

What is the method of choice for ventilating a patient non invasively? This is one of the most commonly asked questions and yet no one is able to answer since no comparative studies have been published except for a few physiological studies which did not show statistically significant differences between the techniques, except better patient-ventilator synchrony in a few cases. Certainly it is easier to state that the pressure modes (i.e., pressure support and pressure controlled) are much more widely used in clinical practice. Table 6.1 shows estimated percentages of use of the various different modes during episodes of acute respiratory failure, based on published studies.

In this chapter, we describe the main characteristics of the most important types of ventilation, recalling that only the assisted modes (i.e., modes in which the patient can trigger the ventilator) are discussed, since NIV, by definition, can only be applied in patients who have a minimum of respiratory autonomy. There is a lot of confusion between the various abbreviations used for the different modes because, for problems of copyright, the same type of ventilation is named differently depending on the ventilator. For example, proportional-assisted ventilation (PAV) is called that with some ventilators, but by other names with other machines. Another term that creates considerable confusion is BiPAP<sup>®</sup>, which written in this way is the name of a ventilator, but which has now become synonymous with bilevel ventilation. Furthermore, this acronym should not be confused for BiPAP<sup>®</sup>, a mode that we shall describe later, developed and available under this name with *Draeger* ventilators. So much for wanting to keep things simple...

---

## 6.1 Continuous Positive Airway Pressure

It may surprise some readers, but we have not included CPAP under the section of ventilation modes (see below). This is because it is not actually a true method of ventilation.

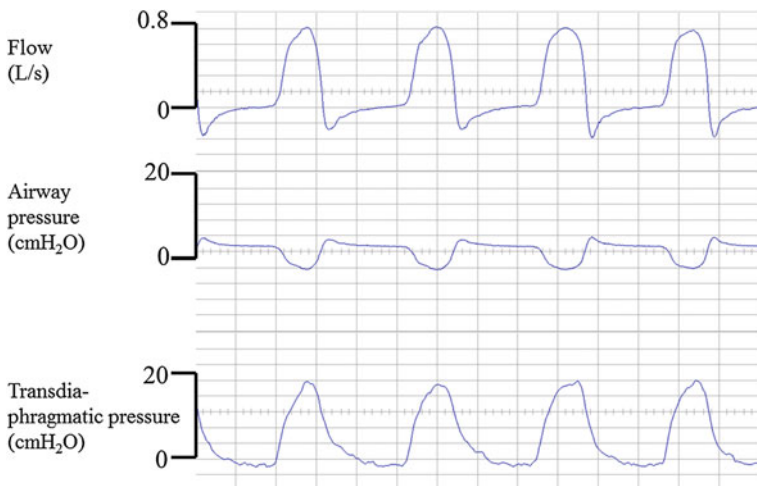
**Table 6.1** Estimated percentage use of different modes of NIV during acute respiratory failure

• Pressure support	54 %
• Pressure controlled	14 %
• Volume assisted	4 %
• Proportional assisted	3 %
• CPAP	23 %
• Others	2 %

CPAP is, in fact, spontaneous breathing in which ventilation is entrusted entirely to the patient, while the ventilator or pressure generator has the task of maintaining a pre-set positive pressure, i.e., higher than atmospheric pressure, constant for the whole of inspiration (Fig. 6.1). During CPAP, no inspiratory aid is delivered at a positive pressure and for this reason it is incorrect to define CPAP as ventilatory support, according to the previously described equation of motion.

The operator must simply regulate the established level of pressure and the sensitivity of the ventilator, which varies depending on the system used (continuous or on-demand flow). CPAP is often confused in common language with extrinsic PEEP.

The former, as its name indicates, is continuous delivery of pressure, while the latter is involved only in the expiratory phase during some other methods of positive pressure ventilation, such as volume assisted/controlled (A/C) ventilation or pressure support ventilation (PSV), pressure controlled ventilation (PCV), or proportional assist ventilation (PAV).

