Continuous Monitoring of Respiratory Flow and CO₂

Challenges of On-Airway Measurements

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In this article, the challenges of simultaneous respiratory gas concentration and flow measurements in a breathing circuit are reviewed. The tradeoffs that were considered in the development of a clinically useful on-airway combination CO₂/flow sensor are discussed as well as the applications enabled by this on-airway combination CO₂/flow sensor.

Continuous respiratory gas measurements during the administration of anesthesia, intensive care, and other clinical environments provide valuable information for assessment of cardiorespiratory function as well as breathing circuit integrity. In particular, measurements of gas concentrations, flows, volumes, and pressures proximal to a patient’s airway can often better reflect the underlying pathophysiology of the patient than measurements made more distally. Continuous monitoring of gas composition and volume in the complex breathing circuit environment, where changes in humidity and temperature can distort the measurement and instrumentation is further contaminated by sputum, pathogens, blood etc., presents a number of difficulties/complications that have led to compromises and less than optimal clinical and technical solutions. This environment demands simplicity, reliability, ease of use, and ability to continue working in wet, often mucous-filled circuits for long periods of time without operator intervention. Because these in-circuit devices are typically disposed of after each patient use to avoid cross-contamination, they should be relatively inexpensive, lightweight, and disposable. Furthermore, these devices need to have minimal volume so as not to interfere with therapy and should work over wide flow ranges, while contributing minimal resistance to air flow, and require minimal or no calibration. Devices typically designed for the pulmonary function laboratory employ sensors designed for brief procedures lasting for a few minutes rather than for continuous monitoring [1].

With respect to flow, volume, and pressure measurements, it has become increasingly clear that to accurately deliver tidal volumes to a critically ill patient, it is preferable to perform these measurements as close to the patient as possible [2]. Traditionally, the measurements of the delivered and expiratory flows and volume have been, for technical reasons, located in the ventilator. Proximal flow (i.e., measured at the patient’s airway) can be substantially different from flow measured inside or at the ventilator due to the wasted gas compression volume, breathing hose expansion, and differences due to humidification. This wasted portion of the tidal volume, i.e., compression and hose expansion volume, does not ventilate the patient, but rather remains within the breathing circuit tubing. A correction for this effect which is proportional to the inspiratory peak pressure is applied by some ventilator manufacturers given that the breathing circuit volume and compliance is known. However, the compliance may also depend on the inspiratory flow rate [3]. Even with this correction applied, the precise estimation of the compression volume is difficult because of variations between individual breathing circuits, use of humidifiers, heat-moisture exchange (HME) devices, and other circuit components. In a typical breathing circuit, gas conditions such as temperature may vary from room. Air-to-body temperature and humidity may vary from dry air to fully saturated air. Water vapor phase changes within the breathing circuit hoses also contribute to differences in volume measurements between the distal (within the ventilator) and proximal (patient airway) measurements. Thus, for more accurate monitoring of delivered volumes and of the patient’s expired volume, the flow sensor should be placed between the breathing circuit wye and the endotracheal tube (ET). For neonatal and pediatric patients, this problem has been widely recognized by ventilator manufacturers who generally offer proximal flow measurements for these patient populations.

The clinical benefits of on-airway measurements were understood early in the development of clinical respiratory instruments [4]. These clinical benefits include faster signal response and precise time alignment between the flow and gas concentration signal. Early respiratory gas benches used in anesthesia were nondiverting on-airway (i.e., mainstream) devices. Bulky and heavy, the size of these mainstream benches obscured the patient’s head from the surgeon [5]. For these reasons, gas concentration measurements have traditionally been made in breathing circuits using diverting (or sidestream) gas benches. However, with advances in technology, the size and weight concerns of these early devices have been overcome. The clinician need no longer accept the limitations of sidestream approaches [6], [7], such as delayed and dampened waveforms and susceptibility to clogging of the sampling line.

We have developed a family of integrated, disposable airway adapters (Figure 1) that are capable of monitoring CO₂
concentration in real time, breath by breath, using infrared (IR) absorption techniques in combination with monitoring respiratory flow with differential pressure flowmeters under diverse inlet conditions. These airway adapters interface to an on-airway capnometer (Figure 2) and spirometry measurement module (Figure 3). Our solution to the challenges of on-airway flow CO₂ and the combination of these two measurements are reviewed with respect to the challenges highlighted in this article.

