\Delta P_{\text{mus}}/\Delta t$ is constant over the interval $T_{-1}$ to $T_0$. This assumption can be in error for a variety of reasons. These, and possible ways to minimize these potential errors, are discussed next.

a. Termination of inspiratory effort (neural $T_1$) during the pulse: This can potentially produce the largest errors in estimated R. Should it occur, Pmus would actually fall between $T_0$ and $T_1$, instead of continuing to rise, with the possibility of greatly overestimating Pmus at $T_1$ and, hence, greatly underestimating resistance.

Because of the potentially large magnitude of this error, it is necessary to ensure that peak Pmus (end of Ti) does not occur between $T_{-1}$ and $T_1$. This is easy to accomplish during PAV (4). In this mode the ventilator provides assist in proportion to instantaneous Pmus and the end of ventilator cycle is automatically synchronized with patient effort and is constrained to occur during the declining phase of Pmus (4). So long as pulses are not delivered in the last fraction (approximately 30%) of ventilator Ti, one is assured that neural Ti termination did not occur within the pulse. With pressure support ventilation (PSV) and assisted volume-cycled ventilation such synchrony is not assured, however, and Ti may terminate at any point within or even beyond the inflation phase.

b. Shape of the rising phase of Pmus: The rate of rise of Pmus during the rising phase in humans is not constant (6). Differences between $\Delta P_{\text{mus}}/\Delta t$ in the interval $T_0$ to $T_1$ (i.e., $\Delta T_1$) and $T_{-1}$ to $T_0$ (i.e., $\Delta T_{-1}$) would cause errors in estimated R for the same reasons discussed under (a) above. Such errors can be minimized by delivering the pulse beyond the first 0.3 s of inspiratory effort. The rationale for this conclusion is given in Section D3b of the online data supplement.

c. Behavioral responses: The change in Pmus after the initiation of the pulse may deviate dramatically from that expected from the preceding time interval if the patient perceives the pulse and reacts behaviorally to it. We (18) and others (19) have shown previously that the minimal latency for behavioral responses to changes in Paw and flow is approximately 0.2 s in very alert normal subjects. It follows that errors related to perception of the pulse, with consequent behavioral responses, can be avoided if measurements are restricted to the 0.2-s interval after initiation of the pulse. Behavioral responses can, however, occur without perception if the change is anticipated. The occurrence of anticipatory responses can be minimized by randomizing the order of pulse applications.

d. Nonbehavioral neuromuscular responses to changes in flow: The rapid reduction in flow in the course of an ongoing inspiratory effort may, theoretically, elicit reflex changes in neural output with much shorter latencies than behavioral responses. In addition, the change in flow and, consequently, in time course of volume, may elicit changes in Pmus, independent of changes in electrical activation, through the operation of the intrinsic properties of respiratory muscles (force–length and force–velocity relations). An important contribution from either of these responses after the onset of the pulse (between $T_0$ and $T_1$) could alter the time course of Pmus relative to the course predicted from the prepulse interval and introduce errors in estimated Pres. We believe, however, that the impact of these responses on estimated resistance should be minimal, particularly if $\Delta T_1$ is brief (e.g., 0.1 s) and the pulse is delivered fairly early in inspiration, where Pmus is relatively low (see Section D3d in the online data supplement).

In summary, the foregoing considerations led us to believe that transient reductions in flow, with estimation of the change in Pmus during the transient from data obtained in the immediately preceding period, have a reasonable likelihood of providing reliable estimates of airway resistance. These considerations have also pointed out a variety of ways by which systematic and random errors may be minimized. These include the use of the PAV mode, application of the pulse as early as possible during inspiration but avoiding the first 0.3 s of inspiratory effort, ensuring that the interval between $T_0$ and $T_{-1}$ is $\leq 0.2$ s, randomizing the order of pulse application, maximizing the drop in V between $T_0$ and $T_1$, and designing the pulse so that there is a nearly flat flow region in the vicinity of $T_0$ and $T_1$. In the current study, the proposed approach was applied using, as much as possible, the aforementioned features. Subprotocols were incorporated to test the impact of timing of pulse application, level of assist, and different signal filtering techniques on the results. The results were compared with resistance values obtained during CMV. Testing was done on a large number of patients (71 patients) with a very wide range of clinical problems, mechanical properties, and level of alertness. In addition, in the last 30 patients, the technique was applied using a fully automated system to simulate application under field conditions (suction, patient repositioning, and other ICU interventions and situations), and monitoring was continued for relatively long periods (hours) to permit determination of trends in resistance under typical ICU conditions.

METHODS

Patients

Seventy-one ventilator-dependent patients in the medical ICU were studied. Patients were not preselected on the basis of disease type or...
The ventilator was used as a custom-built, piston-based, flow-triggered multimode ventilator capable of delivering PAV (The Winnipeg Ventilator: University of Manitoba, Winnipeg, Canada). More details about this ventilator can be found elsewhere (20). Flow was measured by a pneumotachograph, linear to 160 L/min (3600 series; Hans Rudolph, Kansas City, MO), inserted between the Y connector and the ET tube. Volume was obtained by electrical integration of flow. Paw was measured from a side port between the pneumotachograph and the ET tube. Flow and Paw were passed through an 8-Hz low-pass filter. The frequency response of the two signals was identical. In response to a square-wave pressure change the output of the two measuring systems changed with a time constant of 20 ms.