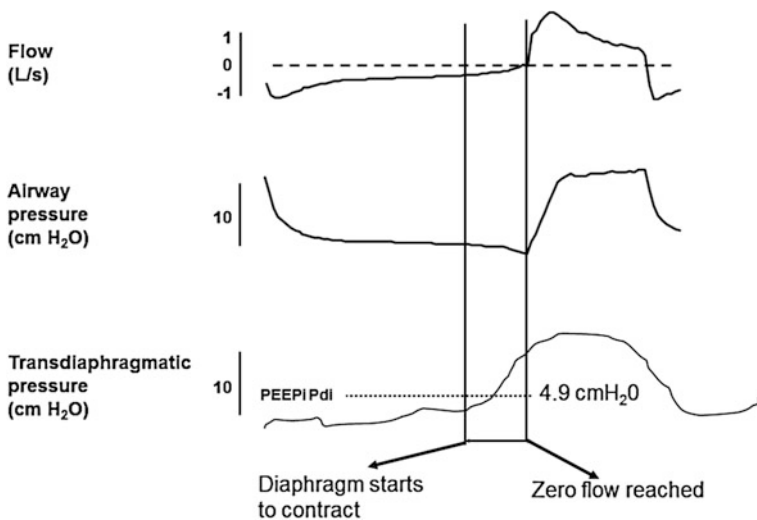


**Fig. 6.1** Patient ventilated with CPAP

### 6.1.1 Applications

Since it is a totally spontaneous mode, it is clear that the CPAP must only be applied in patients with an intact respiratory drive whose respiratory muscles function well. The physiological alterations induced by CPAP, and, therefore, its indications, differ according to the underlying pathology.

In patients with COPD with hypercapnic acute respiratory failure, CPAP can offset the negative effect of the intrinsic PEEP ( $PEEP_i$ ), which we recall contributes substantially (by even more than 60 %) to the work of the inspiratory muscles, during an episode of acute respiratory failure. In any case, great care must be given to the value set, since this must not exceed that of the  $PEEP_i$ , in order to avoid further hyperinflation in subjects who are already working with increased lung volumes. This entails a reduction in the maximal force of the respiratory muscles which then have to work in a still more unfavorable part of the length/tension curve and an increase in the threshold load that the patient has to overcome before starting a breath. Remember that the dynamic  $PEEP_i$  recorded in these patients with acute respiratory failure rarely exceeds the threshold of 6–8  $cmH_2O$ , while we sometimes see patients with COPD who are being ventilated with levels of CPAP over 10  $cmH_2O$ . This is probably because it is impossible to monitor the value of  $PEEP_i$  adequately, except by measuring transdiaphragmatic pressure ( $P_{di}$ ), as illustrated in Fig. 6.2. This figure shows clearly that the  $PEEP_i$  is defined as the part of the transdiaphragmatic pressure expended “uselessly” before the flow returns to normal, i.e., to the value at which the respiratory system is in an equilibrium.



**Fig. 6.2** Recognition of intrinsic PEEP

CPAP is still sometimes used in intensive care units in attempts to wean patients with COPD from mechanical ventilation, but the risk of hyperinflation with this level of pressure must never be underestimated.

To our knowledge, there is only one published study on the use of CPAP in hypercapnic acute respiratory failure and we do not, therefore, feel that we can suggest its use in this pathology, except perhaps in association with inspiratory support.

The most rational use of CPAP is in those disorders characterized by nonhypercapnic acute respiratory failure, above all in cases of acute cardiogenic pulmonary edema, but also in cases of thoracic trauma complicated by rib fractures, burns, and in the treatment or prevention of atelectasis. The mechanism through which CPAP improves the state of oxygenation in these conditions is related to the effect that the positive pressure has in contributing to improving lung compliance (“keeping the alveoli open”). In the case of acute cardiogenic pulmonary edema, the hemodynamic effect is equally important and is discussed in detail in the chapter dedicated to the use of NIV in this disorder.

There are three systems through which CPAP can be delivered. The first is the so-called CPAP circuit, or continuous flow system, which includes a series of components (gas blender, reservoir, humidifier, and PEEP valve) through which fresh gases pass at a flow rate of about 30 L/m. This apparatus has the advantage of being inexpensive, easily constructed, and can be assembled by hand. The other two systems of administering CPAP depend on the characteristics of the ventilator.

Some of the old ventilators had an on-demand system (*demand flow*), whereas the more recent ones use a continuous flow system called, depending on the manufacturer, *flow-by* or *bias-flow*. The advantage of this latter system is that it reduces the work of the inspiratory muscles considerably and is widely used when CPAP is delivered via a traditional ventilator, particularly during trials of spontaneous breathing in patients intubated with a T tube. In practice, as far as regards the use of CPAP in NIV, the *stand-alone system*, that is, separate from the ventilator, is definitely the most widely employed, because of its ease of use.