This solution has been nearly 20 years in the making, requiring a number of key developments that leveraged on internal technical developments, such as a novel thick-film IR source enabling a solid-state on-airway capnometer [5]; external alliances that resulted in a robust, fixed orifice flow sensor [8]; a single piece-combined CO₂/flow sensor [9]; and technological developments including cost-effective and robust, yet extremely sensitive differential pressure sensors; and increasingly integrated digital signal processing chips. The Philips-Respironics devices for on-airway volumetric capnography have evolved since the early 1990s from separate flow and CO₂ sensors placed together in the breathing circuit, with each connected to a separate device (e.g., Ventrak 1500 and Ventrak 1550 systems and Capnoguard or CO₂SMO monitors from Novametrix Medical Systems) [10] to integrated CO₂/flow-airway adapters interfaced to the same host system.

**On-Airway Flow Measurement**

Various technologies have been used to measure airway flow. Many of these techniques were developed strictly for precise short-term laboratory measurements. These applications require meticulous attention to detail, including calibration, placement of a disposable filter element, and operator attendance at all times. Laboratory airflow measurement systems assume relatively dry gas and well-characterized gas inlet conditions. The operators of these systems are expected to pay great attention to accuracy, calibration, repeatability, and precision when taking a laboratory measurement. Overall, in respiratory research, the most widely used flow measurement device is the Fleisch or Lilly-type differential pressure pneumotach with a heated microtube or screen orifice. A continuous, bidirectional-airway flow measurement device that can be placed proximal to the patient and used in critical care environments has been of great interest. Because of the requirements of continuous long-term monitoring in the critical care environment, a different type of flow device was required. To address the requirements of the critical care environment, fixed or variable orifice (or aperture) differential pressure pneumotachometers have been developed for the last 20 years.

The Philips-Respironics family of fixed orifice flow and CO₂/flow sensors grew from an alliance with a research group in the Department of Anesthesiology at the University of Utah. Early prototypes consisted of adding pressure-sensing ports on both the proximal and distal sides of the optical window in a mainstream CO₂ cuvette [11]. Later designs followed an iterative design process including modeling and testing. This testing often resulted in features being added for improved performance under varying inlet conditions and flow-path contamination testing. Scaled-up models of the adult flow design were constructed, and airflow patterns were visualized by introducing filaments of smoke into the airstream.

Measurement of low flows using a fixed orifice design requires extreme sensitivity in the differential pressure measurement signal. Commercially available low-cost, low-pressure differential pressure sensors of the early 1990s were drifty, noisy, and sensitive to orientation. Early analog-to-digital (A/D) converters were limited in resolution. Early designs of the flow-measurement systems used clever designs to compensate for these limitations. New generations of differential pressure sensors due to improvements in fabrication and sensor design have effectively overcome these limitations.

Fixed orifice type of flow-measurement sensors are simpler in construction than alternative types of flow sensors, low cost due to the ability to manufacture as a single piece of molded plastic, and thus can be disposable. They can be designed to operate in wet, mucus-filled patient airway circuits and as such not sensitive to moisture or subject to drift when used for many hours on a patient. Most importantly, fixed orifice devices do not require individual calibrations using a syringe as do variable orifice devices.

The Philips-Respironics fixed orifice flow sensors were first developed as flow-only devices. Shortly after introduction of
the flow-only devices, sensors combining the differential pressure flow-sensor geometry with an integrated carbon dioxide (CO₂) measurement cuvette with different size airway adapters optimized for neonatal/infant, pediatric, and adult patients were released. In the adult-combined sensor, the CO₂ cuvette was placed on the patient side of the flow sensor so as to provide known inlet geometry during expired flow. Test data showed that the variability of the flow signal caused by differences in inlet geometry was more pronounced for the breathing circuit components likely to be placed between the patient and the sensor. Kofoed et al. [12] indicated variations in inlet conditions (i.e., variations in the velocity profile of the flow gas incident to the flow sensor) can lead to significant (e.g., up to 15%) error in the flow and volume measurement of some flowmeters. For example, changing the proximal connections from a direct ET connection to a connection via an elbow has a dramatic effect on the cross-sectional profile of the flow entering the flow sensor. A robust flow-sensor design should tolerate such variations with minimal effect on the measurement of gas flow (Figure 4).

