A method of reconstruction of clinical gas-analyzer signals corrupted by positive-pressure ventilation

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Farmery, A. D., and C. E. W. Hahn. A method of reconstruction of clinical gas-analyzer signals corrupted by positive-pressure ventilation. J Appl Physiol 90: 1282–1290, 2001.—The use of sidestream infrared and paramagnetic clinical gas analyzers is widespread in anesthesiology and respiratory medicine. For most clinical applications, these instruments are entirely satisfactory. However, their ability to measure breath-by-breath volumetric gas fluxes, as required for measurement of airway dead space, oxygen uptake, and so on, is usually inferior to that of the mass spectrometer, and this is thought to be due, in part, to their slower response times. We describe how volumetric gas analysis with the Datex Ultima analyzer, although reasonably accurate for spontaneous ventilation, gives very inaccurate results in conditions of positive-pressure ventilation. We show that this problem is a property of the gas sampling system rather than the technique of gas analysis itself. We examine the source of this error and describe how cyclic changes in airway pressure result in variations in the flow rate of the gas within the sampling catheter. This results in the phenomenon of “time distortion,” and the resultant gas concentration signal becomes a nonlinear time series. This corrupted signal cannot be aligned or integrated with the measured flow signal. We describe a method to correct for this effect. With the use of this method, measurements required for breath-by-breath gas-exchange models can be made easily and reliably in the clinical setting.

Breath-by-breath analysis; capnography; sidestream

Breath-by-breath analysis of respiratory gas flux requires integration of contemporaneous airway flow and gas concentration signals. In addition, both signals need to have sufficiently fast response characteristics (11) so that errors in the process of integration are minimized throughout the time course of any signal “transient.” Methods to improve the signal response in gas analyzers have been described previously (1, 3, 6, 17). Despite this, however, accurate breath-by-breath analysis of gas flux with most sidestream infrared and paramagnetic clinical gas analyzers, although possible in spontaneous ventilation, is not easily practicable in ventilated patients, although it is frequently described in the literature (2, 4, 9, 10, 17). This problem has not been addressed previously. The reasons for it and a means to overcome it are described below.

Background

Problems with the performance of sidestream clinical gas analyzers in ventilated patients came to our attention during work in this laboratory using the single-breath test for CO₂ (7) and in the development of the sine wave inspiratory forcing technique (15, 16) for use in the clinical environment with nonspecialized gas monitors. These techniques require breath-by-breath volumetric analysis of CO₂, O₂, and N₂O. Our initial experiments gave disappointingly inaccurate results for alveolar volume and dead space because of errors in the computation of mixed-inspired and -expired gas concentrations. However, we could ascribe the observed error neither to deficiencies in signal response time nor to misalignment of the flow and concentration signals, both of which were rigorously assessed and optimized (5, 6). A clue to the problem was revealed when it was noticed that, in spontaneously breathing individuals, the mixed-expired concentration computations gave accurate results in all cases. Clearly, some property of positive-pressure ventilation was affecting the performance of the gas analyzer. It was demonstrated experimentally that pressure fluctuations (of the magnitude seen clinically) at the sampling site did not cause significant alterations in the magnitude of the measured concentration value, and so it was still not immediately clear how variations in breathing system pressure could corrupt the gas concentration signal. The remaining possibility was that the gas concentration signal was being corrupted, not in the ordinate but in the abscissa; i.e., the signal was being distorted in the time domain.

The concept of time compression

Ozanne et al. (13) noted that, when mass spectrometry was used in “multiplex mode,” the practice of sampling and analyzing at different sample flow rates produced a phenomenon that they called “time compression.” The time compression ratio is given by the
ratio of the rates at which the sample was aspirated at the proximal end and discharged from the distal end of the catheter. It can be shown theoretically that, if the sample flow rate of our clinical gas analyzer were to be sensitive to cyclic fluctuation in breathing system pressure, then time compression or dilation would corrupt the signal in the time domain within a breath.

