Classical Respiratory Monitoring 12

12.1 Monitoring Oxygenation of Ventilated Infants and Children

John Salyer

Educational Goals

- Describe a basic understanding of the oxygen transport chain.
- Understand the various technologies for oxygenation monitoring during mechanical ventilation.
- Describe the limitations associated with various monitoring technologies.

Karl Wilhelm Scheele first discovered oxygen in 1772.[1] This immense milepost in the history of science and medicine set into motion events that have led us to the present in which the delivery and monitoring of oxygen is a mainstay of critical care. It is now possible to continuously measure many key aspects of the complex movement of oxygen molecules from the atmosphere to the lungs, to the blood, to the tissues, and finally, to the cellular structures that use oxygen and nutrients to create the energy molecules that fuel our biological engines. This chapter will focus on the most commonly used oxygenation monitoring techniques including their measurement principles, utility, and limitations. However, before we explore a brief review of what *can* be monitored, it is useful to consider what *should* be monitored. Sometimes, our technology develops at a pace that far exceeds our wisdom in how to use it. "New technologies and procedures have developed so rapidly—and there are such economic and social incentives to use them—that the evaluation of their safety, efficacy, and cost-effectiveness as well as the consideration of their social and ethical consequences have lagged far behind" (Mosteller and Institute of Medicine 1985). Another term for this is technology creep,

[1] Although still debated, evidence suggests that Scheele discovered oxygen independently and earlier than Joseph Priestly who has been widely credited with this breakthrough because he published his findings prior to Scheele. Others have suggested that oxygen was discovered even earlier by a Michał Sędziwój, a Polish alchemist and natural philosopher in the late sixteenth century.

P.C. Rimensberger (ed.), *Pediatric and Neonatal Mechanical Ventilation*,
DOI 10.1007/978-3-642-01219-8_12, © Springer-Verlag Berlin Heidelberg 2015

which refers to the continuing addition of technology that is both qualitatively and quantitatively more complex. Moreover, this often happens without any rigorous testing of the effect of this technology on patient outcomes. Most new instrument/device testing mandated by regulatory agencies prior to approval is focused on ensuring patient safety and measurement accuracy and precision, as opposed to proving that the device in question will alter patient outcomes or improve processes of care.[2]

Some clinicians have adopted a "more is better" philosophy, wanting to monitor nearly everything possible (Hess 1998). Excessive numbers of monitors at the bedside can produce so much information for clinicians to process that the sheer volume can outpace their ability to analyze and integrate this information into timely decision making (East et al. 1991; Graham and Cvach 2010). There can be up to 40 different monitoring alarms assaulting the intensive care clinician (Chambrin 2001). It is reported that only 15 % of all monitor alarms in an intensive care environment are clinically relevant (Siebig et al. 2010).

Add this complexity to the fact that clinicians are often not adequately trained to understand the physiology and measurement principles related to the monitors they are using. In a survey of more than 4,300 responders, 70 % of neonatal care providers acknowledged that they do not have a complete education in oxygenation and have insufficient knowledge of basic concepts (Sola et al. 2008). In the same survey, 92 % did not know how SpO_2 monitors work and the differences between various brands of SpO_2 monitors. Knowledge (or the lack thereof) about pulse oximetry has been tested among pediatric clinicians, and the results have mostly been disappointing (Teoh et al. 2003; Popovich et al. 2004; Elliott et al. 2006).

To better understand the way in which oxygenation is monitored, the clinician must first understand the basic physiology of oxygen transport in the blood. In healthy humans, every 100 mL of arterial blood carries about 20 mL of oxygen at sea level. At rest, the body extracts about 5 mL of oxygen per 100 mL of arterial blood. This reserve allows for adequate tissue oxygenation during periods of high oxygen demand (i.e., exercise) or periods of low oxygen delivery (i.e., pulmonary and/or cardiac disease, or high altitude).

Entering the arterial blood in gaseous form, oxygen diffuses across the alveolar capillary membrane and dissolves into the plasma. But the oxygen carrying capacity of plasma alone is insufficient to sustain life. In 100 mL of plasma (with no hemoglobin), at a partial pressure of oxygen of 100 mmHg, there is only 0.3 mL of dissolved oxygen. Once dissolved in the plasma, oxygen quickly binds with hemoglobin molecules on the erythrocytes. The remarkable stereochemical properties of the hemoglobin molecule render it capable of binding to, carrying, and offloading much more oxygen than can be dissolved in plasma alone. Once the erythrocytes have been transported through the arterial system to the capillary beds, the oxygen off-loads from the hemoglobin back into the plasma and thus diffuses across the capillary membranes into the adjacent tissues and finally through the cell membrane and into the mitochondria. Figure 12.1 visually describes some of the complex mechanisms involved in oxygen transport from the atmosphere to the tissues.

The movement of oxygen molecules through our biological systems is governed by pressure gradients. The atmosphere has a higher partial pressure of oxygen than the plasma, which is higher than the interstitial partial pressure and so on. This is illustrated in Fig. 12.2. Oxygen transport to the cells depends on the partial pressure of oxygen in the alveoli, the amount of hemoglobin in the blood, the degree to which the hemoglobin is saturated, and the cardiac output. There can also be regional variations in blood flow that can

[2] Not long ago, I stood at the doorway of a room in our cardiac intensive care unit watching the care of a post-op cardiac surgery patient who was on extracorporeal membrane oxygenation. I counted 21 different LCD displays in the immediate beside area. These included cardiorespiratory monitors, infusion pumps, oxygen monitors, ventilation monitors, and the ECMO system. And of course, each of these was connected to the tiny patient by tubing, cables, lines, and sensors. It is a tribute to the focus and dedication of the clinical staff that there are no more mishaps in this complex visual environment.

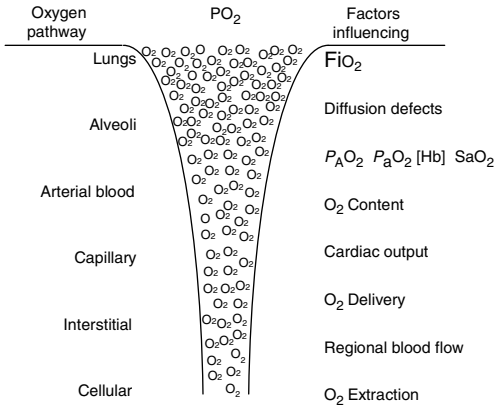

Fig. 12.1 Visual representation of the oxygen movement of oxygen from the atmosphere to the cellular level. *CO* cardiac output, *SVR* systemic vascular resistance (Used with permission from Sola et al. (2008))

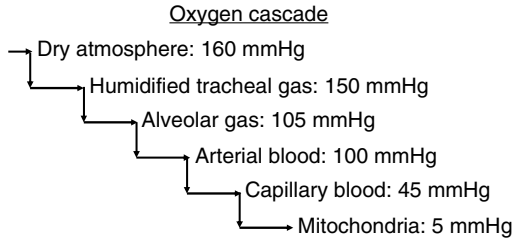

Fig. 12.2 The oxygen cascade is a conceptual rendering of the movement of oxygen from the atmosphere to the mitochondria down a descending pressure gradient. The partial pressure of oxygen in various parts of the oxygen transport chain is displayed. Various types of oxygenation monitoring systems monitor different parts of this cascade either directly or indirectly

affect oxygen transport. Finally, the diffusion of oxygen out of the plasma across the capillary membranes, into the interstitial space, into the cell, and finally into the mitochondria can be affected by interstitial fluid balances, capillary permeability, and anything else that increases the distance oxygen has to travel from the capillary wall to the adjacent cells.

Blood gas studies assess oxygenation by measuring the partial pressure of oxygen dissolved in the plasma alone (PO_2). But this is only a small part of the oxygen transport chain. The utility of blood gas measurements are based on assumptions about the relationship between the partial pressure of dissolved oxygen in plasma and the amount of oxygen bound to hemoglobin. This relationship is described by oxyhemoglobin dissociation curve (Fig. 12.3). The curve is sigmoid shaped to facilitate that loading of oxygen onto hemoglobin in the lungs and off-loading oxygen from the hemoglobin in the somatic capillaries. Many factors affect the shape and position of the dissociation curve. These include temperature, pH, chronic hypoxemia, dyshemoglobinemias, and the availability of 2,3 diphosphoglycerate (2,3-DPG), a compound that affects the affinity of oxygen for hemoglobin (Hsia 1998). Decreased levels of 2,3-DPG are found in cases of erythrocytosis and nonspherocytic hemolytic anemia and 2,3-DPG phosphatase deficiencies. The effect of transfusion of stored RBCs on oxygen delivery is complex, and views about its effect are divergent. Historically, it was reported that 2,3-DPG levels were depleted in stored RBCs, but others have found no relationship between the length of time of storage of RBCs and biochemical markers of oxygenation in the critically ill (Tinmouth et al. 2006; Ibrahim et al. 2005a; Walsh et al. 2004). Increased levels of 2,3-DPG are found in conditions in which the body needs more oxygen, such as obstructive lung disease, cystic fibrosis, congenital heart disease, and hyperthyroidism. High altitudes and participating in exercise sessions can also elevate 2,3-DPG levels.

In general, those factors that shift the curve to the right are advantageous to the patient since this reflects a reduced affinity of oxygen for hemoglobin resulting in more oxygen released from hemoglobin to the tissues (Peter et al. 1991). The position of the curve is usually expressed by measurement of P50, which is defined as the PaO_2 at which the hemoglobin is 50 % saturated with oxygen at a pH of 7.40, $PaCO_2$ of 40 mmHg, and temperature of 37 °C.

It has been known for many years that there is large variation in affinity of oxygen for hemoglobin and thus the shape and position of the dissociation curve (Gøthgen et al. 1990; Wilkinson et al. 1980). No less than Ole Siggaard-Andersen, one of the principle developers of blood gas technology has said (Gøthgen et al. 1990), "…it is essential to know the actual position of the hemoglobin-oxygen dissociation curve, as well

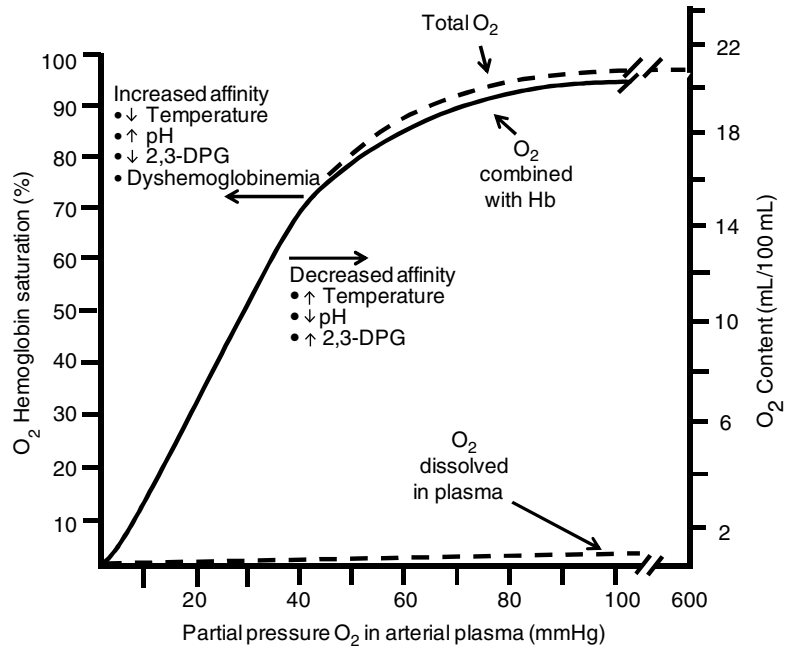

Fig. 12.3 Oxyhemoglobin dissociation curve. Note that the overwhelming majority of the total oxygen content is carried as oxygen bound to hemoglobin. The curve will shift left or right as affinity of oxygen for hemoglobin increases or decreases. Changes in temperature, pH, and levels of 2,3-diphosphoglycerate cause the affinity of oxygen for hemoglobin to change. Increased affinity is associated with decreased availability of oxygen to tissues (Brashers 2002). Recent work has called into question some of the assumptions about the relationship between pH and 2,3-DPG (Ibrahim et al. 2005b)

as the hemoglobin concentration in the individual patient, for correct interpretation of PO_2..... in arterial blood." Yet, historically, we have relied heavily on P_aO_2 alone for assessing oxygenation. Unfortunately, the actual measurement of p50 is not widely available and requires the tonometry of blood. There are calculators for P50, but these are based on assumptions about oxygen hemoglobin affinity which can vary widely (Gøthgen et al. 1990).

As clinical practice has evolved, the focus on P_aO_2 as the most widely used measure of oxygenation has been enhanced by the appreciation that SaO_2 is a broader assessment of the oxygen transport chain. This value assesses a much larger portion of the mechanism of oxygen transport. It is also clear that a thorough assessment of oxygenation cannot be made without knowing the total serum hemoglobin. This can be seen when one considers the equations for oxygen content and oxygen delivery. These equations describe the volume of oxygen in a given amount of whole and the volume delivered (or available) to the tissues by the cardiovascular system:

Oxygen content (*the volume of oxygen* (*in mL*) *carried in 100 mL of whole blood*):

$$CaO_2 = \left(Hb \times 1.34 \times SaO_2\right) + \left(P_aO_2 \times 0.0031\right)$$

where

CaO_2	oxygen content of arterial blood, expressed as mL/dL (normal values are 16–22 mL/dL)
Hb	total serum hemoglobin in g/dL
1.34	the volume of oxygen (in mL) that can be carried by a gram of hemoglobin that is fully saturated with oxygen
SaO_2	the degree to which the hemoglobin is saturated in percent which should be expressed as a decimal for the mathematics of the formula
P_aO_2	partial pressure of oxygen in arterial blood in mmHg
0.0031	the oxygen solubility coefficient in plasma (the number represents the mL of oxygen that will be dissolved in plasma for each mmHg of partial pressure of oxygen dissolved in plasma)

Table 12.1 Measures and derivatives of oxygenation

Measures		Normal range
Partial pressure of arterial oxygen (P_aO_2)		80–100 mmHg
Partial pressure of arterial CO_2 (P_aCO_2)		35–45 mmHg
Arterial oxygen saturation (SaO_2)		95–100 %
Mixed venous saturation (SvO_2)		60–80 %
Arterial oxygen content (CaO_2)	$(Hb \times 1.34 \times SaO_2) + (0.0031 \times P_aO_2)$	17–20 mL/dL
Venous oxygen content (CvO_2)	$(Hb \times 1.34 \times SvO_2) + (0.0031 \times PvO_2)$	12–15 mL/dL
A–V oxygen content difference ($C[a-v]O_2$)	$CaO - CvO_2$	4–6 mL/dL
Oxygen delivery (DO_2)	$CaO_2 \times CO \times 10$	950–1,150 mL/min
Oxygen delivery index (DO_2I)	$CaO_2 \times CI \times 10$	500–600 mL/min/m^2
Oxygen consumption (VO_2)	$(C(a-v)O_2) \times CO \times 10$	200–250 mL/min
Oxygen consumption index (VO_2I)	$(C(a-v)O_2) \times CI \times 10$	120–160 mL/min/m^2
Oxygen extraction ration (O_2ER)	$[(CaO_2 - CvO_2)/CaO_2] \times 100$	22–30 %
Oxygen extraction index (O_2EI)	$[SaO_2 - SvO_2]/SaO_2 \times 100$	20–25 %

Oxygen delivery:

$$DO_2 = CaO_2 \times CO \times 10$$

where

DO_2 oxygen delivery expressed as mL/min

CaO_2 oxygen content of arterial blood expressed as mL/dL

CO cardiac output expressed in mL/min

These formulae and other measures and derivatives of oxygenation, and their normal values are listed in Table 12.1. Careful review of these formulae reminds us that oxygen delivery is dependent on many factors including serum hemoglobin levels, cardiac output, oxygen saturation, and P_aO_2.

12.1.1 Effects of Altitude

As altitude increases, barometric pressure decreases. Thus, even though the concentration of oxygen in the atmosphere is the same regardless of altitude, the partial pressure of oxygen decreases at increasing heights above sea level (Gallagher and Hackett 2004). As the P_aO_2 decreases, so does the SaO_2. Figure 12.4 demonstrates the effect of altitude on the pressure of inspired oxygen (P_IO_2), P_aO_2, and SaO_2 (Hackett et al. 2001).

The effect of altitude on "normal" pulse oximetry readings in infants and children has been studied (Beebe et al. 1994; Niermeyer et al. 1993, 1995; Thilo et al. 1991; Gamponia et al. 1998). Thilo reported that at an altitude of 1,610 m, healthy newborns had a mean SpO_2 of 92–93 % and that the lower end of the reference range was as low as 86 % during quiet sleep at 1–3 months of age (Thilo et al. 1991). Niermeyer et al. studied serial SpO_2 at an altitude of 3,100 m, measured from birth to 4 months in healthy infants. SpO_2 ranged from 80.6 ± 5.3 to 91.1 ± 1.7 % during the 4 months period (Niermeyer et al. 1993).

The clinician is challenged with knowing how low SpO_2 must go before supplemental oxygen is indicated at various altitudes. Subhi and colleagues did a systematic review of published normal SpO_2 for children at various altitudes above sea level (Subhi et al. 2009). Tables 12.2 and 12.3 and Fig. 12.4 are adapted from their work. Figures 12.4 and 12.5 offers threshold values below which a child may be considered hypoxemic adjusted for altitude and thus requiring supplemental oxygen. The risk of the development of retinopathy of prematurity in low-birth-weight infants requires that different target values for SpO_2 be used. See the section below on pulse oximetry.

Table 12.2 Normal (reference) ranges for blood gases in neonatal and pediatric populations

Age range	Neonatal			Pediatric	
Source	Arterial	Venous	Capillary (Cousineaua et al. 2005)	Arterial	Venous
pH	7.35–7.45	7.31–7.41	7.31–7.47	7.35–7.45	7.31–7.41
PCO_2	35–45 mmHg	41–51 mmHg	29–49 mmHg	35–45 mmHg	41–51 mmHg
PO_2	50–90 mmHg	30–40 mmHg	33–61 mmHg	80–100 mmHg	30–40 mmHg

Table 12.3 Normal pulse oximetry values for children 1–5 years of age at various altitudes

Age of study group	Number of children studied	Altitude above sea level (m)	Reported SpO_2 mean (SD)
2–60 months	153	3,750	88.9 (2.9)
2–23 months	80	1,500	98.9 (1.0)
0–2 months	302	1,584	97.1 (2.7)
1–60 months	151	1,600	95.7 (2.7)
1 month	100	1,610	93.4 (2.0)
7 days–36 months	87	1,670	95.7 (1.6)
0–24 months	189	2,640	93.3 (2.1)
0–18 months	55	2,600	93.2 (3.0)
0–60 months	150	2,800	92.0 (2.0)
2 days–22 months	72	2,800	91.7 (2.1)
0–60 months	152	4,018	87.8 (3.8)

Adapted with permission from Subhi et al. (2009)

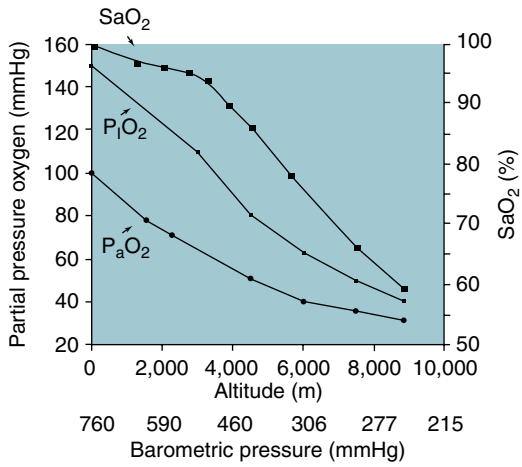

Fig. 12.4 Relationship between altitude, barometric pressure, pressure of inspired oxygen (P_IO_2), P_aO_2, and SaO_2 (Adapted with permission from Hackett et al. (2001))

12.1.2 Blood Gas Measurements

12.1.2.1 Intermittent

Intermittent sampling and analyses of the pH, PCO_2, and PO_2 of arterial, venous, or capillary blood are some of the most frequently ordered laboratory tests. There have been tremendous advances in blood gas technology including miniaturization of components, improved quality control, simplified maintenance techniques, reduced sample size, decreased throughput time, and portability. But the measurement principles for blood gases remain the same. Blood gas machines actually measure only three variables, pH, PCO_2, and PO_2. All other variables reported on a blood gas, i.e., base excess, bicarbonate, and oxygen saturation,[3] are calculated.

Blood gas machines use electrochemical sensors which are covered with selectively permeable membranes that allow the passage of either O_2 or CO_2. These gases then chemically react with reagents in their respective sensors to create voltages that are proportional to the amount of the respective gas that has entered the electrode, which correlates with the partial pressure of gas in the blood that has come in contact with the semipermeable membranes.

Advantages of intermittent blood gas sampling include well-known accuracy and precision, simplicity, convenience, relatively low cost, and a generally good understanding of the basics of blood gas measurement. Typically, PO_2 electrodes are less accurate and precise than PCO_2 electrodes. Intra-instrument imprecision[4] is much improved in newer models of blood gas analyzers. For PO_2 samples <150 mmHg, most instruments can produce measurements within ±2 % (Hansen et al. 1989; Scuderi et al. 1993). This imprecision worsens in $PO_2 > 150$ mmHg.

Disadvantages include the need for an invasive blood sample, either through repeated

[3] Later in this chapter, the limitations of the calculation of oxygen saturation are discussed in detail.

[4] Intra-instrument imprecision can be thought of as the variability of repeated samples of the same blood run consecutively in the same instrument.

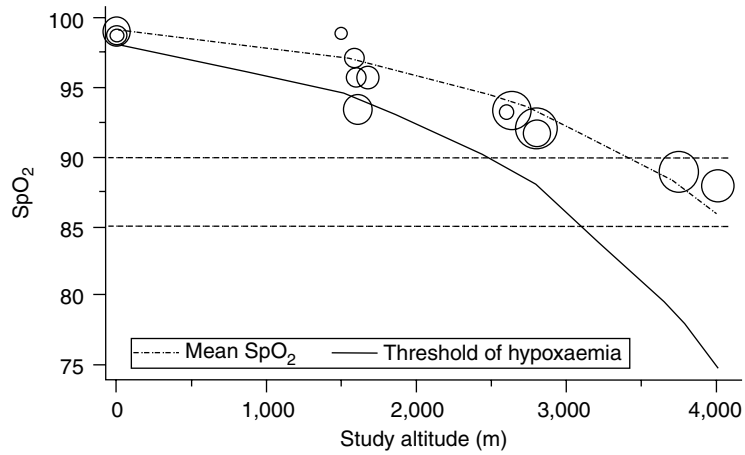

Fig. 12.5 Estimated threshold of hypoxemia at different altitudes. Study estimates are plotted as *circles*, with size proportional to the precision of the transformed study estimate (Used with permission from Subhi et al. (2009))

percutaneous arterial or capillary sticks. Patients on ventilators for many days, can have much bruising and skin injury from repeated sticks, which can be very disturbing to parents, even though they typically heal without difficulty. Arterial lines obviate the need for repeated sticks, but in infants and children, utilization of arterial lines is not as prevalent as in adults. This is probably related to many factors including the pain of insertion, the limitations of the size of the patients, the risk of infection and mishap, and the known sequela of arterial lines.