The Winnipeg Ventilator was modified so that its pressure output could be increased or decreased, relative to what is dictated by the PAV algorithm, using an external input. The external input took the form of a brief (0.2-s) negative voltage that was gated to the ventilator after an adjustable delay from the onset of inspiration (zero flow crossing). The shape of the negative external pulse was designed to result in a trough in Paw and flow between 100 and 200 ms from the onset of the pulse. Given the response characteristics of the ventilator this required a trapezoidal external input of the pattern shown in Figure 1. The rate of increase in voltage was adjusted to produce relatively broad Paw and flow troughs. Pulses were gated to the ventilator at random intervals. In the first 41 patients, gating was done by manually activating an external switch. In the remaining 30 patients, gating was carried out by a microcontroller, using a random number generator. Signals corresponding to Paw, V, and the output of the pulse generator (Figure 1) were digitized at 125 or 200 Hz and stored on computer using a CODAS data acquisition system (DATAQ Instruments, Akron, OH). The signals were also continuously displayed on the computer monitor during the study.

Protocol
Positive end-expiratory pressure (PEEP) and fraction of inspired oxygen (FIO2) were maintained at the levels used before the study. The first step was to determine passive respiratory mechanics during a period of CMV. The patient was placed in the volume-cycled mode, at a tidal volume slightly greater than the one received before the study. Back-up rate was increased in steps until respiratory efforts ceased, as evidenced by lack of trigger artifacts, a reproducible Paw waveform during inflation, and a monotonic decline in expiratory flow in the deflation phase (21). A series of end-inspiratory plateau maneuvers was performed. Before each plateau maneuver the ventilator rate was reduced to permit expiratory flow to approach zero. In most cases, the flow or volume of the breath to be occluded was temporarily changed to permit determination of passive mechanics over a range of flows and tidal volumes.

Preliminary estimates of passive E and R were then made from the stored CMV data using standard equations (2) 

\[ E = (P_{\text{plat}} - \text{PEEP})/V_{i} \]

and

\[ R = (P_{\text{peak}} - P_{\text{plat}})/V_{i} \]

The ventilator was then switched to PAV. Volume assist (VA) and flow assist (FA) were set initially at 80% of the VT. Paw and inspired volume were measured at the point where flow reached 0.05 L/s in the early part of the plateau (Ppeak, VR). Justification for the use of this point to measure R in CMV is given in Section E1 of the online data supplement. Peak flow (Vpeak) and Paw and inspired volume at the time of peak flow were determined (Ppeak, Vpeak). Vpeak is invariably less than VR in view of continued inspiratory flow in the early part of occlusion (22, 23). Passive E was calculated from (P_{\text{peak}} - P_{\text{PEEP}})/VR. Passive resistance (Rcmv) at VL was calculated from: Rcmv = [(P_{\text{peak}} - P_{\text{plat}} + (V_{r} - V_{peak})E)/V_{peak}]. This modification of the standard equation allows for the difference in volume, and hence elastic recoil pressure, between the time of peak flow and the time of P_{\text{plat}} (22, 23).

According to Rohrer’s equation: R = K1 + K2V. In all patients we estimated K1 by assuming that K1 was similar to the value reported for a clean ET tube. Thus:

\[ K1 = (\text{average Rcmv}) - (\text{average V}_{\text{peak}} \cdot K2 \cdot \text{ET}) \]  

where average Rcmv is the average of Rcmv values obtained from all nonrejected occlusions, average V_{peak} is the average peak flow in the same occlusions, and K2·ET is the K2 value reported for the ET tube size used in the patient. The latter values were obtained from Wright and coworkers (24) and are as follows: ET no. 9 = 2.0, ET no. 8 = 5.5, ET no. 7.5 = 7.0, ET no. 7 = 9.5, ET no. 6.5 = 15.
When the CMV data included a wide range of $V_{peak}$ (coefficient of variation [CV] > 0.20), linear regression analysis was done between Rcmv and $V_{peak}$. The slope of this relation provided actual $K_2$ (as opposed to an assumed $K_2$ of a clean tube) and the intercept represented actual $K_1$. $K_2$ was considered different from $K_2$ ET if the 95% confidence interval (CI) of the slope was narrow (i.e., < 30% of slope value or < 3 cm H$_2$O · L$^{-1}$ · s$^{-2}$) and did not include the $K_2$ value of a clean tube.

