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REVIEW

A new mode of mechanical ventilation: positive + negative synchronized ventilation

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ABSTRACT

Supporting patients suffering from severe respiratory diseases with mechanical ventilation, obstacles are often encountered due to pulmonary and/or thoracic alterations, reductions in the ventilable lung parenchyma, increases in airway resistance, alterations in thoraco-pulmonary compliance, advanced age of the subjects. All this involves difficulties in finding the right ventilation parameters and an adequate driving pressure to guarantee sufficient ventilation. Therefrom, new mechanical ventilation techniques were sought that could help overcome the aforementioned obstacles. A new mode of mechanical ventilation is being presented, *i.e.*, a Positive + Negative Synchronized Ventilation (PNSV), characterized by the association and integration of two pulmonary ventilators; one acting inside the chest with positive pressures and one externally with negative pressure. The peculiarity of this combination is the complete synchronization, which takes place with specific electronic modifications. The PNSV can be applied both in a completely non-invasive and invasive way and, therefore, be used both in acute care wards and in ICU. The most relevant effect found, due to the compensation of opposing pressures acting on the chest, is that, during the entire inspiratory act created by the ventilators, the pressure at the alveolar level is equal to zero even if adding together the two ventilators' pressures; thus, the transpulmonary pressure is doubled. The application of this pressure for 1 hour on elderly patients suffering from severe acute respiratory failure, resulted in a significant improvement in blood gas analytical and clinical parameters without any side effects. An increased pulmonary recruitment, including posterior lung areas, and a reduction in spontaneous ventilatory rate have also been demonstrated with PNSV. This also paves the way to the search for the best ventilatory treatment in critically ill or ARDS patients. The compensation of intrathoracic pressures should also lead, although not yet proven, to an improvement in venous return, systolic and cardiac output. In the analysis of the study in which this method was applied, the total transpulmonary pressure delivered was the sum of the individual pressures applied by the two ventilators. However, this does not exclude the possibility of reducing the pressures of the two machines to modulate a lower but balanced total transpulmonary pressure within the chest.

Key words: PNSV; iron-lung; cuirass; ponchowrap; alveolar pressure (P_A); transpulmonary pressure (P_L); negative pressure (P_{neg}); NIPPV, NPV, ARDS.

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Introduction

Bearing in mind our long experience with iron-lungs and ICU ventilators in the Intensive Respiratory Care Unit of Foggia has led us to develop the idea of combining the two methods in order to increase their benefits and reduce their limits and their side effects. The result was an innovative mode of mechanical ventilation, never tried before, which paved the way for new studies of respiratory physiopathology and ventilatory mechanics. With this type of mechanical ventilation, two ventilators are used simultaneously, one delivering a positive pressure inside the airways (in a non-invasive or invasive way) and the other a negative pressure, externally to the thorax.

The main feature of these two ventilators is their synchronization, as they act simultaneously on both sides of the thorax (internal and external), while retaining the possibility of modulating the delivery of the respective flows and pressures, adjusting, the best possible way, to the ventilatory needs of the patient to be treated.

The idea arose from the observation, in many cases, of the limits and possible side effects of both modes of ventilation, respectively (positive and external negative), especially when dealing with more complicated cases from a resuscitation point of view. Naturally, at the basis, there is also the study of human physiology and ventilatory mechanics during extra-thoracic positive and negative pressure ventilation.