---

## 6.2 Volume Modes

A simple rule for understanding how a ventilator mode works is to ask yourself what is/are the variable/s determined by the operator (independent variable/s) and what are their consequences (dependent variable/s). In the final analysis, the person who determines the dependent variables is the patient, through involuntary mechanisms (the mechanical properties of the respiratory system) or voluntary ones (respiratory drive, respiratory rate, etc.).

## 6.2.1 Assisted/Controlled Ventilation

### 6.2.1.1 Independent and Dependent Variables During A/C Ventilation

During A/C ventilation, the independent variables (Fig. 6.3) are, logically, the tidal volume set by the operator, the sensitivity of the inspiratory trigger (when this setting is possible) and the time in which this volume is delivered, expressed as the inspiratory time ( $T_i$ ) or, in some ventilators, as flow.

Remember that the volume is nothing other than the integration of the flow; thus, for a set tidal flow, the velocity of the flow determines the  $T_i$  and vice versa. The dependent variables are the airway pressure and respiratory rate.

### 6.2.1.2 Applications

This is the oldest mode of ventilation but, as mentioned earlier, is now not often used for NIV. It is still popular in North America and countries with a similar school of thought (Australia, South Africa, India, and Central-Southern America) in patients ventilated invasively, while in Europe PSV, PCV, or BiPAP are currently used after the first few days of ventilation even in patients with acute respiratory distress syndrome.

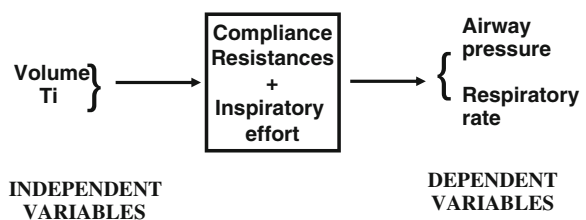
A/C ventilation is a so-called volume-related mode of ventilation. As implicitly indicated from its abbreviation, it can be totally controlled when the sensitivity of the trigger is cancelled and the patient cannot interact with the ventilator, or assisted.

In some ventilators, the two modes are separate and are denoted by the abbreviations CMV and AMV (for controlled mechanical ventilation and assisted mechanical ventilation, respectively), while in most cases they are grouped as a single mode under the abbreviation ACV or A/C with the possibility of excluding or not the trigger.

In the case of “pure” controlled ventilation, most patients also need sedation or even neuromuscular blockade to obtain greater adaptation to this mode, which is typically used only in the first hours of ventilation in severely hypoxic patients.

During assisted ventilation, the sensitivity of the trigger is determined by the operator and the patient is able, having overcome the threshold value with an inspiratory effort, to activate the ventilator. In any case, a minimum frequency is set in order to allow effective ventilation if the patient does not start to take a breath in a period of time that depends on the respiratory rate which has been set. For example, if a minimum respiratory rate of 10 breaths/min is set, every full

**Fig. 6.3** Volume assisted ventilation



breath is quantified as taking 6 s (60/10); if, after this period, the ventilator is not triggered, it automatically starts inflation at a constant volume. Too high a back-up frequency can cause alkalosis, inhibit the patient's respiratory drive or, in the case of a patient with COPD, induce dynamic hyperinflation. There are no apparent advantages of volume A/C ventilation during NIV compared to the more classical pressure methods, since physiological studies have disproven a commonplace belief that the work of respiratory muscles is reduced more during A/C than during other modes of ventilation such as pressure support. It is, therefore, an error to think that volume A/C is the mode of ventilation that minimizes the effort of inspiratory muscles.

The major disadvantages of A/C ventilation include its hemodynamic effects. The cardiac output depends predominantly on venous return, which is determined by the pressure gradient between the right atrium and the systemic venous pressure. Volume-targeted ventilation causes an increase in intrathoracic pressure during inspiration, with a consequent increase in right atrial pressure and decrease in venous return.

One field in which A/C ventilation is still very popular is home ventilation of the patient who cannot be weaned and is, therefore, being ventilated through a tracheotomy tube.