**Pulse data.** Analysis was done with a custom program. Each breath receiving a pulse was identified from the gated pulse channel (Figure 1). The point at which Paw changed from rising to falling ($\Delta$Paw/\Delta t = 0) was identified ($T_0$). The point at which Paw reached its lowest value within the pulse period was also identified ($T_1$). Paw, P, V, and $V$ were measured at $T_0$, $T_1$, and at a point 100 ms before to $T_2$ ($T_{-1}$, Figure 1), and were tabulated. Measurements were made either from discrete data points at these three times (unfiltered data) or from a moving average of the respective channels. The averaging interval was selected by the user (e.g., ± 8 ms, ± 16 ms, ± 24 ms, etc.). Separate tables were kept for unfiltered data and for data obtained with each averaging interval. The time interval between $T_0$ and $T_1$ (i.e., $\Delta T_1$) was also tabulated. The highest Paw value between $T_1$ and the end of inspiration was also noted ($P_1$, Figure 1). The pulse was rejected if:

a) $(V_0 - V_{-1}) < 0.05 \text{ L} \cdot \text{s}^{-1}$. This criterion was to ensure that analysis was limited to pulses applied during the rising phase of flow and, hence, $P_{mus}$.

b) $(P_1 - P_2) < 3$ cm H$_2$O. This criterion was to ensure that the inflation phase resumed after the withdrawal of the pulse. Failure of Paw to rise again may be due to ventilator resetting during the pulse (flow decreasing below triggering off level) or, in the PAV mode, to termination of the patient's neural Ti during the pulse. In either case the $T_1$ values are corrupted.

Equation 8 was solved for each unrejected pulse using an elastance value obtained from end-inspiratory occlusions during PAV $[(P_{plat} - PEEP)/V_l]$. We have shown earlier that this agrees well with elastance measured during CMV (25). An equation having the form of Equation 9 was thus generated for each pulse ($K_1$ · $X + K_2$ · $Y = Z$). $K_1$ was calculated by assuming $K_0 = K_2$ ET and inspiratory resistance at a standard flow of 1 L · s$^{-1}$ ($R_l$) was calculated from $K_0 + K_2$ ET.

The same analysis was done on data obtained from filtered Paw, V, and $V$ signals. Unless otherwise indicated, all resistance values ($R_l$) will be reported as $[K_1 + K_2$ ET].

When all pulses in a given patient were analyzed, the mean, SD, and CV of $R_l$ were obtained separately for unfiltered and filtered data. The impact of filtering on average $R_l$ and on between-pulse variability could then be assessed. When more than one level of assist was applied in a given patient, the results were also averaged separately for each assist level.

In studies lasting more than 30 min the moving average of $R_l$ was obtained to characterize time-dependent trends. For this purpose a 10-pulse moving average was generated for the V term, $V^2$ term, and Pres. The moving average of $K_1$ was estimated from these values, assuming $K_0 = K_2$ ET.

**Supplementary analysis.** Two supplementary approaches were used to explore possible reasons for the difference between $R_l$ obtained during CMV and during PAV:

1. Time-dependent differences in resistance: To the extent that CMV and PAV were applied at different times, we felt that differences in observed $R_l$ may, in part, be real (i.e., not due to difference in technique). This possibility was explored by using $R_e$ as a surrogate for $R_l$. Accordingly, $R_e$ was calculated during CMV and during PAV and, provided certain conditions were met, the difference in $R_e$ between the two conditions was used to correct $R_l$. The methods used to estimate $R_e$ and the conditions under which $R_e$ was accepted as a surrogate for $R_l$ are given in Section E2 of the online data supplement.

2. Differences related to the presence and magnitude of inspiratory muscle activity. As indicated earlier, pulse application may actively induce changes in $P_{mus}$. Such changes would alter the values of calculated resistance relative to the passive state. To the extent that these responses are a function of intensity of respiratory muscle contraction (26), differences between active and passive resistance are expected to be related to level of $P_{mus}$ at the time of pulse application.

To assess the extent to which level of respiratory muscle contraction results in differences between active and passive resistance, we estimated $P_{mus}$ as described in Section E3 of the online data supplement. An example of the calculated $P_{mus}$ tracing is shown in Figure 1. The onset of inspiratory effort was visually identified from the point at which $P_{mus}$ clearly deviated upwards from its baseline value. $P_{mus}$ at the onset of the pulse (i.e., $T_0$) was calculated as the difference in $P_{mus}$ between $T_0$ and onset of inspiratory effort. These tracings were also used to determine the delay for pulse application, relative to onset of neural inspiration.

Group averages will be reported as mean ± SD, unless otherwise indicated. Results of comparisons between resistance values under different conditions are given as mean difference with 95% CI (± 1.96 SD), as recommended by Bland and Altman (27). Differences are expressed in absolute resistance units and as percentage of the average of the two values being compared (27). The slope, intercept, and correlation coefficient will be given as well.