The Philips-Respironics flow-sensor designs have sought to minimize the effects of changing inlet conditions. These adult flow and combined CO₂/flow sensors (Figure 5) feature a target geometry composed of a center strut and side-mounted flow restrictions mounted on the side of the center strut (having a notch in the strut) designed to minimize localized streamline effects about the pressure sensor aperture. Initial tests of potential flow-sensor designs showed that the worst inlet condition error occurs when flow at low velocity exiting from a small diameter (6 mm) endotracheal tube forms a highly variable flow profile. If the center of this profile strikes the differential pressure generator, then an erroneous flow measurement was observed. The flow-sensor designs incorporate a strut intended to break up a laminar flow profile ahead of the differential pressure measurement ports with the side-mounted flow restriction centered between the differential pressure-sensing ports. This strut-port-restriction design significantly improves its performance compared to variable orifice flowmeters, which have varying signal strength with changes in upstream geometry. This design allows for immunity to unpredictable flow-velocity profiles, without the need to add excessive length to the flow-sensor adapter (minimal dead space). Additionally, placing the pressure taps and flow obstruction on a strut, rather than on the wall of the adapter, reduces the potential effects of moisture and sputum on the measurement.

The Philips-Respironics neonatal flow and combined CO₂/flow sensors feature a target geometry composed of a center strut without the side-mounted flow restrictions to maintain an acceptable level of flow resistance. With the neonatal and pediatric-combined CO₂/flow sensors (Figure 6), the pressure ports are located on opposite sides of the CO₂ measurement cell section of the sensor, thereby using the pressure perturbation and pressure loss of the CO₂ measurement cell section of the sensor as part of the flow signal. A first port is placed on the proximal (nearer to the patient) side, and the second port is placed on the distal (farther from the patient) side of this section. This design is particularly advantageous for use in situations where the respiratory tidal volumes are extremely small, because it reduces the volume of rebreathed expired gases. In both the neonatal and pediatric combined sensor design, a flow-conditioning strut is placed at the inlet of the flow sensor to break up jetting in the flow profile of the gas.
As the equipment (i.e., apparatus) dead space in the ventilator circuit (Figure 7) can be substantial relative to the total tidal volume, especially when large HME filters are used, a design goal for each of the flow sensors was to keep the added dead space to a minimum. As such, the combination pediatric/adult and neonatal CO2/flow sensors described are single piece designs. Two pressure-sensing lines, one on each side of the target geometry, are used to measure differential pressure. The proximal pressure sensing is tapped to a gauge pressure sensor and used to measure airway pressure.

Even small changes in the geometry of the breathing circuit tubing relative to the flow sensor can potentially have a significant effect on the measured flow. The adult and neonatal flow sensor are only slightly affected by such changes, whereas other devices can be significantly affected. Figure 8 illustrates the various upstream breathing circuit components on the adult flow sensor during exhalation. Typical design rules for an annular fixed orifice gas flow sensor recommend a length of 5–10 diameters of straight tubing upstream of the differential flow ports as an inlet flow conditioner [13]. Such a large-volume flow conditioner is not viable in the critical-care application. Therefore, a design that is less sensitive to variations in inlet geometry was needed. For example, it has been demonstrated that Fleisch pneumotachographs connected between the wye and ETs exhibit a flow rate-dependent error in measured flow up to 10% [14]. If sufficient entrance length is provided in the flow sensor, then laminar flow and a consistent flow velocity profile can be achieved. However, this is usually not practical, so entrance length to a flow sensor must be traded off against the design requirement of minimal dead space.

The addition of a flow sensor to a breathing circuit should have a minimal impact on the measured quantity—flow. One of the design goals was to minimize the resistance as measured by the pressure loss across the sensor while maintaining as large as possible recoverable differential pressure drop between the ports. It is important to remember that the pressure loss associated with the flow sensor is different than the measured differential pressure (Figure 9).

With a fixed orifice device, the differential pressure measured between two pressure taps varies roughly as the square of the flow [8]. The measured flow should be corrected by use of empirically determined coefficients because of variations from this relationship and the assumptions made in developing the flow equations that include incompressibility, given the very low differential pressures, and inviscid flow, given that the cross-sectional area of the device is large relative to the boundary layer. The relationship between the measured differential pressure to flow (L/min) can be derived by applying Bernoulli’s equation to the upstream and the downstream pressure taps, equating each equation, rewriting the pressures at the two taps as a differential pressure, and applying the continuity equation for mass flow yielding the measured flow up to 10% [14]. If sufficient entrance length is provided in the flow sensor, then laminar flow and a consistent flow velocity profile can be achieved. However, this is usually not practical, so entrance length to a flow sensor must be traded off against the design requirement of minimal dead space.