From the early days when 10 mL of blood and 45 min was required to obtain and analyze a sample, we now have instrumentation that allows for blood gas measurements on far less than 1 mL of blood with results available within 90 s using handheld point of care analyzers. Whether or not having all blood gas results this rapidly ultimately affects patient outcomes remains largely unproven (Giuliano and Grant 2002).

Kendall and colleagues (1998) randomized 1,728 patients to be managed in the emergency room using either point of care or central laboratory testing. They found that point of care testing (which included blood gas, hematological, and chemical studies) reduced the time until lab results were available (for blood gases, a 20 min reduction). But they deemed that change in management in which timing was critical involved only 7 % of all samples. Moreover, there was no difference between groups in hospital admission rate, length of stay in the emergency department, hospital length of stay, and mortality.

In a very interesting study, Thomas and colleagues (2009) compared P_aO_2 and P_aCO_2 values from a point of care testing system to values obtained from a central laboratory with regard to running a ventilator management algorithm in 446 ventilated adult intensive care patients. In other words, would the recommendations of the ventilator management algorithm be different when using point of care values or central laboratory-derived blood gases? They concluded that the use of point of care blood gases versus central blood gas laboratory values produced equivalent ventilator management algorithm recommendations. Their study included no cost analyses.

Despite increased proliferation of handheld, point of care blood gas analyzers, there remains tremendous variation in the use of these devices. Some intensive care units rely exclusively on point of care testing for blood gas analysis. Others use little or no point of care testing, relying instead on near patient, bench blood gas analyzers, or analyses done in a central laboratory.

A search has been underway for more than 10 years to prove that point of care testing is cost effective. Results have been divergent depending on what type of point of care testing is being studied (O'Connell et al. 2008; Macnab et al. 2003; Englander et al. 2006). Clearly, there are some cases where immediate testing results at the bedside seem likely to make a meaningful difference in outcomes, such as in surgery, during ECMO, or during transport. But my observations have led me to conclude that in a typical intensive

care setting, the vast majority of point of care blood gas testing is not emergent and that results within 15–30 min would be completely acceptable. Additionally, any potential savings of implementing point of care blood gases systems would be dependent on elimination of the instrumentation and labor costs of other blood gas analysis systems. Most applications of point of care blood gas testing I have seen simply layered the point of care capabilities on top of existing laboratory blood gas systems, resulting in cost increases with no proven effect on patient outcomes. Most of the published financial analyses of the impact of point of care testing are not sophisticated and often confuse the cost of the blood gases with the charges for blood gases. The interested learner is directed to a thorough review of the general topic of point of care testing by Kost (1998).

Many blood gas instruments do not actually measure SaO_2, but instead calculate (or estimate) the SaO_2 based on assumptions about the shape of the oxygen dissociation curve. Wilkinson et al. showed that in some newborns, when P_aO_2 was less than 50 mmHg, calculated SaO_2 could be >90 %, whereas in others <75 % (Wilkinson et al. 1980). My colleagues and I showed that in pediatric ICU patients, calculated oxygen saturation levels were unreliable, particularly when true saturation levels were <90 % (Salyer et al. 1989). Clinicians are advised not to rely on *calculated* oxygen saturation values derived from blood gas measurements.

The most common method of direct laboratory measurement of SaO_2 requires the use of a CO-oximeter. This name can be a little misleading since it was derived from early instruments designed to measure carboxyhemoglobin (HbCO). Laboratory CO-oximeters use multiple wavelength spectrophotometry of hemolyzed blood samples to measure SaO_2. This measurement principle is basically the same as is used in pulse oximetry, which we will discuss in detail later. Typically, point of care blood gas tests do not actually measure SaO_2 so care must be taken in interpreting low saturation values from point of care devices. Some of the latest bench blood gas analyzers incorporate spectrophotometry into their measurement capabilities and thus can report actual measured SaO_2. The interested clinician should check and ensure that the SaO_2's reported with blood gas results are actually measured using CO-oximetry versus calculated.

12.1.2.2 Continuous Blood Gas Monitoring

Continuous intravascular monitoring of blood gases became widely available in the 1990s and has been steadily improving since then (Ganter and Zollinger 2003). This technology uses various techniques to miniaturize blood gas measurement sensors sufficiently to allow them to be imbedded in a catheter that can be placed in the radial, brachial, and femoral artery for continuous monitoring. Measurement principles may be electrochemical (as in bench blood gas analyzers) or photochemical/optical (also called optodes). Optodes use sample chambers that contain dyes which are illuminated with light of a certain wavelengths. The illuminating light will be transmitted, reflected, absorbed, and reemitted proportionally to the concentration of oxygen, carbon dioxide, and hydrogen ions in the sample.

The radial artery is the most common site for catheter insertion in adults and the femoral artery in children <5 years old. The disadvantages of the radial approach include increased susceptibility to motion artifact, vasospasm, and changes in peripheral blood flow. Nevertheless, this approach is chosen routinely in adults and older children, because of easy access, the double blood vessel supply of the hand, and low complication rates. For newborns, the umbilical artery is used.

Proponents of this technology argued that substantial changes in arterial blood gases can be missed by intermittent blood gas analyses (Zaugg et al. 1998). Moreover, it is suggested that continuous blood gas monitoring could (1) allow for more rapid identification of changing trends in blood gases, (2) decrease therapeutic decision time, (3) reduce blood loss from repeated sampling, and (4) make it possible to use the continuous blood gas results for closed loop control of ventilator settings using feedback-control algorithms (Mahutte 1998). As is the case with so

much new technology, little systematic investigation has been done to validate these assumptions.

These systems are very costly. The instruments themselves cost as much as a bench blood gas analyzer and yet can only be used on one patient at a time. The catheters are also very costly, and some patients end up needing more than one because of catheter failure. They are also very invasive and prone to technical problems such as kinked or clotted catheters and problems with poor regional blood flow. In my experience in the USA visiting many pediatric intensive care units, I have seen very few in use.

12.1.3 Pulse Oximetry

One of the more remarkable advances in oxygenation monitoring technology is the development of the pulse oximeter (Salyer 2003). Pulse oximeters use principles of spectrophotometry to estimate arterial oxygen saturation noninvasively using sensors that can be clipped to an ear or finger or, for smaller patients, can be wrapped around digits, palms, and feet. Pulse oximetry *estimates* arterial oxygen saturation by measuring the absorption of light of two wavelengths, approximately 660 nm (red) and 940 nm (infrared), in human tissue beds. As light passes through human tissue, it is absorbed in various degrees by the skin, tissues, bone, fluids, and blood. The amount of blood in the tissue beds changes with each beat of the heart. This change in volume causes a change in spectral absorption, which the oximeter can detect and thus estimate heart rate. As the relative amounts of oxygenated and deoxygenated hemoglobin changes in the tissue bed, the spectral absorption also changes, and thus the oximeter can estimate SaO_2.

The accuracy of pulse oximetry has been studied extensively in various populations (Choe et al. 1989; Morris et al. 1989; Faconi 1988; Hay et al. 1989; Nickerson et al. 1988; Severinghaus et al. 1989; Hannhart et al. 1991; Taylor and Whitman 1988; Wouters et al. 2002a, b; Deckardt and Steward 1984; Jennis and Peabody 1987; Walsh et al. 1987; Southall et al. 1987; Solimano et al. 1986; Ramanathan et al. 1987; Praud et al. 1989; Boxer et al. 1987; Carter et al. 2001) and is generally about ±1–2 % of readings >85 % (Severinghaus 1993; Emergency Care Research Institute 2003; Van de Louw et al. 2001). During periods of profound desaturation (typically below 70–80 %), bias and precision of oximeters deteriorates significantly, being highly variable depending on brand (Faconi 1988; Severinghaus et al. 1989). This limitation has never been particularly problematic for most clinicians since an SpO_2 of 40 % versus 60 % will illicit the same aggressive interventions to improve oxygenation.

As we have learned more and more about the behavior of oximeters during continuous monitoring, it has become apparent that there are serious performance problems with some types of pulse oximeters that are not related to accuracy, but instead to precision and reliability, e.g., the ability of the devices to produce credible readings over time. More about this are discussed below.

Continuous monitoring with a pulse oximeter was originally mostly confined to the perioperative period. But it has now grown in many places to include all intensive care patients, any child on oxygen, anyone undergoing procedural sedation, anyone presenting with respiratory symptoms in the emergency department, or anyone on patient-controlled anesthesia, to name a few. Indeed, SpO_2 readings have become a de facto fifth vital sign. In terms of processes, pulse oximetry has been shown to sometimes reduce the number of arterial blood gas samples obtained in various populations (King and Simon 1987; Kellerman et al. 1991; Inman et al. 1993; Bourdelles et al. 1998; Roizen et al. 1993; Niehoff et al. 1988).

But as the use of pulse oximetry spread, little evidence was developed demonstrating the effect of continuous monitoring with a pulse oximeter on outcomes of care. It has been said that "absence of evidence is not evidence of absence."[5] Many technologies have not been thoroughly tested, and thus their effect on outcomes has been suspect. But it is risky to then build arguments

[5] This quote should be interpreted to mean that having not looked for something, and thus not found it, does not necessarily mean that it is not there.

based on the assumption that this absence of evidence is a result of having looked for it and not found it. But in the case of oximetry, there has been a decade long search for proof that continuous monitoring changes the outcomes of care. For most of this time, no such effect has been found (Ochroch et al. 2006; Pedersen et al. 2009).

Moeller et al. enrolled more than 20,800 surgical patients and randomized them to receive continuous pulse oximetry during the perioperative period. The two groups did not differ significantly in cardiovascular, respiratory, or neurologic complications; length of hospital stay; or in-hospital deaths (Moller et al. 1993a).

It is possible that not using the pulse oximeter and, thereby, not identifying and treating episodic hypoxemia might have more subtle effects on the higher brain functions of memory and cognition. In a follow-up study, Moeller and colleagues studied this question by randomizing 736 surgical patients to continuous pulse oximetry during the perioperative period (Moller et al. 1993b). Cognitive function was evaluated before surgery, at 7 days and 6 weeks following surgery. The authors concluded that ". . . subjective and objective measures did not indicate less postoperative cognitive impairment after perioperative monitoring with pulse oximetry."

Bowton et al. studied (1991) the effect of continuous pulse oximetry on a population of general medical–surgical patients. Reviews of the oximeter records were compared with the nurses' charting, doctors' progress notes, and doctors' orders. Desaturations that were identified by the pulse oximeter were noted in the nursing notes only 33 % of the time and in the doctors' progress notes 7 % of the time. Changes in the orders for respiratory therapy were noted in only 20 % of patients who desaturated to <85 %.

A Cochrane systematic review of the effect of pulse oximetry in the perioperative period by Pedersen et al. (2009) concluded, "…studies confirmed that pulse oximetry can detect hypoxaemia and related events. However, we have found no evidence that pulse oximetry affects the outcome of anaesthesia for patients. The conflicting subjective and objective results of the studies, despite an intense methodical collection of data from a relatively large general surgery population, indicate that the value of perioperative monitoring with pulse oximetry is questionable in relation to improved reliable outcomes, effectiveness, and efficiency. Routine continuous pulse oximetry monitoring did not reduce either transfer to ICU or mortality, and it is unclear if there is any real benefit from the application of this technology in patients who are recovering from cardiothoracic surgery in a general care area."

However, both my observations of how oximeters are actually used and a careful reading of the literature lead me to conclude two important things about the impact of continuous pulse oximetry on patient outcomes. First, not all oximeters perform the same, and second, an oximeter will not substantially alter patient care unless it is used by people who are thoroughly trained and in conjunction with a systematic methodology for how to set oximeter alarms and how to react to oximeter alarms. We know that clinicians are generally not very well trained in exactly what a pulse oximeter measures, and they know very little about performance differences between brands (Sola et al. 2008; Teoh et al. 2003; Popovich et al. 2004). And collectively, we are beginning to understand that superimposing additional technology on top of unreliable clinical processes will not necessarily improve the process at all, but may instead simply create a more technologically advanced unreliable process (Stapleton et al. 2009; Thompson et al. 2003).

Anyone who has long worked in the quality assurance field of health care will appreciate that policy and practice may often not be well acquainted. In the case of pulse oximeter alarm limits, this is particularly true. It has been shown that compliance with pulse oximetry alarm limit policies is as low as 9 % of patients (Clucas et al. 2007). This has certainly been my clinical experience. This is probably largely due to the propensity of some brands of pulse oximeters to generate lots of false desaturations. The clinicians are simply setting the alarm limits at levels that will keep the oximeters from driving them to distraction. Even so, there is still a great deal of alarm desensitization because of the poor performance of some brands of pulse oximeters. This noncompli-

ance is also probably a contributing factor in why it was originally difficult to show an influence of pulse oximetry on patient outcomes. But as technology and clinical processes have improved and standardized, the impact of pulse oximetry has become more detectable.

As an example, Durbin and Rostow demonstrated that using motion-resistant[6] pulse oximetry technology in conjunction with a standardized process of postoperative weaning resulted in a reduction in oximeter failure rates, arterial blood gas utilization, and oxygen weaning time in adult cardiovascular surgery patients when compared to a conventional pulse oximeter (Durbin and Rostow 2002).

Chow et al. also demonstrated improved outcomes associated with the implementation of an oxygen management protocol while switching to motion-resistant pulse oximetry (Chow et al. 2003). In this study of low-birth-weight infants, retinopathy of prematurity rates went from 12.5 to 2.5 % after introduction of new pulse oximeter technology and a rigorous oxygen management protocol.

Taenzer et al. reported that unplanned transfers to the intensive care unit decreased by 48 % after introduction of motion-resistant pulse oximetry *and* a centralized monitoring system[7] to an orthopedic unit (Taenzer et al. 2010). This system sends all pulse oximetry data via wireless technology to a central computer server that notifies nurses by pager when their patients desaturated.

12.1.3.1 Limitations of Pulse Oximetry

Not all pulse oximeters are created equal. Although the accuracy of pulse oximeters has been demonstrated repeatedly, there are serious issues with the ongoing precision and reliability of the readings produced. Most studies of oximetry performance have focused on comparing single SpO_2 readings to the SaO_2 of simultaneously drawn arterial blood samples that are measured in a CO-oximeter. When this is done, accuracy is typically ±2 % (actual reading). The more important issue for monitoring critically ill patients is the reliability of continuous readings over time. False alarms can be a major problem in critical care units (Lawless 1994; Bohnhorst and Poets 1998). It turns out that in neonatal, pediatric, and adult populations, some pulse oximetry technology is prone to increased false desaturation readings and data dropout, which is defined as the amount of time the pulse oximeters display no reading at all.

In infants and children, the most common limitation is the effect of motion and low perfusion (Petterson et al. 2007). As children move the extremity being monitored, wiggling their fingers and toes, or experience periods of low perfusion, the absorption being measured by the oximeter is constantly changing in an environment where the signal-to-noise ratio of the changes in absorption is very low. These changes can be misinterpreted by oximeters as false desaturations or even cause some oximeters to display no readings at all (data dropout). Some pulse oximeters use sophisticated signal processing algorithms to filter and analyze these signals and determine through statistical modeling if the readings are reliable enough to be displayed. This is typically called motion resistance, and it is claimed by a number of manufacturers (Bohnhorst and Poets 1998). The computer in the oximeter must decide if the data at hand should be displayed, and the complex confidence arbitration algorithms for this are proprietary and thus the exact details of how this is done are often not available. How well these various algorithms work is a point of great debate among manufacturers.

The clinicians must also be aware that pulse oximetry software is frequently changing, and although your hospital may have only one brand of oximetry, you may have many different software versions that perform differently. Another confounder when thinking about pulse oximeter performance is the misleading use of one manufacturer's sensors by another manufacturer. As an example, if you buy Philips multiparameter monitoring systems, you can get many different software and hardware configurations. You can get their monitors equipped with Nellcor, Masimo, or Philips oximetry signal processing software.

[6] Motion-resistant pulse oximetry will be discussed in detail in a later section of this chapter.

[7] Both the oximetry and the monitoring system were manufactured by Masimo Inc, Irvine CA, USA.

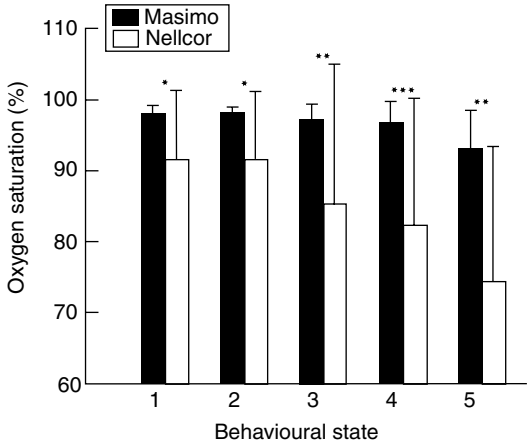

Fig. 12.6 Oxygen saturation measurements (means (SD)) with Masimo and Nellcor pulse oximeters in 15 healthy infants during different behavioral activity states: *1* quiet sleep, *2* indeterminate sleep, 3 active sleep, *4* awake, *5* crying. *p, 0.02; **p, 0.005; ***p, 0.0005 (Used with permission from Sahni et al. (2003))

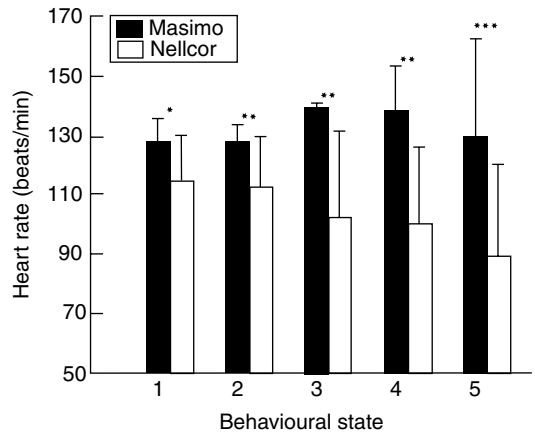

Fig. 12.7 Heart rate measurement (means (SD)) with Masimo and Nellcor pulse oximeters in 15 healthy infants during different behavioral activity states: *1* quiet sleep, *2* indeterminate sleep, *3* active sleep, *4* awake, *5* crying.*p, 0.005; **p, 0.0005; ***p, 0.00005 (Used with permission from Sahni et al. (2003))

You can also use Nellcor probes with Philips signal processing. Thus, clinicians may look at the Nellcor sensor and assume they have Nellcor signal processing in their multiparameter, which they may not. Sometimes, the front-line manufacturer representatives are not forthcoming with this information.

Ahlborn et al. (2000) showed that the use of the motion-resistant pulse oximetry of Masimo Signal Extraction Technology (SET)[8] in a population of low-birth-weight infants resulted in a 75 and 47 % reduction in false alarm rates compared to two other brands of oximeters.

Sahni and colleagues (2003) studied a population of 15 healthy infants during various activity states. They showed that the use of Masimo SET resulted significantly less artifact. Figures 12.6 and 12.7 show SpO_2 and heart rate readings from the two brands of oximeters in these healthy infants during various activity states.

In another study which compared neonatal transcutaneous PO_2 (T_CPO_2) measurements to SpO_2, Bohnhorst and colleagues showed that episodes of hyperoxia detected by T_CPO_2 were missed by the Masimo SET technology in only 0.5 % of episodes compared to 5.4 % by another brand (Bohnhorst et al. 2000).

[8] Masimo Inc. Irvine California, USA.

Table 12.4 Incidence of performance problems of four new-generation pulse oximeters in a neonatal population

	Masimo SET	Nellcor N-395	Novametrix MARS	Philips Viridia
False hypoxemia	1	42	35	10
Data drop outs	1	10	95	21

Used with permission from Hay et al. (2002)

In another study of the utility of various brands of pulse oximeters in neonates, Hay and colleagues (2002) showed that there were 86 % fewer false hypoxemias with the Masimo SET than other brands. Table 12.4 shows the results of this study for four different brands of oximeters. Data dropouts have also been shown to be much lower with the Masimo SET technology compared to some brands of oximeters (Workie et al. 2005).

Torres et al. compared Masimo SET technology to another brand in postoperative pediatric cardiopulmonary bypass patients and reported that the SpO_2 failure rates were 10 % in the Masimo and 41 % in the other brand (Torres et al. 2004).

Another important limitation of pulse oximeters is presence of elevated levels of dyshemoglobins such as carboxyhemoglobin, methemoglobin, and sulfhemoglobin. These variants of hemoglobin arise out of various clinical conditions such

Table 12.5 Pulse oximetry readings, P_aO_2, actual arterial saturation, and methemoglobin (MetHb) levels in a 12-month-old infant suffering from phenazopyridine hydrochloride ingestion

Time	P_aO_2 (mmHg)	SpO_2 (%)	SaO_2 (%)	MetHb (g/dL)
Admission	155	63	44	55
4 h	102	81	66	30
16 h	110	89	82	15
24 h	100	95	93	6

Used with permission from Watcha et al. (1989)

as carbon monoxide inhalation, nitric oxide therapy, and the ingestion of certain poisons. These dyshemoglobins cannot bind adequately with oxygen and when elevated can cause a patient to have a very low true oxyhemoglobin desaturation in the presence of very high P_aO_2's. Thus, relying on P_aO_2 alone, the clinician may have a false sense of security regarding the patient's level of saturation. Table 12.5 demonstrates this phenomenon in a 12-month-old child. Nearly all currently available pulse oximeters cannot distinguish oxyhemoglobin from these dyshemoglobins and thus will read falsely high in the presence of elevated levels. To measure these, an oximeter would have used more than two wavelengths of light (as does a CO-oximeter). Masimo has marketed a pulse oximeter that purports to measure total serum hemoglobin, carboxyhemoglobin, and methemoglobin noninvasively. Little controlled scientific data has yet been subjected to peer review on this product. Early reports are promising (Annabi and Barker 2009; Barker et al. 2006; Rabe et al. 2010) but the technology needs to subjected to more testing under more challenging conditions in various populations.