**RESULTS AND DISCUSSION**

**CMV Data**

In four patients, review of the stored data failed to identify any occluded breaths that met the criteria of passivity. In the absence of a reliable reference with which to compare pulse data, the results of these patients were not analyzed further. In the remaining 67 patients $P_{mus}$ averaged (± SD) 28.6 ± 9.2 cm H$_2$O · L$^{-1}$ · s$^{-2}$ (range 12.2 to 64.4 cm H$_2$O · L$^{-1}$ · s$^{-2}$). $R_l$ (i.e., $K_2$ ET) averaged 14.8 ± 4.2 (range 7.7 to 25.8 cm H$_2$O · L$^{-1}$ · s$^{-2}$). In 29 patients a sufficiently wide flow range (CV > 0.20) was tested and the regression between flow and $R_l$ was sufficiently tight to estimate $K_2$ with confidence. In 11 of these patients $K_2$ was not significantly different from $K_2$ ET. In the remaining 18 patients, $K_2$ obtained from the regression was significantly different from $K_2$ ET. In these patients the average $K_2$ ET was 6.5 (± 1.7) whereas the actual $K_2$ was 12.7 (± 2.8) cm H$_2$O · L$^{-2}$ · s$^{-2}$. The average (± SD) difference was 6.2 ± 2.5 cm H$_2$O · L$^{-2}$ · s$^{-2}$ and the largest difference was 13.4 ($K_2$ of a clean tube = 5.5, actual $K_2$ = 18.9 cm H$_2$O · L$^{-2}$ · s$^{-2}$).

Data on the relation between $R_l$ and $P_{mus}$ during CMV were available in all patients. In 47 patients flow-corrected ($R_e$, i.e., $K_1 + K_2$ ET) was within 25% of $R_l$ and did not increase significantly at lower volumes. In the remaining 20 patients, $R_e$ was considerably higher than $R_l$ or increased significantly at lower volumes. In these patients $R_e$ averaged (± SD) 25.6 ± 14.2 cm H$_2$O · L$^{-1}$ · s, representing 157 ± 47% of $R_l$ (range 115 to 285%).

**PAV Data**

The average duration of data collection was 73.5 ± 52.0 min (range 4.5 to 222.5 min). Average elastance during PAV was 27.2 ± 9.1 cm H$_2$O · L$^{-1}$, not significantly different from the CMV values. The number of pulses examined per patient averaged 63.1 ± 67.2 (range 9 to 227). 10.5 ± 28.6% of pulses were rejected because the ventilator reset during the pulse interval. This occurred usually when the amplitude of the external negative pulse was too large, resulting in flow decreasing below the reset flow limit of the ventilator (0.05 to 0.1 L/s). Another 15.9 ± 20.4% of pulses were rejected because they were delivered too late in the inflation phase and occurred during the declining phase of flow. These events were primarily encountered in early studies in which different delays were used to assess the effect of timing of pulse application on the results.

**Pulse characteristics.** The average delay between onset of inspiratory flow and pulse application was 0.23 ± 0.07 s. This corresponded to 26 ± 8% of Ti. When measured from the onset of neural Ti, as detected from the $P_{mus}$ tracing, the average delay was 0.37 ± 0.1 s, corresponding to 35 ± 10% of Ti.
The average flow at which the negative pulse was initiated (i.e., at $T_0$) was $0.60 \pm 0.17 \text{ L} \cdot \text{s}^{-1}$. The average flow at the trough of the pulse (i.e., at $T_1$) was $0.29 \pm 0.15 \text{ L} \cdot \text{s}^{-1}$. The average reduction in flow during the pulse was $0.31 \pm 0.11 \text{ L} \cdot \text{s}^{-1}$. The average time interval between $T_0$ and $T_1$ was $0.12 \pm 0.03 \text{ s}$. All measurements relevant to calculation of resistance were, accordingly, completed within the latency of behavioral respiratory responses (18, 19). The pulses were well tolerated by all patients.

Comparison of Pulse and CMV Resistance

The average $R_I$ obtained with the pulse technique was $16.2 \pm 4.9 \text{ cm H}_2\text{O} \cdot \text{L}^{-1} \cdot \text{s}$ compared with $14.8 \pm 4.2 \text{ cm H}_2\text{O} \cdot \text{L}^{-1} \cdot \text{s}$ during CMV ($p = 0.0002$ by paired t test, $n = 67$). Figure 2 is a scatter plot of the results obtained with the two techniques. There was a highly significant correlation between the two measurements ($p = 5.0 \times 10^{-15}$). The slope was not significantly different from 1.0 but the intercept was significantly higher than zero ($p = 0.02$).

Notwithstanding the good correlation, there was considerable scatter. The average difference ($\pm$ SD) was $1.3 \pm 3.0 \text{ cm H}_2\text{O} \cdot \text{L}^{-1} \cdot \text{s}$ with a 95% CI of $-4.7$ to $7.2 \text{ cm H}_2\text{O} \cdot \text{L}^{-1} \cdot \text{s}$. These values correspond to $7.8 \pm 18.2\%$ of average $R_I$ with a 95% CI of $-27.9$ to $43.4\%$. There are several reasons that may account for the differences between the two measurements:

True differences in passive resistance. The CMV and pulse data were obtained at different times and it is quite possible that resistance changed in the interim. There are reasons to believe that resistance did change, at times substantially, over relatively short periods independent of technique, in these patients. First, in the 24 patients in whom duplicate CMV measurements were made at two different times, once before and once after PAV, a comparison of the results from the two CMV sets also showed considerable scatter (Figure 3). The average ($\pm$ SD) difference was $1.1 \pm 2.8 \text{ cm H}_2\text{O} \cdot \text{L}^{-1} \cdot \text{s}$ ($7.8 \pm 19.0\%$) with a CI of $-4.4$ to $6.6 \text{ cm H}_2\text{O} \cdot \text{L}^{-1} \cdot \text{s}$ ($-29.5$ to $45.1\%$). These differences are comparable to those of the $R_{Ipulse}$ versus $R_{Icmv}$ relation (Figure 2). Second, in patients in whom monitoring of resistance with the pulse technique spanned a reasonably long interval, substantial spontaneous changes in measured $R_{Ipulse}$ were often observed (e.g., Figure 4; see Time-dependent Changes in $R_{Ipulse}$).