Theoretical Analysis of the Consequences of the Pressure Dependency of Sample Aspiration Rate of the Datex Ultima

See Table 1 for glossary of terms. The acceleration of a sample within the sampling catheter, as breathing system pressure increases, causes the sample to exit the catheter at a greater rate than that at which it was aspirated. This acceleration or deceleration does not affect the magnitude of the concentration signal but has the effect of compressing and dilating time. We can think of gas concentration data as “quantal” entities in that for this purpose we are not interested in the magnitude of the signal but in the distortion of the time intervals between these quanta. Consider the sampling catheter shown in Fig. 1. If a gas concentration signal is digitized at 100 Hz, we can consider that a quantum of gas leaves the distal end of the catheter every 10 ms. This quantum will have occupied, throughout its passage in the catheter, a volume that we will call \( \delta V \), which equals \( V_s(t) \cdot \delta t \), where \( V_s \) is the sample flow rate, \( t \) is time, and \( \delta t \) is the reciprocal of the digitization frequency. However, when this quantum was originally aspirated into the proximal end of the catheter, the time taken would have been \( \delta t' \), which is the time interval over which each 10-ms digital quantum was aspirated from the airway, which equals \( \delta N V_s(t - TT) \), where \( TT \) is the transit time of the sample within the catheter. Hence

\[
\delta t' = \delta t \cdot \frac{V_s(t)}{V_s(t - TT)}
\]

This means that data that appear to have been sampled over time \( \delta t \) were in fact aspirated over a period \( \delta t' \). This represents either a dilation or contraction of time, depending on the relative magnitudes of the real-time sample flow rate and the sample flow rate at the time of aspiration. In other words, the capnograms, oxygrams, etc., as displayed by the analyzer, appear as if they are plotted as nonlinear time series. It follows from this that the “widths” of the real and measured capnogram, oxygram, etc. will differ. To reconstruct the linear time series, each digitization sample is no longer plotted against the time variable \( n \cdot \delta t \) (where \( n \) is the digitization sample number) but against

\[
\sum_{0}^{n} \delta t'
\]

Effect of Time Distortion on the Process of Integration

This discrepancy is important when one considers the integration of airway flow and concentration that occurs at each 100-Hz digitization to yield the volume of tracer gas.

\[
\text{Volume of tracer gas} = \int_{0}^{V_T} c(V) \, dV
\]

where \( V_T \) is tidal volume and \( c(V) \) is the actual concentration of tracer gas as a function of volume \( V \). When data are sampled digitally and when flow and concentration data points are separated by a common time interval (i.e., 10 ms for a 100-Hz digitization), then this integration is affected as follows

\[
\text{Volume of tracer gas} = \sum [c(t) \cdot \dot{V}(t) \cdot \delta t]
\]

where \( \dot{V} \) is airway gas flow rate. Digital integration is only possible in this way if the \( \delta t \) values are constant.

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**Table 1. Glossary of terms**

<table>
<thead>
<tr>
<th>Symbol</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>( c(t) )</td>
<td>Actual concentration of the tracer gas (%) as a function of time ( t )</td>
</tr>
<tr>
<td>( t_{0.1-0.9} )</td>
<td>10–90% Rise time (s)</td>
</tr>
<tr>
<td>( \dot{V} )</td>
<td>Airway gas flow rate (ml/s)</td>
</tr>
<tr>
<td>( V_s )</td>
<td>Sample flow rate (ml/s)</td>
</tr>
<tr>
<td>( V_T )</td>
<td>Tidal volume (ml)</td>
</tr>
<tr>
<td>( \delta t )</td>
<td>Time interval of each “quantum” of digitized concentration data, equals 1/digitization frequency (i.e., 10 ms)</td>
</tr>
<tr>
<td>( \delta t' )</td>
<td>Time interval over which each 10-ms digital quantum was aspirated from the airway (ms)</td>
</tr>
<tr>
<td>( TT )</td>
<td>Transit time; time for gas sample to traverse the catheter (ms)</td>
</tr>
<tr>
<td>( \Delta T_{\text{apparent}} )</td>
<td>Apparent time interval between end-expiratory point on concentration signal and start of inspiration on flow signal (ms)</td>
</tr>
<tr>
<td>( P(t) )</td>
<td>Airway pressure (mbar)</td>
</tr>
</tbody>
</table>

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**Fig. 1.** Schematic diagram of a “quantum” of gas being aspirated into and ejected from a sampling catheter. \( V_s(t) \), flow rate at time of emission; \( \dot{V}_s(t - TT) \), flow rate at time of aspiration, where \( TT \) is transit time. \( \delta V \), volume occupied by quantum.
and common to both flow and concentration signals. With time distortion, the time separator is the inconstant $\delta t'$ for concentration and constant $\delta t$ for flow.