12.1.4 Summary

The movement of oxygen through the human body is a complex phenomenon. It is important for the clinicians to understand which part of the oxygen transport chain is being measured by various oxygenation monitoring technologies. Heavy reliance on P_aO_2 measurements alone may give a limited view of oxygenation monitoring. Other factors to consider are cardiac output, serum hemoglobin levels, and the oxygen saturation of hemoglobin. Normal oxygen saturation diminishes with increasing altitude.

Point of care blood gas testing has gained widespread acceptance without any compelling evidence that it has substantially altered patient outcomes.

Pulse oximetry has greatly simplified oxygenation monitoring and can be a powerful and convenient tool for oxygenation monitoring. However, there continue to be knowledge deficits of the clinicians regarding what oximeters actually measure and how the performance of oximeters vary between and within brands. While pulse oximetry accuracy has been well established, there are significant problems with the reliability of readings over time with some brands. Motion-resistant pulse oximetry (Masimo SET) has been shown to significantly reduce false desaturations and data dropout when compared to other pulse oximeters.

Essentials to Remember

- The movement of oxygen through the human body is complex.
- The most common measures of oxygenation, P_aO_2, and SaO_2 only measure certain aspects of the oxygen transport system. A more thorough understanding of the oxygen transport system and oxygenation monitoring technology will help clinicians make decisions based on the data from continuous or intermittent oxygenation monitoring.
- Point of care invasive oxygenation studies like blood gases have not been shown to substantially alter the outcomes of care when compared with centralized laboratory testing.
- The most widely used measure of oxygenation is pulse oximetry.
- There are important performance differences between brands of oximeters.
- Motion-resistant oximeters are superior and reduce false desaturations, false alarms, and data dropout. When used with carefully controlled clinical protocols, they can also alter care processes and improve patient outcomes.

12.2 Ventilation: Adequacy of Breathing Assessment

Gerd Schmalisch, Ira M. Cheifetz

Educational Aims

- Understand the differences between time-based and volume-based (volumetric) capnography.
- Review technologic considerations of capnography.
- Understand the interpretation of the various phases of the time-based capnogram.
- Discuss the unique aspects of carbon dioxide monitoring in the premature infant population.
- Understand the interpretation of the phases of the single-breath carbon dioxide waveform associated with volumetric capnography.
- Review the effects of both ventilation and perfusion on carbon dioxide elimination.
- Discuss the various clinical applications of time-based and volume-based capnography.
- Review the prognostic value of the dead space to tidal volume ratio (V_d/V_t).

12.2.1 Capnography

Noninvasive carbon dioxide monitoring provides valuable clinical information for the neonatal, pediatric, and adult patient populations. Capnography is an essential monitoring system for critically ill patients and is increasingly being described as the fifth vital sign.

Capnometry is the digital display of data, while capnography is the graphical display of data which can be presented time based or volume based (i.e., volumetric; see Sect. 12.2.3). Capnography refers to the visual depiction via waveforms of exhaled CO_2 during the entire respiratory cycle and is a better indicator for dynamic changes in a patient's gas exchange than capnometry. When capnography is used, proper clinical interpretation of the data and waveforms is essential to provide optimal management of the ventilator as well as safe patient care.

Time-based capnography is commonly known as end-tidal carbon dioxide ($etCO_2$) monitoring. A time-based capnogram provides qualitative information on the waveform patterns associated with invasive ventilation and a quantitative estimation of the partial pressure of expired CO_2. Volumetric capnography utilizes a CO_2 sensor and a pneumotachometer in combination. This approach permits the calculation of the net volume of CO_2 expired and is expressed as a volume exhaled per unit time (most commonly mL/min) rather than a partial pressure or gas fraction. Additionally, volumetric capnography allows for the calculation of the airway dead spaces, including the dead space to tidal volume ratio (V_d/V_t).

12.2.2 Time-Based Capnography/ End-Tidal Carbon Dioxide Measurements

12.2.2.1 Methods, Waveforms, and Nomenclature

End-tidal carbon dioxide measurement is one of the primary variables obtained from time-based capnography. For these measurements, the required interface with the ventilator circuit is called a capnograph. Carbon dioxide elimination can be measured by either mainstream or sidestream technology.

Several studies, in particular in infants, have demonstrated that mainstream measurements are superior to sidestream measurements from the technical perspective (Pascucci et al. 1989). Mainstream sensors have a faster response time, such that reliable single-breath CO_2 measurements, even at high respiratory rates, are possible. However, the additional apparatus dead space (V_{Dapp}) of the CO_2 analyzer chamber leads to rebreathing of the exhaled CO_2, which should be considered; however, V_{Dapp} is generally only clinically significant in very small infants. Mainstream sensors have become the more typical approach for capnography in mechanically ventilated larger infants, children, and adults.

Sidestream measurements utilize a sample port at the endotracheal tube (ETT) and are void of dead space; however, the suction flow rate required to sample exhaled gas may adversely affect measurement accuracy and response time. In neonates with a minute ventilation of about 200 mL/min/kg body weight, the suction flow must be sufficiently low to prevent dilution by surrounding air that will occur when the expiratory gas flow rate falls below the suction flow rate. A microstream capnograph using a suction flow of 30 mL/min and a miniaturized sample chamber has been developed, thus, improving the measurement accuracy for intubated infants (Hagerty et al. 2002; Kugelman et al. 2008).

Several techniques to measure the CO_2 in expired air have been developed (Gravenstein et al. 2004). Currently, infrared (IR) spectrography and mass spectrometry (mainly for multiple gas analyses) are most frequently used. However, only IR spectrography utilizes miniaturized, low-cost main- and sidestream sensors optimized for measurements in the infant population. An alternative fast method could be the molar mass measurement of the breathing gas by ultrasound spirometry. Of note, ultrasonic flow meters have a very short response time without a time delay between the measured air flow and molar mass of the breathing gas. Theoretically, such devices are well suited for volumetric capnography in small lungs. However, molar mass techniques utilize a surrogate signal which is influenced by all components of the expired gas, and, thus, it is difficult to separate the CO_2 signal (Thamrin et al. 2007).

Capnographs measure either the partial pressure (PCO_2) (IR analyzer) or the CO_2 fraction (FCO_2) of the breathing gas (mass spectrometers). The relationship is given by Dalton's law:

$$PCO_2 = \left(P_B - 47\,\text{mmHg}\right) \cdot FCO_2 \quad (12.1)$$

where P_B is the barometric pressure and 47 mmHg is the water vapor pressure at 37 °C. However, with a dry gas (e.g., calibration gas from a gas cylinder), PCO_2 is calculated by:

$$PCO_2 = P_B \cdot FCO_2 \quad (12.2)$$

The time-based waveform of the measured PCO_2 (or FCO_2) is called a capnogram and can be divided into four phases as shown in Fig. 12.8. Phase I starts with inspiration and represents, after a short CO_2 rebreathing, mainly the CO_2-free inspired gas. Phase II starts with exhalation and consists of a rapid S-shaped upswing on the tracing due to mixing of dead space gas with alveolar gas. Phase III describes the so-called alveolar plateau representing CO_2-rich gas from the alveoli. In older infants and adults, phase III almost always has a slightly positive slope, indicating a rising PCO_2 due to the delayed emptying of alveoli with a low ventilation/perfusion ratio (high PCO_2). In ventilated newborns, this slope is rarely seen due to their typically fast exhalation times. An exaggerated positive slope is seen in patients with pulmonary inhomogeneity, high airway resistance, and/or mechanical obstruction of the airway as alveoli empty carbon dioxide at a variable rate in these conditions. This is discussed in more detail below. Phase IV is actually a component of phase I and describes the decrease of the exhaled CO_2 to zero at the beginning of inspiration.

12.2.2.2 $P_{et}CO_2$ Monitoring

Since capnography is noninvasive, its utilization to monitor gas exchange in ventilated infants, children, and adults is very attractive, and the most typical parameter monitored is end-tidal CO_2 ($P_{et}CO_2$). The various factors that increase or decrease $P_{et}CO_2$ are summarized in Table 12.6 (Shapiro and Kacmarek 1998).

Under ideal conditions, $P_{et}CO_2$ accurately represents alveolar PCO_2. However, this relationship is dependent on the delivery of carbon dioxide to the lung via the circulatory system (i.e., perfusion) and its removal from the lung (i.e., ventilation). Thus, the relationship between alveolar PCO_2 and $P_{et}CO_2$ is a reflection of the ventilation/perfusion ratio ($\dot{V}/\dot{Q}$) as assessed by the dead space to tidal volume ratio (V_D/V_T) (McSwain et al. 2010).

An important prerequisite for a $P_{et}CO_2$ measurement is the presence of a stable alveolar plateau at end expiration. Only if the capnogram shows such a plateau can we assume that the $P_{et}CO_2$ accurately reflects the alveolar PCO_2. However, in ventilated infants and some ventilated

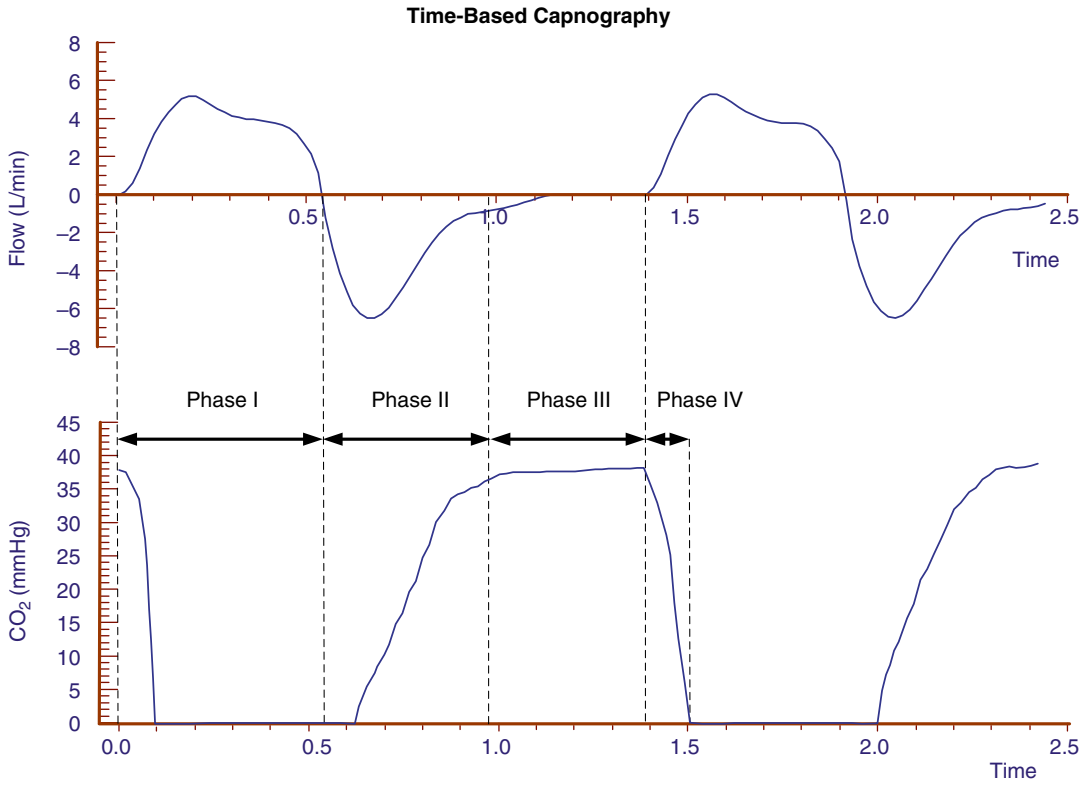

Fig. 12.8 A typical time-based capnogram of a ventilated neonate divided in 4 phases

Table 12.6 Clinical factors that affect $P_{et}CO_2$ (Shapiro and Kacmarek 1998)

	Increases $P_{et}CO_2$	Decreased $P_{et}CO_2$
CO_2-production and delivery to the lung	Increased by • fever • sepsis • bicarbonate administration • seizures	Decreased by • hypothermia • pulmonary hypoperfusion • cardiac arrest • pulmonary embolism • hemorrhage • hypotension
Alveolar ventilation	Decreased by • increased deadspace • hypoventilation • ventilatory inhomogeneity	Increased by • hyperventilation
Equipment malformations	• CO_2-rebreathing due to apparatus deadspace	• ventilator disconnection • esophageal intubation • complete airway/ endotracheal tube obstruction • poor gas sampling • too low response time • endotracheal tube leakage

children with increased airways resistance, this is not guaranteed as the adjusted expiratory time of the ventilator can be longer than the actual exhalation time of the patient (i.e., premature termination of exhalation). In such a situation, there is no patient flow at end expiration (Fig. 12.9), and, thus, $P_{et}CO_2$ cannot be determined (Proquitte et al. 2004). Confounding variables do exist in the

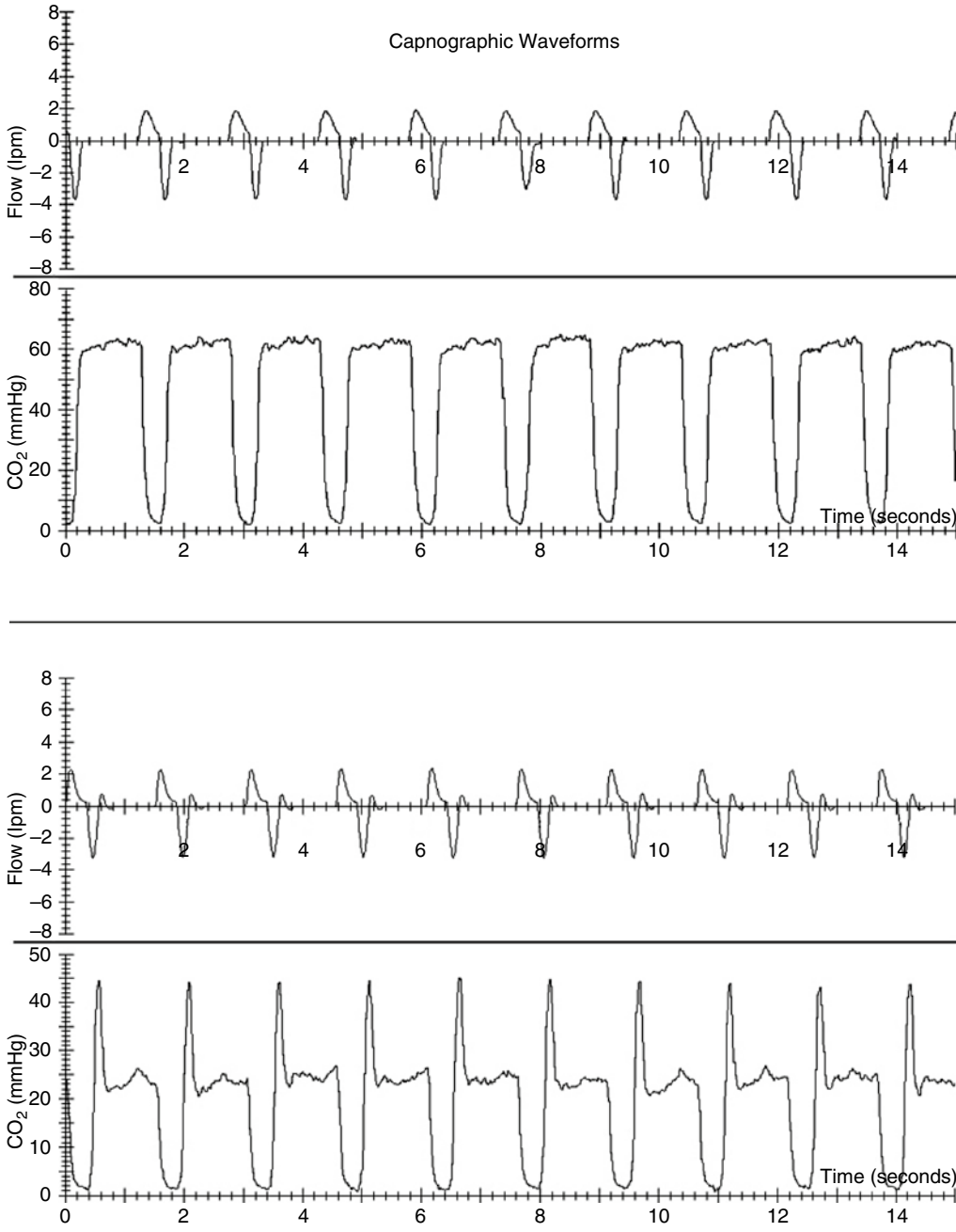

Fig. 12.9 Capnogram of a ventilated surfactant-depleted tracheotomized piglet with a stable alveolar plateau even during the expiratory pause (*top*) and a capnogram where $P_{et}CO_2$ was falsified by CO_2 washout of the sample cell during the expiratory pause (*bottom*). Data from Proquitté et al. (2004)

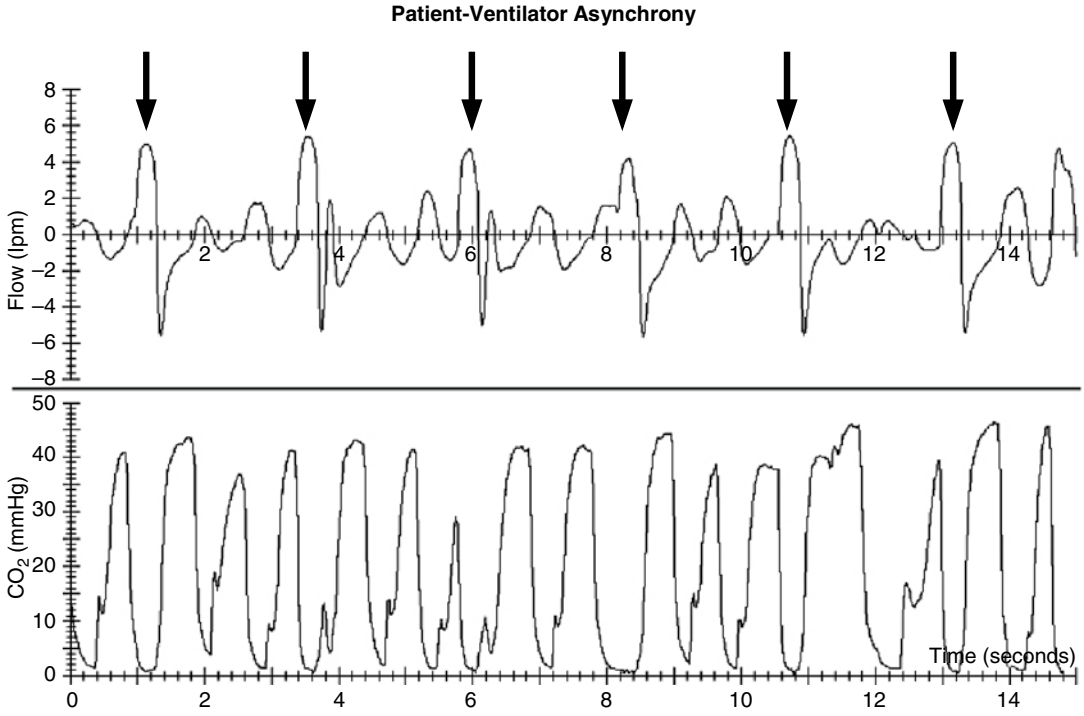

Fig. 12.10 Capnogram of a ventilated newborn with a mismatch of mechanical breath (*black arrows*) and spontaneous breathing

neonatal and pediatric populations. The presence of large endotracheal tube air leaks makes the measurement of "end-tidal" values less reliable (Schmalisch et al. 2012). Additionally, significant patient–ventilator dyssynchrony (Fig. 12.10) can make the accurate determination of $P_{et}CO_2$ difficult.

Therefore, $P_{et}CO_2$ measurements in ventilated patients are only useful if the shape of the capnogram is considered. Automated measurements of $P_{et}CO_2$ without monitoring the waveform should be used with caution as the resultant data can be misleading. Similarly, we should interpret $P_{et}CO_2$ values published in older literature with caution as the technical options for adequate monitoring of the capnogram were often very limited.

12.2.2.3 A Practical Approach to Interpreting Capnograms

What information can the capnogram offer the bedside clinician? At first, the presence of a physiologic meaningful $P_{et}CO_2$ should be assessed. If such a $P_{et}CO_2$ is not present, failure to ventilate the patient's lungs must be assumed. Table 12.7 summarizes typical causes of absent CO_2 elimination (Schmalisch 2004). Second, the shape of the capnogram must be compared with a typical pattern as shown in Fig. 12.8 by inspecting the inspiratory CO_2 baseline, steepness of phase II, alveolar plateau of phase III, and decline of the capnogram at the beginning of the next inspiration. Third, depending on the capnograph and the monitoring software utilized, the clinician should assess the characteristic parameters derived from the capnogram, for example, $P_{et}CO_2$, CO_2 elimination (VCO_2), $P_{a-et}CO_2$, and dead space (anatomic and alveolar).

12.2.2.3.1 The Inspiratory Baseline (Phase I)

Inspired gas should be void of carbon dioxide. Thus, the displayed CO_2 level should be zero; otherwise, there must be either rebreathing of CO_2 from the patient due to high apparatus dead space or the administration of exogenous carbon dioxide. Especially in very small infants, CO_2 rebreathing can occur if the tidal volume is

Table 12.7 Differential diagnostic causes of absent end-expiratory CO_2

	Patient	Capnograph
Immediately after intubation, CO_2 absent or very minimal	• Inadvertent esophageal intubation	• Calibration error • Disconnection of the CO_2 analyzer or the sample tube
Exhaled CO_2 present, then suddenly absent	• Accidental tracheal extubation • Disconnection of breathing circuit • Apneic spells • Cardiac arrest • Severe bronchospasm • Complete obstruction of ETT (e.g., mucous plugging or kinking)	• Disconnection of the CO_2 analyzer or the sample tube • Water condensation or secretions the CO_2 analyzer or in sampling tube • Failure of the capnograph

relatively low compared to the apparatus dead space. A leak around the endotracheal tube may reduce CO_2 rebreathing (Claure et al. 2003); however, it may dampen both tidal volume and $P_{et}CO_2$ measurements considerably (Schmalisch et al. 2012).

12.2.2.3.2 The Expiratory CO_2 Increase (Phase II)

During expiration, the first gas is eliminated from the CO_2-free anatomic dead space. Subsequently, in healthy lungs, the CO_2 curve rises with a steep upward slope. Phase II can be prolonged when the delivery of CO_2 from the lung is delayed, for example, due to pulmonary inhomogeneities, high resistances of the small airways, and mechanical obstructions, such as a blocked or kinked ETT. A prolonged phase II can also be caused by technical problems related to the capnograph. Technical limitations are most commonly seen in patients with stiff lungs and a low respiratory time constant when the response time of the capnograph is inadequate to follow the fast expiration.

