Precision medicine is coming to town: personalising home ventilatory equipment in COPD patients with chronic hypercapnic respiratory failure

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Discharging a patient under mechanical ventilation is a risky procedure if the clinician does not have control of the prescription. In this review we assess the problems that a clinician may encounter when the payer is the main driver of the choice.

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ABSTRACT Discharging a chronic critically ill patient is a risky procedure if the clinician does not have full control of his prescription. This is even more important when applying a machine to replace a failing organ, as is the case for home ventilation. Even if modern home ventilators fulfil quality and safety criteria and, ‘on paper’, ventilators and masks look very similar, performance and scenarios of applicability are not always equivalent. In the case of ventilators, the type of circuit, accessories provided and available modes vary between devices. Bench studies comparing ventilators have shown large differences in triggering, rise time, pressurisation capacities, maximal flow provided, cycling and level of authorised expiratory positive airway pressure. Automated algorithms to deal with leaks also vary and have not been sufficiently evaluated. In the case of interfaces, the choice of mask requires careful evaluation of the underlying disease and of the type of ventilator and circuit, which could have a potentially major impact on patient compliance and clinical effectiveness. This could explain different results in the same clinical situation.

The choice of ventilator and type of mask represents a medical prescription and should be respected by the provider and not subject to financial constraints.

Preface: a clinical lesson
A 62-year-old man with known COPD for 8 years developed chronic respiratory failure 3 years ago that rapidly became hypercapnic. In the past 12 months he was admitted to hospital three times for an acute exacerbation. His arterial carbon dioxide tension (\(P_{\text{aCO}_2}\)) is now stable and >60 mmHg.
Persistent hypercapnia (i.e. \(P_{aCO2} >45\) mmHg) after an exacerbation of COPD may be linked to a higher mortality and frequent hospitalisation in the following months.

In patients like this, the chronic use of noninvasive ventilation (NIV) has been shown not only to reduce the occurrence of exacerbation but also to improve 12-month survival [1].

Therefore, the patient’s attending physician decided to suggest home NIV, which he was very willing to accept. For this reason, he underwent a brief hospital admission to perform a full-night polysomnography and customisation to the ventilator.

Despite there being a pressure mode that compensates for nonintentional leakage better than the volume mode, a constant tidal volume (\(V_T\)) may not be provided when changes in respiratory impedance occur [2]. For this reason, the clinician decided to overcome the problem using a guaranteed \(V_T\) delivered with a ventilator with a single-limb circuit with an intentional leak (or “vented”) system.

This kind of circuit has been shown to keep a constant \(V_T\), increasing the inspiratory pressure; however, this was not the case when a guaranteed \(V_T\) was applied using a circuit without an intentional leak (or “non-vented”) circuit, as the ventilator fails to maintain the target volume due to a fall in the inspiratory pressure [3].

During hospitalisation the patient was accustomed to a X-ventilator that used a vented system, and was discharged with a complete correction of nocturnal hypoventilation (assessed with a sleep study), perfect synchrony with the machine, good tolerance to ventilation (which is essential for long-term use) and favourable clinical outcomes.

The patient lives in an area located in central Italy, where the homecare provider awarded the tender was providing only Y-ventilators. In the prescription paper that should be delivered to the local healthcare agency, the attending physician could only specify the mode of ventilation (i.e. guaranteed \(V_T\)), while there was no possibility to suggest a specific commercial brand.

It so happened that the Y-ventilator company could only provide a machine that for the prescribed ventilator mode was using a non-vented circuit.

During NIV, leaks are almost inevitable and one morning, shortly after discharge, owing probably to the continuous onset of nonintentional leaks during the night, the patient’s wife could not wake him up.

She immediately called the emergency number so that he could be rapidly admitted to the emergency room where arterial blood gases showed marked acidosis (i.e. pH 7.24) with abnormally elevated hypercapnia (i.e. \(P_{aCO2} 87\) mmHg).