**Effect of Time Distortion on the Identification of End Expiration and on Concentration-Flow Signal Alignment**

Not only does time compression (or dilation) create errors in integrating the concentration and flow signals, it also distorts the timing of the point on the concentration signal that is nominated as being “end expiratory.” For CO$_2$, the exact identification of end-expiratory time is, of course, important for the correct alignment of concentration and flow signals (5, 9). If there were no time distortion, then the correct time delay would equal the apparent time difference ($\Delta T_{\text{apparent}}$) between the end-expiratory point of the concentration signal and the onset of inspiratory flow. However, if the concentration signal is a nonlinear time series, the real-time delay equals

$$\sum_{0}^{N} \delta t'$$

where $N = \Delta T_{\text{apparent}}/\delta t$. The purpose of this series of experiments was to examine the relationship between breathing system pressure and sample flow rate and to devise a means of reconstructing or linearizing the concentration time series. Because this latter aim depends on the results of the former, we shall describe the two parts separately.

**METHODS**

**Part 1. Determination of the Relationship Between Sample Flow Rate and Breathing System Pressure**

A bench lung (14) was ventilated with a Siemens Servo 900C constant-flow generator ventilator (Siemens, Solna, Sweden) as shown in Fig. 2. Breathing system pressure was measured with the pressure transducers within the ventilator and with a Datex Ultima analyzer, which also measured airway flow and sampled airway gas via the standard 2-m sampling catheter (internal diameter, 1.2 mm). The sample flow rate was measured by a differential pressure transducer (Validyne Engineering) across a miniature flow transducer (Gould Godart BV, Bilthoven, The Netherlands), which was calibrated with a precision flowmeter (Timeter, Allied Healthcare) at both the proximal (inlet) and distal (outlet) ends of the sample catheter. Analog data from the Ultima, differential pressure transducer, and ventilator were digitized by an analog-to-digital converter (DAQ 700 PCM-CIA card, National Instruments) at 100 Hz and logged with LabView software. This was repeated for a series of breaths of different volumes and flow rates. The relationship between proximal and distal sample flow rate and breathing system pressure (and its derivative) was examined by using multivariate regression analysis with SigmaPlot version 4 (SPSS, Chicago, IL).

**Part 2. To Validate a Means of Reconstructing Gas Concentration Signals Corrupted By Cyclic Variations in Airway Pressure**

Method based on a first-order model. Measurements of airway pressure, flow, and gas (CO$_2$, N$_2$O, and O$_2$) concentration were made using the Datex Ultima instrument described above from a series of 10 patients being ventilated

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Fig. 2. Schematic diagram of apparatus used. A-D, analog to digital.
Corruption of Gas-Analyzer Signals by Airway Pressure


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tidally in volume-control mode with a Siemens Servo 900 ventilator. All patients were receiving general anesthesia for vitreoretinal surgery, and all but one were otherwise healthy. One patient was obese (95 kg) and had chronic, stable asthma. In addition, arterial CO₂ was measured simultaneously with a fast (10–90% response time, 70 ms) mainstream capnometer (COSMO+, Novametrix), a device that is unaffected by problems of time compression, because no sample is aspirated. The sidestream analyzer and mainstream analyzer sampled at exactly the same point, with the sample catheter of the former being inserted via a port drilled into the airway cuvette of the latter. Analog data were converted and logged digitally by the method described above.

The data were processed automatically by a Matlab code (Matlab version 5, The Math Works) in the following steps: 1) enhancement of the rise time of the gas concentration signal (6); 2) differentiation of the pressure signal; 3) determination of the value of the compressed or dilated time step, which is $\delta t'$ at each digitization as described in Part 1 of RESULTS and Eq. 4; 4) association of the concentration value at each digitization step with a new running-time value, which equals

$$\sum_{n} n \delta t_n$$

rather than $n \delta t$, where $n$ is the sample number; and 5) use of linear interpolation to linearize to the time series described in step 4 above so that sequential concentration data points were separated by uniform time intervals of 10 ms once again. This step is necessary for correct integration of the flow and concentration signals.

