Mechanical Ventilation

8

Educational Goals

- Understand the differences between conventional and high-frequency ventilation.
- Comprehend constant- and variable-flow delivery systems.
- Appreciate the importance of monitoring.

8.1 Conventional Mechanical Ventilation

8.1.1 Classification of Mechanical Ventilators

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8.1.1.1 Introduction

A mechanical ventilator is an automated device that provides all or part of the work of breathing for patients with impaired respiratory or neurologic function. In order to safely apply a mechanical ventilator to a patient for continuous use, four requisites must be met (Table 8.1). First, there must be a way to create a stable attachment of the device to the patient, referred to as the interface. Second, there must be an energy source to drive the device. Third, the size and timing of the inflation must be regulated or controlled. Fourth, there must be a system to adequately monitor the performance of the ventilator and the status of the patient. This should include adjustable alarms to alert the clinician to undesirable and potentially dangerous conditions Chatburn (2003).

8.1.1.2 Mechanical Ventilators

Mechanical ventilators can be broadly classified into two major categories based upon the size of the delivered inflation (Table 8.2). Conventional mechanical ventilators deliver tidal volumes, which are within the normal physiological range.

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Table 8.1 Requisites for mechanical ventilators

1. Stable patient–ventilator interface
2. Energy source
3. Control and regulation of size and timing of inflation
4. Monitoring and alarm system

Table 8.2 Classification of mechanical ventilators

Conventional mechanical ventilator (tidal)
Negative-pressure ventilation
Positive-pressure ventilation
Continuous flow
Pressure limited
Variable flow
Pressure control
Pressure support
Constant flow
Volume targeted
Hybrids
High-frequency ventilation (*nontidal*)
Jet ventilation
Oscillatory ventilation
Flow interruptors or percussive ventilators such as the Bronchotron

This is referred to as tidal ventilation, and it comprises the majority of mechanical ventilatory devices. High-frequency ventilators deliver much smaller tidal volumes. (Bunnell 2006). Actual measurements show the VT during HFOV is often > 2 ml/kg in patients with significant lung disease (Zimová-Herknerová and Plavka 2006). These will be considered in more detail in a subsequent chapter.

Conventional mechanical ventilators may also be subdivided based upon the method by which gas flow is introduced into the airway and lung. A gradient may be established by the application of positive pressure, in which gas is delivered to the patient through a circuit. Conversely, the gradient can be achieved through the creation of negative pressure. The patient is placed inside an incubator or chamber and sealed from the neck down. Pressure within the chamber is cyclically decreased (usually by a vacuum pump), forcing gas to enter the airway. Negative-pressure devices, such as the iron lung, were commonly used during the poliomyelitis epidemic of the 1950s but are seldom utilized today. Thus, the overwhelming majority of mechanical ventilation performed on pediatric populations is provided by conventional positive-pressure ventilators.

Positive-pressure ventilation is usually powered by an electrical or compressed gas source. Electricity may be used to run compressors, which in turn create the driving force for ventilation. Compressed gas may also come from separate sources, such as tanks or wall outlets, allowing the blending of air and oxygen (Chatburn 2003). Because compressed gas is devoid of humidity and is damaging to the respiratory epithelial tissues, a heated source of humidification is added to the ventilator circuit (Schulze 2006).

The control system is used to be sure that the patient receives the desired pattern of respiration. The clinician chooses the pressure (peak inflation pressure, PIP) or volume (tidal volume, V_T) to be delivered, the baseline pressure (positive end-expiratory pressure, PEEP), the mandatory rate of mechanical inflation, how long the breath lasts (inspiratory time, T_i), and how much effort the patient has to exert (assist sensitivity) to trigger the ventilator. If the breath is triggered by the patient, it is referred to as a spontaneous breath; if it is initiated by the ventilator, it is referred to as a mandatory or control breath. Ventilator modes refer to the pattern of how spontaneous and mandatory inflation are delivered to the patient (Chatburn 2003).

Monitoring systems consist of both alarms, which notify clinicians when set parameters have been breached, and data displays, which may be digital or graphic. Alarms may signal disconnection of the patient from the ventilator or the ventilator from its power source. Circuit control alarms may indicate electronic failures

or ventilator settings which may be incompatible with ventilator function. Output alarms may warn of pressure, volume, or flow that exceeds or cannot meet the preset limits. Graphic displays include waveforms (or scalars) for flow, volume, and pressure over time, and numerous pulmonary "loops," such as pressure volume or flow volume. Digital displays exist for multiple parameters, including peak pressure, end-expiratory (or baseline) pressure, inspiratory time, rate, and tidal volume. Many devices are also capable of calculating physiological measurements, such as mean airway pressure and minute ventilation, or pulmonary mechanics measurements, such as dynamic compliance or resistance. Storage of data and displays of trends over time may assist in the interpretation of data and management of the patient (Fig. 8.1).

8.1.1.3 Continuous-Flow Systems

The creation of a device that offered continuous flow in the ventilator circuit enabled the development of neonatal mechanical ventilation. Because the intrinsic respiratory rate of the newborn is high relative to an older child or adult, the baby required a source of fresh gas to breathe between mechanical inflation. This is referred to as bias flow, and the rate is set by the clinician. When the ventilator exhalation valve closes during inspiration, the bias flow is diverted to the patient and the lungs are actively

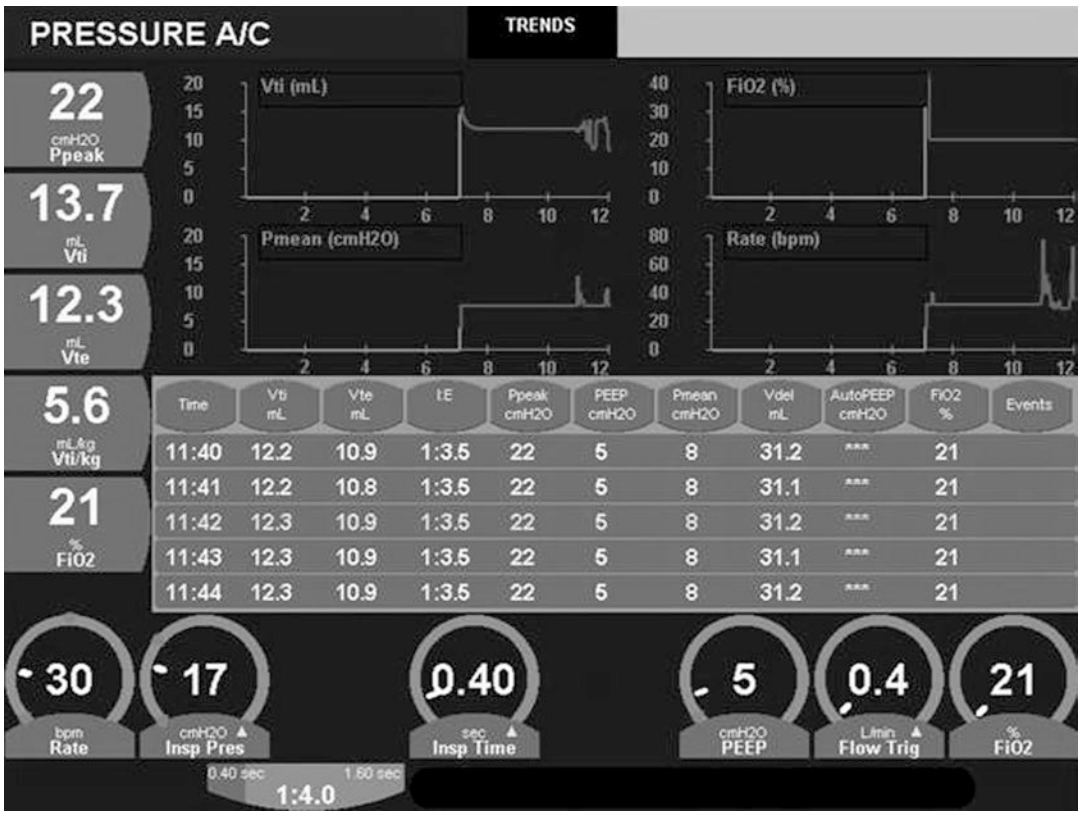


Fig. 8.1 Trend monitoring. Both graphic and analog data are trended here on a minute-to-minute basis

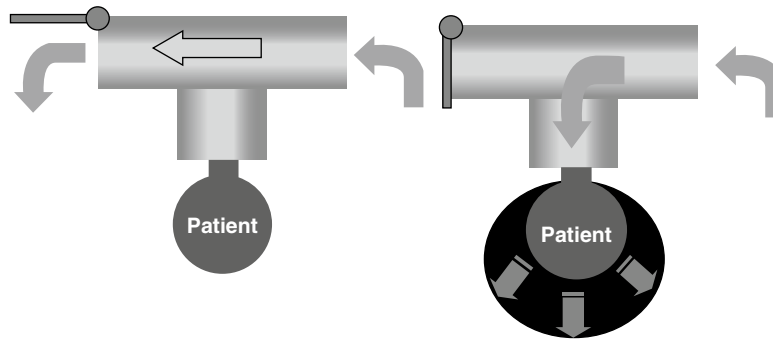


Fig. 8.2 Schematic drawing of continuous-flow, intermittent mandatory ventilation. On the *right side*, expiratory valve closes and gas flow is diverted to the baby, filling the lungs. On the *left side*, inspiration has ended, the exhalation valve has opened, and the lungs are passively deflating

inflated. At the end of inspiration, the valve opens, and the lungs are passively deflated by elastic recoil (Fig. 8.2).

The flow rate (in L/min) should be set high enough to allow the ventilator to reach the PIP in the allotted time. If it is set too low, the patient may develop air hunger and increased work of breathing. If it is set too high, it can create turbulence and ineffective gas exchange, lead to inadvertent PEEP, and result in overdistension of the lungs. Inappropriate circuit flow may result in rheotrauma (Donn and Sinha 2006), a component of ventilator-induced lung injury (Attar and Donn 2002).

Continuous flow is used during pressure-limited ventilation. This was the most common method of providing mechanical ventilation to neonates for more than a quarter of a century. Since the advent of microprocessor-based technology, two new ways to provide gas flow have been introduced into neonatal respiratory care.

8.1.1.4 Variable-Flow Systems

Variable-flow ventilation can be accomplished by actually controlling inspiratory flow through the use of proportional solenoid valves. This creates an inspiratory flow waveform that has a sharply accelerating phase followed by a rapidly decelerating phase (Fig. 8.3). This flow pattern is utilized in pressure-controlled ventilation and

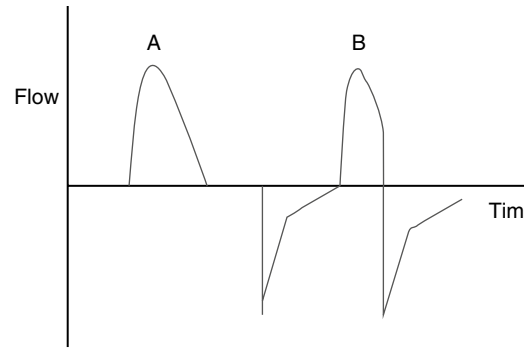


Fig. 8.3 Flow waveform, generated by measuring flow vs time. This is variable-flow ventilation, producing a rapidly accelerating then decelerating flow waveform. (**A**, **B**) On the left, breath is time cycled; on the left it is flow cycled

pressure-support ventilation. It results in rapid pressurization of the ventilator circuit and rapid delivery of gas to the lung, with peak pressure and peak volume delivery occurring early in inspiration. It may be thought of as a "front-end loaded" breath. Intuitively, this should be beneficial in pathophysiological states characterized by homogeneous lung disease where compliance is low and resistance is high (Donn and Boon 2009). Because flow is variable, some devices offer a qualitative way to control it through an adjustable rise-time feature. This alters the slope of the inspiratory pressure waveform. If the rise time is

too flat, air hunger may result. If it is too steep, pressure overshoot may occur. Careful adjustment helps to achieve the appropriate degree of hysteresis in the pressure–volume loop.

A major drawback of both continuous- and variable-flow ventilation is that although pressure is well controlled, volume will vary. At the same pressure, volume will be proportional to compliance. When the lung is stiff, tidal volumes will be low; when compliance improves, tidal volume will increase, and the clinician will need to make the appropriate adjustments.

8.1.1.5 Constant-Flow Systems

Constant-flow ventilation is utilized to provide volume-targeted or volume-controlled ventilation. Inspiratory flow accelerates at the start of inspiration but is held constant at the peak flow rate, creating a square flow waveform. This results in a ramping effect of both volume and pressure delivery, where both peak pressure and maximum volume delivery occur at the end of inspiration (Fig. 8.4). Thus, in contrast to pressure-targeted inflation, volume-targeted inflation are "back-end loaded." They result in a slower inflation of the lung, and they may be more suitable to pathophysiological states characterized by nonhomogeneous lung disease, where rapid inflation would preferentially deliver more gas to the more compliant areas of the lung, creating or contributing to ventilation–perfusion mismatch.

True volume cycling (where inspiration ends after the delivery of a specific volume of gas to the patient) is not yet feasible in the neonate. Because endotracheal tubes are uncuffed, there is almost always some degree of leak around the endotracheal tube. In addition, the ventilator must be able to measure the volume of gas at the proximal airway, not at the machine. Some of the gas leaving the machine will be compressed in the ventilator circuit, especially when the lungs are stiff. This is referred to as compressible volume loss and can be substantial.

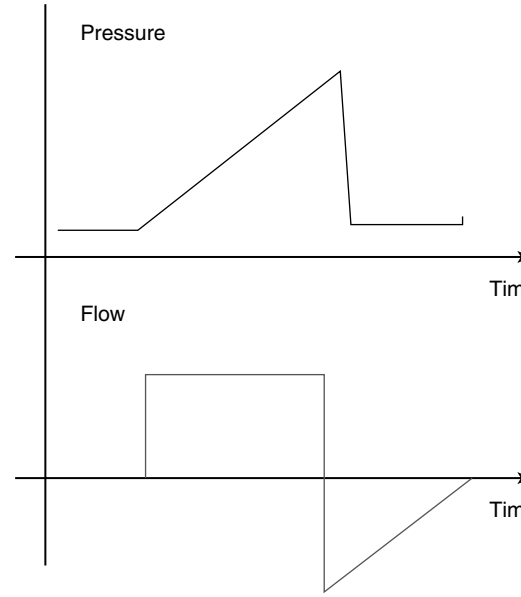


Fig. 8.4 Flow and pressure waveforms for constant-flow (volume-targeted) ventilation. Note the square configuration of the volume flow wave and the gradual increase (ramping) of pressure, creating a "shark's fin" appearance

Constant-flow (volume-targeted) ventilation was briefly popular in the late 1970s, but technological limitations precluded its widespread use, and it was largely abandoned until the development of microprocessor-based ventilation and small, lightweight, low dead-space transducers. Recent clinical evidence suggests that this might be a better way to ventilate preterm infants with respiratory distress syndrome. One feature of constant-flow ventilation is the auto-weaning of pressure. As compliance improves, less pressure is required to deliver the desired tidal volume, and the machine adjusts the peak inspiratory pressure instantaneously. Theoretically, this should be advantageous in avoiding both barotrauma (by weaning pressure) and volutrauma (by limiting volume). Indeed, early meta-analysis of volume vs pressure trials has shown a decreased incidence of air leak, a decreased duration of mechanical

ventilation, and a strong trend toward decreased chronic lung disease. Recent trials are summarized in Table 8.3.

Conclusions

Neonatal mechanical ventilation has advanced dramatically over the past 10 years. The advent of microprocessor-based technology has revolutionized the concepts of ventilating newborns in respiratory failure. Strategies are now formulated based on the underlying pathophysiology and subsequently modified by the response of the patient and the interaction between the patient and the ventilator. Enhanced monitoring has improved patient safety. Long-term outcomes are still under investigation, but early information suggests that the future is indeed bright.

Essentials to Remember

- Conventional ventilation refers to systems that deliver gas volumes that approach physiological tidal volumes.
- High-frequency devices deliver gas volumes less than anatomical dead space.
- Constant-flow ventilation is used to provide volume-targeted ventilation.
- Variable-flow ventilation is used to provide pressure-controlled and pressure-support ventilation.
- Monitoring systems are critical to patient safety and ventilator performance.

8.1.2 Patient–Ventilator Interface

Steven M. Donn

8.1.2.1 Introduction

The interface refers to the way in which the ventilator circuit is connected to the patient. The interface is classified as *invasive* when the ventilator circuit attaches to a tube that is placed directly into the patient's hypopharynx (endotracheal tube) or trachea (tracheostomy tube) for the delivery of positive-pressure ventilation. *Noninvasive* ventilation refers to positive-pressure ventilation that is delivered to the patient by a mask that covers the nose and mouth or by prongs or cannulas that are inserted into the nares. Systems that deliver negative-pressure ventilation may or may not use an interface with the airway (Chatburn 2003). This chapter will focus only upon invasive ventilation interfaces.

Educational Goals

- Understand the concepts of the patient–ventilator interface.
- Differentiate invasive and noninvasive ventilation.
- Comprehend the effects of the patient circuit and endotracheal tube on mechanical ventilation.

8.1.2.2 Effects of the Patient Circuit

The patient circuit consists of tubing which conducts gas flow from the ventilator to the patient (inspiratory limb) and from the patient to the atmosphere (expiratory limb). The inspiratory limb may also pass through a heated source of humidification.

The ventilator circuit has its own characteristics regarding compliance and resistance. This impacts the actual volume of gas which reaches the patient. If the circuit is very flexible and is easily distorted and the compliance is greater than that of the patient, less gas will reach the patient compared to a more rigid circuit. On the other hand, if the circuit is very rigid and the patient's lungs are very stiff, some of the gas within the circuit will be compressed and not reach the patient (Chatburn 2003). This is referred to as compressible volume loss and represents the difference between the volume of gas that leaves the ventilator and the volume of gas that actually reaches the patient airway.

Thus, the pressure, flow, and volume that actually reach the proximal airway are different from the settings that the clinician sets on the ventilator. A portion of this may result from errors in calibration or inaccuracy of measurement, but most relates to circuit compliance and resistance.

Table 8.3 Summary of key trials evaluating volume-targeted ventilation

Study	Randomization	Participants	Intervention	Outcome measures
Cheema and Ahluwalia, (2001)	Randomized double crossover trial	40 infants <34 weeks' gestation requiring mechanical ventilation for RDS Exclusions: Infants requiring muscle relaxants or with lethal congenital anomalies	SIPPV alone vs SIPPV + VG, or SIMV alone vs SIMV + VG	Primary: Peak airway pressure Secondary: Mean airway pressure, expired tidal volume, minute volume, FiO_2, and transcutaneous CO_2 and O_2 pressure
D'Angio et al. (2005)	Randomized controlled trial	213 infants who required mechanical ventilation and were at least 24 weeks' gestational age and weighed 500–1,249 g at birth	PRVC vs TCPL SIMV	Primary: Proportion of infants who were alive and extubated at 14 days of age Secondary: Proportion of infants who were alive and extubated at 28 days of age or 36 weeks post-conceptual age, age at final extubation, mortality, failure of ventilatory mode, incidence of BPD, air leaks, pulmonary hemorrhage, PDA, IVH, PVL, NEC, ROP, home oxygen use, and numerous other parameters
Herrera et al. (2002)	Randomized crossover trial	17 infants between 600 and 1,200 g with respiratory failure Exclusions: Severe congenital anomalies, perinatal asphyxia, sepsis, symptomatic PDA, Grade 3–4 IVH, sedation, and clinical instability as defined by attending neonatologist	First nine infants: SIMV alone vs SIMV + VG (4.5 mL/kg) Next eight infants: SIMV alone vs SIMV + VG (4.5 mL/kg) vs SIMV + VG (3 mL/kg)	Peak inspiratory pressure, mean airway pressure, number of ventilator and patient generated inflation, tidal volume, FiO_2, SPO_2, and $TcPO_2$
Keszler and Abubakar, (2004)	Randomized controlled trial	18 infants <34 weeks' gestation with RDS on mechanical ventilation Exclusions: Patients with congenital anomalies, receiving neuromuscular paralysis or narcotic agents, or with >30 % endotracheal tube leak	Assist control only vs assist control + VG	Primary: Percentage of time that tidal volume and $PaCO_2$ were outside target range (4–6 mL/kg and 35–45 Torr, respectively)

(continued)

Table 8.3 (continued)

Study	Randomization	Participants	Intervention	Outcome measures
Lista et al. (2004)	Randomized controlled trial Stratified by treatment center and gestational age (25–28 weeks and 29–32 weeks)	53 infants between 25 and 32 weeks' gestational age, on mechanical ventilation for severe RDS Exclusions: Lethal anomalies, use of paralytic agents, IVH (Grade 3–4), sepsis, or suspected infection	PSV alone vs PSV + VG (5 mL/kg)	Primary: Concentrations of IL-6, IL-8, and TNF-ÿ in tracheal aspirates on days of life 1, 3, and 7 Secondary: Duration of ventilation, airway pressure, incidence and rate of treatment for PDA, number of surfactant doses, incidence of air leaks, IVH, PVL, ROP, oxygen dependency at 28 days and/or 36 weeks post-conceptual age, and survival
McCallion and Morley (2005)	Meta-analysis of the following four trials: Keszler and Abubakar (2004) Lista et al. (2004) Piowtrowski et al. (1997) Sinha et al. (1997)	178 infants <37 weeks' gestation Exclusions: Lethal congenital anomalies, muscle relaxation, suspected sepsis, lack of arterial access, narcotic use, ETT leaks >30 %, severe IVH, asphyxia, pneumothorax, and meconium aspiration syndrome	Volume-targeted vs pressure-limited ventilation	Primary: Hospital mortality Death or need for supplemental oxygen at either 28 days of life or 36 weeks' post-conceptual age Secondary: Failure of ventilatory mode or need for new use of muscle relaxants, duration of respiratory support, adverse blood gas measurements, PDA, air leaks, growth, IVH, PVL, neurodevelopmental outcome, need for supplemental oxygen at either 28 days of life or 36 weeks' post-conceptual age among survivors, and impact of mode of volume-targeted ventilation
Piowtrowski et al. (1997)	Randomized controlled trial	60 infants with RDS or congenital pneumonia requiring mechanical ventilation and weighing <2,500 g Exclusions: Terminal state of infant at admission, air leaks, congenital anomalies, sepsis, and meconium aspiration	PRVC vs TCPL IMV	Primary: Duration of ventilation and incidence of BPD Secondary: Incidence of air leaks, IVH, hypotension, NEC, PDA, and need for sedation
Singh et al. (2006)	Randomized controlled trial A priori stratification into two groups according to birth weight (600–1,000 g and 1,001–1,500 g)	109 infants weighing between 600 and 1,500 g with gestational ages between 24 and 31 weeks, requiring mechanical ventilation and surfactant therapy Exclusions: Severe congenital malformations	VCV vs TCPLV Tidal volumes maintained between 4 and 6 mL/kg for both groups	Primary: Time from study entry until achievement of either an alveolar–arterial oxygen gradient <13 kPa (100 mmHg) or a mean airway pressure <8 cm H_2O for at least 12 h Secondary: Duration of ventilation or respiratory support, survival to discharge, incidence of CLD, IVH, PVL, PDA, or NEC

Singh et al. 2009	Long-term outcomes from prior RCT (Singh et al. 2006)	90 of the 109 infants in the 2006 study were followed Median corrected age at follow-up was 22 months	VCV vs TCPLV Patients prospectively followed with medical assessments and parental interviews via a structured questionnaire	Mortality, readmission rate, pulmonary outcomes (including the frequency of cough or wheeze and use of pulmonary medications), and gross neurodevelopmental outcome
Sinha et al. (1997)	Randomized controlled trial	50 preterm infants with RDS and birth weights of at least 1,200 g, requiring mechanical ventilation and surfactant therapy Exclusions: Pneumonia, sepsis, congenital malformations, lack of arterial access.	VCV vs TCPLV Tidal volumes maintained between 5 and 8 mL/kg for both groups	Primary: Time from study entry until achievement of either an alveolar–arterial oxygen gradient <13 kPa (100 mmHg) or a mean airway pressure <8 cm H_2O for at least 12 h Secondary: Incidence of IVH, PVL, PDA, or BPD at 36 weeks post-conceptual age

From Donn and Boon (2009), copyright Daedalus Enterprises Inc., used by permission of the American Association for Respiratory Care

SIPPV synchronized intermittent positive-pressure ventilation, *VG* volume guarantee, *PRVC* pressure-regulated volume control, *BPD* bronchopulmonary dysplasia, *PDA* patent ductus arteriosus, *IVH* intraventricular hemorrhage, *PVL* periventricular leukomalacia, *NEC* necrotizing enterocolitis, *ROP* retinopathy of prematurity, *SPO_2* pulse oximetry saturation, *$TcPO_2$* transcutaneous partial pressure of oxygen, *RDS* respiratory distress syndrome, *$PaCO_2$* partial pressure of arterial oxygen, *VCV* volume controlled ventilation, *TCPLV* time-cycled, pressure-limited ventilation, *CLD* chronic lung disease

Volume and flow leaving the ventilator is greater than that measured at the airway because of circuit compliance, whereas the pressure measured at the inspiratory side of the ventilator will be higher than that at the proximal airway because of circuit resistance (Chatburn 2003). Differences will also result from gas leaks anywhere in the circuit or connectors.

This is especially important during volume-targeted ventilation (see Sect. 8.1.3). Although the clinician orders a set volume of gas to be delivered to the patient, the actual volume reaching the proximal airway will be considerably less. For instance, even if a patient has reasonably compliant lungs and the circuit compliance is 0.5 mL/cm H_2O, less than half of the delivered gas volume will reach the patient. For this reason, it is imperative that measurements of tidal volume be performed at the airway and not calculated from the machine, especially in small, preterm babies, where even a small variance can have a huge impact (Cannon et al. 2000) (Fig. 8.5).

Because medical grade oxygen and air contain virtually no water, it is imperative that inspiratory gas be heated and fully humidified before delivery to the patient to avoid damage to the respiratory epithelium. Optimally, the temperature of the gas should be close to body temperature by the time it reaches the airway (Schulze 2006). Condensation (rainout) in the ventilator circuit can be troublesome. It may disrupt laminar flow, causing turbulence and ineffective gas exchange. It may also be the source of auto-cycling in patient-triggered ventilation (see Sect. 8.1.3). Humidification will also affect the viscosity of the delivered gas and thus contribute to circuit resistance.

8.1.2.2.1 The Endotracheal Tube

During invasive ventilation, the ventilator circuit is ultimately attached to an endotracheal or tracheostomy tube. In neonatal intensive care, the most commonly used endotracheal tubes range from 2.5- to 4.0-mm internal diameter. They are inserted from 7 to 10 cm, measured from the lip (for orotracheal tubes), depending upon the size of the baby. It should be remembered that flow through a tube is proportional to the fourth power of the radius and is related linearly to the length. Choosing the proper tube size is important. If the tube is too small, resistance will increase substantially (Oca et al. 2002), the tube will be more prone to become obstructed, and there may be a significant leak around the uncuffed endotracheal tubes used in newborns and small infants. Leaks may interfere with proper functioning of the ventilator and result in significant discrepancies between inspiratory and expiratory tidal volumes.

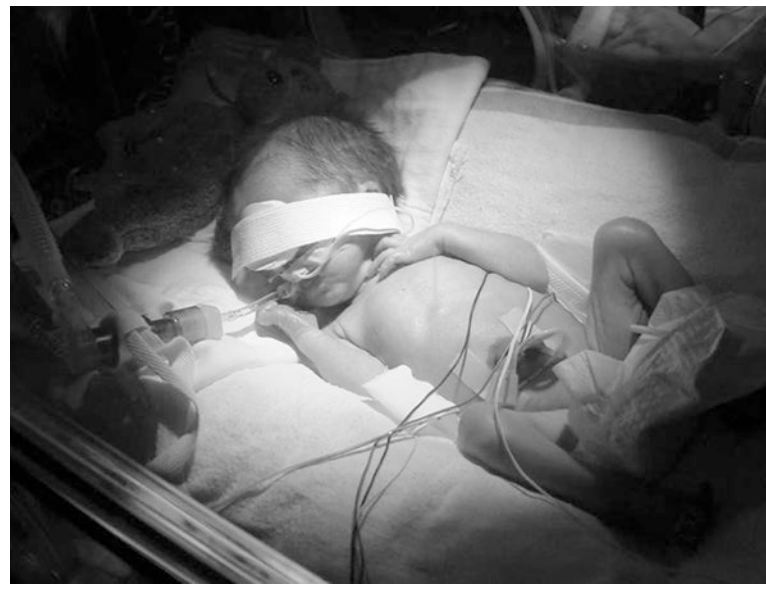


Fig. 8.5 Preterm newborn infant receiving mechanical ventilation. Note the interface between the ventilator and the baby, consisting of ventilator circuit and its connection to the oral endotracheal tube

If the leak exceeds the trigger threshold, auto-cycling may occur (see Sect. 8.1.3). Conversely, if the endotracheal tube is too large, damage may occur to the anatomical structures of the airway. The depth of insertion is also important. If too high, inadvertent extubation may occur and gas leak may be more prominent. If too low, right main bronchus intubation may occur, with subsequent atelectasis of the left lung and overdistension of the right lung.

Clinicians must also be aware that despite adequate external fixation at the lip, the endotracheal tube is still mobile within the trachea, and the location of its tip changes with respect to changes in position of the head and neck. When the head is flexed, the endotracheal tube tip will move deeper into the airway; when the head and neck are extended or laterally rotated, the tip will be withdrawn (Donn and Kuhns 1980). Although it seems intuitive that better fixation can be accomplished with a nasotracheal intubation, this is not the case (Donn and Blane 1985).

Endotracheal tube position can be ascertained using a disposable capnometer to detect exhaled carbon dioxide, followed by radiographic confirmation. The capnometer is temporarily attached to the endotracheal tube connector and undergoes a color change from purple to yellow when exposed to carbon dioxide (Aziz et al. (1999). Because of the aforementioned tube movement, radiographs should be obtained with the patient's head and neck in a neutral position and in the midline (Donn and Kuhns 1980). Once verified in appropriate position, excess external length of the tube should be trimmed for the reasons cited in Table 8.4.

Table 8.4 Complications of long external endotracheal tube length

Increased dead space
Increased resistance
Less efficient gas exchange
Increased work of breathing
Higher risk of kinking (obstruction)
Greater risk of inadvertent and self-extubation
Increased risk of infection (pooling of secretions)
More difficult to suction
Increased risk of auto-cycling

8.1.2.3 Apparatus Dead Space

Dead space classically refers to parts of the respiratory system that do not participate in gas exchange. Within the lung, gas exchange only occurs in the alveoli and terminal portions of the smallest airways. Gas exchange does not take place in the conducting airways, and this is often referred to as anatomical dead space. If, within the lung, there are areas of underperfused alveoli that are not participating in gas exchange, they are referred to as alveolar dead space. The anatomical and alveolar dead-space volumes are collectively referred to as total or physiological dead space. Wasted ventilation, the proportion of tidal gas that is delivered to the patient but not utilized in gas exchange, is defined by the ratio of dead-space volume to tidal volume (Chatburn 2003).

In this regard, the ventilator circuit and any attached apparatus can be thought of as an extension of the anatomical dead space, since not all of the gas flowing through it is involved in pulmonary gas exchange. This has also been referred to as mechanical dead space. Unless a way can be found to compensate for the increase in dead space, the imposed work of breathing will also increase.

Several devices, primarily used for monitoring, can now be added to the ventilator circuit but at the cost of additional dead space (Table 8.5). These include external transducers to measure flow, volume, or pressure; capnometers to measure end-tidal carbon dioxide; and stand-alone pulmonary function or mechanics devices, which are capable of measuring multiple parameters, including volumetric carbon dioxide (enabling the calculation of dead space to alveolar ventilation ratios). There are two types of capnometers: mainstream and sidestream. The mainstream capnometer may add considerable dead space, depending on the model, whereas sidestream capnometers do not. However, the risk of dilution by expired gas through entrainment of ambient air may adversely affect measurements (Sinha and Donn 2006a). Many centers prefer to use closed system suctioning devices, which are placed in line and add dead space to the circuit.

Table 8.5 Devices which add mechanical dead space

Flow, pressure, or volume transducers
Capnometers
Stand-alone pulmonary function or mechanics devices
Closed suctioning devices
Hygroscopic heat and moisture exchangers

Hygroscopic heat and moisture exchangers are sometimes used in place of a heated humidification system and can also add appreciable dead space (Schulze 2006).

8.1.2.4 Imposed Work of Breathing and Pressure-Support Ventilation

The imposed work of breathing refers to the amount of work needed to overcome the collective effects of the endotracheal tube, ventilator circuit, and demand valve, if a demand system is used (Sinha and Donn 2006a). It may be thought of as the "tax" a patient must pay for receiving mechanical ventilation. The age-old adage of "breathing through a straw" is a suitable analogy for the imposed work of breathing.

The imposed work of breathing becomes more significant the more a patient breathes spontaneously. Spontaneous inflation must be supported in some way to overcome the imposed work of breathing. During most forms of mandatory mechanical ventilation, spontaneous inflation are supported only by PEEP, and thus, it is not hard to understand why weaning the ventilator rate and shifting the burden of respiratory work to the patient often fails as a weaning technique (Sinha and Donn 2006b).

Pressure-support ventilation (PSV) was developed to assist spontaneous breathing by overcoming the imposed work of breathing. It is an inspiratory pressure assist applied to spontaneous inflation. It is patient triggered, flow cycled, and pressure limited (see Sect. 8.1.3). Thus, the patient controls its onset by triggering it, its duration of inspiration (by flow cycling), and its frequency. The clinician sets the pressure limit (and thus controls the degree to which the breath is supported) and an inspiratory time limit, which the patient may not exceed. It may be used in conjunction with synchronized intermittent mandatory ventilation (SIMV) or alone, if the patient has reliable respiratory drive. If the pressure is set high enough to provide a full tidal volume breath, the level of support is described as PS_{max}; if the level is just enough to overcome the imposed work of breathing, it is described as PS_{min} (Sinha and Donn 2006a). The best estimate of PS_{min} in the newborn is the pressure required to deliver a tidal volume of 3–4 mL/kg (Fig. 8.6).

Although PSV is relatively new to the neonatal intensive care unit, there are multiple studies which have examined its mechanisms and clinical role in weaning newborns from mechanical ventilation (Nicks et al. 1994; Osorio et al. 2005; Reyes et al. 2006, Sarkar and Donn 2007, Gupta et al. 2009).

8.1.2.5 Summary

The patient–ventilator interface and ventilator circuit play important roles in determining the success of assisted mechanical ventilation. Careful attention must be paid to selecting the proper interface for invasive ventilation and to assuring its optimal location and fixation. The ventilator circuit and various devices, which can be added to it, such as capnometers and closed suctioning systems, also add mechanical dead space and increase the imposed work of breathing. Clinicians must find ways to compensate for this, by either adding more flow or volume or assisting spontaneous breathing by adding pressure support to spontaneous inflation.

Essentials to Remember

- The patient–ventilator interface and ventilator circuit are key elements of mechanical ventilation.
- Components added to the ventilator circuit add dead space and increase the imposed work of breathing.
- PSV is a novel way to help overcome the imposed work of breathing.

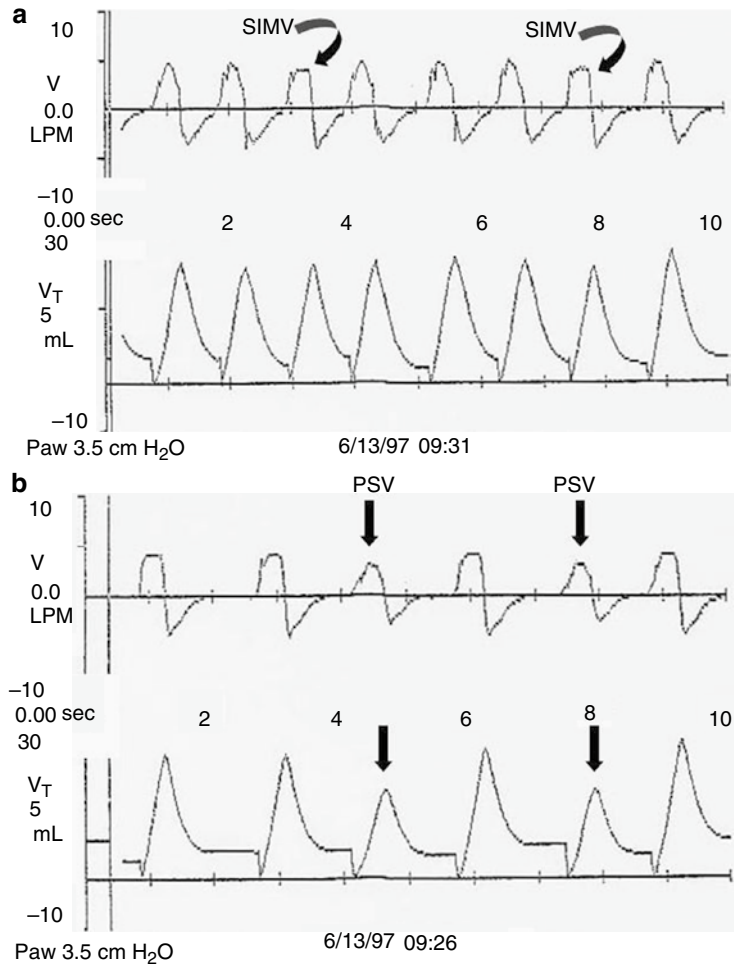


Fig. 8.6 Pressure support ventilation. Real-time pulmonary graphics showing flow and volume waveforms. (**a**) Patient is receiving PS_{max}. Note that the tidal volumes received during both the volume (*square wave*) SIMV inflation (*arrows*) and the pressure-support inflation are the same. (**b**) The patient is receiving pressure support to partially support spontaneous inflation (PSV). Note that the tidal volume delivery is less than that delivered during SIMV

8.1.3 Ventilator Modes

Steven M. Donn and Sunil K. Sinha

8.1.3.1 Introduction

Ventilator modes refer to the specific patterns of spontaneous and mandatory mechanical inflation. Spontaneous inflation are those initiated by the patient. They may or may not result in a mechanical breath, depending upon whether or not the patient is receiving triggered ventilation. Mandatory inflation are initiated by the ventilator based on an initiating factor, usually time.

Controlled ventilatory modes include intermittent mandatory ventilation (IMV), synchronized intermittent mandatory ventilation (SIMV), and assist/control ventilation (A/C). In spontaneous ventilatory mode, pressure support ventilation (PSV) involves mechanical support applied only to spontaneous inflation, which may be combined with SIMV or used as a singular mode (Sinha and Donn 1996; Donn and Sinha 2001).

Educational Goals

- Understand the specific patterns of spontaneous and mandatory mechanical inflation.
- Recognize the three component waveforms: pressure, volume, and flow.
- Differentiate phase and control variables, and understand trigger variables.

8.1.3.2 Controlled Ventilation

8.1.3.2.1 Waveforms

The three airway signals, pressure, volume, and flow, may be plotted against time to produce graphic waveforms. An understanding of the waveforms is essential to comprehending how controlled ventilation works (Donn 1997; Sinha et al. 1996; Bhutani 2002).

The pressure waveform displays changes in airway pressure over time. If positive end-expiratory pressure is utilized, the baseline pressure will serve as the starting point for inspiration. As airway pressure increases during inspiration, the waveform will increase until it reaches its highest value, referred to as the peak inspiratory pressure (PIP). Pressure subsequently declines until it reaches the end-expiratory level. The area under the curve represents the mean airway pressure. Since oxygenation is a function of mean airway pressure, ventilatory maneuvers which increase the area under the curve may improve oxygenation. These include raising the PEEP, increasing the PIP, lengthening the inspiratory time, and to a lesser extent, increasing the rate.

The volume waveform looks similar to the pressure waveform, except that in the ideal situation, the waveform should reach the zero baseline at end expiration. Failure to do so indicates the presence of a volume leak around the endotracheal tube. The volume waveform peaks earlier in inspiration when pressure is controlled in contrast to the situation in which volume or flow is controlled, where the slope will be less.

The flow waveform differs from both the pressure and volume waveforms by having components that are both above the baseline (inspiration) and below the baseline (expiration). In other words, positive flow represents gas delivered into the airway, and negative flow represents gas egressing from the airway. As inspiration commences, there is a rapid flow of gas into the airway producing a sharp upswing in inspiratory flow, referred to as accelerating inspiratory flow. At its most positive level, this is referred to as peak inspiratory flow. Inspiratory flow then decelerates. However, note that this is still a positive value, thus airflow is still inspiratory although slower, and this component is referred to as decelerating inspiratory flow. Between the end of inspiration and the start of expiration, the flow waveform reaches a zero flow state (baseline) (An exception to this occurs during flow cycling discussed below). As expiration begins, there is an acceleration of expiratory flow, the sharp downward deflection below baseline, which at is most negative value is referred to as peak expiratory flow. Following this, expiratory flow decelerates, and although this scalar is in an upward direction, it is still negative and represents decelerating expiratory flow.

8.1.3.2.2 Control Variables

A control variable is the primary variable that the ventilator utilizes to produce the inspiratory phase of a mechanical breath. According to the equation of motion, there are three possible variables that can be controlled: pressure, volume, or flow. However, only one of these can be directly controlled at a time (Carlo et al. 2006; Chatburn 1995).

If pressure is the control variable, the pressure waveform will remain constant, even if there are changes in lung mechanics (compliance and resistance), and flow and volume will be variable. Positive-pressure ventilators control airway pressure, whereas negative pressure ventilators control body surface pressure.

If volume is the control variable, both the volume and flow waveforms will remain constant, and changes in lung mechanics will result in variability in airway pressure. True volume controllers must measure volume and use this measurement to control volume delivery. Volume may be controlled directly, using a device such as a piston or bellows, or indirectly by controlling airway flow (flow is defined as the time rate of volume delivery). Thus, true volume control is not technically possible in neonatal ventilation because cuffed endotracheal tubes are not used, and there is almost always some degree of volume leak around the endotracheal tube. For this reason, it is more appropriate to refer to this type of ventilation as volume-targeted or volume-limited (Sinha and Donn 2001).

If flow is the control variable, again both the volume and flow waveforms will remain constant, with pressure varying as lung mechanics change. The means for controlling flow include

simple flow meters or more technical proportional solenoid valves.

8.1.3.2.3 Phase Variables

Each breath, whether spontaneous or mechanical, consists of four phases: the initiation of inspiration, inspiration itself, the end of inspiration, and expiration. Phase variables refer to parameters that are measured and utilized to initiate, sustain, or terminate some phase of the ventilatory cycle. They consist of a trigger variable that initiates inspiration, a limit variable that restricts the magnitude of some parameter (i.e., pressure) during inspiration but which does not terminate inspiration, and a cycle variable that causes inspiration to end. Positive end-expiratory pressure is sometimes referred to as the baseline variable (Carlo et al. 2006).

8.1.3.2.3.1 Trigger Variables

A mechanical breath may start in response to a spontaneous breath (patient-triggered breath) or it may be initiated by the ventilator (mandatory or control breath). Patient-triggered inflation are initiated by a signal derived from the patient, which represents spontaneous respiratory activity, such as a change in airway pressure or flow. In the absence of a trigger mechanism, time is used as a trigger, where a mechanical breath is provided at intervals chosen by the clinician (Hird and Greenough 1991a; Hummler et al. 1996).

8.1.3.2.3.2 Limit Variables

Typically, limit variables restrict or maintain a parameter within the limits preset by the clinician. Pressure, flow, or volume can all be used as limit variables. An important distinction is that the limit variables are applied *during* inspiration but do not end it. It is a misnomer to consider time as a limit variable, because it actually *ends* inspiration and is thus a cycle variable.

8.1.3.2.3.3 Cycle Variables

When some variable reaches a preselected level, the inspiratory phase ends and the breath is *cycled* into expiration. The cycle variable refers to this measured variable used to end inspiration.

Time has been the most common cycle variable. The clinician chooses an inspiratory time limit, and the inspiratory phase of the breath is terminated when this time elapses. Some devices allow the clinician to prolong inspiration through the use of an inspiratory hold. Inspiratory gas flow occurs during the inspiratory flow time, but during the inspiratory hold time, the exhalation valve remains closed, but there is no inspiratory gas flow. Here, the inspiratory time will be the sum of the inspiratory flow time and the inspiratory hold time. Time cycling is used as a "backup" mechanism during assist/control and pressure support ventilation, where flow is the primary cycle variable (see below). Phase variables refer to parameters that are measured and utilized to initiate or terminate some phase of the ventilatory cycle, e.g., cycling mechanisms.

Pressure cycling is used primarily for alarms. During pressure cycling, inspiratory flow is delivered until the preset pressure level is attained. Inspiratory flow then ceases and expiratory flow begins.

Volume cycling delivers inspiratory flow until a preset volume of gas has been delivered to the airway, after which inspiratory flow stops and expiratory flow begins. Some volume-cycled devices allow the clinician to maintain inspiration beyond this point by using an inspiratory hold, but in this case the cycle variable is time. An important distinction must be made between the volume of gas which leaves the ventilator and the actual volume that reaches the patient. These are not the same because of compression of gas within the ventilator circuit. Even if delivered volume is measured at the proximal airway, true volume cycling cannot be accomplished without a cuffed endotracheal tube because of gas leaks around an uncuffed tube (Sinha and Donn 2001; Hird and Greenough 1991a).

Flow cycling is a technique used to terminate inspiration when decelerating inspiratory flow has declined to a certain percentage of peak inspiratory flow. During flow cycling, inspiration cycles directly into expiration at this point, and there is only an instantaneous zero flow state between inspiration and expiration. Flow cycling allows the patient to control the duration of inspiration and thus improve patient–ventilator synchrony by adding expiratory synchrony, often called

an expiratory trigger (see below). Flow cycling also enhances patient safety. Because inspiration is terminated as a percentage of peak flow, the risks of inversion of the inspiratory-to-expiratory ratio (*I*:*E*), gas trapping, and inadvertent PEEP during patient-triggered ventilation (if the patient becomes tachypneic) are considerably less than with time cycling. During flow cycling, the actual inspiratory time will be less than the set inspiratory time when inflation are terminated by the flow change (Prinainak et al. 2003).

8.1.3.2.4 Controlled Modes of Ventilation

8.1.3.2.4.1 Intermittent Mandatory Ventilation

The original mode of mechanical ventilation was IMV. In this mode, the clinician chooses a set rate at which mechanical inflation will be delivered to the patient, and the ventilator will deliver the inflation at regular intervals. In between the mechanical inflation, the patient may breathe spontaneously. However, the spontaneous and mechanical inflation have no fixed relationship to one another and function independently. This may lead to asynchronous breathing and significant variability in delivered gas volumes. For instance, if the patient initiates a spontaneous breath while a mechanical breath is also in the inspiratory phase, the delivered gas volume will be considerably larger than in the situation where the patient is actively attempting to exhale against an incoming mechanical breath. This is frequently described as "fighting the ventilator."

Asynchrony has been shown to produce numerous problems, including inefficient gas exchange, increased work of breathing, gas trapping and a higher incidence of thoracic air leaks (Greenough and Morley 1984), and irregular arterial blood pressure and cerebral blood flow velocity patterns. The latter have been associated with the development of intraventricular hemorrhage in preterm newborns with respiratory distress syndrome (Perlman et al. 1985).

Infants managed with IMV are frequently weaned from ventilatory support by reducing the IMV rate. This needs to be done cautiously. If done too rapidly, the baby may become increasingly fatigued during the weaning process and may not tolerate extubation.

8.1.3.2.4.2 Synchronized Intermittent Mandatory Ventilation

In SIMV, the clinician also sets a rate at which the mandatory inflation will be delivered, and the patient may also breathe spontaneously between the mandatory inflation. However, the ventilator attempts to synchronize the onset of the inspiratory phase of the mechanical breath to the onset of a spontaneous breath if one occurs within a timing window (Donn and Becker 2003). For example, if the SIMV rate is set at 30 inflation/min, a mandatory breath will be delivered approximately every 2 s. When it is time to deliver that breath, the ventilator will respond to the start of a spontaneous breath that occurs shortly before or shortly after that point. If no patient effort is detected within the timing window, a mechanical breath will be provided. Thus, SIMV removes much of the inspiratory asynchrony of IMV, but if the set inspiratory time is longer than the patient's own inspiratory time, expiratory asynchrony will still occur. This can be alleviated by using flow cycling.

As with IMV, spontaneous breathing between mandatory inflation is supported only by the baseline pressure (PEEP). Because babies have intrinsically high respiratory rates, both IMV and SIMV provide a higher work of breathing for the baby compared to A/C, because a large proportion of inflation are insufficiently supported. Use of either A/C or PSV (alone or in combination with SIMV) can overcome this problem. Problems similar to those for IMV also occur during weaning from SIMV.

8.1.3.2.4.3 Assist/Control Ventilation

During A/C, inflation initiated by the patient are "assisted" by the mechanical breath, while those that occur as mandatory inflation are "controlled." Assist/control ventilation is accomplished by utilizing a trigger variable to respond to patient effort. In the newborn, this is most commonly derived from a change in airway flow (see below). If the spontaneous effort exceeds the

trigger threshold, the ventilator will respond by delivering a mechanical breath, which has a limit and cycling variable chosen by the clinician. If the patient fails to breathe or if the breath effort is insufficient to reach the trigger threshold, a control breath will be delivered at a rate set by the clinician. Thus, every patient breath that meets the trigger threshold will result in the delivery of a synchronized mechanical breath. The level of support during the assisted breath will be the same as during a control breath and is determined by the limit variables. For instance, inflation may be fully supported and deliver a full tidal volume or they may be partially supported (by adjusting pressure or volume) (Donn and Becker 2003; Greenough and Pool 1988).

Weaning during A/C is different from IMV or SIMV. As long as the patient is breathing above the control rate, further reductions in the rate will have no effect on the mechanical ventilatory rate (Sinha and Donn 2002). The primary weaning strategy during A/C is a reduction in pressure or volume. Some clinicians will extubate directly from A/C, while others prefer to switch to SIMV/PS during the weaning stage of illness.

Combining A/C with flow cycling can achieve complete synchrony between the baby and the ventilator. Inflation are initiated by spontaneous patient effort and they are likewise terminated in very close proximity to the end of the spontaneous inspiratory phase. Every breath is virtually identical, and numerous short-term physiological advantages have been demonstrated for A/C compared to either IMV or SIMV (Donn et al. 1994; Donn and Sinha 1998).

8.1.3.2.5 Synchronization Principles and Trigger Systems

8.1.3.2.5.1 Introduction

The concepts of patient-triggered and synchronized ventilation were practiced in adult and even pediatric respiratory care long before they became available to neonatal patients. Technological limitations precluded the ability to derive appropriate trigger signals and monitoring systems to safely accomplish synchronized ventilation until the decade of the 1990s.

As described above, one of the major problems with mechanical ventilation is asynchrony between the patient and the machine. Asynchrony results not only inefficient gas exchange but also contributes to respiratory and neurologic morbidity and increased cost of care. Until the advent of patient-triggered ventilation, clinicians had limited options to deal with asynchrony. Ventilator settings could be increased to try to "capture" or "overbreathe" the patient, but this was at the risk of increasing ventilator-induced lung injury. Patients could be sedated, but this often depressed the respiratory drive and prolonged the duration of mechanical ventilation. In severe cases, skeletal muscle relaxants could be used, but long-term administration resulted in numerous problems, including muscle atrophy, edema, and ventilator dependence.

8.1.3.2.5.2 Principles of Synchronization

Synchronized ventilation is an attempt to match spontaneous and mechanical breathing as closely as possible. It allows the patient to have control over some ventilator variables that were previously set by the clinician and which overrode the patient's own breathing contributing to asynchrony.

The primary principle of synchronized ventilation is the use of a marker or surrogate of spontaneous breathing as a mechanism to trigger the delivery of a mechanical breath in as close proximity as possible to the spontaneous breath and to mimic the patient's own pattern of breathing. Ideally, this should occur for both the onset of inspiration and the termination of inspiration. Thus, it should include both the trigger and cycle variables in its design (Greenough and Pool 1988).

There are additional concepts that are important to the performance of patient-triggered ventilation. First, the trigger signal needs to be a reliable indicator of spontaneous breathing and not an artifact resulting from movement of nonrespiratory musculature. Second, the trigger sensitivity has to be appropriate for the patient; if it is too difficult to achieve, the work of breathing will be higher, as spontaneous inflation will not be supported beyond the baseline pressure,

and if it is too sensitive, auto-cycling may occur (see below). Third, there needs to be a very short system response time or trigger delay. This time refers to the interval between reaching the trigger sensitivity and the rise in pressure at the proximal airway. If the trigger delay is too long, the patient may be nearly finished with the spontaneous inspiratory phase before help from the ventilator arrives. Finally, there should be minimal auto-cycling (false triggering) (Donn and Sinha 1998; Hird and Greenough 1990; Donn et al. 2000).

8.1.3.2.5.3 Trigger Systems

Various trigger systems were introduced into neonatal practice during the 1990s. As technological refinements occurred, several of these were replaced by systems with better sensitivity, shorter trigger delays, and less auto-cycling. In general, most systems now have trigger delays under 50 ms and work well on even the smallest patients (Laureen and Ronald 2000; Servant et al. 1992).

8.1.3.2.5.4 Abdominal Motion

One of the first trigger systems utilized in neonatal patients used a signal derived from abdominal motion during breathing (Hummler et al. 1996). An applanation transducer, such as the Graseby capsule, was placed on the abdomen and used to trigger a mechanical breath in response to spontaneous breathing. It appeared to work best in patients >2,000 g, but sensor placement was critical, and artifacts such as hiccups produced mechanical inflation unrelated to spontaneous breathing. In addition, there was only a single sensitivity setting, and tidal volume could not be measured. This technique has been largely abandoned.

8.1.3.2.5.5 Thoracic Impedance

Another early trigger system utilized changes in thoracic impedance, determined by standard electrodes used for electronic cardiorespiratory monitoring, to trigger inflation. In turn, the inspiratory cycle was terminated by active expiration. It, too, was dependent upon proper lead placement and maintenance of contact gel beneath them. It was also unable to measure tidal volume (Ferguson 2006).

8.1.3.2.5.6 Airway Pressure

Changes in airway pressure are also utilized to trigger mechanical inflation. As the patient begins to breath, there is a slight reduction in airway pressure, which serves as the marker of a spontaneous breath. Proper setting of the sensitivity level is a key. Compared to flow-triggered systems, pressure triggering requires more patient effort and is less suitable for the smaller babies. This system is relatively easy to use and can provide data from numerous airway metrics (Hird and Greenough 1990; Laureen and Ronald 2000).

8.1.3.2.5.7 Airway Flow

The most popular method of providing neonatal patient-triggered ventilation involves the use of a signal derived from changes in airway flow (Laureen and Ronald 2000; Hird and Greenough 1991a). As the patient initiates a spontaneous breath, there is a slight acceleration of flow at the proximal airway. This can be detected by one of the two transduction methods. The first of these uses a pneumotachograph (a variable orifice, differential flow transducer). In the center of the transducer, there is a membrane, which is distorted proportional to the amount of flow. This signal is used to trigger the ventilator, and it can be integrated to provide volume measurements. The second of these uses a heated wire anemometer. As gas flows over it, it is cooled, and the amount of current needed to return the wire to baseline temperature can be converted to a flow and volume signal.

Flow transducers are extremely sensitive, detecting flow changes as small as 0.1–0.2 L/min. This is about the amount of flow necessary to propel a dust ball. They are ideally suited for the tiny patients in the neonatal intensive care unit. The downside of flow transducers is the higher tendency for auto-cycling described below.

8.1.3.2.5.8 Neural Triggering

Another means of triggering mechanical ventilation is the utilization of neural impulses. One such system uses a *neurally adjusted ventilatory assist technology in which a signal is derived when the vagus nerve stimulates the diaphragm. The* electrical activity of the diaphragm is captured, transmitted to the ventilator, and used to assist the patient's breathing. Both the ventilator and the diaphragm work with the same signal, minimizing trigger delay and theoretically reducing the risk of auto-cycling (see Sect. 8.1.3.3.4). There has been limited investigation of the technique in newborns, but it is an attractive hypothesis (Bernstein et al. 1995).

8.1.3.2.5.9 Auto-cycling

Auto-cycling is a phenomenon of patient-triggered ventilation. It occurs when something other than the patient's effort triggers the ventilator in a repetitive fashion, often producing a string of rapid, identical inflation on graphic monitoring.

Flow-triggered systems have the highest incidence of auto-cycling, most likely as a consequence of their extreme sensitivity. Auto-cycling most commonly occurs because of leaks, either in the ventilator circuit or around the endotracheal tube. If the leak exceeds the trigger threshold, the trigger system will interpret this as patient effort and provides a mechanical breath. If the leak persists, another breath is provided, and so on. Auto-cycling can also occur if there is excessive condensation in the ventilator circuit, as the oscillating water can create a flow change that exceeds the trigger sensitivity.

Clinicians must learn to recognize auto-cycling and distinguish it from simple tachypnea. The major graphic feature of auto-cycling is its regularity and similarity of all the inflation. Tachypnea usually shows some degree of breath-to-breath variability in both rate and configuration.

There are several ways to deal with auto-cycling. First, try to eliminate any source of leaks in the circuit or equipment and be sure that there is no condensation in the ventilator circuit. Second, if it appears that the leak is originating from the airway, decreasing the trigger sensitivity may solve the problem. Some devices enable a measurement of the leak, and setting the sensitivity at a level that is slightly greater than this value can "fool" the ventilator and cease the auto-cycling (Donn and Becker 2003; Donn and Sinha 1998).

It is also important to realize that leaks may play havoc with flow cycling. If the leak is significant, the decline in the decelerating inspiratory flow waveform may not reach the termination point. This problem is eliminated by employing effective variable leak compensation in certain ventilators specifically designed for newborns with uncuffed ETT.

8.1.3.2.5.10 Clinical Evidence

Synchronized ventilation, whether provided by SIMV or A/C is clearly superior to IMV (Bernstein et al. 1994, 1996; Chan and Greenough 1994; Greenough et al. 2008). Virtually, every clinical trial has demonstrated short-term physiological benefit, including a shorter duration of ventilation, decreased thoracic air leaks, need for less sedation, and reduced hospital costs. Although there is a trend towards less chronic lung disease, it has been difficult to demonstrate this, as studies have been small and underpowered. It may also be affected by changing demographics, as smaller and more premature babies are now surviving. Nevertheless, IMV should be a mode of the past.

Essentials to Remember

- Modes of ventilation include IMV, SIMV, A/C, and PSV.
- The control variable is the primary variable utilized to produce the inspiratory phase of a mechanical breath.
- The phase variables refer to parameters that are measured and utilized to initiate, sustain, or terminate some phase of the ventilatory cycle.
- Synchronized ventilation is advantageous compared to IMV.