Later, the data download from the ventilator showed that the patient developed clinically significant hypventilation because of a decrease in inspiratory pressure to the minimum set value, as the ventilator was reading an abnormally elevated \(V_T\), while this was not obviously the case but was due to the occurrence of nonintentional leaks during sleep.

Introduction
What did this story tell us? It tells that discharging a patient with severe stable COPD on long-term NIV is a risky procedure if the clinician does not have full control of what has been prescribed. We know from real life that a car is a vehicle to drive and that you use it to travel; however, under the umbrella of the name “car” and even within the same category (e.g. horse power, SUV, four-wheel drive, manual gear, etc.) the performance and reliability may vary greatly as well as the driver’s ease of use and safety.

Simplifying the prescription of the ventilator under the specification of the mode (i.e. guaranteed \(V_T\)), as was the case for this patient, may not only interfere with the patient’s tolerance, but may also harm the patient.

“One size does not fit all” is the paramount principle of so-called personalised medicine that has been summarised by the former US President Barack Obama during the 2015 Speech to the Nation: “Doctors have always recognised that every patient is unique, and doctors have always tried to tailor their treatments as best they can to individuals. You can match a blood transfusion to a blood type (that was an important discovery). What if matching a cancer cure to our genetic code was just as easy, just as standard? What if figuring out the right dose of medicine was as simple as taking our temperature?” [4].

This is even more important when we need to apply a machine when a vital organ is failing. In patients with COPD and chronic respiratory failure, the ventilator has two main functions: 1) to alleviate the inspiratory effort of a patient, relieving dyspnoea at the same time; and 2) to act as full support to artificially sustain life when the organ totally failed. This may be obviously linked with a better quality of life and, eventually, improved survival.
Now, basing our choices of prescribing a ventilator on what it is written in a manual is not only very superficial but also not respectful of the patient’s need.

Not only are leak compensations calculated differently according to the ventilator algorithm, but also the same mode of ventilation may be very heterogeneously delivered, so that the efficacy on gas exchange and the patient’s tolerance may be different [5].

Everything “on paper” looks very similar, so that in the era of financial constraints the healthcare agency or, in general, the payer, is very likely to choose a device on the basis of an economical evaluation.

**The technology: friend or foe?**

Ventilators have made major progress since their first use in the home setting in the 1960s. In the earliest days of ventilation we only had access to a few devices with very basic settings, and no realistic way to monitor the patients’ use. Currently, the settings and modes of operation are not very well understood by physicians, healthcare providers, the patients themselves and those that attempt to “help” them [6, 7]. This is caused by various problems: 1) no mandatory training sessions are required for students, senior physicians or caregivers in the correct use of mechanical ventilation; and 2) distributors and manufacturers create their own terms to describe the functions of specific machines, often using different terms for the same principle or defining different functions for similar actions, thus leading to confusion (e.g., the S/T mode). For the moment, there is no foreseeable solution because of the absence of an international standard from, for example, the International Organization for Standardisation, which leads to increased misunderstanding of terms.

In a report by SRINIVASAN et al. [8] in the USA, 189 problems were detected among 150 patients in a 1-year period. Overall, 30% of the cases were due to incorrect usage of equipment, 13% to damaged machinery and 16% were “false alerts”. Only two (1%) of the cases required hospitalisation, with no lasting negative outcomes; no deaths or serious injuries occurred that were attributed to failing machinery. There was an increase in the workload of the homecare provider: 14% of the ventilating devices were replaced for psychological comfort, while stress and anxiety control were required in 10% of the caregivers, who often required only re-education and adaptation to the ventilator.