Model-free method. The same data as described above were processed automatically by a Matlab code in the following steps: 1) enhancement of the rise time of the gas concentration signal (6); 2) identification of the midpoint (or some other defining point; see APPENDIX) of the upstrokes of the Novametrix mainstream and enhanced Datex capnograms (see Fig. 6A in RESULTS); 3) similar identification of the downstrokes of the mainstream and Datex capnograms (see Fig. 6A in RESULTS); 4) shift of point c forward in time so that it coincides with point a; 5) shift of point d forward in time so that it coincides with point b; 6) use of linear rescaling to readjust the time interval of all the intervening points on the Datex signal between points c and d to “stretch” the Datex signal over the Novametrix template; the readjusted time intervals are made to be constant and equal to $\delta t' (n_{Nov}/n_{Datex})$, where $n$ denotes the number of samples between points a and b and points c and d for the Novametrix and Datex signals, respectively; and 7) by use of linear interpolation, the Datex signal is interpolated to yield a signal whose data points occur at 10-ms intervals (and synchronous with the flow data, etc.).

This process was repeated for the other gases measured by the instrument, namely, O₂ and N₂O.

Evaluation of correction methods. For three successive breaths in each patient, the sums of the squares of the differences (SSD) between the reconstructed Datex and the fast, undistorted mainstream capnogram were calculated. This was expressed as a percentage of the SSD for the “rise-time enhanced” but unreconstructed Datex signal. In addition, the effect of time distortion on measured mixed-expired CO₂ concentration and airway dead space using Fowler’s technique (8) was assessed by using the Novametrix mainstream and reconstructed Datex signal.

RESULTS

Part 1. Determination of the Relationship Between Sample Flow Rate and Breathing System Pressure

The inconstancy of sample flow rate, measured at the proximal site during positive-pressure ventilation, is demonstrated in Fig. 3A, where the measured flow rate is shown as a solid line. The resting gas-analyzer sample flow rate was 195 ml/min in this example. However, as the breathing system pressure increased...
to its peak of 30 cmH₂O (3 kPa), the gas sample flow increased to ~250 ml/min. The relationship between sample flow and breathing system pressure does not appear to be a simple one. There are noticeable “spikes” in the flow signal occurring at the points of maximum rise and fall in the pressure signal. Because it appeared that the sample catheter was behaving as an “impulse line,” i.e., that flow is a function of both breathing system pressure and its first derivative (dP/dt), a first-order regression equation was fitted (SigmaPlot version 4, SPSS) of the form

\[ V_{s(\text{proximal})} = k_1 + k_2 \cdot P(t) + k_3 \cdot \frac{dP(t)}{dt} \]  

where \( V_{s(\text{proximal})} \) is proximal sample flow rate, \( k_1 \) is the baseline flow rate, \( k_2 \) and \( k_3 \) are the appropriate regression coefficients (see Fig. 3A legend), and P is pressure.

The regression function (derived from a number of breaths of different sizes and pressures) is also plotted in Fig. 3A (dotted line) and is overlaid on the real data. Figure 3B shows the same treatment applied to the sample flow measured at the distal site \([V_{s(\text{distal})}].\) The regression equation in this case is

\[ V_{s(\text{distal})} = k_4 + k_4 \cdot P(t) + k_5 \cdot \frac{dP(t)}{dt} \]  

where \( k_4 \) and \( k_5 \) are the appropriate regression coefficients (see Fig. 3B legend).

With knowledge of both of these relationships, Eq. 1 can be written as follows

\[ \delta t' = \frac{k_1 + k_2 \cdot P(t) + k_3 \cdot \frac{dP(t)}{dt}}{k_4 + k_4 \cdot P(t - \text{TT}) + k_5 \cdot \frac{dP(t - \text{TT})}{dt}} \cdot \delta t \]  

Hence, by plotting each concentration data point against \( t_0 + \sum \delta t' \) instead of against \( t_0 + n \cdot \delta t \), any signal can be reconstructed to resemble a linear time series. One potential problem with this approach is that one needs to know the value of TT so that the appropriate value for proximal flow can be substituted in the denominator of Eq. 4. Because the sample flow is not constant, TT is not readily known. We have used two solutions to this problem: one reductionist and one iterative. The details are given in the APPENDIX, where it is shown that, if only a single expiration is considered [as in the single-breath test (7)], it is a valid simplification to set the denominator in Eq. 4 to equal the constant \( k_1 \).