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\[ \text{Flow} = \frac{P_m T_{\text{std}}}{P_{\text{std}} T_m} K \sqrt{\Delta P}, \]

where \( P_m, P_{\text{std}}, T_m, \) and \( T_{\text{std}} \) are the measured and standard pressures (in mmHg) and temperatures (in °K), respectively; \( K \) is a correction factor that is flow dependent and includes gas composition, flow-discharge coefficients, and other factors, and \( \Delta P \) is the differential pressure (in mmHg). The \( P_m T_{\text{std}}/P_{\text{std}} T_m \) is the ideal gas law correction of calculated flow to standard conditions. Inspiratory and expiratory phases are treated separately with regard to temperature and gas composition. For example, in an unheated breathing circuit supplied with room air, inspiratory air may be considered to be at near room temperature and consisting of nominally 21% oxygen and balance nitrogen and expiratory air at body temperature (or near body temperature less than 2–4 °C for temperature drop from lungs to sensor) and consisting of nominally 16% oxygen, 5% carbon dioxide, and balance nitrogen. While in a heated circuit with elevated oxygen (such as 60% FiO2), the values used for both temperature and gas composition would be quite different.

![Fig. 7. Anatomic and apparatus dead space in an intubated patient (image courtesy of Philips-Respironics).](image)

![Fig. 8. Effect of various inlet conditions for the adult flow sensor at a flow rate of 20 L/min (with average percent error ±2 standard deviation limits shown). Note that the effect of the elbow adapter was tested at four angles (image courtesy of Philips-Respironics).](image)
Additionally, the design of the front end was simplified so that each flow-sensor type (e.g., adult, pediatric, neonatal) generated the same maximal recoverable differential pressure drop for its maximum flow rate (e.g., 10 in H_2O). One of the challenges in choosing a fixed orifice design was the extreme range of the differential pressures that must be accurately measured. Dynamic range of flow for each sensor type was approximately 200:1, which required a measurable pressure range of more than 10,000:1. However, because of the relationship between differential pressure and flow, this resulted for most respiratory flows a resulting differential pressure of less than 1 in H_2O. For example, adult flow sensor with a full-scale output of 10 in H_2O at 180 L/min has an output of 3 × 10^{-4} in H_2O at 1 L/min. Therefore, a low-noise front end with a high-resolution A/D converter (≥20 b) needs to be utilized.

**On-Airway Gas Concentration Measurements**

IR gas measurement has been the preferred technology for on-airway CO2 gas sensors, since the filter wheel based Hewlett-Packard CO2 sensor was introduced in the 1970s [5]. Many of the disadvantages of on-airway (i.e., mainstream) gas sensors presented by some authors in the past are primarily technologically in nature and often relate to prior generations of that technology. These disadvantages are often listed in older reviews [15], [16] of the technology while more recent reviews note otherwise [17]. This includes possible damage during handling, increased mechanical dead space, issues of weight on airway, and use limited to only intubated patients.

For example, mainstream IR benches in the past have been termed vulnerable to costly damage [16]. While earlier IR benches were vulnerable primarily due to the use of moving parts such as chopper or filter wheels, some newer mainstream IR benches utilize all solid-state designs that have been shown to be robust enough to survive repeated drops onto hard floors and have been in use for decades now in high-impact areas such as the emergency room, ambulances, and transport. Historically, the primary concerns of mainstream-based systems are related to size and weight. However, the reductions in both size and weight have alleviated these concerns. Current-generation mainstream devices, besides being relatively light and low in dead space, have generally demonstrated better performance than conventional sidestream system in terms of signal fidelity and end-tidal measurements, particularly at higher respiratory rates in small children [18]. Airway adapter design and advances in microelectronics and optical technology incorporated in the latest generation of on-airway IR sensors have reduced the concerns for dead space and weight, even as the functionality and complexity of these sensors has increased.