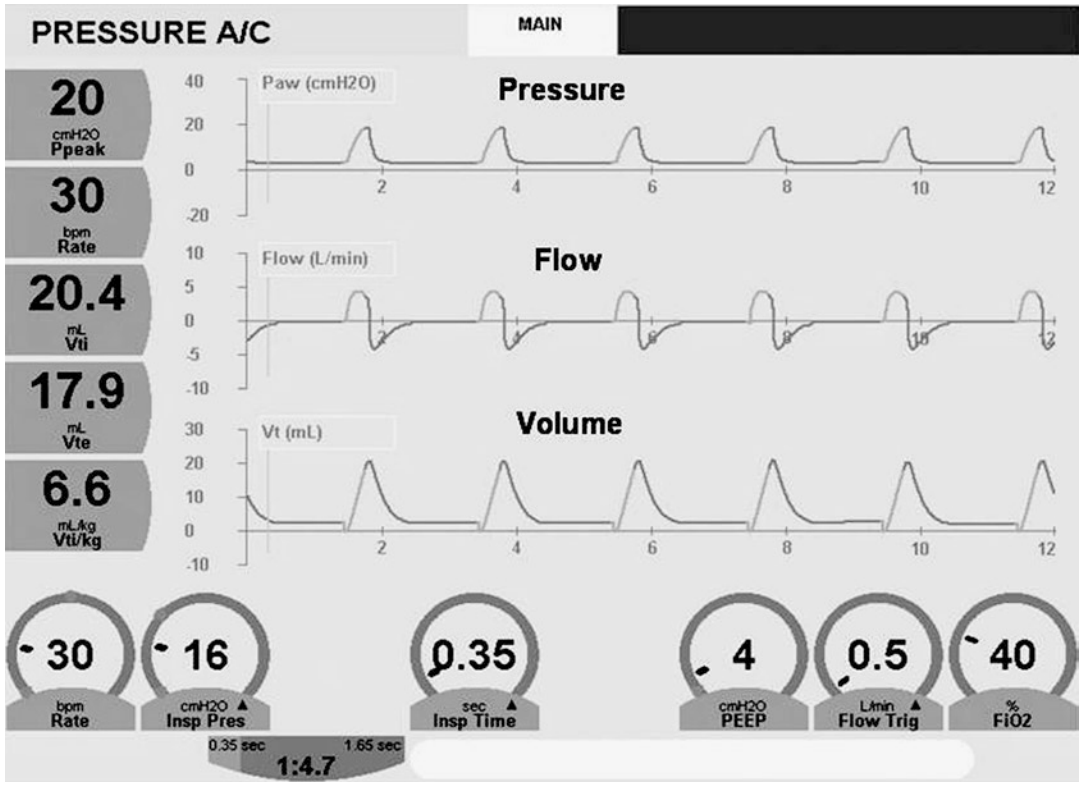


Fig. 8.7 Graphic waveforms. Pressure and volume (*top* and *bottom*) are similar and are always above the baseline. Flow waveform (*middle*) has two components. Inspiration is above the baseline and represents flow going into the patient (positive). This has accelerating (*upward*) and decelerating (*downward*) phases. Expiration is below the baseline and represents flow coming from the patient (negative). It also has accelerating (*downward*) and decelerating (*upward*) phases

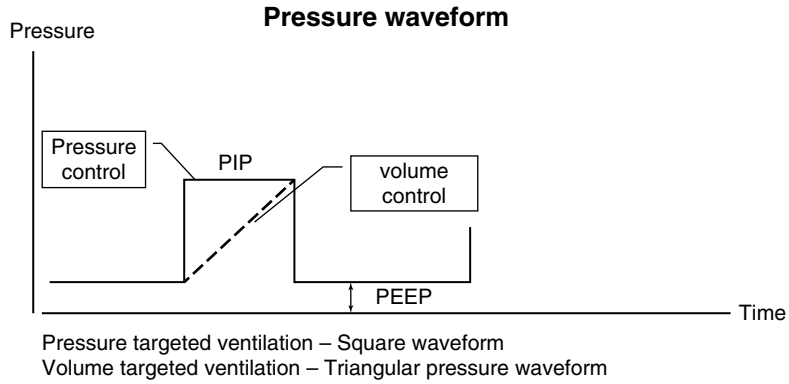


Fig. 8.8 Pressure waveform. Solid line represents pressure-targeted ventilation, which produces a square waveform. *Dotted line* represents volume-targeted ventilation, which produces a triangular or "shark's fin" pressure waveform. Note that the expiratory portion of the waveform is above the baseline representing positive end-expiratory pressure (*PEEP*). The area under the curve, bounded by the peak inspiratory pressure (*PIP*) and PEEP, is the mean airway pressure

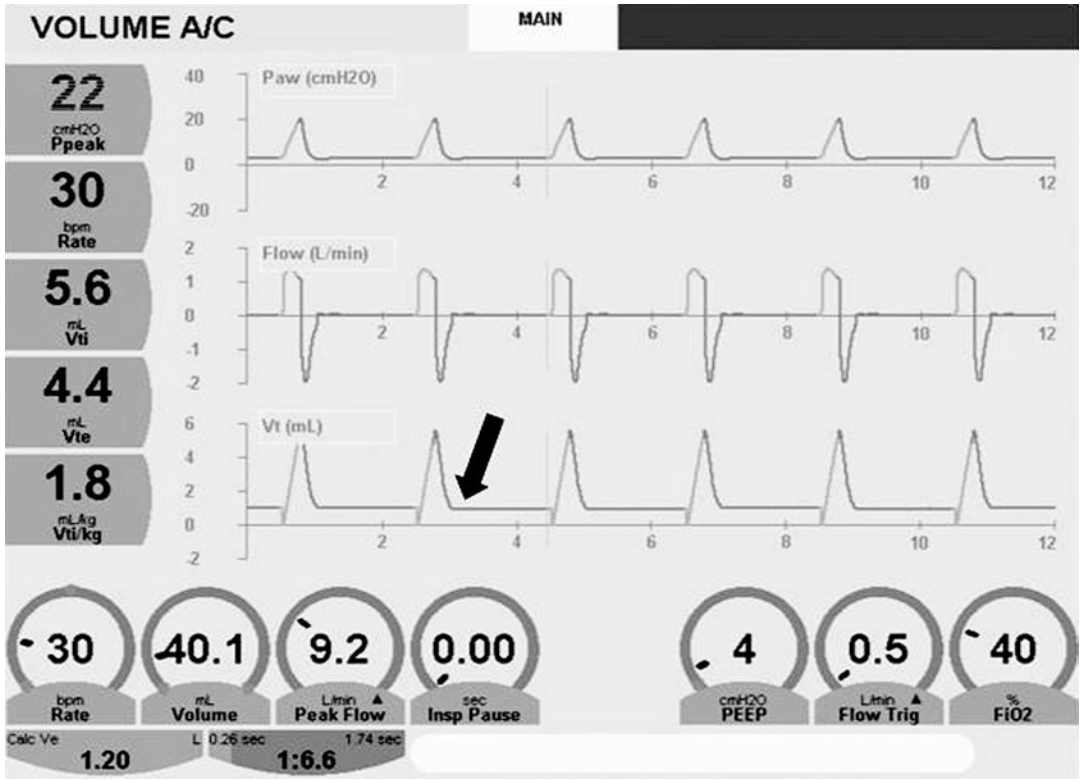


Fig. 8.9 The volume waveform fails to reach the baseline (*arrow*) because of a large endotracheal tube leak. Note discrepancy between the inspiratory (V_{ti}) and expiratory (V_{te}) tidal volumes

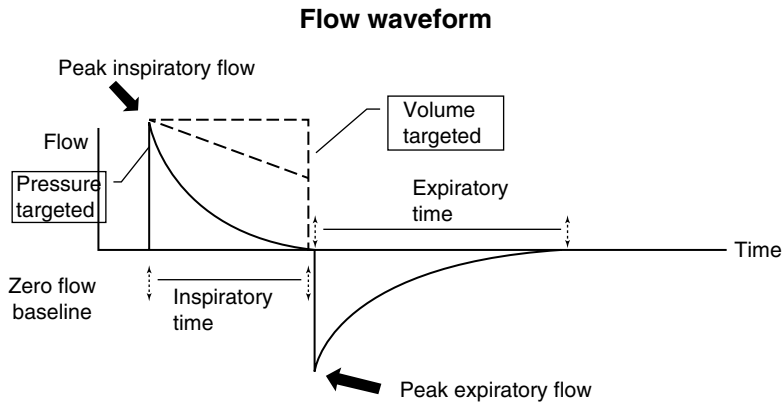


Fig. 8.10 Anatomy of the flow waveform. See text for description

Volume targeted ventilation – Constant square or deceleration flow
Pressure targeted ventilation – Variable decelerating flow

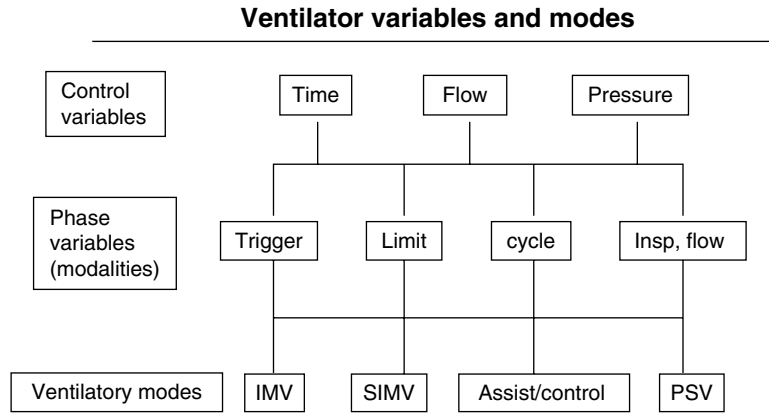


Fig. 8.11 Hierarchical classification of ventilator variables and modes. Although pressure support ventilation (*PSV*) is shown, it is a spontaneous and not a controlled mode

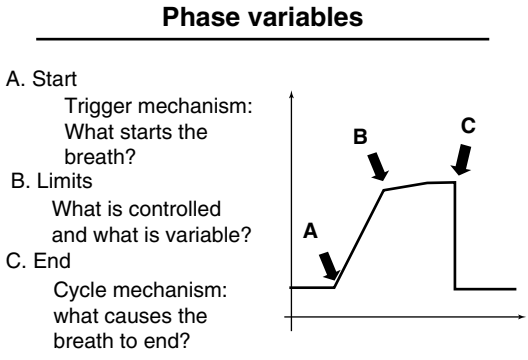


Fig. 8.12 Schematic diagram of a single ventilatory cycle noting points at which phase variables act

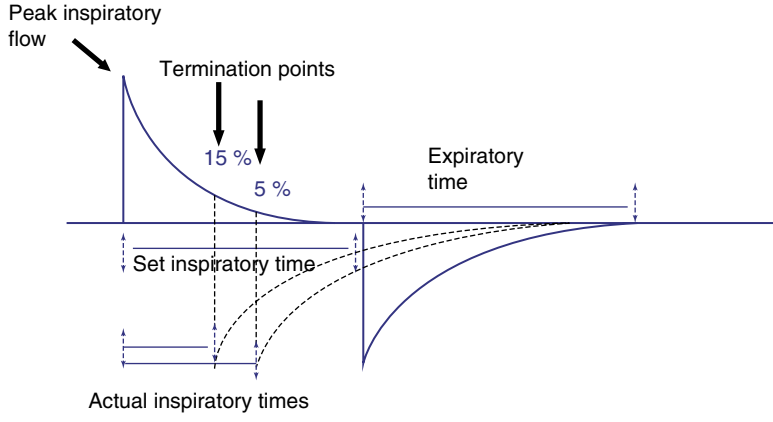


Fig. 8.13 Time versus flow cycling. When time is used to cycle a mechanical breath, inspiration ends when the preset limit has been reached. This may produce a prolonged zero flow state at the end of inspiration. When flow is used to cycle the breath, inspiration ends at a preselected termination point as a percentage of peak inspiratory flow. The actual inspiratory time is less than the set inspiratory time and is controlled by the patient

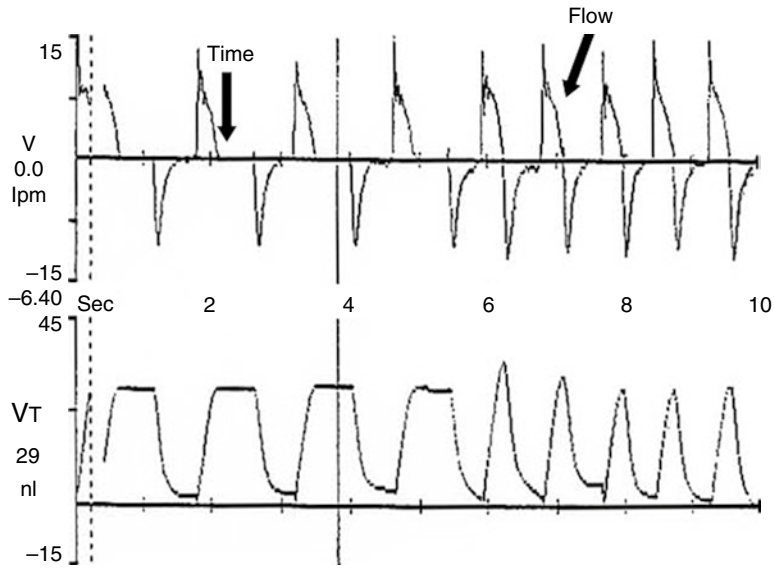


Fig. 8.14 Graphic display of the differences between time and flow cycling. The first four inflation are time cycled. Note the prolonged zero flow state at the end of inspiration (*time arrow*), which produces a plateau of volume delivery. The last five inflation are flow cycled. Note how the decelerating inspiratory flow waveform transitions immediately into expiration at the termination point (*flow arrow*) producing a spiked volume delivery waveform

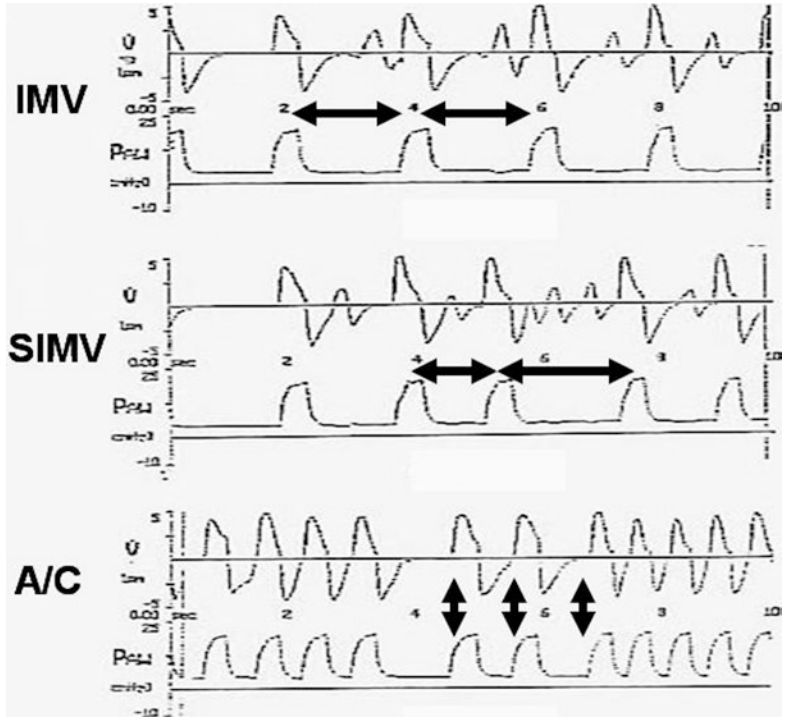


Fig. 8.15 Comparison of flow and pressure waveforms for intermittent mandatory ventilation (*IMV*), synchronized intermittent mandatory ventilation (*SIMV*), and assist/control ventilation (*A/C*). In IMV, mechanical inflation are delivered at regular intervals in accordance with the rate chosen by the clinician. Here, a breath is given every 2 s (note the intervals between the *horizontal arrows*), and the patient breathes spontaneously in between these inflation supported only by PEEP. In SIMV, the ventilator has a "timing window." If the patient makes a detectable spontaneous effort, the ventilator will respond with a mechanical breath that is synchronized to the onset of the spontaneous breath. If the patient fails to breathe, a mandatory breath is provided. Note how this produces an irregularity in the breath rate (differences in the *horizontal arrows*). Again, the patient may breathe between the mechanical inflation supported only by PEEP. In A/C, each spontaneous breath that meets the trigger sensitivity results in a synchronously delivered mechanical breath. If flow cycling is also used, complete patient–ventilator synchrony can be achieved. Note the complete relationship of the flow and volume waveforms (*vertical arrows*), whether the patient breathes at a slow or fast rate

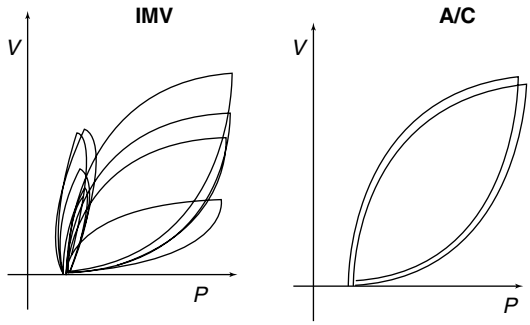


Fig. 8.16 Comparison of IMV and A/C. Note the variability in tidal volume delivery with IMV. Despite the fact that each breath reaches the same peak pressure, asynchrony results in wide differences in tidal volumes. During A/C, every breath is identical

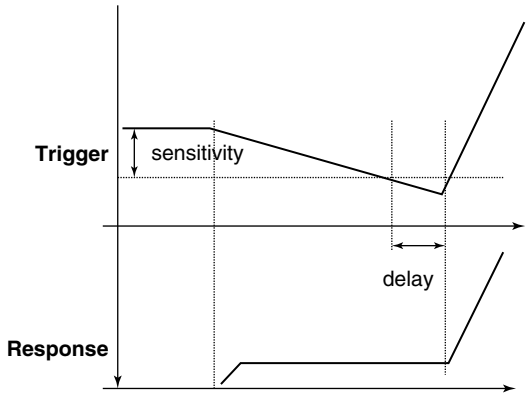


Fig. 8.17 Graphic representation of patient-triggered ventilation. The trigger responds when the patient meets the trigger sensitivity resulting in the delivery of a mechanical breath. The system response time, or trigger delay, is the interval between the trigger event and the rise in pressure at the proximal airway

8.1.3.3 Assisted Ventilation

Katherine C. Clement, Mark J. Heulitt, Andreas Schulze, Eduardo Bancalari, Jean-Michel Arnal, and Guillaume Emeriaud

8.1.3.3.1 Pressure-Support Ventilation

Katherine C. Clement and Mark J. Heulitt

Education Aims

- Understand the characteristics of a pressure-support breath.
- Understand the three major phases of PSV.
- Understand the physiological effects on the breathing pattern, oxygenation and ventilation, and work of breathing.
- Understand the types of asynchrony during PSV and how it can be identified.

8.1.3.3.1.1 Introduction

Pressure-support ventilation (PSV) is a support mode used for spontaneously breathing patients. It augments inflation initiated by the patient which may improve patient–ventilator synchrony, reduce sedation needs, prevent disuse atrophy of respiratory muscles, and facilitate weaning (Brochard and Lellouche 2006; Sassoon et al. 2004). PSV may also improve work of breathing (Kornecki and Kavanagh 2007) and improve patient comfort (MacIntyre 1986; Thille et al. 2008).

8.1.3.3.1.2 Definition

PSV is a patient-triggered, pressure-limited, and flow-cycled form of mechanical ventilation used in patients with intact respiratory drive (Kornecki and Kavanagh 2007). A preset amount of positive pressure is delivered by the ventilator in synchrony with patient effort to raise airway pressure to a certain level (Brochard and Lellouche 2006). This preset pressure is known as the "pressure-support level" (Brochard and Lellouche 2006). A patient must generate a minimum negative inspiratory force that exceeds the preset ventilator flow or pressure sensitivity in order to trigger a breath from the ventilator (Kornecki and Kavanagh 2007). The set level of pressure support is then delivered and sustained until the ventilator senses the end of expiration, which is ideally a reflection of the end of patient demand (Brochard and Lellouche 2006). When inspiratory flow drops below a set threshold, which may be suggestive of relaxation of inspiratory muscles, the ventilator will cycle to the expiratory phase, open the expiratory valve, and release the pressure support (Brochard and Lellouche 2006).

With this mode of ventilation, patients are able to control their own rate, inspiratory time, and tidal volume (Kornecki and Kavanagh 2007). There are no mandatory inflation delivered; however, there is a safety feature on most modern ventilators in the case of apnea where the ventilator will automatically shift into a control mode (Brochard and Lellouche 2006).

The three major phases of PSV (initiation, pressurization, and cycling off) may vary among ventilators, may be altered by patient effort, and/or may be adjusted by the clinician in some circumstances. Patients must trigger the ventilator with their own active effort. Trigger sensitivity may be adjusted to improve a patient's ability to initiate a breath. Trigger delay is the time between the start of patient effort and the start of ventilator pressurization of the breath. Most ventilators respond in less than 100 ms, but there is some variability among ventilator models (Brochard and Lellouche 2006). The rate of pressurization also varies among ventilator models, but many allow for clinician adjustment. A regulatory mechanism should ensure the appropriate flow reaches the set pressure-support level and keeps the pressure constant until expiration occurs (Brochard and Lellouche 2006). A high speed of pressurization will produce a square pressure wave, whereas a lower speed of pressurization will attenuate this square shape (Iotta et al. 1991). Cycling off usually occurs when inspiratory flow falls below a specific threshold. This threshold can be changed on many ventilators (Brochard and Lellouche 2006). Sensing a small change in pressure above the set pressure-support level, which may represent patient expiratory effort, may be used alone or in combination with the flow threshold for cycling off. There is also typically a time limit set for the duration of inspiration (Brochard and Lellouche 2006).

8.1.3.3.1.3 Physiological Effects (Breathing Pattern, Ventilation/Oxygenation, Work of Breathing)

Because patients can control their own respiratory rate and partially control their own tidal volume, PSV would seem to provide a more "physiologic" means of ventilatory assistance (Brochard and Lellouche 2006). However, the use of PSV actually changes the pattern of spontaneous breathing (Brochard et al. 1989; Ershowsky and Krieger 1987; Tokioka et al. 1989; Van de Graff et al. 1991; Hurst et al. 1989; MacIntyre 1987). Most patients will have an increase in tidal volume with a decrease in respiratory rate as the level of pressure support increases (MacIntyre 1986; Brochard et al. 1989; Ershowsky and Krieger 1987; Tokioka et al. 1989; Van de Graff et al. 1991). These findings suggest that breathing patterns rapidly change when respiratory muscles are faced with a new workload (Tobin et al. 1986) and imply that PSV can be adjusted according to the patient's breathing pattern response (Brochard and Lellouche 2006). Breathing patterns may change significantly with increasing PSV; however, minute ventilation may increase slightly or not change at all (Brochard et al. 1989; Ershowsky and Krieger 1987; Tokioka et al. 1989; Van de Graff et al. 1991; Hurst et al. 1989).

Gas exchange in PSV can be improved by enhancing alveolar ventilation, which results from an increased dead space to tidal volume ratio (Brochard and Lellouche 2006). PSV corrects $PaCO_2$ and respiratory acidosis for patients with hypercapnic respiratory failure (Brochard et al. 1989), and in healthy non-intubated patients, PSV of 10 cm H_2O decreases $PaCO_2$ significantly (Lofaso et al. 1992). Oxygenation is not significantly affected by changes in PSV compared to other modes of ventilation (Brochard and Lellouche 2006).

A major goal of PSV is to provide respiratory assistance while improving a patient's work of breathing. The decrease in work of breathing is significant and is proportional to the level of PSV (Brochard and Lellouche 2006). In one study, large swings in esophageal pressure generated only small tidal volumes, but when 20 cm H_2O of pressure support was added, small changes in esophageal pressure were related to larger tidal volumes (Brochard et al. 1989). These results support that the addition of PSV improves patient effort. The change in the pressure–volume ratio of the work of each breath decreases

progressively with increasing levels of pressure support in a lung model (MacIntyre 1986). Providing 5–10 cm H_2O of pressure support may reduce the work needed to overcome resistance in the ventilator circuitry and demand valve (Sassoon et al. 1991–1992). Individual patients have an upper limit of pressure support, above which work of breathing is worsened (Brochard and Lellouche 2006). Excessive pressure support can lead to asynchrony, apnea, desaturation, and ineffective efforts (Ershowsky and Krieger 1987).

8.1.3.3.1.4 Clinical Applications, Advantages, and Limitations

There are no exact guidelines for the clinical use of PSV (Brochard and Lellouche 2006). Adding PSV augments the pressure differences between the alveoli and the ventilator circuit, resulting in higher tidal volumes and inspiratory flow rates than spontaneous breathing alone (Brochard and Lellouche 2006). Often, the PSV is adjusted to achieve a tidal volume of 6–8 mL/kg (Brochard and Lellouche 2006). Assessment of accessory muscle activity and respiratory rate may assist in determining the ideal level of PSV (Brochard and Lellouche 2006; Brochard et al. 1989). Targeting a respiratory rate less than 32 inflation per minute (bpm) may be associated with decreased work of breathing (Brochard et al. 1989); however, a lower target rate (<25 bpm) may prolong weaning duration (Brochard and Lellouche 2006).

PSV is commonly used during weaning and assessment of extubation readiness, although evidence remains mixed. A low level of PSV can be used to simulate spontaneous breathing trials (Brochard and Lellouche 2006). PSV can also be used in combination with SIMV as a means for weaning, but there is not much data to support this (Brochard and Lellouche 2006). Using a low level of PSV has been shown to be equivalent or superior to T-piece trials in adults and infants (Esteban et al. 1997; Farias et al. 2001; Matic and Majeric-Kogler 2004).

Noninvasive ventilation (NIV) delivers gas through a face or nasal mask, providing ventilatory support without endotracheal intubation (Yañez et al. 2008). NIV is beneficial as an alternative to endotracheal intubation for adults with neuromuscular disorders, chronic obstructive pulmonary disease, respiratory distress, and cardiogenic pulmonary edema (Brochard and Lellouche 2006; Antonelli et al. 1998; Minuto et al. 2003). PSV is the usual mode of ventilation utilized with NIV. There is less data available for the use of NIV in children, but the initial studies are promising. In a retrospective series of 114 children with varying disease processes requiring NIV with PSV, Essouri et al. found a 77 % success rate in improving respiratory distress and avoiding endotracheal intubation (Essouri et al. 2005). Similarly, in a randomized, prospective study, Yanez et al. demonstrated improved oxygenation and respiratory effort in children with acute hypoxemic respiratory failure (Yañez et al. 2008). They also had a 47 % reduction in the rate of intubation (Yañez et al. 2008).

The advantages of PSV have been briefly mentioned earlier in this chapter. Patients are allowed to breathe in a more "physiologic" way since they control their own respiratory rate and partially control their own inspiratory time and tidal volume (Brochard and Lellouche 2006). This feature may provide improved patient–ventilator synchrony. In a comparison of SIMV and PSV, patients in PSV demonstrated improved subjective comfort, slower respiratory rates, and reduced muscle work (MacIntyre 1986). PSV also avoids disuse atrophy of respiratory muscles that can often result from controlled modes of ventilation (Sassoon et al. 2004). PSV does not have adverse effects on cardiovascular function in patients after cardiac surgery or with respiratory failure (Brochard and Lellouche 2006).

The primary disadvantage of PSV is that tidal volume is not guaranteed. Delivered tidal

volume depends, in part, on patient effort, which may continuously change with modifications in neurologic status (increased/decreased sedation), or altered respiratory mechanics (Kornecki and Kavanagh 2007). Oxygen demand and minute ventilation may also change over time, secondary to fever, stress, or pain, but preset pressure support remains constant (Kornecki and Kavanagh 2007). Additionally, if pressure support is high, a patient will decrease their respiratory rate and tidal volume and increase the risk of barotrauma. If pressure support is low, a patient will increase their respiratory rate and reduce their tidal volume, which will increase oxygen consumption and work of breathing (Marraro 2003). If there is inhomogeneous lung pathology, PSV favors ventilation of better aerated areas without affecting collapsed lung areas, potentially worsening ventilation–perfusion mismatch (Marraro 2003). PSV may not be highly recommended for pediatric or neonatal patients because the tidal volume cannot be controlled from breath to breath (Marraro 2003). Hypoventilation may alternate with hyperventilation. In small patients, maintaining appropriate tidal volume is critical for maintenance of alveolar ventilation and avoidance of ventilator-induced lung injury from volutrauma (Marraro 2003).

Volume support ventilation (VSV) is a volume-targeted form of PSV. Breath by breath, VSV adapts the inspiratory pressure support based on changes of the mechanical properties of the lung to ensure that the lowest possible pressure is used to deliver a preset tidal volume (Marraro 2003). As lung pathology improves, the ventilator automatically adjusts the amount of pressure needed to generate the set tidal volume, avoiding the risk of volutrauma associated with high preset pressures (Marraro 2003).

8.1.3.3.1.5 Asynchrony

Patient–ventilator synchrony is an ideal matching of patient demand with ventilator support. Asynchrony is deleterious for patients because it may lead to increased need for sedation, increased work of breathing, respiratory muscle injury, ventilation–perfusion mismatch, dynamic hyperinflation, delayed weaning, increased length of hospital stay, and higher hospital costs (Nilsestuen and Hargett 2005). Asynchrony occurs in all modes of ventilation when a patient has spontaneous respiratory effort. PSV is thought to provide excellent synchrony with patient needs because it can identify both the beginning and end of a breathing effort (Brochard and Lellouche 2006). However, many types of asynchrony are still seen in PSV when the settings are not appropriate for patient demand. Three primary reasons for dyssynchrony in PSV are inappropriate pressure levels, inappropriate flow delivery, and inappropriate cycling-off criterion (Kacmarek and Chipman 2006).

The overall incidence of asynchrony during PSV in neonatal and pediatric patients is not well documented. In a recent animal study performed in young pigs recovering from lung injury, we found that when animals were healthy, the incidence of asynchrony occurred in 8 % of pneumatically triggered inflation (Heulitt 2012). When inflation were triggered via a neural signal from an EMG signal from the diaphragm, asynchrony was still low at 6 % of inflation. However, when the animal's lung was injured and after undergoing a recruitment procedure, the incidence of asynchrony in the pneumatically triggered inflation increased to 27 % of all inflation, while the neurally triggered inflation remained at 6 %. The level of asynchrony was directly related to increased response time and trigger delay in the pneumatically triggered inflation.

Inspiratory trigger delay is the time from when a patient starts their breath to when the inspiratory valve opens on the ventilator and the ventilator starts supporting the breath. Thus, it relates to the time from the beginning of inspiratory muscle activity to the beginning of mechanical inflation.

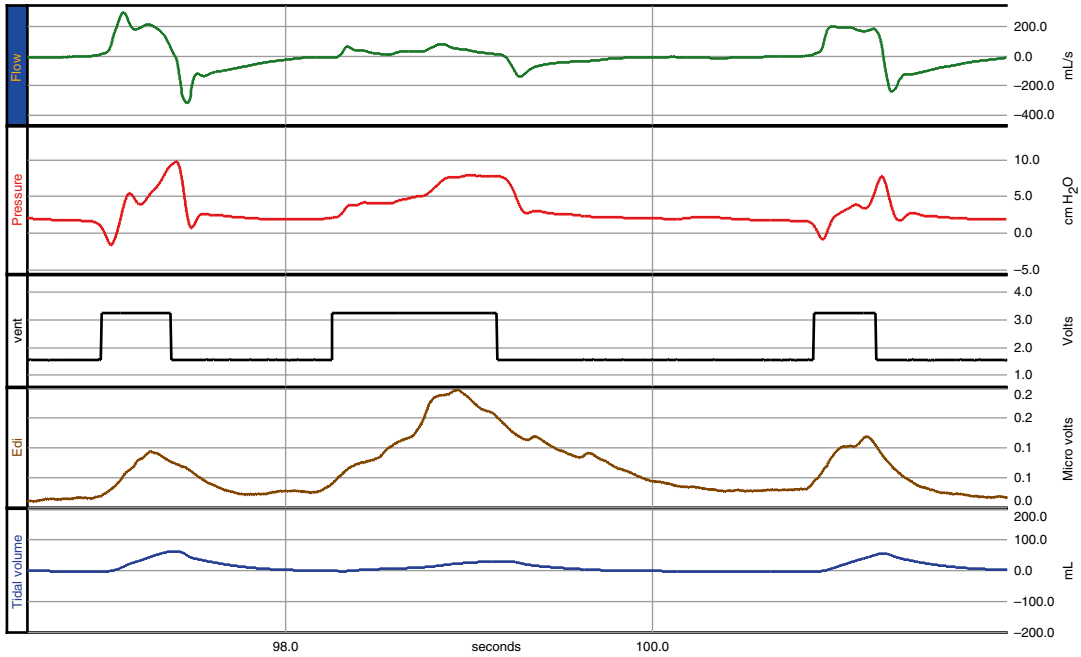


Fig. 8.18 Example of prolonged cycle due to trigger delay. Figure illustrates three inflation with waveforms of airway flow, pressure, and volume and ventilator trigger signal and diaphragm EMG tracing. In this example, trigger delay caused the inspiratory time in the second breath to be greater than two times previous and subsequent inflation causing a prolonged cycle

This delay can lead to patient–ventilator asynchrony. Figure 8.18 is an example of trigger delay. In this example of recordings of flow, pressure ventilator trigger signal (duration of inspiratory valve opening), muscular response measured by EMG activity of the diaphragm, and volume asynchrony are demonstrated when the inspiratory time is twice the mean inspiratory inflation for other inflation during the same time sequence. As illustrated in this example, the second breath has a markedly prolonged inspiratory time as compared to the breath before and after.

Table 8.6 lists potential factors affecting duration of trigger delay. These causes relate to ventilator characteristics and settings, patient characteristics, and circuit characteristics and interfaces. Ventilator characteristics relate to the type and setting of the trigger. Flow-triggering systems require less patient effort (and thus have less trigger delay) than pressure-triggered systems (Brochard and Lellouche 2006). Triggering effort is 10–30 % of a patient's total work of breathing, although the clinical implications of this are unclear (Brochard and Lellouche 2006). Inspiratory trigger delay can vary from 40 to 200 ms among different ventilator brands

Table 8.6 Factors affecting duration of trigger delay

Ventilator characteristics and setting	Type and setting of trigger
	Site of signal recording
	Ventilator valve design
	Level of pressure assistance
	Ventilator mode
Patient characteristics	Presence of dynamic hyperinflation
	Patient respiratory drive during trigger phase
	Upper airway resistance limited to noninvasive ventilation
Circuit characteristics and interfaces	Additional resistance (e.g., endotracheal tube, ventilator circuit, air sensor, HME)
	Presence of air leaks
	Accumulation of water in ventilator tubing

(Richard et al. 2002; Aslanian et al. 1998). If a patient has intrinsic PEEP, he will have to expend even more effort for triggering (Aslanian et al. 1998).

Ineffective triggering is when a patient's inspiratory effort does not trigger a ventilator breath (Thille et al. 2006). This type of asynchrony is directly influenced by the level of PSV and the amount of dynamic hyperinflation (Brochard and Lellouche 2006). It is probably the most common form of asynchrony seen in patients on PSV. Excessive assistance will lead to hyperinflation of the lungs and will depress respiratory drive because of high tidal volumes and prolonged inspiration beyond the end of patient effort (Thille et al. 2006). If a patient is weak and/or the level of support is too high, he will be unable to decrease pressure or reverse expiratory flow enough to trigger the ventilator, and his effort will be wasted (Brochard and Lellouche 2006). Leung et al. found there were very few ineffective efforts below 60 % of assistance, but the number of ineffective efforts increased steadily as assistance increased (Leung et al. 1997). Respiratory cycles before these wasted efforts had higher tidal volumes and lower inspiratory times, both of which will lead to increased levels of hyperinflation (Leung et al. 1997). In a study by Thille, 85 % of asynchrony events were due to ineffective triggering (Thille et al. 2006). High pressure support levels and high tidal volumes were associated factors for ineffective triggering in these patients (Thille et al. 2006). In a second study, reducing the pressure support level completely eliminated ineffective triggering in 2/3 of patients and decreased tidal volume to 6 mL/kg predicted body weight (Thille et al. 2008). There was no increase in respiratory muscle energy expenditure and alveolar ventilation remained unchanged (Thille et al. 2008).

During auto-triggering, the ventilator is falsely triggered by a signal not related to a patient's inspiratory effort. This asynchrony is a type of trigger asynchrony and can be caused by leaks in the ventilator circuit, motion in the circuit, cardiac oscillations, or excessively sensitive trigger sensitivity settings (Thille et al. 2006; Imanaka et al. 2000). A sudden increase in respiratory rate, a persistently high respiratory rate, or an absence of airway pressure drop at the start of an inspiration are all clues that the ventilator may be auto-triggering (Brochard and Lellouche 2006).

Two or more ventilator inflation delivered with a single patient effort are called multiple cycles or "double triggering" (Thille et al. 2006). Double triggering is also termed "stacked inflation" and is exemplified when the delta time between the ventilator trigger is less than one half the mean inspiratory time for inflation during time studied. Stacked inflation can occur with and/or without expiratory flow between the triggers. Figure 8.19 is an example of stacked inflation. Auto-triggering is one cause of this type of asynchrony as is a short ventilator refractory period (Brochard and Lellouche 2006). Double triggering often occurs when a patient's respiratory demand is high and the ventilator inspiratory time is too short (Tokioka et al. 2001). Tokioka et al. described multiple cycles during PSV when the cycling-off criteria were high (Tokioka et al. 2001).

The rate of the pressurization of a breath determines the initial upstroke of the pressure–time curve and is primarily dependent on the initial peak flow rate set on the ventilator (Brochard and Lellouche 2006). Flow dyssynchrony is related to the rise time, patient respiratory drive, and ventilator performance (Brochard and Lellouche 2006). Choosing a low rate of pressurization results in a greater length of time to reach goal levels of PSV and a convex initial airway pressure curve (Kacmarek and Chipman 2006). The longer it takes to reach the set pressure level, the greater the work of breathing for patients with both obstructive and restrictive lung disease (Bonmarchand et al. 1999). Figure 8.20 is an example of the convexity of the initial pressurization. In this example the presence of the convexity occurs after the inspiratory valve closes, and diaphragm muscular activity continues despite this closure. It is important to note that excessively fast pressurization, however, will lead to an initial overshoot beyond

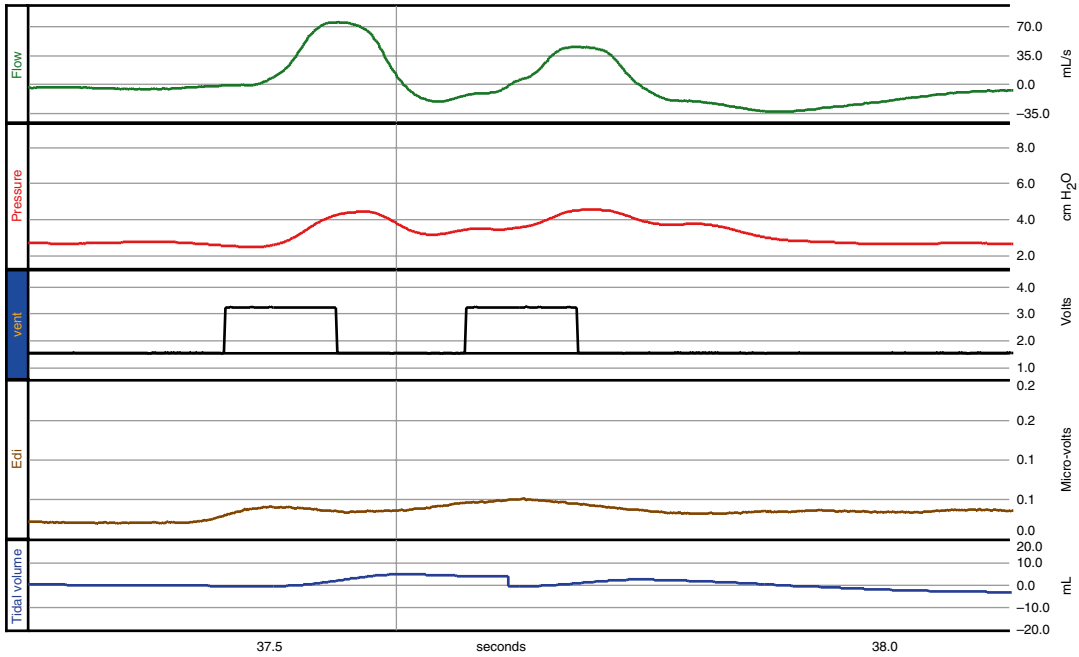


Fig. 8.19 Example of trigger asynchrony with stacked inflation. Figure illustrates two inflation with waveforms of airway flow, pressure, and volume and ventilator trigger signal and diaphragm EMG tracing. In this example delta time between the ventilator triggers is one half of the mean inspiratory time for other inflation in the study. Stacked inflation occur with or without expiratory flow between the triggers

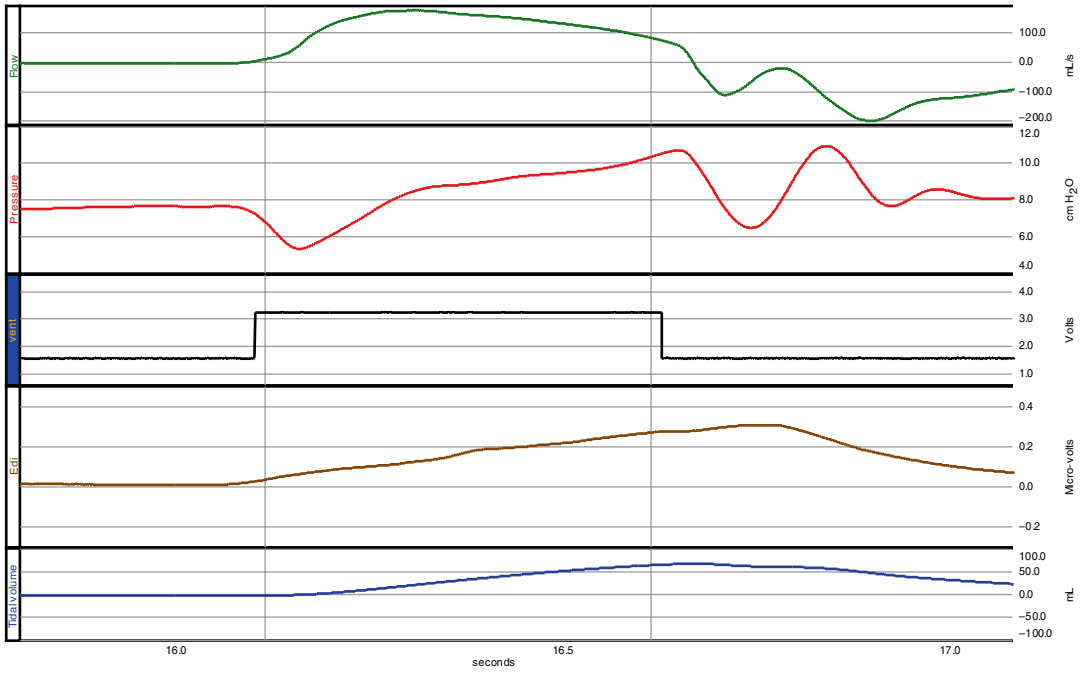


Fig. 8.20 Example of trigger asynchrony with effort without response. Figure illustrates two inflation with waveforms of airway flow, pressure, and volume and ventilator trigger signal and diaphragm EMG tracing. In this example there is evidence of concavity of the pressure waveform. It is important to note that the muscular activity exemplified as the diaphragm activity occurs after the inspiratory valve closes

the goal pressure level, leading to potential early cycle termination related to high pressure and thus asynchrony (Brochard and Lellouche 2006).

If the cycling-off criterion is reached too early, the ventilator stops insufflation and opens the expiratory valve, while patient inspiratory effort continues (Brochard and Lellouche 2006). This type of asynchrony is referred to as early cycling off. It occurs when the cycling-off criterion is based on flow decay or time, as it is during PSV (Brochard and Lellouche 2006). If the expiratory valve opens while a patient is still actively inspiring, there is an initial drop in airway pressure and flow, followed by an increase, which results in a characteristic contour to the pressure–time curve (Tokioka et al. 2001). This type of asynchrony causes increased patient effort and prolonged neural inspiratory time (Brochard and Lellouche 2006).

Conversely patient characteristics such as dynamic hyperinflation may lead to delayed expiration which is the difference between the end of a patient's neural inspiratory time and the termination of inspiration by the ventilator (Brochard and Lellouche 2006). In PSV, the cycling-off criterion is typically a percentage of peak inspiratory flow rate, which often differs between patients with obstructive vs restrictive lung disease (Brochard and Lellouche 2006). Tokioka found an increase in tidal volume and decrease in respiratory rate when the cycling-off criterion was decreased from 45 to 1 %, and work of breathing was less with this low cycling-off criterion as well (Tokioka et al. 2001). This finding suggests that low cycling-off parameters should be considered in patients with acute lung injury (Brochard and Lellouche 2006). However, in patients with obstructive lung disease, a higher cycling-off criteria may be better (Tassaux et al. 2003). Low cycling-off criteria may cause insufflation to continue beyond patient neural inspiratory time, resulting in activation of a patient's expiratory muscles before the end of the ventilator breath, leading to short expiratory times and increased dynamic hyperinflation (Jubran et al. 1995).

For patients on noninvasive ventilation, prolonged inspiration can also occur, typically due to leaks around a mask (Calderini et al. 1999). The cycling-off criterion can never be reached because of the leaks, and the ventilator continues to deliver a breath until the maximum inspiratory time (several seconds) is reached (Brochard and Lellouche 2006). Patients may then fight the ventilator in this situation (Brochard and Lellouche 2006).

Future Perspectives

Pressure support was introduced as mechanical ventilator mode in the 1980s. Since that time different technical advances have been introduced to allow patients to breathe spontaneously during PSV, for example, by the introduction of flow triggering. Currently patients breathing on PSV have a high incidence of asynchrony. Future advances have focused on redirecting the site of triggering from a generated at the patient's airway to one from an EMG signal from the patient's diaphragm. This signal theoretically has the advantage of decreasing trigger delay and allowing a closed-loop system to adjust the level of support to the strength of this signal.

Essentials to Remember

- PSV is a patient-triggered, pressure-limited, and flow-cycled form of mechanical ventilation used in patients with intact respiratory drive.
- The three major phases of PSV (initiation, pressurization, and cycling off) may vary among ventilators, may be altered by patient effort, and/or may be adjusted by the clinician in some circumstances.
- A major goal of PSV is to provide respiratory assistance while improving a patient's work of breathing. The decrease in work of breathing is significant and is proportional to the level of PSV.

8.1.3.3.2 Proportional Assist

Andreas Schulze and Eduardo Bancalari

Learning Objectives: To Understand

- The basic concept of proportional assist ventilation and respiratory mechanical unloading
- How the clinician can select ventilator settings with these modes that are specific for the individual type and extent of disease-related derangements in pulmonary mechanics (compliance, resistance, functional residual capacity)
- That volume-proportional assist (elastic unloading) is indicated in restrictive lung disease (low lung compliance)
- That flow-proportional assist (resistive unloading) is indicated in obstructive airway disease (high airway resistance)
- That PEEP influences the functional residual capacity during proportional assist as it does with other modalities
- Safety features during proportional assist ventilation such as backup ventilation modes and airway pressure limits

8.1.3.3.2.1 General Aspects

Patient-triggered ventilation typically synchronizes one or two events of the ventilator cycle to certain points in the spontaneous respiratory cycle. For example, the ventilator attempts to identify the onset of a spontaneous breath and subsequently delivers an upstroke in ventilator pressure. Other characteristics of the ventilator pressure contour such as peak inflation pressure and others remain preset by the clinician and may or may not match patient needs. The strategy of "proportional assist ventilation" (PAV) is fundamentally different from the conventional perception of a ventilator being a "pump" that is ignited by a trigger event. With PAV, the ventilator pressure steadily follows a continuous input signal that is derived from the infant's spontaneous breathing effort. This is achieved by an ongoing servo control of the ventilator pressure. The delivered pressure rises during inspiration in a fashion that is proportionate with a patient-derived signal at any point in time. During full-cycle "respiratory mechanical unloading" (RMU), the airway pressure is servo controlled throughout the entire respiratory cycle, not just during inspiration (Schulze and Schaller 1997). For such proportional amplification modes, the ventilator pressure has to track the input signal virtually without a time lag. This implies that near-perfect synchrony between the patient's spontaneous effort and the ventilator can be achieved (Fig. 8.21). In addition, a relief in work of breathing ensues.

8.1.3.3.2.2 Clinical Application in Infants

When applying PAV/RMU, the clinician selects three *independent* settings to address *the individual degree* of impairment in compliance, resistance, and FRC:

1. The gain of elastic unloading (volume-proportional assist) which relieves elastic work of breathing for patients with "stiff lungs" (Schulze et al. 1993a). This gain is adjusted on a continuous scale in cm H_2O/mL (applied ventilator pressure per unit of tidal volume) (Fig. 8.22).
2. The gain of resistive unloading (flow-proportional assist) which relieves resistive work of breathing for patients with obstructive airway disease or those with a high-resistance endotracheal tube (Schulze et al. 1990). This is adjusted in cm H_2O/L/s (applied ventilator pressure per unit of airflow) (Fig. 8.23).
3. The PEEP which influences the FRC as it does during conventional mechanical ventilation (Schulze et al. 1993b).

A simple way to initiate PAV/RMU in a clinical setting is to start with zero gains so that the patient briefly breathes without the assist at constant positive airway pressure (CPAP). The elastic unloading gain is then gradually increased to a level judged as "appropriate" by clinical criteria such as reduction in chest wall

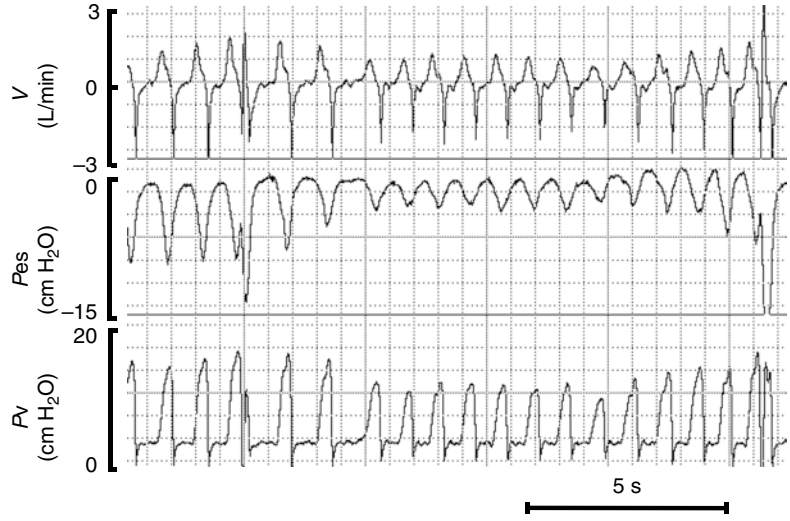
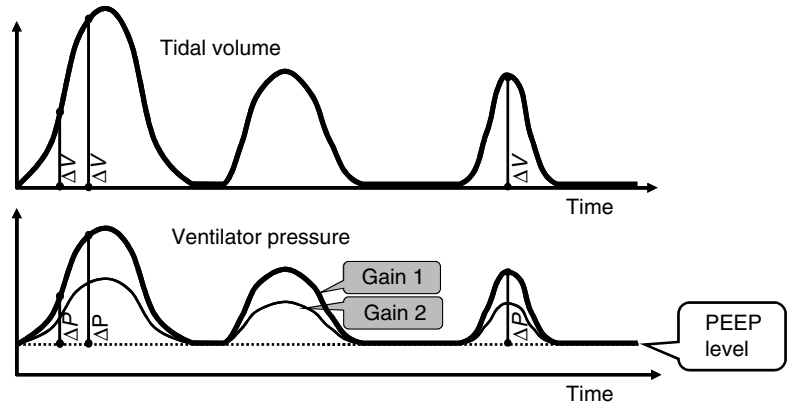


Fig. 8.21 Tracings for a preterm infant supported by proportional assist ventilation. Note the breath-by-breath variability in ventilator pressure which reflects the changing strength of the respiratory effort between inflation in this infant. Sighs (third and last breath on this recording) fail to induce major increases in ventilator pressure because upper ventilator pressure limits are in place as safety feature. The ventilator pressure is aborted to the PEEP level when the upper pressure limit is reached, *V'* airflow as measured at the ventilator Y, *Pes* esophageal pressure, P_v ventilator pressure



$$\text{Gain} = \frac{\Delta \text{ Ventilator pressure } (P, \text{ cm } H_2O)}{\Delta \text{ Tidal volume } (V, \text{ mL})}$$

Fig. 8.22 Schematic representation of spontaneous breathing during volume-proportional assist (elastic unloading) at two different settings (gain 1 and gain 2) of the assist gain level. Vertical lines demonstrate that the gain (ratio of change in ventilator pressure per unit of change in tidal volume) is maintained constant over time while the tidal breathing pattern varies. Gain setting two represents a lower level of the assist

distortion, physiological tidal volume, and regularity of breathing. It should be considered that smaller infants will need higher gains of elastic unloading (in absolute terms, i.e., in cm H_2O/mL) because tidal volume and compliance relate to body weight. As a general rule, infants below 1,000 g of body weight usually need about 1 cm H_2O/mL or more of elastic unloading gain while larger infants need less (Schulze and Bancalari 2001). The selected gain of resistive unloading should at least compensate for the resistance imposed by the endotracheal tube. This is about 20–30 cm H_2O/L/s of resistive unloading for a 2.5-mm ID endotracheal tube. Higher gains may be required when pulmonary resistance is elevated.

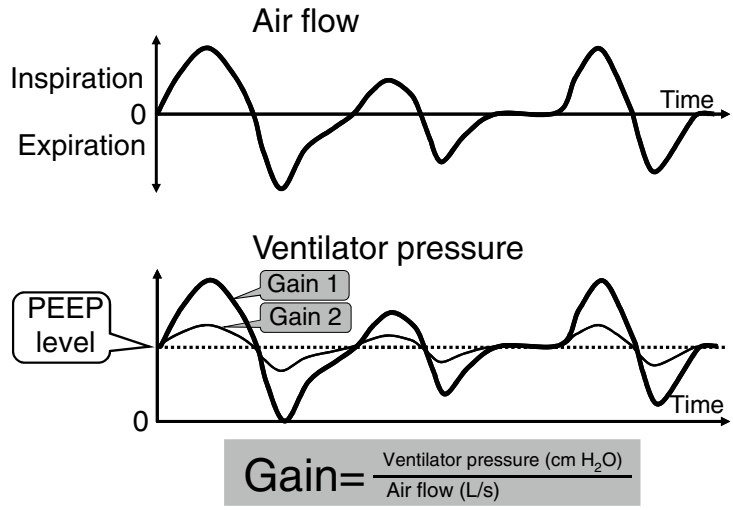


Fig. 8.23 Schematic representation of spontaneous breathing during flow-proportional assist (full-cycle resistive unloading) at two different settings (gain 1 and gain 2) of the assist gain level. *Vertical lines* indicate that ventilator pressure changes occur virtually without a time lag to the airflow signal. The gain (ratio of change in ventilator pressure per unit of airflow) is maintained constant over time while the tidal breathing pattern varies. Gain 2 represents a lower level of the assist

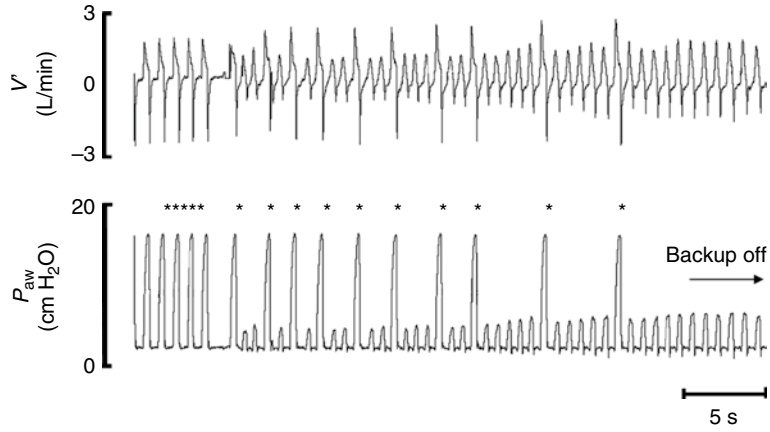


Fig. 8.24 Tracing of airflow ($\dot{V}$), airway pressure (P_{aw}), and oxygen saturation (SpO_2) from an 840 g infant during backup ventilation and resumption of spontaneous breathing. Backup is gradually weaned by a stepwise reduction in the mechanical inflation rate until the full spontaneous breathing is recovered. Each spontaneous breath is supported by PAV. *Asterisks* indicate mechanical backup inflations

8.1.3.3.2.3 Backup Conventional Ventilation for Apnea and Hypoventilation

An automatic initiation of backup conventional ventilation is required not only during apneic episodes but also in the event of hypoventilation. Small inspiratory efforts will receive little ventilator pressure assist, and hypoventilation will occur if respiratory efforts decrease significantly. PAV modalities for infants should therefore include:

1. Initiation of backup ventilation in response to cessation of spontaneous breathing. The interval between the last detected breath and the onset of backup should be user adjustable because smaller and sicker infants tolerate less unsupported time.
2. Initiation of backup in response to a decrease in tidal volume below an adjustable threshold.
3. Gradual weaning from backup support when spontaneous breathing is resumed. This is necessary because breathing after an apnea is often initially weak and needs time to regain its former strength (Fig. 8.24). The ventilator should provide a feature which allows the user to adjust how fast backup is withdrawn (Herber-Jonat et al. 2006).

8.1.3.3.2.4 Technology

Spontaneous breathing activity drives the ventilator pressure output in the PAV/RMU modes by means of a feedback circuit. The driving signal can theoretically be obtained anywhere along the

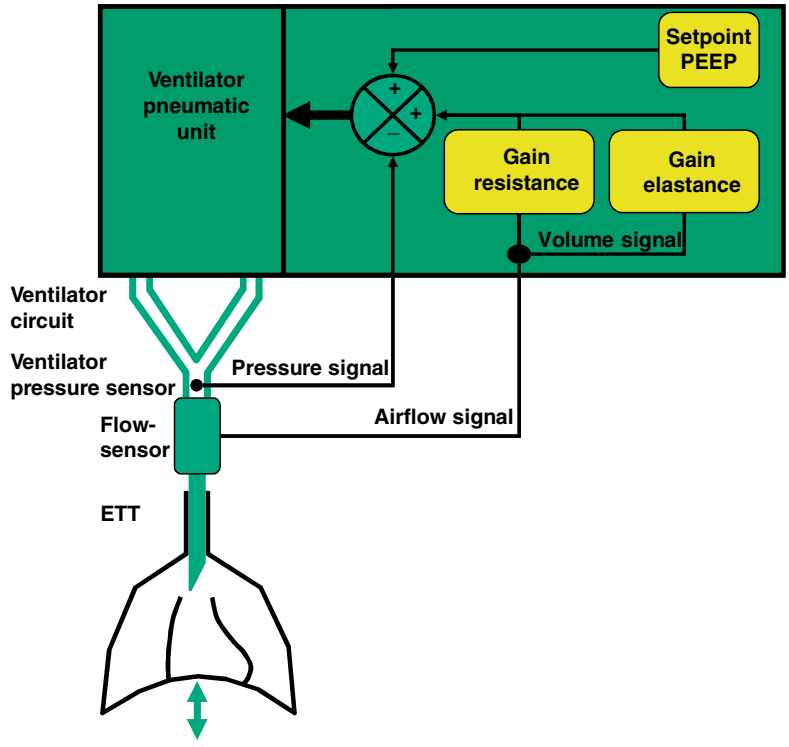


Fig. 8.25 Scheme of a ventilator system for PAV/RMU in infants. Airway pressure is sensed close to the endotracheal tube adapter and the signal is fed into a rapid negative feedback loop. To generate resistive unloading, i.e., flow-proportional assist, the airflow signal as measured at the endotracheal tube adapter is superimposed on the (negative) pressure-feedback circuit such that the airway pressure rises above CPAP during inspiration and decreases below CPAP when there is expiratory flow. To generate elastic unloading, i.e., volume-proportional assist, the tidal volume signal is obtained by integration of the airflow signal. After processing, it is superimposed on the pressure-feedback circuit such that the airway pressure rises in proportion with the tidal volume. The user sets amplification factors (gains, K_R in cm H_2O/L/s and K_E in cm H_2O/mL) for resistive and elastic unloading. The generated airway pressure is a servo-controlled, moving variable which is at any point in time a weighted sum of the airflow and tidal volume signal, added to the CPAP set point value $P_{aw} = (K_R \times \dot{V}) + (K_E \times V) + (\text{CPAP setpointnt})$ (where $\dot{V}$ = airflow and V = volume). Because the system is software driven, almost every ventilatory modality can be generated provided that the hardware response times are sufficiently short

pathway from the respiratory center to the end organ, i.e., recorded as phrenic nerve activity, diaphragmatic electric activity, but also as tidal volume and airflow signals from probes inside the airway or from plethysmography. In this chapter, proportional amplification techniques will be explained that are based on tidal volume and airflow signals of spontaneous breathing. This is volume-proportional assist ventilation and flow-proportional assist ventilation, which is also called elastic and resistive unloading. Commonly, the driving signals are derived from flow probes mounted between the endotracheal tube and the ventilator Y (Fig. 8.25). Ideally, ventilator pressure changes should occur in phase with the command signal derived from the airflow/volume signals. However, some mechanical delay is dictated by the system's inherent compliance, resistance, and inertance and will inevitably occur. PAV/RMU for preterm infants with their typical high respiratory rates and very small tidal volumes require exceptionally rapid feedback circuitry, low internal ventilator circuit compliance, and precise airflow/volume tracking.