Part 2. To Validate a Means of Reconstructing Gas Concentration Signals Corrupted By Cyclic Variations in Airway Pressure

Method based on a first-order model. Figure 4 shows capnograms measured by the Datex Ultima sidestream and the Novametrix mainstream instruments for a series of breaths from the obese patient with chronic, stable asthma. This example is chosen because the phase 3 plateau is markedly sloping, and thus the fidelity of any correction of time-domain distortion is more readily demonstrable. The breathing system pressure is also displayed. The signal from the sidestream instrument is delayed relative to the pressure signal, as is typical. It is also narrower than the mainstream signal. Figure 5A shows an individual breath from this series. The response time of the raw Datex signal (solid line) has been enhanced according to the method of Farmery and Hahn (6); thus it is of a similar order as the mainstream instrument (75 ms; dotted line). All signals in Fig. 5A have been aligned at their apparent end-expiratory points (see APPENDIX for details of this technique), which gives the impression that the “front edge” of the sidestream capnogram is delayed. This latter signal is then reconstructed according to Eq. 4.

The SSD between the reconstructed Datex and the “true” mainstream signals is shown in Table 2. The effect of time distortion and its correction on the volumetric capnogram [and hence on the computation of mixed-expired concentration and on airway dead space using Fowler’s method (8)] is shown in Fig. 5B. A summary of these data from all patients is shown in Table 3.
Model-free method. Figure 6A shows an individual breath from the series shown in Fig. 4. The raw Datex CO₂ signal has been enhanced according to the method of Farmery and Hahn (6) so that its response time is of a similar order as the mainstream analyzer (75 ms). This enhanced signal is then reconstructed according to the algorithm described in the METHODS section. After linear rescaling and interpolation, the reconstructed sidestream signal is shown in Fig. 6B. The SSD between the reconstructed Datex and the true mainstream signals is also shown in Table 2. The effect of time distortion and its correction on the computation of mixed-expired concentration and on airway dead space using Fowler’s method in these patients is also shown in Table 3.

Table 2. Effect of time distortion on measured capnograms for positive-pressure ventilation and performance of methods to correct it

<table>
<thead>
<tr>
<th>Signal</th>
<th>SSD as Percentage of Uncorrected Signal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enhanced response time only</td>
<td>100</td>
</tr>
<tr>
<td>Reconstructed Datex signal, first-order model</td>
<td>9.2 ± 8.1</td>
</tr>
<tr>
<td>Reconstructed Datex signal, model-free approach</td>
<td>5.1 ± 0.85</td>
</tr>
</tbody>
</table>

Values are means ± 2 SD. The sum of the square of the distances (SSD) between each point of the reconstructed signal and the respective point for the Novametrix mainstream (“true”) signal was calculated over a suitable range for each breath (e.g., 3–8 s in Figs. 5A and 6B).

DISCUSSION

Figure 3 demonstrates how the sample aspiration rate is not constant under conditions of positive-pressure ventilation. This relationship between airway pressure and aspiration flow rate approximates to a first-order or impulse line system, and this has been modeled with reasonable closeness by the regression functions (Eqs. 2 and 3), which are also shown in Fig. 3. The reason that some mass spectrometers are not similarly affected is that their sampling catheters have a very fine bore and, consequently, a high resistance (and low-flow rate; ≤20 ml/min). This high-resistance catheter buffers the variation in flow rate in the face of cyclically varying airway pressure. However, some mass spectrometers, e.g., the Marquette RAMS 200 (12), have high-flow (250 ml/min), low-resistance catheters. This instrument has a pulsed crystal-driven sample inlet valve designed to stabilize the pressure within the ionization chamber. We do not know whether the output of this instrument is sensitive to cyclic airway pressure.

The sampling-catheter flow rate varies not only in time, but also with distance along the catheter, and so a sample will be aspirated and discharged from the catheter at different rates. This differential results in the phenomenon of time compression (or dilation), which will occur with each digitization, resulting in a nonlinear output.