In Spain, FARRÉ et al. [9] demonstrated that the percentage of patients with a discrepancy between the prescribed and measured main ventilator variable was 17%. In 25% of the ventilators, the integrated alarm systems were incorrectly set. Readmissions to hospitals that had not been programmed the year prior to the study did not correlate with the ventilator errors. In the UK, CHATWIN et al. [10] confirmed that ventilator alarms were not always available or set correctly for patients using NIV, therefore creating an increase in the homecare providers workload. Overall, 75% of enquiries concerning equipment dysfunction were instigated, again because the patient or caregiver found the NIV performing poorly and not the result of an activated alarm.

Mechanical devices used for homecare have become more widely accepted and used as design and technology has evolved. Sadly, the technical advances have not been matched by ergonomic advances; at best, this is a major source of risk for the patient, at worst a cause of insufficient use by physicians and caregivers. GONZALEZ-BERMEJO et al. [6] demonstrated that with 11 home ventilator models, errors occurred in almost 50% of cases during the ventilation mode and testing settings recognition. This group also demonstrated that unexpected and unknown settings are capable of creating dangerous situations [11, 12]. In addition, in France, LOFASO et al. [13] demonstrated that 28% of those using NIV technology, were unable to correctly designate their mode as a volume or a mode controlled by pressure. Clinically speaking, this is a major revelation, as the more wellbeing perceived by the patient, the more the patient will comply with the treatment, which is critical in the domain of home NIV. SENENT et al. [7] reported major variations in appreciation while testing 10 home NIVs.

The technical differences that were responsible for perceived variations exceed the scope of this work. Nonetheless, it is interesting to remark that the best rated ventilator among those tested also demonstrated the quickest rise in pressure in benchmark studies. Patients reporting that an established NIV had become ineffective, for subjective reasons should be able to compare other ventilators, or at least given the chance to try another ventilator, if all things are termed equal.

Home-installed ventilators are multi-faceted in terms of their technical performance from both the doctor’s and patient’s viewpoint and are also very useful in terms of monitoring the patient’s adherence to treatment.

JANSENS et al. [14] claim that ventilator data that are downloaded into specific software applications can conceivably be an element of clinical decision making in the successful management of home NIV. Using ventilator data downloads could help promote a wider usage for outpatient set-ups for their domestic NIV;
in fact, downloaded data from a ventilator transmitted via a modem will be a future element for telemedicine. Data are available via both a secure data card download, as well as by way of modem technology with some auxiliary devices. Several bench studies demonstrate that NIV data parameters that are already integrated into the manufacturers’ software are reliable, as well as clinical studies that demonstrate the apnoea index recorded by software built into ventilators. Two studies of patients with amyotrophic lateral sclerosis have demonstrated that survival is often related to the quality of home NIV, defined with ventilator data downloads [15, 16]. More recently, two new studies that carefully monitored ventilator download data can predict an exacerbation of COPD [17, 18]. The use of download data in domestically ventilated patients facilitates early and objective assessments concerning leaks and other ventilator problems. When outpatient NIV is established and reviews undertaken there rather than in a traditional and more costly inpatient environment, ventilator data downloads have the possibility of providing clinicians with essential information, and thus can be used as a useful interventional adjunct in the clinicians’ toolkit, and should be available in every ventilator installed in homes.

Are all the ventilators similar?
Nowadays, commercialised home ventilators fulfil the criteria of quality and safety; however, performance and scenarios of applicability of different ventilators are not equivalent and different ventilators are not interchangeable.

Two types of circuits can be used to deliver NIV. The first is analogous to those used in intensive care unit ventilators and includes either simple or double tubing. Inspiration and expiration are independent, and they use an expiratory valve (non-vented circuit). The second type does not have a true exhalation valve but a single-limb circuit. This system includes a calibrated leak (vented circuit) and needs to set a minimal expiratory positive airway pressure (EPAP) of 4 cmH₂O [19], both are conditions needed to avoid rebreathing. Some ventilators allow only one type of circuit (mostly vented ones), while others could be used in a vented or non-vented configuration.