## **6.2.2 Synchronized Intermittent Mandatory Ventilation**

Intermittent mandatory ventilation (IMV) or SIMV is a mode of ventilation that was already studied in the 1950s and that had some success until the 1980s when it was more or less abandoned in clinical practice in many European countries, although remaining very popular in North America and other non-European countries. There are no studies on the use of SIMV during NIV. SIMV was a ventilatory mode originally proposed for the ventilatory treatment of neonates and was used later for weaning post-operative patients and others in whom weaning was difficult.

### **6.2.2.1 Independent and Dependent Variables During SIMV**

Some mandatory breaths, which are set in volume or pressure support or controlled ventilation, are established by the operator (independent variables). Thus, some dependent variables are derived from the type of SIMV used (pressure or volume), as is the timing of these breaths. During the nonassisted breaths, it is the patient who determines his respiratory pattern. In practice, SIMV is a ventilatory support in which a series of breaths are supplied obligatorily with a volume- or pressure-targeted mode by the ventilator but, between one breath and another, the patient can breathe without any support or with a set level of CPAP. In this way, the patient can autonomously vary his breathing pattern and if the mandatory rate is relatively low, the patient may also be able to regain total control of the ventilation. In contrast, when the respiratory rate set by the operator is high, the patient's

spontaneous activity is, in practice, suppressed. Between these two extremes there are, of course, ample possibilities for partial support.

### 6.2.2.2 Applications

SIMV is definitely more advantageous than controlled ventilation. In particular, the patient-ventilator coordination is better since all the patient's inspiratory efforts are picked up by the machine; furthermore, some studies have shown that the risk of barotrauma or volume trauma and the reduction of cardiac output related to high inflation pressures are decreased during SIMV, since the mandatory breaths are interspersed by spontaneous breaths and the mean pressure over a given period of time is lower. Furthermore, SIMV seems to reduce the risk of respiratory alkalosis, improve the distribution of gas within the lungs and prevent disuse atrophy.

The advantages of SIMV with respect to assisted modes of ventilation are less clear.

As far as concerns the comparison with volume-assisted ventilation, the few studies that have been published do not document substantial differences between the two modes with regard to cardiac output, oxygen consumption, and the prevention of respiratory alkalosis. There are no comparative studies of SIMV and PSV during episodes of acute respiratory failure, while a trial in post-operative patients showed that the peak pressure in the airways was lower during PSV. Considering the most common use of SIMV, that is, weaning from mechanical ventilation, it appears to be clearly inferior to both PSV and a trial with a T-tube.

With regard to NIV, many volume-regulated home ventilators include the SIMV option, but to our knowledge this method has never been applied non invasively.

---

## 6.3 Pressure Modes

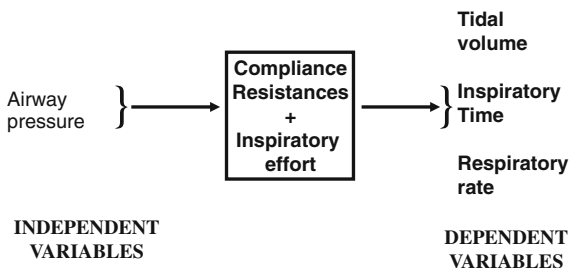
### 6.3.1 Pressure Support Ventilation

The advent of portable pressure ventilators for NIV, e.g., bilevel ventilators, has increased the enthusiasm for this mode of ventilation and also made it popular among pulmonologists. The clinical advantages of PSV are clear even to the uninitiated, given its good adaptability to the needs of the patient who tolerates it well, both in the early stages of ventilation and during weaning. It is, however, often overlooked that this type of ventilation can have some limitations.

#### 6.3.1.1 Independent and Dependent Variables During PSV

Here we pick up the concept of dependent and independent variables again. During PSV, the independent variables (Fig. 6.4), that is, those set by the operator, are the inspiratory pressure and possibly the expiratory pressure, the threshold of the inspiratory trigger and possibly that of the trigger that controls the cycling between

**Fig. 6.4** Flow-cycled pressure support ventilation



inspiration and expiration. The dependent variables are the inspiratory time, expiratory time, tidal volume, and respiratory rate.

PSV is, therefore, a method of ventilation in which every one of the patient's spontaneous breaths receives an inspiratory pressure support. The inspiratory pressure of the airways is maintained constant at the level established by the operator and since the passage to the expiratory phase is regulated by a drop in flow, the patient should theoretically have complete control of the respiratory timing and tidal volume. This should, at least in theory, improve not only tolerance of the ventilation, but also the interaction between the patient and the machine. Given its characteristics, in some ventilators the PSV mode is, improperly, called "Spontaneous Breathing."