The beginnings of the Philips-Respironics mainstream CO2 sensor can be found in a company started in 1981 as a division of hybrid circuit manufacturer (including thermal print heads), which was “looking for the most direct method to measure breathing and... came up with was an inexpensive way to measure exhaled CO2” [5]. This device, introduced as an infant respiration monitor, was a qualitative CO2 detector based on nondispersive infrared (NDIR) technology, which was nonratiometric, nonchopped, and somewhat drifty. After three years, the parent company sold the assets to a Midwest-based company (now known as BCI), and the founders of this division found themselves unemployed. Still believing in the technology, they put together a team at a new company called Cascadia Technology Corporation to build a quantitative system that was a true ratiometric, chopped, and stable NDIR system. This required a number of innovations, including building an IR source with sufficient IR energy and very low thermal mass that could also be pulsed on/off at rates of up to 100 Hz [5]. The original prototype Capnostat CO2 sensor has undergone significant changes over the past 20 years resulting in the current highly integrated Capnostat 5 CO2 sensor.

**Airway Adapter**

The measurement cell, referred to as the cuvette, also serves as the airway adapter that defines the flow path for the gases being monitored obviating the need for gas sampling, drying, water trapping, and scavenging. The optical path, shown in Figure 10, crosses the flow path of the gases through windows in the sidewalls of the cuvette aligned along opposite sides of the flow passage, allowing the beam of IR radiation to pass through the cuvette. The fraction of IR radiation absorbed is dependent upon the path length of the radiation through the gases, the wavelengths...
of radiation being measured, and the gas molecule itself. This path is constrained by dead space, resistance, and inner bore (i.e., flow path) requirements. Also, the optical path length must be sufficient to have adequate sensitivity to measure the gas. One study using a simplified formula for cuvette path length optimized for the received radiation intensity with CO₂ of 4–6% resulted in a path length of approximately 7 mm [19], which is close to the distance between windows for existing designs. Additionally, the end openings of the cuvette need to conform to International Organization for Standardization (ISO) 5356-1 [20], which specifies connections for 15 and 22 mm sizes intended for general use in breathing systems. Condensed water or waterlike mixtures can affect the windows of the cuvette for some optical designs. If droplets appear within the cuvette optical path, severe scattering and absorption can occur. Furthermore, the capnometer head may incorporate a heater to heat the gas in the cuvette or hydrophobically treat the cuvette, thereby discouraging condensation of droplets in the area of CO₂ measurement.

With the combined neonatal and pediatric CO₂/flow sensors from Philips-Respironics, the measurement cell with small restrictions located on each side of cell chamber serves a dual function by adding a differential pressure flow signal to CO₂ measurement. With the adult CO₂/flow sensor, dead space is less critical and as such the CO₂ measurement cell and flow measurement portions are separate.

In reusable cuvettes, the windows are formed from materials such as sapphire with a broad transmission range (up to 5 μm) and high optical transmission (>80%). The cost of these cuvettes has been reduced by replacing the relatively expensive sapphire windows with windows fabricated from a polymer with consistent IR-transmission characteristics and robust mechanical properties. The major problems encountered in replacing sapphire cuvette windows with polymer windows is twofold: 1) establishing and maintaining a precise optical path length through the sample being analyzed affected by such factors as dimensional stability in the polymeric material, the potential of wrinkles in the windows, and the need for a system for retaining the windows at precise locations along the optical path and 2) choosing a polymer with sufficiently broad transmission range and high optical transmission. Using elastically compressible snap-in retainer rings in conjunction with malleable homopolymer windows allows a precise optical path through the sample to be maintained. Selecting an appropriate polymer allows a significant portion of the IR radiation impinging upon it to be transmitted as well as appropriate spectral transmission characteristics (i.e., similar absorbance at the data and reference wavelengths).

**On-Airway IR Bench**

The measurement cell interfaces directly to the IR bench, which consists of a source and detector assembly located on opposite sides of the CO₂ cuvette. The source emits IR radiation that includes the absorption band for carbon dioxide. Carbon dioxide has a very strong absorption band at 4.26 μm, due to the fundamental asymmetric O=\(\text{C} = \text{O}\) stretch, which lies between the two very-intense water vapor bands. The IR radiation, after passing through the gas sample flowing in the cuvette, is often filtered using narrow-band optical filters and measured by appropriate detectors configured as a single-beam ratiometric design. With such a design, both the reference (or non-CO₂ sensitive) and data (or CO₂ sensitive) channels see IR radiation after passing through the measurement cell. The reference channel uses a filter with a center wavelength at which little or no CO₂ is absorbed, and data channel uses a filter with center wavelength at which CO₂ is strongly absorbed. Using the ratio of these two measurements helps to allow for cancellation of the effects of changes in the spectrally independent optical properties of the system such as signal strength, sample chamber contamination, and thermal drift. Thus, in principle, only the presence of CO₂ will affect the data channel while leaving the reference channel unaffected, allowing CO₂ gas concentration to be distinguished from the often larger effects mentioned above.