To assess the possible contribution of true changes in resistance to the differences observed between $R_{Ipulse}$ and $R_{Icmv}$, we used the results of $R_E$ in those patients in whom this approach was feasible. $R_E$ could not be used in 20 patients because it was deemed not to be representative of $R_I$ (see CMV data). The approach could also not be used in nine patients because no inspiratory hold maneuvers were carried out during the collection of the pulse data, and in another three patients because there was no period during which PAV assist was high enough to produce optimal conditions for measuring $R_E$.

Figure 5A shows the relation between $R_E$ determined during CMV and $R_E$ determined later during PAV. The differences were bidirectional. The average difference ($\pm$ SD) was $0.7 \pm 2.6 \text{ cm H}_2\text{O} \cdot \text{L}^{-1} \cdot \text{s}$ ($3.9 \pm 16.8\%$) with a 95% CI of $-4.5$ to $5.8 \text{ cm H}_2\text{O} \cdot \text{L}^{-1} \cdot \text{s}$ ($-29.0$ to $36.9\%$). The range of these differences was similar to that observed in comparisons between CMV$_1$ and CMV$_2$ (Figure 3) (SD 2.6 versus 2.8). In patients in whom a lengthy period of pulse data collection was available, changes in $R_E$ closely mirrored the changes in $R_{Ipulse}$ (e.g., Figure 4, open symbols). This suggests that both methods were reflecting true changes in resistance.

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To assess the extent to which time-dependent changes in resistance contributed to the differences observed between \( R_{\text{ICMV}} \) and \( R_{\text{PULSE}} \) (i.e., as shown in Figure 2), the values of \( R_{\text{ICMV}} \) were corrected by an amount corresponding to the change in \( R_t \) in those patients in whom \( R_t \) data were available (n = 35). The new relation between corrected \( R_{\text{ICMV}} \) and \( R_{\text{PULSE}} \) is shown in Figure 5B. As can be seen, the correlation improved considerably with the correlation coefficient increasing from 0.78 to 0.90 (\( r^2 = 0.82 \)). The mean difference was 1.0 ± 2.0 cm H\(_2\)O \( \cdot \) L\(^{-1} \) \( \cdot \) s \( (6.1 \pm 13.5\%) \) with a 95% CI of −3.0 to 5.0 cm H\(_2\)O \( \cdot \) L\(^{-1} \) \( \cdot \) s \( (−20.3 \text{ to 32.4}\%) \). This improvement indicates that the differences observed initially between \( R_{\text{ICMV}} \) and \( R_{\text{PULSE}} \) were, to a considerable extent, related to true changes in resistance.

**Differences between actual and assumed \( K_2 \).** In comparisons between \( R_{\text{ICMV}} \) and \( R_{\text{PULSE}} \) (e.g., Figure 2 and 5B) all resistance values were adjusted to a standard flow of 1.0 L \( \cdot \) s\(^{-1} \) assuming that \( K_2 \) was similar to that of a clean, in vitro, ET tube. In the event actual \( K_2 \) was different, owing to secretions or kinking, for example, false differences between \( R_{\text{ICMV}} \) and \( R_{\text{PULSE}} \) can result with a magnitude that depends on differences between actual \( K_2 \) and \( K_2 \) ET and on differences between the average flow during CMV and pulse measurements (Equation 10). It was possible to assess the impact of this potential error in 18 patients in whom actual \( K_2 \) was significantly higher than \( K_2 \) ET (see CMV results). Figure 6 shows the impact of using actual \( K_2 \) (versus \( K_2 \) ET) on estimated \( R_{\text{PULSE}} \) in the 18 patients in whom actual \( K_2 \) was different from \( K_2 \) ET. In 15 patients the impact of using an assumed \( K_2 \) ET, instead of the actual \( K_2 \), was minimal (<15%). In three patients, however, the use of an assumed \( K_2 \) ET resulted in important errors; \( AR \) amounted to 3.5, 5.0, and 6.1 cm H\(_2\)O \( \cdot \) L\(^{-1} \) \( \cdot \) s, corresponding to 22%, 25%, and 30% error, respectively. These relatively large errors reflect large differences between actual \( K_2 \) and \( K_2 \) ET and, also, a large difference in the flow at which CMV and pulse measurements were made. From these observations it may be concluded that the use of an assumed \( K_2 \) ET results in important errors in only a minority of patients (3 of 29 patients in whom actual \( K_2 \) was known with certainty; see CMV results). In the great majority of patients the error is negligible because differences between actual and assumed \( K_2 \) are small or the flow at which pulse measurements are made is not sufficiently different from 1.0 L \( \cdot \) s\(^{-1} \) to result in an important error.