### 6.3.1.2 Applications

PSV is the most frequently used mode during NIV, perhaps because it is erroneously thought to be the easiest and quickest to set.

From a clinical point of view, the change from any other mode of ventilation to PSV is usually associated with greater comfort and better compliance by the patient. This has been demonstrated in numerous studies, although these have been limited to the acute effect and have not gone further into the longer term effects.

The other major advantage of PSV is that the work of the inspiratory muscles can be graded and personalized according to individual needs by varying the level of pressure support. The addition of extrinsic PEEP or CPAP during PSV can further reduce the work of the respiratory muscles, both during an episode of acute respiratory failure in patients with marked dynamic hyperinflation and during periods of clinical stability. The success of non invasively applied PSV may also be related to the fact that with almost all the most popular so-called home pressure ventilators, an expiratory pressure can also be set (i.e., extrinsic PEEP or CPAP), whereas this is not always possible with home volume ventilators.

As we know, neuromuscular blockade or heavy sedation cannot be used in patients being ventilated non invasively and it is, therefore, important that these patients have a very comfortable and physiological ventilatory support. The field of clinical applications of PSV during NIV is so broad that there are in fact no limitations to its use in either hypoxic or hypercapnic acute respiratory failure. It is, however, clear that in the case of decreased respiratory drive or alterations in breathing during sleep, a back-up frequency, or a switch to a controlled pressure,



could be advisable. Having said this, setting all the independent variables correctly is the key to the success of PSV which, as we shall see in the chapter on this subject, is not always as simple as “*I only have to turn a few knobs*”.

In line with this, in some cases, PSV can cause major problems of patient-ventilator interaction. For example, asynchrony between the ventilatory demand of the patient and the response of the ventilator during PSV has now been extensively described in patients with COPD, especially, but not only, if they have considerable emphysema. In particular, it has been demonstrated that numerous ineffective efforts can be made, or the double trigger phenomenon may occur. Intubated patients who develop these anomalous interactions are those who have greater problems with being weaned from ventilation and in whom tracheotomy is more often required. How much the presence of asynchronies affects patients' clinical outcome, in terms of survival, has not yet been studied.

As far as concerns, the hemodynamic effects of this mode of ventilation in patients who are or who are not intubated, minor alterations in the major cardiovascular parameters have been described using a range of pressures. Higher inspiratory pressures ( $\sim 30$  cmH<sub>2</sub>O) and respiratory rate (20 breaths/min) were recently adopted to ventilate chronic hypercapnic COPD patients in order to achieve the maximal PaCO<sub>2</sub> reduction. This type of approach called high-intensity positive pressure mechanical ventilation (Hi-NPPV), has been shown to improve spontaneous diurnal blood gases better than the traditional lower pressures approach (Li-NPPV). It was, however, found in a later physiological study, that a significant reduction of cardiac output was present, when a total reduction of inspiratory effort, with an increased in intrathoracic pressure was achieved.

### 6.3.2 Pressure Controlled Ventilation

PCV is a mode of pressure ventilation which approaches, with due differences, the volume A/C mode. Its underlying principle, like that of PSV, is to supply a pressure support in which the cycling between inspiration is not caused by a decrease in flow and, therefore, in the final analysis, by the respiratory mechanics of the patient but are pre-set by the operator.

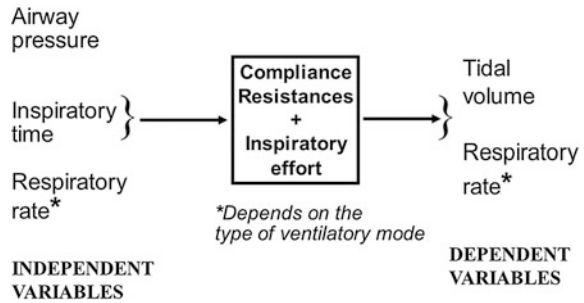
The most widely used form of PCV during NIV is time-cycled and it is this that we discuss below.

#### 6.3.2.1 Independent and Dependent Variables During PCV

During PCV, the independent variables (Fig. 6.5), that is, the variables set by the operator, are inspiratory pressure and possibly also expiratory pressure, the threshold of the inspiratory trigger and the inspiratory time for which this pressure is maintained.