Depending on the selected gains, the ventilator amplifies the output (which is the ventilation)

of the driving signal (which is the respiratory effort) more or less. Similar systems are widely used in electronic engineering. For example, a microphone–loudspeaker system works on the same principle: Sound waves are received, electronically transformed, their signal proportionally amplified, and used to drive the output of a sound wave generator. The gain, i.e., the degree of amplification, can be adjusted to suit individual circumstances.

8.1.3.3.2.5 Terminology and Therapeutic Objectives

While the basic concept of mechanical unloading for conditions characterized by impaired respiratory mechanics dates back to the 1950s (Biernson and Ward 1958), servo-controlled respiratory unloading devices with an appropriate dynamic response for adults (Poon and Huang 1987) and infants (Schaller and Schulze 1991) have been designed since the 1980s.

Investigators have used diverse terminology such as negative impedance ventilation, negative ventilator elastance and negative ventilator resistance, or resistive/elastic unloading (Schulze et al. 1993b). The term "proportional assist ventilation" as introduced in 1992 (Younes 1992) was meant to specifically denote a method of support in which the ventilator provides only *inspiratory* support in proportion to the instantaneous pressure generated by the respiratory muscles (P_{mus}), i.e., the simultaneous use of *both* flow- *and* volume-related assist with gains below the patient's resistance and elastance.

However, all these devices share a common essential feature: They generate airway pressure in proportion to the instantaneous tidal airflow and/or volume with their respective proportionality factors (weights, gains) selectively adjustable by the user. Nevertheless, the different groups of investigators did have different specific objectives: Younes et al. primarily saw the technique as a means to amplify respiratory muscle effort (P_{mus}) and applied it in adults (Younes et al. 1992). Schulze et al. intended to use an infant ventilator to restore impaired lung mechanics to an "apparently" normal state. They therefore suggested to calculate the magnitudes of "negative ventilator resistance and elastance" required to specifically compensate for the degree of an individual patient's obstructive and/or restrictive lung disease. This concept of returning apparent respiratory mechanics back to normal also implied the use of unloading throughout the entire respiratory cycle (Schulze et al. 1990, 1993a).

8.1.3.3.2.6 Physiological Effects of PAV/RMU Effect on Elastance

"Elastance" (E) describes a behavior of a system in which a certain change in pressure occurs necessarily with a given change in volume. It can be measured in units of cm H_2O per mL. Lung elastance (E_l) causes a rise in lung elastic recoil pressure per unit of tidal volume gained. During a normal inspiration, a decreasing pleural pressure needs to be generated by the respiratory muscles to overcome the rising lung elastic recoil pressure. The inspiratory rise in elastic recoil pressure can be opposed by a rise in positive airway pressure. If the rise in positive airway pressure is applied by a ventilator such that it increases in proportion to the tidal volume, the ventilator itself exerts an "elastic behavior" characterized by the change in ventilator pressure per unit of tidal volume. This elastance of the ventilator (E_v) is equally quantifiable in cm H_2O/mL. However, while lung elastic recoil pressure tends to collapse the lung, the ventilator pressure acts in the opposite direction in the elastic unloading mode. Relative to lung elastance, the elastic "behavior" of the ventilator is therefore "negative." When a patient is connected to a ventilator in the elastic unloading mode, the overall elastance of the combined system of lung and ventilator is equal to the arithmetic sum of the two elastic elements (because they are interconnected "in series"):

$$E_c = E_l + E_v$$

with E_v being a negative term.

The respiratory muscles work against this overall elastance of the combined system which becomes lower than lung elastance itself when the negative elastic behavior of the ventilator is added. If ventilator elastance is adjusted such that the overall elastance approaches the magnitude

of a normal lung's elastance, respiratory muscles will work on a system of apparently normal elastance. It follows that the patient's elastic work of breathing will then be in the normal range while the disease-related part of the elastic work of breathing is eliminated by the ventilator. To calculate the magnitude of ventilator elastance needed to achieve a "normal" overall elastance, the equation has to be solved for E_v:

$$E_v = E_c + E_l$$

For example, an infant weighs 750 g and has a measured respiratory system compliance of 0.3 mL/cm H_2O. The following steps are required to calculate precisely the gain of elastic unloading that returns the infant's elastic work of breathing to normal:

1. It is assumed that a normal lung of a newborn infant has a compliance of 2 mL/cm H_2O/kg. In a 750-g infant, a "normal" lung should therefore have a compliance of 1.5 mL/cm H_2O. Because *elastance* is the inverse of *compliance*, the target overall system elastance ("normal" lung elastance) should be $E_c = 1/1.5 = 0.67$ cm H_2O/mL.
2. Because the infant's measured lung compliance was 0.3 mL/cm H_2O, the elastance was $E_l = 1/0.3 = 3.33$ cm H_2O/mL, the applied ventilator elastance should be

$$E_v = 0.67 - 3.33 = -2.66\,\text{cm}\,H_2O/\text{mL}$$

Thus, if the ventilator is set to raise the airway pressure by 2.66 cm H_2O for each mL of tidal volume, this infant's elastic work of breathing would be in the "normal range."

This example shows that the required level of elastic unloading (gain) in cm H_2O/mL depends not only on the absolute stiffness of the lungs but also on body weight. Smaller infants will require higher gains. This is because "normal" lung compliance varies directly with body weight. Because the normal tidal volume in infants also varies directly with body weight, the respiratory muscle pressure amplitude required to generate a normal tidal volume is relatively constant across different body weights.

For clinical purposes, it is sufficient to base the estimate of the required elastic unloading gain on measurements of *total respiratory system compliance* rather than *lung compliance*. The former variable is easier to measure because it does not require esophageal pressure manometry. Total respiratory system compliance is not very different from lung compliance in premature infants because of their soft chest wall (high chest wall compliance).

Effect on Resistance

Similar to elastic unloading, the applied ventilator pressure waveform during resistive unloading is in close relation to the *airflow* of spontaneous breathing, and this "behavior" can be described as a "negative resistance," i.e., a certain change in applied pressure per unit of airflow (cm H_2O of ventilator pressure per L/s). For a patient on a ventilator, the overall resistive load on respiratory muscles is the sum of the different components:

$$R_c = R_{aw} + R_{ETT} + R_v$$

with R_{aw} being the airway resistance, R_{ETT} the endotracheal tube's resistance, and the ventilator's resistance R_v, the latter being a negative term.

For example, an infant is intubated with a 2.5-mm inner diameter endotracheal tube. This endotracheal tube has an estimated resistance of 20 cm H_2O/L/s. If the gain of resistive unloading is set at – 20 cm H_2O/L/s, the infant can breathe as if the endotracheal tube's resistance would not be in place. The ventilator specifically relieves the amount of additional resistive work of breathing associated with this endotracheal tube.

Effect on Chest Wall Distortion

Impairment of respiratory mechanics in infants is associated with increased chest wall distortion (CWD). CWD further increases respiratory muscles' work of breathing because work is "wasted" in distorting the chest. This reduces the efficiency of the respiratory muscles' to generate ventilation. Compensating for impaired respiratory mechanics by unloading decreases CWD and therefore improves the efficiency of respiratory muscles. This has been demonstrated in small adult and newborn animals who were intubated and had their lungs injured with

meconium (Schulze et al. 1998b) and in very low-birth-weight infants with acute respiratory illness (Musante et al. 2001). These studies have also shown that compared to unassisted breathing, a larger fraction of the tidal volume enters the chest compartment while the displacement of the abdominal compartment does not change much with respiratory mechanical unloading. Unloading can therefore provide a "stenting pressure" and stabilize the preterm infant's highly flexible chest wall during spontaneous breathing.

Effects on Control of Breathing

Respiratory center output is increased in lung disease with impaired respiratory mechanics. It has been shown in animal models with severe pulmonary parenchymal failure that PAV/RMU decreases phrenic nerve activity while tidal volume rises and blood gases improve (Schulze et al. 1999b).

Overcompensation of Lung Elastic Recoil and Pulmonary Resistance

Magnitudes of unloading that equal or surpass lung elastic recoil (or pulmonary resistance) may induce a runaway of the ventilator pressure. In such situation, a small initial change in volume (airflow) triggers an increase in ventilator pressure higher than the accompanying rise in lung elastic recoil (flow-resistant airway pressure gradient) which in turn further increases lung volume (airflow). This positive feedback self-perpetuates because the negative elastance of the ventilator exceeds the positive elastance of the respiratory system. With such excessive gain settings, artifacts on the volume/airflow signal may initiate ventilator pressure runaway up to the set ventilator pressure limit or a set tidal volume limit. Unless ventilator pressure limits are in place, overcompensation of lung elastic recoil (excessive gains of volume-proportional assist) will lead to a self-perpetuating passive inflation. This process will not be terminated until overinflation leads to stiffening of the lung (increased lung elastance, decreased lung compliance) so that the ventilator pressure finally equals lung elastic recoil pressure (lung elastance equals the magnitude of the set "negative" ventilator elastance). As lung recoil pressure is completely balanced by the ventilator pressure at this point, passive expiration will still not ensue even though the inspiratory effort may be long over. Therefore, besides tidal volume limits, an airway pressure limit and an inflation time limit should always be in place during PAV/RMU (Schulze et al. 1998a).

Full compensation of pulmonary resistance (when negative ventilator resistance equals pulmonary resistance in magnitude) induces sinusoidal oscillations of the respiratory system near its resonant frequency. This phenomenon can be explained by electrical or mechanical analogies of the respiratory system. The amplitude of the oscillations increases with higher gains of resistive unloading so that a variant of high-frequency oscillatory ventilation near the resonant frequency may be generated (Schulze et al. 1991).

Effect of Endotracheal Tube Leaks

A leak around the endotracheal tube will be measured as inspiratory airflow and volume by the pneumotachograph that is mounted at the endotracheal tube adapter. In the PAV/RMU modes, this will cause a rise in airway pressure out of proportion to the airflow and volume entering the lung. In case of a substantial leak, the ventilator pressure will rise rapidly to the set pressure limit and then fall to the PEEP level and may rise again repetitively. However, the leak component of the airflow signal can be estimated by the ventilator so that the airway pressure changes can then be based on a corrected flow signal (Fig. 8.26). With appropriate algorithms, PAV/RMU devices for infants can perform satisfactorily in the presence of variable leaks of up to 20–30 % of the tidal volume.

8.1.3.3.2.7 Studies on PAV/RMU in Small Animal Species and Infants

PAV/RMU has been extensively studied in small adult and newborn animals with normal lungs and in various models of neonatal lung diseases such as surfactant deficiency and meconium aspiration. A clinical study on preterm infants compared PAV to assist control and to conventional mechanical ventilation in a crossover design in 36 infants (body weight 600–1,200 g) with mild

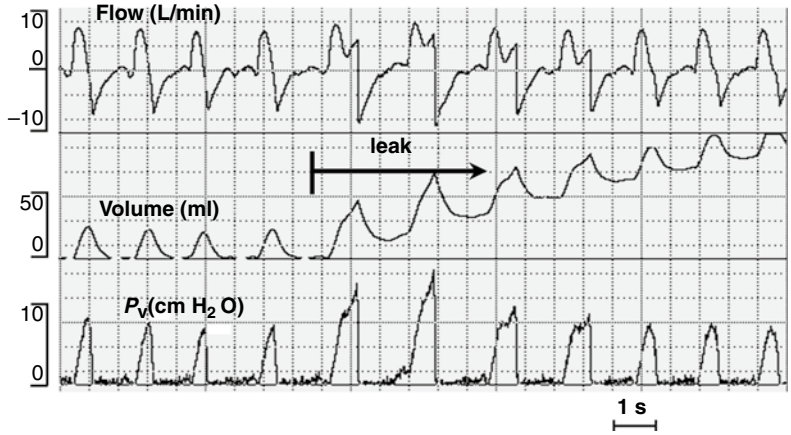


Fig. 8.26 Sudden opening of a substantial endotracheal tube leak during proportional assist ventilation: Note that the ventilator pressure increases during inspiration out of proportion with the tidal volume signal and reaches the upper ventilator pressure limit. Four inflation later, however, it returns to its pre-leak contour although the leak persists. An algorithm in the ventilator software recognizes the air leak, calculates its average size, and subsequently subtracts leak flow from the measured total inspiratory airflow. Recording from a normal piglet

to moderate acute respiratory illness (Schulze et al. 1999a). Short-term physiological outcome variables were evaluated. During PAV, required mean airway pressures and transpulmonary pressures were lower at equivalent oxygen exposure, equivalent pulmonary oxygen uptake, and a similar CO_2 removal rate. Under the strictly controlled conditions of the study, PAV appeared safe and at least as effective as the comparison conventional modes. Infants on PAV typically showed a "fast and shallow" respiratory pattern, with respiratory rates about between 50 and 80/min. Tidal volumes were usually smaller than 5 mL/kg. Because preterm infants with their immature renal function are often slightly acidotic, it had been suspected that infants might hyperventilate when enabled to do so with PAV. This, however, was not corroborated. PAV was subsequently investigated in 22 chronically ventilator-dependent preterm infants (mean birth weight 705 g) in a crossover study design with conventional patient-triggered ventilation (Schulze et al. 2007). Ventilator pressure cost of ventilation was statistically significantly lower during PAV compared to the conventional triggered control mode. Recently, improved adaptive backup ventilatory strategies for episodes of cessation of the respiratory drive and oxygen desaturation during PAV have been shown to be effective in preterm infants (Herber-Jonat et al. 2006). In addition, PAV has been used in studies investigating various aspects of the regulation of spontaneous breathing in preterm infants. However, PAV has not been formally evaluated as the initial and sole ventilatory modality in preterm infants with respiratory failure. Also, its utility in infants with other types of pulmonary or cardiac diseases has not been studied.

8.1.3.3.3 Adaptive Support Ventilation

Jean-Michel Arnal

Educational Aims

- Understand the physiological background and the principle of functioning.
- Know how to set, adjust, and monitor.
- Review the evidences for passive and active breathing patients in adult and pediatric.

8.1.3.3.3.1 Adaptive Support Ventilation Introduction

Closed-loop ventilation modes are designed to adjust automatically some settings based on measurement obtained from the patient. A lot of closed-loop control of ventilation (Saxton

and Myers 1953; Frumin 1957; Mitamura et al. 1971; Coles et al. 1973; Schulz et al. 1974; Coon et al. 1978; East et al. 1982; Ohlson et al. 1982; Chapman et al. 1985; Rudowski et al. 1991), mechanical pump (Younes 1992; Dojat et al. 1992; Iotti et al. 1996), oxygenation (Yu et al. 1987; East et al. 1991), or combined systems (Mitamura et al. 1975; East et al. 1986; Strickland and Hasson 1991; Waisel et al. 1995) have been described, but few of them are commercially available. Adaptive support ventilation (ASV) is at the present time the only closed-loop ventilation mode to accommodate both for passive and active breathing patients. Based on continuous measurement of pulmonary mechanics, it is conceptually capable of following the disease process automatically and delivers a breath pattern adapted to the respiratory system mechanics.

Japanese authors were the first to report adjustment of tidal volume (V_T) and respiratory rate (RR) to control CO_2 and to introduce work of breathing (WOB) as a parameter to select the breath pattern (Mitamura et al. 1971, 1975). Laubscher et al. carried the idea further and made the transition from passive to active ventilation an integral part of their adaptive lung ventilation (ALV) and its commercial implementation of ASV (Laubscher et al. 1994a). Although ASV has been available for more than 10 years, clinical experience reported was mainly in the adult population, and pediatric experience remains scarce.

Principles of ASV

The basic principle of ASV stems from the work by Otis et al. (1950) and Mead (1960) demonstrating that, for a given level of alveolar ventilation, there is a particular RR that minimize the WOB. This optimal RR is the best compromise between elastic WOB and resistive WOB (Fig. 8.27) and depends on the minute volume (MV), the expiratory time constant (RC_{exp}), and the dead space (V_D). To initiate ASV, the clinician sets the patient's predicted body weight (PBW) and the percentage of minute ventilation (100 % being equal to 100 mL/kg PBW/min in adult patients). V_D is computed by the Radford monogram at 2.2 mL/kg PBW. The ventilator then delivers five test inflation to determine RCexp by analysis of the expiratory flow–volume curve (Brunner 2001; Brunner and Iotti 2002; Laubscher et al. 1994b; Brunner et al. 1995; Lourens et al. 2000). Thereafter, the ventilator compute the target V_T and RR, and mechanical ventilation starts using an interbreath negative control of V_T and RR to drive the patient's breath pattern to the target V_T and RR (Brunner 2002). In passive patients unable to trigger a breath, the ventilator generates pressure-controlled inflation and automatically adjusts the inspiratory pressure (P_{insp}) and timing to achieve the target V_T and RR. In active patients able to trigger a breath, the ventilator switch to pressure support inflation, automatically adjusting P_{insp} to achieve the target V_T, and it delivers additional pressure-controlled inflation if the patient's RR is below the target RR. During the maintenance, RCexp is estimated on a breath-by-breath basis to reassess the target and adjust P_{insp}, I:E ratio, and mandatory RR to maintain the target MV and RR within a frame designed to avoid both rapid shallow breathing and excessive inflation volumes. These safety limits to prevent markedly abnormal ventilator settings are automatically determined or can be manually adjusted. The limits are (min–max) as follows: inspiratory pressure (5 cm H_2O above PEEP to 10 cm H_2O below set P_{max}), V_T (4.4 mL/kg PBW to 22 mL/kg PBW), mandatory respiratory rate (5/min to 20/RC_{exp}/min), inspiratory time (0.5–2 s), expiratory time (3 RC_{exp} to 12 s), and inspiratory/expiratory time ratio (1:4–1:1). The rather high value of 22 mL/kg PBW for the upper limit of tidal volume can be set at a lower level to avoid lung overdistension by setting P_{max}.

Settings, Adjustments, and Monitoring

At initiation, clinician has to set MV by setting PBW and %MV. It is crucial to set properly the PBW and not the actual body weight. A large discrepancy between PBW and set body weight may result in large V_T delivered (Dongelmans et al. 2008). Usually, %MV is set at 100 % as a starting point (110 % if an HME or heat and moisture exchanger is used on the ventilatory circuit).

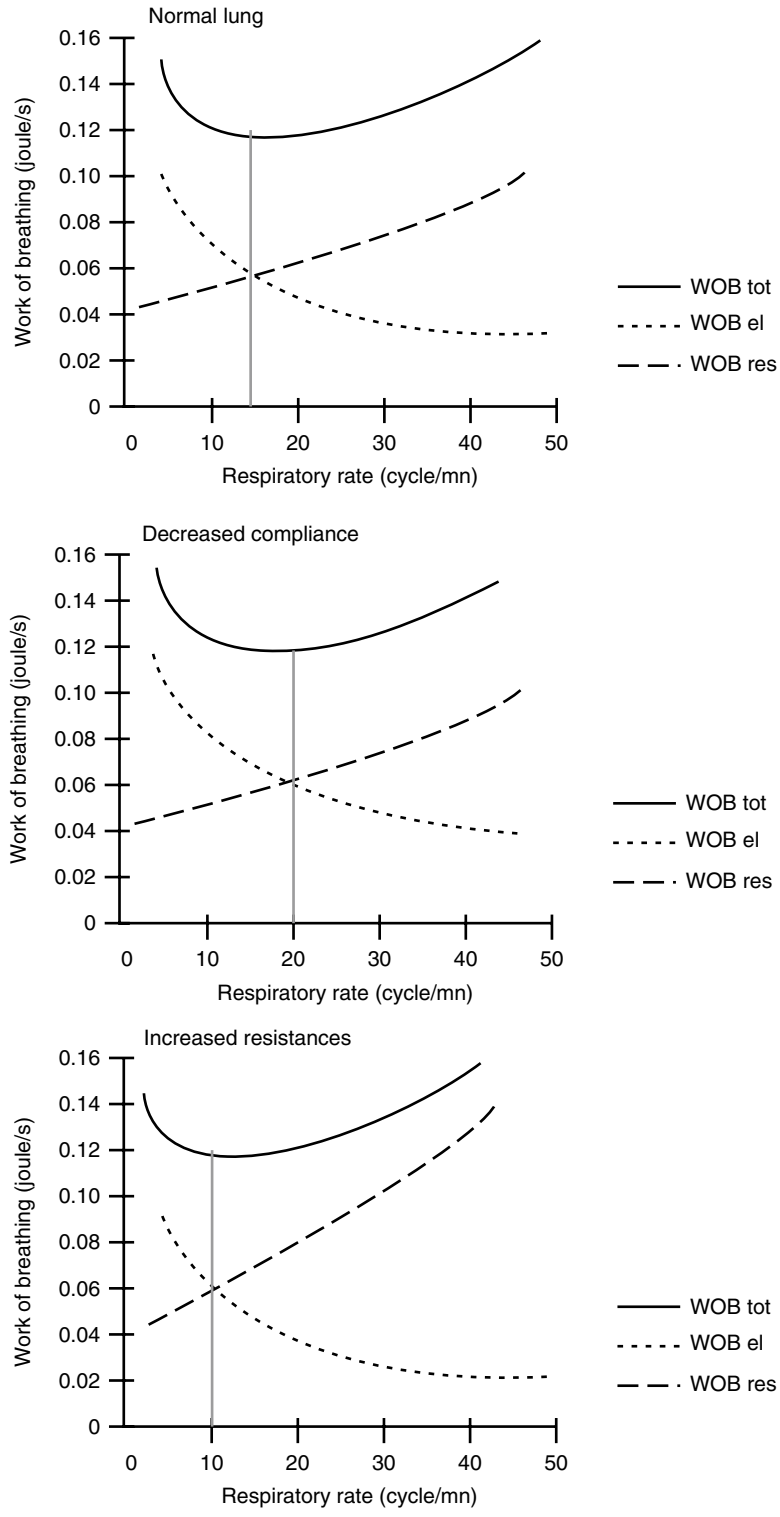


Fig. 8.27 Principle of ASV. ASV is based on Otis' physiological work (Otis et al. 1950) which determined that for a given minute ventilation, resistive work of breathing (*WOB*) increases when respiratory rate (RR) increases (*dotted line*). Reversely, elastic WOB decreases when RR increases (*dash line*). Thus, total WOB (resistive WOB + elastic WOB) (*plain line*) has a U shape with an optimal RR associated with the least WOB (*grey line*). *Upper panel* is for normal lung patients. *Middle panel* is the relationship between RR and WOB in decreased compliance patients (e.g., ARDS): the optimal RR is higher than normal lungs. *Lower panel* is the relationship between RR and WOB in increased resistances patients (e.g., asthma): the optimal RR is lower than normal lungs

Later, %MV is adjusted by 10–20 % according to the $PaCO_2$ measured on blood gas analysis. In addition, settings of PEEP, FiO_2, P_{max}, inspiratory trigger sensitivity, rise time, and expiratory trigger sensitivity are required. In passive patient, monitoring is similar to the pressure control mode. Plateau pressure is estimated by P_{insp} if inspiratory flow reach zero at the end of inspiration, otherwise an end-inspiratory occlusion is required. Total PEEP is assessed by an end-expiratory occlusion maneuver, especially in asthmatic and COPD patients (Brochard 2002). In active patient, monitoring is similar to pressure support. P_{insp} required to reach the target V_T informs on the readiness to wean the patient. If the ASV screen shows that the patient's RR is far above the target RR, it means a high ventilatory drive that may require increasing the %MV in addition to the etiologic treatment (Wu et al. 2004) (Fig. 8.28). In all cases, monitoring of RCexp inform of the respiratory mechanics. The normal value for intubated adult patient is around 0, 75 s (Arnal et al. 2008). A longer RCexp suggests an obstructive disease (asthma, COPD, bronchospasm, etc.) if not an excess of secretion or an endotracheal tube kicking. A shorter RCexp suggests a restrictive disease either due to the lung (atelectasis, ARDS, etc.) or to the chest wall (morbid obesity, kyphoscoliosis, etc.).

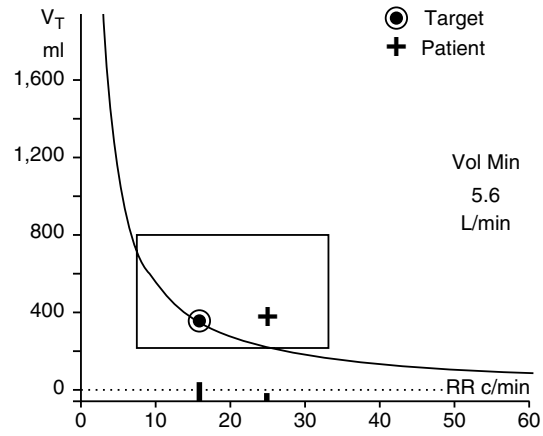


Fig. 8.28 The ASV screen displays respiratory rate (*RR*) versus tidal volume (V_T). In this example, minute ventilation (MV) set is 5.6 L/min. The curve represents all the V_T–RR combination to achieve the MV. The *circle* is the target calculated by the ventilator according to the expiratory time constant. The square is the safety window automatically calculated by the ventilator, which can be also manually adjusted. The cross is the actual breath pattern of the patient. In this case, the patient is actively breathing with a spontaneous RR above the target RR. In order to match spontaneous RR and target RR, clinician can increase the %MV which will increase the ventilatory support

Studies in Passive Condition

A multicenter trial tested the safety of ASV as compared to volume control mode (VC) in 48 passive adult patients (Iotti et al. 2005). In term of peak pressure, Pplat, and intrinsic PEEP, ASV was at least as safe as VC. Furthermore, in one-third of these patients, ASV was more effective than VC in clearing CO_2. An observational study in a cohort of 243 adult patients with different lung conditions reported different V_T–RR combination delivered according to the respiratory mechanics. V_T delivered was 8.3, 9.3, and 7.6 mL/kg PBW for normal lung condition, COPD, and ARDS condition, respectively (Arnal et al. (2008). In ARDS patients, a bench study compared V_T and Pplat delivered by ASV versus a strict 6 mL/kg PBW strategy (Suleymanci et al. 2008). Result showed that in the most severe cases of low compliance, high PEEP, and high MV, ASV was able to keep Pplat lower than the 6 mL/kg strategy. This is in favor of a good adaptation of the breath pattern delivered according to the respiratory mechanics with a V_T delivered below 6 mL/kg PBW for the most severe cases. A subsequent observational study focusing on 51 unselected ARDS patients confirmed the previous result with V_T delivered at 7.8 mL/kg PBW on the first day of mechanical ventilation correlated to the static compliance. In addition, Pplat was kept ≤28 cm H_2O during all the ventilation duration (Arnal et al. 2006). Two preliminary studies in large numbers of patient report the use of ASV in 98 % of ICU patients (Arnal et al. 2004) with a rate of failure of 3 % (Sviri et al. 2007). To resume, ASV can be used with safety in all conditions of passive ventilated ICU patient. The breath pattern selected is adapted to the respiratory mechanics and is in line with recommendations regarding protective ventilation strategy in ARDS patients (Yilmaz and Gajic 2008).

Studies in Active Condition and Weaning

In stable patients spontaneously breathing, the ASV algorithm will progressively and automatically reduce the inspiratory pressure as the patient's respiratory mechanics improve. A bench study determined that ASV effectively maintains minute ventilation and alveolar ventilation under various conditions of spontaneous ventilation, compliance, and airway resistances (Lawson et al. 2001). A physiological study in ten patients during early weaning with partial ventilatory support suggested an improvement in patient–ventilator interaction and reduced signs of dyssynchrony with ASV compared with SIMV–PS (Tassaux et al. 2002). Another physiological study in 14 adult patient during weaning phase showed that ASV and PSV behaved differently but ended up with similar pressure level facing acute changes in ventilatory demand by contrast to dual modes (volume-guaranteed pressure-control mode), in which an increase in ventilatory demand results in a decrease in the pressure support provided by the ventilator (Jaber et al. 2009).

Preliminary studies in adults suggest that ASV can simplify ventilator management and reduce the time to extubation in predominantly postoperative patient populations. Two RCTs involving 49 and 34 post-cardiac surgery patients, respectively, found that compared to protocols using SIMV and PS, ASV resulted in fewer changes in the ventilator settings from the ICU team providing care (Sulzer et al. 2001; Petter et al. 2003). Additionally, the first one noted that ASV resulted in significantly fewer high-inspiratory pressure alarms (Sulzer et al. 2001), while the second one also noted that ASV significantly reduced the duration of endotracheal intubation [3.2 (2.5–4.6) vs. 4.1 (3.1–8.6) h; $P=0.02$] and resulted in more fast-track successes (successful extubation at 6 h) (Petter et al. 2003). Two recent RCT performed in post-cardiac surgery patients found conflicting results (Gruber et al. 2008; Dongelmans et al. 2009). The first one included 50 patients after elective coronary artery bypass grafting and found earlier extubation associated with the use of ASV, without an increase in clinical intervention, when compared with pressure-regulated volume-controlled ventilation (Gruber et al. 2008). The second one compared ASV with pressure support for the post-cardiac surgery weaning in 128 patients and did not find any benefit in terms of ventilation duration (Dongelmans et al. 2009). In all these study, the weaning protocol associated with the use of ASV interfere with the results.

Studies in Pediatrics

To test the response of ASV in small pediatric patients with a sizeable endotracheal tube leak, a bench study found that MV delivered was not affected by leaks as high as 50 % for patients whose PBW is 5 kg (Watson et al. 1999). From 10 to 20 kg, MV delivered is affected if leaks are above 25 %. A short-term crossover designed study compared ASV with SIMV in 13 children (mean age 2.3 years, actual body weight 12.3 kg) (Parret et al. 2000). Both V_T and peak pressure were decreased with ASV associated with an increase in inspiratory time and a decrease in expiratory time. At the present time, ASV can be used in children in the same way as in adult. In neonates, the experience is too scarce to recommend its use.

Limitations. The absolute contraindication of ASV is an important leak on the circuit as the monitoring of the V_T would be disturbed. Thus, ASV is currently not recommended in noninvasive ventilation and in case of bronchopleural fistula. ASV is more and more used around the world both in adult and pediatric population. Still, data are lacking concerning the weaning duration in ICU (beside postoperative patients), workload, cost, and outcomes especially in pediatrics.

Future Perspectives

The rational for using closed-loop ventilation is becoming stronger. It will become unavoidable in ICU aiming to achieve cost-efficiency, quality, and safety. The challenge is how to make that change effortless, friendly, and as fast as possible. Introducing novel graphical user interfaces and providing data displays that are pertinent, integrative, and dynamic will reduce

cognitive resources of the clinician and have the potential to make ventilation safer (Wysocki and Brunner 2007). They may be the key for adopting closed-loop ventilation in everyday practice. Furthermore, new closed-loop control will be integrated in the algorithm to control ventilatory pump and oxygenation.

Essentials to Remember

ASV is currently the only closed-loop ventilation mode available for both passive and active breathing patient. The algorithm selects automatically a V_T–RR combination associated with the least WOB with designed safety features. Initial settings and adjustments are simple. The monitoring is very similar to conventional ventilation modes. Clinical studies in adult ICU patients have shown a good adaptation of the breath pattern delivered in different lung condition without any safety issue. In some settings, ASV was associated with a faster weaning for post-cardiac surgery patients. Beside many potential advantages, data are still lacking, especially in pediatric population.

8.1.3.3.4 Neurally Adjusted Ventilatory Assist (NAVA)

Guillaume Emeriaud

Educational Aims

- To highlight the importance of the electrical activity of diaphragm (EAdi), its physiological relevance, and its recording method
- To describe the global concept of neurally adjusted ventilatory assist (NAVA)
- To discuss specific points (benefits or problems) concerning NAVA, from the theoretic basics to the clinical data, including patient–ventilator synchronization, concept of diaphragm unloading, and settings of the NAVA level and PEEP
- To describe how NAVA could generate clinical benefits, already demonstrated or in future perspectives
- To present practical use of NAVA

Mechanical ventilation can induce deleterious effects on lung parenchyma (Dreyfuss and Saumon 1998) or inspiratory muscles (Levine et al. 2008). Emerging evidence suggests that physiological and clinical benefits could be obtained by (1) maintaining spontaneous breathing during mechanical ventilation (Allen 2006; Putensen et al. 2006), (2) avoiding excessive respiratory support (Petrucci and Iacovelli 2007), and (3) reducing patient–ventilator asynchrony (Thille et al. 2006). Pneumatically triggered ventilation modes are universally used, but patient–ventilator synchrony remains poor in both adults and pediatric patients (Thille et al. 2006; Beck et al. 2004). In order to improve patient–ventilator synchrony, Sinderby et al. described in 1999 (1999) the neurally adjusted ventilatory assist (NAVA), a mode that provides a ventilatory support triggered by and proportional to the electrical activity of the diaphragm (EAdi). NAVA has first been developed and extensively evaluated in healthy volunteers and animals. It has recently become available on the Servoi ventilators (Maquet Critical Care, Solna, Sweden) and preliminary experiences of NAVA in ICU patients commence to be reported. In this chapter, the NAVA theoretical concept will first be explained. The potential benefits and problems with NAVA will then be discussed, from theoretic basis to clinical data when available. Last, practical considerations and future perspectives will be presented.

8.1.3.3.4.1 Theoretical Aspects

Electrical Activity of Diaphragm (EAdi)

Unlike the conventional ventilatory modes which adapt the assistance to airway pressure or flow, NAVA is adjusted by the neural drive

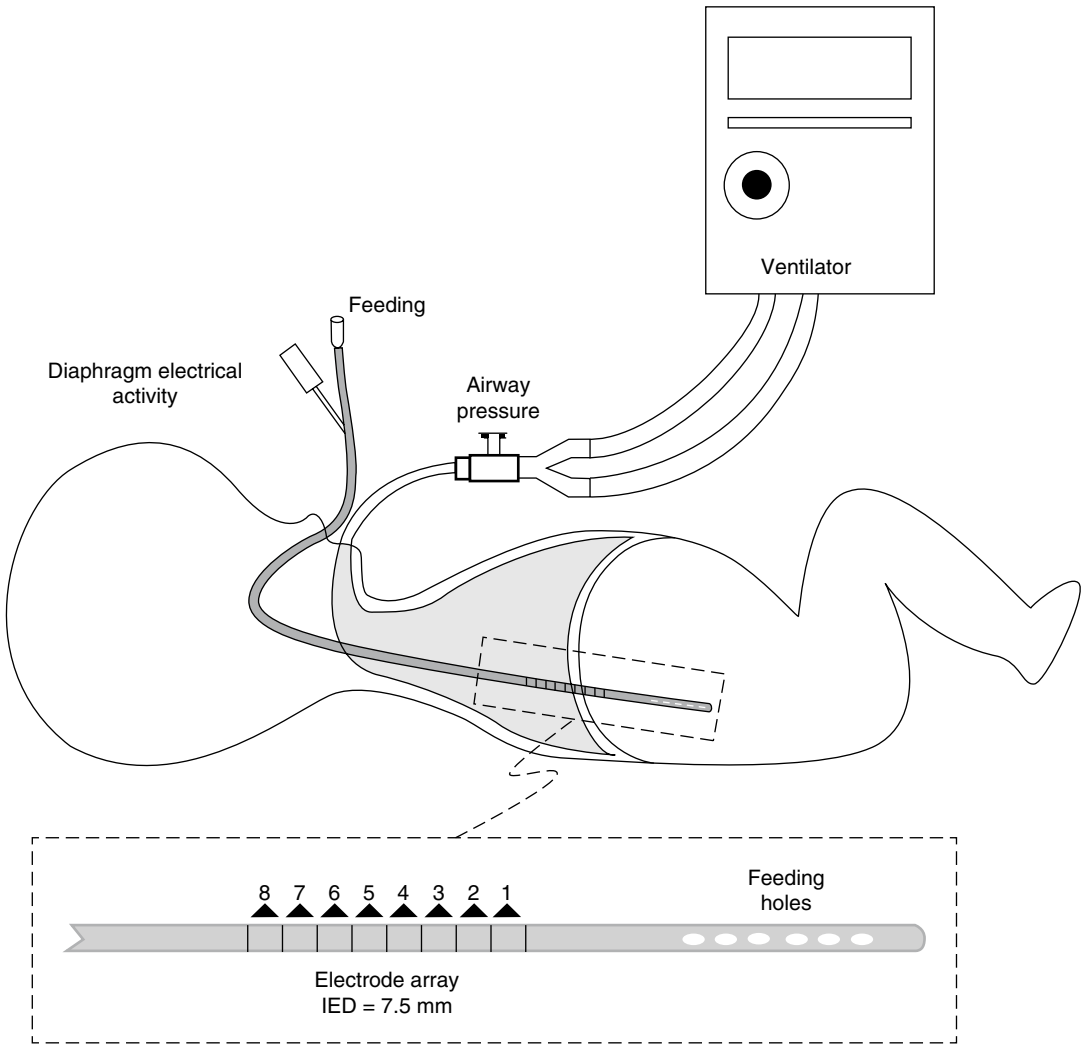


Fig. 8.29 Arrangement of the electrode array on the specific gastric catheter inserted in the lower esophagus

to the diaphragm. The key parameter is the EAdi, which is assumed to reflect the patient respiratory center demand. EAdi signal is continuously recorded using an array of nine miniaturized electrodes mounted on a conventional feeding tube positioned in the lower esophagus (Fig. 8.29). An automated method for online acquisition and processing of EAdi signal has been developed to obtain a high signal-to-noise ratio, to limit electrocardiogram influence, and to maintain an optimal muscle-to-electrode distance despite the diaphragm displacement. Briefly, a cross-correlation analysis of signals measured by each electrode pair permits to identify the diaphragm position (along the array): The most negative correlation value is obtained from the electrode pairs located on either side of the diaphragm (Beck et al. 1996; Sinderby et al. 1997). The signals given by the electrode pairs the closest to the diaphragm are subtracted and filtered, and the remaining heart artifacts are suppressed by replacement (Sinderby et al. 1995, 1998). The final EAdi signal is transferred to the ventilator.

EAdi reflects the respiratory center demand, as illustrated by the EAdi increase observed when the respiratory load is artificially augmented, or in patients with restrictive or obstructive respiratory diseases (Sinderby et al. 1998). Good quality

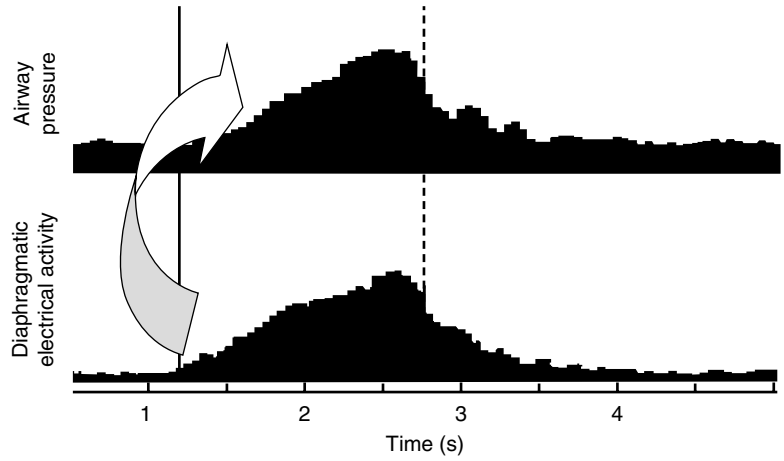


Fig. 8.30 EAdi and airway pressure during a single breath with NAVA. The ventilatory assist is triggered when EAdi exceeds a threshold level (*vertical solid line*). The magnitude of inspiratory support is proportional to EAdi, with a modifiable gain factor called the NAVA level (*arrow*). The inspiratory interruption occurs when EAdi decreases below 70 % of peak EAdi (*vertical dashed line*)

EAdi signals have been successfully recorded in healthy volunteers, critically ill adult patients, pediatric patients including premature infants (Beck et al. 2009; Emeriaud et al. 2006), and small animal species (Allo et al. 2006). Adequate EAdi has also been recorded in patients with severe neuromuscular disease (Beck et al. 2006).

NAVA Principle

During NAVA, the ventilatory assist is triggered when EAdi exceeds a threshold level (Fig. 8.30). The magnitude of the mechanical support during inspiration is adapted every 60 ms, corresponding to the EAdi multiplied by a proportionality factor that can be selected, called the NAVA level. Inspiratory support is interrupted when EAdi decreases below 70 % of the peak EAdi, and the selected PEEP is then applied. Experiences of short periods (maximum 8 h) of ventilation with NAVA have been reported in healthy volunteers (Moerer et al. 2008), critically ill adult patients (Brander et al. 2009a; Colombo et al. 2008; Spahija et al. 2010), pediatric patients (Breatnach et al. 2010; Bengtsson and Edberg 2010), premature infants (Beck et al. 2009), and small animal species (Beck et al. 2008; Lecomte et al. 2009).

8.1.3.3.4.2 Specific Advantages and Difficulties with NAVA

Patient–Ventilator Synchronization

One major advance with NAVA concerns the patient–ventilator synchronization. The electrical activation of the diaphragm precedes its contraction and the modification of pressure or flow in the respiratory circuit; cycling-on delay is intrinsically lower with NAVA than with conventional ventilation based on pneumatic triggering. An important point is that this synchrony should not be affected by the presence of leaks nor by unfavorable mechanical conditions like overdistension with intrinsic PEEP.

The improvement in patient–ventilator synchrony has been confirmed in lung-injured rabbits, with lower trigger delay and fewer non-assisted inflation with NAVA than with pressure-support ventilation (PSV) (Beck et al. 2007). In adult critically ill patients, NAVA was associated with lower asynchrony than PSV, particularly at high level of assistance (Colombo et al. 2008; Spahija et al. 2010); shorter delays were also observed with NAVA for both triggering the assist and cycling off (Spahija et al. 2010). In 7 premature infants (weight 976 ± 249 g), trigger delays were also similar with NAVA or PSV, but the cycling off was more synchronous in NAVA (Beck et al. 2009). Importantly in the same study, the trigger and cycling-off delays in NAVA were not altered after extubation (Beck et al. 2009). In pediatric patients, the synchrony has been less evaluated, but it has been shown that the neural triggering precedes the pneumatic triggering in more than 2/3 inflation during NAVA (Breatnach et al. 2010; Bengtsson and Edberg 2010).

During noninvasive helmet ventilation, an improved patient–ventilator synchrony has also been demonstrated in volunteers (Moerer et al. 2008).

Concept of Diaphragm Unloading

The patient–ventilator synchrony is also improved with NAVA in a second dimension: The assist is delivered proportionally in response to the patient respiratory center demand. This relation relies on the concept of unloading the diaphragm during the period of increased respiratory load, in order to prevent a diaphragm fatigue. This concept is quite different than other conventional modes used in pediatric and neonatal patients, like pressure support with volume guarantee, assist-control ventilation, and volume assist. With these modes, when the patient efforts augment, the ventilator progressively decreases its assistance after a few cycles. This can be considered an indication of weaning readiness, but this can also augment the diaphragm fatigue or the oxygen consumption if the situation is prolonged. In contrast, an increase in EAdi during NAVA ventilation is considered like an augmented demand, and the response is a higher assistance. This concept has first been validated in healthy volunteers, with the adjustment of pressure-support amplitude in order to maintain EAdi in an optimal target during exercise (Spahija et al. 2005). Studies in adult (Brander et al. 2009a; Colombo et al. 2008), pediatric (Breatnach et al. 2010; Bengtsson and Edberg 2010), and premature patients (Beck et al. 2009) have confirmed the clinical applicability of NAVA concept. However, the clinical benefit of this concept remains to be demonstrated.

The adjustment of the ventilatory assist to the patient demand implies that this demand is continuously appropriate. Feasibility of NAVA may be impaired in particular during profound sedation. The minimal level of sedation which permits NAVA ventilation has to be studied, but individual evaluation can be done with the monitoring of EAdi during conventional ventilation. A particular concern for pediatric physicians is the immaturity of the central respiratory centers, especially during the neonatal period. Apneas are detected during NAVA, and backup ventilation is activated. However, periodic breathing risks inducing periods of low ventilation. This phenomenon remains to be evaluated, and alarms of minimal ventilation have to be set with caution.

Nava Level Setting

The NAVA level is the main ventilator setting during NAVA. This proportionality factor permits to augment the ventilatory support when EAdi increases. There is a theoretic risk of excessive pressure or tidal volume. However, it has been well established in human volunteers (Beck et al. 2001), in animals (Allo et al. 2006; Beck et al. 2008; Lecomte et al. 2009), and in adult patients (Brander et al. 2009b; Colombo et al. 2008; Spahija et al. 2010) that a downregulation prevents excessive ventilation when NAVA level is elevated. When the NAVA level is titrated from zero to high level in cases of acute lung injury (Brander et al. 2009b; Lecomte et al. 2009), a two-phased response is observed (Fig. 8.31). At lower levels, airway pressure and tidal volume progressively increase, unloading the diaphragm as illustrated by a decrease of EAdi which probably return to its normal level. When the NAVA level is further augmented, the EAdi decreases further, illustrating the lower demand, and the inspiratory pressure and tidal volume will plateau. In animals, when NAVA level is at the breakpoint between the two response phases, esophageal pressure, EAdi, and $PaCO_2$ are similar to their baseline normal values.

The ventilatory support adjustment to the patient demand does not result in excessive ventilation. It has been shown, in premature infants (Beck et al. 2009) as in adults (Brander et al. 2009a; Colombo et al. 2008), that patients with acute lung injury ventilated with NAVA spontaneously chose a protective tidal volume (6–7 mL/kg). In pediatric patients, peak inspiratory pressures were lower during NAVA as compared to PSV, with similar minute ventilation (Breatnach et al. 2010; Bengtsson and Edberg 2010). It is however possible that very high NAVA levels induce transiently high tidal volumes or pressures, and corresponding alarms should be activated.

PEEP Setting

PEEP setting remains a challenge in intensive care. Two particularities have to be addressed with NAVA. The first point concerns the intrinsic PEEP and hyperinflation. With conventional ventilation, patients have to overcome the intrinsic

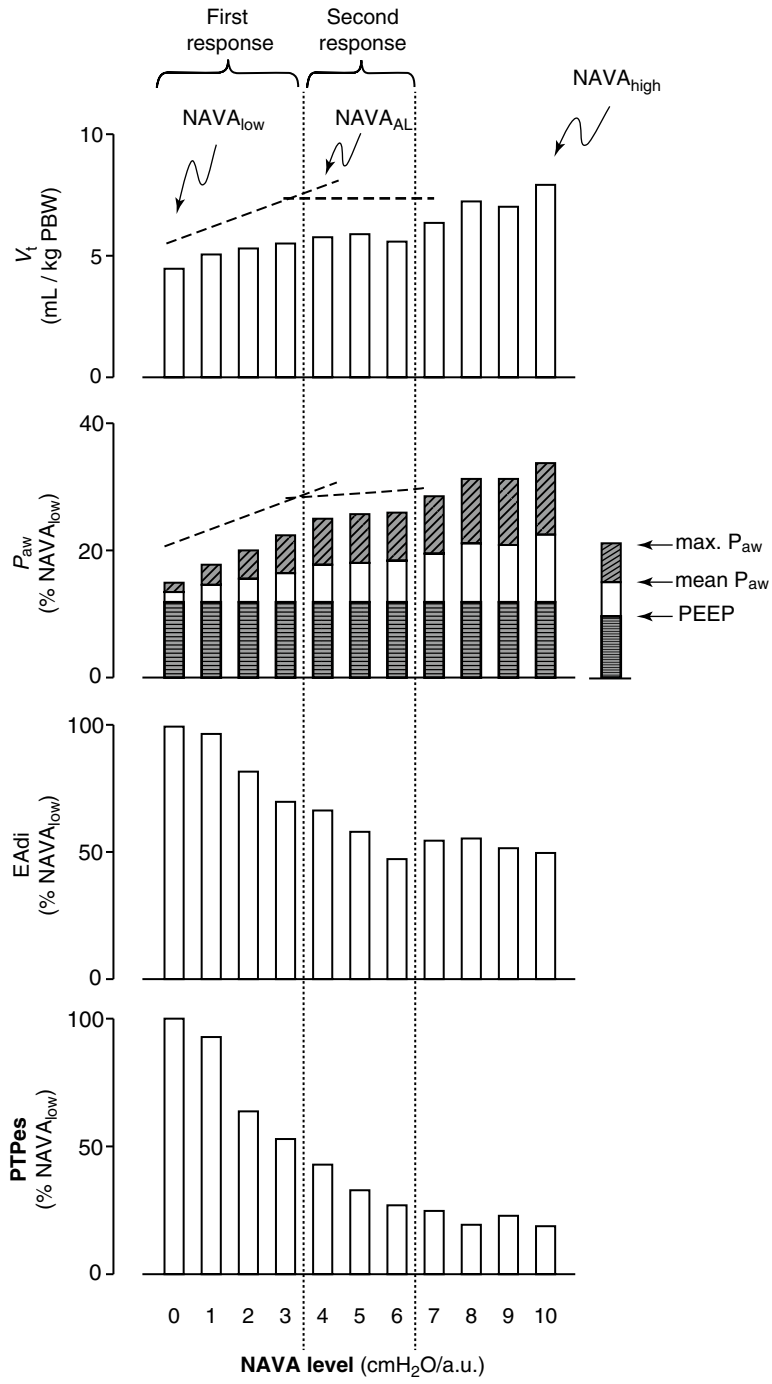


Fig. 8.31 Changes in tidal volume (V_t), mean airway pressure (P_{aw}), EAdi, and esophageal pressure–time product (PTPes) during NAVA level titration in a patient. A biphasic response can be observed. At low level of assistance (NAVA low), P_{aw} and V_t increase progressively with the NAVA level, with a progressive reduction of EAdi illustrating the diaphragm unloading. Above the breakpoint (considered the adequate NAVA level, NAVAal), V_t and P_{aw} reach a plateau despite NAVA level increase, due to the downregulation on EAdi (From Brander et al. 2009a, published with permission)

PEEP before the respiratory effort can be detected. To lower this trigger delay, it is recommended to add an external PEEP. In NAVA, the trigger delay should not be altered by overdistension and this PEEP indication has probably to be reevaluated.

The second point concerns the tonic EAdi. In intubated infants, around 15 % of the inspiratory EAdi remain active at the end of expiration (Emeriaud et al. 2006). This tonic EAdi is probably involved in the control of the end-expiratory lung volume, by braking

the expiratory flow. When PEEP is lowered to zero, tonic EAdi increases (Emeriaud et al. 2006; Beck et al. 2008), suggesting that tonic EAdi reflects the patient's effort to maintain an appropriate end-expiratory lung volume. It can be hypothesized that high levels of tonic EAdi correspond to insufficient levels of PEEP. This remains to be evaluated, but tonic EAdi may become a valuable tool for the adjustment of PEEP in the future.

Clinical Benefits

It has to be noticed that no data concerning periods of ventilation superior to eight hours have yet been published. The feasibility of long-term ventilation with NAVA appears good but has to be confirmed, and in particular the stability of EAdi recording.

The improvement in patient–ventilator synchrony is well established with NAVA. The clinical benefits resulting from this synchrony in terms of comfort, sleep quality, sedative use, and ventilation duration have to be evaluated with long-term ventilation periods with NAVA.

NAVA seems also to generate a "safe" ventilation with low tidal volumes. This aspect has recently been confirmed in a study with lung-injured rabbits, in which lower tidal volumes, lower airway pressures, and better PaO_2/FiO_2 were observed with NAVA as compared to protective conventional ventilation (6 mL/kg), with similar prevention of ventilator-induced lung injury markers (Brander et al. 2009a).

NAVA seems also to augment the respiratory variability (Schmidt et al. 2008). Respiratory variability is likely beneficial in ICU patients (Wysocki et al. 2006) and this effect of NAVA will have to be studied as well.

8.1.3.3.4.3 Practical Considerations

NAVA is available on the Servoi ventilators (Maquet Critical Care, Solna, Sweden). All the preparation steps are conducted while the patient breathes on its preceding conventional mode. The first step is the insertion of the special gastric catheter. The correct positioning of the catheter is based on pre-calculated distance of insertion and confirmed using a specific window on the ventilator where the signals of four electrode pairs are displayed. The catheter is correctly positioned when the blue diaphragmatic signals appear mostly in the two middle tracings. Once a correct EAdi signal is displayed in the lower part of the screen, the second step is the setting of the NAVA level. This is generally achieved from a special function which permits to display both actual airway pressure (in conventional mode) and the estimated airway pressure that would result from NAVA ventilation. The NAVA level can be adapted in order to produce the desired pressure. An alternative (but more complex) way to set the NAVA level is to use the titration method described above and in Fig. 8.31. At that point, the NAVA mode can be activated after accurate selection of alarm levels (for maximal pressure, and minimal and maximal minute ventilation).

Of note, the ventilatory assist is triggered by the first activated trigger (EAdi or pneumatic). In case of loss of EAdi signal (e.g., displacement of the tube), pressure-support ventilation will be activated. It is therefore important to correctly set the pressure-support settings. A backup ventilation has also to be set (apneas).

Future Perspectives

NAVA is a new ventilation mode that will probably strongly modify the ventilation practice in intensive care. First experiences with NAVA have only recently been published, and most of the potential benefits are to be studied. Some future perspectives have been mentioned above; the most important one concerns the evaluation of clinical benefits with long-term NAVA. The selection of the patients who will best benefit from NAVA has also to be established. The development of NAVA in noninvasive context seems of paramount importance as well, as this situation is usually associated with a very poor patient–ventilator synchrony in pediatric patients (Essouri et al. 2005). Another perspective relies on the utility of the EAdi signal as a monitoring tool, which reflects very interestingly the patient respiratory center demand.

Essentials to Remember

- EAdi is an essential parameter in NAVA, which reflects the patient respiratory center demand. It is continuously recorded with an array of electrodes mounted on a specific gastric tube and with a standardized and automated signal processing algorithm.
- During NAVA, the patient–ventilator synchrony is optimized in two dimensions: (1) EAdi is used to trigger (on and off) the ventilatory assist, and (2) the assistance amplitude is proportional to EAdi (with a gain factor, called the NAVA level).
- The improved patient–ventilator synchrony with NAVA has been demonstrated in animals, in volunteers, and in adult and pediatric patients. The synchrony is not affected by large leaks – which could be highly valuable for noninvasive ventilation – nor by altered respiratory mechanics like overdistension.
- In contrast with other ventilation modes, when the respiratory drive augments in NAVA, the ventilatory assistance is increased. This concept of diaphragm unloading is not associated with excessive ventilation. The tidal volume spontaneously "chosen" by the patients is 6–7 mL/kg in both pediatric and adult patients.
- EAdi signal could also be used as a monitoring tool, reflecting the respiratory center demand. The tonic EAdi level may reflect the appropriateness of the PEEP level.
- Clinical benefits of long periods of ventilation with NAVA have to be evaluated.

8.1.3.4 Bi-level and Airway Pressure Release Ventilation

Mark J. Heulitt and Ronald C. Sanders Jr.

Educational Aims

- To understand the physiological principles associated with airway release ventilation/bi-level
- To understand the indications and contraindications of its use
- To understand how settings are manipulated to effect oxygenation and ventilation

8.1.3.4.1 Introduction

For the purpose of this chapter, we will use the terms airway pressure release ventilation (APRV) and bi-level interchangeable. These modes do differ according to the type of support allowed during the spontaneous inflation, with bi-level incorporating the option of pressure-support in the airway pressure waveform to augment spontaneous breathing. This discussion will be limited to these two modes and not include as reported modes such as BIPAP, IMPRV, and intermittent CPAP. These modes are relatively new, released in the early 1990s (Downs and Stock 1987; Stock et al. 1987), with no studies demonstrating its use reducing mortality or morbidity in ARDS, but has demonstrated improvement in gas exchange at lower airway pressures (Rasanen et al. 1987; Stock et al. 1987). The fundamental principles of both modes differ from conventional ventilation in regard to the starting point of the breath and where within the breath cycle spontaneous breathing can occur. Unlike conventional mechanical ventilation where the breath begins at a baseline pressure and then pressure is elevated to deliver a tidal volume, the APRV breath begins at an elevated baseline pressure and follows with a deflation from high pressure to deliver the tidal volume. Further, and

Table 8.7 Airway pressure release ventilation parameters

Term	Definition	Unit of measure
Pressure high (P_{High})	Baseline airway pressure level Higher of two airway pressures	cm H_2O
Pressure low (P_{Low})	Airway pressure level resulting from pressure release The lower of the two airway pressures	cm H_2O
Time high (T_{High})	Length of time for which P_{High} is maintained	Seconds
Time low (T_{low})	Length of time for which P_{low} is maintained	Seconds
Mean P_{aw}	$\frac{\left(P_{High}\times T_{High}\right)\pm\left(P_{Low}\times T_{Low}\right)}{\left(T_{High}\pm T_{Low}\right)}$	cm H_2O

more importantly, spontaneously breathing in contrast to conventional ventilation can occur at either the high-pressure or low-pressure levels. When spontaneously breathing is not present, APRV is not different from conventional time-cycled, pressure-controlled ventilation (Stock et al. 1987; Baun et al. 1989).

8.1.3.4.2 Definition

Practically APRV can be described as the application of continuous positive airway pressure (CPAP) with regular, brief intermittent releases of the airway pressure (Rasanen 1994; Burchardi 1996). However, unlike CPAP, APRV facilitates both oxygenation and CO_2 clearance. It is best described using Chatburn criteria (Chatburn and Primiano 2001), as a time-triggered, pressure-limited, time-cycled mode of mechanical ventilation. Theoretically, APRV is capable of complete support in the apneic patient or augmentation of alveolar ventilation in the spontaneously breathing patient. Table 8.7 summarizes the terms utilized in APRV. The degree of ventilatory support with APRV is determined by the duration of the two CPAP levels and the mechanically delivered tidal volume. Even though the terms can be confusing between manufacturers and publications, certain terms and principles are the same. These terms include measures of pressure and time: pressure high (P_{High}) the upper CPAP level analogous to MAP, pressure low (P_{Low}) is the lower pressure setting, time high (T_{High}) is the inspiratory time or phase for the high CPAP level (P_{High}), and time low (T_{low}) is the release time allowing for CO_2 elimination (Sydow et al. 1994). P_{High} is the higher of the two airway pressure levels and is the pressure at baseline. The pressure resulting from the pressure release is P_{Low}. T_{high} corresponds with the length of time which P_{High} is maintained; T_{low} is the length of time for which P_{low} is held or the time airway pressure is released (Fig. 8.32).