The filters used, usually of the narrow band type, are typically manufactured using multiple thin-film vapor depositions on a silicon substrate. The data channel filter with a center bandpass wavelength of 4.26 μm and a half power bandwidth typically less than 0.2 μm can effectively eliminate any interference from water vapor or even closer bands of N₂O. One of the most common detectors in use today, a photodiode semiconductor material, is lead selenide (PbSe). PbSe works well for on-airway...
CO₂ measurement, in part due to the adequate spectral response and fast response time constant. The bulk resistance of this material drops proportionately to the amount of incident IR energy. As this material is extremely temperature sensitive, a feedback temperature control system is used to assure a stable detector temperature, enabling accurate measurements.

The monitor has traditionally contained the electronics associated with control and measurement functions of the IR bench. Newer designs including the Capnostat 5 sensor from Philips-Respironics, incorporating advancements in electronics packaging and components, have moved these electronics into the measurement head, turning the sensor into a complete headless (i.e., lacking only display and controls) CO₂ analysis system. This results in greater complexity in the sensor but greater simplicity to the original equipment manufacturer (OEM) customer and the end user by enabling concepts such as plug and play capnography; that is, the user can choose between the most appropriate type of CO₂ measurement technology for the patient at hand. An on-airway CO₂ sensor can be selected for monitoring patients on mechanical ventilation, and a side-stream solution for monitoring patients using nasal cannulas.

The Philips-Respironics Capnostat 3 and Capnostat 5 CO₂ sensors also employ a coaxial light path design, wherein a dichroic beam splitter oriented at 45° to the IR light path is employed to direct the appropriate band of wavelengths to each of the two detectors such that each detector receives light through precisely the same path. This prevents contaminants in the cuvette from influencing the light reaching only one of the detectors, causing a ratiometric shift that would otherwise cause CO₂ measurement errors.

On-Airway Flow and Gas Measurement—Combining the Signal

Challenges of combining flow and CO₂ signals in volumetric capnography include the following:

- compensating for the rebreathing of gas in the tubing that will cause CO₂ excretion rate (VCO₂) to be overestimated if not corrected
- correcting for the delay of CO₂ signal relative to the flow signals (much more of a consideration with sidestream systems) requiring proper frequency matching of the signals
- consideration of the variations in temperature and vapor content of expired gas affecting volume correction and mixed expired CO₂ values (FECO₂) (more of an issue with sidestream systems that measure CO₂ and flow at different points).

Issues of dead space and resistance as well as robustness to the challenging environment (discussed earlier) at the airway must also be kept in mind. Devices such as the combined CO₂/flow airway adapters allow for minimizing the added dead space between the wye and elbow and permit accurate and continuous measurement of carbon dioxide elimination and volumetric capnogram-derived parameters such as dead space to tidal volume ratios (Vd/Vt) [21].

During normal conditions, the lung will excrete CO₂ at the same rate as the total body production rate and there will be no net change in body CO₂ stores. CO₂ elimination (VCO₂), which is often incorrectly referred to as CO₂ production, is the net volume of CO₂ measured at the mouth or airway, and calculated as the difference between expired and inspired CO₂ normalized to a minute. VCO₂ is computed by taking integral of the dot-product of the flow and CO₂ waveforms over the entire breath cycle and usually reported at standard temperature and pressure dry (STPD) conditions. For breath-by-breath measurements it is calculated as

\[
\dot{V}{\text{CO}_2} = \sum \text{FCO}_2(t) \times V(t) \times \Delta t \times RR,
\]

where FCO₂(t) and V(t) are the sampled individual values of the CO₂ and flow waveforms summed over the entire breath, RR is the respiratory rate, and \(\Delta t\) is the sampling interval. When present, inspired CO₂, if not accounted for could result in an error in the calculation of VCO₂ of several percent [22]. In anesthesia and intensive care, components such as filters, HMEs, connecting tubes, elbows, airway adapters, and suction adapters are placed between the ET connector and wye, causing partial rebreathing and therefore inspired CO₂. Placing the sampling site more proximal (e.g., on-airway) will potentially allow the end-tidal CO₂ value to better reflect the alveolar concentration. If the inspiratory carbon dioxide volume is ignored, the overestimation of VCO₂ will increase with decrease in tidal volume and/or increase in apparatus dead space.