Moreover, the field of application of those different ventilators varies from use as an isolated nocturnal ventilatory support in a patient with ventilatory autonomy (no batteries or alarms are needed) to life-support use (batteries and alarms are mandatory).

Another difference concerns the available modes. Classically, NIV was provided by using volume-targeted modes or pressure-targeted (PTM) modes.

The limitation of a volume-targeted mode is that it does not take into account patients’ varying requirements and that the effective volume falls during leaks.

The disadvantage of PTM is that it cannot guarantee a $V_T$ [20]. Recently, manufacturers proposed a plethora of hybrid modes that combine characteristics of both modes and are theoretically committed to overcome those limitations.

These modes, called volume-targeted pressure ventilation (VTPV), provide a predetermined target volume while ensuring the physiological benefits of PTM. The ventilator estimates expiratory volume on a breath-by-breath basis by automatically adjusting inspiratory pressure within a predetermined range to ensure a stable $V_T$ [21].

Some ventilators, but not all, proposed VTPV both when using a single-limb circuit with intentional leaks and a single or double circuit limb with an expiratory valve. Moreover, some new devices also allow setting variable back-up respiratory rates and automated EPAP levels. The different devices allowing those modes vary not only in terms of the type of targets and range of settings, but also show large technical differences; not only are the algorithms of those different devices different but they also differ in the method used to estimate $V_T$ and to detect events, in the methods used for leak estimation and in their reactivity and response threshold (i.e. the time to reach the target and the time to decrease pressure) [22–24].
In real life, VTPV does not seem to be very popular [25] as most clinicians are prescribing simpler solutions (such as pressure support or pressure control modes) before thinking of more complex ones.

During mechanical ventilation, two ventilatory pumps act together; on the one hand the ventilator and on the other hand the patient’s respiratory muscles. These two pumps may work in agreement but in fact they can interact in any number of ways, many of which will create difficulties rather than solving them.

Moreover, when compared with invasive ventilation, NIV has two unique features: the non-hermetic nature of the system that carries the potential risk of nonintentional leaks, and the fact that the ventilator–lung assemblage could not be considered as a mono-compartment model because of the presence of a
fluctuating resistance represented by the upper airway [20]. Both situations by themselves may compromise the patient ventilatory asynchrony even more.

To analyse how the patient–ventilator interaction is realised, it is useful to analyse the different phases of a classic positive pressure ventilatory cycle (figure 1).

Several bench studies comparatively evaluated ventilator response in these different phases [5, 26–33]. These studies showed significant differences in terms of: triggering (trigger sensitivity, triggering delay, response to leaks); rise time and pressurisation capacities reactivity; maximal flow capacity of the blowers (mainly during leaks); cycling (criteria used to switch from inspiration to expiration and the possibility or not to set a maximal inspiratory time to avoid an inappropriate lengthening of inspiratory time, in particular during leaks); and the level of minimal and maximal EPAP levels allowed by the device.

Concerning leaks, even if the latest generation blowers can attain flows >200 L·min⁻¹ and are able to deal with very high levels of leaks, this capacity is variable among different devices and has not been sufficiently evaluated [34, 35].

Borel et al. [36] demonstrated the incapacity of some ventilators to even deal with intentional leaks when using masks with >40 L·min⁻¹ of intentional leaks at 14 cmH₂O.

To improve patient–ventilator synchrony, in particular during leaks, some ventilators offer automated complex trigger algorithms (the flow waveform method of triggering).

With those systems, triggering occurs when the inspiratory effort of the patient distorts the flow waveform. Even if this way is supposed to be more sensitive than classical flow triggering, the algorithms vary among different devices and comparative studies between those devices are lacking. Moreover, most of those algorithms are real black boxes.

This heterogeneity of algorithms could explain a different response of different ventilators to the same clinical situation, challenging the possibility of interchanging different devices.