8.1.3.4.3 Physiological Effects

Since one of the potential advantages of APRV is to increase the time patients spend breathing spontaneously, we need to review the theoretical advantages of allowing patients to breathe spontaneously during mechanical ventilation. It has been demonstrated that spontaneous breathing provides ventilation to dependent lung regions that get the best blood flow, as opposed to PPV with paralyzed patients (Froese 1974). During spontaneous respiration, there is improved ventilation–perfusion by preferentially ventilating the peri-diaphragmatic regions that receive disproportional blood flow. This effect may vary with the intensity of the breathing efforts and the vigor of the expiratory muscle activity (Kleinman et al. 2002). In patients with ARDS, arterial hypoxemia has been explained by the intrapulmonary shunting due to alveolar collapse in the

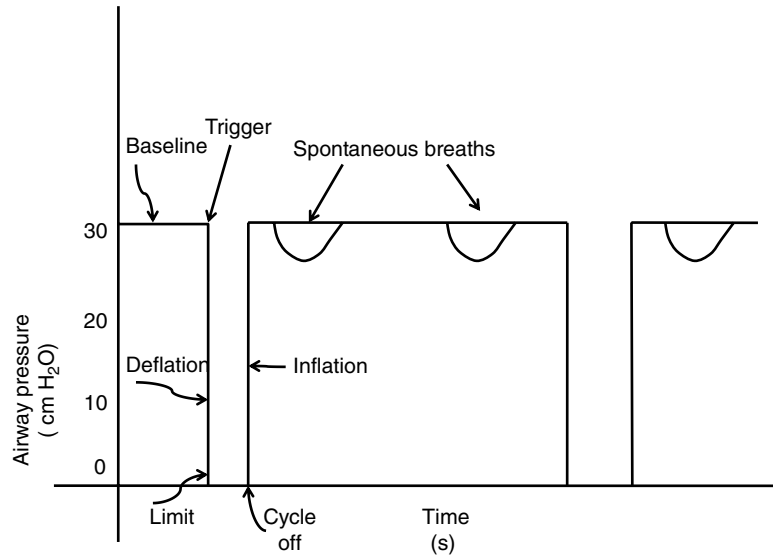


Fig. 8.32 Airway pressure release ventilation differs from conventional modes because trigger initiates a drop in airway pressure rather than a rise. The amount of pressure changes will be the limit. The cycle off will occur because of time. Airway pressure then returns to the baseline

dependent regions of the lungs demonstrated on computed tomography (CT) (Gattioni et al. 1986). These changes appear to improve with less atelectasis and increased end-expiratory lung volumes as seen in end-expiratory CT of the lungs in experimental ARDS in animals breathing spontaneously in APRV (Wrigge et al. 2003). It has been suggested that the recruitment demonstrated during spontaneous breathing during APRV may be caused by an increase in transpulmonary pressure secondary to a decrease in pleural pressure (Henzler et al. 2004). These effects would lead to reduced atelectasis.

Both animals in experimental models and patients with ARDS breathing spontaneously on APRV have demonstrated improvement in intrapulmonary shunting and arterial oxygenation (Putensen et al. 1999, 1994a, b). Both these settings with improved arterial oxygenation and less atelectasis, thus improved pulmonary compliance, are indicative of lung recruitment. It is important to note that in patients these changes may progress over a period of time and not be instantaneous (Putensen et al. 1999).

Mechanical ventilation with a positive-pressure breath can have detrimental effects on the patient's cardiovascular status, especially in normo- and hypovolemic patients. This detrimental effect causes decreased stroke volume, cardiac output, and oxygen delivery due to a reduction in right and left ventricular filling. Consequently, any type of ventilatory support that could cause a reduction of intrathoracic pressure would promote venous return to the heart and would reverse these detrimental effects. Reduction in intrathoracic pressure is seen in patients (Putensen et al. 1999; Sydow et al. 1994) and animals breathing spontaneously. Thus, these results would suggest that one should use lower PIPs in order to maintain oxygenation and ventilation without compromising the patient's hemodynamics (Sydow et al. 1994).

8.1.3.4.4 Clinical Applications

There is little direction on the application of APRV or bi-level. There are theoretical principles within recommendations for protective lung strategy that can be applied to the use of these modes (Artigas et al. 1998; Heulitt et al. 1995; Heulitt and Desmond 1998). First, the clinician must choose initial settings; in these examples we will use examples from Bi-vent, but the principles are the same with other manufacturers. APRV can provide full or partial ventilatory support with low peak airway pressure.

Proper application of APRV requires adjustment of CPAP to a level that results in optimum pulmonary gas exchange and lung mechanics. First select settings for P_{High}, T_{High}, and T_{PEEP}. For P_{High} in adults, this would be the plateau pressure

Table 8.8 Strategies used in APRV to change PaO_2 and $PaCO_2$

	P_aO_2	P_aCO_2
Increase	1. Increase FiO_2 2. Increase MAP by increasing P_{High} in 2 cm H_2O increments 3. Increase T_{high} slowly (0.5 s/change) 4. Recruitment maneuvers 5. *Maybe* shorten T_{PEEP} (T_{low}) to increase PEEPi in 0.1 s. increments (this may reduce V_T and affect $PaCO_2$)	1. Increase T_{high} (fewer releases/min) 2. Decrease P_{High} to lower delta pressure
Decrease		1. Decrease T_{High} 2. Increase P_{High} to increase delta pressure and volume exchange (2–3 cm H_2O/change) 3. Check T_{low}. If possible, increase T_{low} to allow more time for "exhalation"

or mean airway pressure in pediatrics. Typically this setting would be about 20–25 cm H_2O. In larger patients with $P_{plateau}$ at or above 30 cm H_2O, it is recommended to set it at 30 cm H_2O. It is important to recognize that overdistension of the lung must be avoided. There is no agreement on what the maximum P_{High} should be, but high settings may be expected in patients that have morbid obesity and decreased thoracic or abdominal compliance (ascites).

For T_{High} the inspiratory time (T_{high}) is set at a minimum of 2.0 s in children and about 4.0 s in older patients. T_{high} is progressively increased (every 10–15 s) with a target being improved oxygenation. These changes should be progressed slowly, for example, 5 s T_{high} to 0.5 s T_{low}, is a 10:1 ratio. So if you increase T_{High} to 5.5 s and T_{Low} to 0.5 s, this only changes the ratio to 11:1. In children use a T_{High} of 2 s. Target is oxygenation.

For release time, it has been proposed in patients with ARDS not to let exhalation go to complete emptying, i.e., do not let expiratory flow return to zero. Thus, regional auto-PEEP is a desirable outcome with Bi-vent. Set T_{PEEP} (T_{Low}) so that expiratory flow from the patient ends at about 50–75 % of peak expiratory flow. This can be determined by saving a screen on the ventilator and calculating the peak expiratory flow from it, or it can be estimated from the ventilator graphics. T_{PEEP} should be set to 0.5–0.8 s in adults and in 0.2–0.6 s in pediatric and neonatal patients. Another way to set it is to use one time constant ($TC = C \times R$). It is important to note that too long a release time could cause the lung to collapse and interfere with the patient's oxygenation. Thus, it is important to monitor tidal volume and oxygenation so that sufficient time is allowed for reinflation of the lung and that the fall in mean airway pressure and transpulmonary pressure resulting from increasing the release rate does not impair arterial oxygenation. If alveolar ventilation is adequate, but average lung volume is insufficient to maintain oxygenation, the CPAP and the release pressure should be increased simultaneously in equal amounts until the desired effect on oxygenation is seen. In Table 8.8, there are specific recommendations in making ventilatory changes to affect oxygenation or ventilation.

8.1.3.4.5 Weaning

FiO_2 should be weaned first before any other parameters are weaned. A goal is to reduce FiO_2 to 0.50 or less. Weaning the support level of APRV may be accomplished by either reducing the frequency of pressure release or increasing the release pressure so that it is close to the level of CPAP. This is accomplished by manipulation of P_{High} and T_{High}. P_{High} is lowered 2–3 cm H_2O at a time to a goal to below 20 cm H_2O, and T_{High} will be lengthened in 0.5–2.0 s increments depending upon the patient tolerance to allow for 5 releases per minute. Thus, the patient is transitioned to CPAP with very few releases. It is important to add pressure support judiciously. Pressure support can be added to P_{High} to decrease work of breathing while avoiding

overdistension. It is important that P_{High} plus pressure support be maintained less than or equal to 30 cm H_2O. Patient needs to be monitored closely to document an increase for the patient's spontaneous rate to compensate for the APRV weaning.

8.1.3.4.6 Contraindications and Disadvantages

APRV and bi-level can be utilized in a diverse clinical population with acute respiratory failure. Due to the fact that the goal of APRV is to allow the patient to breathe spontaneously during a prolonged phase with increased intrathoracic pressure with a brief release of this pressure, conditions where these physiological effects may adversely affect the patient this mode must be used with caution.

Considerations of the advantages of APRV relates to the limitations of pressure-controlled ventilation, effects of airway and circuit resistance, decrease in transpulmonary pressure, and interference with spontaneous ventilation.

8.1.3.4.7 Pressure-Controlled Ventilation

The generation of tidal volume during APRV is primarily from generation of airway pressure. The magnitude is dependent upon adequacy of inspiratory and expiratory time associated with pressure–volume characteristics of the lungs. Thus, acute changes in pulmonary compliance will alter tidal volume, necessitating clinician-directed changes in settings. This limitation is not unique to APRV, but applies to all forms of pressure-controlled ventilation that has been demonstrated in patients with acute lung injury (Cane et al. 1991).

8.1.3.4.8 Effects of Airway and Circuit Resistance on Ventilation

In APRV, there must be adequate time to allow sufficient emptying of the lungs. There is no experience with the use of this mode in patients with obstructive lung disease. There is no reason to believe that the characteristics of this mode would be beneficial in patients with prolonged expiratory time constants. The rate of volume changes in the lungs depends on their time constants that are a product of pulmonary compliance and resistance. In patients with significant airway obstruction, a longer release time may be required to allow adequate emptying of the lungs. It is important to note though that a longer release time may limit the mechanical minute volume that can be achieved by decreasing the maximum frequency of airway pressure release. Thus, one should use the shortest release time that allows expiratory flow to stop by the end of pressure release. Unfortunately, the optimum release time has not been established and must be adjusted depending upon the patient's clinical condition.

One final concern for neonatal and pediatric patients which is not clear is the role of APRV in patients with mixed conditions where there is both increased airway resistance and poor pulmonary compliance such as bronchopulmonary dysplasia.

8.1.3.4.9 Decrease in Transpulmonary Pressure

Another theoretical concern with APRV is the potential for a decrease in transpulmonary pressure and lung volume due to the fall in airway pressure. This effect could adversely impair oxygenation due to decreased lung volume affecting the ventilation–perfusion relationship. Reviewed studies utilizing APRV compared to conventional mechanical modes with similar mean airway pressure have not demonstrated a detrimental effect to oxygenation with patient during APRV (Garner et al. 1988; Valentine et al. 1991).

8.1.3.4.10 Interference with Spontaneous Breathing

Theoretically, there are distinct physiological advantages to patients breathing spontaneously on positive-pressure mechanical ventilatory support. During APRV, spontaneous breathing is unrestricted due to the design of the APRV circuit. However, the timing of spontaneous inflation could be problematic. For example, just as in nonsynchronized intermittent mandatory ventilation, advertent patient effort not timed to

inspiration or expiration could cause discomfort and increased work of breathing. These theoretical disadvantages have been demonstrated in lung models, but not in reported clinical trials.

Also to ensure spontaneous breathing by the patient, minimal sedation is utilized, and this could be detrimental in conditions where it is required to maintain the patients at levels of deep sedation. For example, in increased intracranial pressure where the goal is to reduce intracranial pressure and maintain cerebral perfusion pressure, intracranial pressure can be dependent on the transmitted pressure in the low-pressure, high-capacitance venous system; increased intrathoracic pressure may impair venous drainage from the brain and could worsen increased intracranial pressure and reduce cerebral perfusion pressure. For the clinician faced with a patient with acute hypoxic respiratory failure and traumatic brain injury, there must be a balancing between the needs to increase intrathoracic pressure to enhance lung recruitment and the possible adverse effects on the injured brain.

Other conditions where it may be contraindicated or unclear if there would be benefit are patients with neuromuscular disease or large bronchopleural fistula.

Future Perspective

Modifications to compensate for the limitations of APRV/bi-level have been proposed. Intermittent mandatory pressure release ventilation (IMPRV) is a combination of pressure-support ventilation, CPAP, and APRV. The mechanical cycle is patient triggered and begins with a pressure-support breath. Synchronization of spontaneous and mechanical inflation, breath-to-breath ventilatory support, and the ability to alter airway pressure both above and below a given level of CPAP are potential advantages over APRV. However, like APRV further study is required before it can be utilized routinely in infants and children.

Essentials to Remember

- APRV utilizes a release of airway pressure from an elevated baseline to simulate expiration. The elevated baseline facilitates oxygenation and the timed release aid in carbon dioxide removal.
- Advantages of APRV include lower P_{aw} for a given tidal volume, lower minute ventilation, limited adverse cardiovascular effects, potential decreased sedation use, and reduced need for neuromuscular blockade.
- Potential disadvantages are lung volume change with alterations in pulmonary compliance and resistance and the patient needs to be monitored closely for these changes.

8.1.3.5 Waveform Analysis

Mark Heulitt, Paul Ouellet, and Steve M. Donn

Educational Aims

- Understand the physiological principles responsible for gas delivery during positive-pressure mechanical ventilation.
- Understand the functional characteristics of mechanical ventilation including the control, phase, limit, and cycle variables.
- Understand the relationship between control and phase variables and their effect on displayed waveforms and calculated indices.

8.1.3.5.1 Introduction

Current ventilators have the ability to display breath-by-breath airway pressure, flow, and volume as a function of time necessary to overcome the elastic and resistive forces of the patient, ventilator, and circuit. It is important to note that of pressure, flow, and volume, only flow and pressure are measured and volume is calculated from flow by the ventilator. Further, current ventilators also may display calculated values from

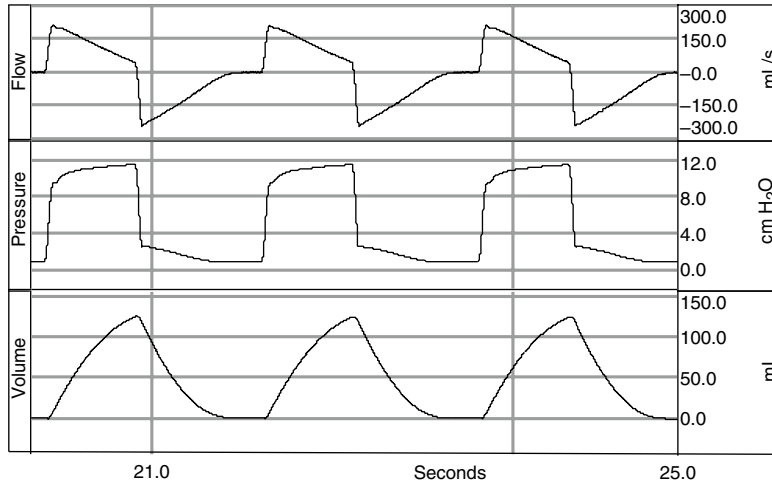


Fig. 8.33 Constant pressure normal; flow, pressure, and volume waveforms under normal conditions. During the inspiratory phase there is a rapid increase to peak inspiratory flow (PIF), and then flow decelerates through the inspiratory phase with an exponential decay to baseline. During the expiratory phase peak expiratory flow (PEF) demonstrates a rapid decrease with again an exponential decay to baseline with end-expiratory flow being zero at the end of expiration

the above displayed parameters. Modern ventilators are equipped with a graphical display intended to allow the clinician to evaluate interactions between the mechanical ventilator and the patient. These interactions can be specific to the patient's disease state, the equipment (e.g., modality of ventilation being used), or the decisions of the clinician (e.g., adequacy of settings determined by the clinician). It is important for the clinician to recognize that the displayed and calculated parameters may be influenced by predetermined factors not in their control, such as sampling frequency of the sensor and filtering of the displayed waveform. Also effects of adapters or filters placed in the ventilator circuit may influence the displayed and calculated parameters. In order for the clinician to evaluate and interpret values and waveforms displayed by the ventilator, the clinician must understand the physiological basis of those displayed values and waveforms.

8.1.3.5.2 Applied Physiology

The respiratory system, like most biological systems, is closely associated with exponential functions. An exponential function is a mathematical expression that describes an event where the rate of change of one variable is proportional to its magnitude.

An example, in a passive breath, expiratory flow will be higher at the beginning of expiration than at the end, as the lung volume decreases toward functional residual capacity (FRC).

There are various forms of exponential functions, but the two most important ones for the clinician in mechanical ventilation are the rise and the decay of exponential functions.

Rising exponential function expresses an increase of one variable as a function of time (flow, pressure, or volume versus time). A rising exponential expresses the behavior of a physical system, where the rate of change of one variable is proportional to its magnitude and a constant. In this relationship, the largest rate of change is always observed at the beginning of the event, and the smallest rate of change is always observed at the end of the event. This relationship is demonstrated in Fig. 8.33 of a flow–time waveform during a constant pressure modality. The change in flow is most rapid at the beginning of the breath and slows at the end. Exponential functions are often described with time constants. A time constant is a time interval. Short time constants imply a fast rate of change and long time constants reflect a slow rate. In a rising exponential function, after one time constant there is a rise of 63.3 % of its final value. After two time

constants it increases to 86.5 %, at three it is 95.1 %, and after four it increases to its final value 98.2 %. In mechanical ventilation, for practical purposes, an event is considered complete after three time constants (Rodarte and Rehder 1986).

Decaying exponential function expresses a decrease of one variable as a function of time (flow, pressure, or volume versus time). An example of this relationship can be seen with the pressure decrease during lung deflation in a passive expiration. Flow returns to a baseline during a passive expiration reflecting a negative decay function. This expression of a physical system is expressed where the rate is proportional to its magnitude only. Thus, the rate of change will always have the largest value at the beginning of the event and smallest at the end of the event. The rate of change is not constant over time as it is seen in rising exponential function.

During various forms of ventilation, the flow, pressure, and volume will vary with time as an exponential function. Depending on the modality of ventilation, compliance and resistance will affect both phases of each variable. During inspiration, flow and pressure patterns are directly related to the forces generated by the ventilator. Thus, the clinician can control flow and pressure through ventilation strategies in order to optimize ventilation according to the compliance and resistance of the patient's respiratory system. However, during expiration, flow, pressure, and volume patterns cannot be directly manipulated by the clinician, except for determining the duration of each cycle when using a control mode. Passive expiration is then directly governed by the elastic and resistive characteristics of the respiratory system. Thus, during mechanical ventilation, for practical reasons, the value of the expiratory time constant reflects characteristics of the global respiratory system, which consists of a multitude of zones each with different time constants. This is clearly evident in a disease state like ARDS where the lung pathology is nonhomogeneous with lung zones with different levels of compliance and resistance. Therefore, diseased zones will have shorter time constants than normal zones with normal compliance. However, ventilator strategies are directed at obtaining adequate ventilation according to the global time constants of the total respiratory system. The respiratory system is governed by the laws of physics that involve the description of various dynamic forces involved in the movement of the system. In physiology, force is measured as pressure (), displacement is measured as volume, and the relevant rate of change is measured as flow (average flow=; instantaneous flow = d*v*d*t*; the derivative of volume with respect to time). The pressure necessary to cause flow of gas into the airway and to increase the volume of the gas in the lung is the key component in positive-pressure mechanical ventilation. The volume of gas to any lung unit and the gas flow is related to the applied pressure by where R is the airway resistance and C is the lung compliance. This equation is known as the equation of motion for the respiratory system (RL Chatburn 1998 and Bates 1998). The applied pressure to the respiratory system measured at the inlet is the sum of the muscle pressures P_{mus} (pressure generated by the patient's spontaneous muscular forces) and the ventilator pressure ($P_{Applied}$ pressure generated by ventilator). Muscle pressure is patient generated, cannot be directly measured, and represents the pressure generated by the patient to expand the thoracic cage and lungs. In contrast, ventilator pressure is the trans-respiratory pressure generated by the ventilator during inspiration. Combinations of these pressures are generated when the patient is breathing with positive-pressure ventilation. In spontaneously breathing patients, the pressure measured at the airway is a mix of the two pressures depending upon the mode of ventilator support utilized. For example, in CPAP all pressure generated will be by the patient's muscles as opposed to pressure support, where the pressure generated will be a mix of the pressure generated by the patient's respiratory muscles and that generated by the ventilator. For example, when respiratory muscles are at complete rest, the muscle pressure is 0; therefore, the ventilator must generate all the pressure necessary to deliver the inspiratory flow and tidal volume. The converse is also true, and there are degrees of support depending upon the amount of force generated by the patient's respiratory muscles. The application of the equation of motion to the generation of gas

Table 8.9 Equation of motion for the respiratory system

Airway opening pressure =	Elastic component +	Resistive component
Pressure =	Elastic pressure +	Resistive pressure
Pressure =	Elastance × Volume +	Resistance × Flow
Pressure =	$\frac{\text{Volume}}{\text{Compliance}}$	Resistance × Flow

flow is the next important step. Therefore, total pressure applied to the respiratory system (PRS) of a ventilated patient is the sum of the pressure generated by the ventilator (measured at the airway) PAO and the pressure generated by the respiratory muscles (P_{mus}) Table 8.9. Therefore,

$$P_{RS} = P_{Applied} + P_{mus}$$

where PRS is the respiratory system pressure, $P_{Applied}$ is the applied pressure by the ventilator, P_{mus} is the pressure developed by the respiratory muscles, is flow, R is airway resistance, is respiratory system compliance, and k is the pressure. $P_{Applied}$ and can be measured by the pressure and flow transducer in the ventilator. Volume is derived mathematically from the integration of the flow waveform.

To generate a volume displacement, the total forces have to overcome elastic and resistive elements of the lung and airway/chest wall represented by and, respectively. Depends upon both the volume insufflated in excess of resting volume and the respiratory system compliance Table 8.10. To generate gas flow, the total forces must overcome the resistive forces of the airway and the endotracheal tube against the driving pressure gradients. At any moment during inspiration, there must be a balance of forces opposing lung and chest wall expansion, measured as the airway pressure (P_{AO}). The opposing pressure can be summarized as the sum of elastic recoil pressure ($P_{elastic}$), flow-resistive pressure ($P_{resistive}$), and inertance pressure ($P_{resistance}$) of the respiratory system:

$$P_{AO} = P_{elastic} + P_{resistive} + P_{inertance}$$

Inertial forces, which are usually negligible during conventional ventilation, depend upon bulk convective flow unlike in high-frequency ventilation, where volumes are at the level of dead space. Therefore, for conventional ventilation, the forces exemplified in the equation of motion can be expressed as

$$P_{AO} = P_{elastic} + P_{resistive}$$

If elastic forces are recognized as the product of elastance and volume ($P_{elastic} = E \times V$) and the resistive forces as the product of flow and resistance (Resistive $= V \times R$), the formula can be written as

$$P_{AO} = (\text{Elastance} \times \text{Volume}) + (\text{Resistance} \times \text{Flow})$$

If compliance (the inverse of elastance) is substituted for elastance, the equation of motion becomes

$$P_{AO} = +\text{Resistance} \times \text{Flow}$$

This relationship is demonstrated in Tables 8.9 and 8.10.

The quotient of volume displacement over compliance of the respiratory system represents the pressure necessary to overcome the elastic forces above the resting lung volume or functional residual capacity (FRC), the quantity of air remaining in the lungs at the end of a spontaneous expiration. Pressure, flow, and volume are all measured relative to their baseline values. Therefore, the pressure necessary to cause inspiration is measured as the change in airway pressure above positive end-expiratory pressure (PEEP). For example, in a patient breathing spontaneously on continuous positive airway pressure (CPAP), the ventilator pressure is 0; the patient must utilize his respiratory muscles to generate all the work of breathing (WOB). The same can be applied to the volume during inspiration or the tidal volume, which is the change in volume above FRC. The pressure necessary to overcome the resistive forces of the respiratory system is the product of the maximum airway resistance (R_{max}) and inspiratory flow. Flow is measured relative to its end-expiratory value, which is usually 0, unless intrinsic PEEP ($PEEP_i$) is present.

Table 8.10 Manipulation of the equation of motion

Elastic components	Resistive components
$\text{Pressure} = \frac{\text{Volume}}{\text{Compliance}}$ or $\text{Volume} = \text{Pressure} \times \text{Compliance}$ or $\text{Compliance} = \frac{\text{Volume}}{\text{Pressure}}$	$\text{Pressure} = \text{Resistance} \times \text{Flow}$ or $\text{Flow} = \frac{\text{Pressure}}{\text{Resistance}}$ or $\text{Resistance} = \frac{\text{Pressure}}{\text{Flow}}$

8.1.3.5.3 Functional Characteristics of Mechanical Ventilators

For a discussion of waveform analysis during mechanical ventilation, there must be a differentiation between those variables that are directly controlled by clinicians and those that are indirectly controlled. For example, pressure, volume, and flow are directly controlled variables, as opposed to constants such as resistance and compliance, which are dependent upon the resistive and elastic properties of the respiratory system. For patients who are spontaneously breathing, partially or totally supported on mechanical ventilation, dynamic mechanics may be derived (Iotti et al. 1995a, b).

Each ventilator is a controller of pressure, flow, or volume in the equation of motion (Chatburn and Primiano 2001). The manner, in which each variable is controlled, described as the mode of ventilation, determines how the ventilator delivers the mechanical inflation. In the equation of motion, the forms of any of the variables (pressure, volume, or flow) are expressed as functions of time and can be predetermined. This serves as the theoretical basis for classifying ventilators as pressure, volume, or flow controllers. It is important to recognize that according to the equation of motion, any ventilator can only directly control one variable at a time: pressure, volume, or flow. Therefore, a ventilator is simply a technology that controls the airway pressure waveform, the inspired volume waveform, or the inspiratory flow waveform. Therefore, pressure, volume, and flow are referred to in this context as control variables.

Most clinicians think of ventilators in terms of modes of ventilation. However, the mode of ventilation is a description of the way a mechanical breath is delivered. The determinants of how a mechanical breath is delivered are summarized not only in the control variables but also in the phase and conditional variables. Conditional variables are determinants of a response to a preset threshold. Control variables are the independent variables. In each phase, a particular variable is measured and is used to start, sustain, and end the phase. The phase variable includes the trigger variable (determines the start of inspiration), limit variable (determines what sustains inspiration), and the cycle variable (determines the end of inspiration).

To understand the interpretation of waveforms, the clinician needs to understand the relationship between the control and phase variables as it relates to the parameters that are either displayed or calculated and shown on the ventilator screen. First, the control variables must be identified for each type of controller, including what the dependent and independent variables are, in order for the clinician to identify the proper waveform (pressure–time, flow–time, or volume–time) representing either the elastic or resistive changes of interest (Tables 8.11 and 8.12).

8.1.3.5.3.1 Control Variables

The control variable must overcome the elastic and resistive forces to allow gas delivery to the patient. The elastic components of the equation of motion related to pressure is

$$\text{Pressure} = \text{Volume} \times \text{Elastance}$$

If a clinician sets pressure as a function of time, volume varies directly with the compliance of the respiratory system. Pressure is the

Table 8.11 Controllers

	Flow controller modes (Constant-flow controller)	Pressure controller modes (Constant pressure controller)	Volume controller modes (Variable-flow controller)
	Volume control, SIMV-VC	Pressure control, PRVC, SIMV-PC	Volume control
Equation	Flow = Pressure/Resistance	Flow = Volume/Compliance Pressure = Resistance × Flow	Flow = Pressure × Compliance
Independent variable	Flow	Pressure	Volume
Dependent variable	Pressure	Volume	Pressure
		Flow	
Limiting variable	Volume	Pressure	Volume
Trigger variables			

Table 8.12 Controller waveform analysis

Flow controller waveform analysis	Pressure controller waveform analysis	Volume controller waveform analysis
Pressure–time waveform is affected by resistance changes	Pressure–time waveform is not affected by resistance and compliance changes	Pressure–time waveform is affected by compliance changes
Flow–time waveform is not affected by compliance and resistance changes	Flow–time waveform is affected by compliance and resistance	Flow–time waveform is not affected by resistance changes
Volume–time waveform is not affected by compliance and resistance changes	Volume–time waveform is affected by compliance and resistance	Volume–time waveform is not affected by compliance and resistance changes

independent variable set by the clinician, and volume is the dependent variable determined by the level of pressure. When the clinician presets the pressure pattern, the ventilator operates as a pressure controller. The volume becomes a function of compliance, so that a decrease in compliance allows less volume to be delivered at the same pressure. During expiration, the elastic and resistive elements of the respiratory system are passive, and expiratory waveforms are not directly affected by the mode of ventilation or controller.

For the resistive components of the equation of motion:

$$\text{Pressure} = \text{Flow} \times \text{Resistance of the total system}$$

The clinician sets pressure as a function of time, allowing flow to vary with resistance. If resistance increases, flow is ultimately limited. Pressure is referred to as the independent variable and flow as the dependent variable. As previously discussed, expiration is passive and the expiratory profile is not directly affected by the mode of ventilation but rather by compliance and resistance. However, because the respiratory cycle is a set period, any change in the inspiratory time can influence expiratory time and, to a certain point, the expiratory profile.

When a ventilator operates as a constant pressure controller (e.g., in pressure control, pressure-regulated volume control [PRVC] and synchronized intermittent mandatory ventilation-pressure control [SIMV-PC]), pressure is an independent or controlled variable. The set pressure will be delivered and maintained constant throughout inspiration, independent of the resistive or elastic forces of the respiratory system. Although pressure is constant, the delivered tidal volume is a function of compliance and resistance, and the flow varies exponentially with time.

For a waveform illustrated in Fig. 8.33 from a ventilator operating as a pressure controller, volume and flow become the dependent variables, and their patterns will depend upon compliance and resistance of the respiratory system.

Characteristics of the flow–time waveform shows a rapid increase to peak inspiratory flow (PIF) with flow decelerating through the inspiratory time with exponential decay to baseline. During expiration there is a rapid decrease to peak expiratory flow (PEF) with exponential decay to baseline with normal end-expiratory flow being zero. Increased airway resistance is evident when flow persists at the end of expiration with a slow and linear expiratory decay to baseline.

With this waveform evidence of patient–ventilator interactions is identified. Secretions in the airways or water in the connecting tubing can cause evidence of a sawtooth (noisy) pattern in the inspiratory and or expiratory profile. Also use of respiratory muscles during expiration can change both the duration and pattern of expiratory flow profile.

In a pressure–time waveform during a constant pressure mode, there is a rapid increase to PIP with pressure being constant during the inspiratory time. During the expiratory time flow is exponential to baseline. Elastic and resistive components are not reflected in the inspiratory profile, but an increase in expiratory resistance is associated with a linear decay to baseline.

Patient–ventilator interactions are evident by fluctuations in triggering efforts suggesting asynchrony between the patient and the ventilator. Evidence of plateau pressure not reaching set pressure may be evidence of a leak.

Flow and resistance are only associated with the resistive components of the equation of motion. The elastic components refer to volume and compliance. The resistive components of the equation of motion are

$$\text{PIP} - \text{P}_{\text{plateau}} / \text{Peak inspiratory flow}$$

$$\text{Flow} = \text{Pressure}/\text{Resistance or}$$
$$\text{Pressure} = \text{Resistance} \times \text{Flow}$$

Therefore, if the clinician sets flow as a function of time, pressure then varies with resistance. Flow is the independent variable, and pressure is the dependent variable. When a flow pattern is preset, the ventilator operates as a flow controller, the pressure is a function of resistance, and the inspiratory-pressure–time waveform varies linearly with time. Volume increases linearly with time but does not have a direct relationship to flow. Volume does have an indirect relationship to flow because volume is the integral of flow and flow is derivative of volume.

Expiration is passive, and the expiratory profile is not directly affected by mode of ventilation but rather by compliance and resistance, although the set inspiratory time can influence the expiratory time and to a certain point the respiratory profile.

When a ventilator operates as a constant-flow controller (e.g., SIMV-VC), flow is the independent variable. Regardless of what the resistive or elastic forces of the respiratory system are, the set flow will be delivered and maintained constant throughout inspiration. Pressure and tidal volume will vary with time but are functions of compliance and resistance.

Figure 8.34 illustrates the waveform from a ventilator operating as a flow controller. Flow is the independent variable (controlled variable); pressure and volume are dependent variables. With a preset flow pattern, pressure and volume vary linearly with time and are affected by compliance and resistance.

In the pressure–time waveform, during inspiration there is an exponential increase in the first portion with a linear increase to PIP with an exponential decrease from PIP to P_{pause}. During expiration there is an exponential decay to baseline or level of PEEP. Dynamic characteristics of elastic and resistive components are reflected in the inspiratory profile. An increase in expiratory resistance is associated with a linear decay to baseline. Evidence of fluctuations in PIP and triggering effort reflects asynchrony.

If one examines the flow–time waveform for a constant-flow modality in Fig. 8.34, different characteristics can be identified in each phase of ventilation. In the inspiratory phase, there is a rapid rise to peak inspiratory flow (PIF), with

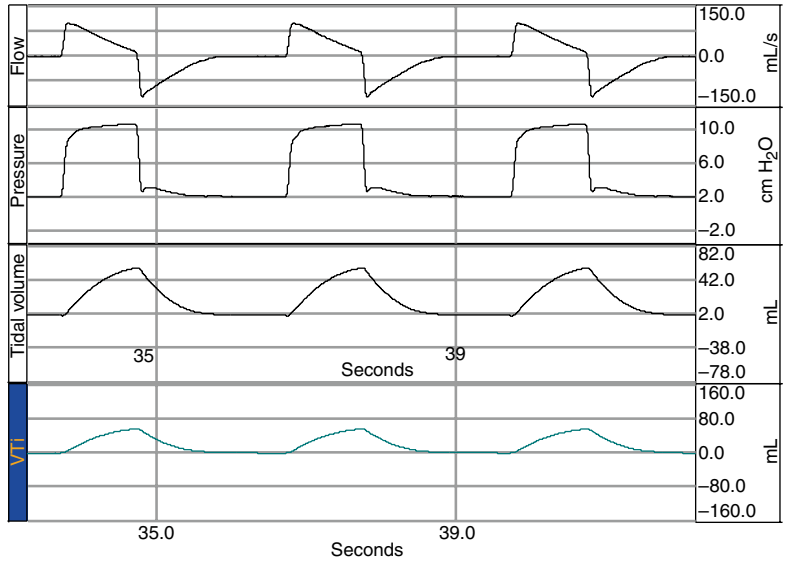


Fig. 8.34 Flow–time, pressure–time, and volume–time waveforms during a constant pressure mode under normal conditions. Flow characteristics are similar to a constant-flow mode in the flow–time waveform. The pressure–time waveform demonstrates a rapid increase to peak inspiratory pressure and exponential decay to baseline. It is important to note that elastic and resistive components are not reflected in the inspiratory profile. An increase in expiratory resistance is associated with a linear decay to baseline. Also unreached pressure plateau is associated with evidence of leakage at the airway or ventilator system. For the volume–time waveform, there is an exponential rise to inspired tidal volume and decay to baseline during expiration. Elastic and resistive components are reflected in the inspiratory and expiratory profiles. A sudden return to baseline at the start of inspiration is associated with evidence of leakage

flow being constant during inspiration. No flow occurs during the pause time. During expiration, there is a rapid decrease to peak expiratory flow (PEF) with an exponential decay to baseline. End-expiratory flow should be zero; flow present at the end of expiration is evidence of increased resistance. This is further evident with the presence of a slow linear expiratory decay to baseline.

Like the pressure–time waveform, secretions in the airways or water in the connecting tubing can cause turbulent flow, resulting in a sawtooth pattern in the inspiratory and/or expiratory profile. Also, the use of respiratory muscles during expiration can change both the duration and pattern of the expiratory flow profile.

Modern ventilators operate as either flow or pressure controllers. As a flow controller, the most common pattern is constant flow, also referred to as a square wave flow pattern (Fig. 8.33 square waveform). As a pressure controller, the only pressure pattern is a constant pressure, also referred to as square wave pressure pattern (Fig. 8.34).

From the equation of motion, one can infer that with ventilator operating as a constant-flow controller, the pressure and volume are linear functions of time. Different ventilators have the possibility of delivering various flow patterns.

Alternative flow patterns, beyond constant and exponentially decelerating flow, need to be controlled by a microprocessor that sequentially adjusts flow using an algorithm to create the decelerating ramp, ascending ramp, and sinusoidal flow patterns. These flow patterns are used in various volume-targeted modes. The decelerating rate controlled by the algorithm

produces a linear deceleration that does not reflect elastic and resistive elements of the respiratory system. A linear deceleration is often associated with flow-starvation asynchrony because flow is not a dependent variable in such a mode. Not all ventilators can produce these flow patterns. The exponentially decreasing flow pattern is available with a pressure-control or dual-control modality.

Theoretically, it has been proposed that a decelerating flow favors better gas exchange and improves distribution of ventilation among lung units with heterogeneous time constants. However, neither animal nor clinical studies have documented this advantage.

Volume is associated with the elastic component of the equation. The resistive components refer to resistance and flow. The elastic components can be rearranged to indicate how volume is determined.

If the clinician sets volume as a function of time, pressure then varies with compliance. Volume is an independent variable and pressure is a dependent variable. Expiration is passive, and the expiratory profile is not directly affected by the mode of ventilation but rather the compliance and resistance, although the set inspiratory time can influence the expiratory time and, to a certain extent, the expiratory profile.

When a ventilator sets a volume pattern, it operates as volume controller. However, to truly be a volume controller, the ventilator must measure volume directly to set the volume pattern. Most ventilators do not directly measure volume; rather, they calculate volume over a period of time. Most ventilators use volume as a limit variable; that is, inspiration stops when the preselected volume is reached. When inspiration stops at the preset volume, the ventilator is referred to as being volume cycled but is actually a flow controller. Additionally, true volume cycling cannot occur with an uncuffed endotracheal tube, as there will be a variable degree of leak around the tube, especially during inspiration.

The relationship between the gas delivery and the resistive and elastic elements of the patient and ventilator system is important for understanding the delivery of a positive-pressure breath to a patient.

8.1.3.5.3.2 Phase Variables

Phase variables control the ventilator between the beginning of one breath and the initial phase of the next breath. Phase variables are important determinants of how a ventilator initiates, sustains, and ends inspiration and what it does between cycles. A specific variable is measured and used to initiate, sustain, and end each phase. The phase variable includes the trigger, which determines the initiation of inspiration; a limit variable, which determines what sustains inspiration; and a cycle variable, which determines the termination of inspiration. Changes in the phase variable can affect and be reflected by forces and influence the patient's work of breathing. Work of breathing is discussed elsewhere; we will focus on the effects in the phase variables displayed in ventilator waveforms that reflect patient–ventilator asynchrony.

8.1.3.5.3.3 Limit Variable

The limit variable sustains inspiration. Inspiratory time is defined as the interval from the beginning of inspiratory flow to the beginning of expiratory flow. During inspiration, pressure, volume, and flow increase above their end-expiratory values. If one or more of these variables increase no higher than the preset value, this is referred to as the limit variable. However, it is important to recognize that the limit variable determines the factors that sustain inspiration but differs from the cycle variable, which determines the end of inspiration. Therefore, a limit value does not terminate inspiration but increases it to a preset value. A limit variable that is set below the level desired by the patient can lead to patient–ventilator asynchrony and will be discussed below.

8.1.3.5.3.4 Cycle Variables

The cycle variable terminates inspiration once a preset value is obtained. The cycle variable differs for various modes of ventilation. In pressure support, the termination of the breath is

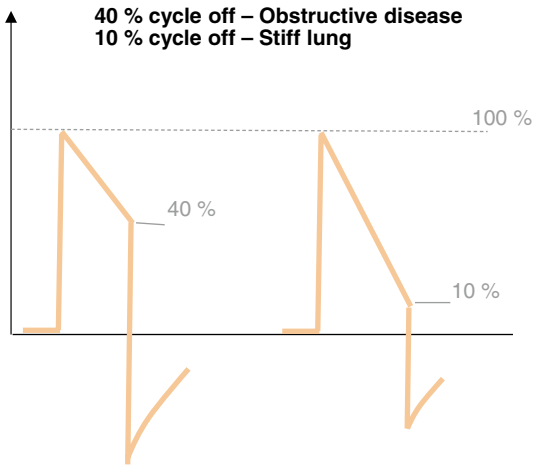


Fig. 8.35 The cycling-off parameter. The cycling-off parameter is based on a percentage of peak flow. Thus, at 10 % inspiratory time is prolonged and at 40 % it is shortened. If the cycle parameter is set at 40 %, the patient spends a greater time during expiration which would be advantageous in a patient with obstructive disease. If the cycling-off parameter is set at 10 %, then there is a longer inspiratory phase which would be advantageous in a patient with decreased pulmonary compliance or stiff lungs

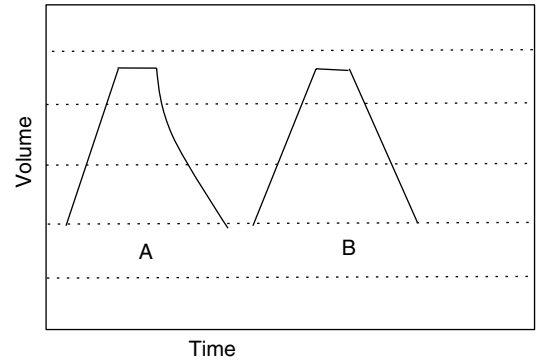


Fig. 8.36 A volume–time waveform during a constant-flow mode. *A* illustrates increased resistance and *B* normal resistance. The effects of increased resistance can be seen in *A* with a slower exponential decay to baseline

traditionally triggered by the absolute level of flow or by decay to a fixed percentage of peak inspiratory flow. Until recently, clinicians had little control over inspiratory time because it relates to the patient's pathology. For example, for a patient with increased airway resistance and dynamic hyperinflation, it may be desirable to shorten the inspiratory time and use a prolonged expiratory phase. By changing the cycle variable, as illustrated in Fig. 8.35, the patient's inspiratory phase can be shortened, allowing a longer expiratory phase. The opposite is also true for patients with decreased pulmonary compliance, where the clinician might want to prolong the inspiratory phase.

8.1.3.5.4 Monitoring Increased Airway Resistance

During mechanical ventilation the delivery of a positive-pressure breath requires overcoming both resistive and elastic forces. Increased airway resistance causes the resting volume at the end of exhalation to be increased because of lower expiratory flows and short expiratory times. To understand resistance during positive-pressure mechanical ventilation, airflow during both inspiration and expiration (as a measure of the flow-resistive elements of the respiratory system) needs to be considered. Resistance can be expressed as

$$\text{Pressure}/\text{Flow}$$

Flow, tidal volume, and the dimensions of the gas delivery system, including the patient's endotracheal tube, affect airway resistance. In pediatric patients, resistance to gas flow is primarily caused by the endotracheal tube. In the neonate, small diameter airways are also contributory. When delivering a positive-pressure breath with a set tidal volume and flow, the resistance created by the endotracheal tube is directly related to both the diameter and length of the tube. In examining resistance during positive-pressure mechanical ventilation, the type of controller delivering the mechanical breath must be considered. For example, if a mechanical breath operates as a pressure controller [e.g., pressure control (PC), pressure-regulated volume control (PRVC), or synchronized intermittent mandatory ventilation (SIMV)-PC], the following relationship from the equation of motion occurs:

$$\text{Flow} = \text{Pressure}/\text{Resistance}$$

The dependent variables are volume and flow and the independent variable is pressure (Tables 8.11 and 8.12). The resistive elements of both within the respiratory system and breathing circuit are visualized in flow–time and volume–time waveforms (Figs. 8.36, 8.37, 8.38,

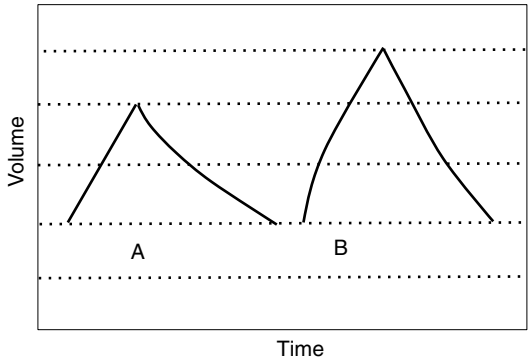


Fig. 8.37 A volume–time waveform during a constant pressure mode. *A* illustrates increased resistance and *B* normal resistance. The effects of increased resistance can be seen in *A* during linear increase vs exponential increase to inspired tidal volume. Also in expiration with a linear decay vs exponential decay seen in normal resistance

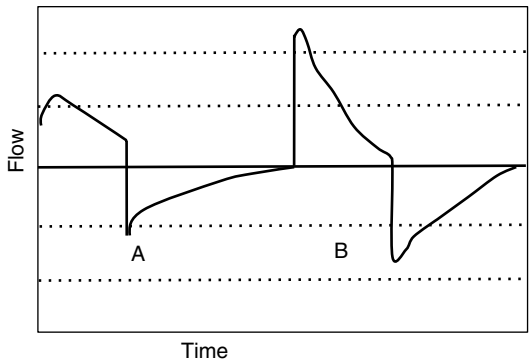


Fig. 8.38 A flow–time waveform during a constant pressure mode. Tracing *A* illustrates increased resistance. During the inspiratory phase PIF is decreased with a linear and slower decay to baseline. Inspiration stops before baseline. During expiration PEF is decreased and there is a linear decay to baseline. Tracing *B* illustrates normal resistance with higher PIF with an exponential decay and faster decay to baseline. During expiration there is a higher PEF and an exponential decay to baseline

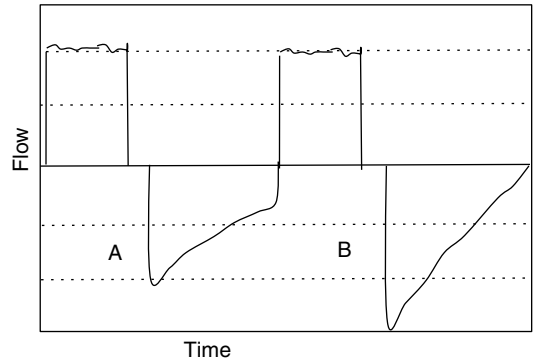


Fig. 8.39 A flow–time waveform during a constant-flow mode. Tracing *A* illustrates increased resistance. During the inspiratory phase tracing *A* is similar to tracing *B*. During expiration PEF is lower with a linear and slower decay to baseline as compared to tracing *B*. Nonzero flow at the end of expiration is illustrative of auto-PEEP. Tracing *B* illustrates normal resistance with inspiration similar to tracing *A*. During the expiratory phase PEF is higher with decay being exponential and faster to baseline. There is zero flow at end of expiration

and 8.39). Because pressure is the independent variable, it is held constant during inspiration, and a pressure–time waveform does not illustrate the effects of resistance. In contrast, because the rate of decay of flow is a function of resistance, a flow–time waveform illustrates resistance. For ventilator modes that use a flow controller (e.g., volume control, SIMV-VC), Flow = Pressure/Resistance, the independent variable is flow and the dependent variable is pressure. When a ventilator operates in a constant-flow mode, the resistive elements of the respiratory system and breathing circuit can be visualized and calculated with a pressure–time waveform, which begins with an exponential rise to a first step, followed by a linear rise to peak inspiratory pressure (PIP).

During the initial portion of inspiration, the first step is a function of flow and resistance, with the size of the step directly related to the degree of resistance. The second portion of the waveform is a linear increase to PIP and is a function of flow being constant throughout inspiration, and it represents the elastic properties of the respiratory system.

As PIP is reached, a pause time or plateau is maintained while pressure inside the airways and the breathing circuit equilibrates at plateau pressure ($P_{plateau}$). Flow then stops while pressure equilibrates.

Figure 8.38 is a pressure–time waveform from constant-flow ventilation and illustrates various elements related to resistive and elastic properties of the respiratory system.

Inspiratory resistance (R_I) is the difference between the PIP and the $P_{plateau}$ divided by peak

inspiratory flow at PIP, as expressed by the following equation:

$$\text{PIP} - \text{P}_{\text{plateau}} / \text{Peak inspiratory flow}$$

Expiratory resistance is the difference between P_{plateau} and total PEEP over flow value at the onset of exhalation, as expected from the following equation:

$$\text{P}_{\text{plateau}} - \text{total PEEP} / \text{Flow (at onset of expiration)}$$

Figure 8.39 demonstrates flow–time and pressure–time waveforms for constant-flow ventilation and illustrates various landmarks for resistance calculations.

8.1.3.5.4.1 Patients with Increased Airway Resistance

Airway resistance (R_{AW}) is the sum of periphery airway resistance peripheral airway resistance (peripheral intrathoracic airways <2 mm diameter R_{awp}), the central airway resistance, and extrathoracic airway resistance. In intubated patients receiving mechanical ventilation, the patient's airway resistance has to take into account the endotracheal tube and resistive components of the circuit and triggering system. Obstructed airway disease may result from an obstruction at an extrathoracic or intrathoracic site. For diagnostic purposes, flow–volume loops can be diagnostic and help to guide therapeutic interventions.

Extrathoracic obstruction involving the airway primarily limits airflow from entering the lungs on inspiration. Non-intubated patients will present with stridor, as seen in croup, laryngomalacia, tracheomalacia, and epiglottitis. In contrast, variable intrathoracic airway obstruction primarily limits gas from exiting the lung during exhalation. Patients breathing through narrowed airways impose an additional load on the respiratory muscles that is exacerbated with increased airway resistance.

In patients with increased airway resistance, the resting volume at the end of exhalation is increased because of lower expiratory flows and short expiratory times. As a result, a positive recoil pressure (PEEP_{i}) is created at the end of expiration, and a new resting state is established. This state of air trapping or dynamic hyperinflation is common in patients with obstructive disease such as asthma or bronchopulmonary dysplasia. Initially in these patients, hyperinflation tends to keep airways open, reduces airway resistance, increases elastic recoil, and tends to improve expiratory flow. However, hyperinflation has several deleterious effects. The positive pressure within regions of hyperinflated lung increases the mean intrathoracic pressure and causes the inspiratory muscles to operate at a volume higher than the resting volume. Respiratory muscle function becomes impaired because dynamic hyperinflation places respiratory muscles at a considerable mechanical disadvantage. PEEP_{i} imposes a substantial inspiratory threshold, as flow is limited because of negative intrapleural pressure equal to the level of PEEP_{i} that has to be generated before inspiratory flow can begin within the alveoli. This threshold load imposed by PEEP_{i} may interfere with ventilator triggering requiring the patient to overcome the imposed PEEP_{i} before the trigger to threshold is reached. Moreover, the ventilation–perfusion relationship can be impaired because the hyperinflated lung may compress adjacent areas of the normally inflated lung. PEEP_{i} also decreases cardiac output by increasing intrathoracic pressure, thereby reducing venous return, and predisposes the patient to barotrauma by causing dynamic hyperinflation. Therefore, the mainstay of therapy in patients with obstructive lung disease requiring mechanical ventilation is the reduction of dynamic hyperinflation.

When a ventilator operates in a constant pressure mode, the resistive elements of the respiratory system/breathing circuit can be visualized with the flow–time and volume–time waveforms. The inspiratory part of the pressure–time waveform does not offer any indication of resistance, since pressure is constant throughout inspiration. However, the flow–time waveform will reflect the resistive element of the respiratory system since the rate of decay of flow is a function of resistance. For measuring resistance, the expiratory flow–time waveform aids the clinician in detecting the presence of dynamic hyperinflation or detecting the presence of dynamic hyperinflation or intrinsic PEEP. Expiratory flow shows air trapping when it fails to return to zero. When the expiratory time is not long enough to allow exhalation of all the tidal volume, auto-PEEP is generated. In a flow–volume loop, air trapping is characterized by a truncated expiratory phase that does not return to baseline (Blanch et al. 2005; Dhand 2005).

8.1.3.5.4.2 Measuring Resistance in Constant-Flow Mode of Ventilation

Traditionally, resistance has been measured by the interrupter technique. Flow is interrupted at the end of inspiration while pressure is held constant during a period of time (pause). The interrupter technique is only valid when the ventilator operates in a constant-flow mode.

When a ventilator operates in a constant-flow mode, the resistive elements of the respiratory/breathing circuit can be visualized and calculated with the pressure–time waveform. The pressure–time waveform begins with an exponential rise to a first step, followed by a linear rise to peak inspiratory pressure (PIP).

The first step is a function of flow and resistance during the initial portion of inspiration. The higher the step, the larger the resistance. The second portion of the waveform is a linear increase to PIP and is a function of flow being constant throughout inspiration. This second portion represents the elastic properties of the respiratory system. As seen in Fig. 8.40, PIP is reached, a pause time or plateau is maintained, while pressure inside the airways and the breathing circuit equilibrates at plateau pressure ($P_{plateau}$). Flow then stops while pressure equilibrates.

Inspiratory resistance is the difference between PIP and $P_{plateau}$, as expressed by the following equation:

$$\text{PIP} - \text{P}_{plateau}$$

Expiratory resistance is the difference between $P_{plateau}$ and total PEEP divided by flow value at the onset of exhalation, as expressed by the following equation:

$$\text{P}_{plateau} - \text{total PEEP}/\text{Flow (at onset of expiration)}$$

Specific measuring conditions must be met for a valid inspiratory and expiratory resistance value: (1) passive tidal volume (inspiration and expiration), (2) constant flow over a fixed inspiratory time, (3) T_i (for inspiratory resistance only), and (4) $P_{plateau}$ must have an end-inspiratory pause of at least 1 s with a stable pressure within 0.5 cm H_2O over two readings at least 10 ms apart.

The pressure–time waveform under a constant-flow mode with a pause time has been previously described. The pause time can be analyzed in detail and brings subdivisions in the resistance concept. The pressure decrease from PIP to the end of $P_{plateau}$ can be magnified. Two segments of resistance can be calculated: the maximum resistance index (R_{max}) and the minimum resistance index (R_{min}).

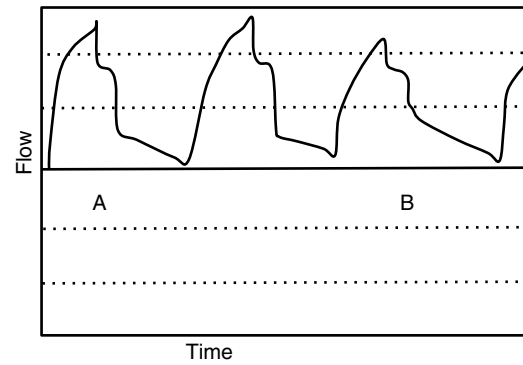


Fig. 8.40 A pressure–time waveform during a constant-flow mode of ventilation. Tracing *A* illustrates increased resistance. During the inspiratory phase there is a linear increase to the first portion and an exponential increase to PIP. The difference between PIP and P_{pause} is increased. During expiration the exponential decay is slower and almost linear with baseline reaching the set PEEP

Figure 8.41 shows flow–time and pressure–time waveforms from constant-flow ventilation and illustrates various landmarks for resistance calculations. In this figure, PIP is the peak inspiratory pressure and represents the peak dynamic pressure. P_Z is the airway pressure when flow stops (zero flow) during pause time. The exact location of P_Z is not yet clearly identified. $P_{plateau}$ is the end-inspiratory pause pressure (representing the static airway pressure) and is often referred to as a close estimate of the alveolar pressure. The slow decay after the drop from PIP to P_Z depends on the viscoelastic properties of the system and on the pendulum-like movement of the air (pendelluft) (Rossi et al. 1985a, b; Milic-Emili and Polysongsang 1986; D'Angelo et al. 1989; Bates et al. 1988; Stenqvist 2003).

In contrast, R_{max} is the difference between PIP and $P_{plateau}$ at peak inspiratory flow. R_{max} represents the resistance caused by the endotracheal tube, the breathing circuit, pulmonary tissues, and the thoracic cavity at maximum lung volume.

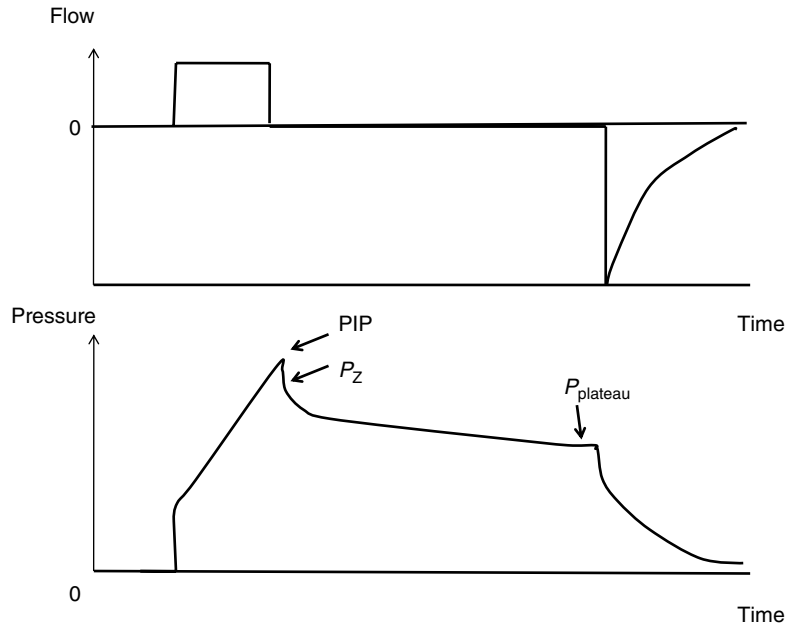


Fig. 8.41 Flow–time and pressure–time waveforms during a constant-flow mode

Table 8.13 Values of R_{max} and R_{min} in adults

Adults	R_{max} (cm H_2O/L/s)	R_{min} (cm H_2O/L/s)
Normal	7	2.5
ARDS	12–15	8.0
COPD	26	15
Pulmonary edema	7–18	4–12

Table 8.14 Values of R_{max} for intubated and extubated infants

	R_{max} (cm H_2O/L/s)	
Infants	Intubated	Extubated
3.0-mm ID	128	75
3.5-mm ID	73	37
Tube size not specified	50–150	20–30

R_{max} is calculated using the following equation:

$$\text{PIP} - \text{P}_{\text{plateau}}\,(\text{at peak inspiratory flow})$$

R_{max} constitutes the overall resistance of the respiratory system/breathing circuit traditionally calculated during mechanical ventilation. Table 8.13 illustrates various values of R_{max} and R_{min} for adults under specific conditions. Table 8.14 illustrates various R_{max} clinical values for infants under specific conditions.

Minimum resistance index (R_{min}) is the difference between PIP and P_z at peak inspiratory flow. P_z is the pressure value when the expiratory valve closes and flow stops. R_{min} describes a specific component of the R_{max} and reflects only the resistance of the airways. R_{min} is calculated by the following equation:

$$R_{min} = \text{PIP} - \text{P}_z\,(\text{at peak inspiratory flow})$$

The calculation of R_{min} itself presents certain difficulties as to precisely identifying the location of P_z. P_z has value greater than the $P_{plateau}$. The difference between P_z and $P_{plateau}$ represents the gas distribution of alveolar regions with different time constants. However, the zones are ventilated even though the flow in larger airways seems to have stopped.

This phenomenon is often referred to as the pendelluft, the German word for pendulum of air. The larger the difference between R_{max} and R_{min}, the larger the zones of discrepancies. In ARDS, the differences between P_z and $P_{plateau}$ generally differ by 10–20 %.

8.1.3.5.5 Monitoring Compliance in Mechanical Ventilation

Compliance expresses the elastic components as a volume change divided by a pressure change and can be expressed by the following equation:

Compliance = $\Delta V/\Delta P$

Respiratory system compliance (C_{RS}) is related to lung compliance (C_{pulm}) and chest wall compliance (C_{CW}) by the following equation:

$$C_{RS} = \Delta\text{Volume}/\Delta(P_{AO}\text{ airway opening}) - P_{bs}\text{ pressure at the body surface or atmospheric pressure}$$

C_{RS} may be used to evaluate and modify various therapeutic interventions such as tidal volume and PEEP titration, skeletal muscle relaxation, and patient positioning. In the preterm newborn, the chest wall is usually more compliant than the lung.

Chest wall compliance (CCW) is not commonly calculated during mechanical ventilation; it requires an estimate of intrapleural pressure changes not requiring an indwelling esophageal catheter.

Chest wall compliance describes the changes in tidal volume relative to the pleural pressure, reflected by the esophageal pressure (Peso), and is expressed by the following equation:

$$\text{Chest wall compliance} = \Delta V/\Delta P$$

Chest wall compliance can usually be estimated at 4 % of the vital capacity per cm H_2O. Normal value for chest wall compliance is approximately 200 mL/cm H_2O.