The impact of errors related to the use of the wrong \( K_2 \) on the relation between \( R_{\text{PULSE}} \) and \( R_{\text{ICMV}} \) (Figure 5B) was assessed by recomputing both \( R_{\text{PULSE}} \) and \( R_{\text{ICMV}} \) using actual \( K_2 \), as opposed to \( K_2 \) ET, in the 29 patients in whom actual \( K_2 \) was known. As may be expected from the foregoing analysis, the effect of this correction was small; \( r \) increased from 0.90 to 0.92 (\( r^2 = 0.85, p = 8E−28 \)). The slope (1.01) and intercept (0.77) of the relation were not significantly different from 1.0 and zero, respectively. The average difference was 0.9 ± 2.0 cm H\(_2\)O \( \cdot \) L\(^{-1} \) \( \cdot \) s \( (5.4 \pm 12.6%) \) with a 95% CI of −2.9 to 4.7 cm H\(_2\)O \( \cdot \) L\(^{-1} \) \( \cdot \) s \( (−19.3 \text{ to 30.1}\%) \). This plot is not shown because it is not visibly different from that of Figure 5B.

**Active versus passive resistance.** The calculations used to estimate \( R_{\text{PULSE}} \) do not take into consideration the possible effects of changes in flow on the pressure output of the active inspiratory muscles. Thus, it is assumed that \( PMuS \) will continue rising during the flow perturbation at the same rate obtaining before the perturbation. As discussed elsewhere (see THEORY), changes in flow may alter \( PMuS \) by reflexly changing muscle activity or through the intrinsic properties of respiratory muscles. In the presence of such effects the true change in \( PMuS \) during the pulse may differ from the value estimated from extrapolation of an earlier segment, thereby resulting in differences between calculated \( R_{\text{PULSE}} \) and passive \( R \). These differences need not be considered as technical errors. To the extent that intrinsic muscle properties and reflex responses operate during natural changes in flow, and not only during artificial flow changes, resistance of the active respiratory system may be different from that of the passive system. We believed, therefore, that some of the remaining differences between \( R_{\text{PULSE}} \) and \( R_{\text{ICMV}} \) may be due to the fact that \( R_{\text{PULSE}} \) reflects active resistance whereas \( R_{\text{ICMV}} \) reflects passive resistance. This possibility was addressed by determining whether the difference between \( R_{\text{ICMV}} \) and \( R_{\text{PULSE}} \) was related to the magnitude of active pressure generation (\( PMuS \)) at the onset of the pulse (i.e., \( T_0 \)). Thus, we reasoned that the more \( PMuS \) the patient is generating the more pronounced the effects of changes in flow on \( PMuS \) will be, resulting in greater difference between \( R_{\text{ICMV}} \) and \( R_{\text{PULSE}} \). This reasoning is valid at least in the case of intrinsic muscle responses (26).

The impact of \( PMuS \) at the onset of the pulse was assessed in two ways: (1) Interindividual differences in \( PMuS \): The 67 patients studied were subjected to a wide range of assist and also displayed a wide range of respiratory drive; minute ventilation on PAV ranged from 6.2 to 24.0 L \( \cdot \) min\(^{-1} \). As a result, the extent of \( PMuS \) generated at the onset of the pulse varied considerably among patients (0.5 to 16.2 cm H\(_2\)O, \( \bar{x} \) (± SD) =
5.8 ± 3.2 cm H2O). We determined the relation between individual Pmus values and the individual differences between RIpulse and RImv (n = 67). There was no significant relation between the two variables (r = 0.19, p = 0.13). (2) In 17 patients there were two or more steady-state periods at different levels of assist. As a result different levels of Pmus were obtained in the same patients. We determined RIpulse and Pmus during the highest and lowest assist in each of these patients and the results were compared by the paired t test. RIpulse was not different (17.4 ± 6.1 versus 16.3 ± 6.3 cm H2O · L⁻¹ · s in high and low assist, respectively; p < 0.1) even though Pmus was significantly higher during low assist (6.0 ± 3.1 versus 9.2 ± 2.7 cm H2O in high and low assist, p < 0.0001).

Collectively, these observations indicate that any effect prevailing Pmus has on RIpulse estimates is too small to be of concern. This is of relevance in the clinical setting where respiratory drive and level of assist change frequently. This finding should facilitate interpretation of changes in Rtl that would, otherwise, have to be corrected for possible changes in Pmus. We believe that a number of technical features in the current approach have contributed to this insensitivity to Pmus. First, the pulse was applied early in inspiration where Pmus is relatively low (mean Pmus = 5.8 cm H2O). Second, the change in flow (approximately 0.3 L · s⁻¹) was small relative to the gain of the force–velocity relation [0.24 ± 63 cm H2O · L⁻¹ · s (28)]. Third, the pulse was designed so that ∆V in the intervals ∆T₂₋₁ and ∆T₁ are small and roughly equal in magnitude. This minimized the impact differences in ∆V between the two intervals may have had on the Pmus trajectory through the force–velocity relation; the volume effect on Pmus is considerably less reliable than those delivered early in inspiration.