Table 3. Effect of time distortion on measured mixed-expired CO₂ concentration and on Fowler dead space for positive-pressure ventilation and performance of methods to correct it

<table>
<thead>
<tr>
<th>Signal</th>
<th>%Error (Overestimation) in Fowler Vb</th>
<th>%Error (Underestimation) in Mixed-expired CO₂ Concentration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enhanced Datex response time only</td>
<td>55 ± 16</td>
<td>15.2 ± 5</td>
</tr>
<tr>
<td>Reconstructed Datex signal, first-order model</td>
<td>7.9 ± 4.5</td>
<td>2.0 ± 1.4</td>
</tr>
<tr>
<td>Reconstructed Datex signal, model-free approach</td>
<td>3.2 ± 1.0</td>
<td>0.9 ± 0.5</td>
</tr>
</tbody>
</table>

Values are means ± 2 SD. Vb, dead space volume.
Time Compression

Having modeled the first-order relationship between airway pressure and sample flow rate at proximal and distal sites (Eqs. 2 and 3), we used this model to test the hypothesis that time compression (described by Eq. 1) was responsible for the observed effect on the capnogram, oxygram, etc., by attempting to reconstruct the sidestream signal using Eq. 4 (and using a mainstream signal as a comparator). The first-order model of the pressure dependency of sample flow fits the data closely, as shown in Fig. 3. That sample flow rate should be related to airway pressure is intuitive, but its relationship to dP/dt is less so. A detailed discussion of impulse line theory is beyond the scope of this paper.

Signal Reconstruction: First-order Model

Using knowledge of the relationship between pressure and flow, and from the theory of time compression (Eq. 1), it is possible to devise an algorithm to reconstruct signals distorted by positive-pressure ventilation. There are a number of assumptions involved in this approach. First, the coefficients in regression equations in Eq. 4 are derived from experimental data, which are imperfect and whose derivatives are sensitive to the frequency response and averaging of the measurement system. Second, the time delay (TT) between aspiration and emission is not precisely known; thus the regression function in the denominator of Eq. 4 cannot be determined a priori. We have used two approaches to this problem, one reductionist and one iterative, which are detailed in the APPENDIX. Despite this, however, the calculation of d't' and the reconstruction and interpolation of the signal do produce a reasonable correction, sufficient at least to support our hypothesis of the time-compression mechanism for the observed phenomenon. The mean SSD is 9.2% of the unreconstructed signal, but there is a wide spread of values, with the coefficient of variation being 0.45. Reconstructing the signals using this model improves the estimation of series dead space by Fowler’s method. The Datex signal gives a marked error, with a mean overestimation of 55%. The maximum error observed in one individual case was 75%. This error is reduced to a mean of 7.9% by signal reconstruction, although there was some variation in this error.

Signal Reconstruction: Mainstream CO₂ Signal Template and Linear Rescaling

Although the first-order model is useful in characterizing the nature and cause of the signal distortion, it is unlikely to be a practical correction algorithm because of the complexity of the processing required and the variability in the coefficients in Eq. 4, which are likely under different experimental conditions and with different catheters. For this reason, we sought to use the mainstream CO₂ signal as a template to reconstruct other gas signals in the time domain. Reconstructing the Datex CO₂ signal by this method may seem pointless because, as it requires a mainstream CO₂ template, nothing is gained because one might as well use the mainstream instrument for making measurements in the first place. However, for a multigas analyzer such as the Ultima, O₂ and N₂O signals can be processed in the same way (steps 1–7 in METHODS, Part 2 section). This is particularly straightforward in the case of N₂O because, in the Ultima, the signal has a rise time identical to that of CO₂ and is contemporaneous with it. Therefore, whatever process is required to reconstruct the CO₂ signal can be applied directly to the N₂O signal without having to identify the upstrokes and downstrokes of the latter.

Practical Outcome

This model-free method of reconstruction has a number of advantages. First, no assumptions are made
about a first-principles model, and so it is likely to be more robust. Indeed, the errors in estimation of mixed-expired concentrations and dead space in Table 3 show not only a smaller error (3.2%), but also a smaller variance, in keeping with the more robust nature of this technique. Second, not only does this method correct for the effects of time distortion, but it automatically aligns flow and concentration signals because it fits the signal to a (near) real-time template. Third, there is less uncertainty about the output of the method in practice, because it can be compared with the mainstream signal at a glance. Fourth, the execution of this code (in Matlab in our case) is considerably more straightforward.