Lung compliance is also not commonly calculated in patients on mechanical ventilator support because of the same limitations that apply to the calculation of chest wall compliance. Lung compliance describes a change in tidal volume relative to alveolar pressure reflected as plateau pressure and esophageal pressure under quasi-static conditions. This is reflected in the following equation:

$$C = \Delta V/\Delta P$$

Total static compliance (during a no-flow activity at the end of inspiration and expiration) and total dynamic characteristics (during active inspiration) are two conditions when the volume–pressure relationship is most often monitored in mechanical ventilation.

In order to measure static compliance during mechanical ventilation, specific conditions must be met including that tidal volume must be passive (both inspiration and expiration), compressible volume of the ventilator circuit must be corrected, and plateau must have an end-inspiratory pause of at least 1 s with a stable pressure within 0.5 cm H_2O over two readings at least 10 ms apart.

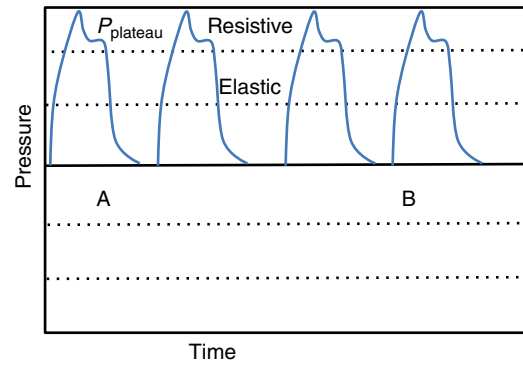


Fig. 8.42 A pressure–time waveform during a constant-flow mode of ventilation illustrating areas related to resistive and elastic properties of the respiratory system

Total static compliance is reflective of changes in lung elasticity and describes the delivery of tidal volume relative to the airway pressure under static conditions and is expressed as

$$C_{stat} = \Delta V / P_{plat}\text{PEEP}$$

The status of compliance at the bedside can be observed with flow–time and pressure–time waveforms and pressure–volume loops. Pressure–volume loops will be discussed in another section. It is important to note that compliance values are affected by a number of parameters including patient size, state of relaxation, lung volume, and flow, thus necessitating caution when applying actual values of compliance. Thus, trended values offer more accurate clinical guidance than a specific value at any time point. Also specific waveforms illustrated below can be reflective of changes in dynamic characteristics (Suter et al. 1978) which represents the tidal volume relative to the peak airway pressure.

Figure 8.42 is a pressure–time waveform from constant-flow ventilation and illustrates areas related to resistive and elastic properties of the respiratory system.

Figure 8.43 demonstrates a flow–time waveform from constant-flow ventilation with decreased and normal compliance. Decreased compliance can be detected by examining the slope of the second portion of expiratory flow, which is sharper.

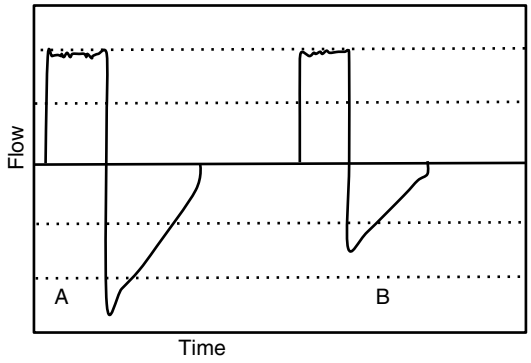


Fig. 8.43 A flow–time waveform during a constant-flow mode of ventilation. Tracing *A* illustrates decreased compliance. The inspiratory phase is similar to tracing *B* but the expiratory phase demonstrates a linear and faster decay to baseline

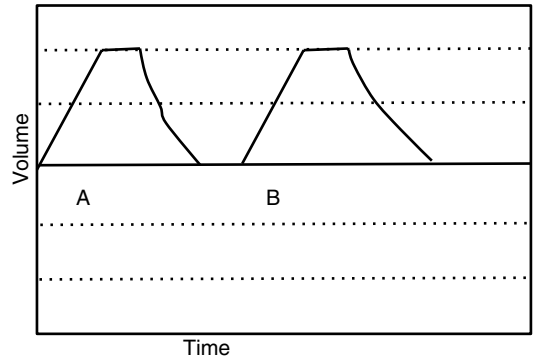


Fig. 8.45 A volume–time waveform utilizing a constant-flow mode. Tracing *A* illustrates decreased compliance. The inspiratory phase is similar between the two tracings. The expiratory phase for tracing *A* has a faster exponential decay to baseline than tracing *B*

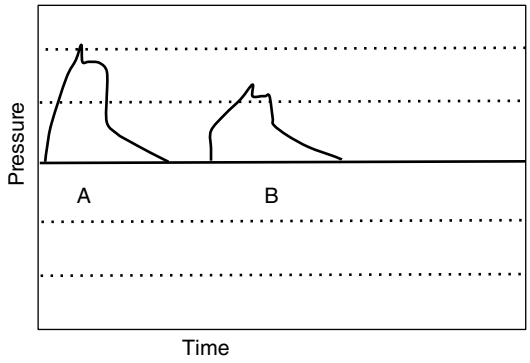


Fig. 8.44 A pressure–time waveform from a constant-flow mode of ventilation with decreased and normal compliance. Tracing *A* illustrates decreased compliance. During inspiration the first portion is similar to normal compliance tracing but the slope of the second portion is steeper. In this example PIP minus P_{pause} is identical to tracing *B*. During the expiratory phase there is a steeper exponential decay to baseline

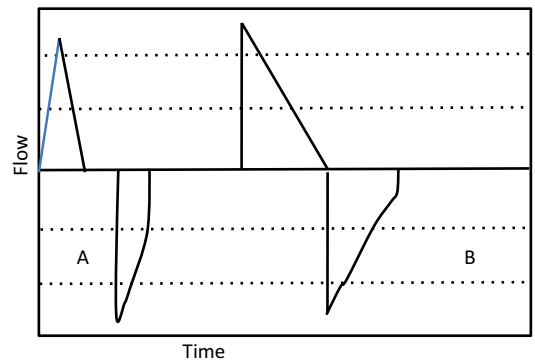


Fig. 8.46 A flow–time waveform during a constant pressure mode. Tracing *A* illustrates decreased compliance. During inspiration there is a rapid decay to baseline before end of set inspiratory time. Tracing *A* has lower tidal volume than in tracing *B*. During the expiratory phase the slope is steeper than in the second portion of tracing *B*

Figure 8.44 demonstrates a pressure–time waveform utilizing constant flow; decreased compliance is detected by examining the second portion of the expiratory waveform where the slope is steeper.

Figure 8.45 demonstrates a volume–time waveform utilizing a pressure mode of ventilation; decreased compliance is detected by examining the peak of the waveform. With decreased compliance the peak has a plateau because flow reaches zero before the elapsed inspiratory time.

Figure 8.46 demonstrates a flow–time waveform utilizing pressure ventilation; decreased compliance is detected by examining both the inspiratory and expiratory waveforms. With decreased compliance, there is a rapid decay to baseline before the set inspiratory time has elapsed; subsequently, tidal volume is lower than seen in a normal tracing despite the same peak pressure. During expiration with decreased compliance, the slope is steeper.

During constant-flow ventilation (volume control ventilation) in a completely relaxed patient, the time course of P_{aw} depends linearly on the total respiratory system compliance. The mathematical analysis of the shape of the dynamic pressure–time profile or visualization of the shape of the P_{aw} curve allows detection of hyperinflation or lung recruitment by changing morphology of the curve turning from concave to convex, respectively (Milic-Emili

Table 8.15 Flow–time waveform from a constant-flow mode of ventilation

Characteristics	Potential interventions
Dynamic hyperinflation	Adjusting respiratory rate is indicated Adjusting inspiratory time if indicated Check for auto-PEEP
Auto-PEEP	Adjusting respiratory rate if indicated Adjusting external PEEP if indicated Decrease airway resistance by use of bronchodilator
Dynamic airway compression	Bronchodilator therapy if indicated Suctioning if indicated
Increased inspiratory resistance	Adjusting inspiratory time if indicated Checking mode of ventilation if indicated
Patient–ventilator asynchrony	Changing mode of ventilation if indicated Reviewing patient's level of sedation Reviewing triggering modality if indicated
Leakage	Faulty breathing circuit connections Anatomical leakage

et al. 1987; Ranieri et al. 1994). Ranieri et al. (Ranieri et al. 2000; Grasso et al. 2004) described these changes mathematically as the stress index in an animal study predicting lung recruitment.

8.1.3.5.6 Detection of Air Leaks

The presence of an air leak may affect the ability to interpret ventilator waveforms or lead to malfunction of the ventilator by causing auto-triggering, inability to maintain PEEP, hypoventilation, or lung de-recruitment from loss of inspired volume. The source of the leak could be caused by an endotracheal tube leak, cuff failure, or loose connection in the ventilator circuit or humidification system. A leak can be detected by comparing the difference between the displayed inspired and expired tidal volume, failure of closure of flow–volume and/or pressure–volume loop, or a volume waveform that fails to return to zero baseline.

8.1.3.5.7 Clinical Interventions

The ultimate goal of utilizing mechanical ventilation waveforms is both to guide the clinician in identifying possible changes in the patient's respiratory status and to guide interventions. As discussed previously, the detection of changes in the patient's clinical condition such as increased resistance or decreased compliance requires an understanding of the mode of ventilation and the displayed waveform. Table 8.15 illustrates potential clinical characteristics that can be identified from a flow–time waveform during a constant-flow mode of ventilation.

Conclusion

This chapter illustrates the basic principles of respiratory mechanics and how they pertain to the interpretation of pulmonary waveforms. Use of pressure, flow, and volume waveforms is a useful – and necessary – adjunct to mechanical ventilation and provides the clinician with important information regarding pulmonary pathophysiology and the patient's response to and interaction with mechanical ventilation.

Future Perspectives

Over the past 10 years, mechanical ventilators have been developed that offer the clinician increasing information regarding the patient's physiological status and the effects of clinical interventions. The key to future development will be to further integrate information generated from the ventilator and patient into computerized control algorithms to allow for rapid changes in ventilator support to meet the patient's clinical needs. Future advances will include integration of currently unused physiological signals and power of the processing by the computer in the ventilator.

Essentials to Remember

- In waveform analysis during mechanical ventilation, there must be a differentiation between those variables that are directly controlled by clinicians and those that are indirectly controlled. For example, pressure, volume, and flow are directly controlled variables, as opposed to constants such as resistance and compliance, which are dependent upon the resistive and elastic properties of the respiratory system.
- During inspiration, flow and pressure patterns are directly related to the forces generated by the ventilator.

- During expiration, flow, pressure, and volume patterns cannot be directly manipulated by the clinician, except for determining the duration of each cycle when using a control mode.
- A ventilator is simply a technology that controls the airway pressure waveform, the inspired volume waveform, or the inspiratory flow waveform.
- To understand the interpretation of waveforms, the clinician needs to understand the relationship between the control and phase variables as it relates to the parameters that are either displayed or calculated and shown on the ventilator screen.

8.2 Nonconventional Ventilation Modes

8.2.1 High-Frequency Ventilators

Martin Keszler, Jane J. Pillow, and Sherry E. Courtney

Educational Aims

- Describe the principles of function of clinically available high-frequency ventilators.
- Review basic principles of gas exchange and how gas exchange is affected by the specific characteristics of the various devices.
- Describe the limitations of available devices and possible future developments.

High-frequency ventilation (HFV) nominally refers to those ventilator modalities utilizing breathing rates greater than 150 inflation/min and tidal volumes near or even below the anatomical dead-space volume. There are three main types of high-frequency ventilation in clinical use including high-frequency oscillatory ventilation (HFOV), high-frequency jet ventilation (HFJV), and high-frequency flow interruption (HFFI). In this chapter, we will define the different forms of high-frequency ventilators highlighting similarities and differences in operation and functionality that influence optimal ventilator strategy to be used with each modality. A thorough understanding of these differences and the operation and limitations of these ventilators is necessary to interpret differences in clinical trials and to avoid causing injury to the patient when changing between HFO ventilators or ventilatory modalities. New and improved ventilators are likely to emerge with further technological advances which may overcome current limitations of contemporary high-frequency ventilation devices.

8.2.1.1 High-Frequency Oscillatory Ventilators

8.2.1.1.1 Principles of Functioning and Gas Exchange

8.2.1.1.1.1 Classification of HFO Ventilators

High-frequency oscillation (HFO) is the most well-known and used form of high-frequency ventilation. While some clinical reports of HFOV use stem from the 1970s, more widespread utilization of HFOV as a neonatal ventilator modality stems from the first large randomized controlled trial in the mid-1980s. Since then, HFOV has been subjected to extensive *in vitro* and *in vivo* clinical evaluation.

In general, HFO ventilators are designed to provide ventilation through an endotracheal tube (ETT). They have a clearly defined active inspiratory and expiratory phase that generates biphasic pressure waveforms and diverts small volume packages of fresh bias flow to the patient at frequencies equal to or greater than 3 Hz (typically 6–15 Hz in newborn infants, 4–10 in pediatric patients). Despite this simple description, there has been a long-standing controversy about how to classify certain HFO devices. This controversy stems in part from continued confusion regarding the definition of what exactly constitutes "oscillatory ventilation." There is general agreement that to qualify as an oscillator, a device has to generate a waveform that has both positive and negative pressure deflection. The biphasic

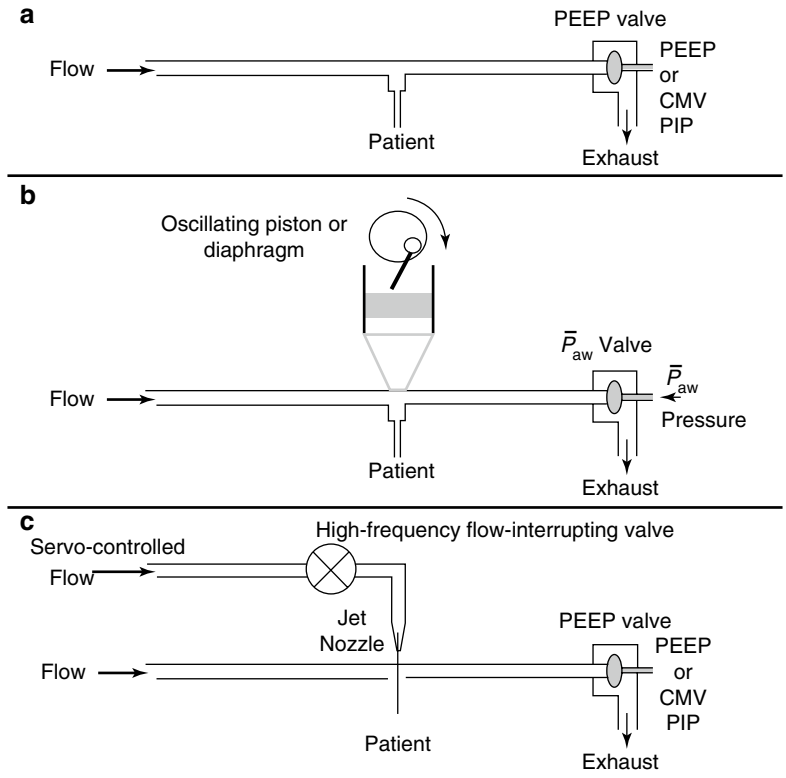


Fig. 8.47 Principles of gas delivery for different modes of ventilation: (**a**) During pressure-limited conventional ventilation, closure of the expiratory (*PEEP*) valve diverts the full bias flow to the patient circuit. Volume delivery to the patient is determined by the peak pressure that develops and the mechanical properties of the intubated respiratory system. During expiration, resistance through the expiratory (*PEEP*) valve determines the level of PEEP applied. Expiratory flow is determined by passive recoil of the chest and the resistance through the expiratory (*PEEP*) valve; (**b**) During high-frequency oscillatory ventilation, a constant bias flow is maintained across the circuit throughout inspiration and expiration. An oscillating piston or vibrating diaphragm diverts small parcels of this fresh bias flow to the patient circuit at high frequency. The oscillatory action of the piston/diaphragm results in active inspiration and expiratory phases – such that expiration is independent of the chest recoil mechanics. Mean airway pressure is determined by the amount of resistance offered to egress of the bias flow through the mean airway pressure valve in the expiratory limb; (**c**) In high-frequency jet ventilation, the jet ventilator is coupled to a conventional ventilator. PEEP is determined by the resistance to flow through the PEEP valve generated by the conventional ventilator. Intermittent closure of the PEEP valve facilitates delivery of low rate conventional ventilator inflation as required for volume recruitment. A separate servo-controlled flow is interrupted at high frequency to send high-velocity small volume jets of fresh gas to the patient, accounting for more than 90 % of the fresh gas delivery, and is the principle determinant of the removal of carbon dioxide

pressure waveform can be generated by a piston moving back and forth, in continuity with the patient's airway, or by a variety of venturi and jet injector configurations. To be a true oscillator, the magnitude of the negative pressure wave deflection should be roughly equal to that of the positive pressure deflection when operating with equal inspiratory and expiratory cycle durations. Such matching of positive and negative pressure deflections can be achieved by a linear motor piston pump, an electromagnetically driven vibrating diaphragm device or an expiratory venturi jet. Examples of contemporary piston HFO ventilators include the SM 3100A, SM 3100B, Humming V, the Flowline Dragonfly, the Heinen and Löwenstein Leoni plus, and the Stephan SHF 3000. The non-piston oscillators generally function much the same as piston oscillators; the

Table 8.16 Comparison of main features of CMV, HFOV, and HFJV

	CMV	HFOV	HFJV
Frequency (Hz)	0–2.5	3–15[a]	4–11
t_I :t_E	3:1–1:300[a]	1:2.5–1:1[a]	1:12 to 1:3
t_I (s)	0.1–2 s[a]	0.02–0.17[a]	0.02 (to 0.034)
Waveform	Variable	Square/sinusoidal/mixed	Peaked, complex
Exhalation	Passive	Active/venturi	Passive
CV needed	Yes	Not required	Yes
V_E and O_2 uncoupled	No	Yes	Partial
TT adapter	No	No	Yes

[a]Values are given for the Babylog 8000+ (CMV) and the SM 3100A (HFOV) and may vary with different ventilators within a specific class of ventilation. t_I inspiratory time, t_E expiratory time, V_E ventilation, O_2 oxygenation, *TT* tracheal tube

variables that influence gas exchange, the mechanisms of gas exchange, as well as applicable ventilation strategies are very similar among these devices. Contemporary non-piston oscillators include the SLE5000, the Drager Babylog 8000+ (BL8000+), and the Babylog VN500.

For both piston and non-piston oscillators, each device has its own unique operating characteristics and limitations. It is therefore crucial that the clinician be familiar with the key features of each device. The differences between HFO ventilators and those that provide conventional pressure-limited ventilation or HFJV are shown in Fig. 8.47 and highlighted in Table 8.16. The important features of HFO ventilators include largely independent manipulation of oxygenation (via adjustments to mean airway pressure) and removal of carbon dioxide (via adjustments to oscillatory amplitude and frequency), and the active expiratory phase.

8.2.1.1.1.2 Ventilation

Ventilation at tidal volume (V_T) equal to or less than anatomical dead space can and does occur during HFOV, although in infants with more severe disease, the tidal volume is often slightly greater than dead space (Dimitriou et al. 1998). Whereas minute volume (respiratory rate × tidal volume) is the determinant of CO_2 removal when breathing at conventional breathing rates, the efficiency of gas mixing is greatly increased at breathing frequencies greater than 3 Hz, such that carbon dioxide elimination is more closely related to $f \cdot V_T^2$ (Slutsky et al. 1981; Slutsky 1984). The mechanisms responsible for this highly efficient ventilation during HFO were elegantly outlined in the classic article by Chang (1984) and more recently by Slutsky and Drazen (2002) and are summarized in Fig. 8.48. Briefly, direct alveolar ventilation from bulk movement of gas occurs proximally. Turbulent flow also contributes to proximal gas transport. Asymmetric velocity profiles that occur due to the parabolic shape of gas moving back and forth in the airways enhance distal penetration of fresh oxygen-rich inspiratory gas and egress and radial mixing of CO_2. Movement of gas between alveoli with differing time constants leads to out-of-phase mixing (pendelluft) in more distal units, further enhanced by collateral ventilation via pores of Kohn. Cardiogenic mixing may further enhance gas mixing, particularly in the left lingular and left lower lobe. Distally, where flow becomes more laminar, molecular diffusion occurs at the alveolar–capillary membrane (Khoo et al. 1984).

Tidal volume delivery can be influenced by both amplitude and frequency (decreasing as frequency increases) as well as by other circuit and mechanical properties of the intubated respiratory system, including the size of the ETT and airway resistance (Pillow et al. 2001). At high frequency, tidal volume is largely independent of compliance (except at very low compliance); however, tidal volume becomes increasingly dependent on lung compliance as frequency is decreased (Pillow et al. 2001).

Under normal conditions, HFO ventilation is characterized by marked damping of oscillatory pressure waveform by the relatively high impedance (resistance and inertance) associated with turbulent flow through the tracheal tube. The degree of that attenuation is principally

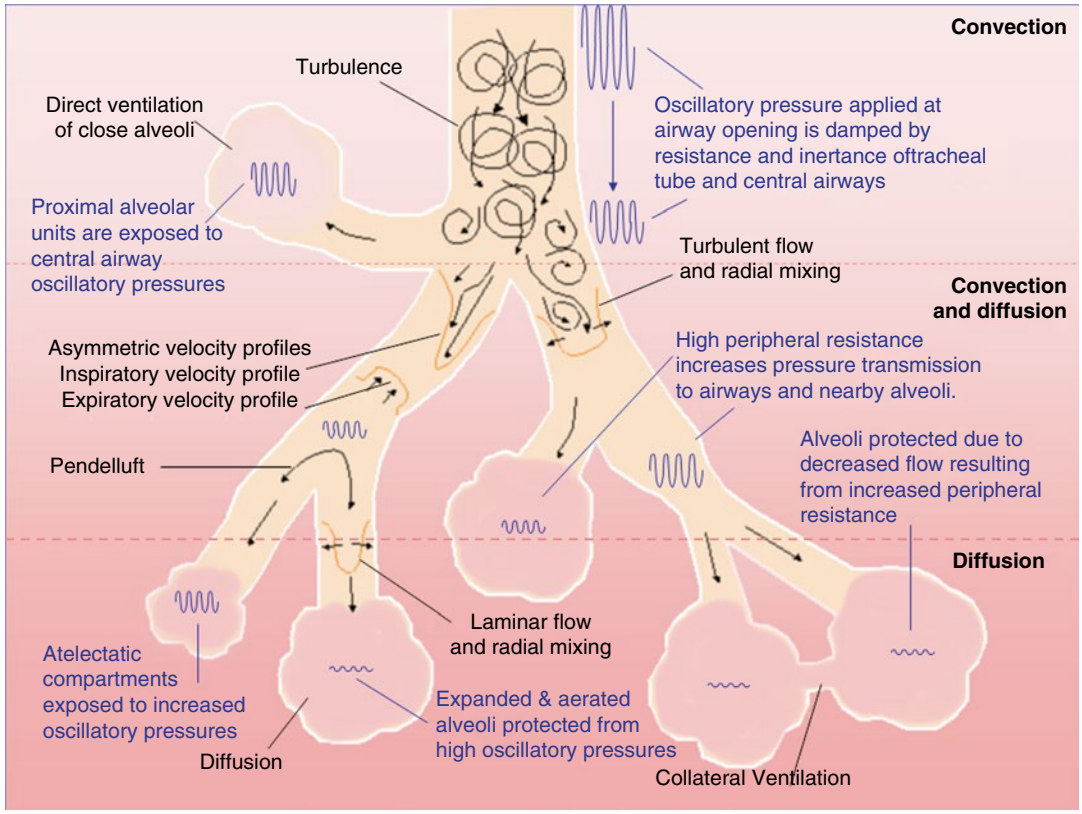


Fig. 8.48 Gas-transport mechanisms and pressure damping during high-frequency oscillatory (HFO) ventilation: The major gas-transport mechanisms operating during HFOV in convection, convection–diffusion, and diffusion zones include the following: turbulence, bulk convection (direct ventilation of close alveoli), asymmetric inspiratory and expiratory velocity profiles, pendelluft, cardiogenic mixing, laminar flow with Taylor dispersion, collateral ventilation between neighboring alveoli, and molecular diffusion (see text for details). The extent to which the oscillatory pressure waveform is damped is influenced by the mechanical characteristics of the respiratory system. Atelectatic alveoli will experience higher oscillatory pressures than normally aerated alveoli, whereas increased peripheral resistance increases the oscillatory pressures transmitted to proximal airways and neighboring alveolar units (Adapted with permission from Slutsky and Drazen 2002)

determined by the internal diameter of the ETT and the frequency employed (Fig. 8.49). However, an often poorly appreciated fact is that the transmission of oscillatory pressure amplitudes to the lung can be markedly increased in the presence of abnormal lung mechanics. The main effects are summarized in Figs. 8.48 and 8.49.

The optimal frequency of ventilation will vary, therefore, according to the mechanical properties of the intubated respiratory system. Optimal frequency selection is best estimated by considering the oscillatory pressure cost of achieving flow (Venegas and Fredberg 1994): This falls rapidly with increasing frequency, reaching a minimum at the resonance frequency of the lung. However, in overdamped lungs, minimal additional damping of the oscillatory pressure waveform is achieved above the corner frequency (f_c) of the lung: $f_c = 1/2\pi RC$ where R is the respiratory resistance and C is the lung compliance. Thus, there is benefit in increasing frequency up to, but not beyond, the corner frequency of the lung (Pillow 2005). Low-compliance lungs are optimally ventilated within a limited range of high frequencies, while lower frequencies are more appropriate in high-resistance systems, to avoid barotrauma to the proximal airways and neighboring alveoli while still achieving adequate volume delivery

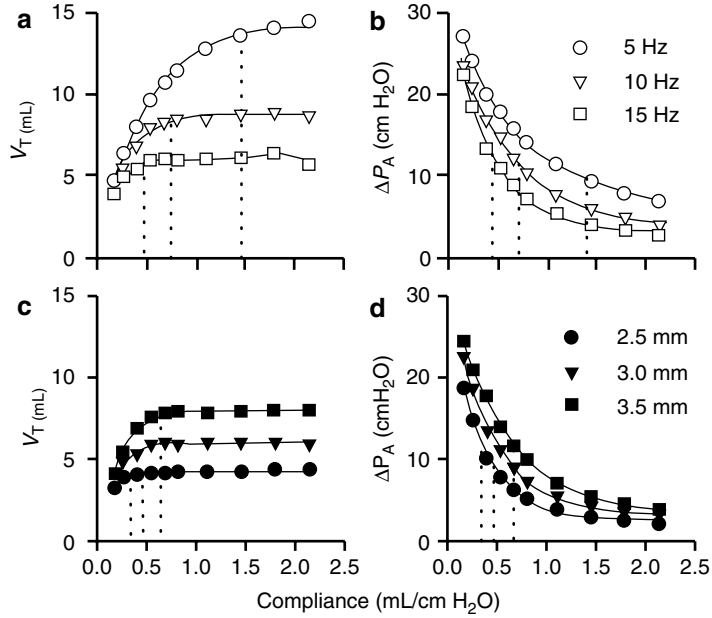


Fig. 8.49 Effect of compliance on V_T and DP_A at different frequencies and ETT sizes: Graphs show tidal volume (V_T: **a**, **c**) and amplitude of the alveolar pressure waveform (ΔP_A: **b**, **d**) at different frequencies and tracheal tube sizes, using a mathematical model (Reproduced with permission from Pillow et al. 2002)

to effect adequate gas exchange. In contrast, a healthy lung will tolerate a wider frequency selection without significant injury.

8.2.1.1.1.3 Oxygenation and Optimal Lung Volume

Mean airway pressure is the primary determinant of oxygenation during HFO ventilation, and its appropriate selection to achieve optimal lung distension (avoiding atelectasis and overdistension) is a critical consideration in minimizing the pressure and flow cost of ventilation during HFO ventilation (Venegas and Fredberg 1994). Mean pressure measured at the airway opening (patient connector – P_{ao}) is used as an approximation of mean airway pressure; however, this may overestimate mean airway pressure when t_I:t_E ratios less than 1:1 are used (Pillow et al. 1999; Gerstmann et al. 1990; Thome and Pohlandt 1998), and the magnitude of this pressure drop will increase with decreasing ETT size and increasing frequency (Pillow et al. 1999) (Fig. 8.50).

Optimal P_{ao} is attained when fractional inspired oxygen (FiO_2) is at a minimum, and the chest radiograph shows maximal resolution of atelectasis without evidence of hyperinflation. Clinically, this point is best obtained at initiation of HFOV in an atelectatic lung by focused volume recruitment maneuvers. The most common approach is to increase the P_{ao} and to wean the FiO_2 according to peripheral oxyhemoglobin saturations (SpO_2) until the FiO_2 reaches a minimum value then starts to increase. P_{ao} is then decreased until FiO_2 is again at minimum. At this point the lung is being ventilated at the point of maximum curvature on the descending limb of the pressure–volume curve, often referred to as "optimal lung volume" (see Fig. 8.51). An alternative approach is to use "sigh" recruitment maneuvers to raise the resting volume of the lung up to optimal lung volume. Videomicroscopy illustrates clearly how the use of a constant distending pressure sufficient to keep the airways and alveoli open throughout the respiratory cycle potentially avoids atelectotrauma that may occur more easily when using conventional ventilator modes (see Fig. 8.52).

An accurate and easy-to-use bedside measure of distending lung volume during HFOV is desperately needed. Current methods used in research and clinically in selective units include electrical impedance tomography and respiratory inductance plethysmography (Wolf and Arnold 2005). Indirect measures including nonlinear lung mechanics (Habib et al. 2002), intermittent oscillatory mechanics (Pillow et al. 2004),

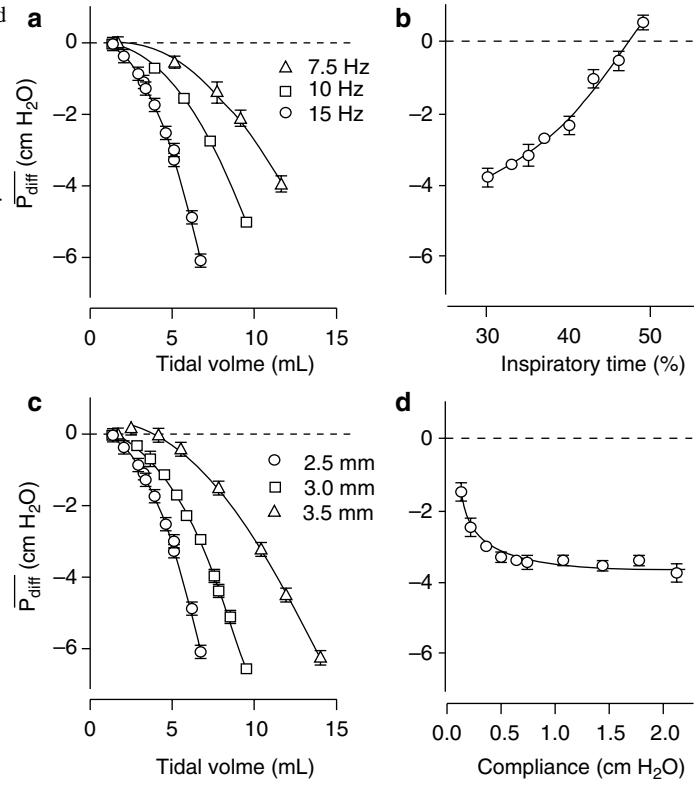


Fig. 8.50 Effect of ventilator settings and respiratory mechanics on mean pressure drop: Graphs illustrate the magnitude of the difference in mean pressure between the airway opening and the lung (P_{diff}) attributable to change in ventilation frequency (**a**), % inspiratory time (**b**), endotracheal tube internal diameter (**c**), or lung compliance (**d**) in an in vitro model lung (Reproduced with permission from Pillow et al. 1999)

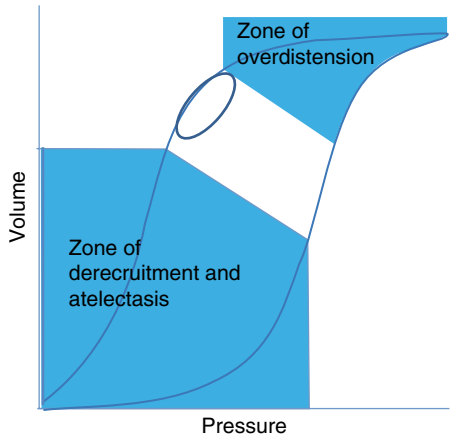


Fig. 8.51 Zone of ventilator-induced lung injury (VILI) relative to distending lung volume: Small cyclic volume changes at the point of maximal curvature on the deflation limb of the volume–pressure relationship may protect the lung from injury arising from overdistension (volutrauma) or atelectasis (atelectotrauma) (Reproduced with permission from Froese 1997)

and measurement of the oscillatory pressure ratio (OPR) can also identify the optimal lung volume (van Genderingen et al. 2002) (see Fig. 8.53). Of each of these methods, the oscillatory pressure ratio (ratio of tracheal pressure amplitude to airway opening pressure amplitude: $\Delta P_{tr}/\Delta P_{ao}$) is likely to be the most easily achieved at the bedside in a wide range of clinical units – but requires the measurement of ΔP_{tr}, which is not yet a routine measurement in the NICU.

8.2.1.1.2 Contemporary HFO Ventilators

8.2.1.1.2.1 Piston HFO Ventilators

A range of contemporary piston HFO ventilators are available for clinical and research use. They differ with respect to generation of oscillatory flow, frequency, amplitude, mean airway pressure, inspiratory to expiratory ratio, monitoring options, and integration with a conventional ventilator.

Sensor Medics

The SensorMedics 3100A (SensorMedics, CareFusion, San Diego, CA) is indicated for use in neonates and children less than 35 kg.

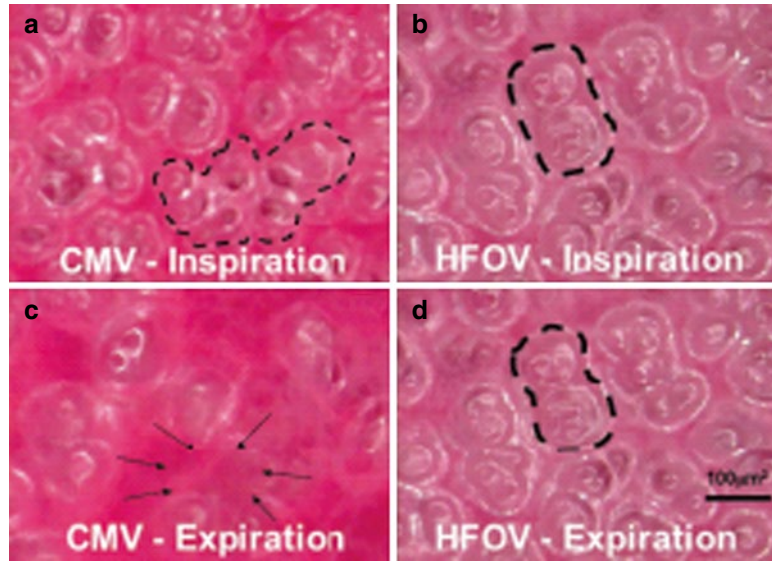


Fig. 8.52 Videomicroscopy of alveolar morphology during conventional ventilation and HFO ventilation: Figure shows subpleural alveoli in the rat after lung injury by saline lavage ventilated with either conventional mechanical ventilation (*CMV*) or high-frequency oscillatory (HFO) ventilation. With CMV, alveoli inflated during inspiration (*dots*, panel **a**) collapse with expiration (*arrows*, panel **b**). In contrast, alveoli remain open and stable with HFO ventilation throughout inflation (panel **c**) and exhalation (*dashes*, panel **d**) (Reproduced with permission from Carney et al. 2005)

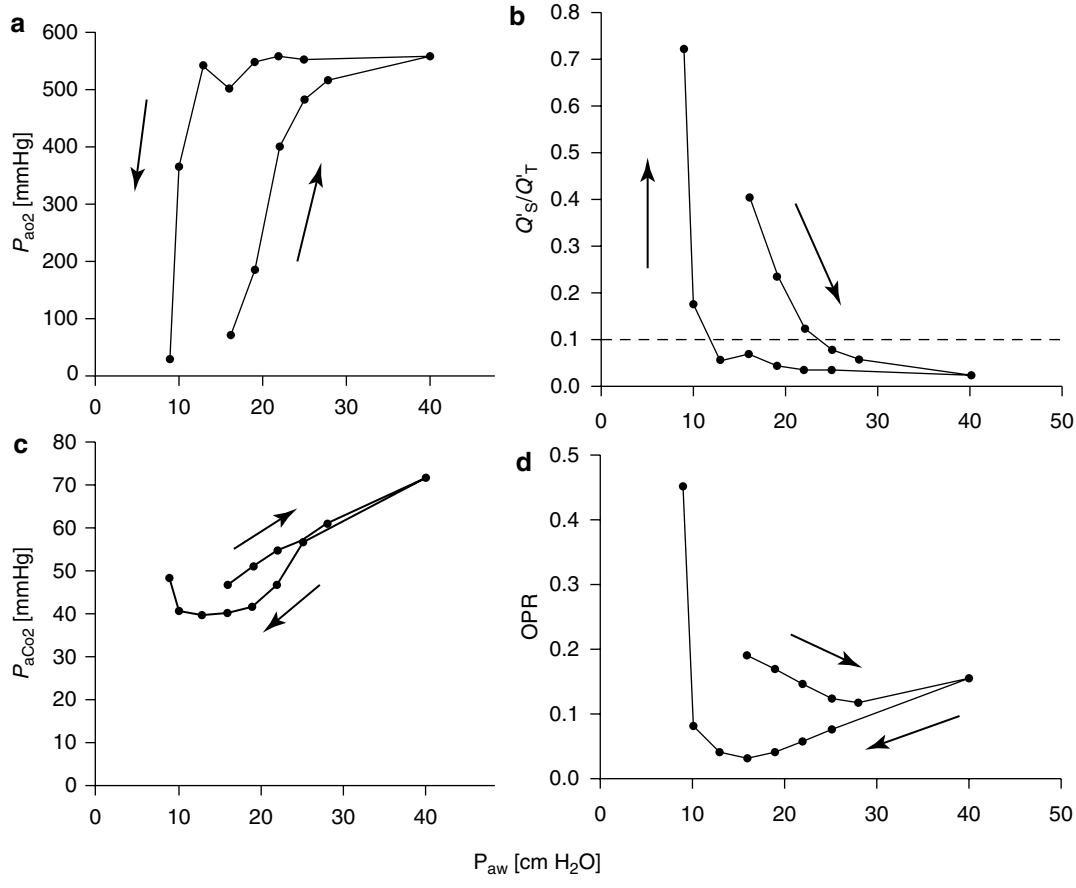


Fig. 8.53 Relationship between P_{aw} and (**a**) PaO_2, (**b**) physiological shunt fraction, (**c**) $PaCO_2$, and (**d**) oscillatory pressure ratio: The arrows indicate the order in which values change in response to increments and subsequent decrease in P_{aw}. The minimum oscillatory pressure ratio (OPR: $\Delta P_{tr}/\Delta P_{aw}$ where ΔP_{tr} is tracheal pressure amplitude and ΔP_{aw} is airway pressure amplitude measured at airway opening) coincides with optimum $PaCO_2$, PaO_2, and minimum physiological shunt fraction (Q'_s/Q'_T) (Adapted from van Genderingen et al. 2002)

An electromagnetic piston diaphragm is oscillated back and forth, very similar to a permanent magnet loudspeaker. It produces a complex square pressure waveform with multiple frequency harmonics. The ventilator is the most powerful stand-alone neonatal oscillator and cannot be used as a conventional ventilator. Capabilities include a frequency range of 3–15 Hz, proximal amplitudes of 10–110 cm H_2O, and mean airway pressures of 3–45 cm H_2O using bias flow of 3–40 L/min. Mean airway pressure is achieved by a continuous bias flow of gas past the resistance (inflation) of the balloon on the mean airway pressure-control valve. Inspiratory time is set as percent of the duty cycle; it can be varied from 30 % to a maximum of 50 %; however, the manufacturer recommends using 33 % as few data are available on the safety of using 50 % with this device. There is no facility for a sigh maneuver; hence, volume recruitment with the SM 3100A requires adjustments to the mean airway pressure. The current commercially available ventilator does not provide demand flow, which can interfere with spontaneous breathing efforts. Tidal volume is not monitored. Operative noise levels are relatively high compared to most other HFOV ventilators.

The SensorMedics 3100B is indicated for use in children and adults greater than 35 kg, though it can also be used in neonates and small children. It functions similarly to the 3100A, though it is much more powerful. Bias flow capability of up to 60 L/min allows provision of P_{aw} of 5–55 cm H_2O and amplitudes of >90 cm H_2O in adult patients. Frequency range is 3–15 Hz and inspiratory time can range from 30 to 50 % of the duty cycle. Tidal volume is not monitored.

Metran Ventilators

The Hummingbird oscillators are the most well-known oscillators produced by Metran (Saitama, Japan). They are piston oscillators (linear motor generators) with inspiration and expiration each accounting for 50 % of the duty cycle. The Humming V (current model) can function as both a conventional ventilator (SIMV) and an oscillator. The HFO pressure waveform is sinusoidal. During HFOV, frequency range in the Humming V is limited to 13–17 Hz which limits its application in situations of high resistance (e.g., meconium aspiration). Inspiratory to expiratory time ratio is limited to 1:1 (although can be changed to 1:3 by altering dip switch settings). The Humming V has an output equal to that produced by the SM 3100A (Pillow et al. 2001; Hatcher et al. 1998). Sighs can be delivered manually or programmed to be delivered as infrequently as once every 5 min. Synchronized breathing is easier on the Humming V than with the SM 3100A. Tidal volume is not monitored.

More recently, Metran has produced two other HFO ventilators including the Calliope α and the R100 (or Vision α in Europe by Novalung GmbH, Talberg, Germany). The Calliope α provides enhanced mean airway pressure capabilities (up to 40 cm H_2O), smaller adjustments of stroke volume, a wider frequency range (5–17 Hz), and quieter operation and includes PSV as a conventional ventilation mode. The R100 (Vision α) offers both CMV and HFOV. The new rotary valve associated with the R100 (or Vision α) produces square wave oscillations sufficiently powerful to be used not only in small children (≥5 kg) but also in adults. Capabilities include a frequency range of 5–15 Hz, oscillatory stroke volumes (that are to be set by the operator instead of a pressure amplitude) that range from 2 to 350 mL (and vary with the oscillatory frequency), and mean airway pressures of 5–60 cm H_2O. Operative noise levels are very low compared to the SensorMedics 3100 A and B.

Stephan

Stephan-GmbH (Gackenbach, Germany) offers two neonatal ventilators capable of HFO, those being the Stephanie and the Sophie ventilators. Both are combined conventional/HFO ventilators and have the same HFO performance. Adjustable settings include waveform (Stephanie, square or sinusoidal; Sophie, square only), frequency (5–15 Hz), inspiratory to expiratory time ratio (Stephanie 1:1, 2:3, 1:2; Sophie from 1:1 to 1:2), and mean airway pressure (maximum P_{aw} 30 cm H_2O). Stroke volume is somewhat more limited (max stroke volume of 20 mL) than the abovementioned HFO ventilators, limiting their HFO use to infants up to 10 kg. Combined HFO and conventional ventilation is possible. Tidal volume is monitored.

Heinen + Löwenstein

Heinen + Löwenstein (Bad-Ems, Germany) offers the Leoni plus which is a neonatal ventilator capable of HFO and CMV. The integrated HFO module works according to the diaphragm principle (double membrane). The waveform is sinusoidal. Adjustable settings include frequency (5–20 Hz), inspiratory to expiratory time ratio (1:1, 2:3, 1:2, 1:3), and mean airway pressure (maximum P_{aw} 40 cm H_2O). Stroke volume is somewhat more limited than the abovementioned HFO ventilators, limiting its HFO use to infants up to 10 kg. Combined HFO and conventional ventilation is possible with oscillation provided during the inspiratory and expiratory cycle. Tidal volume is monitored. The requirement for a pressure supply of 2.0–6.5 BAR (29–63 PSI), low gas-flow requirements of 7 L/min to support the mean airway pressure, and an inbuilt battery (30 min backup in the HFO mode, 1-h backup in the CMV mode) allow for short intrahospital transfer (e.g., NICU to operating theater).

Acutronic

Acutronic Medical Systems (Hirzel, Switzerland) offers the Fabian HFO which provides HFOV in addition to CMV for neonates and children up to 30 kg. The integrated HFO module works according to the diaphragm principle (large single membrane). The waveform is sinusoidal. Adjustable settings include frequency (5–20 Hz), inspiratory to expiratory time ratio (1:1, 1:2, 1:3), mean airway pressure (maximum P_{aw} 40 cm H_2O), and amplitude settings from 5 to 80 cm H_2O. During HFOV, a volume guarantee mode can be chosen in the tidal volume range of 1–30 mL (suitable for patients up to 10 kg). Combined HFO and conventional ventilation is possible with oscillation provided during the inspiratory and expiratory cycle. Tidal volume is monitored. The requirement for relatively low pressure supply (< 2.0 BAR/< 29 PSI), a low base flow of only 2–10 L/min, an inbuilt battery (1-h backup in the HFO mode, 4-h backup in the CMV mode), and a relative low unit weight (only 18 kg) allows for intrahospital (e.g., NICU to operating theater) and short interhospital (e.g., ambulance and air ambulance) transfers.

Flowline

The Dragonfly (Shreeyash Electro Medical, India) represents the start of a new generation of HFO ventilators. Offering servo-controlled bias flow, mean airway pressure, and piston positioning, it is a more user-friendly option for the clinician due to reduced need for manual adjustment and correction of ventilator settings, which otherwise may change in response to alterations to any one of these factors. It offers a frequency range of 5–18 Hz and inspiratory to expiratory time ratios of 1:2 and 1:1. Bias flow is adjustable from 4 to 60 L/min and mean airway pressure is servo controlled up to 40 cm H_2O. It is a moderately powerful ventilator with a maximum piston volume of up to 500 mL. Tidal volume is monitored. The requirement for low pressure supply (only 1.5 PSI) and an inbuilt battery (2-h backup) facilitates the use of the ventilator for intrahospital transfers (e.g., NICU to operating theater).

8.2.1.1.2.2 Non-piston HFO Ventilators

Babylog 8000+

The BL8000+ (Draeger, Lubeck, Germany) is a device capable of producing both conventional and high-frequency oscillatory ventilation alone or in combination. During HFOV, mean airway pressure and the positive pressure deflection of the oscillatory waveform are generated by continuous flow of gas from a bank of precision solenoid valves. The inspiratory flow is automatically adjusted based on choice of mean airway pressure (maximum of 25 cm H_2O) and frequency (5–20 Hz). Superimposed on this is an intermittent negative pressure generated by a venturi effect of the high-flow jet injector at the expiratory valve causing active exhalation. Thus, circuit pressure fluctuates from positive to negative based on the activation of the expiratory valve venturi. The inspiratory flow is not interrupted during the expiratory phase; it is overcome by the negative pressure of the active expiratory flow. Therefore, the BL8000+ is clearly NOT a flow interrupter, although it has commonly been described as such. The t_I:t_E ratio is not directly set, but is a function of the set frequency, varying from 1:1 at 15 Hz to as much as 1:5 at the lowest

frequencies. At the typical frequency of 8–10 Hz, the ratio is close to 1:2. The amplitude is set as a percentage of peak output, which is calculated as a percentage of the difference between mean airway pressure and 60 cm H_2O. For example, if the mean airway pressure is 15 cm H_2O, then 100 % amplitude would be 45 cm H_2O with a pressure range from −7.5 to 37.5 cm H_2O. However, the actual amplitude is limited at low mean airway pressure by a safety limit valve that does not permit the negative pressure to drop below −4 cm H_2O. The practical consequence of this is that once the trough pressure reaches −4 cm H_2O, further increases in % amplitude do not increase delivered tidal volume, unless the mean airway pressure is also increased. The effective amplitude is very frequency dependent. Limited tidal volume is produced at frequencies above 10 Hz; therefore, in larger infants, frequencies below 8 Hz may be needed to achieve adequate tidal volume. The waveform is a true sinusoidal waveform with equal positive and negative deflection at 1:1 ratio and quasi-sinusoidal at the shorter inspiratory ratios. The device monitors tidal volume (V_T) during HFOV using a hot wire anemometer at the airway opening; this is a distinct advantage over some commonly available HFV devices. A calculated value of DCO_2 (rate of CO_2 removal) is displayed, allowing the clinician to easily recognize changes in minute ventilation.

VN500

Virtually all the limitations of the BL8000+ were effectively addressed in the recently released (late 2009) Draeger *VN500*. The new device is much more powerful, reaching 80 % of the output of the SensorMedics 3100A in bench tests at 5 Hz using optimal circuit configurations (J Pillow, unpublished data, 2012). In the VN500, the circuit inflow is actively modulated during the expiratory phase, and the larger, reconfigured expiratory valve is capable of generating much stronger active exhalation. The t_I:t_E ratio is now user controlled in the range of 1:1 to 1:3. The pressure amplitude is set directly by the user and is no longer a percentage of an abstract maximum value. The −4 cm H_2O safety valve is neutralized during HFOV, allowing the device to generate large amplitudes even at low mean airway pressure. However, mean airway pressure should not be too low or atelectasis will develop as with any form of ventilation. Additionally, as in all devices, airway collapse can potentially result from active exhalation at low mean airway pressure and this could lead to air trapping. Inappropriately low mean airway pressure should therefore be avoided. Conventional sigh inflation can be combined with HFOV to aid in lung volume recruitment.

An important new development is the ability to servo control the delivered V_T (measured as exhaled tidal volume at the airway opening) by means of HFOV + Volume Guarantee (VG) option. This allows the user to preset a V_T during HFOV, much like with conventional volume guarantee. It should be noted that activating VG eliminates the effect of changes in frequency on delivered VT seen in other HFOV devices. The calculated value of DCO_2 (rate of CO_2 removal) is displayed as in the 8000+. As with other HFOV devices intrahospital transport is possible. Due to its very recent release, there are no clinical studies at this time to support the clinical benefits of the new Draeger VN500 high-frequency oscillator.

SLE 5000

The SLE 5000 (SLE corporation, South Croydon, UK) is also a combination conventional and high-frequency ventilator. Continuous flow of heated, humidified gas at 8 L/min in the ventilator circuit is opposed by a reverse jet of gas in the expiratory block, resulting in positive end-expiratory pressure. Adjustment of the gas flow controls the mean airway pressure. Oscillations are produced at the expiratory block by a rotating ball valve that directs a second jet alternately against the continuous gas flow or with it, resulting in positive and negative pressure deflections, in essence acting as a pneumatic piston. This design results in a fixed 1:1 inspiratory to expiratory ratio and results in a true sinusoidal waveform with active exhalation. The device is sometimes referred to as a "valveless jet ventilator," but that is a misleading term, because the jet does not reach the patient and does not directly participate in gas exchange. Frequency is adjustable from 3 to 20 Hz. Airway opening pressure amplitude (ΔP_{ao}) range is

4–180 cm H_2O and mean airway pressure range is 4–35 cm H_2O. Oscillations can be delivered in isolation or superimposed on conventional inflation which may be patient triggered. The manufacturer claims the ability to support infants from 300g to 20 kg, depending on lung mechanics. Tidal volume is monitored. The inbuilt battery (1-h backup) allows the use of the ventilator for intrahospital transfers.

8.2.1.1.3 Performance Characteristics of HFO Ventilators

Several *in vivo* and *in vitro* studies have highlighted important differences in performance characteristics between different HFO ventilators (Pillow et al. 2001; Hatcher et al. 1998; Fredberg et al. 1987; Jouvet et al. 1997). An understanding of these differences is essential for clinicians treating patients with HFO. In particular, it is important for practitioners to know the specific characteristics and capabilities of (and differences between) the machine(s) used in their unit. For example, the Humming V has a limited frequency range, and thus, volume output is limited, which in turn limits the size of the patient for whom this machine can be used. It also limits the applicable clinical situations given that lower frequencies may be needed when airway resistance is high (Pillow 2005; Hatcher et al. 1998).

Utilization of an inspiratory to expiratory time ratio less than 1:1 (e.g., 1:2) (SM 3100, Stephanie, Sophie, Leoni Plus, BL8000+ and VN500, Dragonfly) may produce mean intrapulmonary pressures that are lower than those at the airway opening (Pillow et al. 1999; Gerstmann et al. 1990; Thome and Pohlandt 1998; Hatcher et al. 1998). This arises due to flow dependence of resistance through the tracheal tube and the increased inspiratory resistance relative to expiratory resistance seen assuming airways are stented open by use of sufficient mean airway pressure (removing the normal increased resistance associated with partially collapsed airways at low PEEP in conventional ventilation). Contrary to widely held beliefs, with an inspiratory to expiratory time ratio of 1:1, mean intrapulmonary pressure is very similar to that displayed at the airway opening during HFOV provided that sufficiently high mean airway pressures are employed to avoid choke point formation (Pillow et al. 1999; Hatcher et al. 1998). Differences in algorithms used for tidal volume calculation may also result in overestimation (SLE 5000) or underestimation (Stephanie) of the delivered volume by between 5 and 20 %, and the inaccuracy of this display may also increase as frequency is increased (Leipala et al. 2004).

A further important consideration is the nature of the ventilator circuit. Unlike the SM 3100 and the Dragonfly, the Stephan and Metran piston oscillators and the non-piston oscillators use a conventional ventilator circuit. This means that ventilator circuits and humidifiers need to have minimal compliance and compressible volume; nonstandard circuits and humidifiers could adversely affect performance. A potential advantage of ventilators capable of both conventional and HFOV is the option of combining low rate of conventional sighs with HFOV, which may be useful in maintaining an open lung strategy without excessive mean airway pressure. However, the benefits of this strategy have not been systematically evaluated.

8.2.1.1.4 HFO Ventilator Developments and Future Directions

Many sick newborns require transport to other institutions for surgery, extracorporeal membrane oxygenation (ECMO), or other special care. If these infants have already been started on HFO, transporting them on conventional ventilation may not be tolerated. Current oscillators are not configured for use in transport, requiring a change to a jet ventilator (Bunnell Life Pulse) or flow interrupter (Bronchotron), both discussed later in this chapter. An oscillator that could be used for transport would be an important future development. While intrahospital (e.g., ICU to theater) transport is now possible (Dragonfly, VN500, Leoni plus, Fabian HFO), further research and development is required to provide a reliable ventilator for long-distance interhospital transfers. Incorporation of low gas pressures and flows into such a ventilator would be an important consideration.

Although HFOV has been in clinical use for 25 years, many issues relating to optimum clinical application still remain to be resolved. Focus

on inspiratory to expiratory ratio has largely related to gas trapping and intrapulmonary pressures, but this aspect may also have implications for gas-transport efficiency and shear stress, due to differences in inspiratory and expiratory flow profiles. It is also unclear whether the complex frequency content of a square pressure waveform offers specific advantage/disadvantage over a sinusoidal waveform. The optimal method of volume recruitment (sigh versus increased mean airway pressure) is also unclear. Finally, increased awareness of the lack of patient-initiated breathing and stretch on diaphragm dysfunction have highlighted the desirability of allowing superimposition of HFO on gentle spontaneous breathing movements without additional sedation. Therefore, enhanced patient–ventilator interactions need to be a focus of future HFO ventilator development.

New ventilators are constantly being developed, and by the time this book is in press, almost certainly new machines capable of providing HFO will be available. As these new ventilators emerge, it is important that their performance characteristics are fully evaluated and that the practitioner understands the machine being used and how it may differ from other HFO ventilators, in order to optimize patient care.

8.2.1.2 High-Frequency Jet Ventilators

High-frequency jet ventilation is a distinct form of high-frequency ventilation that has been widely used in newborn infants for more than 25 years. It shares the basic principles of gas exchange with other HFV devices but differs in some important ways, which will be discussed in detail below. The "Sanders bronchoscope jet" was the first practical device that used the basic principle of jet ventilation and thus is the true forerunner of modern jet ventilators. This simple device was based on an observation that when oxygen was delivered via the side arm of a bronchoscope in short bursts rather than continuously, the CO_2 accumulation that previously limited bronchoscopy to only a few minutes was markedly reduced (Sanders 1967). True HFJV was first applied in adults in the mid-1970s using an electronically controlled solenoid valve jet ventilator (IDC VS-600, Instrument Development Corporation, Pittsburgh, Pennsylvania) (Klain and Smith 1977). Subsequently, this device and two prototype jet ventilators based on fluidic technology were used in newborn infants in the early 1980s (Pokora et al. 1983). The initial application was in severely ill infants who were failing conventional ventilation and typically suffered from severe air leak complications (Spitzer et al. 1989). The emphasis was on reducing airway pressure, something for which HFJV is uniquely suited because of the very short inspiratory time and relatively long expiratory time. As treatment expanded to less severely affected infants and different disease processes, new strategies evolved that were more appropriate for these pathophysiologies (Keszler and Durand 2001). This section will focus on the Bunnell Life Pulse ventilator, because it is the only jet ventilator that is widely used and approved by regulatory agencies and for the treatment of newborns and young infants. The device is currently almost exclusively used in North America, although small numbers of these ventilators are in use in Europe and Australia.

8.2.1.2.1 HFJV: Principles of Functioning and Gas Exchange

HFJV shares the basic principles of gas exchange with other HFV devices, specifically the use of rapid respiratory rate and very small tidal volume. Mean airway pressure is the key determinant of oxygenation and CO_2 elimination is proportional to $f \cdot V_T^2$. However, the different mechanisms by which these devices generate high-frequency pulses or oscillations lead to some important differences in their function.

Unique to HFJV is the concept of spike formation. Henderson first described this phenomenon nearly 100 years ago (Henderson et al. 1915). He demonstrated that a high-velocity impulse of gas penetrates through the dead-space gas resident in the upper airway, rather than pushing it ahead, as occurs with gas flow at low velocities. Spike formation enhances bulk flow of gas in the upper airway by largely bypassing anatomical dead space and provides more efficient gas mixing in the more distal lung. Enhanced

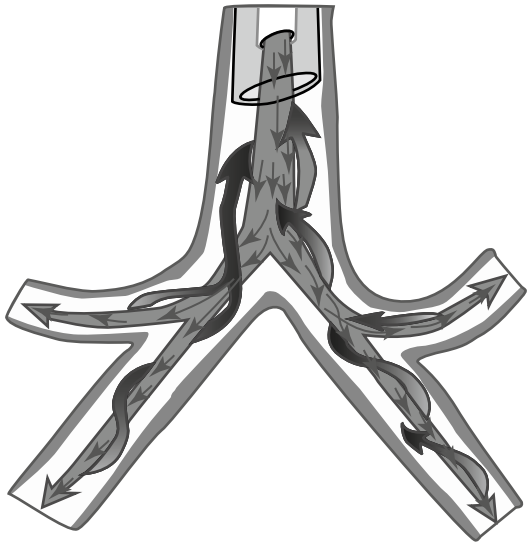


Fig. 8.54 Schematic of gas transport during HFJV. The diagram illustrates the principles of gas transport through the major airways during HFJV with a central high-velocity inspiratory jet stream, and the spiraling of expiratory gases in the reverse direction around this central inspiratory gas stream. The unique "spike" of gas penetrates the dead space of the upper airway, rather than pushing dead space ahead of it, as occurs with conventional ventilation at lower frequencies

molecular diffusion probably plays an important role in the gas exchange occurring in the distal airways and alveoli. Mathematical models predict and empirical observations support the concept that exhalation to a significant degree is concurrent with inspiration; high-velocity gases stream down the center of the larger airways with outward coaxial rotational flow occurring simultaneously (see Fig. 8.54) . Bidirectional flow is likely the mechanism responsible for the ability of the jet ventilator to prevent aspiration, enhance clearance of meconium from the upper airways, and achieve effective alveolar ventilation even in the face of large airway disruption, as well as its ability to allow for faster resolution of pulmonary interstitial emphysema (Keszler et al. 1991). The position and curvature of the endotracheal tube appears to be important in the efficiency of spike formation and gas mixing. Other factors that reduce the effectiveness of spike formation and impair ventilation include the presence of thick secretions and debris in the airways.