12.2.2.3.3 The Alveolar Plateau (Phase III)

In adults and older infants, the shape of the alveolar plateau is one of the most interesting portions of the capnogram because the steepness of the slope is a function of morphometric structure and respiratory mechanics (Neufeld et al. 1992; Schwardt et al. 1991). Early phase III contains gas from the well-ventilated, low-resistance regions of the lung. Later in phase III, gas from poorly ventilated, high-resistance regions is exhaled which causes a slope of the alveolar plateau. Thus, the steepness of the alveolar plateau is commonly used as an indicator for inhomogeneities in the alveolar time constants and $\dot{V}/\dot{Q}$ ratio (Ream et al. 1995). A flat phase III indicates relatively homogeneous exhalation from airways throughout the lung. It should be noted in very small infants that phase III should be interpreted with caution as the plateau (if it exists at all) is often small, and steepness is also a function of lung growth (Ream et al. 1995). Therefore, the diagnostic value of a phase III analysis in the small neonatal population may be limited. Nevertheless, the appearance of phase III in the capnogram indicates that alveolar gas has been sampled.

12.2.2.3.4 The Decrease of Exhaled CO_2 at the Beginning of Inspiration (Phase IV)

After expiration, the fresh gas from the breathing circuit rinses out the carbon dioxide from the previous exhalation. Thus, there should be a quick decrease of the end-expiratory CO_2 at the initiation of inspiration. Several techniques (e.g., tracheal gas insufflation) (Davies and Woodgate 2002; Miller et al. 2004) have been developed to reduce rebreathing and dead space ventilation such that the tidal volume is more efficiently used for gas exchange. However, for various reasons, these techniques have seen limited application in the neonatal and pediatric populations. A delayed decrease of the expired CO_2 may be caused by a respiratory circuit with low flow, such that CO_2 may accumulate in the inspiratory limb of the circuit. Furthermore, a prolonged phase IV can also be associated with technical failures of the capnograph (e.g., a slow response time of the CO_2 analyzer).

12.2.2.4 Relationship Between $P_{et}CO_2$ and P_aCO_2

In infants with normal pulmonary function and well-matched $\dot{V}/\dot{Q}$, the $P_{et}CO_2$ can provide an accurate estimate of the PCO_2 in arterial blood (P_aCO_2) (Wu et al. 2003; McDonald et al. 2002; Bhat and Abhishek 2008), for all patient populations from the extremely low-birth-weight infant (Amuchou and Singhal 2006) through adults (McSwain et al. 2010; Wu et al. 2003; McDonald et al. 2002; Bhat and Abhishek 2008; Amuchou and Singhal 2006). Noninvasive measurement of $P_{et}CO_2$ clearly allows for an accurate estimation of P_aCO_2 in patients with minimal dead space ventilation without the inherent need for the time delay or the blood removal associated with performing an arterial blood gas analysis. The relationship between $P_{et}CO_2$ and P_aCO_2 in patients with elevated dead space is discussed in more detail below.

$P_{et}CO_2$ monitoring has several advantages for all patients requiring intensive care, from preterm newborns through elderly adults (McDonald et al. 2002; Rozycki et al. 1998), which include:

- Decreased blood loss by arterial sampling for blood gas analysis
- Lower risk of infection related to a decreased number of central venous line or arterial line entries
- Decreased costs
- Availability of continuous data

However, as shown in Table 12.6, several physiologic and technical factors as well as disease states can affect $P_{et}CO_2$ measurements and potentially make it less reliable as a surrogate for blood gas interpretation.

The lack of consistency in the agreement between $P_{et}CO_2$ and P_aCO_2 has led to significant controversy in the medical literature with regard to the usefulness of $P_{et}CO_2$ measurements in ventilated patients, especially in the neonatal population. McDonald et al. (2002) and Wu et al. (2003) have shown in large clinical studies in critically ill mechanically ventilated infants that $P_{et}CO_2$ correlates with P_aCO_2 and provides a clinically relevant, reliable estimation of ventilation for most infants. Similar results were found by Rozycki et al. (1998) investigating 45 newborn infants receiving mechanical ventilation. They suggest that capnography in these patients may be useful for trending or screening patients for abnormal arterial CO_2 values. In contrast, Tobias et al. (Tobias and Meyer 1997a) found in intubated infants that $P_{et}CO_2$ does not accurately predict P_aCO_2 and that transcutaneous carbon dioxide ($P_{tc}CO_2$) measurements are more accurate. To the same result came Tingay et al. (2005) during neonatal transport as there was an unacceptable under-recording of the P_aCO_2 likely due to the technical limitations of the sidestream technology used.

A distinct improvement in the agreement between $P_{et}CO_2$ and P_aCO_2 was obtained by Kugelman et al. (2008) by using a double lumen endotracheal tube and a microstream sidestream capnograph. They demonstrated in 27 newborns (body weight 490–4,790 g) that distal end-tidal CO_2 measurements correlate significantly better with P_aCO_2 than when $P_{et}CO_2$ is measured with a mainstream capnograph. This improved agreement remained reliable in conditions of severe lung disease. However, such measurements can be difficult as the required cannula is small and may be occluded with secretions while continuously sampling. Unfortunately, the sampling equipment cannot be flushed with air to avoid damage to its filters.

Across a heterogeneous critically ill population of infants, children, and adolescents, McSwain et al. (2010) demonstrated a close correlation between $P_{et}CO_2$ and P_aCO_2. As a key component of their results, McSwain and colleagues noted that as dead space (V_D/V_T) increased, the mean gradient between $P_{et}CO_2$ and P_aCO_2 increased as physiology would dictate; however, the excellent correlation persisted. In contrast, a poor agreement between $P_{et}CO_2$ and P_aCO_2 in magnitude as well direction was observed in ventilated dogs undergoing thoracotomy (Wagner et al. 1998), during cardiac surgery (Russell et al. 1990), and neurosurgery (Grenier et al. 1999) and in mechanically ventilated adults with multisystem trauma (Russell and Graybeal 1994) due to highly variable $\dot{V}/\dot{Q}$ matching. A survey about misleading $P_{et}CO_2$ values during anesthesia and surgery has been provided by Wahba and Tessler (1996).

It appears that in neonatology (especially for the smaller preterm infants), $P_{et}CO_2$ measurements

may not be replacements for arterial or transcutaneous blood gases; however, in most of these patients, capnography can be helpful in monitoring the PCO_2 trend and assessing the integrity of the airway and ventilator circuit (e.g., monitoring for inadvertent extubation and circuit disconnections/blockages). Within the pediatric critical care environment, $P_{et}CO_2$ can be a suitable substitute for arterial blood gas analyses, if dead space ventilation and the expected gradient between $P_{et}CO_2$ and P_aCO_2 is considered (McSwain et al. 2010).

12.2.2.5 The $P_{a-et}CO_2$ Difference and Ventilation/Perfusion Abnormalities

$P_{et}CO_2$ is commonly lower than P_aCO_2, and the difference ($P_{a-et}CO_2$) can be caused by $\dot{V}/\dot{Q}$ mismatching in the lungs (e.g., dead space ventilation) as a result of temporal, spatial, and alveolar mixing effects. The $P_{a-et}CO_2$ gradient is normally 4–6 mmHg, if ventilation and perfusion are reasonably matched. However, when the alveoli are not properly ventilated (i.e., shunt perfusion) or, much more significantly, when lung perfusion is decreased (globally or regionally) as compared to ventilation (i.e., dead space ventilation), the increased $\dot{V}/\dot{Q}$ mismatch will result in an increased $P_{a-et}CO_2$ difference. It should be noted that a variable air leak around the endotracheal tube or within the ventilator circuit (as discussed below), hypothermia, and other variables may result in a falsely decreased $P_{et}CO_2$ and, subsequently, an exaggerated $P_{a-et}CO_2$ gradient.

In several studies, the $P_{a-et}CO_2$ difference has been used to monitor $\dot{V}/\dot{Q}$ matching during mechanical ventilation. Wenzel et al. (1999a) found in ventilated rabbits a strong correlation between $P_{a-et}CO_2$ and alveolar dead space. Both increased significantly after surfactant depletion by bronchoalveolar lavage and decreased significantly after surfactant application with a return nearly to the baseline. Skimming et al. (2001) demonstrated in ventilated sheep that the vasodilator effects of nitric oxide (NO) inhalation improved the efficiency of CO_2 elimination in acutely injured lungs by a decrease in $P_{a-et}CO_2$, and these effects, including alveolar dead space, were relatively dose independent between 5 and 20 ppm. Due to the strong correlation between $P_{a-et}CO_2$ and alveolar dead space, these authors state that from a clinical perspective, measuring $P_{a-et}CO_2$ to monitor NO inhalation therapy is simpler than measuring alveolar dead space as an ordinary end-tidal CO_2 monitor can substitute for a sophisticated system of dead space measurements requiring simultaneous measurements of CO_2 elimination and tidal volume.

Hagerty et al. (2002) found a higher $P_{a-et}CO_2$ gradient when comparing newborns with pulmonary disease and those who received mechanical ventilation for non-pulmonary conditions. However, McDonald et al. (2002) showed in a large study in 129 ventilated infants using 2,184 arterial blood and gas samples that in most of the patients, $P_{a-et}CO_2$ is small enough such that $P_{et}CO_2$ monitoring enables the clinician to adequately monitor ventilation and gas exchange.

The $P_{a-et}CO_2$ difference can also be used as a minimally invasive monitor of pulmonary blood flow. A reduction in cardiac output causes a reduction in pulmonary blood flow, which produces a high $\dot{V}/\dot{Q}$ ratio and an increased alveolar dead space resulting in a lower $P_{et}CO_2$ and an increased $P_{a-et}CO_2$ difference. As pulmonary blood flow increases, thereby improving the $\dot{V}/\dot{Q}$ ratio, $P_{et}CO_2$ increases and $P_{a-et}CO_2$ decreases. Sanders et al. (1989) have shown that $P_{a-et}CO_2$ monitoring can be effectively utilized to predict successful resuscitation after cardiac arrest. During cardiac arrest, circulation and $P_{et}CO_2$ disappear. A subsequent increase in $P_{et}CO_2$ indicates effective cardiopulmonary resuscitation or return of spontaneous circulation. Berg and colleagues (1996) have confirmed these observations in an animal model.

In summary, an increase of the $P_{a-et}CO_2$ gradient is one of the most sensitive indicators of decreased pulmonary blood flow, which may be caused by acute pulmonary embolism (Napolitano 1999), air embolism, fat embolism, pulmonary hypertension, and/or, more commonly, a global decrease in cardiac output. Overall, poor cardiac output, decreased pulmonary blood flow for other reasons, and/or significant lung disease will result in high alveolar dead space, and, thus, $P_{a-et}CO_2$ will be increased. This is clinically seen as a poor correlation between $P_{et}CO_2$ and P_aCO_2.

12.2.2.6 Alveolar Ventilation and Dead Space

Only one portion of the total delivered tidal volume from a ventilator participates in gas exchange with pulmonary capillary blood (i.e., alveolar ventilation). The difference between minute ventilation and alveolar ventilation is dead space ventilation—the portion of the delivered tidal volume of which gas exchange is negligible. Dead space consists of the conducting airways (anatomic dead space), the endotracheal tube and other adaptors (apparatus dead space), and the non-perfused or underperfused alveoli (alveolar dead space). Anatomic and apparatus dead space may be combined into the term airway dead space. In ventilated neonates and young children, the dead space fraction (V_D/V_T) is higher than in adults which impairs both the alveolar ventilation and the homogeneity of the alveolar ventilation visibly by a higher lung clearance index (Schmalisch et al. 2006). Since areas of physiologic dead space (airway and alveolar) do not participate in gas exchange, expired CO_2 must derive from alveolar gas.

The first calculations of alveolar ventilation and airway dead space in neonates from the breathing gas were performed using the chemical CO_2 absorption method by Haldane and Scholander assuming that alveolar CO_2 can be approximated by the arterial CO_2 (Karlberg et al. 1954; Cook et al. 1957; Nelson et al. 1962). Chu et al. (1967) were the first to use a rapid capnograph to measure the $P_{et}CO_2$ in neonates and to calculate the anatomic and physiologic dead space using the Bohr equation:

$$V_{\text{Dana}} = V_{\text{T}} \frac{P_{et}\text{CO}_2 - P_{\text{mean}}\text{CO}_2}{P_{et}\text{CO}_2} \qquad (12.3)$$

or the Bohr/Enghoff equation by substituting arterial CO_2 for $P_{et}CO_2$:

$$V_{\text{Dphys}} = V_{\text{T}} \frac{P_{\text{a}}\text{CO}_2 - P_{mean}\text{CO}_2}{P_{\text{a}}\text{CO}_2} \qquad (12.4)$$

where mean $P_{\text{mean}}CO_2$ is the mean CO_2 tension of the mixed expired air. The difference of both dead space represents the alveolar dead space:

$$V_{\text{Dalv}} = V_{\text{Dphys}} - V_{\text{Dana}} \qquad (12.5)$$

These calculations can be routinely used for all patient populations. It should be acknowledged that the calculation of the alveolar dead space requires simultaneous measurement of the arterial CO_2 tension (P_aCO_2), and the mixed expired carbon dioxide concentrations ($P_{\text{mean}}CO_2$) obviously limit the relative noninvasiveness of the technique as well as its ability to provide breath-to-breath information (Arnold 2001).

The Bohr and the Bohr/Enghoff equations use only three measured parameters to calculate dead space. Basing on earlier work by Aitken and Clark-Kennedy (1928), Fowler (1948) and Fletcher et al. (1981) were the first who considered the shape of the entire CO_2 curve during expiration for dead space calculations. They plotted exhaled CO_2 as a function of the exhaled volume and calculated different airway dead space from a single breath by the area under the curve as discussed in Sect. 12.2.3. This single-breath CO_2 ($SBCO_2$) technique is now commercially available and can be used for dead space measurements for all patient populations (McSwain et al. 2010; Ream et al. 1995; Riou et al. 2004).

Theoretically, Fletcher's method is optimal, provided that phases I–III are clearly defined. However, determination of dead space by the $SBCO_2$ method can be foiled if there is no alveolar plateau or if the transition from phase II to III cannot be clearly identified. This is predominantly a problem in very small lungs. Wenzel et al. (1999b) found in ventilated preterm infants that the $SBCO_2$ technique failed in 67 % of the infants studied. In contrast, the dead space calculations by the Bohr or the Bohr–Enghoff equations are independent of the shape of the volumetric capnogram and are preferentially used by several authors for dead space calculation (Ream et al. 1995; Rozycki et al. 1998; Arnold et al. 1993, 1995; Lum et al. 1998). However, this advantage may be deceptive because until recently it has not been known to what extent the missing alveolar plateau leads to dead space errors. As such, the failure rate of capnography to determine dead space as well as

the calculated dead space itself may depend on the method used (Wenzel et al. 1999b).

12.2.2.7 Specific Considerations During Noninvasive Ventilation

Noninvasive ventilatory support (i.e., ventilation without intubation), including noninvasive ventilatory pressure ventilation (NPPV) and continuous positive airway pressure (CPAP), has been successfully applied to patients with acute or acute-on-chronic respiratory failure of various etiologies. During recent several years, there is a clear shift to noninvasive respiratory support in all patient populations as it has become widely accepted as an effective means to improve pulmonary and non-pulmonary outcomes, including a reduction in the risk of ventilator-induced lung injury (VILI) (Davis et al. 2009; Mahmoud et al. 2011). In preterm infants, the use of noninvasive CPAP for respiratory support has provided an improvement in survival rates and morbidity, compared to endotracheal intubation (Gittermann et al. 1997; Dani et al. 2004; Geary et al. 2008; Morley et al. 2008). Unfortunately, definitive data are lacking in the pediatric population. In the adult population, noninvasive ventilation has been demonstrated to reduce mortality, ventilator-associated pneumonia (VAP), and intubation rates (Keenan et al. 2004; Hess 2005).

In addition to improvements in lung mechanics and gas exchange, noninvasive ventilation aims to reduce CO_2 rebreathing by the flushing of airway dead space and to improve alveolar gas exchange by a reduction of alveolar dead space. Theoretically, capnography should be a suitable method to monitor the effectiveness of this therapy. However, capnography is only rarely used during noninvasive-ventilator support due to the very difficult measuring conditions. The patient interface (e.g., binasal prongs, nasopharyngeal tubes, or masks) limits the usefulness of the capnographic measurements as exhaled CO_2 is diluted by the driving inspiratory flows of the system and accurate measurements are limited by the leakage of expired gas around the monitoring device (as described in more detail below). Both of these limitations of noninvasive ventilation hamper precise measurements.

Due to these technical difficulties, there are only a few reports of the use of capnography during noninvasive ventilation in the medical literature, mainly in adults. Schettino et al. (2003) used mainstream capnography in an in vitro model to optimize face masks for adults with regard to CO_2 rebreathing. Henke et al. (1991) investigated the effect of CPAP in sleeping adults with obstructive airways by $P_{et}CO_2$ sidestream measurements, and Bratzke et al. (1998) compared controlled mechanical ventilation (CMV) with CPAP during anesthesia using $P_{et}CO_2$ and dead space measurements.

Capnographic measurements in neonatal/pediatric animal models have been performed using the combination of intubation with noninvasive devices to facilitate CO_2 measurements. Miller et al. (2004) investigated the effect of tracheal gas insufflation-augmented CPAP on CO_2 elimination in intubated piglets, and Pillow et al. (2007) compared bubble CPAP with constant pressure CPAP using mainstream capnography in intubated preterm lambs. Thus, the efficiency of ventilatory support in most studies of non-intubated patients is assessed by conventionally measured arterial blood gas analyses, transcutaneous monitoring, and/or pulse oximetry (Gozal 1997; Criner et al. 1999; Regnis et al. 1994).

As previously noted, a principal difficulty of capnography with noninvasive ventilatory support is that the site of CO_2 and air flow measurements depends on the patient interface used (e.g., facial mask, head box, mono- or binasal prongs, or pharyngeal tubes). With all of these patient interfaces, large air leaks can occur. When using nasal prongs, oral air leaks can lead to highly variable leak flows which prevent reliable CO_2 and air flow measurements. Hückstädt et al. (2003) performed air flow measurements in 69 neonates during nasal CPAP using differential pneumotachography, and in 49 (71 %) infants, measurements were not possible due to uncorrectable air leaks. In contrast to measurements of ventilation during noninvasive ventilatory support (Fischer et al. 2008, 2009;

Schmalisch et al. 2009), nothing is known about the effect of air leaks on the measured $P_{et}CO_2$ or dead space. Overall, capnography during noninvasive ventilation support seems to be highly doubtful, and, therefore, it cannot be recommended for clinical use at this time.

12.2.2.8 Specific Considerations in the Neonatal Patient

The developing neonatal lung differs in many respects from older children and adults, and this may influence CO_2 measurements significantly. It is essential to understand these age-related deviations to minimize misleading interpretations of a capnogram.

12.2.2.8.1 Small Airways

In healthy adult lungs, there is a rapid rise in CO_2 concentration during phase II of the capnogram with only a negligible contribution of the upper airways to gas exchange. In neonates, the diameter of the airways is inherently much smaller. The smaller the airway diameter, the higher is the impact on the exhaled CO_2. With a larger airway diameter, the ratio between inner surface and volume suffices to prevent a fast CO_2 exchange between gas and tissue. However, in much smaller airways, there is already an inner-bronchial PCO_2 exchange. This may explain why neonates have an exaggerated phase II and a reduced, or even missing, phase III (Tirosh et al. 2001).

12.2.2.8.2 Lung Growth

Lung growth during infancy also affects phase III (if even present) of the capnogram. Ream et al. (1995) found a steeper slope of phase III in small infants as compared to adults. This result is supported by the modeling studies of Schwardt et al. (1991) and Neufeld et al. (1992) which demonstrated that a morphometric decrease of the airway cross-section is associated with an increase in the diffusional resistance within the airways resulting in an increase in the phase III slope. However, the steeper phase III, the more difficult it is to distinguish between phase II and III, and the more difficult becomes the calculation of the dead space from the volumetric capnogram by Fletcher's method.

12.2.2.8.3 Respiratory Time Constant

The main problem of capnography in ventilated neonates is the fast exhalation time such that the response time of the capnograph may not be sufficient to reach an alveolar plateau in the capnogram. This is especially true in preterm newborns with stiff lungs where the respiratory time constant can be shorter than 50 ms and exhalation completed within 200 ms. The influence of the stiffness of the lungs on the incidence of capnograms without alveolar plateau was investigated by Proquitté et al. (2004) in 21 ventilated surfactant-depleted piglets (body weight 560–1,435 g). This study noted that the incidence of capnograms without alveolar plateau increased considerably with decreasing exhalation time. If the exhalation time was shorter than 200 ms, an alveolar plateau was not seen in more than 75 % of all recorded files. This agrees well with a study by Tirosh et al. (2001) which demonstrated that with decreasing gestational age, the number of capnograms without alveolar plateau increased significantly.

12.2.2.8.4 Breathing Pattern

Relatively higher respiratory rates and smaller tidal volumes encountered in neonates, as compared to older infants and adults, make capnography much more difficult. Technical requirements of the capnograph for use in neonates and small children are higher and include:

- Minimal dead space of mainstream sensors because of the lower delivered tidal volumes
- Low suction flow of sidestream monitors because of the low expiratory flow rates
- Fast response time of the CO_2 analyzer because of the short exhalation times, especially in preterm neonates with stiff lungs
- High sample rate of the signals to obtain sufficient graphic resolution of the capnogram, especially in infants and young children with elevated respiratory rates

The concept of capnography was initially developed for adults with a well-defined capnogram. Ventilation and gas exchange in smaller lungs may differ from adult lungs in many respects. Particularly in premature neonates, in which the phase II is widened and phase III reduced or

absent, we will need imaginative physiologic concepts to interpret such capnograms.

12.2.2.9 Current Technical Limitations of Capnography in the Neonatal Patient

An important difference of capnography in ventilated newborns compared to older infants, children, or adults is the use of uncuffed endotracheal tubes (ETT). This practice leads to air leakages around the ETT which are observed in about 70 % of all ventilated neonatal infants (Bernstein et al. 1995). In the past, several studies were preformed to investigate the effect of ETT leakages on the measurement of ventilation and lung mechanics and to develop suitable correction algorithms (Schmalisch et al. 2009; Kondo et al. 1997; Herber-Jonat et al. 2008); however, little is known about the effects of ETT leaks on capnographic measurements. Depending on the used ventilator, tidal volume measurements are reliable up to 5–20 % endotracheal tube air leaks (Mahmoud et al. 2009). In contrast to volume measurements, it is not possible to give an upper limit of ETT leaks which may be tolerated for capnographic measurements with clinically applicable results. The leak-dependent CO_2-measuring error depends on the shape of CO_2 plateau in the exhaled air. If there is a wide alveolar plateau, capnographic measurements may be reliable for ETT leaks up to 20 % (Schmalisch et al. 2012). However, in mechanically ventilated newborns with low compliant, stiff lungs, there is only a small (if any) CO_2 plateau at the end of expiration. Therefore, the presence of ETT leak in these infants' capnographic measurements should be interpreted with caution, and the $P_{et}CO_2$ is the most falsified capnographic parameter by the ETT leak.