To achieve the goal of being able to use the two ventilators in a synchronized manner, we sought and had the collaboration of an Italian company (DIMA Italia) manufacturer of machines with both ventilation modes. Therefore, thanks to the willingness and dedication on the part of the engineering and technical staff, some modifications were made with the result of obtaining ventilators that can be completely synchronized with each other, each retaining, however, all their respective electronic, physical and mechanical characteristics. Subsequently, the two ventilators, both used in a non-invasive mode, were applied, both independently and jointly, on patients with hypoxemic-hypercapnic respiratory insufficiency to observe the functional, therapeutic and clinical aspects. This resulted in a study that has been the subject of scientific publication [1]. This work, despite the small sample of cases studied, has demonstrated unequivocally the clear superiority of the combination of the two ventilators in obtaining clinical and blood gas analytical improvements compared to the use of the same ventilators used separately, and with no side effects being observed. At the same time as this study [1], carried out in a completely non-invasive way, this type of positive + negative synchronized pulmonary ventilation was also applied to intubated or tracheostomized patients, i.e. in invasive mechanical ventilation, with equivalent benefits. The study of these patients, however, due to the onset of the COVID-19 epidemic, has been temporarily suspended so that, currently, statistical evaluations are not possible. However, the possibility of applying extra-thoracic negative pressure ventilation to patients already on invasive mechanical ventilation remains certain.

Extra-thoracic negative pressure ventilation and positive pressure ventilation

The main difference between extra-thoracic negative pressure ventilation (NPV) and positive pressure ventilation (PPV) lies in the physiological principles that underpin these two types of ventilation. With negative pressure ventilation, after positioning the patient inside a special container, a negative pressure is created outside the chest and, in the case of the iron-lung, also in the abdomen. This extra-thoracic negative pressure causes a lifting of the thorax and an enlargement of the internal volume with a consequent reduction of the pleural pressure (P_{pl}) and, thus, of the alveolar pressure (P_A). The difference between the negative pressure which is present at the alveolar level (P_A) and the one present at the level of the upper airways (P_{awo}), in close contact and, therefore, equal to that of the ambient air, will determine the inspiratory act which will consists in an aspiration of air from the external environment towards the alveoli. This mechanism emulates exactly natural breathing and, therefore, respects normal respiratory physiology.

The measurement of the pressure differential between the upper airways and the alveoli is indicated as trans-airway pressure ($P_{TA} = P_{awo} - P_A$), while the difference between the alveolar pressure and the pleural pressure is indicated as trans-pulmonary pressure ($P_L = P_A - P_{pl}$). Both indicate the force required to perform a complete inspiratory act.

If the patient is subjected to ventilation with the steel lung, the negative pressure will involve also the abdomen. The lifting of this part of the human body causes a lowering of the diaphragm which, associated with the lifting of the chest, increases even more the negativity inside the chest and, therefore, an increase in the volume and flows of the inspired air. Positive pressure ventilation has a physiological mechanism that can be said to be opposite to the mechanism of negative pressure ventilation. In fact, in this case, it is the positive pressure created by a ventilator and applied in the upper airways (P_{awo}) that determines a flow and a volume of a mixture of air that is introduced into the chest with consequent expansion. As it can be seen also in this case, there is a pressure differential between the upper airways and the alveoli, and the trans-airway pressure ($P_{TA} = P_{awo} - P_A$) will be the expression of the force imposed by the ventilator, with the difference that, at the moment of its application, the pressure in the upper airways will be high and the alveolar pressure will be equal to atmospheric pressure. Throughout the ventilatory cycle, with the exception of the end of expiration, there will always be an increase in pressure at the alveolar and bronchial levels. Positive pressure ventilation occurs with the use of ventilator circuits and prostheses that allow the connection of the ventilator to the patient and which, in non-invasive mechanical ventilation, include various face masks (nasal, oro-nasal, total-face masks) or helmets and, in invasive mechanical ventilation, various tracheal tubes, tracheostomy cannulas or laryngeal masks.

These two modes of ventilation also differ during the expiratory phase of the ventilatory cycle. In fact, positive pressure ventilation interrupts the supply of air and passively exploits the elastic pressure of the chest and lung to ensure that the air previously introduced in the inspiratory phase is completely exhaled until the start of the new inspiratory act, while the extra-thoracic negative pressure ventilation, in the expiratory phase, in addition to the passive mode (simple interruption of the negative pressure), has the possibility of delivering also an extra-thoracic positive pressure, which can facilitate the elastic return of the thoraco-pulmonary system and, therefore, the exhalation.