Figure 11 illustrates the cross-multiplication process with the plot of actual flow and CO₂ waveforms versus time of a mechanical breath delivered in a volume control mode. Because of apparatus dead space from the mainstream sensor, wye, and other circuit components, a small volume of end-expiratory CO₂ (from the previous breath) is rebreathed upon the initiation of inspiration. Note that, in this patient, the expiratory CO₂ waveform rises rapidly to a plateau and the CO₂ volume curve follows that of the expiratory portion of the flow waveform. VCO₂ would then be the difference between the expiratory and inspiratory areas of the dot products. If we plot PCO₂ and volume instead, carbon dioxide elimination (VCO₂), the net volume of CO₂ eliminated can be viewed as the area between the expiratory and inspiratory curves (Figure 12). With no rebreathing, the volume of CO₂ eliminated during a breath is the area under the volumetric capnogram. However, the presence of inspiratory CO₂ must be accounted for when reporting and interpreting VCO₂ [22].

VCO₂ does not accurately reflect the underlying physiology when there are leaks in the collecting system or where
conditions exist such that all the gas that is considered part of the alveolar ventilation volume cannot be measured i.e., pneumothorax with leak or ET cuff leaking on exhalation. Because of the complex interaction between tidal volume, physiological dead space, and alveolar ventilation, the volume of CO\(_2\) excreted by each breath is variable. The results of several breaths are often averaged in an attempt to decrease the effect of normal breath-to-breath changes in volume. Depending on how V\text{CO}_2 is used (metabolic measurements versus ventilator adjustments) [23], different averaging intervals may be required including a range of averaging intervals such as one breath, eight breaths, 1 min, 3 min, and longer.

During steady-state conditions, the lung will excrete CO\(_2\) at the same rate as the total body production rate, and there will be no net change in body CO\(_2\) stores. In this case, measured V\text{CO}_2 is representative of total body production and is proportional to metabolic rate. Because the body retains a large amount of CO\(_2\) relative to the rate at which CO\(_2\) is produced, eliminated CO\(_2\) can be different from metabolically produced CO\(_2\) for a long time (up to 1 h) following a change in ventilation. However, changes in V\text{CO}_2 can provide an instantaneous indication of the change in effective alveolar ventilation [23].

With robust mainstream sensors for flow and carbon dioxide located at or very close to the same point in the gas stream the principal issue is one matching the frequency response of the flow and gas analyzers [24]. Note that, since integration of the dot product of the flow and CO\(_2\) signals over an entire breath generates a significant low pass filter, there is little need to provide low-pass filtering of the input signals prior to integration. The frequency response characteristic of the flow measurement is primarily limited by the pneumatic pathways between the fixed orifice sensor and the differential pressure transducer as well as the sampling rate and front-end hardware and software low-pass filtering. The frequency response of the carbon dioxide measurement is limited by the size of the measurement cell (i.e., volume interrogated by the IR beam) as well as the thermal characteristics of the IR source and time constant of the detector (if certain technologies are employed). By properly delaying and filtering the respective signals, a reasonable degree of frequency matching can be achieved.

**Applications Enabled**

The combination of flow, pressure, volume, and gas measurements at the airway with a single integrated sensor provides a powerful array of measurements to the clinician for the management of both the spontaneously breathing and mechanically ventilated patient. These measurements include bedside spirometry, lung mechanics, and volumetric capnographic measurements such as carbon dioxide elimination and dead space. Applications enabled by volumetric capnography include prediction of outcome with ARDS [25], a screening test for pulmonary embolism [26] and determining disease staging of chronic obstructive pulmonary disease (COPD) [27]. Additional measurements requiring perturbations to the systems also include noninvasive cardiac output via partial CO\(_2\) rebreathing and functional residual capacity measurement [28].
Future Challenges
With the competitive pressures for increasing miniaturization, greater regulation, and the future inclusion of new on-airway measurements (e.g., oxygen) for enhanced capabilities (e.g., metabolic measurements), additional technological, and user interface/ease-of-use hurdles will need to be overcome. However, advances in microelectronics and other technologies suggest that these hurdles will be surmounted in the not-distant future.

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