For example, a recent bench study comparatively evaluating different home ventilators showed that a critical leak (i.e. a leak inducing an asynchrony rate >25%) was significantly different among different ventilators. Therefore, the difference in coping with leaks and the capacity of estimating leaks may account for the differences between devices in the effectiveness of NIV [5].

All that is still complicated as nomenclature issues and operating processes of ventilator modes proposed by modern ventilators are far from clear [6].

While mechanical ventilation has largely evolved in recent years, what has not changed is a standard classification able to describe this complexity. This issue is more pronounced in the field of NIV. Due to growing evidence for NIV effectiveness in an extensive range of indications, the number of patients receiving NIV at home is increasing. As “a victim of its own success”, NIV has become a widespread practice and is not unusual that it might be carried out by nonspecialised centres.

When NIV was introduced, there were a limited number of modes and ventilators with few possible settings. But as a consequence of market evolution, >30 models offering numerous setting options are now available [6].
Moreover, there are no marketing directives for ventilators. This leaves manufacturers free to name the same modes and settings in their own way and even fashion new modes that frequently correspond to only minor modifications in an existing mode. This explains the wide variety of existing terminology describing NIV modes that is rather confusing, with no common classifications. It is even the case that the same acronyms can correspond to different modes and that the same mode can be called something different by other manufacturers.

An additional paraphernalia of terms and acronyms were used such as inspiratory peak airway pressure, EPAP, pressure support ventilation, S/T devices, bilevel pressure assist, continuous positive airway pressure plus pressure support and pressure support with positive end-expiratory pressure. This is somewhat problematic in clinical practice when a nonspecialised physician is challenged with an incomprehensible plethora of designations and machines [37].

Moreover, nomenclature differences also relate to setting issues. The mode of setting inspiratory trigger sensitivity, pressure rise time and inspiratory–expiratory cycling shows huge differences between available devices. As an example, rise time is expressed in flow rate (L·s⁻¹) in some ventilators, as time (ms) in others and even in arbitrary values (1/2/3) in some others. In fact, few data are available on the equivalence of those different settings among different ventilators [5]. Bench tests to establish equivalent settings between different devices are still lacking.

Last but not least, nowadays, almost all home ventilators include monitoring systems that allow the assessment of many ventilatory parameters, and the ability to either view them online or storing the data in the memory for subsequent use [38, 39].

However, there is a large spectrum of data provided by these devices and high interdevice variability, with data available in some devices but not in others. Moreover, the algorithms applied vary among different devices [39, 40] and are expressed in different ways.

As an example, some devices estimate total leaks, others estimate nonintentional leaks (by subtracting the estimation of instantaneous intentional leaks at each pressure). The type of leak estimated also varies, with some devices estimating leaks in the whole cycle and others at the end of expiratory phase [39].

In addition, the significance of data values (maximal, mean, median, thresholds) of those different built-in monitoring systems need to be clarified. In fact, even if data obtained by some of those devices were validated [38, 39, 41, 42], the validity of several other parameters is questionable and must be validated by independent clinical and/or bench test studies.

Given this variability in technology, algorithms and available information, these different modules are not equivalent and so are not interchangeable among different ventilators.

**Beyond the ventilators**

*Selecting the right interface*

Patient tolerance is extremely important for NIV success in both the acute and chronic settings. Since the interface (mask, helmet or mouthpiece) is a connection between the native airways and the artificial ones of the ventilator, the choice of the interface may represent a major issue on the patient’s tolerance and clinical efficacy.

A perfect interface that is best for all patients in all situations, does not exist and will probably never exist. The type (oral, nasal, oronasal), size, design, material and securing system of the interface may affect the patient’s comfort with respect to many aspects, such as air leaks, claustrophobia, skin erythema, eye irritation and skin breakdown.