One of the most important obstacles in the use of mainstream capnography in ventilated newborns is the additional dead space of the CO_2 analyzer chamber. For most neonates, current technology allows for the use of capnography. However, in preterm infants with low tidal volumes, rebreathing of exhaled CO_2 with the potential of generating false inspiratory and expiratory CO_2 measurements may occur. This was a significant problem in the past using volumetric capnography by serial connection of a CO_2 analyzer and a flow sensor where the resulting dead space could exceed 30 % of the tidal volume (Wenzel et al. 1999b). Combined sensors for volumetric capnography are now available (e.g., neonatal sensor of the NM3, NICO, and CO_2SMO+ respiratory monitors, Philips Respironics, Murrysville, PA, USA) with dead space of about 1 mL. Except for premature neonates, these new flow sensors have essentially eliminated the dead space concern of the capnostats. If the tidal volume is less than 5 mL (e.g., ventilated preterm newborn <1,000 g), a dead space of 1 mL is an undesirable load (Nassabeh-Montazami et al. 2009).

Sidestream measurements are dead space-free, and special microstream devices (e.g., NBP-75, Nellcor Puritan Bennett, Pleasanton, CA, USA) have been developed for use in neonates with low sampling flows and rapid response times (Hagerty et al. 2002; Kugelman et al. 2008). When a sidestream capnograph is used, the sampling tube needs special care to prevent measuring errors. During mechanical ventilation, water droplets and secretions can be aspirated, significantly affecting accuracy of the carbon dioxide measurements. In the extreme situation, the sample port or the sampling tube can become completely occluded.

Some capnographs either increase the sampling flow or, to clear contaminants from the tube, reverse the flow (purge) when they sense a drop in pressure from a flow restriction. If this fails, the sampling port and/or the tubing requires replacement. Occasionally, liquids enter the CO_2 analyzer chamber despite the presence of a water trap. This can affect the performance of the CO_2 monitor and produce abnormal capnograms. It should be noted that cleaning the CO_2 analyzer chamber can be difficult. Positioning of the sampling tubing upwards (i.e., away from the patient and against gravity) decreases the risk of liquids entering in the tubes and the analyzer chamber. When abnormal capnograms are noted, clinicians should ensure that there is no system fault. In clinical practice, a common, but less accurate, bedside method to check the capnograph is to record a normal CO_2 tracing (e.g., one's own) to confirm the proper functioning of the capnometer (Bhavani-Shankar et al. 1992).

Independent of which measuring principle is used, the response time of the capnograph must be sufficiently high so that the magnitude and shape of the signal are not falsified. Due to the short respiratory time constants in neonates and young infants, a capnograph should have an adequate response time, which has two components—transit time and rise time (Tang et al. 2005).

In sidestream measurements, the transit time is the time taken by the gas sample to travel from the sample port to the CO_2 analyzer and depends on ventilator pressures, suction flow, and length and diameter of the tube. The transit time can be numerically corrected provided that it is nearly constant. Nevertheless, a volumetric capnograph is hardly possible due to remaining errors in the synchronization of the volume and CO_2 signals.

The rise time is the time of the CO_2 analyzer taken from 10 to 90 % of the final value. Unfortunately, the possibilities of improving the rise time by signal filtering are marginal and are limited by the rapid increase of the noise in the signal (Wong et al. 1998). Capnographs used in neonates currently have rise times ($T_{10–90\ \%}$) of 50–80 ms depending on the airflow used for testing. This can be too long for preterm neonates with low expiratory flow and respiratory rates of 60/min and higher (i.e., expiratory time, t_E, <500 ms). If the rise time of the capnograph is too high as compared to the exhalation time, the alveolar plateau is not reached and $P_{et}CO_2$ is underestimated. Therefore, older results using capnographs with much higher rise times should be viewed with reservation.

As many capnographs are developed for children and adults with a relatively low sampling rate of the signals, the specifics of the technology used must be assessed before employing such devices in the neonatal and infant populations. A sampling rate of 50/s for CO_2 and gas flow may be sufficient in adults with an expiratory time of several seconds; however, such a sampling rate would provide only 25 sample values in a preterm newborn with an expiratory time of 500 ms. Such a situation would put into doubt the ability to cleanly distinguish phase I, II, and III of the capnograms. To accurately record breathing signals of premature infants, a sampling rate of at least 200 Hz is required. For full-term neonates and infants, a sampling rate of 100 Hz is generally adequate. These limits are necessary for a precise evaluation and an accurate graphic presentation of the signals (Bates et al. 2000). As already shown, the graphic assessment of a capnogram is an essential prerequisite for a valid interpretation of capnogram-derived parameters.

12.2.2.10 Time-Based Capnography and Endotracheal Tube Placement

Although practical applications of end-tidal CO_2 monitoring in the ICU setting include adequacy of alveolar ventilation during mechanical ventilation and respiratory monitoring of spontaneously breathing patients, one could argue that the most important use for this monitoring technology in the ICU setting is to assess proper endotracheal tube (ETT) positioning and patency. The use of capnography at intubation for a rapid assessment of appropriate ETT placement by confirming the presence of exhaled carbon dioxide is standard of care. Knapp et al. (1999). demonstrated capnography as the most rapid and reliable method for evaluation of appropriate ETT placement (Clark et al. 1992). One could argue that capnography should be used through the duration of mechanical ventilation to ensure the continued integrity of the ventilatory system (Cheifetz and Myers 2007). However, only a small subset of centers use capnography throughout the duration of mechanical ventilation to monitor for inadvertent ETT dislodgement or discontinuity of the ventilator circuit. It should be noted that volumetric capnography, as described below, is a more sensitive indicator of appropriate ETT placement than time-based (i.e., end-tidal CO_2) monitoring.

12.2.3 Volume-Based (Volumetric) Capnography

With volume-based or volumetric capnography, a Capnostat (i.e., carbon dioxide sensor) and a pneumotachometer (i.e., gas flow sensor) in combination measure the quantity of CO_2 exhaled as

a function of the total expired volume of gas. The net quantity of CO_2 expired (VCO_2) is calculated and expressed as a volume of gas, generally in units of mL/min, rather than as a gas fraction or partial pressure (as occurs with time-based capnography). In the unusual circumstance in which carbon dioxide is present in the inspired gas, the difference between inspired and expired carbon dioxide is used to calculate VCO_2. Volumetric capnography would be expected to be an improved indicator of dynamic changes in gas exchange as compared to time-based capnography (Proquitte et al. 2004; Schmalisch 2004).

Volumetric capnography is often referred to as single-breath carbon dioxide ($SBCO_2$) elimination because the quantity of carbon dioxide eliminated per breath is used for most of the calculations. The $SBCO_2$ waveform includes three distinct phases enabling clinicians to assess clinical issues of cardiorespiratory concern (see Fig. 12.11). Phase 1 depicts gas exhaled from the upper airways (i.e., gas exhaled from the combined anatomic and apparatus dead space), which is generally void of carbon dioxide. An increase in the duration of phase 1 is consistent with an increase in anatomic/apparatus (i.e., airway dead space) dead space. As an example, a prolongation of phase I can be seen with excessive PEEP leading to distension of the upper airways. Phase 2 depicts a transitional phase of ventilation from the upper to the lower airways and tends to depict alterations in perfusion. A slower rise of phase 2 tends to correlate with decreased pulmonary capillary blood flow. Phase 3 represents alveolar gas exchange and may indicate abnormalities in gas distribution due to heterogeneous lower airway and/or alveolar disease. An upsloping of phase 3 generally indicates maldistribution of gas delivery throughout the lung regions. Such an upsloping can be seen with significant lower airways disease (i.e., bronchospasm).

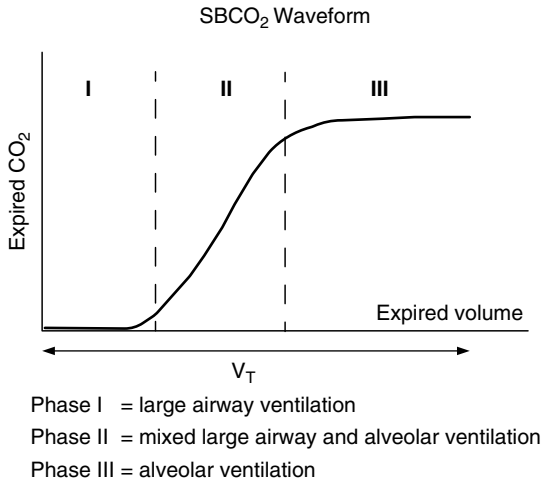

Fig. 12.11 Single breath carbon dioxide ($SBCO_2$) waveform

12.2.3.1 Technique

Volumetric capnography is the continuous monitoring of carbon dioxide elimination per unit time. CO_2 elimination (VCO_2) is affected by ventilation, circulation/pulmonary perfusion, and, to a much lower degree, diffusion as carbon dioxide diffuses so rapidly across the epithelial–endothelial junction. Carbon dioxide elimination can be a valuable clinical marker for acute changes in the cardiorespiratory status of an invasively ventilated patient. Basic physiology states that VCO_2 indicates pending alterations in P_aCO_2.

Devices that monitor VCO_2 and display volumetric capnograms provide bedside clinicians with a breath-by-breath indicator of gas exchange in response to changes in a patient's cardiorespiratory status in relation to variations in the trajectory of clinical illness and/or in response to alterations in the medical management of a patient (Taskar et al. 1995). Overall, volumetric capnography provides a global picture of the physiologic effects of cardiorespiratory interactions for the mechanically ventilated patient.

12.2.3.2 Carbon Dioxide Production/Metabolism

An underlying principle of capnography (time-based and volume-based) is that carbon dioxide elimination and carbon dioxide production must always equilibrate, with carbon dioxide production being primarily determined by cellular metabolism. Normally, carbon dioxide production is dependent on a person's activity level and weight. For a resting, healthy, normal person with a respiratory quotient of 0.8, carbon dioxide production minute is estimated by Brody's formula, $8 \times \text{patient weight}^{0.75}$, where CO_2 production is

calculated in mL/min and patient weight is measured in kilograms. Thus, an average size, resting adult produces carbon dioxide at approximately 200–250 mL/min (Arnold et al. 1993). However, there are no equations to predict carbon dioxide production for an invasively ventilated patient, who may have injured lungs and be pharmacologically sedated as Brody's formula simply does not apply. Thus, it is important to stress that much of the interpretation of volumetric capnography is based on trends over time and patterns of change rather than absolute numbers.

Clinical conditions which directly affect metabolism would be expected to predictably decrease or increase CO_2 production accordingly. Thus, CO_2 production decreases with pharmacologic sedation, natural or pharmacologic sleep, and hypothermia (except if shivering occurs) and increases with agitation, fever, shivering, and excessive caloric intake.

Carbon dioxide balance in the body (i.e., production versus elimination) at any point in time is dependent on the intricate balance between CO_2 production, transport (cells to blood, then to lungs), storage (skeletal muscle, fat, and bone), and exhalation. In a normal, healthy individual, CO_2 produced from metabolism rapidly equilibrates with CO_2 elimination via the lungs. However, the time to re-equilibration can vary greatly with the degree of alterations in pulmonary capillary blood flow and/or lung volume. Thus, acute changes in VCO_2 and the return to an equilibration with carbon dioxide production will vary in relation to both the timeframe and magnitude of the cardiorespiratory change(s). This time variability can be a hurdle in the interpretation of volumetric capnography.

12.2.3.3 Clinical Applications

The volumetric capnogram (i.e., single-breath carbon dioxide waveform) has been successfully used in the measurement of anatomical dead space, pulmonary capillary perfusion, global cardiac output, and effective ventilation (Arnold et al. 1993; Blanch et al. 2006). By analyzing volumetric capnograms, clinicians can easily and quickly assess cardiorespiratory issues of concern. In Fig. 12.11, phase 1 represents gas exhaled from the upper airways (i.e., gas exhaled from anatomic dead space), which is generally void of carbon dioxide (Proquitte et al. 2004). Therefore, an increase in phase 1 indicates an increase in anatomic dead space ventilation (V_{Dana}). Such a situation can occur with excessive PEEP, which may overdistend the upper airways (as well as the alveoli). Phase 2 is the transitional phase from upper to lower airway ventilation and tends to depict changes in perfusion. For example, a decrease in phase 2 slope would be indicative of reduced perfusion. Phase 3 is the area of alveolar gas exchange and represents changes in gas distribution. For example, an increase in the slope of phase 3 is indicative of increased maldistribution of gas delivery.

As with oxygen consumption, CO_2 production and elimination (VCO_2) is a continuous process. VCO_2 rapidly reflects changes in both ventilation and perfusion regardless of clinical etiology. As such, VCO_2 reflects the body's physiologic response to changes in a patient's cardiorespiratory status and can be a useful monitor to assess response to changes in mechanical ventilator settings as well as therapies that affect pulmonary perfusion (including global cardiac output). Thus, volumetric capnography is a sensitive clinical tool useful for reflecting acute changes in the cardiorespiratory status and metabolic state of a mechanically ventilated patient (Breen et al. 1996a, b), as discussed in more detail below.

12.2.3.3.1 Endotracheal Intubation

Although time-based capnography has become the standard of care for determining endotracheal intubation (Holland et al. 1993; Birmingham et al. 1986; Knapp et al. 1999; Anonymous 2006), one could speculate that volumetric capnography would be superior as it provides data on both carbon dioxide elimination and the movement of gas flow in and out of the airways (Sum-Ping et al. 1989; Grmec 2002). It should be noted that

time-based capnography can provide false-positive results for the determination of endotracheal intubation when carbon dioxide is present in the stomach. Although somewhat rare, this typically occurs after ingestion of a carbonated beverage or prolonged bag-mask ventilation. Volumetric capnography would be much less likely to provide a false-positive result as expiratory gas flow would be unlikely to be detected with a misplaced endotracheal tube.

12.2.3.3.2 Mechanical Ventilation

Volumetric capnography may assist the clinician in managing the mechanical ventilator as changes in VCO_2 predict changes in P_aCO_2. As the patient's exhalation of carbon dioxide increases (i.e., increased VCO_2), the level of carbon dioxide in the blood must decrease (i.e., decreased P_aCO_2). Likewise, any decrease in VCO_2 would predict an increase in P_aCO_2. As P_aCO_2 obviously cannot decrease to zero or increase to infinity, the changes seen in VCO_2 and P_aCO_2 must be transient until carbon dioxide elimination re-equilibrates with carbon dioxide production. One of the more difficult aspects of utilizing volumetric capnography in the clinical setting is evaluating the variable of time. The time for re-equilibration of CO_2 production and elimination varies with the patient's clinical status as well as the degree and timing of ventilator changes. Baseline lung volume and changes in lung volume are an inherent component of the required equilibration time.

Although data are limited, it would be anticipated that volumetric capnography could assist with PEEP management as lung volume is a key component of carbon dioxide elimination. As the lung collapses or overdistends, carbon dioxide elimination would be anticipated to decrease. In contrast, carbon dioxide elimination would be expected to increase as the lung approaches a more optimal lung volume. Although this concept is based on physiology, clinical application becomes difficult as the time to CO_2 re-equilibration is considered. A more detailed discussion of PEEP titration by the use of volumetric capnography is beyond the scope of this chapter.

From a weaning perspective, volumetric capnography may provide objective data to assist clinicians. Successful weaning using volumetric capnography is demonstrated by an increase in spontaneous alveolar minute ventilation in association with a stable (or slightly increased) elimination of carbon dioxide. If seen, an increase in VCO_2 with weaning often correlates with an increase in CO_2 production (i.e., increased respiratory muscle activity) with the patient being able to exhale the additional carbon dioxide produced. In such situations, an arterial blood gas would demonstrate a stable P_aCO_2. A significant increase in VCO_2 with weaning from mechanical ventilation would suggest excessive work of breathing and the potential for impending respiratory decompensation. This scenario would be consistent with a visual assessment of increasing respiratory distress (e.g., retractions, tachypnea, and potentially agitation).

With the failure of weaning from mechanical ventilation as the ventilator settings are decreased, the patient is no longer able to maintain an adequate degree of spontaneous ventilation, and, hence, total minute ventilation falls. This decrease in minute ventilation is associated with a decrease in carbon dioxide elimination, and an arterial blood gas would, thus, reveal an elevated P_aCO_2. Volumetric capnography enables the bedside clinician to more easily and quickly identify weaning failure and, in response, increase mechanical ventilator support promptly and often without the requirement for an arterial blood gas determination.

12.2.3.3.3 Pulmonary Blood Flow

Physiology dictates that any clinical condition which alters pulmonary blood flow will alter CO_2 elimination. A decrease in pulmonary capillary blood flow (regardless of etiology) results in a decrease in VCO_2. Such conditions include a decrease in RV output (which would include a

decrease in global cardiac output), pulmonary hypertension, and/or pulmonary (including thrombus, fat, and air) embolus. VCO_2 can be used as an effective monitor for pulmonary blood flow as long as minute ventilation is stable.

One of the key difficulties of volumetric capnography occurs when there are competing cardiorespiratory variables. For example, if pulmonary capillary blood flow increases (which should increase VCO_2) and minute ventilation decreases (which should decrease VCO_2 as described above), then VCO_2 will move in the direction of the primary pathophysiology, which the clinician must then determine. The same would be true for a decrease in pulmonary blood flow and an increase in minute ventilation or other competing physiologic changes.

12.2.3.3.4 Assessment of Dead Space Ventilation

One of the most important applications of volumetric capnography is the calculation of physiologic dead space and the total dead space to tidal volume ratio (V_D/V_T) (see Eqs. 12.3. and 12.4). Total physiologic dead space equals airway (anatomic and apparatus) dead space plus alveolar dead space. Thus, alveolar dead space can be calculated once one knows the V_D/V_T ratio, delivered tidal volume, and airway dead space. It should be noted that although volumetric capnography is generally a noninvasive monitoring technique, the calculations of physiology dead space and the V_D/V_T ratio do require an arterial blood gas.

The V_D/V_T ratio has been successfully used to predict extubation readiness in a heterogeneous population of infants and children as reported by Hubble et al. (2000). A V_D/V_T ratio of less than 0.50 correlated with a 96 % chance for successful extubation, while V_D/V_T ratios of 0.51–0.65 and greater than 0.65 correlated with successful extubation rates of 60 and 20 %, respectively. The V_D/V_T ratio has also been used to assess the survival likelihood of adult patients with acute respiratory distress syndrome with a $V_D/V_T \leq 0.55$ representing increased survival (Kallet et al. 2004; Nuckton et al. 2002).

Essentials to Remember

- Capnography is an essential monitoring system for critically ill patients and is increasingly being described as the fifth vital sign.
- Time-based capnography represents carbon dioxide elimination as expressed as CO_2 partial pressure or CO_2 fraction over time. Volume-based (volumetric) capnography represents carbon dioxide elimination over exhaled volume.
- Recent technologic advances have allowed for noninvasive carbon dioxide monitoring for all patient populations, although limitations do exist for the small premature infant.
- The clinical use of carbon dioxide monitoring should allow for decreased blood loss related to a lower need for arterial sampling for blood gas analysis, lower risk of infection related to a decreased number of central venous line or arterial line entries, decreased costs, and availability of continuous data.
- Both time-based and volume-based capnography provides clinical information concerning both ventilation and perfusion. Overall, volumetric capnography provides a global picture of the physiologic effects of cardiorespiratory interactions.
- Basic physiology states that carbon dioxide elimination (VCO_2) indicates pending alterations in the arterial carbon dioxide concentration (P_aCO_2).
- Much of the interpretation of volumetric capnography is based on trends over time and patterns of change rather than absolute numbers.
- Elevated dead space to tidal volume ratio (V_D/V_T) has been correlated with extubation failure in the pediatric population and increased mortality in the adult ARDS population.

12.3 Transcutaneous Carbon Dioxide Monitoring in Infants and Children

Joseph D. Tobias

Educational Aims

- The reader will be familiar with the various techniques available for the continuous, noninvasive monitoring of PCO_2.
- The reader will understand the advantage sand disadvantages of the different techniques for continuous monitoring of PCO_2.

12.3.1 Introduction

The equipment and techniques to accurately measure transcutaneous PCO_2 (TC-CO_2) were first developed and described in 1960 by Dr. Severinghaus (Severinghaus 1960). This pioneering work was later applied to clinical trials which demonstrated a linear correlation between skin surface PCO_2 and arterial CO_2 (P_aCO_2) in the range of 20–74 mmHg (Johns et al. 1969). The initial investigations involving TC-CO_2 monitoring were performed using a specially designed temperature-stabilized tissue PCO_2 electrode. However, it was later determined that it was feasible to noninvasively and continuously measure transcutaneous oxygen (TC-O_2) and later TC-CO_2 by using an electrode that provided local heating of the skin. The initial applications of these devices were in the neonatal population in whom the continuous monitoring of PO_2 was necessary to limit the deleterious effects of excessive tissue oxygen concentrations on the eye (Eberhard et al. 1976). Similar technology was subsequently applied to the continuous measurement of TC-CO_2 thereby resulting in the commercially available monitors which combined the ability to provide the continuous measurement of TC-O_2 and CO_2 being introduced into clinical practice in the 1980s (Eberhard and Schafer 1980). Although the largest application of TC-CO_2 monitoring remains in the neonatal population (Cassady 1983), a greater appreciation of the potential utility of this technology has resulted in several potential applications outside of the newborn population. Suggested applications outside of the neonatal population have included continuous CO_2 monitoring during mechanical ventilation including high-frequency oscillatory ventilation, in spontaneously breathing patients with respiratory insufficiency related to various pathologic processes, during noninvasive ventilatory support, with apnea testing during brain death examination, and in the assessment of patients with diabetic ketoacidosis (DKA) (Tobias 2009).