The jet ventilator has a set inspiratory time (t_I), unlike HFOV where the inspiratory time is a fixed percentage of the respiratory cycle. Therefore, as the Life Pulse rate is adjusted, the only thing that changes is exhalation time. The frequency dependence of pressure amplitude and tidal volume seen with oscillatory-type devices is less problematic with HFJV, except at very low compliance (Pillow J., personal communication, 2010). The exhalation is passive; therefore, the optimal operating frequency of the jet ventilator is lower than that for HFOV and, as with other ventilators, needs to be lowered further in patients with prolonged time constants.

It is important to recognize that because of the extremely short inspiratory to expiratory time ratio (t_I:t_E), mean airway pressure ($\overline{P}_{aw}$) with the Life Pulse ventilator is primarily determined by the positive end-expiratory pressure (PEEP). Therefore, at equivalent peak inflation pressure (PIP), the PEEP must be substantially higher to maintain the same $\overline{P}_{aw}$ as on conventional ventilation and to prevent atelectasis in patients with atelectasis-prone lung disease. Failure to recognize this fact is the reason why HFJV acquired an unjustified reputation for being poor at achieving good oxygenation. While $\overline{P}_{aw}$ is predominantly determined by PEEP, it also receives a contribution from the HFJV peak insufflation pressure: Thus, $\overline{P}_{aw}$ and therefore oxygenation is not independent of ventilation. A reduction in HFJV ΔP_{aw} may need to be achieved by decreasing the HFJV peak insufflation pressure in parallel with an increase in positive end-expiratory pressure, if simultaneous weaning of $\overline{P}_{aw}$ is not desired.

The ability to combine conventional sigh or background inflations with HFJV is a potential advantage of the technique over some HFOV ventilators. Sighs are useful in initial lung volume recruitment and perhaps in maintenance of optimal lung inflation with slightly lower $\overline{P}_{aw}$. Once good lung volume has been achieved, the rate should be reduced to no more than 2 sighs/min or the sighs may be discontinued altogether. Background IMV at a higher rate is used by some clinicians to compensate for low mean airway pressure, but that is clearly a more injurious way of ventilation and therefore this practice should be discouraged.

8.2.1.2.2 Contemporary HFJ Ventilators

The Bunnell Life Pulse is the most widely used infant HFJV device. There are also several niche devices used infrequently in pediatric patients (Paravent, Chirajet, Monsoon).

8.2.1.2.2.1 Bunnell Life Pulse

The Bunnell Life Pulse HFJV (Bunnell Inc. Salt Lake City, UT) delivers short pulses of heated and humidified gas at high velocity to the upper airway through a narrow injector lumen in the LifePort adapter. This is a special 15-mm endotracheal tube adapter that contains a proximal jet injector port and a distal pressure monitoring port, eliminating the previous need for reintubation with a triple lumen endotracheal tube (Figs. 8.55 and 8.56). The clinician sets the same variables on the front panel of the Bunnell Life Pulse HFJV as he or she is accustomed to setting on conventional ventilators, namely, peak insufflation pressure (PIP, range 8–50 cm H_2O), respiratory rate or frequency (range 240–660 cycles/min or 4–11 Hz), and jet valve "on time," which is comparable to inspiratory time (range 0.020–0.034 s). The Life Pulse t_I:t_E varies from 1:3.5 at 660 cycles/min to 1:12 at 240 cycles/min (Harris and Bunnell 1993).

When introduced in the mid-1980s, the Life Pulse was the first microprocessor-controlled infant ventilator. Servo control of PIP is accomplished by the ventilator's microprocessor, which compares the PIP level set by the operator with the actual PIP measured continuously in the distal airway and the driving or "servo" pressure behind the inspiratory pulses is raised or lowered in proportion to the difference between the set and actual PIP. These moment-to-moment adjustments in servo pressure are accomplished by an array of precision solenoid valves supplying the pressure chamber that supplies gas to the jet circuit.

Actual delivery of the jet pulses is by way of an electromagnetically controlled pinch valve in the "patient box" controlled by the same microprocessor. Moving the pinch valve and pressure transducer into the patient box placed close to the patient was an important advance, resulting in much less dampening of the jet pulse and more accurate pressure monitoring. More efficient jet pulse delivery allows the ventilator to operate efficiently at much higher frequencies and smaller tidal volume than the early prototype jet ventilators. The humidification system for the ventilator is also feedback controlled for maintaining appropriate temperature, humidity, and water level. The temperature of the humidification cartridge and circuit can be adjusted independently to prevent excessive condensation. The disposable humidifier cartridge and circuit are designed to withstand

Fig. 8.55 Bunnell Life Pulse HFJ ventilator

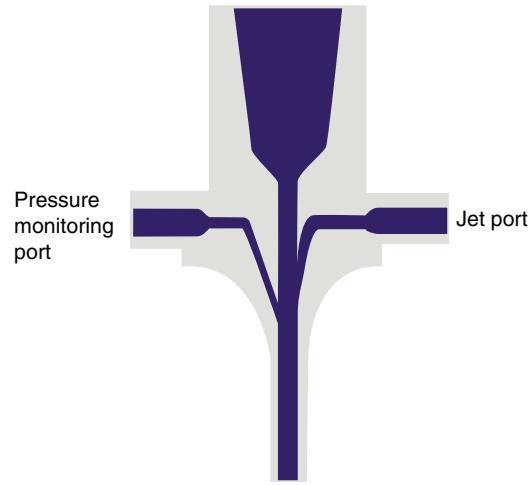


Fig. 8.56 LifePort adapter. The schematic shows the narrow injector port used to inject high-velocity small volume gas jets into the patient airway. The adapter includes a pressure monitoring port

the relatively high servo pressure and have a very small compressible volume. Prior to the introduction of this efficient heating and humidification system, inadequate humidification of inspired gas with prototype HFV devices resulted in a series of reports of necrotizing tracheobronchitis that led to a temporary dampening of enthusiasm for HFJV (Ophoven et al. 1984).

A conventional ventilator is used in tandem with the Life Pulse and serves as a source of bias gas flow for entrainment and to generate positive end-expiratory pressure (PEEP). When desired, it also provides intermittent sighs in the form of background intermittent mandatory ventilation (IMV) inflations, typically at a rate of two to ten inflations per minute. The amplitude of the HFJV pulses is determined by the difference between the jet peak insufflation pressure and the conventional ventilator PEEP. The FiO_2 of the two ventilators is adjusted separately but should be maintained at the same value. The actual PIP, $\bar{P}_{aw}$, ΔP_{aw}, and servo pressure are displayed in the monitoring window on the face of the ventilator. Alarms are automatically set 15 % above and below current levels for PIP, $\bar{P}_{aw}$, and servo pressure once the values stabilize and the ventilator reaches the "Ready" state. Subsequently, the alarm limits can be adjusted manually.

8.2.1.2.2.2 Paravent PAT Ventilator

The Paravent PAT ventilator (Elmed, Prelouc, Czech Republic) has been in limited use in Europe for some time (Zahorec et al. 2009). It is a pneumatically controlled high-frequency jet ventilator with a distally located jet nozzle and a constant frequency of 120 inflation/min. This device is primarily used for short-term procedures, such as laryngeal surgery, bronchoalveolar lavage, and endobronchial procedures in adults and children. The gas is delivered through the multinozzle jet injector that is available in different sizes and has three inspiratory jets with different degrees of pressure reduction. Insufflation pressure, ratio of inspiratory to expiratory time (t_I:t_E: 1:2, 1:1, and 2:1), and ventilating pressure limit are set. Airway pressure is monitored through a catheter connected to the jet injector. There is no heating or, humidification of inspired gas.

8.2.1.2.2.3 Chirajet Ventilator

The Chirajet (Chirana, Stará Turá, Slovakia) has been used primarily for laboratory investigation but has seen limited clinical use. It is an electronically actuated device with adjustable rate (0.33–10 Hz), inspiratory time, and pressure. It may be more suitable for prolonged support because, unlike the Paravent Pat, it incorporates a heating and humidification system.

8.2.1.2.2.4 Monsoon Jet Ventilator

The Monsoon jet ventilator (Acutronic Medical Systems AG Hirzel, Switzerland) has been used primarily for ENT surgery and thoracic surgery and has seen limited applications in intensive care for patients with severe lung injury and air leak complications. The ventilator has an integrated humidification and heating system, which is automatically adjusted according to the actual minute volume delivered to each patient, making it potentially suitable for extended use. It is capable of frequencies of 0.2–10 Hz, % inspiratory time 20–70 %, PEEP 10–40 cm H_2O and uses driving pressure of 0.4–3.5 bar. No systematic evaluation of safety and effectiveness is available.

8.2.1.2.3 Performance Characteristics of HFJ Ventilators

There are limited data on the performance characteristics of modern jet ventilators. Boros et al. compared the Bunnell Life Pulse jet ventilator to the Gould HFOV device (forerunner of the SensorMedics) in cats with normal lungs and found that equivalent gas exchange was accomplished with much lower peak and mean pressures with HFJV, and at equivalent airway pressures there was more efficient CO_2 elimination (Boros et al. 1989). Fredberg et al. compared eight different HFV devices, including the Bunnell Life Pulse, using a test lung (Fredberg et al. 1987). They found that the HFJV V_T increased at higher frequencies, in contrast to most other devices, where the V_T fell with increasing frequency. HFJV V_T delivery was more affected by lung compliance, in contrast to the oscillatory devices. These findings are contrary to what might be expected with a fixed inspiratory time, and

more recent *in vitro* studies suggest that V_T actually decreases with increasing frequency of the Life Pulse at any given inspiratory time, likely due to the increase opposing impedance arising from the exhaled gas stream at higher frequencies (Prof J. Pillow, 2010). Similarly, whereas V_T delivery during HFJV is highly dependent on compliance, when compliance is low, the threshold compliance (reflecting the point at which there is minimal additional change in V_T with increasing compliance) is independent of frequency during HFJV (Prof. J. Pillow, unpublished data), presenting a stark contrast to HFO ventilators such as the SM 3100A (Pillow 2001). All ventilators delivered larger V_T with increased endotracheal tube size. HFJV required the highest proximal pressure owing to the extremely short inspiratory time. Bancalari et al. documented more air trapping with HFJV, compared to HFOV (Bancalari et al. 1987). However, this study was not an optimal comparison as the devices were tested at frequencies of 10 and 15 Hz, well above the optimal frequency range of the jet ventilator. Theoretically, at least, gas trapping with HFJV is critically dependent on the balance between inertive, resistive, and elastic forces within the lung. Of the existing jet ventilators, only the Bunnell Life Pulse ventilator has been subjected to clinical evaluation (Keszler 1991, 1997; Wiswell 1996). The Paravent, Chirajet, and Monsoon devices have not been subjected to systematic clinical evaluation, and therefore, it is not possible to formulate meaningful conclusions regarding their safety and effectiveness.

8.2.1.2.4 HFJV: Technical Limitations and Ongoing Developments

The need for tandem conventional ventilator is more of an inconvenience than a technical limitation. While more cumbersome than a single device, it makes changing to and from HFV to conventional ventilation very easy. The technical limitation of most high-frequency ventilators, including the Bunnell Life Pulse, is the lack of tidal volume monitoring that is now routine with conventional ventilators. Although technically feasible, continuous tidal volume measurement is not incorporated into the ventilator, and this is a significant potential limitation, given the geometric relationship between tidal volume and CO_2 elimination that is responsible for the ease with which inadvertent hyperventilation can occur. The passive exhalation used with HFJV is considered a technical limitation by some. It should rather be simply seen as a specific characteristic that may have advantages in infants prone to airway collapse where the active exhalation of oscillatory ventilation may be counterproductive. The passive exhalation does result in a modestly lower optimal frequency range for HFJV, compared to HFOV.

A new Whisper Jet patient box has recently been introduced to reduce the noise associated with the pinch-valve action. The new box brings the noise level to around 40 dB, well within acceptable limits and substantially below earlier versions. As part of the process of obtaining regulatory clearance in the European Union countries and elsewhere, which is currently underway, the device has also been updated with a more current microprocessor, internal battery, and a smaller, lighter, lower profile box. These developments should pave the way for wider availability of this device throughout the world and increase its utility during transport (Mainali et al. 2007).

8.2.1.3 High-Frequency Flow Interrupters

High-frequency flow interrupters (HFFI) deliver pulses of fresh gas down the endotracheal tube with only a positive pressure deflection and passive exhalation. Unlike jet ventilators, gas flow in HFFI devices does not pass through a narrow injector cannula. The difficulty is that some high-frequency interrupters have a small negative pressure deflection that straddles the definition of HFFI and HFOV. The Infant Star ventilator was the chief example of that phenomenon. Although the device is no longer manufactured or supported, it is still in use in many parts of the world, especially in the developing countries. Other HFFI devices include the Bronchotron and the Volumetric Diffusive Respirator.

8.2.1.3.1 HFFI: Principles of Gas Exchange

A detailed appraisal of the principles of gas exchange during HFFI has not been undertaken. However, the general principles of gas exchange during HFFI straddle the concepts covered for both HFOV and HFJV in that mean airway pressure controls oxygenation, and carbon dioxide removal is proportional to $f \cdot V_T^2$. The passive expiratory phase demands utilization of lower frequencies than in HFOV to facilitate completion of the expiratory phase and avoidance of inadvertent PEEP.

8.2.1.3.2 Contemporary HFFI Ventilators

8.2.1.3.2.1 Infant Star 950

For many years, the Infant Star 950 (IS950) (Infrasonics, San Diego, USA) ventilator, a high-frequency flow interrupter combined with a conventional ventilator, was widely used in the USA, Europe, and elsewhere. By briefly opening the solenoid proportioning valves, the device generates pulses of fresh gas in the inspiratory limb of the circuit at a frequency ranging from 2 to 22 Hz (usual range 6–15 Hz) and adjustable pressure amplitude. The inspiratory time is fixed at 18 ms. Consequently, the inspiratory to expiratory time ratio ranges from 1: 8 at 6 Hz to 1: 3 at 15 Hz. A venturi placed at the exhalation valve assists the return of pressures to expiratory baseline and results in a modest negative deflection. However, exhalation is largely passive and inadvertent gas trapping is not completely avoided by this method, judging by the increased incidence of air leak complications (Craft et al. 2003; Thome et al. 1999).

8.2.1.3.2.2 Bronchotron

The Bronchotron (Percussionaire, Sandpoint, ID) is a pneumatically powered high-frequency flow interrupter, also referred to as percussive ventilator (HFPV) developed in the 1980s by Dr. Forrest Bird. It is increasingly accepted as a neonatal transport ventilator because of its light weight, ability to function as both conventional and high-frequency ventilator, and relatively low gas consumption. The ventilator has an internal pneumatic timing device which cycles high-pressure gas flow at a frequency of 3–10 Hz. Rate and amplitude are continuously adjustable while the inspiratory time is not, being determined by the frequency and the mechanical properties of the lungs. The high-frequency gas pulses enter a sliding piston mechanism called a Phasitron through a venturi cavity in its central axis. The Phasitron creates an oscillatory waveform by the rapid movement of a spring mechanism that balances inspiratory and expiratory pressures within preset pressures for PEEP or $\bar{P}_{aw}$. The Phasitron acts as both an inspiratory and expiratory valve. In the inspiratory phase, the pulse of gas is augmented by entrained gas proportional to the pressure difference before and after the venturi. During expiration, the piston springs back opening an exhalation port, and gas is allowed to exit the patient through an adjustable resistor that provides PEEP and regulates mean airway pressure. The mean airway pressure, frequency, and flow (which adjust the gas flow to the Phasitron and control the pulse amplitude) are continuously adjustable.

The main limitation of the Bronchotron is the lack of actual values for the ventilator variables – all dials are marked with values of 1–10, but these numbers do not readily translate to values to which a clinician can relate. Adjustments are made by clinical observation of chest movement and patient response. Frequency is displayed as inflation/min (not Hz) and mean airway pressure can be measured intermittently by flipping a toggle switch changing the phasic pressure display to an integrated mean. The phasic pressure displayed by the rapidly oscillating needle of a mechanical gauge is difficult to read. The other major concern is a lack of alarms or other safety features.

There are limited published data to support the safety and efficacy of the Bronchotron, which was approved by the US Food and Drug Administration (FDA) based on its substantial equivalence to a device in existence prior to the effective date of the law (1979). In a study comparing the SensorMedics 3100A and the Bronchotron in saline lavaged newborn piglets, similar oxygenation and ventilation were achieved, when the devices were adjusted to deliver identical V_T at same mean airway pressure and frequency, but a higher pressure amplitude was needed with the Bronchotron (Messier et al. 2009).

One center recently reported their experience of 134 infants in whom 96 % were successfully transported using HFPV with improvement in oxygenation, ventilation, and acid–base status during the time that the patients were on the transport ventilator (Honey et al. 2007).

8.2.1.3.2.3 Volumetric Diffusive Respirator

The Volumetric Diffusive Respirator – VDR 4 (Percussionaire Corp, Sandpoint, ID) – is a time-cycled, pressure-limited, pneumatically driven high-frequency flow interrupter ventilator similar to the Bronchotron, but more complex and designed for hospital use. The device delivers gas from a pressurized source (25–65 psi) through a pneumatic timing cartridge system. The source gas is interrupted to produce a pulsatile flow which enters the breathing circuit via the Phasitron. Warmed, humidified gas is entrained to augment tidal volume. Tidal volume delivery is determined by flow velocity, inspiratory duration, and supplementary gas entrainment. The VDR 4 is composed of two ventilator systems: conventional and high frequency. The conventional component can deliver up to 70 inflations per minute with independent control of inspiratory time and pressure. The high-frequency component allows programming of frequencies from 0.5 to 30 Hz and amplitudes from 0 to 100 cm H_2O and inspiratory to expiratory time ratio from 1:1 to 1:5. A variety of conventional and high-frequency combinations can be selected. Like the Bronchotron, the VDR was approved by the FDA without requiring proof of safety and efficacy.

There are only anecdotal patient series supporting the putative benefits of the device. In one study, 48 pediatric burn patients with failing respiratory status were changed from conventional ventilation to the VDR. Both ventilation and oxygenation were significantly improved with $PaCO_2$ decreasing from 47 ± 3 mmHg to 39 ± 11 mmHg and PaO_2 increasing from 105 ± 8 to 171 ± 12 mmHg after transition to VDR while peak inflation pressures (PIP) dropped from 52 ± 2 to 38 ± 2 cm H_2O (Rodeberg et al. 1994). A small randomized, controlled study compared efficacy of percussive ventilation with incentive spirometry in reducing number of days of antibiotic use in adolescents with neuromuscular disease. A total of 18 patients were enrolled (9 per group). Antibiotic use was significantly higher with incentive spirometry (24/1,000 patient-days) compared with percussive ventilation (0/1,000 patient-days). The incentive spirometry group spent more days hospitalized (4.4/1,000 patient-days versus 0/1,000 patient-days) than the percussive ventilation group and had no episodes of pneumonia or bacterial bronchitis compared with three events in the incentive spirometry group, supporting the hypothesis that percussive ventilation may have benefits in helping to clear secretions (Reardon et al. 2005).

8.2.1.3.3 Performance Characteristics of HFFI Ventilators

The IS950 is the only HFFI that has been subjected to an evaluation of performance characteristics. Like the SM 3100A, the IS950 has a complex waveform with multiple harmonics. However, the IS950+ is less powerful than either the SM 3100A or the Humming V, and tidal volume delivery is more dependent on compliance than the SM 3100A, the Humming V, or the Drager BL800+ (Pillow et al. 2001). There was little change in tidal volume between 5 and 15 Hz at a constant ventilator-displayed amplitude, although it decreased slightly at higher frequencies. In contrast to the other three ventilators studied, independently measured amplitude increased with increasing frequency, despite maintaining ventilator-displayed amplitude at a constant value.

Conclusions

A large variety of sophisticated high-frequency ventilators are available to clinicians. All of these devices are capable of supporting gas exchange with small V_T and at least short-term improvement in the patient's condition. For HFFI, evidence of safety and efficacy remains very limited. As conventional ventilation has become more sophisticated, any significant advantages of HFV will be more difficult to demonstrate conclusively. The situation is made more difficult by the increased use of noninvasive respiratory support modalities, resulting in fewer ventilated patients available for clinical

trials. Limited evidence of efficacy notwithstanding, there remain clinical situations that warrant a trial of high-frequency ventilation. Intensivists are by nature inclined to actively intervene. In order to optimize the chance of benefiting our patients and minimize the risk of adverse consequences, a thorough understanding of the operating principles of each device, including their limitations, is critical. Frequently, physicians try several different devices with little benefit, when a good understanding of pathophysiology would have allowed them to optimize the strategy used on any given device to greater advantage. Often, it is true that the best device to use is the one you know best!

Essentials to Remember

- Each high-frequency ventilator has its own unique operating characteristics.
- Clinical data on non-piston oscillators and flow interrupters are limited.
- The clinician must be familiar with the high-frequency ventilators available in his or her unit so that the particular machine employed can be utilized optimally for the clinical situation of the patient.

8.2.2 Negative Pressure Ventilation: Physiological Aspects

Francesco Grasso and Brian P. Kavanagh

Educational Aims

- Negative ventilation works by decreasing the intrapleural pressure thereby creating a gradient for air to move into the alveoli.
- In experimental data in ARDS models, negative ventilation may have the capability to better recruit the lungs and create less overdistension.
- Negative ventilation (as spontaneous ventilation) can increase the cardiac output because of an increased right ventricular filling and may be better tolerated than positive ventilation when right heart preload is critical.
- Negative ventilation increases the left ventricular afterload by increasing the aortic transmural pressure; this can be adverse when the left ventricular function is depressed.
- Full body negative-pressure devices do not affect hemodynamics, but "chest only" devices have similar effects as spontaneous ventilation.

8.2.2.1 Introduction

Positive pressure mechanical ventilation via an endotracheal tube is the conventional gold standard for treatment of acute respiratory failure. While endotracheal intubation may expose the patient to complications such as ventilator-associated pneumonia which in turn may prolong hospital length of stay (Fagon et al. 1993), such problems may be mitigated with noninvasive ventilation (either positive or negative pressure).

Negative pressure ventilation works by exposing the chest and the upper abdomen to subatmospheric pressure, which assists – or results in – inspiration; the negative pressure distends the thoracic cage, causing a decrease in pleural and alveolar pressure, and creates a gradient for inspired air to move into the alveoli.

8.2.2.2 Types of Negative Pressure Ventilation

The important components of a negative pressure ventilator are an airtight chamber to enclose the thorax (or thorax plus abdomen) and a power unit capable of generating negative pressure in the chamber.

There are three basic types of device: the tank, the jacket, and the cuirass. The tank ventilator encloses the whole body up to the neck (Corrado 1996: 9), and a collar is necessary around the neck in order to maintain an airtight seal. Most tank ventilators have portholes and windows which allow observation and access to the patient inside the chamber. The jacket ventilators consist

of a rigid nylon-covered cage which encloses the chest and the upper abdomen (Hill 1986); here, airtight seals are necessary around the neck, the arms, and the abdomen. Finally, the cuirass is a rigid shell positioned over the anterior part of the chest (Corrado and Gorini 2006). The surface area underneath the cuirass – where the negative pressure is applied – is smaller than that of either the jacket or the tank ventilator.

Among the three different devices, the tank ventilators are the most efficient. The tidal volume delivered by any level of applied negative pressure is in the following rank order: tank > jacket > cuirass. Because of greater efficiency among negative-pressure options, the tank ventilator is the method of choice to treat ARF; jackets and cuirasses are more commonly employed for long-term (e.g., home) ventilation (Hill 1986; Shneerson 1991).

Negative pressure ventilation can be provided as two modes: continuous negative extrathoracic ventilation (CNEP), where a constant level of negative end-expiratory pressure is applied in order to prevent end-expiratory alveolar collapse. Alternatively, negative pressure can be applied as cyclic negative ventilation plus CNEP, in which case the ventilator generates subatmospheric pressure cycles (corresponding to inspirations) and maintains a (constant) preset level of CNEP during expiration. Traditionally, negative pressure ventilation is operated in a control mode, thereby providing a set number of respiratory cycles each minute, but reducing the possibility for patient–ventilator interactions (Gorini et al. 2002). Technical improvements over the past few years have centered on triggering ability. For example, temperature-sensing triggers can reliably detect a switch from inspiration to expiration by sensing nasal air flow and are able to provide an improved interface for patient–ventilator interactions, thereby making assisted negative pressure ventilation more comfortable and better tolerated (Gorini et al. 2002).

8.2.2.3 Effects on Transpulmonary Pressure (TPP)

The lungs inflate when the transpulmonary pressure (TPP) is sufficiently increased, and deflate when it is decreased. The pressure applied by a negative-pressure system is immediately directed to the chest wall, and it is the outward movement of the chest wall that causes the increase in TPP and subsequent lung inflation. The chest wall behaves differently if lifted by external negative pressure versus when pushed from inside by positive pressure. The explanation is unclear but it may be related to rib cage distortion due to application of negative pressure on the costovertebral junction, decreasing the chest wall compliance (Borelli et al. 1998). For this reason a higher absolute level of negative pressure needs to be applied to the chest wall to obtain the same level of inflation when compared with positive pressure (Krumpe et al. 1977; Borelli et al. 1998) (Fig. 8.57).

Different effects on chest wall compliance may result from different types of negative-pressure ventilators. For example, a comparison between a chest device and a tank ventilator (Lockhat et al. 1992) reported a lower thoracic compliance with the chest device, possibly because the chest device requires chest wall pressure (by the rigid shell on the rib cage) to maintain an airtight seal (Borelli et al. 1998).

8.2.2.4 Respiratory Effects

Previous reports have indicated that negative pressure ventilation provides effective gas exchange and increased functional residual capacity (FRC) (Sanyal et al. 1977a, b; Sanyal et al. 1975).

Respiratory mechanics during CNEP were studied in self-ventilating newborns with respiratory distress syndrome (RDS) (Bancalari et al. 1973). The key findings were increased oxygenation, maintenance of $PaCO_2$ (despite a reduction in minute ventilation), and an increase in the FRC. The increase in oxygenation corresponds indirectly to recruitment of atelectatic regions. The reduction in minute ventilation without a corresponding increase in $PaCO_2$ indicates that the dead space ventilation was decreased.

A laboratory study of PEEP and CNEP, in a surfactant-depleted animal model of saline-lavaged piglets, compared the two approaches at different steps using the same amount of end-expiratory distending pressure (Easa et al. 1994). At each stage, the transpulmonary pressure was the same between PEEP and CNEP, but the end-expiratory

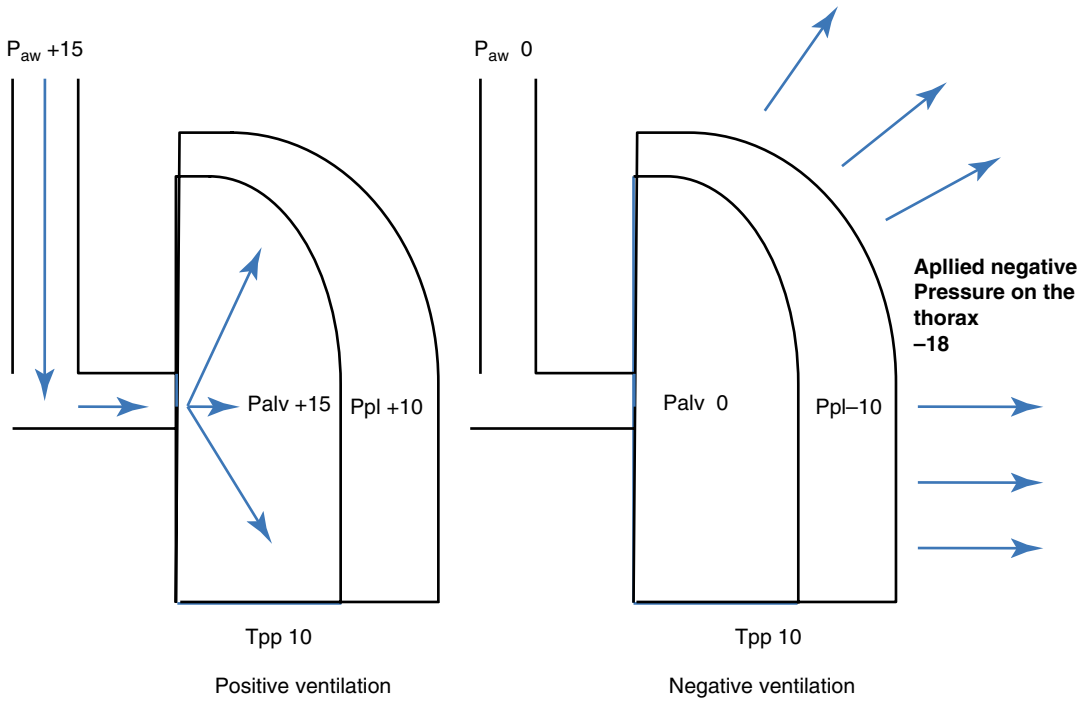


Fig. 8.57 Scheme of the pressure distribution during positive and negative ventilation. In PPV the pressure is transmitted from the airways to the alveoli, and the resultant pleural pressure is positive. In NPV the pressure generated by the ventilator is around the chest and is transmitted to the pleural space. The airway and the alveolar pressure is always zero. Because of the decreased chest wall compliance during negative ventilation, a higher magnitude of applied pressure is required in order to match the TPP. All the pressure values are in cm H_2O

lung volume (EELV) was higher with CNEP. In a clinical study of adult patients with acute respiratory distress syndrome (ARDS), CNEP was used for matching transpulmonary pressure, and no differences were found in terms of oxygenation or FRC, although CNEP was associated with a reduction in respiratory system compliance secondary to reduced chest wall compliance (Borelli et al. 1998).

In the studies cited above, negative pressure has been used as end-expiratory distending pressure. A recent study compared volume-controlled ventilation administered via a positive- versus a negative-pressure system in surfactant-depleted rabbits (Grasso et al. 2008). In that study, the absolute amount of end-expiratory pressure was the same in the two strategies, and the peak pressure was adjusted in order to obtain the desired (high) tidal volume. Negative ventilation was associated with better oxygenation which was attributed to superior lung recruitment (and not to optimized lung perfusion) (Fig. 8.58). These data were supported by CT study of the thorax suggesting less atelectasis during inspiration as well as expiration (Grasso et al. 2008; Helm et al. 2009) (Fig. 8.59). However, precise matching of the pressure–time profile, and especially of the transpulmonary pressure over time, is virtually impossible.

8.2.2.5 Cardiovascular Effects

Spontaneous, as well as controlled, mechanical ventilation induces changes in intrapleural and intrathoracic pressure and in lung volume which can independently affect the key determinants of cardiovascular performance such as ventricular filling (i.e., preload) or the impedance of the ventricle to emptying (i.e., afterload). Such changes in intrathoracic pressure are transmitted to heart, the extrapulmonary large vessels, and the intrapulmonary vasculature. For example, that positive pressure ventilation impedes venous return,

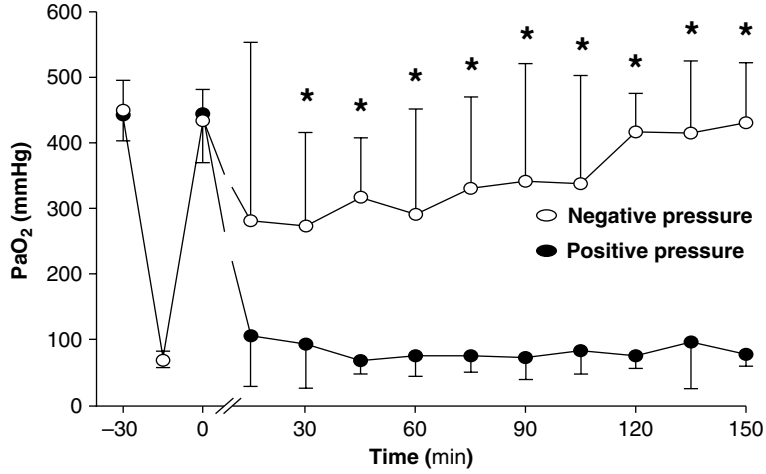


Fig. 8.58 Difference between arterial PO_2 and positive and negative ventilation. Arterial PO_2 was similar in both groups at baseline and during the surfactant depletion process (−30 to time zero). When the two different ventilatory strategies were applied, the PaO_2 was significantly greater in negative versus positive pressure ventilation throughout the remainder of the experiment (*$P<0.05$) (From Grasso et al. 2008)

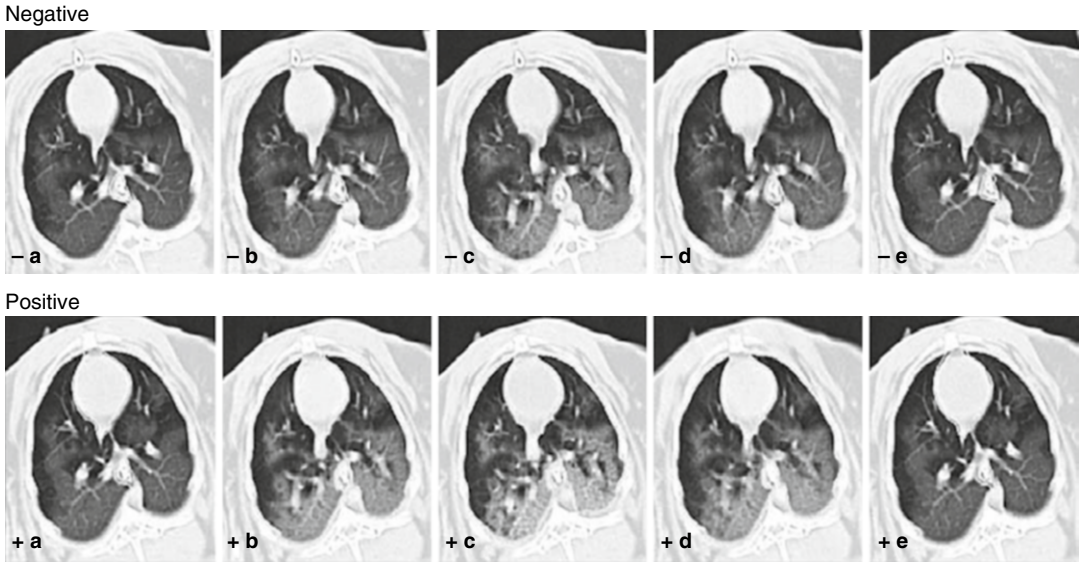


Fig. 8.59 CT comparing positive and negative ventilation at multiple points of the respiratory cycle. Is evident how at end inspiration negative ventilation shows more homogeneous recruitment and less atelectasis at end expiration when compared with positive ventilation. (**a**) End inspiration, (**b**) mid expiration, (**c**) end expiration, (**d**) mid inspiration, and (**e**) end inspiration (From Helm et al. 2009)

thereby reducing cardiac output, has been known for decades (Cournand et al. 1948). The individual elements of cardiovascular performance will be considered below.

Cardiac Output: The cardiac output is the result of a balance among three compartments: the thorax (the pressure in which directly impacts on the pressure in the right atrium); the abdomen (the pressure in which can inhibit venous return and worsen lung compliance); and the peripheral venous pressure (i.e., closely related to the atmospheric pressure).

The movement of blood from one compartment to another is made possible by the difference in pressure – the "driving pressure" – across each one. The difference between intravascular pressure and intrathoracic pressure (i.e., the pleural pressure) is termed the transmural pressure (Ptm). This transmural pressure reflects the pressure in an intrathoracic vessel or in a cardiac chamber

which takes into account the other pressures which are working on that structure. Therefore, for a given compliance, the *P*tm reflects the effective filling status of the structure in question.

During spontaneous ventilation, the activity of the respiratory muscles on the chest and the diaphragmatic contraction combine to create a negative pressure which enables air flow into the lungs. The same negative pressure is conducted, in the thorax, and increases the *P*tm. In addition, the venous return from the lower body is enhanced by the transdiaphragmatic driving pressure. These two elements together enhance right ventricular filling, and thereby increase cardiac output. However, pulmonary inflation – even with negative pressure – has an impact on venous return. A study conducted in self-ventilating patients with emphysema (i.e., prone to hyperinflation) described an obstruction of venous return in the inferior vena cava where it enters the thorax during inspiration and normal flow during the expiration (Nakhajavan et al. 1966; 32). The same phenomenon has been described in dogs with normal lungs when extrathoracic negative pressure was applied with very negative values (Wong 1967; 22).

During positive pressure ventilation, the increased intrathoracic pressure is fully transmitted to the right atrium and superior vena cava; this diminishes right heart filling, thereby decreasing cardiac output. Changes in intrathoracic pressure can affect cardiac output by modifying the ventricular afterload: in this context, negative intrathoracic pressures increase the *P*tm of the ventricles and the ascending aorta (increasing afterload), while positive intrathoracic pressures make it lower (reducing afterload).

Negative pressure ventilation exerts similar effects as spontaneous breathing, but replaces the muscular work by machine (i.e., ventilator) work. However, the hemodynamic effects of negative ventilation depend on the specific mode and timing of application. Ventilation using a chest device (i.e., a cuirass or a jacket) causes hemodynamic effects that closely reflect spontaneous ventilation. However, ventilation with a total body device (e.g., a tank ventilator) results in hemodynamic effects that are comparable to those produced by the PPV; this is because of the loss of the driving pressure between the abdomen and the right atrium caused by the negative pressure applied to the abdominal surface (Lockhat et al. 1992;Skaburskis et al. 1987).

Left Ventricular Afterload: A standard support for cardiac failure is positive pressure ventilation. PEEP increases the intra-alveolar pressure which mitigates the formation of pulmonary edema; in addition, by increasing the intrathoracic pressure, PEEP also decreases the *P*tm in the left ventricle (and ascending aorta) and decreases left ventricular afterload. Conversely, negative pressure lowers intra-alveolar pressure, potentially exacerbating the formation of pulmonary edema; and, the increased *P*tm in the ascending aorta increases left ventricular afterload. For this reason, negative pressure ventilation may be contraindicated in patients with left ventricular dysfunction.

Data from an animal model of heart failure suggest that the cardiac output and the SvO_2 do not change during negative pressure ventilation, but that both are reduced with positive pressure ventilation, especially at high end-expiratory pressures (Skaburskis et al. 1990). The transmural pressure in the left ventricle at the end of diastole tends to be higher with negative pressure, suggesting a higher impact on left ventricular afterload where heart failure may be more severe (Skaburskis et al. 1990). A higher left ventricular end-diastolic *P*tm corresponds to increased afterload which can worsen ventricular function and potentially lead to hydrostatic pulmonary edema formation. Because NPV can increase the left heart pressures and pulmonary artery occlusion pressure, it can cause hydrostatic pulmonary edema or add a hydrostatic component to preexisting permeability edema. In the latter setting, the edema present in the lung is a consequence of an enhanced inflammatory state, and superimposed increases in pulmonary blood flow (augmented by negative ventilation) could increase extravascular pulmonary water. However, variable results have been found in different studies of lung injury. In oleic acid (Skabuskis et al. 1989) and in bacterial toxin-induced lung injury, positive and negative pressure ventilation resulted in comparable degrees

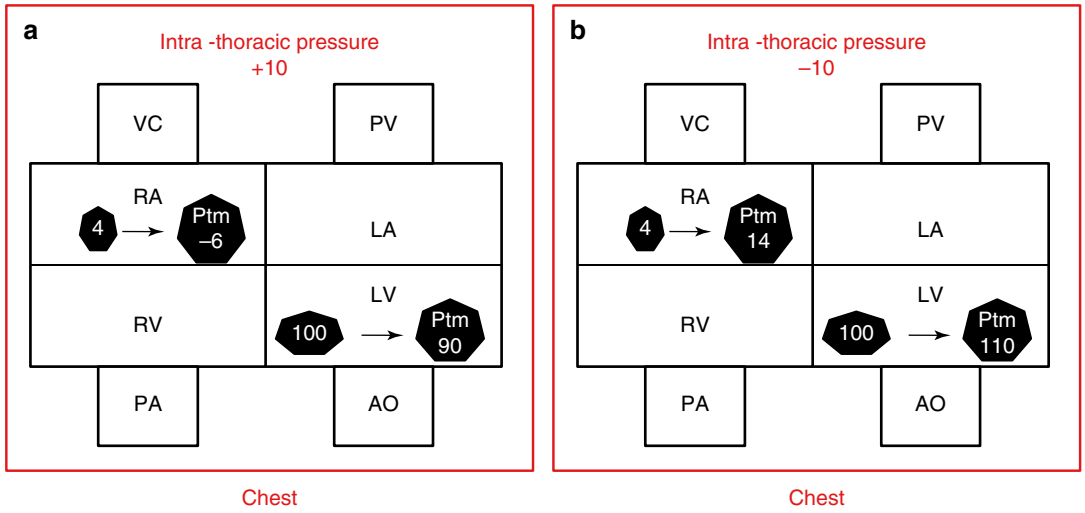


Fig. 8.60 Relationship between intrathoracic pressures and transmural pressures (*P*tm: pressure inside a chamber–pressure outside the same chamber) (*LV* left ventricle, *RV* right ventricle, *RA* right atrium, *LA* left atrium, *PA* pulmonary artery, *AO* aorta, *VC* vena cava, *PV* pulmonary veins). When the intrathoracic pressure is positive, there is a decrease in the LV *P*tm which leads to a lower afterload; at the right atrial level, the RA *P*tm decreased with consequent decreased preload, when the intrathoracic pressure is negative the situation is opposite

of pulmonary edema (Krumpe and Gorin 1981; Kudoh et al. 1992) (Fig. 8.60).

Pulmonary Vascular Resistance: Pulmonary vascular resistance is the ratio of the pulmonary driving pressures to the pulmonary blood flow (i.e., cardiac output). The cardiac output is the function of preload, afterload, contractility, and lung inflation, as well as ventilation. Lung inflation acts, at least in the experimental isolated lung, on both intra-alveolar and extra-alveolar vessels (Burton and Patel 1958). Where lung volume is close to functional residual capacity, loss of volume results in compression of the extra-alveolar vessels which increases overall resistance. In contrast, when inflated to total lung capacity, increase in volume compresses intra-alveolar microvessels, which is "sandwiched" between the inflated alveoli, contribute to increasing the pulmonary vascular resistance. In this scheme, maintaining optimal lung inflation may be important to minimize pulmonary vascular resistance. Positive and negative (Corrado et al. 1996; 9) pressure ventilation can achieve optimal lung inflation; however, in contrast to negative pressure, positive pressure ventilation may, by reducing right ventricular *P*tm, decrease impedance to ejection and improve pulmonary perfusion. However, experimental studies indicate that the effects on pulmonary vascular resistance are identical with positive and negative pressure ventilation, provided that both systems reference pulmonary vascular pressures in the same way (Mundie et al. 1995).

Essentials to Remember

In conclusion, negative pressure ventilation may have advantages (e.g., better tolerated) over positive pressure ventilation, where the right ventricle is critically preload dependent and where the application is to the chest only; in this context, right-sided venous return is augmented and cardiac output enhanced. In contrast, negative pressure applied to the abdomen retards venous return, and at high levels can increase ventricular *P*tm thereby elevating afterload. While chronic application has many advantages, the acute physiological effects on lung injury and gas exchange are not yet fully understood.

8.2.3 Tracheal Gas Insufflation (TGI)

Claude Danan and Xavier Durrmeyer

Educational Aims

- Understand the rational for continuous tracheal gas insufflation (CTGI) as an adjunct to conventional mechanical ventilation.
- Learn about physiological effects and mechanical aspects of CTGI.
- Review specific physiological considerations to take in account during conventional mechanical ventilation with and without CTGI in extremely low-birthweight infants.

8.2.3.1 Introduction

Improving survival of the most immature preterm neonates leads to reaching the limits of conventional ventilation. In that population, for the most severe forms of restrictive respiratory diseases, the high ratio of dead-space to tidal volume (VD/VT) makes efficient CO_2 clearance no longer possible. More exactly, the ventilatory prostheses' dead space is very close to the allowable, in terms of lung protection during mechanical ventilation, tidal volume in neonates (see Sect. 3.4). The CO_2 cleared from the blood at alveolocapillary level stagnates in the anatomic dead space gradually increasing the fraction of inspired CO_2. CO_2 elimination is thus only possible at the risk of increasing the inspired VT. For the most immature preterm neonates, however, aggressive (i.e., larger VT ventilation) artificial ventilation remains a limiting factor with respect to life expectancy and sequelae-free survival (Meredith et al. 1988; Ambalavanan and Carlo 2006). Under those conditions, we have to consider any technique supposed to be efficient for decreasing or even erasing the anatomic dead space. Shortening of the endotracheal tube is often proposed to limit the prosthetic dead space, but its efficiency is very low because each centimeter of reduced length will reduce dead space by only about 0.05 mL. As the sum of the different parts that constitute the equipment-related dead space (i.e., 2.5 tube, adapter, Y-piece, and flow sensor or other sensors) is more than 3 mL, a more efficient solution than only trying to cut out a few centimeters of ETT might be required. Furthermore, removal of sensors and shortening tube length may render the baby less comfortable and, in the absence of a flow sensor that allows not only for volume measurements but also for patient–ventilator synchronization, make the respiratory management more difficult. TGI attempts to minimize the negative effect of the anatomic dead space on ventilation efficiency by washing out expiratory CO_2 trapped in the ventilatory prostheses. This technique will be discussed here in different modalities. However, it must be said that at this time no patented device is available on the market. Some animal and human studies confirm the potential benefit of this method that would deserve to be made available for clinical use, which might be the case in the near future, knowing that some commercial development is heading into this direction.

TGI is still seen as a nonconventional mode of mechanical ventilation but should be seen much more as an adjunct to conventional ventilation since it does, conversely to high-frequency ventilation, not modify the physiological basic effects of conventional ventilation.

8.2.3.2 Mechanism of Action

In the conventionally mechanically ventilated patient, CO_2 concentration does increase during expiration in the anatomic and the instrumental dead space. Given the high VD/VT ratio in neonates and in all situations with severe lung restrictive lung pathology (i.e., pathologies with reduced residual aerated lung volumes), most if not all of the CO_2 trapped in the instrumental dead space will be rebreathed during the next inspiratory phase. TGI attempts to minimize this unwanted effect of the instrumental dead space on ventilation efficiency by flushing out actively the CO_2 during the expiratory phase. The method consists in driving an additional flow at

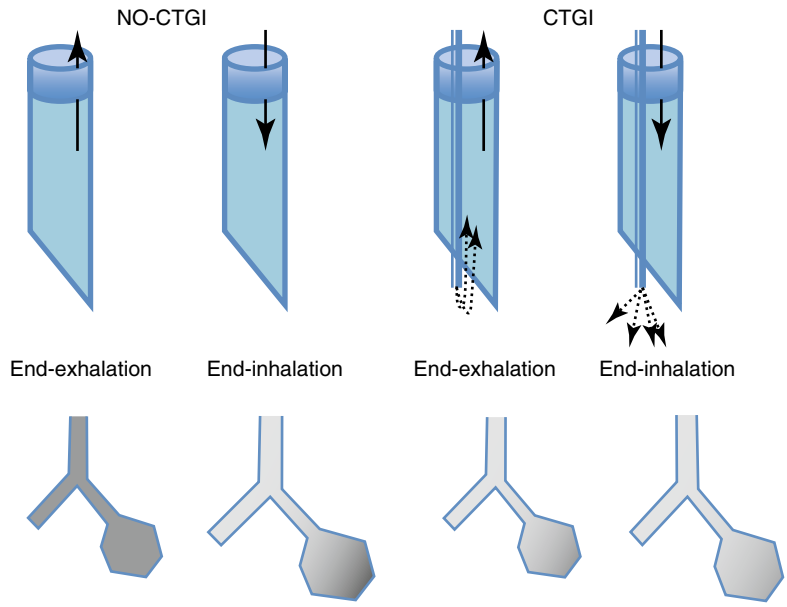


Fig. 8.61 Effect of CTGI on CO_2 removal along respiratory cycles. During mechanical ventilation (*left*), CO_2 (*in grey*) stagnates in the anatomical and prosthetic dead space and is pushed into the alveoli at each insufflation. Adjunction of CTGI (*right*) removes prosthetic and possibly large airways of CO_2 so that CO_2-free gas is pushed into the alveoli at each insufflation

the bottom of the trachea. During the expiratory phase, the expiratory valve is open and the CO_2 trapped in the instrumental dead space is flushed out through the expiratory valve. At the end of the expiratory phase, the prostheses are entirely discharged from CO_2, and the gas volume insufflated during the inspiration phase will be free or almost free of CO_2, increasing the clearance of CO_2 at the alveolar level. This method suppresses the part of additional ventilatory support required to overcome the negative effect of the instrumental dead space, thereby allowing to adjust better the ventilator settings to the real "requirements" of the patient's alveolar disease. If we consider the whole ventilatory cycle, continuous tracheal gas insufflation (CTGI) has different effects depending on the phase of the respiratory cycle (Fig. 8.61). During the expiratory phase of the respiratory cycle, CTGI washes out the instrumental dead space and during inspiration CTGI participates to tidal volume. We can imagine another effect of CTGI considering the turbulence generated by the CTGI flow at the tip of the ETT that can enhance gas mixing in regions distal to the exit of the additional flow (somewhat similar, although limited, to what happens during high-frequency ventilation), thereby contributing to CO_2 removal. This effect is hypothetic, difficult to measure, and clearly marginal if we use low flow rates for CTGI. As we will present in the "lung test" chapter below, the whole system is functions as a system without any instrumental dead space. If we consider that instrumental dead space is two to four times greater than the anatomic dead space in extremely low-birth-weight infants (ELBW), we can imagine the tremendous benefit of erasing this additional dead space might have. Dead space washout is therefore the main if not the exclusive effect of TGI.

8.2.3.3 Data from Bench Tests in a Test Lung

The theoretical main effect of TGI is instrumental dead-space washout. To confirm this and to understand the possible effect of CTGI on airway pressures, tidal volume and minute ventilation, and on gas humidification, a neonatal setup (ventilator, circuit, and test lung) has been used to test CTGI flow-related physical and mechanical effects in the respiratory system. Various compliance values were used for these tests. All values were in the range of normal and sick term and preterm newborns.

8.2.3.3.1 Equipment Characteristics: Catheter or Specific Endotracheal Tube?

In preterm neonates the inlet diameter of usual ETT is 2.5 mm. To provide additional flow to wash out the instrumental dead space, the insertion in the lumen of the ETT of a catheter large enough to avoid high-pressure and high-velocity flow would increase the inspiratory and expiratory resistance by significantly reducing the lumen's diameter. With a thinner catheter than 1.5 mm of outlet diameter, there would be an increased risk of tracheal mucosa injury by direct aggression of the high-velocity jet flow. In this case, humidification would be difficult to maintain and an insufficiently humidified flow could become responsible for drying respiratory gases with a substantial risk of favorizing mucus plugging. For these reasons it is advisable to use multichannel ETTs [e.g., 990.05.1024 EPRT, Vygon, 95440 Ecouen, France] with 6 capillaries inlaid in the ETT wall to be used for TGI (Fig. 8.62). The multiplicity of TGI channels reduces the flow at the tip of the channel and reduces the risk for jet-induced mucosal lesions. Proper humidification and heating of inspired gas can be therefore easier assured.

8.2.3.3.2 Calculation of CTGI Flow Rate to Wash Out the Instrumental Dead Space

Given the volume of the sum of each component of the instrumental dead space, it is theoretically possible to calculate the flow [L/min] necessary to wash out totally this volume [mL] during each expiration time [s] [TGI flow rate = 60 × prosthesis volume (*V*) (mL)/(1,000 × Expiratory time (Texp) (s)]. The following table gives the theoretical TGI flow for various expiratory times and different prosthesis's volumes.

Total efficacy is theoretically reached with less than 0.7 L/min of TGI flow rate and less than 0.5 L/min if the respiratory rate is under 60/min with *I*/*E* ratio under 1/1

8.2.3.3.3 Effect of CTGI Flow Rate on Intratracheal Pressure Rise and on Upstream Pressure

The increase in distal pressure is due to a moment transfer mechanism (Slutsky and Menon 1987) created at the continuous-flow exit in the endotracheal tube lumen. Increasing CTGI flow rates (ranging from 0.5 to 2 L/min) while using various endotracheal tubes (Fig. 8.63) leads to a rapid increase in pressures in CTGI circuit (Fig. 8.63a) and in distal pressures (Fig. 8.63b), limiting CTGI at flow rates of maximal 0.5 L/min. It is important to note that the distal pressure created by CTGI is 0.85 cm H_2O for 0.5 L/min and cannot be detected at the Y-piece level. Therefore, the ventilator display cannot display the more distal created pressure by CTGI. Thus, for all test and clinical trials, PEEP has been reduced from previous setting by 1 cm H_2O when switching on CTGI.

8.2.3.3.4 Efficacy of CTGI on PCO_2 Reduction in an Artificial Lung Model

While adjusting in a test lung model with anatomic dead space the PCO_2 to a steady value of 50 mmHg (■) using a continuous CO_2 supply (Fig. 8.63d), the reduction in PCO_2 induced by CTGI can be analyzed (●) and then be compared to a lung model without any dead space (○). In such a model setup, PCO_2 levels could be measured to be equivalent in the TGI model with a CTGI flow of 0.5 L/min to the PCO_2 levels measured in dead-space-free model. Moreover, the reduction in PCO_2 increases when tidal volume decreases.

Texp/*V*	2.50 (mL)	3.00 (mL)	3.50 (mL)	4.00 (mL)	4.50 (mL)
0.40 s	0.38 (L/min)	0.45 (L/min)	0.53 (L/min)	0.60 (L/min)	0.68 (L/min)
0.50 s	0.30 (L/min)	0.36 (L/min)	0.42 (L/min)	0.48 (L/min)	0.54 (L/min)
0.60 s	0.25 (L/min)	0.30 (L/min)	0.35 (L/min)	0.40 (L/min)	0.45 (L/min)
0.70 s	0.21 (L/min)	0.26 (L/min)	0.30 (L/min)	0.34 (L/min)	0.39 (L/min)
0.80 s	0.19 (L/min)	0.23 (L/min)	0.26 (L/min)	0.30 (L/min)	0.34 (L/min)

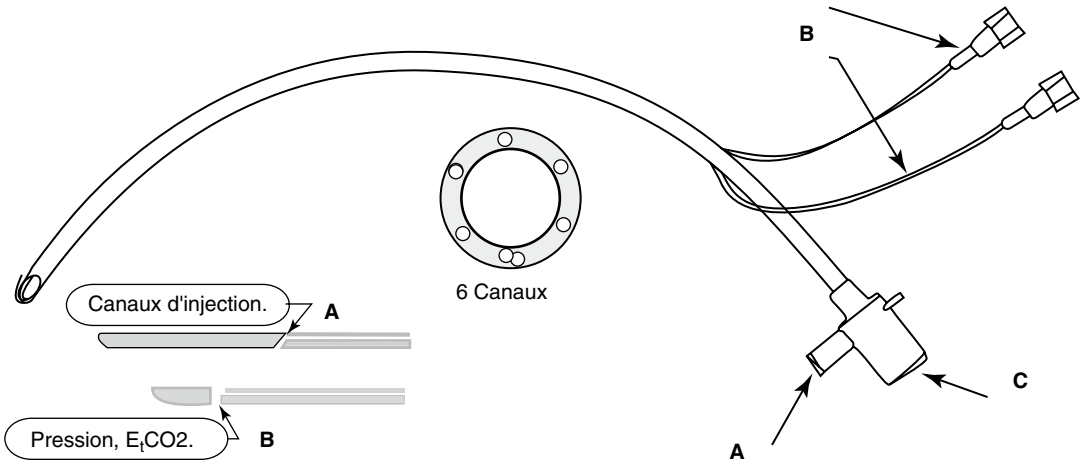


Fig. 8.62 ETT for CTGI. 990.05.1024 EPRT, Vygon endotracheal tube; (*A*) Six capillaries drive the continuous flow for TGI; (*B*) two additional capillaries are used for pressure control and surfactant administration; (*C*) usual connection to the ventilator circuit

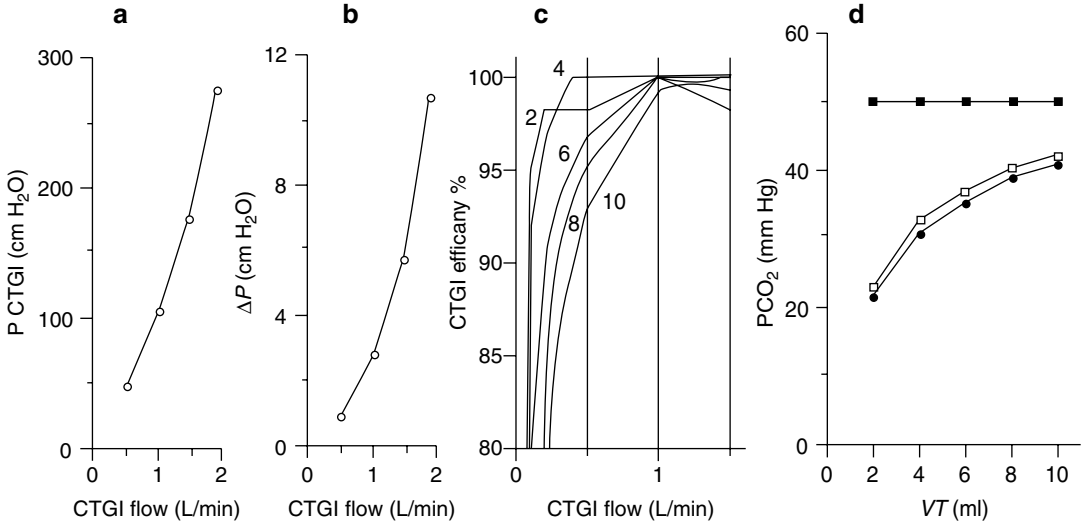


Fig. 8.63 Determination of the optimal CTGI flow rate. (**a**) CTGI flow is represented on the *X*-axis. The pressure inside the CTGI circuit is represented on the *Y*-axis. (**b**) CTGI flow is represented on the *X*-axis. The additional pressure generated at the end of the ETT is represented on the *Y*-axis. (**c**) Efficacy of CTGI at different flows (*X*-axis) and at varying tidal volumes (the number close to each curve denotes the tidal volume used in mL). (**d**) PCO_2 changes in a CO_2-filled test-lung model during conventional ventilation (*full squares*), conventional ventilation plus CTGI (*full circles*), and conventional ventilation in a dead space-free model (*empty circles*) at various tidal volumes (*X*-axis)

A 95 % efficacy for CO_2 washout was obtained with 0.5 L/min, over a big range of VTs (2–10 mL) by variation of the TGI flow rate from 0 to 1 L/min for all chosen VTs, with the exception of 10 mL (Fig. 8.63c). For the smallest VT, 95 % of maximal efficacy can even be achieved with a CTGI flow below 0.5 L/min.

In conclusion, for neonates intubated with a 2.5-ETT, a 0.5 L/min TGI flow rate seems to be the most appropriate. It is sufficient to erase

instrumental dead space, but it increases the pressures all along the ETT by 0.85 cm H_2O. If we want to adapt the flow to specific conditions, it is possible to decrease the flow rate according to the smallest tidal volumes (Fig. 8.63c). Otherwise, for a same volume to wash out during expiration time, the longer expiratory time necessitate the lower CTGI flow rate.