We believe there are two likely reasons for the reduced reliability of pulses delivered late in inspiration. First, the extrapolation technique depends critically on the assumption that ∆Pmus/∆t remains relatively constant between T₂₋₁ and T₁. With late pulses there is a greater likelihood for termination of neural Ti, with progressive reduction in Pmus, to begin during the interval in which measurements are made, thereby introducing errors in the extrapolated Pmus value. This would result in RIpulse underestimated passive Rtl. Second, to the extent that Pmus is higher later in inspiration, the impact of the reduction in flow on Pmus (via intrinsic properties) is expected to be higher. This would result in RIpulse being greater than passive Rtl (see ACTIVE VERSUS PASSIVE RESISTANCE).

**Time-dependent Changes in RIpulse**

Time-dependent changes were examined by calculating a 10-point moving average (and SD) of consecutive RIpulse values in individual patients. Analysis was limited to those patients in whom at least 20 consecutive RIpulse measurements were available (n = 48 patients). Peaks and troughs of the moving average were identified. An important change in RIpulse was defined as a difference in RIpulse of > 2 cm H2O · L⁻¹ · s, or > 20% of average resistance, between a peak (or trough) and the next trough (or peak) and which was also statistically significant.

Important changes in RIpulse during the period of monitoring (1.52 ± 0.77 h) were found in 32 (66%) of the 48 patients. There were a total of 69 important events in a total of 73 h of monitoring, giving an average 0.95 events/h. The average change in RIpulse was 5.4 ± 2.8 cm H2O · L⁻¹ · s (range 1.9 to 14.8 cm H2O · L⁻¹ · s) corresponding to 27.5 ± 13.6% of average resistance (range 8.4 to 68%). The differences between the peak and trough values were highly significant in most cases; p < 0.0001 in 21 of 69 events, p < 0.0001 in 11, p < 0.01 in 6, p < 0.01 in 19, p < 0.02 in 6 and p < 0.05 in 6. The change in RIpulse most commonly took the form of a gradual increase in the moving average. At some point a notation was made that “patient needs suction,” followed by another notation to the effect that patient is being suctioned. Suction was typically followed by rapid decline in RIpulse (solid arrows, Figure 4).

This, to our knowledge, represents the first documentation of the frequency and magnitude of time-dependent changes in resistance in ventilator-dependent ICU patients. Our findings indicate that such changes are frequent and often large. Changes in resistance are evident well before the need for suction becomes clinically evident. These findings suggest that continuous monitoring of resistance may be useful in a majority of patients by making it possible to provide appropriate interventions (suction, bronchodilators, changes in level of as-
sist) in a timely manner. Continuous monitoring of resistance would also be particularly useful in the PAV mode. Unlike the case of volume-cycled ventilation, where the ventilator automatically compensates for changes in resistance by providing more or less pressure, an increase in resistance during PAV is not automatically compensated for; the patient must do the compensation. Having continuous feedback about resistance would make it possible to automatically adjust the flow assist component of PAV to be commensurate with the prevailing resistance.

Variability in \( R_{\text{pulse}} \) Values within Individual Patients

With the proposed technique each pulse provides an estimate of flow-adjusted resistance \( (K_1 + K_2 \cdot ET) \). An important question is how much confidence can be placed in the result of one pulse and, by extension, how much averaging is required to obtain reliable results. To address this issue, the SD of \( R_{\text{pulse}} \) was initially determined from all observations obtained in the patient. The average SD (±SDD) encountered in the 67 patients was 2.4 ± 1.5 cm H\( \text{O} \) \( \cdot \) L\( \text{min} \)\(^{-1} \) \( \cdot \) s and the average CV was 14.7 ± 7.8%. These values are comparable with the variability in lung resistance measured by the esophageal balloon technique \[ CV = 15 ± 6\% \] (29).

We carried out extensive analysis to identify technical and experimental factors that affect or account for between-pulse variability (BPV). The intent of this analysis was to help optimize pulse delivery and data processing so that fewer pulses are required to obtain reliable estimates of \( R_I \). Details of this analysis are provided in Section F of the online data supplement. Only the conclusions are provided here:

1. Some of the variability was related to slow time-dependent changes in \( R_I \) (e.g., Figure 4) and does not, therefore, represent noise. When these slow changes in \( R_{\text{pulse}} \) were filtered out, the average (±) CV decreased to 12.4 ± 5.8%.  
2. A moving average (MA) of 10 \( R_{\text{pulse}} \) values is associated with acceptably narrow 95% CI in all patients (<17% of mean in all patients and <12% of mean in 88% of patients). For most patients a MA of 5 points or less would be associated with acceptably narrow confidence intervals. Given that pulses can be applied at a rate of 1/min or higher, the variability exhibited by this approach is such that changes in resistance can be rapidly and reliably detected.  
3. The use of an 8-Hz low-pass filter for the primary signals (Paw and V) appears optimal.  
4. Pulses delivered in the second half of the inflation phase displayed much greater between-pulse variability (BPV).  
5. For pulses delivered in the first half of the inflation phase BPV was most strongly correlated with Pmus at the time of the pulse (Pmus0). For each 1 cm H\( \text{O} \) increase in Pmus0, the SD of \( R_{\text{pulse}} \) increased by 0.19 cm H\( \text{O} \) \( \cdot \) L\( \text{min} \)\(^{-1} \) \( \cdot \) s \( (p = 3.2\text{E}^{-8}) \). This emphasizes the need to deliver the pulse early in the inflation phase. The timing of pulse application, within the first half of the inflation phase, had no impact on BPV once the independent effect of Pmus (more latency, more Pmus) was accounted for.  
6. BPV was negatively related to the magnitude of decrease in V between \( T_0 \) and \( T_1 \).  
7. BPV was not influenced by the time difference between \( T_0 \) and \( T_1 \) within the range used in this study (0.07 to 0.16 s).  
8. BPV was not significantly influenced by the magnitude of pressure assist once the effect of assist level on Pmus was taken into account.

The results of the analysis summarized above suggest that the relatively low noise level observed in the present study was related in large measure to early application of the pulse which, all else being the same, results in lower Pmus at the time of the pulse, and our use of a relatively large \( \Delta \text{flow} \) (0.31 L \( \cdot \) s\(^{-1} \), on average). These findings also suggest that noise is likely to be greater whenever Pmus is high such as in patients with high respiratory drive or patients on low levels of assist close to weaning.

Finally, we wish to describe an unusual flow pattern, identified in two patients, which has the potential of causing important errors in \( R_{\text{pulse}} \) estimates. Figure 7 shows this pattern in the patient in whom it was most prominent. There was a sharp flow spike soon after triggering. This occurred in all breaths throughout the 63 min of monitoring. Because in the PAV mode the ventilator increases Paw in response to an increase in flow, there was a corresponding peak in Paw that was delayed relative to the flow spike, reflecting the obligate ventilator delay. Flow, however, began decreasing sharply while Paw was still rising so that peak Paw over this artifact period, occurred at a flow that was substantially below the peak flow of the spike (Figure 7B).

We believe that the early flow spike seen soon after triggering in these patients represents reversal of the dynamic airway compression that occurred during the preceding expiration. Both patients had severe chronic obstructive pulmonary disease (COPD) and showed evidence of dynamic compression of airways, and flow limitation, during expiration. Thus, expiratory flow showed an early spike soon after the opening of the exhalation valve both during CMV (not shown) and PAV (Figure 7). After this early expiratory spike, flow was considerably less than expected based on estimated elastic recoil and \( R_I \) (determined by the interrupter technique during CMV). The early expiratory flow spike in severe COPD has long been thought to reflect dynamic compression of the central airways with expulsion of their air content at the beginning of expiration (30–32). As soon as the ventilator triggers, the central airways spring open. During this period, and until the airways are fully expanded, resistance is, in effect, very low because a major part of the flow is directed away from the usual high-resistance pathway (into the alveoli) and into the low-resistance pathway of the central airways. In the PAV mode this results in a temporary resistive runaway (FA > \( R_I \)) which accelerates the process of airway filling. Once dynamic compression ends (i.e., airway circumference becomes circular), all flow must pass through the high-resistance pathway. Flow drops followed by a decrease in Paw. Resistance now assumes its high value for the remainder of inspiration.

The artifact observed in these two patients may result in important errors in \( R_{\text{pulse}} \) estimates if the pulse interval (i.e., \( T_{-1} \) to \( T_1 \)) overlaps the artifact. This is because with the extrapolation technique it is assumed that the resistance coefficients \( (i.e., K_1 \text{ and } K_2) \) are constant over the interval \( T_{-1} \) to \( T_1 \). More details about the possible mechanisms of this artifact, its impact on \( R_{\text{pulse}} \) values, and possible ways to avoid errors in

Figure 7. Tracings showing the pattern of Paw, V, and \( V \) in a patient who displayed a sharp flow spike soon after triggering. Note that the abnormality exists in all breaths. Also note that a flow spike also occurs at the very beginning of expiration. (A) Slow speed. (B) Faster speed.
its presence are provided in Section G of the online data sup¬
plemen
t. In summary, this study confirms that reliable estimates of re-
sistance can be obtained, noninvasively, in mechanically venti-
lated patients with respiratory efforts using a pulse technique in which Paw and V are transiently reduced in the early part of the inflation phase.

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References
10. Farre R, Ferrer M, Rotger M, Navajas D. Servocontrolled generator to measure respiratory impedance from 0.25 to 26 Hz in ventilated patients at different PEEP levels. Eur Respir J 1995;8:1222–1227.
28. Corne S, Webster K, Younes M. Effect of inspiratory flow rate on dia-
31. Gottfried SB, Rossi A, Higgs BD, Calverley PMA, Zocchi L, Bozic C, Milic-Emili J. Noninvasive determination of respiratory system me-
32. Hage R, Aerts JG, Verbraak AF, van den Berg B, Bogaard JM. Detection of flow limitation during tidal breathing by the interrupter tech-