12.3.2 Technical Aspects of Transcutaneous Carbon Dioxide Monitoring

TC-CO_2 monitors apply heat (42–43 °C) to the skin to induce vasodilatation of the capillary bed which results in the equilibration of capillary and arterial PCO_2 levels (Fig. 12.12). Capillary vasodilatation also facilitates the diffusion of CO_2 from the capillary lumen to the membrane of the TC-CO_2 monitor. This externally applied heat alters the true value of the capillary/arterial PCO_2 by changing the solubility of CO_2 in blood and increasing the metabolic rate of the tissue and local CO_2 production (an increase of 4–5 % for every °C). Additionally, a final factor which accounts for the TC-CO_2 being higher than the P_aCO_2 is the local production of CO_2 from the epidermal cells of the skin. Therefore, to provide an accurate reflection of the P_aCO_2, the TC monitor must provide some type of temperature correction to account for these factors. The currently available TC monitors provide an internal temperature correction for the PCO_2 based on the working temperature of the electrode (Severinghaus 1982). At a working temperature of 43 °C, the conversion from P_aCO_2 to TC-CO_2 can be arrived at using the formula PCO_2 = (TC-CO_2 divided by 1.34) + 4 mmHg. Without temperature correction, there is an exaggeration of the normal TC to arterial

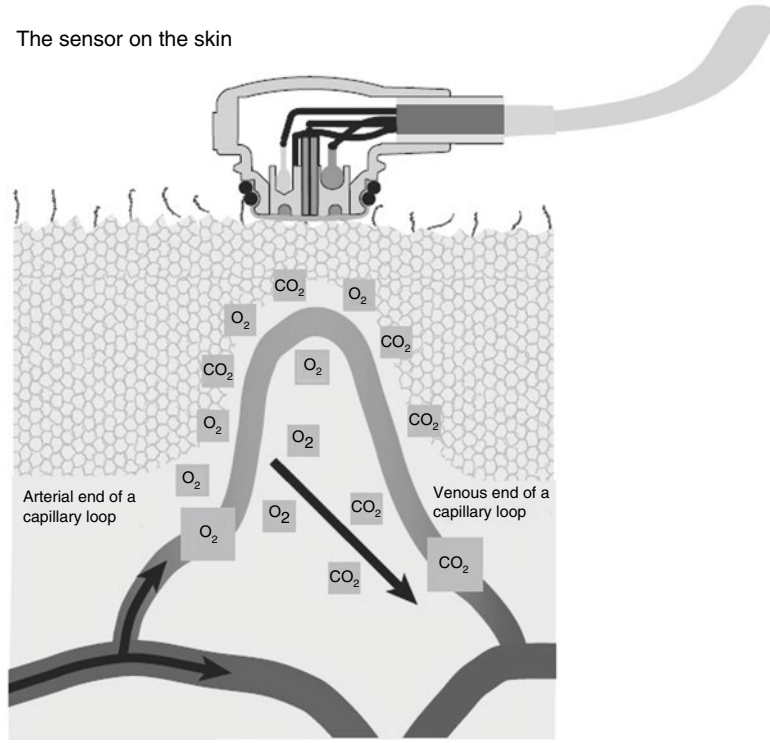

Fig. 12.12 Schematic representation of a transcutaneous O_2/CO_2 device. The heat produced by the sensor dilates the capillary bed thereby increasing local blood flow and facilitating the diffusion of O_2 and CO_2 from the capillary to the sensor. Transcutaneous O_2 and CO_2 are measured electrochemically in the sensor (Figure provided by Radiometer Inc.)

CO_2 gradient, which may lead one to question the validity and utility of such technology (Tremper et al. 1981).

The technology for TC blood gas monitoring was originally developed and described in the 1950s by two groups of investigators (Stow and Randall 1954; Severinghaus and Bradley 1958). TC-CO_2 value is determined by measuring changes in the pH of an electrolyte solution that is separated from the skin by a semipermeable membrane. Following the local application of heat from the surface of the monitoring electrode and the local vasodilatation of the capillary bed, CO_2 diffuses from the capillary lumen across the tissue planes and through the semipermeable membrane of the monitor. The movement of CO_2 into the electrolyte solution changes the pH of the solution. This change in pH is used to calculate the TC-CO_2 value.

Various types of TC-CO_2 monitors are currently available for clinical use. Those initially available for clinical use in the 1980s included the combination of both TC-O_2 and TC-CO_2 monitors. More recently, TC-CO_2 monitors are available as a single TC-CO_2 electrode or as a combined pulse oximeter and TC-CO_2 monitor (Bendjelid et al. 2005; Dullenkopf et al. 2003; Tschupp and Fanconi 2003). The newer devices incorporate the two monitors into an earclip sensor which has found increased applications in the older pediatric and even the adult population. As with any type of monitoring technology, there are specific details of TC-CO_2 monitoring that are required to ensure its accuracy. In comparison to ET-CO_2 monitoring, TC-CO_2 equipment requires a longer preparation time including a calibration period, which varies from 1 to 3 min dependent on the manufacturer, prior to placement. This is followed by an additional 3–5 min equilibration period after placement of the electrode (Fig. 12.13) on the patient. This time is required to allow for heating of the skin to provide an equilibration between the TC and arterial CO_2 values. Additionally, with older generations of the TC-CO_2 monitor, removal of the electrode, recalibration, and placement at another site were recommended to avoid burning the skin. The TC-CO_2 electrode can be placed on any flat skin

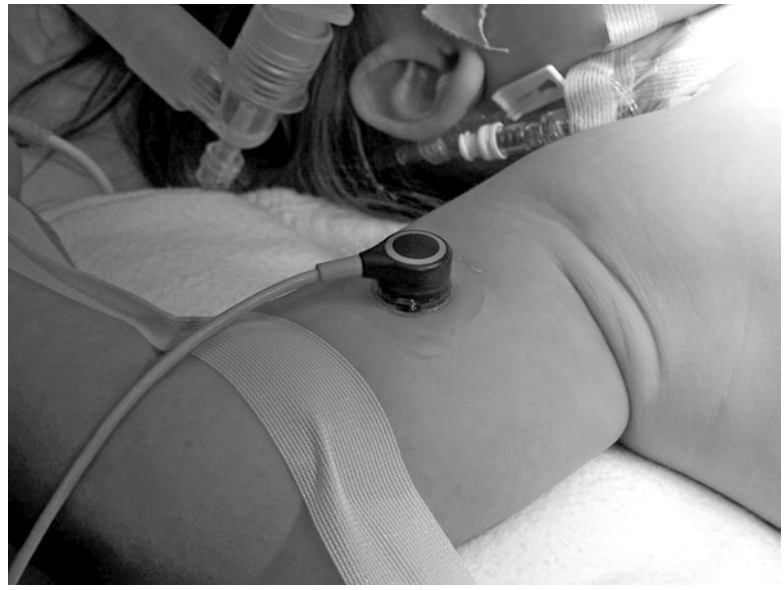

Fig. 12.13 Transcutaneous CO_2 electrode with membrane in use on a patient

surface, or the newer electrodes can be clipped on an earlobe.

As the working temperature of the electrode is less (42 °C) with the newer generation of TC-CO_2 monitors, the need to reposition the electrode has decreased. However, frequent site changes are still suggested in preterm infants or other patient populations at risk for skin breakdown. Factors related to the monitor and electrode which may affect accuracy include technical variables such as trapped air bubbles under the electrode membrane, improper placement technique, damaged membranes, and inappropriate calibration techniques. Patient-related factors may also affect the accuracy of TC-CO_2 monitoring including skin thickness, the presence of edema, tissue hypoperfusion, or the administration of vasoconstricting drugs.

12.3.3 Clinical Applications of TC-CO_2 Monitoring

12.3.3.1 Neonatal Applications

The initial applications of TC blood gas monitoring (PCO_2 and PO_2) were in the neonatal ICU population, most importantly preterm infants with respiratory failure. Given the potential for oxygen toxicity and the development of retrolental fibroplasias as well as the risk of iatrogenic anemia related to repeated blood gas analysis, a device to provide a continuous readout of P_{O2} was a welcome addition to the monitoring provided by pulse oximetry and intermittent blood gas monitoring. In the neonatal population, the correlation of the TC with arterial PCO_2 and PO_2 values is excellent given the thinner epidermis and the limited development of the stratum corneum in neonates compared to older infants and children. Continuous TC-O_2 monitoring in the neonatal periods allows a means of more effectively and accurately maintaining the desired level of oxygenation (P_aO_2 of 50–70 mmHg) as well as a means for the early identification of hypoxemia which may develop during routine care, handling, or invasive procedures. Routine screening with TC-O_2 monitors may also allow for the identification of significant respiratory or cardiac anomalies in otherwise asymptomatic neonates.

12.3.3.2 Monitoring During Mechanical Ventilation (Pediatric ICU)

Outside of the neonatal ICU population, one of the most frequent uses of TC-CO_2 monitoring is to provide a continuous monitor demonstrating the efficacy of ventilation during respiratory

failure in patients who require endotracheal intubation and ventilatory support. Various reports have demonstrated the accuracy of such monitoring in the PICU population (Tobias and Meyer 1997b; Berkenbosch et al. 2001; Tobias et al. 1999; Sivan et al. 1992). In two prospective comparisons involving PICU patients with respiratory failure requiring mechanical ventilation, TC-CO_2 was significantly closer to arterial PO_2 values than the simultaneously measured ET-CO_2 value (Tobias and Meyer 1997b; Berkenbosch et al. 2001). The efficacy of TC-CO_2 monitoring has also been demonstrated following cardiovascular surgery in infants and children with congenital heart disease (CHD) (Tobias et al. 1999). In all of these studies, various physiologic factors including increased dead space ventilation, residual shunt from CHD, and ventilation–perfusion mismatch can be expected to lead to significant inaccuracies with $ETCO_2$ monitoring.

While the previously reviewed studies have used continuous TC-CO_2 monitoring, other investigators have evaluated its utility as an intermittent monitor of PCO_2. As a cost saving measures by avoiding the need to have a TC-CO_2 monitor at each bedside, Rauch et al. used intermittent TC-CO_2 monitoring in a PICU population of 19 patients ranging in age from 5 days to 16 years (Rauch et al. 1999). Prior to obtaining the P_aCO_2 sample, the TC-CO_2 device was applied and left in place for 5 min. The actual P_aCO_2 value varied from 19 to 86 mmHg. The mean difference between the TC and arterial CO_2 value was 1.94 mmHg with a 95 % confidence interval of – 0.12–4.07 mmHg. Scatter plot analysis revealed a regression line characterized by the equation $P_aCO_2 = (\text{TC-}CO_2 \times 1.05) - 4.08$. Additional workup has demonstrated the utility and accuracy of TC-CO_2 monitoring during high-frequency oscillatory ventilation (Berkenbosch and Tobias 2002). Given the inability to use ET-CO_2 monitoring during high-frequency ventilation techniques, the authors demonstrated that TC-CO_2 monitoring can be used in this unique population of pediatric ICU patients. In the 100 paired values (TC and arterial CO_2) obtained from14 patients ranging in age from 1 day to 16 years, the difference between the TC and arterial CO_2 was 2.8 ± 1.9 mmHg. No difference in the accuracy of TC-CO_2 monitoring was noted when the arterial CO_2 was $\leq$50 mmHg versus when it was $\geq$50 mmHg. Given these results, TC-CO_2 monitoring is highly recommended during the use of HFOV.

12.3.3.3 Spontaneous Ventilation

Continuous monitoring of ventilatory function is equally important during spontaneous ventilation or assisted spontaneous ventilation with noninvasive ventilatory techniques. Continuous TC-CO_2 monitoring has been shown to provide evidence of previously unrecognized episodes of hypercarbia in adults during the immediate postoperative period or during the use of patient-controlled or epidural analgesia (Drummond et al. 1997; Kopka et al. 2007; McCormack et al. 2008). Additional reports suggest the utility of TC-CO_2 monitoring in spontaneously breathing pediatric patients with acute airway and respiratory events such as croup and status asthmaticus (Holmgren and Sixt 1992; Fanconi et al. 1991; Wennergan et al. 1986). Holmgren and Sixt evaluated the relationship between TC and arterial CO_2 in 14 children, 7–15 years of age, with status asthmaticus (Holmgren and Sixt 1992). The average TC-CO_2 value was 0.6 kPa (range, 0–1.5 kPa) higher than the P_aCO_2 (1 kPa = 7.3 mmHg). This relationship was not changed by the administration of ß-adrenergic agents. In a cohort of 17 children with croup, a reduction in TC-CO_2 values and croup scores was noted following the administration of inhaled epinephrine (Fanconi et al. 1991). These changes were noted despite no change in other physiologic parameters including heart rate, oxygen saturation, or respiratory rate. The authors also noted a correlation of TC-CO_2 values with the croup scores and suggested that TC-CO_2 monitoring was a reliable and objective tool for managing patients with upper airway obstruction.

TC-CO_2 monitoring has also been used during the provision of noninvasive ventilation (NIV), another situation in which the accuracy of ET-CO_2 may be affected by the presence ventilation–perfusion mismatch due to parenchymal lung disease and sampling issues related to the

apparatus and mask. In a cohort of 26 adults receiving noninvasive ventilation, there was a good correlation ($r = 0.968$) between TC and arterial CO_2 values over a P_aCO_2 range of 26–71 mmHg ($TC\text{-}CO_2 = 1.116 \times P_aCO_2 - 0.46$) (Janseens et al. 1998; Storre et al. 2007). To date, only one study has investigated the use of TC-CO_2 monitoring during NIV in the pediatric population (Paiva et al. 2009). The study population included patient with acute respiratory problems supported with NIV and a second cohort of patients who were on long-term home NIV and required a sleep study evaluation. The first cohort included 65 patients with various respiratory issues including asthma, acute infectious problems, cystic fibrosis, interstitial lung disease, and neuromuscular disorders. Using linear regression analysis, the authors noted a clinically acceptable correlation of the TC and arterial CO_2 in all 3 age groups with $r = 0.931$ in patients 0–6 years of age, $r = 0.630$ in patients 7–12 years of age, and $r = 0.505$ in patients 13–18 years of age. Bland–Altman analysis revealed that the TC-CO_2 value moderately underestimated the P_aCO_2 value with a mean bias of approximately 1 mmHg and a precision of approximately 4 mmHg. In the second cohort of patients, 21 of 50 patients were identified who manifested nocturnal hypercarbia ≥50 mmHg despite no evidence of hypoxemia and normal daytime blood gas measurements.

12.3.3.4 Intraoperative Applications

Although $ETCO_2$ monitoring remains an intraoperative standard of care to document the intratracheal presence of the ETT, various issues affecting ventilation–perfusion matching, the presence of shunt, and technical limitations may affect its accuracy in the operating room setting. When compared with the ICU setting, there are fewer studies reporting intraoperative applications of TC-CO_2 monitoring (McBride et al. 2002; Griffin et al. 2003; Bhavani-Shankar et al. 1998; Reid et al. 1992; Phan et al. 1987; Nosovitch et al. 2002). Nosovitch et al. demonstrated that TC-CO_2 monitoring was more accurate than ET monitoring during intraoperative care in a cohort of 30 pediatric patients (Nosovitch et al. 2002). The potential utility of TC-CO_2 monitoring was demonstrated by one of the patients who developed intraoperative bronchospasm. Despite an ET-CO_2 of 70 mmHg, the TC-CO_2 monitoring was reading 110 mmHg, while a simultaneous P_aCO_2 was 122 mmHg. Using the new combined ear sensor (TC-CO_2 and pulse oximetry), Dullenkopf et al. evaluated intraoperative TC-CO_2 monitoring in a cohort of 60 children receiving general anesthesia (Dullenkopf et al. 2003). Although there was no difference in the accuracy of ET versus TC-CO_2 monitoring in the general population, in a subset of patients with CHD, TC-CO_2 monitoring was more accurate (-0.039 ± 0.56 kPa versus 0.093 ± 0.64 kPa, $p < 0.01$). Another scenario in which the anesthetic technique may impact on the accuracy of $ETCO_2$ is the use of one-lung ventilation (OLV) during thoracic surgical procedures. Four studies have demonstrated improved accuracy of TC compared to ET-CO_2 monitoring in this scenario (Ip Yam et al. 1994; Oshibuchi et al. 2003; Cox and Tobias 2007; Tobias 2003).

12.3.3.5 Apnea Testing

One component of the brain death examination is the demonstration of no ventilatory effort at a $P_aCO_2 \geq 60$ mmHg. To accomplish, an apnea test is performed and an arterial blood gas is drawn to demonstrate a $P_aCO_2 \geq 60$ mmHg. However, as the rate at which the P_aCO_2 increases is variable, it may be problematic to judge when the threshold P_aCO_2 of 60 mmHg has been achieved. Therefore, frequent ABGs are generally obtained to avoid waiting too long given the potential for hemodynamic compromise from hypercarbia or the development of hypoxemia. In both adult and pediatric patients, TC-CO_2 monitoring has been used to determine the appropriate time to obtain an ABG (Tobias 2001; Lang 1998). In a cohort of 8 pediatric patients, TC-CO_2 monitoring was employed during two separate apnea tests (Tobias 2001). In the first 2 patients of the cohort, the ABG was obtained when the TC-CO_2 was 60 mmHg. In all four instances, the P_aCO_2 was less than 60 mmHg. For the subsequent 6 patients, the ABG was drawn when the TC-CO_2 was ≥70 mmHg. In 11 of 12 apnea tests, the P_aCO_2 was greater than 60 mmHg, and in the other one,

the P_aCO_2 was 60 mmHg. In the 16 samples from the 8 patients, the TC to P_aCO_2 difference varied from 2 to 11 mmHg (5.8 ± 2.7 mmHg). If the ABG was obtained when the TC-CO_2 was ≥80 mmHg, the P_aCO_2 was ≥60 mmHg in all cases, and the TC to P_aCO_2 difference varied from 2 to 8 mmHg (5.4 ± 1.9 mmHg).

12.3.3.6 Monitoring of Acid–Base Status

Given the relationship between P_aCO_2, pH, and serum bicarbonate, TC-CO_2 may also have clinical utility as a means of evaluating changes in pH during pathologic processes that result in metabolic acidosis. During diabetic ketoacidosis (DKA), acidosis is partially compensated by a decrease in the P_aCO_2 related to an increase in minute ventilation. With appropriate therapy and resolution of the metabolic acidosis, the P_aCO_2 returns to normal values. In a cohort of 30 children with DKA, it has been demonstrated that TC-CO_2 monitoring can be used to follow changes in pH during treatment and resolution of the metabolic acidosis (McBride et al. 2004). In 2 of the patients, TC-CO_2 monitoring was not feasible due to poor tissue perfusion. In the remaining 28 patients, there was a gradual increase in the TC-CO_2 during correction of metabolic acidosis. Using the equation $P_aCO_2 = (1.5 \times \text{serum bicarbonate}) + 8$, a calculated bicarbonate value was determined and compared to simultaneously obtained serum bicarbonate values. The difference between the calculated and actual serum bicarbonate values was 1.5 ± 1.2 mmol/L. The difference was ≤2 mmol/L in 74.4 % of the sample sets and ≤5 mmol/L in 99.2 % of the sample sets. Linear regression analysis of calculated versus actual serum bicarbonate revealed a slope of 0.95 and an r (Johns et al. 1969) value of 0.88. From this linear regression analysis, the authors suggested that the serum bicarbonate could be calculated from the TC-CO_2 value by using the equation $\text{serum bicarbonate} = 0.61 \times (\text{TC-}CO_2 - 3.9)$.

12.3.3.7 Evaluation of Tissue Perfusion

As noted previously, the accuracy of TC-CO_2 monitoring is affected by tissue perfusion. In the previously mentioned study evaluating the correlation of TC and arterial CO_2 in patients with CHD following cardiovascular surgery, it was noted that TC-CO_2 monitoring could not be used in patients receiving high doses of inotropic agents that resulted in peripheral vasoconstriction and/or in those with poor peripheral perfusion (Tobias et al. 1999). The impact of hemodynamic instability with poor tissue perfusion on TC-CO_2 monitoring has also been reported in a group of adult patients from a mixed operating room and ICU setting (Tremper et al. 1981). When the cardiac index was ≤1.5 L/min/m^2, there was an increase in the TC to arterial CO_2 gradient. The TC-CO_2 value trended inversely with the cardiac index rather than the P_aCO_2. Given this relationship, other investigators have suggested the utility of measuring TC-CO_2 as a means of evaluating tissue perfusion (Greenhalgh and Warden 1992; Tatevossian et al. 2000; Tobias et al. 2006). Greenhalgh and Warden applied intermittent TC CO_2 and O_2 monitoring on the day of surgery and then daily for the next 2 weeks following partial-thickness skin grafts for burn injury in 13 adults (Greenhalgh and Warden 1992). The TC-CO_2 values from the grafts were 80–100 mmHg for the initial few days and then decreased to levels that were slightly higher than those of normal skin (40–50 mmHg) by day 5–6 after grafting. The authors suggested that graft TC-CO_2 levels can be used to provide a noninvasive and objective measure of skin graft vascularization. Other authors have used TC-CO_2 and O_2 values as a means of evaluating peripheral perfusion during resuscitation (Tatevossian et al. 2000). When compared with survivors, non-survivors had lower TC-O_2 and higher TC-CO_2 values. All patients who maintained a TC-O_2 ≥ 150 mmHg survived. A TC-O_2 ≤ 50 mmHg for ≥60 min or a TC-CO_2 ≥ 60 mmHg for ≥30 min was associated with a 90 % mortality.

TC-CO_2 monitoring has also been used to evaluate changes in tissue PCO_2 during aortic cross-clamping for repair of aortic coarctation (Tobias et al. 2006). The study protocol included TC-CO_2 monitoring from a site above the aortic cross-clamp (right chest wall) and a site below

(right thigh). Following placement of the aortic cross-clamp, there was a progressive rise in the tissue CO_2 (TC-CO_2) below the region of the cross-clamp (right thigh), while no change was noted above the cross-clamp. TC-CO_2 increased from 41 ± 4 to 92 ± 41 mmHg during the period of aortic cross-clamping which varied from 12 to 20 min. There was significant variability in the increase of the TC-CO_2 below the cross-clamp (4–127 mmHg), which the authors speculated resulted from the variability of the collateral circulation around the aortic coarctation. There was a correlation between the TC-CO_2 increase and the age of the patient with less of an increase in older patients who likely had time to develop collaterals. The authors suggested that TC-CO_2 monitoring might be able to predict extreme degrees of tissue hypoperfusion distal to the cross-clamp and might therefore be able to identify patients at risk for spinal cord ischemia.

Table 12.8 Potential limitations of TC-CO_2 monitoring

More labor intensive for respiratory therapy staffl
Device requires calibration and setup time
Lag time between change in arterial oxygen and TC oxygen
Depending on type of device used, may require calibration and site change at specific intervals
Accuracy affected by specific patient factors including: Low perfusion states Administration of inotropic agents with vasoconstricting properties Tissue edema or subcutaneous fat
Potential for superficial burns and blistering especially in preterm infants
Limited, but increasing clinical experience outside of neonatal population
Limited clinician familiarity with its use
Device must have intrinsic calibration to eliminate discrepancy due to increased tissue metabolism and CO_2 production from heat.