8.2.3.4 Physiological Consequences of CTGI

8.2.3.4.1 Effect of CTGI-0.5 on PEEP and ΔP

A key issue is to know whether TGI modifies infant's tidal volumes and/or minute ventilation. While using pressure-limited ventilation provided by a continuous-flow apparatus, as is standard practice in neonatal intensive care units, tidal volume is not set directly but is dependent on mechanical characteristics (compliance and resistance) of the respiratory system (ventilation circuit, infant) and on ventilator settings, i.e., peak inspiratory pressure (PIP) and peak end-expiratory pressure (PEEP) and the difference between these two pressures (ΔP), inspiratory time, and flow. Initiating TGI has no effect on most of these parameters: Respiratory system characteristics, PIP–PEEP difference, inspiratory time, and flow remain unchanged in experimental settings (Dassieu et al. 1998) (Fig. 8.64). The only modification in parameters that can be observed is a slight but consistent increase in mean tracheal pressure distal to the outlets of the TGI capillary tubes. The numerous measurements that we performed on test lung and on patients demonstrated that this increase was consistently $\leq$1 cm H_2O. This increase, however, is not detectable in the ventilator circuit and on therefore the ventilator display cannot indicate it. This pressure increase remains stable during the whole respiratory cycle therefore not influencing the ΔP (i.e., the pressure difference between PIP and PEEP). The absence of CTGI-induced VT or minute ventilation changes is confirmed by direct VT and minute ventilation measurements downstream the ETT, taking into account both main and CTGI flows (Dassieu et al. 1998).

8.2.3.4.2 Contribution of CTGI-0.5 to V_T

To determine relative volume distribution of two gas sources injected in one system, a dilution technique can be used. In that two gases with different oxygen concentration, one for the ventilator ($FiO_2 = 0.21$) and the other for the CTGI circuit ($FiO_2 = 1$), have to be used. Determination of the resulting FiO_2 in the test lung allows then calculation of the contribution of CTGI to the delivered V_T as follows: If "A" is the fraction of V_T generated by CTGI, A = (measured $FiO_2 - 0.21$)/(1 − 0.21). CTGI-0.5 does make an important contribution to VT in all test situations (various VTs over a range of 2–10 mL), ranging from 40 to 100 % (Fig. 8.64a). CTGI contribution increases when tidal volume and breathing rate decreases. Furthermore, it increases with CTGI flow rate but is not sensitive to isolated variation of inspiratory time settings.

8.2.3.4.3 Ventilation Gas, Humidity, and Temperature Tests

The temperature and relative humidity were determined with a thermo-hygrometer (Testo 610, Lenzkirch, Germany) in the test lung under various ventilatory conditions, using conventional mechanical ventilation, ventilation and CTGI-0.5 with CTGI gases derived directly from a wall source, and mechanical ventilation and CTGI-0.5 with CTGI-0.5 derived from the humidified inspiratory gases (MR 730 Fisher and Payckel, Auckland, New Zealand). The test lung was placed in an incubator at 37 °C to simulate the conditions of clinical use. Under test conditions (Fig. 8.64b), CTGI-0.5 with non-humidified unwarmed gases induced a marked decrease in relative humidity and, to a lesser degree, a decrease in the temperature measured in the test lung. With humidified and warmed gases in the CTGI circuit, as described later, relative humidity with IPPV plotted against relative humidity with IPPV + CTGI-0.5 (Fig. 8.64c), the humidity was well preserved ($r = 0.92$).

8.2.3.4.4 Continuous-TGI or Intermittent-TGI During the Expiratory Phase?

As it was suggested before, TGI has its major effect in terms of CO_2 washout during expiratory phase, but for different reasons, the additional

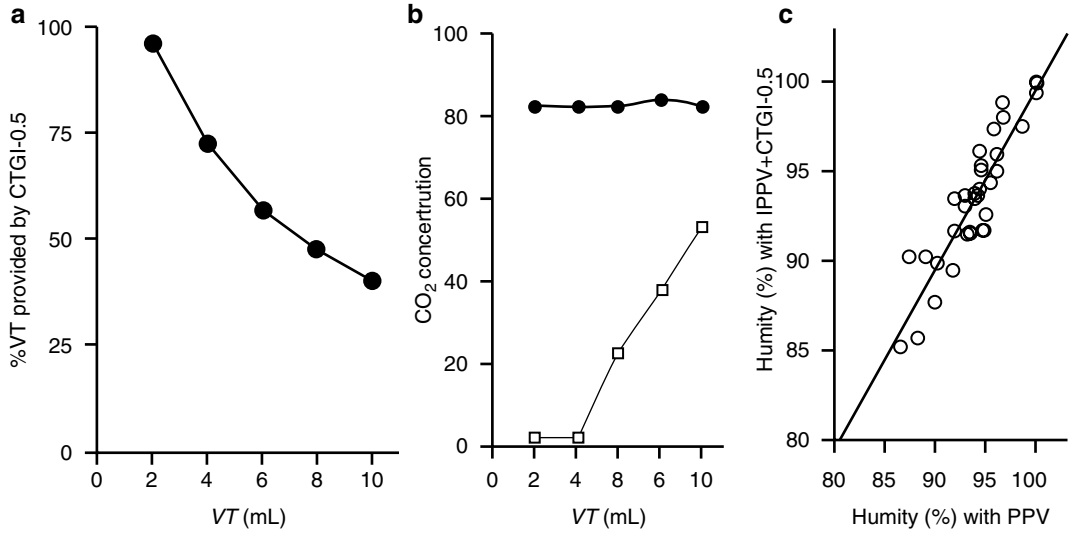


Fig. 8.64 Influence of CTGI on alveolar gases. Contribution of CTGI-0.5 to VT and influence on humidity

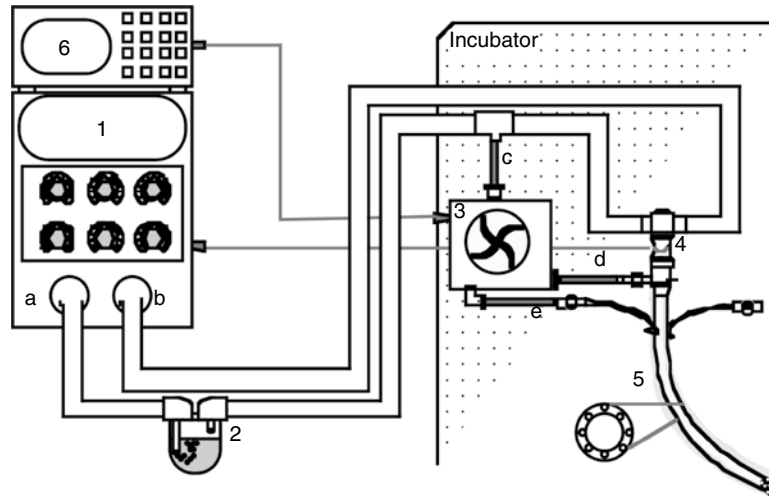


Fig. 8.65 Assembly diagram for controlled positive pressure ventilation and CTGI. *1* Ventilator, *2* heater/humidifier, *3* CTGI pump, *4* spirometer holder, *5* endotracheal tube, *6* monitoring and safety module. *a* Inspiratory circuit, *b* expiratory circuit, *c* inlet CTGI circuit, *d* outlet CTGI circuit, *e* tracheal pressure transducer

flow is as efficient and easier to achieve if it is continuously blown during both expiratory and inspiratory phases.

8.2.3.4.5 Safety Considerations

As the TGI flow exits at the tip of the ETT, any mucus plug in the ETT forbids unrestricted exhalation, thereby increasing the risk of air trapping even if the ventilator would react correctly to this obstruction by reducing delivered tidal volumes if set in a TCPL mode. Therefore, TGI may be appended to conventional mechanical ventilation only if a security device controls the risk of inadvertent hyperinflation. One possible answer is illustrated by our CTGI model (Fig. 8.65).

Dead-space washout was ensured by an ancillary flow rate of 0.5 L/min (CTGI-0.5) injected into the lower part of the endotracheal tube through six capillaries extruded in the tube wall (990.05.1024 EPRT, Vygon, 95440 Ecouen, France). Two further independent capillaries were used to monitor pressure changes at the tube extremity or inject surfactant. Pressure monitoring in the CTGI circuit and at the extremity of the tube (AST 142PC, Vanves, France) was designed to prevent hyperinflation. Any abnormal rise in

the CTGI circuit pressure would trigger an alarm and then cut the power supply to the pump. An electrovalve (Kuhnke 65231, Malente, Germany) would then open to shorten the time to return to zero pressure. Independent reference transducers were used to validate the pressure (Meriam Instrument Meri-cal LP 2001, Cleveland, Ohio, USA) and flow-rate determinations (Sierra Instruments 822-13-ovl, Monterey, CA, USA)

8.2.3.5 Animal Studies

Reduction of dead space in cases of respiratory insufficiency has long been a preoccupation. Slutsky et al. developed an animal model using constant endobronchial insufflation under apneic ventilation with positive expiratory pressure. This technique, using very high flow rates (up to 30–60 L/min), enabled normocapnia to be obtained. Efficacy varied as a function of flow rate (Slutsky and Menon 1987; Watson et al. 1986) and catheter positioning (Slutsky and Menon 1987). Using slightly lower flow rates in paralyzed (Slutsky et al. 1985) or partially paralyzed dogs (Long et al. 1988), the efficacy of the method was found to be the same if the catheter was positioned 1 cm above or below the carina trachea. This gave rise to the idea of applying this type of tracheal gas insufflation, concomitantly with mechanical ventilation, and several animal and a few human clinical studies were conducted. Nahum et al. developed an animal model combining conventional mechanical ventilation with tracheal gas insufflation via a catheter positioned above the carina and inserted in parallel with the ETT. These authors showed that the technique decreased $PaCO_2$ (Nahum et al. 1992a). Efficacy depended on the flow rate used (up to 10 L/min) and was little dependent on catheter positioning. Similarly, the configuration of the end of the catheter (distal versus lateral apertures) did not seem important (Nahum et al. 1992b). The method of insufflation was, however, important. Constant tracheal insufflation was more effective than expiratory insufflation, the latter being more effective than inspiratory insufflation (Burke et al. 1993). In contrast, the use of retrograde insufflation was less effective than anterograde insufflation (Nahum et al. 1993). Using a similar animal model, Snadjer showed that tracheal washout with constant PCO_2 enabled a significant decrease in tidal volume and inspiratory pressures (Sznajder et al. 1989). Jonson obtained the same results with expiratory washout only, using a jet-ventilation tube with a channel included in the ETT wall (Jonson et al. 1990). More recently, Shaffer tested continuous tracheal insufflation, using CTGI appended to conventional ventilation, showing a lung-protective effect based on histological findings after a short duration of CTGI compared to conventional ventilation alone (Miller et al. 2004). Associated to liquid ventilation he showed a synergistic effect on lung protection of the two non-conventional approaches (Zhu et al. 2004). More recently, in a rabbit model of acute lung injury, the same author showed that TGI associated with conventional ventilation decreased ventilatory requirements (PIP, VT, and VD/VT), resulted in more favorable alveolar pulmonary surfactant composition and function and less severity of lung injury than conventional ventilation alone (Zhu et al. 2006).

8.2.3.6 Human Studies

At the end of the 1960s, Stresemann proposed a method for anatomical dead-space washout in tracheotomized patients under spontaneous ventilation, using an intratracheal catheter (Stresemann et al. 1969). More recently, studies have shown that intratracheal administration of gas enabled a reduction in tidal volume, dead space, and minute ventilation in the same type of patients (Benditt et al. 1993; Hurewitz et al. 1991; Bergofsky and Hurewitz 1989). After the Stresemann pilot study, studies in man remained rare. Marini's group, using the method described above in 8 adults under mechanical ventilation, studied the effect of tracheal washout as a function of flow rate (2, 4, and 6 L/min) and catheter positioning. A 15 % decrease in $PaCO_2$ was obtained with the high flow rate (6 L/min) and the most distal catheter position (1 cm above the carina) (Ravenscraft et al. 1993). Nakos obtained equivalent results and showed that tracheal washout at constant $PaCO_2$ enabled a decrease in V_T, peak inspiratory pressure, and mean airway pressure (Nakos et al. 1994).

In children, the only studies have been conducted in patients who could not be weaned from an extracorporeal membrane oxygenator (ECMO). These patients consisted in two newborns presenting with diaphragmatic hernia (Wilson et al. 1993) and a 16-year-old child experiencing an aplastic crisis in a context of sickle-cell anemia (Raszynski et al. 1993). The method used was a technique developed by Kolobow (Muller et al. 1993), in which the entire ventilatory flow rate is administered by a catheter inserted in the ETT. In all three cases, weaning from ECMO was successfully achieved.

8.2.3.7 Specific Insights in Neonates

In neonatology, pressure-limited continuous-flow ventilators are used in the overwhelming majority of patients. The rate of expiratory valve closure can be preset, and the tidal volume is dependent on three adjustable parameters: continuous flow (which determines the pressure increase slope), pressure gradient (PIP–PEEP), and inspiratory time. Each of these parameters can be set individually and has no influence on the other two parameters. Although flows and volumes can be measured, these ventilators do not allow to strictly control tidal volume or minute ventilation. This is an important difference with adult mechanical ventilation and data coming from experimental use of TGI with adult ventilators. The other differences concern the lung and prosthetic volumes in neonates. Physiological dead space is rarely important in preterm newborns, lung pathologies are often restrictive, V_D/V_T ratio is greater than in adults, and instrumental dead space increases this ratio more in the smallest infants than in adults. For all these reasons, TGI is supposed to be more efficient and simpler to understand and to apply in preterm infants than in adults. For other reasons, as the small size of the prosthesis, importance of humidity, and fragility of lung tissues, TGI must be cautiously designed to avoid tracheobronchial mucosa injuries, plugs, and air leaks (Dassieu et al. 1998).

Conclusion

Lung testing enables to understand the very simple incidence of TGI as an adjunct to conventional ventilation. The only one goal is to erase an instrumental dead space incompatible with minimally aggressive ventilation. With pressure-limited ventilation provided by a continuous-flow ventilator, CTGI interferes with conventional ventilation with a slight increment of pressures, easy to correct, without any incidence on minute ventilation. Conversely, gases coming from the TGI flow participate largely to alveolar gases. Subsequently, they have to be precisely enriched with oxygen and optimally heated and humidified. All these considerations, including safety issues, are taken into account in a specific technical assembly proposed in Chap. 22.

Essentials to Remember

High dead space (V_D) to tidal volume (V_T) ratio can limit the efficiency of conventional ventilation especially in extremely low-birth-weight infants in whom V_D/V_T ratio is often greater than in mechanically ventilated adults mainly because of a relative high instrumental dead space. Continuous tracheal gas insufflation (CTGI) appended to pressure-controlled mechanical ventilation aims at removing CO_2 trapped in the instrumental dead space, and by this it allows to reduce tidal volumes during mechanical ventilation below 4–5 mL/kg. However, it must be remembered that the additional gas flow that is best provided through specially designed endotracheal tubes with several very small in-wall channels that allow best to keep correct gas humidity and also reduce the pressure buildup along the neonatal endotracheal tube to less than 1 cm H_2O with TGI flows of 0.5 L/min. Accordingly it is advisable to reduce PEEP settings on the ventilator by 1 cm H_2O when turning on a TGI flow. TGI flow rates of 0.5 L/min seem to be sufficient to compensate in terms of CO_2 washout for the instrumental dead-space effect in the neonatal setting. When using this technique, appropriate safety conditions must be provided.

8.2.4 Liquid Ventilation

Thomas Schaffer

Educational Aims

- To understand the chemical physical properties of perfluorochemical (PFC) liquids
- To understand the concept of liquid ventilation, especially its impact on pulmonary mechanics and gas exchange

8.2.4.1 Chemical Properties

Supporting respiratory function utilizing a liquid to eliminate the liquid–gas interface is a more than 50-year-old concept. Published data from the 1950s and 1960s supported the use of saline as a respiratory medium to accomplish the goals of oxygen delivery and carbon dioxide removal. Mammalian animals have successfully breathed hyperoxygenated saline and returned to air breathing. While these animals were successful in delivering oxygen to hemoglobin, it was noted during experiments that they eventually began to retain carbon dioxide and develop a significant metabolic acidosis. These findings in combination with the detergent-like action of saline in removing pulmonary surfactant led to the abandoning of saline as a liquid breathing medium (Mead et al. 1957; Kylstra et al. 1966, Kylstra 1970, 1974; Shaffer et al. 1976; Shaffer 1987, 2004; Wolfson and Shaffer 1990).

Many other liquid media were investigated as potential alternatives to saline including animal and vegetable oils as well as silicon. None of these alternatives were found to be suitable substitutes for saline as they demonstrated numerous toxic effects on the pulmonary parenchyma (Shaffer 2004; Clark and Gollan 1966; Clark 1985; Moore and Clark 1985).

Perfluorochemical (PFC) liquids were developed during the Manhattan Project and are unique in many ways. PFC liquids are known to have extreme thermal, chemical, and physical stability. They can be stored at room temperature indefinitely and subjected to antiseptic conditioning without alteration, and they are clear, odorless, non-transformable, and generally insoluble in aqueous media. Table 8.17 describes the chemical properties of the PFC liquids as a general class (Shaffer 2004; Lynch et al. 1983)

They are generally formed through the addition of fluorine to cyclic carbon molecules such as benzene through a variety of chemical synthesis reactions. They can be made through vapor phase fluorination, cobalt trifluoride agitation, or electrochemical fluorination. Fluorine replaces carbon-bound hydrogen and it is these carbon–fluorine bonds that give the PFC liquids their unique characteristics (Sargent and Seffl 1970).

In addition to their remarkable chemical characteristics, the PFC liquids as a class demonstrate remarkable gas solubility characteristics. Oxygen dissolves in PFC liquids approximately 20 times more readily than in saline. The solubility of carbon dioxide, however, is much more variable and dependent upon the specific physical properties of each individual PFC (Shaffer 2004)

While the gas solubility properties of PFC liquids make them ideal candidates as a liquid breathing medium, there are several characteristics that limit their ability in a spontaneous breathing application. As a general class these liquids have high density, viscosity, and diffusion

Table 8.17 Physical properties of various PFC liquids

Perfluorocarbon	Formula	O_2 solution mL/100 mL (25 °C)	Vapor pressure mmHg (37 °C)	Viscosity cS (25 °C)
PP2	C_7F_{14}	57.2	180	0.88
PFOB	$C_8F_{17}Br$	52.7	11	1
PCl	$C_7F_{15}Cl$	52.7	48.5	0.82
PFDMA	$C_{12}F_{18}$	39.4	2.6	4.35
APF-100	C_8F_{16}	42.1	64.6	1.11
APF-145	$C_{10}F_{20}$	45.3	8.9	1.44
APF-215	$C_{14}F_{26}$	37	0.2	8

Table 8.18 Ideal properties of a fluid as a respiratory medium

High respiratory gas diffusion coefficient
High respiratory gas solubility
Low density and viscosity
Low vapor pressure
Inertness

coefficients which make the work of breathing during spontaneous respiration significantly greater when compared to gas breathing. In addition these same properties result in longer inspiratory and expiratory times as more time is needed in both phases of the ventilation cycle for the movement of the liquid media.

Table 8.18 presents some of the ideal properties of the fluid for a liquid medium to achieve ventilation (Lynch et al. 1983). There are numerous PFC liquids that can be created by chemical techniques; however, not all are ideally suited to serve as a respiratory medium. Fluids of a higher vapor pressure may evaporate more quickly from the lung than those of a lower vapor pressure. Fluids with a lower spreading coefficient may be more difficult to distribute throughout the lung than those with a higher spreading coefficient. Fluids of a higher density will resist redistribution throughout the lung and offer greater resistance to flow. Finally, the ability of the liquid to dissolve gases and carry large amounts of those gases is crucial in determining the functionality of any liquid's ability as a respiratory medium. All of these factors should be considered when choosing an appropriate liquid PFC (Shaffer 2004).

8.2.4.2 Impact on Lung Mechanics

8.2.4.2.1 Pulmonary Structure and Function

The diseased infant lung often suffers from conditions that limit alveolar recruitment and limit uniform ventilation–perfusion matching. Liquid breathing media offer several benefits to the overall structure and function of the lung. More volume is displaced per unit change in pressure in the fluid-filled lung then in the gas-filled lung. This improvement in overall compliance is exaggerated when surfactant is deficient. The liquid breathing media removes the gas–liquid interface, thus reducing or eliminating the surface forces that result in the need for higher distending pressure. Also, the fluid-filled lung demonstrates similar vascular and alveolar pressures resulting in more uniformly distended vascular structures and an overall improvement in ventilation–perfusion matching.

8.2.4.2.2 Pulmonary Mechanics

Surface tension of the alveolar–capillary interface created by the interface between two phases, gas and the lung surface, is the force resisting expansion and determines the amount of work required to create additional surface for gas exchange. It is by altering these forces that liquid breathing offers its greatest benefit, reducing the surface forces that increases the work of breathing associated with newborn respiratory distress syndrome. By replacing this gas–liquid interface with a liquid–liquid interface, surface forces are reduced but not completely eliminated at this interfacial barrier. The greatest reduction in surface tension is seen with total liquid ventilation where the lung is insufflated to functional residual capacity and free gases are solubilized. However, improvements are also seen during recovery to gas breathing as well as during partial liquid ventilation. Even during partial liquid ventilation when multiple interfacial barriers are present, compliance is always superior to the gas-filled lung (Fig. 8.66) (Shaffer et al. 1983, 1984, Greenspan et al. 1989; Leach et al. 1996; Tarczy-Hornoch 1994, 1995, 1998). The physical properties of liquid breathing necessarily change the way in which breathing need be accomplished. Because of the increase in density and viscosity of these media, the respiratory cycle while breathing liquid necessarily has to be longer with less frequent cycles per minute. PFC breathing is a process in which inspiratory and expiratory times are prolonged, respiratory rate is reduced, and a lengthened exchange period is necessary for gas exchange to occur (Shaffer 2004).

8.2.4.2.3 Gas Exchange

The ability of any media to facilitate oxygen delivery and carbon dioxide removal is dependent upon the ability of the media to move in and out of the

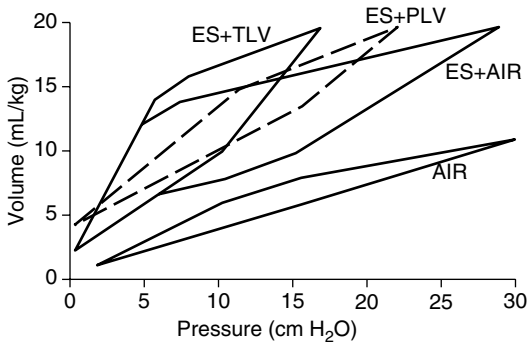


Fig. 8.66 Average pressure–volume curves of excised preterm lamb lung exposed to gas ventilation without (*AIR*) or with (*ES+AIR*) surfactant or with perfluorochemical partial liquid ventilation (*ES+PLV*) or tidal liquid ventilation (*ES+TLV*) (Reprint from Polin et al. 2004)

lung as well as the ability of the media to dissolve and carry gases. In the healthy condition during which surface tension is low and alveolar recruitment is even, ventilation while breathing a gas is ideal. Gases are significantly less dense and viscous and move in and out of the lung easily while efficiently achieving ventilation. However, in a diseased state where surface tension is high and alveolar recruitment is suboptimal, gas breathing results in diminished gas exchange as alveolar hypoventilation and ventilation–perfusion mismatch diminish the effectiveness of ventilation. It is in this condition that liquid breathing offers significant benefits to gas exchange. While liquids are significantly more dense and viscous, they improve ventilation by improving uniformity of alveolar recruitment and perfusion throughout all regions of the lung, thus essentially eliminating both hypoventilation and ventilation–perfusion mismatching (Shaffer et al. 1984; Wolfson et al. 1996).

8.2.4.3 Cardiovascular Impact

Early studies utilizing PFC as a liquid breathing medium in healthy adult animals reported decreases in cardiac output, oxygen consumption, pH, and an increase in pulmonary vascular resistance. The studies suggested that while gas exchange was possible with PFC, the weight of the liquid in the thorax was compressive to the great vessels of the heart as well for pulmonary vasculature (Matthews et al. 1978; Lowe et al. 1979; Sivieri et al. 1981; Lowe and Shaffer 1981, 1986). More recently, however, changes in ventilatory management favoring more moderate recruitment strategies with positive end-expiratory pressure (PEEP) in conjunction with PFC ventilation have reported less compromise in cardiopulmonary function (Curtis et al. 1991, 1993; Wolfson 1995). Current studies would support that cardiopulmonary function is minimally impacted by a moderate recruitment strategy (PFC ~10 mL/kg) and that ventilation–perfusion matching is improved.

Essentials to Remember

- Various PFC liquids have various chemical and physical properties, therefore.
- PFC liquids improve ventilation by improving uniformity of alveolar recruitment and perfusion throughout all regions of the lung, thus essentially eliminating both hypoventilation and ventilation–perfusion mismatching.
- The liquid breathing media removes the gas–liquid interface, thus reducing or eliminating the surface forces that result in the need for higher distending pressure.
- PFC breathing is a process in which inspiratory and expiratory times are prolonged, respiratory rate is reduced, and a lengthened exchange period is necessary for gas exchange to occur.

8.3 Noninvasive Positive-Pressure Ventilation in the PICU

Sandrine Essouri

Noninvasive ventilation is now used as a first-line treatment in the management of acute respiratory failure (ARF). Interface choice can strongly influence the efficacy and tolerance of NIV by air leak, facial skin erythema, skin damage, or eye irritation.

The best choice of interface for children patient is a major challenge for pediatricians and requires careful evaluation of the child. The development of new devices specially designed for small patients can minimize these adverse effects when associated with increased use of the NIV.

The nasal mask is widely used for NIV or CPAP most often in ventilation of chronic respiratory failure. During ARF, patients breathed through the mouth to bypass the nasal resistance, but this increase air leaks and can reduce efficacy of NIV. Thus, oronasal masks are preferred for patients with ARF and these masks have the advantage of eliminating significant oral air leaks which should improve the efficacy of NIV. Another new interface, the helmet, should have a real place in PICU to provide NIV. Because of its comfort and good tolerance, the helmet can be used alternately with masks to provide ventilatory support. Education of pediatricians and nurses along with who install the interfaces to maintain a good seal without side effects should be a goal for NIV users.

Progress in development of specific pediatric interfaces has been made but these are still insufficient. The cooperation between physicians and industry should be developed to create adapted interfaces for the newborn to young adult.

Educational Goals

- Precise respiratory physiological characteristic with implications for the choice of interfaces.
- Make a list of available interfaces for NIV in pediatrics.
- Identify the benefits and side effects of each type of interface.
- Enable the practitioner to choose the most relevant interface to optimize the comfort of the child according to the clinical situation.

Noninvasive ventilation is a technique of ventilatory support that does not use an endotracheal interface. Noninvasive ventilation is now used as a first-line treatment in the management of acute respiratory failure (ARF). Depending on the type of respiratory failure, the child's age, the choice of interface will be an oronasal mask or nasal interface. Interface choice can strongly influence the efficacy and tolerance of NIV by air leak, facial skin erythema, skin damage, or eye irritation.

The best choice of interface for children patient is a major challenge for pediatricians.

8.3.1 Technical Considerations

As its name suggests simplicity, the NIV is in fact a ventilatory assistance requiring specific technical knowledge and experience of practitioners. The increased importance of NIV in pediatric intensive care medicine and the new interfaces for its application led to the development of special modes of intensive care ventilators to overcome the problems related to the type of interface essentially higher air leakage and dead space. Although the basics of the respiratory physiology are similar in adult and older children, major differences do exist, especially between the very young children and adults. Young infants are characterized by a very compliant chest wall that impedes the ability to generate adequate tidal volume and increases the work of breathing by wasting force on chest wall distortion instead of generating effective alveolar ventilation, contributing to muscle fatigue (Davis et al. 1988; Papastamelos et al. 1995). The respiratory system is also hampered by high-flow resistance of the nasal airway and small airway, by hypertrophy of adenoids and tonsil, and by a small zone of apposition of the diaphragm and horizontal ribs; all these physiological properties curtail the endurance of the respiratory system (Devlieger et al. 1991; Hershenson et al. 1990; Openshaw et al. 1984).

NIV is based on the application of a positive pressure (or volume) to the airways and varies with the user effort and the mechanical characteristics of the respiratory system such as compliance, resistance, auto positive end-expiratory pressure, respiratory rate, and potential leakage.

Trigger, usually sensed as flow change in the system, is fundamental to achieve a good patient–ventilator synchrony. In case of small children, inspiratory flow may be insufficient to activate the trigger. This is further complicated by the volume added by the humidifier interposed on the circuit.

The expiratory trigger can be set to inspiratory time or, more often, to a value of inspiratory flow. During pressure-support ventilation (PSV), leaks can hinder achievement of the inspiration termination, thus impeding expiration (Calderini et al. 1999; Mehta and Hill 2001). Air leaks may reduce the efficiency of NIV, increase patient–ventilator asynchrony, and reduce patient tolerance. The management of leakage is therefore a real challenge for the success of the NIV. The management of leaks by applying the mask on the child's face with high pressure is double edged. While the leakage will be reduced, it may seriously alter the skin tolerance and generate short-term skin damage that will impair the patient's tolerance to the NIV. Schettino et al. studied air leaks and estimated the pressure required to seal the mask to the skin and prevent leaks (Schettino et al. 2001). With full-face mask or oronasal mask, a level of pression >2 cm H_2O avoids significant air leaks, whereas with a pressure <2 cm H_2O air leaks become relevant. However, if the mask pressure against the face exceeds the skin capillary pressure, it can impair skin perfusion leading to skin damage (Gregoretti et al. 2002; Li et al. 2000; Schonhofer and Sortor-Leger 2002).

8.3.2 Machine–Patient Interfaces

During NIV for acute respiratory failure (ARF), the patient's comfort may be less important than efficacy, but mask fit and care are needed to prevent air leaks that can reduce efficacy of NIV and skin damage that can decrease patient tolerance.

In the last few years, the industry has made a great effort on interfaces to provide more comfortable, better tolerated, and safer interfaces for adults. In the pediatric population, patient size and anatomy differs dramatically and this piece has a crucial role in NIV. Although great progress in terms of child-friendly interfaces has been made, we are still in a situation where there is a paucity of masks available for pediatric use. The interfaces have included standard commercially masks, ready-to-use models available in various sizes: pediatric and small adult, medium, and large. The interfaces could be also be custom fabricated, molded directly on the patient (McDermott et al. 1989; Tsuboi et al. 1999), but the time required to manufacture the mask does not allow the use of the custom-made mask for critically ill patients in acute respiratory failure (ARF).

Comparative studies on noninvasive interfaces in the pediatric population is absent despite the important role of this piece for NIV.

The classes of NIV interface are resumed in Table 8.19:

Table 8.19

Classes of NIV interface	Characteristics
Mouthpiece	Placed between the patients lips and held in place by lip seal
Nasal prongs	Plugs inserted into the nostrils
Nasal mask	Covers the nose but not the mouth
Oronasal mask	Covers the nose and the mouth
Full-face mask	Covers the mouth, nose, and eyes
Helmet	Covers the whole head and the neck without contact with the face

Among these interfaces, only full-face masks are not available for pediatric intensive care unit use; if small sizes exist, they could be used with children depending on the etiology of the respiratory failure. During acute respiratory distress in children, decrease of compliance and increase of resistance result in a swallow respiratory pattern with breathing both through the nose and the mouth. In these acute clinical situations, nasal masks and mouthpieces should not be used.

The Table 8.20 summarizes the characteristics of an ideal NIV interface.

8.3.2.1 Nasal Mask

The standard nasal mask is a triangular or cone-shaped clear plastic device with the air seal over the skin formed by a soft cuff. Nasal masks are available in various sizes (pediatric to adult) and from many manufacturers. The nasal mask

Table 8.20 Characteristics of an ideal interface

Characteristics of an ideal noninvasive ventilation interface for pediatric patient.
Ideal interface
Minimal leaks
Minimal dead space
Available in various sizes
Nontraumatic
Lightweight
Good stability and easy to fix
Nonallergenic material
Low resistance to airflow
Low cost
Nondeformable + easy cleaning

exerts pressure over the bridge of the nose to achieve an adequate air seal which may cause erythema and skin irritation. To avoid or reduce these complications, a thin hydrocolloid flap is added which creates an air seal with less mask pressure on the nose. When using nasal masks, transparent models should be preferred to allow easy inspection of the nostrils to ensure that they are not partly or totally occluded due to an inadequate position of the mask. This risk is higher in small children where even a small displacement can alter the delivery of the pressure support. Head gear that holds the mask in place is important for patient comfort, many types of straps assemblies are available, but most manufacturers provide head gear that is designed for use with a particular mask. Depending on the interface, head gear is attached in two or as many five points on the mask, increasing the points of attachment adds stability. The use of chin strap in case of mouth leaks is possible.

The nasal mask is widely used for NIV or CPAP most often in ventilation of chronic respiratory failure. During ARF, patients breathed through the mouth to bypass the nasal resistance but this increases air leaks and can reduce efficacy of NIV. Some authors advocate the use of nasal masks because they produce less anxiety in young children but no studies have compared pediatric nasal masks to oronasal masks in terms of tolerance and efficacy during ARF (Teague 2003). In contrast, many studies describe the successful long-term use of nasal masks for home ventilation in young children with neuromuscular disease or congenital central hypoventilation syndrome (Guilleminault et al. 1995; Khan et al. 1996; Marcus et al. 1995; Waters et al. 1995).

8.3.2.2 Oronasal Mask

Many commercial masks are formed by two or more pieces of material: the cushion of soft material that forms the seal against the patient's face composed of polyvinyl chloride, polypropylene, silicon, silicon elastomer, or hydrogel and the frame of stiff material which is transparent in most of the mask and composed of polyvinyl chloride, polycarbonate, or thermoplastic. There are 4 types of face-seal cushion: transparent noninflatable, transparent inflatable, full hydrogel, and full foam.

Oronasal masks are preferred for patients with ARF because they generally breathe through the mouth to bypass nasal resistance (Soo Hoo et al. 1994) and oronasal masks have the advantage of eliminating significant oral air leaks which should improve the efficacy of NIV. In adults, recent engineering advances have improved mask-face seal comfort with added quick-release straps and anti-asphyxia valves to prevent rebreathing in the event of ventilator dysfunction that automatically open to room air when airway pressure falls below 3 cm H_2O. The mask must have a system of fixing to the child's head which is adapted and thus performant. This is a problem for small children for whom the pediatricians are often required to use adult nasal masks in the oronasal position with an inadapted headdress and straps which overlap each other to maintain a stable and correct position of the mask (see Fig. 8.67).

The first concern for the oronasal mask is the higher dead space but, this is not a drawback when the mask is used with a polyvalent ventilator that takes into account all of the compliance of the breathing circuit and has good flow and volume monitoring. Another major concern for the use of oronasal masks in the acute setting is the potential for significant gastric distension and vomiting. However, different clinical experiences show that the systematic use of a gastric tube discharge can, in most cases, avoid these complications.

Fig. 8.67 Oronasal interfaces used in PICU (Respironics)

8.3.2.3 Helmet

It is now well known that air leaks, patient discomfort, and skin breakdown are common problems with face masks which limits the duration and the efficacy of NIV (Mehta and Hill 2001; Mehta et al. 2001) . The helmet was originally designed to deliver high oxygen concentrations during hyperbaric therapy (Bellani et al. 2008) and was then introduce as a tool to deliver noninvasive continuous positive airway pressure. Some advantages of using a helmet are as follows: no need for a seal around the nose and the mouth, an improved tolerability, and the possibility of fitting it to any patient, even the smaller one, regardless of the face contour. The helmet is made of lightweight and transparent biocompatible plastic material joined by means of a rigid ring to a latex-free collar that provides a soft seal around the patient's upper thorax. The helmet is held in place by straps under the patient armpits or layer for an infant. The helmet is fitted with a bidirectional anti-asphyxia valve which opens

automatically when pressure failed. An access port is available to facilitate nursing. The whole apparatus is connected to the ventilator using a conventional respiratory circuit. The two ports of the helmet act as gas inlet/outlets. The transparency of the device allows the children to see and interact with the parents, nurses, and environment (see Fig. 8.68a).

In a physiological study, Patroniti et al. demonstrate, in healthy volunteers, that the CPAP delivered by a helmet is as effective as face mask CPAP, higher inspiratory concentration of CO_2 was decreased with increased flow rates (Patroniti et al. 2003). In recent nonrandomized studies, oxygenation improvements were similar with the face mask and helmet for noninvasive pressure-support ventilation, but tolerance was better with the helmet (Antonelli et al. 2002, 2004). Regarding the work of breathing, the helmet was associated with less inspiratory muscle unloading and with greater patient–ventilator asynchrony in healthy volunteers (Racca et al. 2005). These findings were also described in clinical studies (Chiumello et al. 2003; Patroniti et al. 2003). In a recent physiological study, Vargas et al. confirmed that helmet NPPV was less effective in unloading the inspiratory muscles compared with the face mask when the same ventilator settings were used, but with specific ventilator settings, helmet NIV provided similar reduced effort than face mask (Vargas et al. 2009). Concerning patient–ventilator asynchrony, with specific settings the authors were able to improve the triggering-on delay but not the cycling-off delay with the helmet. The authors suggest that increasing both pressure-support level and positive end-expiratory pressure rate may be useful when providing NIV via a helmet.

In children, only case report (Piastra et al. 2004; Yildizdas et al. 2008) or small clinical studies (Piastra et al. 2004) is available on the helmet for NIV in acute setting. Codazzi et al. described in 15 children with hypoxemic ARF the use of a reduced-size soft helmet, "baby body," which is worn under the pubic region as a pair of pants (see Fig. 8.68b) (Codazzi et al. 2006). The small size for infants <10 kg has an internal gas volume of about 7 L, and the large size for infants >10 kg an internal gas volume of about 9 L. With this system the treatment was effective in improving oxygenation after 2 h. To avoid a high level of CO_2 rebreathing, high inspiratory flow rates are required, 30 L/mn in children and 40–60 L/mn in adults (Taccone et al. 2004).

In practice, the helmet should have a real place in PICU to provide NIV. Because of its comfort and good tolerance, the helmet can be used alternately with masks to provide ventilatory support. It can only be used in the PICU with intensive care ventilators and high gas flow rates to ensure CO_2 clearance.

8.3.2.4 Mouthpiece

A mouthpiece is commonly used in patients with neuromuscular disease who require daytime ventilation in addition to their nocturnal NPPV. When patients with neuromuscular disease are admitted to the ICU for respiratory failure, this interface may thus be proposed if the patient is able to maintain a seal around the mouthpiece. However, this interface is not suited for young or noncooperative children.

8.3.2.5 Humidification During NIV in Children

To avoid adverse effects of cool and dry gas on the airway epithelium, warming and humidification of the inspired gas is useful. Dryness of the upper airways is a common complaint from users of NIV in adult. The nasal mucosa can lose the capacity to heat and humidify inhaled air and the mucosa progressively dries and releases inflammation mediators (leukotrienes) with an increase vascularity. Humidification of inhaled air can prevent these adverse effects. In children, any retention of secretions in small airways is likely to increase significantly the work of breathing and should be avoided so humidification is essential. Two types of humidification devices are available, heated humidifier and heat and moisture exchanger (HME), and should be used for short-term and long-term NIV in adults. In children, only the heated humidifier should be used for NIV in acute setting because it adds less dead space. HME and heated humidifiers were compared by Jaber et al. and Lellouche et al. and they found similar results: HME was associated with significantly higher $PaCO_2$, markedly increased inspiratory effort in hypercapnic

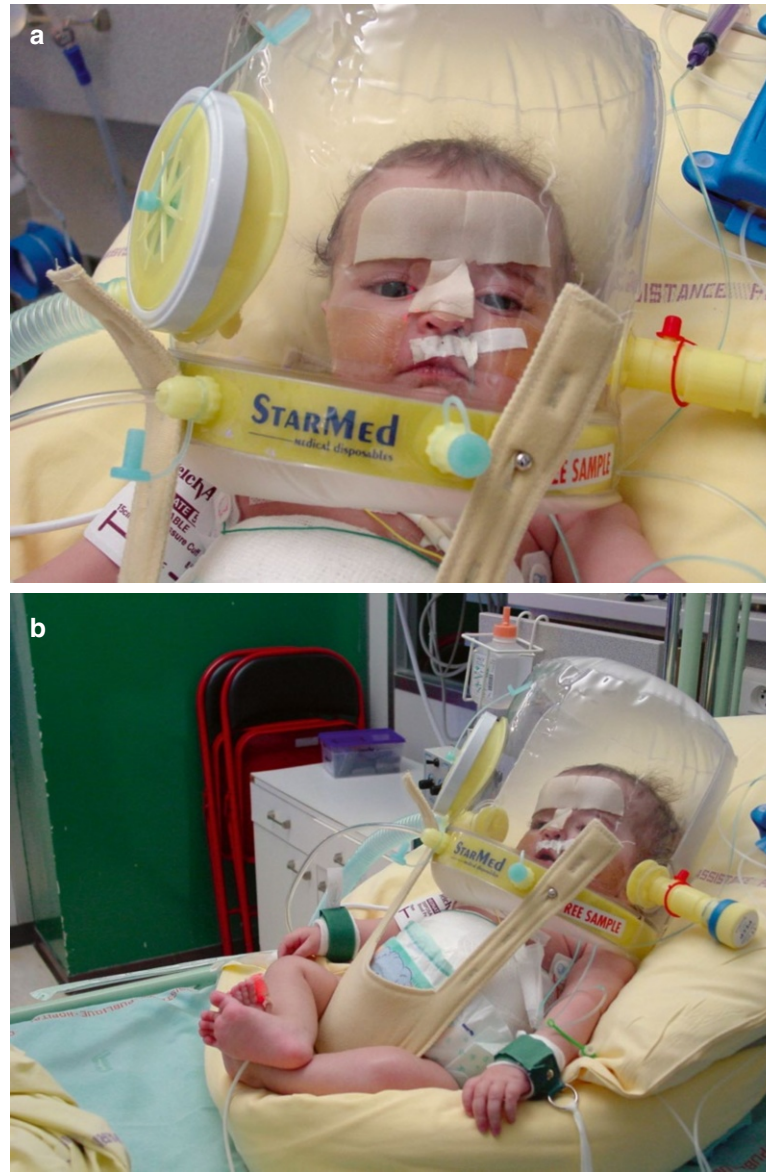


Fig. 8.68 (**a**) Helmet is connected to the ventilator using a conventional respiratory circuit. The two ports of the helmet act as gas inlet/outlets. The transparency of the device allows the children to see and interact with the parents, nurses, and environment. (**b**) Correct fitting is ensured by straps under the patient armpits or layer for infant ("baby body")

patients (Jaber et al. 2002; L'Her et al. 2005). Alveolar ventilation was similar for both but with a greater work of breathing with HME than heated humidifier. These two authors conclude that humidification devices can affect some physiological variable. Nava et al. recently recommended, based on physiological and clinical data, heated humidification during NIV for ARF to minimize work of breathing and maximize CO_2 clearance (Nava et al. 2009).

In pediatric acute setting, only heated humidifiers should be used based on adult data and clinical local experiences.

8.3.2.6 Limitations and Adverse Effects of NIV Interfaces

The noninvasive interface is a crucial determinant of the success of NPPV. It is now well known that most of NIV failure is due to technical problems including mask discomfort, leaks,

and skin lesions (Meduri et al. 1996a). Leaks are systematic in the NIV and target zero leakage is not the goal. However, the key is required to define what level of leakage is acceptable and compatible with efficient ventilation.

Among adverse effects skin lesions is a frequent complication ranging from 2 to 23 % (Gregoretti et al. 2002). Skin breakdown occurs at the areas of mask contact even only after few hours of NIV. In most clinical studies and practical experience, masks are fitted tightly in order to reduce air leaks; however, if the mask pressure exceeds the skin capillary pressure and impairs tissue perfusion, this can cause skin damage. The development of skin lesions is more likely to occur on the nasal bridge where the skin lies upon very little subcutaneous tissue on the nasal bone. Children are growing and, in addition to skin lesions, the NIV may have an impact on the growth of the facial bone of the child with facial flattening and maxillary retrusion present in 68 and 37 % of the patients only during chronic NIV and not when NIV is needed for only a few days.

Eye irritation is another problem, related to mask ventilation but less important than skin breakdown (Gregoretti et al. 2002; Meduri et al. 1996a, b).

With the helmet most of the skin injury should be avoided, but this specific interface has specific adverse effects such as axillae skin damage or the noise arising from turbulent flow at the gas inlet. Cavaliere et al. report noise levels in the helmet equal 100 dB, but the presence of a simple heat and moisture exchange filter on the inlet line significantly decrease the subjective noise perception (Costa et al. 2005).

The most important strategy to prevent adverse effects is to avoid an excessively tight fit. Moreover, having multiple interfaces for children and the ability to toggle these interfaces should avoid skin damage by changing the distribution of pressure and friction. In addition, wound-care dressing has also been used to limit skin damage. Table 8.21 resumes the ways to reduce the risk of skin damage during the NIV.

Gastric distension has been described as an adverse effect of NIV more than an adverse effect of the interface; however, the frequency of this complication is exaggerated. Most pediatricians use a nasogastric tube during ARF and during NIV to avoid gastric distension with great effect (Essouri et al. 2005).

Table 8.21 Tips to reduce the risk of skin damage during NIV in children

Proper interface type and size
Rotate various type of interfaces
Proper harness with correct fitting
Skin and mask hygiene
Thin hydrocolloid on pressure points

Conclusion

Even if the commercial availability of specific pediatric NIV interfaces is increasing, there is no perfect interface for all children in all situations. The choice of the interface requires careful evaluation of the child. The development of new devices specially designed for small patients can minimize these adverse effects when associated with increased use of the NIV.

Future Perspectives

Pressure support was introduced as mechanical ventilator mode in the 1980s. Since that time different technical advances have been introduced to allow patients to breathe spontaneously during PSV, for example, by the introduction of flow triggering. Currently patients breathing on PSV have a high incidence of asynchrony. Future advances have focused on redirecting the site of triggering from a generated at the patient's airway to one from an EMG signal from the patient's diaphragm. This signal theoretically has the advantage of decreasing trigger delay and allowing a closed-loop system to adjust the level of support to the strength of this signal.

Essentials to Remember

- The interface is a piece with a fundamental role for the success of NIV; however, specific pediatric interfaces are not commonly available.
- The right choice of the type and size of interface is a guarantee of performance and compliance with NIV.
- Education of pediatricians and nurses along with who install the interfaces to maintain a good seal without side effects should be a goal for NIV users.
- Progress in development of specific pediatric interfaces has been made, but these are still insufficient. The cooperation between physicians and industry should be developed to create adapted interfaces for the newborn to young adult.

References

Allen GB (2006) To breathe or not to breathe: is spontaneous ventilation the answer for acute lung injury? Crit Care Med 34:1844–1845

Allo JC, Beck JC, Brander L, Brunet F, Slutsky AS, Sinderby CA (2006) Influence of neurally adjusted ventilatory assist and positive end-expiratory pressure on breathing pattern in rabbits with acute lung injury. Crit Care Med 34:2997–3004

Ambalavanan N, Carlo WA (2006) Ventilatory strategies in the prevention and management of bronchopulmonary dysplasia. Semin Perinatol 30(4):192–199

Antonelli M, Conti G, Rocco M, Bufi M, De Blasi RA, Vivino G, Gasparetto A, Meduri GU (1998) A comparison of noninvasive positive-pressure ventilation and conventional mechanical ventilation in patients with acute respiratory failure. N Engl J Med 339:429–435

Antonelli M, Conti G, Pelosi P, Gregoretti C, Pennisi MA, Costa R, Severgnini P, Chiaranda M, Proietti R (2002) New treatment of acute hypoxemic respiratory failure: noninvasive pressure support ventilation delivered by helmet–a pilot controlled trial. Crit Care Med 30: 602–608

Antonelli M, Pennisi MA, Pelosi P, Gregoretti C, Squadrone V, Rocco M, Cecchini L, Chiumello D, Severgnini P, Proietti R, Navalesi P, Conti G (2004) Noninvasive positive pressure ventilation using a helmet in patients with acute exacerbation of chronic obstructive pulmonary disease: a feasibility study. Anesthesiology 100:16–24

Arnal JM, Nafati C, Wysocki M et al (2004) Utilization of adaptive support ventilation (ASV) in a polyvalent intensive care unit [abstract]. Intensive Care Med 30:S84

Arnal JM, Garcin F, Wysocki M et al (2006) Adaptive support ventilation (ASV) automatically adapts a protective ventilation in ARDS patients. Intensive Care Med 32:S120

Arnal JM, Wysocki M, Nafati C et al (2008) Automatic selection of breathing pattern using adaptive support ventilation. Intensive Care Med 34:75–81

Artigas A, Bernard GR, Carlet J et al (1998) The American-European consensus conference on ARDS, part 2: ventilatory, pharmacologic, supportive therapy, study design strategies and issues related to recovery and remodeling. Intensive Care Med 24:378–398

Aslanian P, El Atrous S, Isabey D, Valente E, Corsi D, Harf A, Lemaire F, Brochard L (1998) Effects of flow triggering on breathing effort during partial ventilatory support. Am J Respir Crit Care Med 157:135–143

Attar MA, Donn SM (2002) Mechanisms of ventilator-induced lung injury in premature infants. Semin Neonatol 7:353–360

Aziz HF, Martin JB, Moore JJ (1999) The pediatric disposable end-tidal carbon dioxide detector role in endotracheal intubation in newborns. J Perinatol 19:110–113

Bancalari E, Garcia O, Jesse MJ (1973) Effects of continuous negative pressure on lung mechanics in idiopathic respiratory distress syndrome. Pediatrics 51:485–493

Bancalari A, Gerhardt T, Bancalari E, Suguihara C, Hehre D, Reifenberg L, Goldberg RN (1987) Gas trapping with high-frequency ventilation: jet versus oscillatory ventilation. J Pediatr 110:617–622

Bates JHT (1998) Assessment of mechanics. In: Mrini JJ, Slutsky AS (eds) Physiologic basis of ventilatory support. Marcel Dekker, New York, pp 231–259

Bates JHT, Baconier P, Milic-Emili J (1988) A theoretical analysis of interrupter technique for measuring respiratory mechanics. J Appl Physiol 64:2204–2214

Baun M, Benzer H, Putensen C, Koller W (1989) Biphasic positive airway pressure (Bipap): a new form of augmented ventilation. Anaesthesist 38:452–458

Beck J, Sinderby C, Lindstrom L, Grassino A (1996) Influence of bipolar esophageal electrode positioning on measurements of human crural diaphragm electromyogram. J Appl Physiol 81:1434–1449

Beck J, Gottfried SB, Navalesi P, Skrobik Y, Comtois N, Rossini M, Sinderby C (2001) Electrical activity of the diaphragm during pressure support ventilation in acute respiratory failure. Am J Respir Crit Care Med 164:419–424

Beck J, Tucci M, Emeriaud G, Lacroix J, Sinderby C (2004) Prolonged neural expiratory time induced by mechanical ventilation in infants. Pediatr Res 55:747–754

Beck J, Weinberg J, Hamnegard CH, Spahija J, Olofson J, Grimby G, Sinderby C (2006) Diaphragmatic function in advanced duchenne muscular dystrophy. Neuromuscul Disord 16:161–167

Beck J, Campoccia F, Allo JC, Brander L, Brunet F, Slutsky AS, Sinderby C (2007) Improved synchrony and respiratory unloading by neurally adjusted ventilatory assist (nava) in lung-injured rabbits. Pediatr Res 61:289–294

Beck J, Brander L, Slutsky AS, Reilly MC, Dunn MS, Sinderby C (2008) Non-invasive neurally adjusted ventilatory assist in rabbits with acute lung injury. Intensive Care Med 34:316–323

Beck J, Reilly M, Grasselli G, Mirabella L, Slutsky AS, Dunn MS, Sinderby C (2009) Patient-ventilator interaction during neurally adjusted ventilatory assist in low birth weight infants. Pediatr Res 65:663–668

Bellani G, Patroniti N, Greco M, Foti G, Pesenti A (2008) The use of helmets to deliver non-invasive continuous positive airway pressure in hypoxemic acute respiratory failure. Minerva Anestesiol 74:651–656

Benditt JO, Pollock M, Roa J, Celli B (1993) Transtracheal delivery of gas decreases the oxygen cost of breathing. Am Rev Respir Dis 147:1207–1210

Bengtsson JA, Edberg KE (2010) Neurally adjusted ventilatory assist in children: an observational study. Pediatr Crit Care Med 11(2):253–257

Bergofsky EH, Hurewitz AN (1989) Airway insufflation: physiologic effects on acute and chronic gas exchange in humans. Am Rev Respir Dis 140:885–890

Bernstein G, Heldt GP, Mannino FL (1994) Increased and more consistent tidal volume during synchronized intermittent mandatory ventilation in newborn infants. Respir Crit Care Med 150:1444–1448

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

Bernstein G, Mannino F, Heldt G et al (1996) Randomized multicenter trial comparing synchronized and conventional intermittent mandatory ventilation in neonates. J Pediatr 128:453–463

Bhutani VK (2002) Clinical application of pulmonary function and graphics. Semin Neonatol 7:391–399

Biernson GA, Ward JE (1958) A servopressure control system for the iron lung. Proc IRE 46:628

Blanch L, Bernabe F, Lucangelo U (2005) Measurement of air trapping, intrinsic positive end-expiratory pressure and dynamic hyperinflation in mechanically ventilated patients. Respir Care 50:110–123

Bonmarchand G, Chevron V, Menard JF, Girault C, Moritz-Berthelot F, Pasquis P, Leroy J (1999) Effects of pressure ramp slope values on the work of breathing during pressure support ventilation in restrictive patients. Crit Care Med 27:715–722

Borelli M, Benini A, Denkevitz T, Acciaro C, Foti G, Pesenti A (1998) Effects of continuous negative extrathoracic pressure versus positive end expiratory pressure in acute lung injury patients. Crit Care Med 26:1025–1031

Boros SJ, Mammel MC, Coleman JM, Horcher P, Gordon MJ, Bing DR (1989) Comparison of high-frequency oscillatory ventilation and high-frequency jet ventilation in cats with normal lungs. Pediatr Pulmonol 7:35–41

Brander L, Leong-Poi H, Beck J, Brunet F, Hutchison SJ, Slutsky AS, Sinderby C (2009a) Titration and implementation of neurally adjusted ventilatory assist in critically ill patients. Chest 135:695–703

Brander L, Sinderby C, Lecomte F, Leong-Poi H, Bell D, Beck J, Tsoporis JN, Vaschetto R, Schultz MJ, Parker TG et al (2009b) Neurally adjusted ventilatory assist decreases ventilator-induced lung injury and non-pulmonary organ dysfunction in rabbits with acute lung injury. Intensive Care Med 35:1979–1989

Breatnach C, Conlon NP, Stack M, Healy M, O'Hare BP (2010) A prospective crossover comparison of neurally adjusted ventilatory assist and pressure-support ventilation in a pediatric and neonatal intensive care unit population. Pediatr Crit Care Med 11:7–11

Brochard L (2002) Intrinsic (or auto-) PEEP during controlled mechanical ventilation. Intensive Care Med 28:1376–1378

Brochard L, Lellouche F (2006) Pressure-support ventilation. In: Tobin MJ (ed) Principles and practice of mechanical ventilation. McGraw-Hill, New York, pp 221–250

Brochard L, Harf A, Lorino H, Lemaire F (1989) Inspiratory pressure support prevents diaphragmatic fatigue during weaning from mechanical ventilation. Am Rev Respir Dis 139:513–521

Brunner JX (2001) Principles and history of closed-loop controlled ventilation. Respir Care Clin N Am 7(3):341–362

Brunner JX (2002) History and principles of closed-loop control applied to mechanical ventilation. Neth J Crit Care 8:6–9

Brunner JX, Iotti GA (2002) Adaptive support ventilation (ASV). Minerva Anestesiol 68(5):365–368

Brunner JX, Laubscher TP, Banner MJ et al (1995) Simple method to measure total expiratory time constant based on the passive expiratory flow volume curve. Crit Care Med 23(6):1117–1122

Bunnell JB (2006) High-frequency ventilation: general concepts. In: Donn SM, Sinha SK (eds) Manual of neonatal respiratory care, 2nd edn. Mosby, Philadelphia

Burchardi H (1996) New strategies in mechanical ventilation for acute lung injury. Eur Respir J 9(5):1063–1072

Burke WC, Nahum A, Ravenscraft SA, Nakos G, Adams AB, Marcy TW, Marini JJ (1993) Modes of tracheal gas insufflation. Comparison of continuous and phase-specific gas injection in normal dogs. Am Rev Respir Dis 148:562–568

Burton AC, Patel DJ (1958) Effects on pulmonary vascular resistance of inflation of the rabbit lung. J Appl Physiol 12:239–246

Calderini E, Confalonieri M, Puccio PG, Francavilla N, Stella L, Gregoretti C (1999) Patient-ventilator asynchrony during noninvasive ventilation: the role of expiratory trigger. Intensive Care Med 25:662–667

Cane RD, Peruzzi WT, Shapiro BA (1991) Airway pressure release ventilation in severe acute respiratory failure. Chest 100:460–463