As for the volume-controlled modality, there are ventilators with which the patient cannot interact and so a trigger cannot be set. The dependent variables are

**Fig. 6.5** Time-cycled pressure controlled ventilation



the tidal volume and the respiratory rate, this latter only in the case that the ventilator allows triggering.

Once the parameters have been specified, the mean pressure in the airways and, therefore, also approximately the alveolar pressure, should not exceed a given established value, but as for PSV the  $V_t$ , the minute ventilation and the alveolar ventilation cannot be controlled since these vary depending on the changes in respiratory mechanics.

### 6.3.2.2 Applications

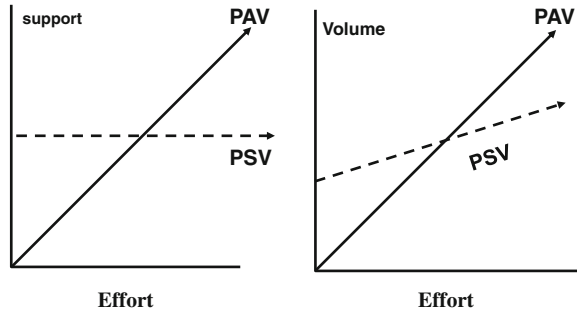
The advantage of PCV is that it can be applied in patients who have reduced respiratory drive or marked muscle weakness, contemporaneously reducing the risk of volume trauma or barotrauma, compared with that of volume-controlled ventilation, in the case that respiratory mechanics change unexpectedly. PCV is also used in cases of air leaks, when the ventilators used (particularly old generation intensive care ones) are not able to compensate for the air-leaks. In fact in the case of PSV the cycling threshold between inspiration and expiration could be reached only after an unacceptably long period of time if, because of the air losses, the flow does not decrease to values pre-established by the ventilator's algorithm. This phenomenon, which is increasingly rare with modern ventilators, is called *hang-up*; the term indicates the patient's inability to finish the inspiratory phase while the machine continues to insufflate air.

### 6.3.3 Proportional Assist Ventilation

This is definitely a very interesting method of ventilation, although honestly it is little used in clinical practice. Why? The first reason is that not all ventilators allow this option, which is not currently registered in the USA since it has not yet been approved by the Food and Drug Administration; secondly, given that it is based on not immediately comprehensible physiological concepts, it is often viewed with suspicion by clinicians.

As shown in Fig. 6.6, unlike PSV, in which the pressure support during inspiration is pre-determined, PAV provides a sort of support proportional to the

**Fig. 6.6** Difference between PAV and PSV



patient’s effort. Theoretically, this mode should allow automatic synchrony with changes in the patient’s ventilatory demand.

**6.3.3.1 Independent and Dependent Variables During PAV**

PAV and PSV have some basic characteristics in common, in particular the fact that both modes were designed to support spontaneous inspiratory efforts by supplying a certain level of pressure support to the airways. It is difficult to establish the independent and dependent variables in this mode. In fact, with PAV no airway pressure, flow or tidal volume is set *a priori*; instead, the aim is to guarantee instant by instant a support in relation to the patient’s effort.

During assisted ventilation, the pressure applied to the respiratory system ( $P_{rs}$ ) is given by the pressure of the respiratory muscles ( $P_{mus}$ ) and by the ventilator ( $P_{aw}$ ), which represents the level of “external” assistance to the patient. Thus:

$$P_{rs} = P_{mus} + P_{aw}$$

All of us, and patients in particular, must overcome an elastic load and a resistive load and so the patient’s effort can be determined by the formula:

$$P_{mus} = R \times V + E \times VT + PEEP_i - P_{aw}$$

where  $V$  is the flow,  $VT$  is the volume generated,  $R$  is the resistance,  $E$  is the elastance and  $PEEP_i$  is the intrinsic PEEP.

In PAV, during the inspiratory phase, the ventilator generates a positive pressure proportional to the flow and volume generated by the patient and, therefore:

$$P_{aw} = FA \times V + VA \times VT$$

Consequently, the more force the patient generates, the more the machine assists him and vice versa.

The operator can set the level of assistance of flow and volume, in this way “modulating” the effort of the patient with respect to his conditions.