12.3.4 Summary

Although still used most commonly in the neonatal period, an improved understanding of the techniques of TC-CO_2 monitoring and the availability of new monitors have led to the increased use of TC-CO_2 monitoring in various clinical scenarios outside of the neonatal population. Despite specific limitations of the technology (Table 12.8), when compared with ET-CO_2 monitoring, TC-CO_2 monitoring is equally as accurate in patients with normal respiratory function and more accurate in patients with shunt or ventilation–perfusion inequalities. Additionally, TC-CO_2 monitoring can be applied in situations that may preclude ET-CO_2 monitoring such as HFOV, apnea testing, and NIV. TC-CO_2 monitoring has been used in spontaneously breathing patients with airway and respiratory issues (croup and status asthmaticus) as well as a means of monitoring metabolic status during treatment of acidosis related to DKA. TC-CO_2 monitoring should not be used to replace ET-CO_2 monitoring as ET-CO_2 monitoring remains the standard of care to demonstrate the intratracheal location of the ETT following endotracheal intubation and as a disconnect alarm in the operating room. Given the complementary nature of these two noninvasive monitors, their combined use should be considered in critically ill pediatric patients in both the pediatric ICU and the operating room settings.

Essentials to Remember

- TC-CO_2 monitors apply heat (42–43 °C) to the skin to induce vasodilatation of the capillary bed which results in the equilibration of capillary and arterial PCO_2 levels.
- Although used most commonly in neonates, improvement in the technology of TC-CO_2 monitoring has led to the increased use of TC-CO_2 monitoring in various clinical scenarios outside of the neonatal population.
- Despite limitations of the technology, when compared with ET-CO_2 monitoring, TC-CO_2 monitoring is equally as accurate in patients with normal respiratory function and more accurate in patients with shunt or ventilation–perfusion inequalities.

- TC-CO_2 monitoring can be applied in situations that may preclude ET-CO_2 monitoring such as HFOV, apnea testing, and NIV and in spontaneously breathing patients with airway and respiratory issues (croup and status asthmaticus). It can also be used to evaluate metabolic status during treatment of acidosis related to DKA.
- TC-CO_2 monitoring should not be used to replace ET-CO_2 monitoring as ET-CO_2 monitoring remains the standard of care to demonstrate the intratracheal location of the ETT following endotracheal intubation and as a disconnect alarm in the operating room. Given the complementary nature of these two noninvasive monitors, their combined use should be considered in critically ill pediatric patients in both the pediatric ICU and the operating room settings.

References

Ahlborn V, Bohnhorst B, Peter CS, Poets CF (2000) False alarms in very low birthweight infants: comparison between three intensive care monitoring systems. Acta Paediatr 89(5):571–576

Aitken RS, Clark-Kennedy AE (1928) On the fluctuation in the composition of the alveolar air during the respiratory cycle in muscular exercise. J Physiol 65:389–411

Amuchou SS, Singhal N (2006) Dose end-tidal carbon dioxide measurement correlate with arterial carbon dioxide in extremely low birth weight infants in the first week of life? Indian Pediatr 43:20–25

Annabi EH, Barker SJ (2009) Severe methemoglobinemia detected by pulse oximetry. Anesth Analg 108(3):898–899

Anonymous (2006) American Heart Association (AHA) guidelines for cardiopulmonary resuscitation (CPR) and emergency cardiovascular care (ECC) of pediatric and neonatal patients: pediatric advanced life support. Pediatrics 117:e1005–e1028

Arnold JH (2001) Measurement of the alveolar deadspace: are we there yet? Crit Care Med 29:1287–1288

Arnold JH, Thompson JE, Benjamin PK (1993) Respiratory deadspace measurements in neonates during extracorporeal membrane oxygenation. Crit Care Med 21:1895–1900

Arnold JH, Bower LK, Thompson JE (1995) Respiratory deadspace measurements in neonates with congenital diaphragmatic hernia. Crit Care Med 23:371–375

Barker SJ, Curry J, Redford D, Morgan S (2006) Measurement of carboxyhemoglobin and methemoglobin by pulse oximetry: a human volunteer study. Anesthesiol 105(5):892–897

Bates JH, Schmalisch G, Filbrun D, Stocks J (2000) Tidal breath analysis for infant pulmonary function testing. ERS/ATS Task Force on Standards for Infant Respiratory Function Testing. European Respiratory Society/American Thoracic Society. Eur Respir J 16:1180–1192

Beebe SA, Heery LB, Magarian S, Culberson J (1994) Pulse oximetry at moderate altitude: healthy children and children with upper respiratory infection. Clin Pediatr (Phila) 33(6):329–332

Bendjelid K, Schutz N, Stotz M et al (2005) Transcutaneous P_{CO2} monitoring in critically ill adults: clinical evaluation of a new sensor. Crit Care Med 33:2203–2206

Berg RA, Henry C, Otto CW, Sanders AB, Kern KB, Hilwig RW, Ewy GA (1996) Initial end-tidal CO2 is markedly elevated during cardiopulmonary resuscitation after asphyxial cardiac arrest. Pediatr Emerg Care 12:245–248

Berkenbosch JW, Tobias JD (2002) Transcutaneous carbon dioxide monitoring during high-frequency oscillatory ventilation in infants and children. Crit Care Med 30:1024–1027

Berkenbosch JW, Lam J, Burd RS, Tobias JD (2001) Noninvasive monitoring of carbon dioxide during mechanical ventilation in older children: end-tidal versus transcutaneous techniques. Anesth Analg 92:1427–1431

Bernstein G, Knodel E, Heldt GP (1995) Airway leak size in neonates and autocycling of three flow-triggered ventilators. Crit Care Med 23:1739–1744

Bhat YR, Abhishek N (2008) Mainstream end-tidal carbon dioxide monitoring in ventilated neonates. Singapore Med J 49:199–203

Bhavani-Shankar K, Moseley H, Kumar AY, Delph Y (1992) Capnometry and anaesthesia. Can J Anaesth 39:617–632

Bhavani-Shankar K, Steinbrook RA, Mushlin PS et al (1998) Transcutaneous CO_2 monitoring during laparoscopic cholecystectomy during pregnancy. Can J Anaesth 45:164–169

Birmingham PK, Cheney FW, Ward RJ (1986) Esophageal intubation: a review of detection techniques. Anesth Analg 65:886–891

Blanch L, Romero PV, Lucangelo U (2006) Volumetric capnography in the mechanically ventilated patient. Minerva Anestesiol 72:577–585

Bohnhorst B, Poets CF (1998) Major reduction in alarm frequency with a new pulse oximeter. Intensive Care Med 24:277–278

Bohnhorst B, Peter CS, Poets CF (2000) Pulse oximeters' reliability in detecting hypoxemia and bradycardia: comparison between a conventional and two new generation oximeters. Crit Care Med 28(5):1565–1568

Bourdelles GL, Estagnasie P, Lenoir F, Brun P, Dreyfuss D (1998) Use of a pulse oximeter in an adult emergency department: impact on the number of arterial blood gas analyses ordered. Chest 113:1042–1047

Bowton DL, Scuderi PE, Harris L, Haponik EF (1991) Pulse oximetry monitoring outside the intensive care unit: progress or problem'. Ann Intern Med 115(5):450–454

Boxer RA, Gottesfeld I, Singh S, Lacorte MA, Parnell VA Jr, Walker P (1987) Noninvasive pulse oximetry in children with cyanotic congenital heart disease. Crit Care Med 15(11):1062–1064

Brashers VL (2002) Structure and function of the pulmonary system. In: McCamce KL, Heuther SE (eds) Pathophysiology: the biologic basis for disease in adults & children, 4th edn. Mosby, St Louis, p 1099

Bratzke E, Downs JB, Smith RA (1998) Intermittent CPAP: a new mode of ventilation during general anesthesia. Anesthesiology 89:334–340

Breen PH, Mazumdar B, Skinner SC (1996a) Comparison of end-tidal PCO2 and average alveolar expired PCO2 during positive end-expiratory pressure. Anesth Analg 82:368–373

Breen PH, Serina ER, Barker SJ (1996b) Measurement of pulmonary CO2 elimination must exclude inspired CO2 measured at the capnometer sampling site. J Clin Monit 12:231–236

Carter BG, Wiwczaruk D, Hochmann M, Osborne A, Henning R (2001) Performance of transcutaneous PCO2 and pulse oximetry monitors in newborns and infants after cardiac surgery. Anaesth Intensive Care 29:260–265

Cassady G (1983) Transcutaneous monitoring in the newborn infant. J Pediatr 103:837–848

Chambrin MC (2001) Alarms in the intensive care unit: how can the number of false alarms be reduced? Crit Care 5:184–188

Cheifetz IM, Myers TR (2007) Respiratory therapies in the critical care setting. Should every mechanically ventilated patient be monitored with capnography from intubation to extubation? Respir Care 52:423–438

Choe H, Tashiro C, Fakumitsu K et al (1989) Comparison of recorded values from six pulse oximeters. Crit Care Med 17(7):678–681

Chow LC, Wright KW, Sola A, CSMC Oxygen Administration Study Group (2003) Can changes in clinical practice decrease the incidence of severe retinopathy of prematurity in very low birth weight infants? Pediatrics 111(2):339–345

Chu J, Clements JA, Cotton EK, Klaus MH, Sweet AY, Tooley WH, Bradley BL, Brandorff LC (1967) Neonatal pulmonary ischemia. I. Clinical and physiological studies. Pediatrics 40:709l–782l

Clark RH, Gerstmann DR, Null DM Jr, deLemos RA (1992) Prospective randomized comparison of high-frequency oscillatory and conventional ventilation in respiratory distress syndrome. Pediatrics 89:5–12

Claure N, D'Ugard C, Bancalari E (2003) Elimination of ventilator dead space during synchronized ventilation in premature infants. J Pediatr 143:315–320

Clucas L, Doyle LW, Dawson J, Donath S, Davis PG (2007) Compliance with alarm limits for pulse oximetry in very preterm infants. Pediatrics 119:1056–1060

Cook CD, Sutherland JM, Segal S, Cherry RB, Mead J, McIlroy MB, Smith CA (1957) Studies of respiratory physiology in the newborn infant III. Measurements of mechanics of respiration. J Clin Invest 36:440–448

Cousineaua J, Anctilb S, Carcellerb A, Gonthierb M, Delvin EE (2005) Neonate capillary blood gas reference values. Clin Biochem 38(10):905–907

Cox P, Tobias JD (2007) Noninvasive monitoring of $PaCO_2$ during one-lung ventilation and minimal access surgery in adults: end-tidal versus transcutaneous techniques. J Minim Access Surg 3:8–13

Criner GJ, Brennan K, Travaline JM, Kreimer D (1999) Efficacy and compliance with noninvasive positive pressure ventilation in patients with chronic respiratory failure. Chest 116:667–675

Dani C, Bertini G, Pezzati M, Cecchi A, Caviglioli C, Rubaltelli FF (2004) Early extubation and nasal continuous positive airway pressure after surfactant treatment for respiratory distress syndrome among preterm infants <30 weeks' gestation. Pediatrics 113:e560–e563

Davies MW, Woodgate PG (2002) Tracheal gas insufflation for the prevention of morbidity and mortality in mechanically ventilated newborn infants. Cochrane Database Syst Rev (2):CD002973

Davis PG, Morley CJ, Owen LS (2009) Non-invasive respiratory support of preterm neonates with respiratory distress: continuous positive airway pressure and nasal intermittent positive pressure ventilation. Semin Fetal Neonatal Med 14:14–20

Deckardt R, Steward DJ (1984) Noninvasive arterial hemoglobin oxygen saturation versus transcutaneous oxygen tension monitoring in the preterm infant. Crit Care Med 12(11):935–939

Drummond KJ, Fearnsdale MR, Chee A (1997) Transcutaneous carbon dioxide measurement after craniotomy in spontaneously breathing patients. Neurosurgery 41:361–365

Dullenkopf A, Dibernardo S, Berger F et al (2003) Evaluation of a new combined SpO_2/$PtcCO_2$ sensor in anaesthetized paediatric patients. Pediatr Anesth 13:777–784

Durbin CG Jr, Rostow SK (2002) More reliable oximetry reduces the frequency of arterial blood gas analyses and hastens oxygen weaning after cardiac surgery: a prospective, randomized trial of the clinical impact of a new technology. Crit Care Med 30:1735–1740

East TD, Morris AH, Wallace CJ et al (1991) A strategy for development of computerized critical care decision support systems. Int J Clin Monit Comput 92:263–269

Eberhard P, Schafer R (1980) A sensor for noninvasive monitoring of carbon dioxide. Br J Clin Equip 5:224–226

Eberhard P, Mindt W, Kreuzer F (1976) Cutaneous oxygen monitoring in the newborn. Paediatrician 5:335–369

Elliott M, Tate R, Page K (2006) Do clinicians know how to use pulse oximetry? A literature review and clinical implications. Aust Crit Care 19(4):139–144

Emergency Care Research Institute (2003) Next-generation pulse oximetry. Health Devices 32:49–103

Englander R, Agostinucci W, Zalneraiti E, Carraccio CL (2006) Teaching residents systems-based practice through a hospital cost-reduction program: a "win-win" situation. Teach Learn Med 18(2):150–152

Faconi S (1988) Reliability of pulse oximetry in hypoxic infants. J Pediatr 112(3):424–427

Fanconi S, Burger R, Maurer H et al (1991) Transcutaneous carbon dioxide pressure for monitoring patients with severe croup. J Pediatr 119:673–674

Fischer HS, Roehr CC, Proquitte H, Wauer RR, Schmalisch G (2008) Assessment of volume and leak measurements during CPAP using a neonatal lung model. Physiol Meas 29:95–107

Fischer HS, Roehr CC, Proquitte H, Hammer H, Wauer RR, Schmalisch G (2009) Is volume and leak monitoring feasible during nasopharyngeal continuous positive airway pressure in neonates? Intensive Care Med 35:1934–1941

Fletcher R, Jonson B, Cumming G, Brew J (1981) The concept of deadspace with special reference to the single breath test for carbon dioxide. Br J Anaesth 53:77–88

Fowler WS (1948) Lung function studies; the respiratory dead space. Am J Physiol 154:405–416

Gallagher SA, Hackett PH (2004) High-altitude illness. Emerg Med Clin North Am 22:329–355

Gamponia MJ, Babaali H, Yugar F, Gilman RH (1998) Reference values for pulse oximetry at high altitude. Arch Dis Child 78:461–465

Ganter M, Zollinger A (2003) Continuous intravascular blood gas monitoring: development, current techniques, and clinical use of a commercial device. Br J Anaesth 91(3):397–407

Geary C, Caskey M, Fonseca R, Malloy M (2008) Decreased incidence of bronchopulmonary dysplasia after early management changes, including surfactant and nasal continuous positive airway pressure treatment at delivery, lowered oxygen saturation goals, and early amino acid administration: a historical cohort study. Pediatrics 121:89–96

Gittermann MK, Fusch C, Gittermann AR, Regazzoni BM, Moessinger AC (1997) Early nasal continuous positive airway pressure treatment reduces the need for intubation in very low birth weight infants. Eur J Pediatr 156:384–388

Giuliano KK, Grant ME (2002) Blood analysis at the point of care: issues in application for use in critically ill patients. AACN Clin Issues 13(2):204–220

Gøthgen IH, Siggaard-Andersen O, Kokholm G (1990) Variations in the hemoglobin-oxygen dissociation curve in 10079 arterial blood samples. Scand J Clin Lab Invest Suppl 203:87–90

Gozal D (1997) Nocturnal ventilatory support in patients with cystic fibrosis: comparison with supplemental oxygen. Eur Respir J 10:1999–2003

Graham KC, Cvach M (2010) Monitor alarm fatigue: standardizing use of physiological monitors and decreasing nuisance alarms. Am J Crit Care 19(1):28–34

Gravenstein JS, Jaffe MB, Paulus DA (2004) Capnography- clinical aspects. Cambridge University Press, Cambridge

Greenhalgh DG, Warden GD (1992) Transcutaneous oxygen and carbon dioxide measurements for determination of skin graft "take". J Burn Care Rehabil 13:334–339

Grenier B, Verchere E, Mesli A, Dubreuil M, Siao D, Vandendriessche M, Cales J, Maurette P (1999) Capnography monitoring during neurosurgery: reliability in relation to various intraoperative positions. Anesth Analg 88:43–48

Griffin J, Terry BE, Burton RK et al (2003) Comparison of end-tidal and transcutaneous measures of carbon dioxide during general anaesthesia in severely obese adults. Br J Anaesth 91:498–501

Grmec S (2002) Comparison of three different methods to confirm tracheal tube placement in emergency intubation. Intensive Care Med 28:701–704

Hackett PH, Roach RC, Hackett PH, Roach RC (2001) High-altitude medicine. In: Auerbach PS (ed) Wilderness medicine. Mosby, Philadelphia, p 5

Hagerty JJ, Kleinman ME, Zurakowski D, Lyons AC, Krauss B (2002) Accuracy of a new low-flow sidestream capnography technology in newborns: a pilot study. J Perinatol 22:219–225

Hannhart B, Haberer JP, Saunier C, Laxenaire MC (1991) Accuracy and precision of fourteen pulse oximeters. Eur Respir J 4:115–119

Hansen JE, Jensen RL, Casaburi R, Crapo RO (1989) Comparison of blood gas analyzer biases in measuring tonometered blood and a fluoroca4rbon containing proficiency-testing material. Am Rev Respir Dis 140:403–409

Hay WWJ, Brock Way JM, Eyzaguirre M (1989) Neonatal pulse oximetry: accuracy and reliability. Pediatrics 83(5):7–17

Hay WW Jr, Rodden DJ, Collins SM, Melara DL, Hale KA, Fashaw LM (2002) Reliability of conventional and new pulse oximetry in neonatal patients. J Perinatol 22(5):360–366

Henke KG, Dempsey JA, Badr MS, Kowitz JM, Skatrud JB (1991) Effect of sleep-induced increases in upper airway resistance on respiratory muscle activity. J Appl Physiol 70:158–168

Herber-Jonat S, von Bismarck P, Freitag-Wolf S, Nikischin W (2008) Limitation of measurements of expiratory tidal volume and expiratory compliance under conditions of endotracheal tube leaks. Pediatr Crit Care Med 9:69–75

Hess D (1998) Selection of monitoring equipment. In: Tobin MJ (ed) Principles and practices of intensive care monitoring. McGraw-Hill, New York, pp 1469–1480

Hess DR (2005) Noninvasive positive-pressure ventilation and ventilator-associated pneumonia. Respir Care 50:924–929

Holland R, Webb RK, Runciman WB (1993) The Australian Incident Monitoring Study. Oesophageal intubation: an analysis of 2000 incident reports. Anaesth Intensive Care 21:608–610

Holmgren D, Sixt R (1992) Transcutaneous and arterial blood gas monitoring during acute asthmatic symptoms in older children. Pediatr Pulmonol 14:80–84

Hsia CC (1998) Respiratory function of hemoglobin. N Engl J Med 338:239–247

Hubble CL, Gentile MA, Tripp DS, Craig DM, Meliones JN, Cheifetz IM (2000) Deadspace to tidal volume ratio predicts successful extubation in infants and children. Crit Care Med 28:2034–2040

Hückstädt T, Foitzik B, Wauer RR, Schmalisch G (2003) Comparison of two different CPAP systems by tidal breathing parameters. Intensive Care Med 29:1134–1140

Ibrahim ED, McLellan SA, Walsh TS et al (2005) Red blood cell 2,3-diphosphoglycerate concentration and in vivo P50 during early critical illness. Crit Care Med 33:2247–2252

Inman SJ, Sibbald WJ, Rutledge FS, Speechley M, Martin CM, Clark BJ (1993) Does implementing pulse oximetry in a critical care unit result in substantial arterial blood gas savings? Chest 104(2):542–546

Ip Yam PC, Innes PA, Jackson M et al (1994) Variation in the arterial to end-tidal P_{CO2} difference during one-lung thoracic anaesthesia. Br J Anaesth 72:21–24

Janseens JP, Howarth-Frey C, Chevrolet JC et al (1998) Transcutaneous PCO2 to monitor noninvasive mechanical ventilation in adults. Chest 113:768–773

Jennis MS, Peabody JL (1987) Pulse oximetry: an alternative method for the assessment of oxygenation in newborn infants. Pediatrics 79(4):524–528

Johns RL, Lindsay WJ, Shephard RH (1969) A system for monitoring pulmonary ventilation. Biomed Sci Instrum 5:119–121

Kallet RH, Alonso JA, Pittet JF, Matthay MA (2004) Prognostic value of the pulmonary dead-space fraction during the first 6 days of acute respiratory distress syndrome. Respir Care 49:1008–1014

Karlberg P, Cook CD, O'Brien D, Cherry RB, Smith CA (1954) Studies of respiratory physiology in newborn infants II. Observations during and after respiratory distress. Acta Paediatr 43:387–411

Keenan SP, Sinuff T, Cook DJ, Hill NS (2004) Does noninvasive positive pressure ventilation improve outcome in acute hypoxemic respiratory failure? A systematic review. Crit Care Med 32:2516–2523

Kellerman AL, Coler CA, Joseph S, Hackman BB (1991) Impact of portable pulse oximetry on arterial blood gas test ordering in an urban emergency department. Ann Emerg Med 20:130–134

Kendall J, Reeves B, Clancy M (1998) Point of care testing: randomised controlled trial of clinical outcome. BMJ 316(7137):1052–1057

King T, Simon RH (1987) Pulse oximetry for tapering supplemental oxygen in hospitalized patients. Chest 92:713–716

Knapp S, Kofler J, Stoiser B, Thalhammer F, Burgmann H, Posch M, Hofbauer R, Stanzel M, Frass M (1999) The assessment of four different methods to verify tracheal tube placement in the critical care setting. Anesth Analg 88:766–770

Kondo T, Matsumoto I, Lanteri CJ, Sly PD (1997) Respiratory mechanics during mechanical ventilation: a model study on the effects of leak around a tracheal tube. Pediatr Pulmonol 24:423–428

Kopka A, Wallace E, Reilly G, Binning A (2007) Observational study of perioperative Ptc_{CO2} and Sp_{O2} in non-ventilated patients receiving epidural infusions or patient-controlled analgesia using a single earlobe monitor (TOSCA). Br J Anaesth 99:567–571

Kost GJ (1998) Point-of-care testing in intensive care. In: Tobin MJ (ed) Principles and practices of intensive care monitoring. McGraw-Hill, New York, pp 1267–1296

Kugelman A, Zeiger-Aginsky D, Bader D, Shoris I, Riskin A (2008) A novel method of distal end-tidal CO2 capnography in intubated infants: comparison with arterial CO2 and with proximal mainstream end-tidal CO2. Pediatrics 122:e1219–e1224

Lang CJG (1998) Apnea testing guided by continuous transcutaneous monitoring of partial pressure of carbon dioxide. Crit Care Med 26:868–872