Cannon ML, Cornell J, Tripp-HameHamel DS et al (2000) Tidal volumes for ventilated infants should be determined with a pneumotachometer placed at

the endotracheal tube. Am J Respir Crit Care Med 162:2109–2112
Carlo WA, Ambalavanan N, Chatburn RL (2006) Classification of mechanical ventilation devices. In: Donn SM, Sinha SK (eds) Manual of neonatal respiratory care. Mosby Elsevier, Philadelphia, pp 74–80
Carney D, DiRocco J, Nieman G (2005) Dynamic alveolar mechanics and ventilator-induced lung injury. Crit Care Med 33:S122–S128
Chan V, Greenough A (1994) Comparison of weaning by patient triggered ventilation or synchronous intermittent ventilation. Acta Paediatr 83:335–337
Chang HK (1984) Mechanisms of gas transport during ventilation by high-frequency oscillation. J Appl Physiol 56:553–563
Chapman FW, Newell JC, Roy RJ (1985) A feedback controller for ventilatory therapy. Ann Biomed Eng 13:359–372
Chatburn RL (1995) Calcification of mechanical ventilators. In: Branson RD, Hess DR, Chatrburn RL (eds) Respiratory care equipment. Lippincott, Philadelphia, pp 264–293
Chatburn RL (2003) Fundamentals of mechanical ventilation. Mandu Press Ltd, Cleveland Heights
Chatburn RL, Primiano FP Jr (1998) Mathmatical models of respiratory mechanics. In: Chatburn RL, Craig KC (eds) Fundamentals of respiratory care research. Appleton & Lange, Norwalk, pp 59–100
Chatburn RL, Primiano FP Jr (2001) A new system for understanding modes of mechanical ventilation. Respir Care 46(6):604–621
Cheema IU, Ahluwalia JS (2001) Feasibility of tidal volume-guided ventilation in newborn infants: a randomized crossover trial using the volume guarantee modality. Pediatrics 107:1323–1328
Chiumello D, Pelosi P, Carlesso E, Severgnini P, Aspesi M, Gamberoni C, Antonelli M, Conti G, Chiaranda M, Gattinoni L (2003) Noninvasive positive pressure ventilation delivered by helmet vs. standard face mask. Intensive Care Med 29:1671–1679
Clark LC (1985) Introduction to fluorocarbons. Int Anesthesiol Clin 23:1–9
Clark LC, Gollan F (1966) Survival of mammals breathing organic liquids equilibrated with oxygen at atmospheric pressure. Science 152:1755–1756
Codazzi D, Nacoti M, Passoni M, Bonanomi E, Sperti LR, Fumagalli R (2006) Continuous positive airway pressure with modified helmet for treatment of hypoxemic acute respiratory failure in infants and a preschool population: a feasibility study. Pediatr Crit Care Med 7:455–460
Coles JR, Brown WA, Lampard DG (1973) Computer control of respiration and anaesthesia. Med Biol Eng 11:262–267
Colombo D, Cammarota G, Bergamaschi V, De Lucia M, Corte FD, Navalesi P (2008) Physiologic response to varying levels of pressure support and neurally adjusted ventilatory assist in patients with acute respiratory failure. Intensive Care Med 34:2010–2018
Coon RL, Zuperku EJ, Kampine JP (1978) Systemic arterial blood pH servocontrol of mechanical ventilation. Anesthesiology 49:201–204
Corrado A, Gorini M (2006) Negative pressure ventilation. In: Tobin MJ (ed) Principles and practice of mechanical ventilation. McGraw Hill, New York, pp 403–419
Corrado A et al (1996) Negative pressure ventilation in the treatment of acute respiratory failure: an old noninvasive technique reconsidered. Eur Respir J 9:1531–1544
Costa R, Navalesi P, Antonelli M, Cavaliere F, Craba A, Proietti R, Conti G (2005) Physiologic evaluation of different levels of assistance during noninvasive ventilation delivered through a helmet. Chest 128:2984–2990
Cournand A, Motley HL, Werko L, Richards DW (1948) Physiologic studies of the effect of intermittent positive pressure breathing on cardiac output in man. Am J Physiol 152:162–174
Craft AP, Bhandari V, Finer NN (2003) The sy-fi study: a randomized prospective trial of synchronized intermittent mandatory ventilation versus a high-frequency flow interrupter in infants less than 1000 g. J Perinatol 23:14–19
Curtis SE, Fuhrman BP, Howland DF, DeFrancisis M, Motoyama EK (1991) Cardiac output during liquid (perfluorocarbon) breathing in newborn piglets. Crit Care Med 19:225–230
Curtis SE, Peek JT, Kelly DR (1993) Partial liquid breathing with perflubron improves arterial oxygenation in acute canine lung injury. J Appl Physiol 75:2696–2702
D'Angelo E, Calderini E, Torri G et al (1989) Respiratory system mechanics in anesthetized-paralyzed humans: effects of flow and volume. J Appl Physiol 67:2556–2564
D'Angio CT, Chess PR, Kovacs SL et al (2005) Pressure-regulated volume control ventilation vs. synchronized intermittent mandatory ventilation for very low-birth-weight infants: a randomized controlled trial. Arch Pediatr Adolesc Med 159:868–875
Dassieu G, Brochard L et al (1998) Continuous tracheal gas insufflation enables a volume reduction strategy in hyaline membrane disease: technical aspects and clinical results. Intensive Care Med 24(10):1076–1082
Davis GM, Coates AL, Papageorgiou A, Bureau MA (1988) Direct measurement of static chest wall compliance in animal and human neonates. J Appl Physiol 65:1093–1098
Devlieger H, Daniels H, Marchal G, Moerman P, Casaer P, Eggermont E (1991) The diaphragm of the newborn infant: anatomical and ultrasonographic studies. J Dev Physiol 16:321–329
Dhand R (2005) Ventilator graphics and respiratory mechanics in the patient with obstructive lung disease. Respir Care 50:246–259
Dimitriou G, Greenough A, Kavvadia V, Laubscher B, Milner AD (1998) Volume delivery during high

frequency oscillation. Arch Dis Child Fetal Neonatal Ed 78:F148–F150
Dojat M, Brochard L, Lemaire F et al (1992) A knowledge-based system for assisted ventilation of patients in intensive care units. Int J Clin Monit Comput 9:239–250
Dongelmans DA, Veelo DP, Bindels A et al (2008) Determinant of tidal volumes with adaptive support ventilation : a multicenter observational study. Anesth Analg 107(3):932–937
Dongelmans DA, Veelo DP, Paulus F et al (2009) Weaning automation with adaptive support ventilation: a randomized controlled trial in cardiothoracic surgery patients. Anesth Analg 108(2):565–571
Donn SM (ed) (1997) Neonatal and paediatric pulmonary graphics: principles and clinical applications. Future Publishing, Armonk
Donn SM, Becker MA (2003) Special ventilator technique & modalities 1. Patient-triggered ventilation. In: Goldsmith JP, Karotkin EH (eds) Assisted ventilation of the neonate, 4th edn. WB Saunders, Philadelphia, pp 203–218
Donn SM, Blane CE (1985) Endotracheal tube movement in the preterm infant: oral versus nasal intubation. Ann Otol Rhinol Laryngol 94:18–20
Donn SM, Boon W (2009) Mechanical ventilation of the neonate: should we target volume or pressure? Respir Care 54:1236–1243
Donn SM, Kuhns LR (1980) Mechanism of endotracheal tube movement with change of head position in the neonate. Pediatr Radiol 9:37–40
Donn SM, Sinha SK (1998) Controversies in patient- triggered ventilation. Clin Perinatol 25:49–61
Donn SM, Sinha SK (2001) Newer modes of mechanical ventilation for neonates. Curr Opin Pediatr 13:99–103
Donn SM, Sinha SK (2006) Minimising ventilator induced lung injury in preterm infants. Arch Dis Child Fetal Neonatal Ed 91:F226–F230
Donn SM, Nicks JJ, Becker MA (1994) Synchronized ventilation of preterm with respiratory distress syndrome. J Perinatol 14:90–94
Donn SM, Greenough A, Sinha SK (2000) Patient triggered ventilation. Arch Dis Child Fetal Neonatal Ed 83:F224–F226
Downs JB, Stock MC (1987) Airway pressure release ventilation: a new concept in ventilatory support. Crit Care Med 15:459–461
Dreyfuss D, Saumon G (1998) Ventilator-induced lung injury: lessons from experimental studies. Am J Respir Crit Care Med 157:294–323
Easa D, Mundie GT, Finn KC, Hashiro G, Balaraman V (1994) Continuous extrathoracic pressure versus positive end expiratory pressure in piglets after saline lung lavage. Pediatr Pulmunol 17:161–168
East TD, Westenskow DR, Pace NL, Nelson LD (1982) A microcomputer based differential lung ventilation system. IEEE Trans Biomed Eng 29:736–740
East TD, Andriano KP, Pace NL (1986) Computer-controlled optimization of positive end-expiratory pressure. Crit Care Med 14:792–797
East TD, Tolle BS, McJames BS et al (1991) A non-linear closed-loop controller for oxygenation based on a clinically proven fifth dimensional quality surface. Anesthesiology 75(3A):A468
Emeriaud G, Beck J, Tucci M, Lacroix J, Sinderby C (2006) Diaphragm electrical activity during expiration in mechanically ventilated infants. Pediatr Res 59: 705–710
Ershowsky P, Krieger B (1987) Changes in breathing pattern during pressure support ventilation. Respir Care 32:1011–1016
Essouri S, Nicot F, Clement A, Garabedian EN, Roger G, Lofaso F, Fauroux B (2005) Noninvasive positive pressure ventilation in infants with upper airway obstruction: comparison of continuous and bilevel positive pressure. Intensive Care Med 31:574–580
Esteban A, Alia I, Gordo F, Fernandez R, Solsona JF, Vallverdu I, Macias S, Alleque JM, Blanco J, Carriedo D, Leon M, de la Cal MA, Taboada F, GonzalezdeValasco J, Palazon E, Carrizosa F, Tomas R, Suarez J, Goldwasser RS (1997) Extubation outcome after spontaneous breathing trials with T-tube or pressure support ventilation. Am J Respir Crit Care Med 156:459–465
Fagon Y, Hance J, Chastre J et al (1993) Nosocomial pneumonia in ventilated patients: a cohort study evaluating attributable mortality and hospital stay. Am J Med 94:281–288
Farias J-A, Retta A, Alia I, Olazarri F, Esteban A, Golubicki A, Allende D, Maliarchuk O, Peltzer C, Ratto ME, Zalazar R, Garea M, Moreno EG (2001) A comparison of two methods to perform a breathing trial before extubation in pediatric intensive care patients. Intensive Care Med 27:1649–1654
Ferguson SD (2006) Sechrist model IV – 200 SAVI ventilators. In: Donn SM Sinha SK (ed) Manual of neonatal respiratory care, 2nd edn. Elsevier, Philadelphia, pp 269–272
Fredberg JJ, Glass GM, Boynton BR, Frantz ID 3rd (1987) Factors influencing mechanical performance of neonatal high-frequency ventilators. J Appl Physiol 62: 2485–2490
Froese AB, Bryan AC (1974) Effects of anesthesia and paralysis on diaphragmatic mechanics in man. Anesthesiology. 41(3):242–55
Froese AB (1997) High-frequency oscillatory ventilation for adult respiratory distress syndrome: let's get it right this time! Crit Care Med 25:906–908
Frumin JM (1957) Clinical use of a physiological respirator producing N2O amnesia-analgesia. Anesthesiology 18:290–299
Garner W, Downs JB, Stock MC, Rasanen J (1988) Airway pressure release ventilation (APRV): a human trial. Chest 94:779–781
Gattioni L, Presenti A, Torresin A et al (1986) Adult respiratory distress syndrome profiles by computed tomography. J Thorac Imaging 1:25–30
Gerstmann DR, Fouke JM, Winter DC, Taylor AF, deLemos RA (1990) Proximal, tracheal, and alveolar pressures during high-frequency oscillatory

ventilation in a normal rabbit model. Pediatr Res 28:367–373
Gorini M, Villella G, Ginanni R et al (2002) Effect of a assist negative pressure ventilation by microprocessor-based iron lung on breathing effort. Thorax 57:258–262
Grasso S, Terragni P, Mascia L et al (2004) Airway pressure–time curve profile (stress index) detects tidal recruitment/hyperinflation in experimental acute lung injury. Crit Care Med 32:1018–1027
Grasso F et al (2008) Negative pressure ventilation, better oxygenation and less lung injury. Am J Respir Crit Care Med 177:412–418
Greenough A, Morley CJ (1984) Pneumothorax in infants who fight ventilator. Lancet 1:689
Greenough A, Pool J (1988) Neonatal patient triggered ventilation. Arch Dis Child 63:394–397
Greenough A, Dimitriou G, Pendergast M et al (2008) Synchronized mechanical ventilation for respiratory support in newborn infants. Cochrane Database Syst Rev (1), CD000456
Greenspan JS, Wolfson MR, Rubenstein SD, Shaffer TH (1989) Liquid ventilation of preterm baby. Lancet 2:1095
Gregoretti C, Confalonieri M, Navalesi P, Squadrone V, Frigerio P, Beltrame F, Carbone G, Conti G, Gamna F, Nava S, Calderini E, Skrobik Y, Antonelli M (2002) Evaluation of patient skin breakdown and comfort with a new face mask for non-invasive ventilation: a multi-center study. Intensive Care Med 28:278–284
Gruber PC, Gomersall CD, Leung P et al (2008) Randomized controlled trial comparing adaptive-support ventilation with pressure-regulated volume-controlled ventilation with automode in weaning patients after cardiac surgery. Anesthesiology 109(1):81–87
Guilleminault C, Pelayo R, Clerk A, Leger D, Bocian RC (1995) Home nasal continuous positive airway pressure in infants with sleep-disordered breathing. J Pediatr 127:905–912
Gupta S, Sinha SK, Donn SM (2009) The effect of two levels of pressure support ventilation on tidal volume delivery and minute ventilation in preterm infants. Arch Dis Child Fetal Neonatal Ed 94:F80–F83
Habib RH, Pyon KH, Courtney SE (2002) Optimal high-frequency oscillatory ventilation settings by nonlinear lung mechanics analysis. Am J Respir Crit Care Med 166:950–953
Harris TR, Bunnell J (1993) High-frequency jet ventilation in clinical neonatology. In: Pomerance JJ, Richardson CJ (eds) Neonatology for the clinician. Appleton & Lange, Norwalk, pp 311–324
Hatcher D, Watanabe H, Ashbury T, Vincent S, Fisher J, Froese A (1998) Mechanical performance of clinically available, neonatal, high-frequency, oscillatory-type ventilators. Crit Care Med 26:1081–1088
Helm E et al (2009) Use of dynamic Ct scan in acute respiratory distress syndrome (ARDS) with comparison of positive and negative ventilation. Eur Radiol 19:50–57
Henderson Y, Chillingworth FD, Whitney JL (1915) The respiratory dead space. Am J Physiol 38:1–19
Henzler D, Dembrinski R, Bensberg R et al (2004) Ventilation with biphasic positive airway pressure in experimental lung injury: influence of transpulmonary pressure on as exchange and hemodynamics. Intensive Care Med 30:935–943
Herber-Jonat S, Rieger-Fackeldey E, Hummler H, Schulze A (2006) Adaptive mechanical backup ventilation for preterm infants on respiratory assist modes – a pilot study. Intensive Care Med 32:302–308
Herrera CM, Gerhardt T, Claure N et al (2002) Effects of volume-guaranteed synchronized intermittent mandatory ventilation in preterm infants recovering from respiratory failure. Pediatrics 110:529–533
Hershenson MB, Colin AA, Wohl ME, Stark AR (1990) Changes in the contribution of the rib cage to tidal breathing during infancy. Am Rev Respir Dis 141:922–925
Heulitt MJ, Desmond B (1998) Lung protective strategies in pediatric patients with ARDS. Respir Care 43(11):952–960
Heulitt MJ, Anders M, Benham D (1995) Acute respiratory distress syndrome in pediatric patients: redirecting therapy to reduce iatrogenic lung injury. Respir Care 40:74–85
Heulitt MJ, Clement KC, Holt SJ, Thurman TL, Jo CH (2012) Neurally triggered breaths have reduced response time, work of breathing, and asynchrony compared with pneumatically triggered breaths in a recovering animal model of lung injury. Pediatr Crit Care Med 13(3):e195–e203, Online publication only. E-PAS2008: [2125.7]
Hill NS (1986) Clinical application of body ventilators. Chest 90:897–905
Hird MF, Greenough A (1990) Causes of failure of neonatal patient triggered ventilation. Early Hum Dev 23:101–108
Hird MF, Greenough A (1991a) Comparison of triggering systems for neonatal patients. Arch Dis Child 66:426–428
Hird MF, Greenough A (1991b) Patient triggered ventilation using a flow triggered system. Arch Dis Child 66:1140–1142
Honey G, Bleak T, Karp T, MacRitchie A, Null D Jr (2007) Use of the Duotron transporter high frequency ventilator during neonatal transport. Neonatal Netw 26:167–174
Hummler HD, Gerhardt T, Gonzales A et al (1996) Patient- triggered ventilation in neonates: comparison of a flow and impedance- triggered systems. Am J Respir Crit Care Med 154:1049–1054
Hurewitz AN, Bergofsky EH, Vomero E (1991) Airway insufflation: increasing flow rates progressively reduce dead space in respiratory failure. Am Rev Respir Dis 144:1229–1233
Hurst J, Branson R, Davis K, Barrette R (1989) Cardiopulmonary effects of pressure support ventilation. Arch Surg 124:1067–1070
Imanaka H, Nishimura M, Takeuchi M, Kimball WR, Yahagi N, Kumon K (2000) Autotriggering caused by

cardiogenic oscillation during flow-triggered mechanical ventilation. Crit Care Med 28:402–407
Iotta GA, Brochard L, Lemaire F (1991) Mechanical ventilation and weaning. In: Zapol W, Tinker J (eds) Care of the critically ill patient. Springer, London, pp 457–478
Iotti GA, Braschi A, Brunner JX et al (1995a) Noninvasive evaluation of instantaneous total mechanical activity of the respiratory muscles during pressure support ventilation. Chest 108:208–215
Iotti GA, Braschi A, Brunner JX et al (1995b) Respiratory mechanics by least square fitting in mechanically ventilated patients: applications during paralysis and during pressure support ventilation. Intensive Care Med 21:406–413
Iotti G, Brunner JX, Braschi A, Laubscher TP et al (1996) Closed-Loop control of airway occlusion pressure at 0.1 s (P0.1) applied to pressure-support ventilation: algorithm and application in intubated patients. Crit Care Med 24:771–779
Iotti G, Belliato M, Polito A et al (2005) Safety and effectiveness of adaptive support ventilation (ASV) in acute respiratory failure. Intensive Care Med 31:S168
Jaber S, Chanques G, Matecki S, Ramonatxo M, Souche B, Perrigault PF, Eledjam JJ (2002) Comparison of the effects of heat and moisture exchangers and heated humidifiers on ventilation and gas exchange during non-invasive ventilation. Intensive Care Med 28:1590–1594
Jaber S, Sebbane M, Verzilli D et al (2009) Adaptive support and pressure support ventilation behavior in response to increased ventilatory demand. Anesthesiology 110(3):620–627
Jonson B, Similowski T, Levy P, Viires N, Pariente R (1990) Expiratory flushing of airways a method to reduce deadspace ventilation. Eur Respir J 3:1202–1205
Jouvet P, Hubert P, Isabey D, Pinquier D, Dahan E, Cloup M, Harf A (1997) Assessment of high-frequency neonatal ventilator performances. Intensive Care Med 23:208–213
Jubran A, Van de Graff WB, Tobin MJ (1995) Variability of patient-ventilator interaction with pressure support ventilation in patients with chronic obstructive pulmonary disease. Am J Respir Crit Care Med 152: 129–136
Kacmarek RM, Chipman D (2006) Basic principles of ventilator machinery. In: Tobin MJ (ed) Principles and practice of mechanical ventilation. McGraw-Hill, New York, pp 72–75
Keszler M, Abubakar K (2004) Volume guarantee: stability of tidal volume and incidence of hypocarbia. Pediatr Pulmonol 38:240–245
Keszler M, Durand D (2001) High-frequency ventilation. In: Donn SM, Wiswell T (eds) Clinics in perinatology: advances in mechanical ventilation and surfactant therapy. W.B. Saunders & Co, Philadelphia, pp 579–607
Keszler M, Donn SM, Bucciarelli RL, Alverson DC, Hart M, Lunyong V, Modanlou HD, Noguchi A, Pearlman SA, Puri A et al (1991) Multicenter controlled trial comparing high-frequency jet ventilation and conventional mechanical ventilation in newborn infants with pulmonary interstitial emphysema. J Pediatr 119:85–93
Keszler M, Modanlou HD, Brudno DS et al (1997) Multi-center controlled clinical trial of high-frequency jet ventilation in preterm infants with uncomplicated respiratory distress syndrome. Pediatrics 100: 593–599
Khan Y, Heckmatt JZ, Dubowitz V (1996) Sleep studies and supportive ventilatory treatment in patients with congenital muscle disorders. Arch Dis Child 74:195–200
Khoo MC, Slutsky AS, Drazen JM, Solway J, Gavriely N, Kamm RD (1984) Gas mixing during high-frequency ventilation: an improved model. J Appl Physiol 57:493–506
Klain M, Smith RB (1977) High frequency percutaneous transtracheal jet ventilation. Crit Care Med 5:280–287
Kleinman BS, Frey K, VanDrunen M et al (2002) Motion of the diaphragm in patients with chronic obstructive pulmonary disease while spontaneously breathing versus during pressure breathing after anesthesia and neuromuscular blockade. Anesthesiology 97:298–305
Kornecki A, Kavanagh BP (2007) Mechanical ventilation. In: Wheeler DS, Wong HR, Shanley TP (eds) Pediatric critical care medicine basic science and clinical evidence. Springer, London, pp 412–425
Krumpe P (1981) Continuous negative external chest pressure decreases transvascular water transport in sheep after pseudomonas bacteriemia. J Clin Invest 67:264–273
Krumpe PE, Zidulka A, Urbanetti J, Anthonisen NR (1977) Comparison of the effect of continuous negative external chest pressure and positive end expiratory pressure on cardiac index in dogs. Am Rev Respir Dis 115:39–45
Kudoh I, Andoh T, Doi H, Kaneko K, Okomura F (1992) Continuous negative extrathoracic pressure ventilation, lung water volume, and central blood volume. Chest 101:530–533
Kylstra JA (1970) Required properties of a liquid for respiration. Fed Proc 29:1724
Kylstra JA (1974) Liquid breathing. Undersea Biomed Res 1:259–269
Kylstra JA, Paganelli CV, Lanphier EH (1966) Pulmonary gas exchange in dogs ventilated with hyperbarically oxygenated liquid. J Appl Physiol 21:177–184
Laubscher TP, Heinrichs W, Weiler N et al (1994a) An adaptive lung ventilation controller. IEEE Trans Biomed Eng 41:51–59
Laubscher TP, Frutiger A, Fanconi S et al (1994b) Automatic selection of tidal volume, respiratory frequency, and minute ventilation in intubated ICU patients as start up procedure for closed loop controlled ventilation. Int J Clin Monit Comput 11(1): 19–30

Laureen H, Ronald GP (2000) Flow- triggering, pressure triggering and auto triggering during mechanical ventilation. Crit Care Med 28:579–581

Lawson RW, Vines DL, Shelledy DC et al (2001) The response of adaptive support ventilation (ASV) to varying spontaneous minute ventilation at different compliance and resistance in a lung model. Respir Care 01:210

Leach CL, Greenspan JS, Rubenstein SD et al (1996) Partial liquid ventilation with perflubron in premature infants with severe respiratory distress syndrome. The LiquiVent Study Group. N Engl J Med 335:761–767

Lecomte F, Brander L, Jalde F, Beck J, Qui H, Elie C, Slutsky AS, Brunet F, Sinderby C (2009) Physiological response to increasing levels of neurally adjusted ventilatory assist (nava). Respir Physiol Neurobiol 166:117–124

Leipala JA, Iwasaki S, Milner A, Greenough A (2004) Accuracy of the volume and pressure displays of high frequency oscillators. Arch Dis Child Fetal Neonatal Ed 89:F174–F176

Leung P, Jubran A, Tobin MJ (1997) Comparison of assisted ventilator modes on triggering, patient effort, and dyspnea. Am J Respir Crit Care Med 155:1940–1948

Levine S, Nguyen T, Taylor N, Friscia ME, Budak MT, Rothenberg P, Zhu J, Sachdeva R, Sonnad S, Kaiser LR et al (2008) Rapid disuse atrophy of diaphragm fibers in mechanically ventilated humans. N Engl J Med 358:1327–1335

L'Her E, Deye N, Lellouche F, Taille S, Demoule A, Fraticelli A, Mancebo J, Brochard L (2005) Physiologic effects of noninvasive ventilation during acute lung injury. Am J Respir Crit Care Med 172:1112–1118

Li KK, Riley RW, Guilleminault C (2000) An unreported risk in the use of home nasal continuous positive airway pressure and home nasal ventilation in children: mid-face hypoplasia. Chest 117:916–918

Lista G, Colnaghi M, Castoldi F et al (2004) Impact of targeted-volume ventilation on lung inflammatory response in preterm infants with respiratory distress syndrome (RDS). Pediatr Pulmonol 37:510–514

Lockhat D, Langleben A, Zidulka D (1992) Haemodynamic differences between continual positive and two types of negative pressure ventilation. Am Rev Respir Dis 146:677–680

Lofaso F, Isabey D, Lorino H, Harf A, Scheid P (1992) Respiratory response to positive and negative inspriatory pressure in humans. Respir Physiol 89:75–88

Long SE, Menon AS, Kato H, Goldstein RS, Slutsky AS (1988) Constant oxygen insufflation (COI) in a ventilatory failure model. Am Rev Respir Dis 138:630–635

Lourens MS, van den Berg B, Aerts JGJV et al (2000) Expiratory time constants in mechanically ventilated patients with and without COPD. Intensive Care Med 26:1612–1618

Lowe CA, Shaffer TH (1981) Increased pulmonary vascular resistance during liquid ventilation. Undersea Biomed Res 8:229–238

Lowe CA, Shaffer TH (1986) Pulmonary vascular resistance in the fluorocarbon-filled lung. J Appl Physiol 60:154–159

Lowe C, Tuma RF, Sivieri EM, Shaffer TH (1979) Liquid ventilation: cardiovascular adjustments with secondary hyperlactatemia and acidosis. J Appl Physiol 47:1051–1057

Lynch PR, Wilson JS, Shaffer TH, Cohen N (1983) Decompression incidence in air- and liquid-breathing hamsters. Undersea Biomed Res 10:1–10

MacIntyre NR (1986) Respiratory function during pressure support ventilation. Chest 89:677–683

MacIntyre N (1987) Pressure support ventilation: effects on ventilatory reflexes and ventilatory muscle work load. Respir Care 32:447–457

Mainali ES, Greene C, Rozycki HJ, Gutcher GR (2007) Safety and efficacy of high-frequency jet ventilation in neonatal transport. J Perinatol 27:609–613

Marcus CL, Ward SL, Mallory GB, Rosen CL, Beckerman RC, Weese-Mayer DE, Brouillette RT, Trang HT, Brooks LJ (1995) Use of nasal continuous positive airway pressure as treatment of childhood obstructive sleep apnea. J Pediatr 127:88–94

Marraro GA (2003) Innovative practices of ventilatory support with pediatric patients. Pediatr Crit Care Med 4:8–20

Matic I, Majeric-Kogler V (2004) Comparison of pressure support and T-tube weaning from mechanical ventilation: randomized prospective study. Croat Med J 45:162–166

Matthews WH, Balzer RH, Shelburne JD, Pratt PC, Kylstra JA (1978) Steady-state gas exchange in normothermic, anesthetized, liquid-ventilated dogs. Undersea Biomed Res 5:341–354

McCallionN, Davis PG, Morley CJ (2005) Volume-targeted versus pressure-limited ventilation in the neonate. Cochrane Database Syst Rev (3):D003666

McDermott I, Bach JR, Parker C, Sortor S (1989) Custom-fabricated interfaces for intermittent positive pressure ventilation. Int J Prosthodont 2:224–233

Mead J (1960) Control of respiratory frequency. J Appl Physiol 15:325–336

MEAD J, WHITTENBERGER JL, RADFORD EP (1957) Surface tension as a factor in pulmonary volume-pressure hysteresis. J Appl Physiol 10:191–196

Meduri GU, Cook TR, Turner RE, Cohen M, Leeper KV (1996a) Noninvasive positive pressure ventilation in status asthmaticus. Chest 110:767–774

Meduri GU, Turner RE, Abou-Shala N, Wunderink R, Tolley E (1996b) Noninvasive positive pressure ventilation via face mask. First-line intervention in patients with acute hypercapnic and hypoxemic respiratory failure. Chest 109:179–193

Mehta S, Hill NS (2001) Noninvasive ventilation. Am J Respir Crit Care Med 163:540–577

Mehta S, McCool FD, Hill NS (2001) Leak compensation in positive pressure ventilators: a lung model study. Eur Respir J 17:259–267

Meredith KS, de Lemos RA et al (1988) Role of lung injury in the pathogenesis of hyaline membrane

disease in premature baboons. J Appl Physiol 66: 2150–2158
Messier SE, Digeronimo RJ, Gillette RK (2009) Comparison of the Sensormedics 3100A and Bronchotron transporter in a neonatal piglet ARDS model. Pediatr Pulmonol 44:693–700
Milic-Emili J, Polysongsang Y (1986) Respiratory mechanics in the adult respiratory distress system. Crit Care Clin 2:573–584
Milic-Emili J, Gottfried SB, Rossi A (1987) Noninvasive measurement of respiratory mechanics in ICU patients. Int J Clin Monit Comput 4:11–20
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(5):386–395
Minuto A, Giacomini M, Giamundo B, Tartufari A, Denkewitz T, Marzorati S, Palandi A, Stabile L, Iapichino G (2003) Non-invasive mechanical ventilation in patients with acute cardiogenic pulmonary edema. Minerva Anestesiol 69:835–840
Mitamura Y, Mikami T, Sugawara H et al (1971) An optimally controlled respirator. IEEE Trans Biomed Eng 18:330–337
Mitamura Y, Mikami T, Yamamoto K (1975) A dual control system for assisting respiration. Med Biol Eng 13:846–853
Moerer O, Beck J, Brander L, Costa R, Quintel M, Slutsky AS, Brunet F, Sinderby C (2008) Subject-ventilator synchrony during neural versus pneumatically triggered non-invasive helmet ventilation. Intensive Care Med 34:1615–1623
Moore RE, Clark LC (1985) Chemistry of fluorocarbons in biomedical use. Int Anesthesiol Clin 23: 11–24
Muller E, Kolobow T, Mandava S, Jones M, Vitale G, Aprigliano M, Yanada K (1993) How to ventilate lungs as small as 12,5% of normal: the new technique of intratracheal pulmonary ventilation. Pediatr Res 34:606–610
Mundie TG, Kuuleialoha F, Venkataraman B, Sneha S, Easa D (1995) Continuous negative extrathoracic pressure and positive and expiratory pressure. A comparative study in Escherichia coli endotoxin-treated neonatal piglets. Chest 107:249–255
Musante G, Schulze A, Gerhardt T, Everett R, Claure N, Schaller P, Bancalari E (2001) Respiratory mechanical unloading decreases thoraco-abdominal asynchrony and chest wall distortion in preterm infants. Pediatr Res 49:175–180
Nahum A, Burke WC, Ravenscraft SA, Marcy TW, Adams AB, Crooke PS, Marini JJ (1992a) Lung mechanics and gas exchange during pressure-control ventilation in dogs. Augmentation of CO2 elimination by an intratracheal catheter. Am Rev Respir Dis 146:965–973
Nahum A, Ravenscraft SA, Nakos G, Burke WC, Adams AB, Marcy TW, Marini JJ (1992b) Tracheal gas insufflation during pressure-control ventilation. Effect of catheter position, diameter, and flow rate. Am Rev Respir Dis 146:1411–1418
Nahum A, Ravenscraft SA, Nakos G, Adams AB, Burke WC, Marini JJ (1993) Effect of catheter flow direction on CO2 removal during tracheal gas insufflation in dogs. J Appl Physiol 75:1238–1246
Nakhajavan FK, Palmer WH, McGregor M (1966) Influence of respiration on venous return in pulmonary emphysema. Circulation 32:8–17
Nakos G, Zakinthinos S, Kotanidou A, Tsagaris H, Roussos C (1994) Tracheal gas insufflation reduces the tidal volume while PaCO2 is maintained constant. Intensive Care Med 20:407–413
Nava S, Navalesi P, Gregoretti C (2009) Interfaces and humidification for noninvasive mechanical ventilation. Respir Care 54:71–84
Nicks JJ, Becker MA, Donn SM (1994) Bronchopulmonary dysplasia: response to pressure support ventilation. J Perinatol 14:495–497
Nilsestuen JO, Hargett KD (2005) Using ventilator graphics to identify patient-ventilator asynchrony. Respir Care 50:202–234
Oca MJ, Becker MA, Dechert RE, Donn SM (2002) Relationship of neonatal endotracheal tube size and airway resistance. Respir Care 47:994–997
Ohlson KB, Westenskow DR, Jordan WS (1982) A microprocessor based feedback controller for mechanical ventilation. Ann Biomed Eng 10:35–48
Openshaw P, Edwards S, Helms P (1984) Changes in rib cage geometry during childhood. Thorax 39:624–627
Ophoven JP, Mammel MC, Gordon MJ, Boros SJ (1984) Tracheobronchial histopathology associated with high-frequency jet ventilation. Crit Care Med 12:829–832
Osorio W, Claure N, D'Ugard C et al (2005) Effects of pressure support during an acute reduction of synchronized intermittent mandatory ventilation in preterm infants. J Perinatol 25:412–416
Otis AB, Fenn WO, Rahn H (1950) Mechanics of breathing in man. J Appl Physiol 2:592–607
Papastamelos C, Panitch HB, England SE, Allen JL (1995) Developmental changes in chest wall compliance in infancy and early childhood. J Appl Physiol 78:179–184
Parret L, Stucki P, Scalfaro P et al (2000) Adaptive support ventilation (ASV) can prevent ventilator-induced lung injury in children. Pediatr Crit Care Med 1:1–41
Patroniti N, Foti G, Manfio A, Coppo A, Bellani G, Pesenti A (2003) Head helmet versus face mask for non-invasive continuous positive airway pressure: a physiological study. Intensive Care Med 29:1680–1687
Perlman JM, Goodman K, Kreusser KL et al (1985) Reduction in intraventricular hemorrhage by elimination of fluctuating cerebral blood-flow velocity in preterm infants with respiratory distress syndrome. N Engl J Med 312:1353–1357
Petrucci N, Iacovelli W (2007) Lung protective ventilation strategy for the acute respiratory distress syndrome. Cochrane Database Syst Rev (3):CD003844

Petter AH, Chiolero RL, Cassina T et al (2003) Automatic "respirator weaning" with adaptive support ventilation: the effect on duration of endotracheal intubation and patient management. Anesth Analg 97:1743–1750

Piastra M, Antonelli M, Chiaretti A, Polidori G, Polidori L, Conti G (2004) Treatment of acute respiratory failure by helmet-delivered non-invasive pressure support ventilation in children with acute leukemia: a pilot study. Intensive Care Med 30:472–476

Pillow JJ (2005) High-frequency oscillatory ventilation: mechanisms of gas exchange and lung mechanics. Crit Care Med 33:S135–S141

Pillow JJ, Neil H, Wilkinson MH, Ramsden CA (1999) Effect of I/E ratio on mean alveolar pressure during high-frequency oscillatory ventilation. J Appl Physiol 87:407–414

Pillow JJ, Wilkinson MH, Neil HL, Ramsden CA (2001) In vitro performance characteristics of high-frequency oscillatory ventilators. Am J Respir Crit Care Med 164:1019–1024

Pillow JJ, Sly PD, Hantos Z, Bates JH (2002) Dependence of intrapulmonary pressure amplitudes on respiratory mechanics during high-frequency oscillatory ventilation in preterm lambs. Pediatr Res 52:538–544

Pillow JJ, Sly PD, Hantos Z (2004) Monitoring of lung volume recruitment and derecruitment using oscillatory mechanics during high-frequency oscillatory ventilation in the preterm lamb. Pediatr Crit Care Med 5:172–180

Piowtrowski A, Sobala W, Kawczynski P (1997) Patient-initiated, pressure-regulated, volume-controlled ventilation compared with intermittent mandatory ventilation in neonates: a prospective, randomized study. Intensive Care Med 23:975–981

Pokora T, Bing D, Mammel M, Boros S (1983) Neonatal high-frequency jet ventilation. Pediatrics 72:27–32

Polin RA, Fox WW, Abman SH (2004) Liquid Ventilation, Fetal and Neonatal Physiology, 3rd edn. Elsevier/Saunders, Philadelphia, p 989

Poon CS, Huang KA (1987) An assist device for selective reduction of the work of breathing. Biomed Sci Instrum 23:161–167

Prinainak G, Kondali E, Georgopoulos D (2003) Effects of the flow wave form method of triggering and cycling on patient – ventilator interaction during pressure support. Intensive Care Med 29:1950–1959

Putensen C, Rasanen J, Lopez FA (1994a) Effects of interfacing between spontaneous breathing and mechanical cycles on ventilation-perfusion distribution in canine lung injury. Anesthesiology 1994(81):921–930

Putensen C, Rasanen J, Lopez FA (1994b) Ventilaiton perfusion distribution during mechanical ventilation with superimposed spontaneous breathing in canine lung injury. Am J Respir Crit Care Med 150:101–108

Putensen C, Mutz NJ, Putensen-Himmer G, Zinserling J (1999) Spontaneous breathing during ventilatory support improves ventilation-perfusion distributions in patients with acute respiratory distress syndrome. Am J Respir Crit Care Med 159:1241–1248

Putensen C, Muders T, Varelmann D, Wrigge H (2006) The impact of spontaneous breathing during mechanical ventilation. Curr Opin Crit Care 12:13–18

Racca F, Appendini L, Gregoretti C, Stra E, Patessio A, Donner CF, Ranieri VM (2005) Effectiveness of mask and helmet interfaces to deliver noninvasive ventilation in a human model of resistive breathing. J Appl Physiol 99:1262–1271

Ranieri VM, Guiliani R, Fiore T et al (1994) Volume-pressure curve of the respiratory system predicts effects of PEEP in ARDS :"occlusion" versus "constant flow" technique. Am J Respir Crit Care Med 149:19–27

Ranieri VM, Zhang H, Mascia L et al (2000) Pressure–time curve predicts minimally injurious ventilatory strategy in an isolated rat lung model. Anesthesiology 93:1320–1328

Rasanen J (1994) Airway pressure release ventilation. In: Tobin MJ (ed) Principles and practice of mechanical ventilation. Mc-Graw-Hill, Inc, New York, pp 341–348

Rasanen J, Downs JB, Stock MC (1987) Cardiovascular effects of conventional positive pressure ventilation and airway pressure release ventilation. Chest 92:390

Raszynski A, Hultquist A, Latif H, Sussmane J, Soler M, Alam A, Brao J, Amor J, Kicheeney B, Kolobow T, Wolsfsdorf J (1993) Rescue from pediatric ECMO with prolonged hybrid intratracheal pulmonary ventilation. A technique for reducing deadspace ventilation and preventing induced lung injury. ASAIO J 39:681–685

Ravenscraft SA, Burke WC, Nahum A, Adams AB, Nakos G, Marcy TW, Marini JJ (1993) Tracheal gas insufflation augments CO2 clearance during mechanical ventilation. Am Rev Respir Dis 148:345–351

Reardon CC, Christiansen D, Barnett ED, Cabral HJ (2005) Intrapulmonary percussive ventilation vs incentive spirometry for children with neuromuscular disease. Arch Pediatr Adolesc Med 159:526–531

Reyes ZC, Claure N, Tauscher MK et al (2006) Randomized, controlled trial comparing synchronized intermittent mandatory ventilation and synchronized intermittent mandatory ventilation plus pressure support in preterm infants. Pediatrics 118:1409–1417

Richard JC, Carlucci A, Breton L, Langlais N, Jaber S, Maggiore S, Fougere S, Harf A, Brochard L (2002) Bench testing of pressure support ventilation with three different generations of ventilators. Intensive Care Med 28:1049–1057

Rodarte JR, Rehder K (1986) Dynamic of respiration. In: Macklem PT, Mead J (eds) Handbook of physiology section 3: the respiratory system, Mechanics of breathing. American Physiologic Society, Baltimore, pp 131–144

Rodeberg DA, Housinger TA, Greenhalgh DG, Maschinot NE, Warden GD (1994) Improved ventilatory function in burn patients using volumetric diffusive respiration. J Am Coll Surg 179:518–522

Rossi A, Gottfried SB, Higgs BD et al (1985a) Respiratory mechanics in mechanically ventilated patients. J Appl Physiol 58:1849–1858

Rossi A, Gottfried SB, Zochi L et al (1985b) Measurement of static compliance of the total respiratory system in patients with acute respiratory failure during mechanical ventilation. Am Rev Respir Dis 131:672–677

Rudowski R, Bokliden A, Carstensen A et al (1991) Multivariable optimization of mechanical ventilation. A linear programming approach. Int J Clin Monit Comput 8:107–115

Sanders RD (1967) Two ventilating attachments for bronchoscopes. Del Med J 39:170

Sanyal SK, Mitchell C, Huges WT, Cacaces J (1975) Continuous negative chest wall pressure as therapy for severe respiratory distress in older children. Chest 68:143–148

Sanyal SK, Avery T, Mohinder K, Hughes W, Harris K (1977a) Continuous negative chest wall pressure therapy for assisting ventilation in older children with progressive respiratory insufficiency. Acta Paediatr Scand 66:451–456

Sanyal SK, Avery TL, Huges WT, Harris KS (1977b) Management of severe respiratory insufficiency due to pneumocystis carinii pneumonitis in immunosuppressed hosts. Am Rev Respir Dis 116:223–231

Sargent JW, Seffl RJ (1970) Properties of perfluorinated liquids. Fed Proc 29:1699–1703

Sarkar S, Donn SM (2007) In support of pressure support. Clin Perinatol 34:117–128

Sassoon CSH, Light RW, Lodia R, Sieck GC, Mahutte CK (1991) Pressure–time product during continuous positive airway pressure, pressure support ventilation and T-piece during weaning from mechanical ventilation. Am Rev Respir Dis 143:459–479

Sassoon CSH, Lodia R, Rheeman CH, Kuei JH, Light RW, Mahutte CK (1992) Inspiratory muscle work of breathing during flow-by, demand-flow, and continuous-flow systems in patients with chronic obstructive pulmonary disease. Am Rev Respir 145:1219–1222

Sassoon CS, Zhu E, Caiozzo VJ (2004) Assist-control mechanical ventilation attenuates ventilator-induced diaphragmatic dysfunction. Am J Respir Crit Care Med 170:626–632

Saxton GA, Myers GH (1953) An electro-mechanical substitute for the human respiratory center. Clin Res Proc 1:116–117

Schaller P, Schulze A (1991) A ventilator generating a positive or negative internal compliance. Ups J Med Sci 96:219–234

Schettino GP, Tucci MR, Sousa R, Valente Barbas CS, Passos Amato MB, Carvalho CR (2001) Mask mechanics and leak dynamics during noninvasive pressure support ventilation: a bench study. Intensive Care Med 27:1887–1891

Schmidt M, Demoule A, Mirkovic T, Duguet A, Bautin N, Straus C, Gottfried S, Similowski T (2008) Effet du neuro-asservissement de la ventilation assistée (nava) sur la variabilité et le chaos ventilatoire. Rev Mal Respir 25:1199, abstract

Schonhofer B, Sortor-Leger S (2002) Equipment needs for noninvasive mechanical ventilation. Eur Respir J 20:1029–1036

Schulz V, Ulmer HV, Erdmann W et al (1974) A system of continuously patient CO2 -controlled ventilation. Pneumonologie 150:319–325

Schulze A (2006) Respiratory gas conditioning and humidification. In: Donn SM, Sinha SK (eds) Manual of neonatal respiratory care, 2nd edn. Mosby, Philadelphia

Schulze A, Bancalari E (2001) Proportional assist ventilation in infants. Clin Perinatol 28:561–578

Schulze A, Schaller P (1997) Assisted mechanical ventilation using resistive and elastic unloading. Semin Neonatol 2:105–114

Schulze A, Schaller P, Gehrhardt B, Mädler HJ, Gmyrek D (1990) An infant ventilator technique for resistive unloading during spontaneous breathing. Results in a rabbit model of airway obstruction. Pediatr Res 28:79–82

Schulze A, Schaller P, Dinger J, Winkler U, Gmyrek D (1991) High frequency oscillatory ventilation near resonant frequency of the respiratory system in rabbits with normal and surfactant depleted lungs. Eur J Pediatr 150:671–675

Schulze A, Schaller P, Jonzon A, Sedin G (1993a) Assisted mechanical ventilation using elastic unloading: a study in cats with normal and injured lungs. Pediatr Res 34:600–605

Schulze A, Schaller P, Töpfer A, Kirpalani H (1993b) Resistive and elastic unloading to assist spontaneous breathing does not change functional residual capacity. Pediatr Pulmonol 16:170–176

Schulze A, Rich W, Schellenberg L, Schaller P, Heldt GP (1998a) Effects of different gain settings during assisted mechanical ventilation using respiratory unloading in rabbits. Pediatr Res 44:132–138

Schulze A, Suguihara C, Gerhardt T, Schaller P, Claure N, Everett R, Bancalari E (1998b) Effects of respiratory mechanical unloading on thoracoabdominal motion in meconium-injured piglets and rabbits. Pediatr Res 43:191–197

Schulze A, Gerhardt T, Musante G, Schaller P, Claure N, Everett R, Gomez-Marin O, Bancalari E (1999a) Proportional assist ventilation in low birth weight infants with acute respiratory disease. A comparison to assist/control and conventional mechanical ventilation. J Pediatr 135:339–344

Schulze A, Jonzon A, Sindelar R, Schaller P, Dammann V, Sedin G (1999b) Assisted mechanical ventilation using combined elastic and resistive unloading in cats with severe respiratory failure: effects on gas exchange and phrenic nerve activity. Acta Paediatr 88:636–641

Schulze A, Rieger-Fackeldey E, Gerhardt T, Claure N, Everett R, Bancalari E (2007) Randomized crossover comparison of proportional assist ventilation and patient-triggered ventilation in extremely low birth weight infants with evolving chronic lung disease. Neonatology 92:1–7

Servant GM, Nicks JJ, Donn SM et al (1992) Feasibility of applying flow-synchronized ventilation to very low birth weight infants. Respir Care 37:249–253

Shaffer TH (1987) A brief review: liquid ventilation. Undersea Biomed Res 14:169–179

Shaffer W (2004) Liquid ventilation. In: Fetal and neonatal physiology. Saunders, Philadelphia, pp 985–1001

Shaffer TH, Rubenstein D, Moskowitz D, Delivoria-Papadopoulos M (1976) Gaseous exchange and acid–base balance in premature lambs during liquid ventilation since birth. Pediatr Res 10:227–231

Shaffer TH, Douglas PR, Lowe CA, Bhutani VK (1983) The effects of liquid ventilation on cardiopulmonary function in preterm lambs. Pediatr Res 17:303–306

Shaffer TH, Lowe CA, Bhutani VK, Douglas PR (1984) Liquid ventilation: effects on pulmonary function in distressed meconium-stained lambs. Pediatr Res 18:47–52

Shneerson JM (1991) Non invasive and domiciliary ventilation: negative pressure technique. Thorax 46:131–135

Sinderby C, Lindstrom L, Grassino AE (1995) Automatic assessment of electromyogram quality. J Appl Physiol 79:1803–1815

Sinderby CA, Beck JC, Lindstrom LH, Grassino AE (1997) Enhancement of signal quality in esophageal recordings of diaphragm EMG. J Appl Physiol 82:1370–1377

Sinderby C, Beck J, Spahija J, Weinberg J, Grassino A (1998) Voluntary activation of the human diaphragm in health and disease. J Appl Physiol 85:2146–2158

Sinderby C, Navalesi P, Beck J, Skrobik Y, Comtois N, Friberg S, Gottfried SB, Lindstrom L (1999) Neural control of mechanical ventilation in respiratory failure. Nat Med 5:1433–1436

Singh J, Sinha SK, Clarke P et al (2006) Mechanical ventilation of very low birth weight infants: is volume or pressure a better target variable? J Pediatr 149:308–313

Singh J, Sinha S, Alsop E et al (2009) Long term follow-up of very low birth weight infants from a neonatal volume versus pressure mechanical ventilation trial. Arch Dis Child Fetal Neonatal Ed 94:F360–F362

Sinha SK, Donn SM (1996) Advances in neonatal conventional ventilation. Arch Dis Child Fetal Neonatal Ed 75:F135–F140

Sinha SK, Donn SM (2001) Volume controlled ventilatory modes for the newborn: variations on a theme. Clin Perinatol 8:547–560

Sinha SK, Donn SM (2002) Weaning newborns from mechanical ventilation. Semin Neonatol 7:421–428

Sinha SK, Donn SM (2006a) Pressure support ventilation. In: Donn SM, Sinha SK (eds) Manual of neonatal respiratory care, 2nd edn. Mosby, Philadelphia

Sinha SK, Donn SM (2006b) Difficult extubation in babies receiving assisted mechanical ventilation. Arch Dis Child Educ Pract Ed 91:ep42–ep46

Sinha SK, Nicks JJ, Donn SM (1996) Graphic analysis of pulmonary mechanics in neonates receiving assisted ventilation. Arch Dis Child Fetal Neonatal Ed 75:F213–F218

Sinha SK, Donn SM, Gavey J et al (1997) Randomised trial of volume controlled versus time cycled, pressure limited ventilation in preterm infants with respiratory distress syndrome. Arch Dis Child 77:F202–F205

Sivieri EM, Moskowitz GD, Shaffer TH (1981) Instrumentation for measuring cardiac output by direct fick method during liquid ventilation. Undersea Biomed Res 8:75–83

Skaburskis M, Helal R, Zidulka A (1987) Haemodynamic effects of external continuous negative pressure ventilation compared with those of continuous positive pressure ventilation in dogs with acute lung injury. Am Rev Respir Dis 136:886–891

Skaburskis M, Rivero D, Fitchett A, Zidulka A (1990) Haemodynamic effects of continuous negative chest pressure ventilation in heart failure. Am Rev Respir Dis 141:938–943

Skabuskis M, Michel RP, Gatensy A, Zidulka A (1989) Effect of negative pressure ventilation on lung water in permeability pulmonary edema. J Appl Physiol 66:2223–2230

Slutsky AS (1984) Mechanisms affecting gas transport during high-frequency oscillation. Crit Care Med 12:713–717

Slutsky AS, Drazen JM (2002) Ventilation with small tidal volumes. N Engl J Med 347:630–631

Slutsky AS, Menon AS (1987) Catheter position and blood gases during constant-flow ventilation. J Appl Physiol 62:513–519

Slutsky AS, Kamm RD, Rossing TH, Loring SH, Lehr J, Shapiro AH, Ingram RH Jr, Drazen JM (1981) Effects of frequency, tidal volume, and lung volume on CO2 elimination in dogs by high frequency (2-30 Hz), low tidal volume ventilation. J Clin Invest 68: 1475–1484

Slutsky AS, Watson J, Leith DE, Brown R (1985) Tracheal insufflation of O2 (TRIO) at low flow rates sustains life for several hours. Anesthesiology 63:278–286

Soo Hoo GW, Santiago S, Williams AJ (1994) Nasal mechanical ventilation for hypercapnic respiratory failure in chronic obstructive pulmonary disease: determinants of success and failure. Crit Care Med 22:1253–1261

Spahija J, Beck J, de Marchie M, Comtois A, Sinderby C (2005) Closed-loop control of respiratory drive using pressure-support ventilation: target drive ventilation. Am J Respir Crit Care Med 171:1009–1014

Spahija J, de Marchie M, Albert M, Bellemare P, Delisle S, Beck J, Sinderby C (2010) Patient-ventilator interaction during pressure support ventilation and neurally adjusted ventilatory assist. Crit Care Med 38:518–526

Spitzer AR, Butler S, Fox WW (1989) Ventilatory response to combined high frequency jet ventilation and conventional mechanical ventilation for the rescue treatment of severe neonatal lung disease. Pediatr Pulmonol 7:244–250

Stenqvist O (2003) Practical assessment of respiratory mechanics. Br J Anaesth 91:92–105

Stock MC, Downs JB, Frolicher D (1987) Airway pressure release ventilation. Crit Care Med 15: 462–466

Stresemann E, Votteri BA, Slatter FP (1969) Washout of anatomical deadspace for alveolar hypoventilation. Respiration 26:425–434

Strickland JH, Hasson JH (1991) A computer controlled ventilator weaning system. Chest 100:1096–1099

Suleymanci DS, Marchese A, Garbarini MS et al (2008) Adaptive support ventilation (ASV): an appropriate mechanical ventilation strategy for ARDS ? Anesthesiology 109:A1598

Sulzer CF, Chiolero R, Chassot PG et al (2001) Adaptive support ventilation for fast tracheal extubation after cardiac surgery: a randomized controlled study. Anesthesiology 95:1339–1345

Suter PM, Fairley HB, Isenberg MD (1978) Effect of tidal volume and positive end expiratory pressure on compliance during mechanical ventilation. Chest 73:158–162

Sviri S, Statz O, Stav D et al (2007) Four year experience with adaptive support ventilation in a medical intensive care unit. Intensive Care Med 33:S89

Sydow M, Burchardi H, Ephraim E, Zielmann S, Crozier TA (1994) Long-term effects of two different ventilatory modes on oxygenation in acute lung injury: comparison of airway pressure release ventilation and volume-controlled inverse ratio ventilation. Am J Respir Crit Care Med 149:1550–1556

Sznajder JI, Becker CJ, Crawford GP, Wood LDH (1989) Combination of constant-flow and continuous positive-pressure ventilation in canine pulmonary edema. J Appl Physiol 67:817–823

Taccone P, Hess D, Caironi P, Bigatello LM (2004) Continuous positive airway pressure delivered with a "helmet": effects on carbon dioxide rebreathing. Crit Care Med 32:2090–2096

Tarczy-Hornoch P (1994) In-situ interfacial tension during liquid ventilation. Pediatr Res 35:355A

Tarczy-Hornoch P (1995) Lung compliance during total and partial liquid ventilation vs. exogenous surfactant. Pediatr Res 37:355A

Tarczy-Hornoch P, Hildebrandt J, Standaert TA, Jackson JC (1998) Surfactant replacement increases compliance in premature lamb lungs during partial liquid ventilation in situ. J Appl Physiol 84:1316–1322

Tassaux D, Dalmas E, Gratadour P et al (2002) Patient–ventilator interactions during partial ventilatory support: a preliminary study comparing the effects of adaptive support ventilation with synchronized intermittent mandatory ventilation plus inspiratory pressure support. Crit Care Med 30(4):801–807

Tassaux D, Michotte J, Gainnier M, Jolliet P (2003) Effects of adjustable expiratory trigger on delayed cycling during pressure support in obstructive disease. Am J Respir Crit Care Med 167:A301

Teague WG (2003) Noninvasive ventilation in the pediatric intensive care unit for children with acute respiratory failure. Pediatr Pulmonol 35:418–426

Thille AW, Rodriguez P, Cabello B, Lellouche F, Brochard L (2006) Patient-ventilator asynchrony during assisted mechanical ventilation. Intensive Care Med 32:1515–1522

Thille AW, Cabello B, Galia F, Lyazidi A, Brochard L (2008) Reduction of patient-ventilator asynchrony by reducing tidal volume during pressure-support ventilation. Intensive Care Med 34:1477–1486

Thome U, Pohlandt F (1998) Effect of the TI/TE ratio on mean intratracheal pressure in high-frequency oscillatory ventilation. J Appl Physiol 84:1520–1527

Thome U, Kossel H, Lipowsky G, Porz F, Furste HO, Genzel-Boroviczeny O, Troger J, Oppermann HC, Hogel J, Pohlandt F (1999) Randomized comparison of high-frequency ventilation with high-rate intermittent positive pressure ventilation in preterm infants with respiratory failure. J Pediatr 135:39–46

Tobin MJ, Perez W, Guenther SM, Semmes BJ, Mador MJ, Allen SJ, Lodato RF, Dantzker DR (1986) The pattern of breathing during successful and unsuccessful trials of weaning from mechanical ventilation. Am Rev Respir Dis 134:1111–1118

Tokioka H, Saito S, Kosaka F (1989) Effect of pressure support ventilation on breathing pattern and respiratory work. Intensive Care Med 15:491–494

Tokioka H, Tanaka T, Ishizu T, Fukushima T, Iwaki T, Nakamura Y, Kosogabe Y (2001) The effect of breath termination criterion on breathing patterns and the work of breathing during pressure support ventilation. Anesth Analg 92:161–165

Tsuboi T, Ohi M, Kita H, Otsuka N, Hirata H, Noguchi T, Chin K, Mishima M, Kuno K (1999) The efficacy of a custom-fabricated nasal mask on gas exchange during nasal intermittent positive pressure ventilation. Eur Respir J 13:152–156

Valentine DD, Hammond MD, Downs JB, Sears NJ, Sims WR (1991) Distribution of ventilation and perfusion with different modes of mechanical ventilation. Am Rev Respir Dis 142:1262–1266

Van de Graff WB, Gordey K, Dornseif SE, Dries DJ, Kleinman BS, Kumar P, Mathru M (1991) Pressure support. Changes in ventilatory pattern and components of the work of breathing. Chest 100:1082–1089

van Genderingen HR, van Vught AJ, Duval EL, Markhorst DG, Jansen JR (2002) Attenuation of pressure swings along the endotracheal tube is indicative of optimal distending pressure during high-frequency oscillatory ventilation in a model of acute lung injury. Pediatr Pulmonol 33:429–436

Vargas F, Thille A, Lyazidi A, Campo FR, Brochard L (2009) Helmet with specific settings versus facemask for noninvasive ventilation. Crit Care Med 37:1921–1928

Venegas JG, Fredberg JJ (1994) Understanding the pressure cost of ventilation: why does high-frequency ventilation work? Crit Care Med 22:S49–S57

Waisel DB, Fackler JC, Brunner JX et al (1995) PEFIOS: an expert closed-loop oxygenation algorithm. Medinfo 8:1132–1136

Waters KA, Everett FM, Bruderer JW, Sullivan CE (1995) Obstructive sleep apnea: the use of nasal CPAP in 80 children. Am J Respir Crit Care Med 152: 780–785

Watson JW, Burwen DR, Kamm RD, Brown R, Slutsky AS (1986) Effect of flow rate on blood gases during constant flow ventilation in dogs. Am Rev Respir Dis 133:626–629

Watson K, Al-Khadra S, Thompson JE et al (1999) Evaluation of the effect of endotracheal tube leak on the performance of Hamilton Galileo ventilator in the adaptive ventilation mode in the pediatric setting. Respir Care R107

Wilson JM, Thompson JR, Schnitzer JJ, Bower LK, Lillehei CW, Perlman ND, Kolobow TJ (1993) Intratracheal pulmonary ventilation and congenital

diaphragmatic hernia: a report of two cases. J Pediatr Surg 28:484–487
Wiswell TE, Graziani LJ, Kornhauser MS et al (1996) High-frequency jet ventilation in the early management of respiratory distress syndrome is associated with a greater risk for adverse outcomes. Pediatrics 98:1035–1043
Wolf GK, Arnold JH (2005) Noninvasive assessment of lung volume: respiratory inductance plethysmography and electrical impedance tomography. Crit Care Med 33:S163–S169
Wolfson MR (1995) Effect of intra-tracheal PFC on pulmonary blood flow in surfactant treated preterm lambs. Physiol Zool 68:71
Wolfson MR, Shaffer TH (1990) Liquid ventilation during early development: theory, physiologic processes and application. J Dev Physiol 13:1–12
Wolfson MR, Greenspan JS, Shaffer TH (1996) Pulmonary administration of vasoactive substances by perfluorochemical ventilation. Pediatrics 97:449–455
Wong M (1967) Effects of continuous pressure breathing on right ventricular volumes. J Appl Physiol 22:1053–1060
Wrigge H, Zinserling J, Neumann P et al (2003) Spontaneous breathing improves lung aeration in oleic-acid induced lung injury. Anesthesiology 99:376–384
Wu CC, Yang SS, Chen CC et al (2004) The setting of minute volume in adaptive support ventilation. Intensive Care Med 30:S19
Wysocki M, Brunner JX (2007) Close loop ventilation: an emerging standard of care? Crit Care Clin 23:223–240
Wysocki M, Cracco C, Teixeira A, Mercat A, Diehl JL, Lefort Y, Derenne JP, Similowski T (2006) Reduced breathing variability as a predictor of unsuccessful patient separation from mechanical ventilation. Crit Care Med 34:2076–2083
Yañez LJ, Yunge M, Emilfork M, Lapadula M, Alcántara A, Fernández C, Lozano J, Contreras M, Conto L, Arevalo C, Gayan A, Hernández F, Pedraza M, Feddersen M, Bejares M, Morales M, Mallea F, Glasinovic M, Cavada G (2008) A prospective, randomized, controlled trial of noninvasive ventilation in pediatric acute respiratory failure. Pediatr Crit Care Med 9:484–489
Yildizdas D, Yilmaz HL, Erdem S (2008) Treatment of cardiogenic pulmonary oedema by helmet-delivered non-invasive pressure support ventilation in children with scorpion sting envenomation. Ann Acad Med Singapore 37:230–234
Yilmaz M, Gajic O (2008) Optimal ventilator settings in acute lung injury and acute respiratory distress syndrome. Eur J Anaesthesiol 25:89–96
Younes M (1992) Proportional assist ventilation, a new approach to ventilatory support. Theory. Am Rev Respir Dis 145:114–120
Younes M, Puddy A, Roberts D, Light RB, Quesada A, Taylor K, Oppenheimer L, Cramp H (1992) Proportional assist ventilation. Results of an initial clinical trial. Am Rev Respir Dis 145:121–129
Yu C, He WG, So JM et al (1987) Improvement in arterial oxygenation control using multiple-model adaptive control procedures. IEEE Trans Biomed Eng 8: 567–574
Zahorec M, Kovacikova L, Martanovic P, Skrak P, Kunovsky P (2009) The use of high-frequency jet ventilation for removal of obstructing casts in patients with plastic bronchitis. Pediatr Crit Care Med 10:e34–e36
Zhu G, Shaffer TH, Wolfson MR (2004) Continuous tracheal gas insufflation during partial liquid ventilation in juvenile rabbits with acute lung injury. J Appl Physiol 96(4):1415–1424
Zhu GF, Zhang W et al (2006) Effects of continuous tracheal gas insufflation during pressure limited ventilation on pulmonary surfactant in rabbits with acute lung injury. Chin Med J (Engl) 119(17): 1415–1420
Zimová-Herknerová M, Plavka R (2006) Expired tidal volumes measured by hot-wire anemometer during high-frequency oscillation in preterm infants. Pediatr Pulmonol 41:428–433