The choice of the interface requires careful evaluation of the patient, underlying disease, type of ventilator and circuit and ventilatory mode and settings; however, it is necessary to understand that the ideal mask varies according to each patient. When buying a shoe, one may want a shoe with certain characteristics (size, material, type of sole, heel, colour), and there will be many models that meet these characteristics, but it is the client who needs to try on the shoe and see if it feels comfortable. The same thing happens when fitting an NIV mask. According to the medical indication, it is the patient who needs to measure the different available models to make sure which mask suits them best.

In general terms, nasal masks are preferred in >80% of the studies evaluating long-term domiciliary NIV [43–45] as they have many advantages in terms of comfort, such as allowing the patient to eat, drink or wear glasses, less pressure over the bridge of the nose, and are less claustrophobic.

Clinical advantages of nasal masks include less risk of aspiration, less interference with cough and no risk of asphyxia in cases of ventilator malfunctioning. However, they may be less effective in cases of nasal obstruction, may also cause nasal irritation and rhinorrhoea and can lead to trouble with monitoring due to mouth leaks.
Air leaks may reduce the efficiency of NIV by reducing the tolerance, increasing patient–ventilator dyssynchrony, altering trigger sensitivity and promoting arousals that lead to sleep fragmentation.

A rotational strategy of different masks can be an excellent option to decrease the risk of skin breakdown in patients with long periods of NIV use.

In a recent observational study, the percentage of patients using nasal versus oronasal or facial masks was 23% versus 77% [24]. Of note, physiological studies revealed better patient compliance with nasal masks, whereas alveolar ventilation was improved with full face masks [46, 47]. The decision to use a full face mask instead of a nasal mask could also be made on the basis of avoiding unintentional leaks when high inspiratory peak airway pressure therapy is applied.

However, it has been shown that some patients undergoing home mechanical ventilation were successfully using a nasal mask, even when they were ventilated with high inspiratory pressure [48].

Vented masks necessitate a positive end-expiratory pressure of ∼4 cmH₂O in order to avoid rebreathing of the exhaled air and require use with a single-limb circuit. Meanwhile, nonvented interfaces are used with double-limb or single-limb circuits with active exhalation valve incorporation (nonvented circuits).

**Humidification**

The importance of heating and humidification for long-term invasive mechanical ventilation is well known [49].

On the contrary, it is less recognised for the patient undergoing long-term NIV. The lack of heating and humidification is one of the main causes of discomfort for patients undergoing chronic NIV therapy, leading to poor compliance to treatment.

In the presence of air leaks, cold dry air causes increased nasal airway resistance owing to the release of inflammatory mediators and increased mucosal blood flow [50–52].

The increase in nasal resistance negatively affects the delivered $V_T$ [53]. These effects are reduced using heated humidification, which improves comfort by attenuating the negative effects of mouth leakage and nasal airway resistance in patients on domiciliary NIV.

Although heated humidification for NIV is preferred, there is no significant difference with respect to NIV compliance, airway symptoms and rate of hospitalisation following acute exacerbation when comparing a heat and moisture exchanger, a passive humidification device, to active systems [54]. In principle, a heat and moisture exchanger should be avoided with nasal NIV because the air leaked through the mouth makes it ineffective. Furthermore, the additional resistance imposed by a heat and moisture exchanger may interfere with ventilator triggering.

**Conclusions**

Even if modern home ventilators fulfil quality and safety criteria and, on paper, ventilators and masks look very similar, the performance and scenarios of applicability are not equivalent. In the case of ventilators, the type of circuits, accessories provided and available modes vary from one device to another. Moreover, bench studies showed large differences between ventilators. Also, the choice of mask requires careful evaluation of the patient and could have a major impact on patient compliance and clinical effectiveness. Given this variability, devices are not interchangeable. The choice of a ventilator and type of mask is a medical prescription and needs to be clearly established and respected by the provider and not subject to financial constraints or economical evaluation.

It also looks like there is may be a gap between the hospital team setting patients up with personalised ventilation and the inexperience of carers in the home setting; however, this is strictly dependent on the local organisation that may vary geographically in European countries.

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