Thus, from a practical point of view, only a single parameter needs to be regulated in PAV, that is, the percentage of the patient’s *compliance* and resistance

that the ventilator must be responsible for. Assuming that the measurements of respiratory mechanics are correct, setting the assistance to 100 % would reduce the patient's respiratory work to a minimum, whereas setting it at zero would maximize the patient's work.

What becomes critical when setting the ventilatory assistance is the measurement of the *compliance* and resistances (those of the endotracheal tube are subtracted). The most scientific method would be to measure these parameters during the brief period of controlled volume ventilation, but if this is not possible, there are two alternatives during PAV.

The first is based on the method of occluding the airways during an inspiration maintained for the whole expiratory cycle. The elastance or *compliance* (its reciprocal) is calculated using mathematical formulae.

The second, more empirical, but practical method for measuring elastance and, thereby choosing the level of respiratory assistance, is the so-called “*runaway*”.

The operator gradually increases the degree of volume assist until the level at which the ventilator can no longer cycle the breath in the usual time and so the inspiratory time becomes prolonged for a long period. This value of volume assist is usually just greater than the patient's elastance and so this latter can be determined without requiring particular equations.

The new PAV*plus* option is able to monitor the resistance and elastance values automatically and, therefore, considerably simplifies setting the ventilator.

### 6.3.3.2 Applications

There are now both physiological and clinical studies that have been able to demonstrate the clinical efficacy of PAV in chronic and acute respiratory failure, and in this latter case in both hypercapnic and hypoxemic forms. Most of the research has focused on the comparison with PSV, showing the “noninferiority” of PAV with respect to the more consolidated method. Furthermore, PAV seems to be better tolerated, at least in the first hours of ventilation, induces better patient-ventilator synchrony and also improves the quality of sleep in the intensive care unit. The new PAV*plus* seems to offer further improvements compared to traditional PAV, by automatically monitoring respiratory mechanics at predetermined intervals and thereby enabling changes of the settings of the flow and volume assists “in course”. However, as said earlier, the presumed easier use of PSV limits the use of PAV in clinical practice. But we also know how difficult it is in medicine to change the ideas and, even more so, the habits of someone who has used a method for years and which has, in any case given satisfaction.

---

## Suggested Reading

Appendini L, Patessio A, Zanaboni S (1994) Physiologic effects of positive end-expiratory pressure and mask pressure support during exacerbations of chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 149(5):1069–1076

- Brochard L (2002) Intrinsic (or auto) PEEP during controlled mechanical ventilation. *Intensive Care Med* 28(1):1376–1378
- Brochard L, Pluskwa F, Lemaire F (1987) Improved efficacy of spontaneous breathing with inspiratory pressure support. *Am Rev Respir Dis* 136(2):411–415
- Dreher M, Storre JH, Schmoor C et al (2010) High-intensity versus low-intensity non-invasive ventilation in patients with stable hypercapnic COPD: a randomised crossover trial. *Thorax* 65:303–308
- Gay PC, Hess DR, Hill NS (2001) Noninvasive proportional assist ventilation for acute respiratory insufficiency. Comparison with pressure support ventilation. *Am J Respir Crit Care Med* 164(9):106–111
- Lukácsovits J, Carlucci A, Hill N, Ceriana P, Pisani L, Schreiber A, Pierucci P, Losonczy G, Nava S (2012) Physiological changes during low and high “intensity” noninvasive ventilation. *Eur Respir J* 39:869–875
- MacIntyre NR, Ho LI (1991) Effects of initial flow rate and breath termination criteria on pressure support ventilation. *Chest* 99(1):134–138
- Nava S, Ambrosino N, Rubini F (1993) Effect of nasal pressure support ventilation and external PEEP on diaphragmatic activity in patients with severe stable COPD. *Chest* 103(1):143–150
- Nava S, Bruschi C, Rubini F (1995) Respiratory response and inspiratory effort during pressure support ventilation in COPD patients. *Intensive Care Med* 21(11):871–879
- Petrof BJ, Legaré M, Goldberg P (1990) Continuous positive airway pressure reduces work of breathing and dyspnea during weaning from mechanical ventilation in severe chronic obstructive pulmonary disease. *Am Rev Respir Dis* 141(2):281–289
- Sassoon C, Zhu E, Caiozzo VJ (2004) Assist-control mechanical ventilation attenuates ventilator-induced diaphragmatic dysfunction. *Am J Respir Crit Care Med* 170(6):626–632