APPENDIX

Identification of End-expiratory CO2 and Flow Points

The capnograms in Fig. 5 are aligned at their respective apparent end-expiratory points so that their SSDs from the comparator (mainstream) signal can be compared. This was achieved by using a version of the method of Cochrane et al. (5) and Jacobson and Breen (9) by identifying when the CO2 signal derivative became negative for 10 successive sample points. The first of these 10 points was nominated as being end expiratory. If much fewer than 10 points are used, a false identification may be made if the signal is noisy or contains cardiogenic oscillations. If much more than 10 samples are used, the conditions may never be met. Similarly, the point on the flow signal corresponding to the onset of inspiration is taken as the first point of a series of 20 successive points where flow is “inspiratory” (negative in our system). For general applicability, if the flow transducer has an offset due to drift, a finite threshold (say, if flow is less than zero in a suitable threshold) can be used.

Identification of Upstrokes and Downstrokes of Gas Signals for the Model-free Method

For each breath \( i \), the maximum and minimum values from the Novametrix signal \( F_{max,i}, F_{min,i} \) are identified. From \( F_{max,i} \), the first of the preceding data points to equal \( \leq F_{max,i} - (F_{max,i} - F_{min,i}) \times (1 - RF) \), where RF is the rise fraction, was nominated as defining the upstroke of the capnogram for breath \( i \) (i.e., point \( a \) in Fig. 6A). Similarly, from \( F_{min,i} \), the first of the subsequent data points to equal \( \leq F_{max,i} - (F_{max,i} - F_{min,i}) \times RF \) was nominated as defining the downstroke of the capnogram for breath \( i \) (i.e., point \( b \) in Fig. 6A). Here RF is the rise fraction, i.e., the fraction of the inspiration-expiration concentration step for breath \( i \), which is taken to define the upstrokes and downstrokes of a capnogram and hence its width. We have used RF values between 0.2 and 0.5 and have found that no significant difference in output can be measured for RF values between these limits. If a small RF value is chosen, say 0.1, a false identification of upstroke and downstroke may be made if the signal is noisy or contains cardiogenic oscillations. If it is much larger than 0.5, the distinction between phase 2 and phase 3 of the capnogram may be blurred (especially if the capnogram has a sloping plateau as in our example in Fig. 6A). This process was repeated for the Datex CO2 and O2 signals to identify points \( c \) and \( d \). For N2O (whose response time and temporal alignment with the Datex CO2 signal are identical), points \( c \) and \( d \) are simply taken as the points contemporaneous with points \( c \) and \( d \) for Datex CO2. Maximum and minimum points were used rather than end inspiratory and end expiratory, because it proved to be more robust and not dependent on any uncertainty in identifying the former, although the system is amenable to modification to the preference of the user.

Approaches to Determine the Value of TT in Eq. 4

Reductionist approach. If one considers a single side-stream capnogram, say, for example, the one whose end-tidal point occurs at about \( t = 8 \) s in Fig. 4, it can be seen that the gas quantum in the side-stream analyzer cell at this time was aspirated from the airway at the instant before inspiration began. At this time (\( t - TT \), airway pressure and its derivative are zero. In fact, the pressure at time \( t - TT \) remains zero for the whole expiratory capnogram, and so the denominator of Eq. 4 can be set to the constant \( k_1 \). The nonlinearity of the capnogram time domain occurs in the latter part of the plateau, from time \( t_{end\,tidal} \) TT to \( t_{end\,tidal} \) and is effected through the changes in airway pressure and \( dP/dt \) in the numerator of Eq. 4. If only the expiratory gas concentration profiles are of interest, then each capnogram or oxygram or other “gasogram” can be analyzed in this way breath by breath and aligned with flow at end expiration. However, the condition that airway pressure is zero at time \( t - TT \) is invalid for the inspiratory gas concentration profile. This problem can be overcome as follows.

Iterative approach. With the reductionist approach above, the expiratory gas concentration profiles of each breath will have the correct width, but the inspiratory profiles will have an incorrect width. This will have the effect of producing a breath-by-breath concentration signal with a progressively changing phase relationship to the ventilatory flow signal. The problem is solved by using an iterative approach to the solution of Eq. 4. By this process, for each breath \( i \), a value of TT in Eq. 4 is selected such that the time difference between end-tidal points for breaths \( i - 1 \) and \( i \) − 1 \( t_{end\,tidal}(i) - t_{end\,tidal}(i - 1) \) is closest (in a least squares sense) to the time difference between the onsets of inspiratory flow for breaths \( i \) and \( i - 1 \). With the enforcement of phase conformity in this way, if the expiratory concentration profile is correct, then so too must be the inspiratory profile.

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