Lawless S (1994) Crying wolf: false alarms in a pediatric intensive care unit. Crit Care Med 22:981–985

Lum L, Saville A, Venkataraman ST (1998) Accuracy of physiologic deadspace measurement in intubated pediatric patients using a metabolic monitor: comparison with the Douglas bag method. Crit Care Med 26: 760–764

Macnab AJ, Grant G, Stevens K, Gagnon F, Noble R, Sun C (2003) Cost: benefit of point-of-care blood gas analysis vs. laboratory measurement during stabilization prior to transport. Prehosp Disaster Med 18(1):24–28

Mahmoud RA, Fischer HS, Proquitte H, Shalaby HM, Schmalisch G (2009) Relationship between endotracheal tube leakage and under-reading of tidal volume in neonatal ventilators. Acta Paediatr 98:1116–1122

Mahmoud RA, Roehr CC, Schmalisch G (2011) Current methods of non-invasive ventilatory support for neonates. Paediatr Respir Rev 12:196–205

Mahutte CK (1998) Continuous intravascular and on-demand extravascular arterial blood gas monitoring. In: Tobin MJ (ed) Principles and practices of intensive care monitoring. McGraw-Hill, New York, pp 243–259

McBride DS, Johnson JO, Tobias JD (2002) Noninvasive carbon dioxide monitoring during neurosurgical procedures in adults: end-tidal versus transcutaneous techniques. South Med J 95:870–874

McBride ME, Berkenbosch JW, Tobias JD (2004) Transcutaneous carbon dioxide monitoring during diabetic ketoacidosis in children and adolescents. Paediatr Anaesth 14:167–171

McCormack JG, Kelly KP, Wedgwood J, Lyon R (2008) The effects of different analgesic regimens on transcutaneous CO_2 after major surgery. Anaesthesia 63:814–821

McDonald MJ, Montgomery VL, Cerrito P, Parrish CJ, Boland KA, Sullivan JE (2002) Comparison of

end-tidal CO2 and PaCO2 in children receiving mechanical ventilation. Pediatr Crit Care Med 3:244–249

McSwain SD, Hamel DS, Smith PB, Gentile MA, Srinivasan S, Meliones JN, Cheifetz IM (2010) End-tidal and arterial carbon dioxide measurements correlate across all levels of physiologic dead space. Respir Care 55:288–293

Miller TL, Blackson TJ, Shaffer TH, Touch SM (2004) Tracheal gas insufflation-augmented continuous positive airway pressure in a spontaneously breathing model of neonatal respiratory distress. Pediatr Pulmonol 38:386–395

Moller JT, Johannessen NW, Espersen K (1993a) Randomized evaluation of pulse oximetry in 20,802 patients: II. Perioperative events and postoperative complications. Anesthesiology 78(3):445–453

Moller JT, Svennild I, Johannessen NW, Jensen PF, Espersen K, Gravenstein JS et al (1993b) Perioperative monitoring with pulse oximetry and late postoperative cognitive dysfunction. Br J Anaesth 7I(3):340–347

Morley CJ, Davis PG, Doyle LW, Brion LP, Hascoet JM, Carlin JB (2008) Nasal CPAP or intubation at birth for very preterm infants. N Engl J Med 358:700–708

Morris RW, Nairn M, Torda TA (1989) A comparison of fifteen pulse oximeters. Part I: a clinical comparison; part II: a test of performance under conditions of poor perfusion. Anaesth Intensive Care 17(2):62–73

Mosteller F, Institute of Medicine (1985) Assessing medical technologies. National Academy Press, Washington, pp vii–ix

Napolitano LM (1999) Capnography in critical care: accurate assessment of ARDS therapy? Crit Care Med 27:862–863

Nassabeh-Montazami S, Abubakar KM, Keszler M (2009) The impact of instrumental dead-space in volume-targeted ventilation of the extremely low birth weight (ELBW) infant. Pediatr Pulmonol 44:128–133

Nelson NM, Prod'hom LS, Cherry RB, Lipsitz PJ, Smith CA (1962) Pulmonary function in the newborn infant: 1. Methods: ventilation and gaseous metabolism. Pediatrics 30:963–974

Neufeld GR, Schwardt JD, Gobran SR, Baumgardner JE, Schreiner MS, Aukburg SJ, Scherer PW (1992) Modelling steady state pulmonary elimination of He, SF6 and CO2: effect of morphometry. Respir Physiol 88:257–275

Nickerson BG, Sarkisian C, Tremper KK (1988) Bias and precision of pulse oximeters and arterial oximeters. Chest 93:515–517

Niehoff J, Delbuericio C, LaMorte W et al (1988) Efficacy of pulse oximetry and capnometry I postoperative ventilatory weaning. Crit Care Med 16:701–705

Niermeyer S, Shaffer EM, Thilo E, Corbin C, Grindlay M (1993) Arterial oxygenation and pulmonary arterial pressure in healthy neonates and infants at high altitude. J Pediatr 123:767–772

Niermeyer S, Yang P, Shanmina, Drolkar, Zhuang J, Moore LG (1995) Arterial oxygen saturation in Tibetan and Han infants born at Lhasa, Tibet. N Engl J Med 333:1248–1252

Nosovitch MA, Johnson JO, Tobias JD (2002) Noninvasive intraoperative monitoring of carbon dioxide in children: end-tidal versus transcutaneous techniques. Paediatr Anaesth 12:48–52

Nuckton TJ, Alonso JA, Kallet RH, Daniel BM, Pittet JF, Eisner MD, Matthay MA (2002) Pulmonary dead-space fraction as a risk factor for death in the acute respiratory distress syndrome. N Engl J Med 346:1281–1286

O'Connell DA, Seikaly H, Harris JR (2008) Central laboratory versus point of care testing in intraoperative monitoring of parathyroid hormone levels: cost comparison. J Otolaryngol Head Neck Surg 37(1):91–97

Ochroch EA, Russell MW, Hanson WC 3rd, Devine GA, Cucchiara AJ, Weiner MG, Schwartz SJ (2006) The impact of continuous pulse oximetry monitoring on intensive care unit admissions from a postsurgical care floor. Anesth Analg 102(3):868–875

Oshibuchi M, Cho S, Hara T et al (2003) A comparative evaluation of transcutaneous and end-tidal measurements of CO_2 in thoracic anesthesia. Anesth Analg 97:776–779

Paiva R, Krivec U, Aubertin G et al (2009) Carbon dioxide monitoring during long-term non-invasive respiratory support in children. Intensive Care Med 35:1068–1074

Pascucci RC, Schena JA, Thompson JE (1989) Comparison of a sidestream and mainstream capnometer in infants. Crit Care Med 17:560–562

Pedersen T, Møller AM, Hovhannisyan K (2009) Pulse oximetry for perioperative monitoring. Cochrane Database Syst Rev (4):CD002013

Peter JA, Hodgkin JE, Collier CR (1991) Blood gas analysis and acid–base physiology. In: Burton GG, Hodgkin JE, Ward JJ (eds) Respiratory care: a guide to clinical practice, 3rd edn. JP Lippincott, New York, pp 181–210

Petterson MT, Begnoche VL, Graybeal JM (2007) The effect of motion on pulse oximetry and its clinical significance. Anesth Analg 105(6 suppl):S78–S84

Phan CQ, Tremper KK, Lee SE, Barker SJ (1987) Noninvasive monitoring of carbon dioxide: a comparison of the partial pressure of transcutaneous and end-tidal carbon dioxide with the partial pressure of arterial carbon dioxide. J Clin Monit 3:149–154

Pillow JJ, Hillman N, Moss TJ, Polglase G, Bold G, Beaumont C, Ikegami M, Jobe AH (2007) Bubble continuous positive airway pressure enhances lung volume and gas exchange in preterm lambs. Am J Respir Crit Care Med 176:63–69

Popovich DM, Richiuso N, Danek G (2004) Pediatric health care providers' knowledge of pulse oximetry. Pediatr Nurs 30(1):14–20

Praud JP, Carofilis A, Bridey F et al (1989) Accuracy of two-wavelength pulse oximetry in neonates and infants. Pediatr Pulmonol 6(3):180–182

Proquitte H, Krause S, Rudiger M, Wauer RR, Schmalisch G (2004) Current limitations of volumetric capnography in surfactant-depleted small lungs. Pediatr Crit Care Med 5:75–80

Rabe H, Alvarez RF, Whitfield T, Lawson F, Jungmann H (2010) Spectroscopic noninvasive measurement of hemoglobin compared with capillary and venous values in neonates. Neonatology 98(1):1–5, Epub 2009 Nov 25

Ramanathan R, Durand M, Larrazabal C (1987) Pulse oximetry in very low birth weight infants with acute and chronic lung disease. Pediatrics 79(4):612–617

Rauch DA, Ewig J, Benoit P et al (1999) Exploring intermittent transcutaneous CO_2 monitoring. Crit Care Med 27:2358–2360

Ream RS, Schreiner MS, Neff JD, McRae KM, Jawad AF, Scherer PW, Neufeld GR (1995) Volumetric capnography in children. Influence of growth on the alveolar plateau slope. Anesthesiology 82:64–73

Regnis JA, Piper AJ, Henke KG, Parker S, Bye PT, Sullivan CE (1994) Benefits of nocturnal nasal CPAP in patients with cystic fibrosis. Chest 106: 1717–1724

Reid CW, Martineau RJ, Miller DR et al (1992) A comparison of transcutaneous, end-tidal and arterial measurements of carbon dioxide during general anesthesia. Can J Anaesth 39:31–36

Riou Y, Leclerc F, Neve V, Dupuy L, Noizet O, Leteurtre S, Sadik A (2004) Reproducibility of the respiratory dead space measurements in mechanically ventilated children using the CO2SMO monitor. Intensive Care Med 30: 1461–1467

Roizen MF, Schreider B, Austin W, Carter C, Polk S (1993) Pulse oximetry, capnography, and blood gas measurements: reducing cost and improving the quality of care with technology. J Clin Monit 9(4):237–240

Rozycki HJ, Sysyn GD, Marshall MK, Malloy R, Wiswell TE (1998) Mainstream end-tidal carbon dioxide monitoring in the neonatal intensive care unit. Pediatrics 101:648–653

Russell GB, Graybeal JM (1994) Reliability of the arterial to end-tidal carbon dioxide gradient in mechanically ventilated patients with multisystem trauma. J Trauma 36:317–322

Russell GB, Graybeal JM, Strout JC (1990) Stability of arterial to end-tidal carbon dioxide gradients during postoperative cardiorespiratory support. Can J Anaesth 37:560–566

Sahni R, Gupta A, Ohira-Kist K, Rosen TS (2003) Motion resistant pulse oximetry in neonates. Arch Dis Child Fetal Neonatal Ed 88(6):F505–F508

Salyer JW (2003) Neonatal and pediatric pulse oximetry. Respir Care 48(4):386–396

Salyer JW, Chatburn RL, Dolcini DM (1989) Measured versus calculated oxygen saturation in a population of pediatric intensive care patients. Respir Care 34:342–348

Sanders AB, Kern KB, Otto CW, Milander MM, Ewy GA (1989) End-tidal carbon dioxide monitoring during cardiopulmonary resuscitation. A prognostic indicator for survival. JAMA 262:1347–1351

Schettino GP, Chatmongkolchart S, Hess DR, Kacmarek RM (2003) Position of exhalation port and mask design affect CO2 rebreathing during noninvasive positive pressure ventilation. Crit Care Med 31:2178–2182

Schmalisch G (2004) Time and volumetric capnography in the neonate. In: Gravenstein JS, Jaffe MB, Paulus DA (eds) Capnography, clinical aspects. Cambridge University Press, Cambridge, pp 81–100

Schmalisch G, Proquitte H, Roehr CC, Wauer RR (2006) The effect of changing ventilator settings on indices of ventilation inhomogeneity in small ventilated lungs. BMC Pulm Med 6:20

Schmalisch G, Fischer H, Roehr CC, Proquitte H (2009) Comparison of different techniques to measure air leaks during CPAP treatment in neonates. Med Eng Phys 31:124–130

Schmalisch G, Al-Gaaf S, Proquitte H, Roehr CC (2012) Effect of endotracheal tube leak on capnographic measurements in a ventilated neonatal lung model. Physiol Meas 33:1–11

Schwardt JD, Gobran SR, Neufeld GR, Aukburg SJ, Scherer PW (1991) Sensitivity of CO2 washout to changes in acinar structure in a single-path model of lung airways. Ann Biomed Eng 19:679–697

Scuderi PE, MacGreggor DA, Bowton DL et al (1993) Performance characteristics and interanalyzer variability for PO2 measurement using tonometered human blood. Am Rev Respir Dis 147:1354–1359

Severinghaus JW (1960) Methods of measurement of blood and gas carbon dioxide during anesthesia. Anesthesiology 21:711–726

Severinghaus JW (1982) Transcutaneous blood gas analysis. Respir Care 27:152–159

Severinghaus JW (1993) History and recent developments in pulse oximetry. Scand J Clin Invest 53(Suppl 214):105–111

Severinghaus JW, Bradley AF Jr (1958) Electrodes for blood PO2 and PCO2 determinations. J Appl Physiol 13:515–520

Severinghaus JW, Naifeh KH, Koh SO (1989) Errors in 14 pulse oximeters during profound hypoxemia. J Clin Monit 5:72–81

Shapiro RS, Kacmarek RM (1998) Monitoring of the mechanically ventilated patient. In: Marini JJ, Slutsky AS (eds) Physiological basis of ventilatory support. Marcel Dekker, Inc, Basel, pp 709–782

Siebig S, Kuhls S, Imhoff M, Gather U, Schölmerich J, Wrede CE (2010) Intensive care unit alarms–how many do we need? Crit Care Med 38(2):451–456

Sivan Y, Eldadah MK, Cheah TE et al (1992) Estimation of arterial carbon dioxide by end-tidal and transcutaneous P_{CO2} measurements in ventilated children. Pediatr Pulmonol 12:153–157

Skimming JW, Banner MJ, Spalding HK, Jaeger MJ, Burchfield DJ, Davenport PW (2001) Nitric oxide inhalation increases alveolar gas exchange by decreasing deadspace volume. Crit Care Med 29: 1195–1200

Sola A, Salden YP, Favareto V (2008) Clinical practices in neonatal oxygenation: where have we failed? What can we do? J Perinatol 28:S28–S34

Solimano AJ, Smyth JA, Mann TK, Albersheim SG, Lockitch G (1986) Pulse oximetry advantages in infants with bronchopulmonary dysplasia. Pediatrics 78(5):844–849

Southall DP, Bignall S, Stebbens VA et al (1987) Pulse oximetry and transcutaneous arterial oxygen measurements in neonatal and paediatric intensive care. Arch Dis Child 62:882–888

Stapleton FB, Hendricks J, Hagan P, DelBeccaro M (2009) Modifying the Toyota Production System for continuous performance improvement in an academic children's hospital. Pediatr Clin North Am 56(4):799–813

Storre JH, Steurer B, Kabitz HJ et al (2007) Transcutaneous PCO2 monitoring during initiation of non-invasive ventilation. Chest 132:1810–1816

Stow RW, Randall BF (1954) Electrochemical measurement of the PCO_2 of blood. Am J Physiol 179:678–681

Subhi R, Smith K, Duke T (2009) When should oxygen be given to children at high altitude? A systematic review to define altitude-specific hypoxaemia. Arch Dis Child 94(1):6–10

Sum-Ping ST, Mehta MP, Anderton JM (1989) A comparative study of methods of detection of esophageal intubation. Anesth Analg 69:627–632

Taenzer AH, Pyke JB, McGrath SP, Blike GT (2010) Impact of pulse oximetry surveillance on rescue events and intensive care unit transfers: a before-and-after concurrence study. Anesthesiology 112(2):282–287

Tang Y, Turner MJ, Baker AB (2005) Effects of lung time constant, gas analyser delay and rise time on measurements of respiratory dead-space. Physiol Meas 26:1103–1114

Taskar V, John J, Larsson A, Wetterberg T, Jonson B (1995) Dynamics of carbon dioxide elimination following ventilator resetting. Chest 108:196–202

Tatevossian RG, Wo CCJ, Velmajos GC et al (2000) Transcutaneous oxygen and CO_2 as early warning of tissue hypoxia and hemodynamic shock in critically ill emergency patients. Crit Care Med 28:2248–2253

Taylor MB, Whitman JG (1988) The accuracy of pulse oximeters: a comparative clinical evaluation of five pulse oximeters. Anesthesia 43:229–232

Teoh L, Epstein A, Williamson B, Morton J, Papadopoulos J, Teng A (2003) Medical staff's knowledge of pulse oximetry: a prospective survey conducted in a tertiary children's hospital. J Paediatr Child Health 39:618–622

Thamrin C, Latzin P, Sauteur L, Riedel T, Hall GL, Frey U (2007) Deadspace estimation from CO2 versus molar mass measurements in infants. Pediatr Pulmonol 42:920–927

Thilo EH, Park-Moore B, Berman ER, Carson BS (1991) Oxygen saturation by pulse oximetry in healthy infants at an altitude of 1610 m (5280 ft). Am J Dis Child 145:1137–1140

Thomas FO, Hoffman TL, Handrahan DL, Crapo RO, Snow G (2009) The measure of treatment agreement between portable and laboratory blood gas measurements in guiding protocol-driven ventilator management. J Trauma 67(2):303–313

Thompson D, Wolf G, Spear S (2003) Driving improvement in patient care: lessons from Toyota. J Nurs Adm 33(11):585–595

Tingay DG, Stewart MJ, Morley CJ (2005) Monitoring of end tidal carbon dioxide and transcutaneous carbon dioxide during neonatal transport. Arch Dis Child Fetal Neonatal Ed 90:F523–F526

Tinmouth A, Fergusson D, Yee IC, Hébert PC, ABLE Investigators; Canadian Critical Care Trials Group (2006) Clinical consequences of red cell storage in the critically ill. Transfusion 46(11):2014–2027

Tirosh E, Bilker A, Bader D, Cohen A (2001) Capnography in spontaneously breathing preterm and term infants. Clin Physiol 21:150–154

Tobias JD (2001) Transcutaneous carbon dioxide measurement during apnea testing in pediatric patients. J Intensive Care Med 16:76–78

Tobias JD (2003) Noninvasive carbon dioxide monitoring during one-lung ventilation: end-tidal versus transcutaneous techniques. J Cardiothorac Vasc Anesth 17: 306–308

Tobias JD (2009) Transcutaneous carbon dioxide monitoring in infants and children. Pediatr Anesth 19:434–444

Tobias JD, Meyer DJ (1997) Noninvasive monitoring of carbon dioxide during respiratory failure in toddlers and infants: end-tidal versus transcutaneous carbon dioxide. Anesth Analg 85:55–58

Tobias JD, Wilson WR Jr, Meyer DJ (1999) Transcutaneous monitoring of carbon dioxide tension after cardiothoracic surgery in infants and children. Anesth Analg 88:531–534

Tobias JD, Russo P, Russo J (2006) An evaluation of acid–base changes following aortic cross-clamping using transcutaneous carbon dioxide monitoring. Pediatr Cardiol 27:585–588

Torres A Jr, Skender KM, Wohrley JD et al (2004) Pulse oximetry in children with congenital heart disease: effects of cardiopulmonary bypass and cyanosis. J Intensive Care Med 19:229–234

Tremper KK, Shoemaker WC, Shippy CR, Nolan LS (1981) Transcutaneous pCO_2 monitoring on adult patients in the ICU and the operating room. Crit Care Med 9:752–755

Tschupp A, Fanconi S (2003) A combined ear sensor for pulse oximetry and carbon dioxide tension monitoring: accuracy in critically ill children. Anesth Analg 96:82–84

Van de Louw A, Cracco C, Cerf C et al (2001) Accuracy of pulse oximetry in the intensive care unit. Intensive Care Med 27:1606–1613

Wagner AE, Gaynor JS, Dunlop CI, Allen SL, Demme WC (1998) Monitoring adequacy of ventilation by capnometry during thoracotomy in dogs. J Am Vet Med Assoc 212:377–379

Wahba RW, Tessler MJ (1996) Misleading end-tidal CO2 tensions. Can J Anaesth 43:862–866

Walsh MC, Noble LM, Carlo WA, Martin RJ (1987) Relationship of pulse oximetry to arterial oxygen tension in infants. Crit Care Med 15:1102

Walsh TS, McArdle F, McLellan SA et al (2004) Does the storage time of transfused red blood cells influence regional or global indexes of tissue oxygenation in anemic critically ill patients? Crit Care Med 32(2):364–371

Watcha MF, Connor MT, Hing AV (1989) Pulse oximetry in methemoglobinemia. Am J Dis Child 143(7):845–847

Wennergan G, Engstrom I, Bjure J (1986) Transcutaneous oxygen and carbon dioxide levels and a clinical symptom scale for monitoring the acute asthmatic state in infants and young children. Acta Paediatr Scand 75:465–469

Wenzel U, Rudiger M, Wagner MH, Wauer RR (1999a) Utility of deadspace and capnometry measurements in determination of surfactant efficacy in surfactant-depleted lungs. Crit Care Med 27:946–952

Wenzel U, Wauer RR, Schmalisch G (1999b) Comparison of different methods for dead space measurements in ventilated newborns using CO2-volume plot. Intensive Care Med 25:705–713

Wilkinson AR, Phibbs RH, Heilbron DC, Gregory GA, Versmold HT (1980) In vivo oxygen dissociation curves in transfused and untransfused newborns with cardiopulmonary disease. Am Rev Respir Dis 122(4):629–634

Wong L, Hamilton R, Palayiwa E, Hahn C (1998) A real-time algorithm to improve the response time of a clinical multigas analyser. J Clin Monit Comput 14:441–446

Workie FA, Rais-Bahrami K, Short BL (2005) Clinical use of new-generation pulse oximeters in the neonatal intensive care unit. Am J Perinatol 22(7):357–360

Wouters PF, Gehring H, Meyfroidt G et al (2002a) Accuracy of pulse oximeters: the European multicenter trial. Anaesth Analg 94:S13–S16

Wouters PF, Gehring H, Meyfroit G et al (2002b) Accuracy of pulse oximeters: the European multicenter trial. Anesth Analg 94(1 suppl): S13–S16

Wu CH, Chou HC, Hsieh WS, Chen WK, Huang PY, Tsao PN (2003) Good estimation of arterial carbon dioxide by end-tidal carbon dioxide monitoring in the neonatal intensive care unit. Pediatr Pulmonol 35:292–295

Zaugg M, Lucchinetti E, Zalunardo MP et al (1998) Substantial changes in arterial blood gases during thoracoscopic surgery can be missed by conventional intermittent laboratory blood gas analyses. Anesth Analg 87:647–653