Both ventilatory methods have the purpose of: i) reducing ventilatory work; ii) improving lung ventilation; iii) increasing gas exchange; iv) improving alveolar recruitment; v) optimizing lung volumes. Nevertheless, when used or applied separately, they offer advantages and disadvantages.

Pros and cons of extrathoracic negative pressure

First of all, let us keep in mind that all ventilators acting extrathoracically determine non-invasive ventilation, therefore one of the advantages is the possibility of intermittent ventilatory treatment even for long periods of time [2-4]. The non-invasiveness of these machines also leads to a reduction in the use of intubation [5] and in the onset of respiratory infectious problems, including pneumonia [6]. Negative mechanical ventilation (NPV) has been widely used in the treatment of COPD respiratory failure [7-8], in neuromuscular patients [9], in neonatology [10-11], in pediatrics [12], in rehabilitation [13], and in endoscopic or surgical treatments of the airways [14-15]. As far as the iron-lung is concerned, negative extra-thoracic ventilation surely has the disadvantage of having to use large and heavy machines which have to contain the whole human body with the exception of the head. In more recent times, however, ventilators made of significantly lighter materials (Porta-Lung TM) have been put on the market and therefore, they are more easily usable and transportable. The main advantages of an iron-lung are: the ability to deliver high levels of negative pressure to the entire body of the patient and the possibility of treating patients with severe respiratory insufficiency, including hypercapnic coma [16]. Much less bulky and lighter are the prostheses such as the cuirass and the so-called "ponchowraps" or simply "ponchos". The former ones are characterized by shells of transparent plastic material, positioned anteriorly on the chest and which are fastened to the patient's back with straps, the latter ones, on the other hand, are garments of light and impermeable but breathable material (Goretex), worn by the patient and equipped with special closures with laces or Velcro, positioned at the level of the neck, at the extremities of the limbs or at the level of the pelvis (hence the name "poncho") to prevent air leaks. In the case of the cuirass, the negative pressure, generated by a machine positioned outside and connected with a tube, is created in the space between the surface of the chest and the shell, anchored on it. In the case of the "poncho", the same pressure is created in the space between the surface of the chest and the inner part of the worn garment, but spaced from the chest by a special metal grid inserted inside it. The "poncho", which is affected by a relative greater extension on the patient's trunk, due to the longitudinal length of the grid, has a part of the abdomen that is affected by the negative pressure created inside it. The cuirass, in general, is less extended in length than the "poncho" so that, the affected part of the abdomen is inferior.

While the old iron-lungs had the disadvantage of being able to ventilate only in "controlled" mode, the more recent models, through the use of flow sensors or thermistors positioned at the level of the nasal cavities or mouth, can also deliver "assisted" ventilation modes, with a considerable advantage for the synchronization and compliance on the part of the patient [17]. The pressures created by the ventilator acting externally on the chest are generally well tolerated, together with a good adaptability on the part of the subject to be treated. A limitation for the iron-lung is that it cannot accommodate large obese people (due to the size of their bodies), tracheostomized patients (possible cannula obstruction) and patients with gastrointestinal bleeding or with recent abdominal surgery. These limitations are reduced in the use of cuirass or the "poncho". Rarely, for clinical reasons, it is necessary to resort to high negative pressures, but even in this case, the side effects are not many. However, it is necessary to point out the possibility of edema phenomena inside the chest with the use of high pressures administered for a long time.

In addition, a certain sense of claustrophobia may be encountered with the iron-lung, as the whole body, with the exception of the head, is inside the ventilator, and this gives a feeling of limited movement. With the iron-lung, obstruction of the upper airways can also occur, favored by the hermetic closure placed at the neck, if too tight, by the supine position and by the negativity within the upper airways. These can cause a posterior fall of the tongue and soft palate and, therefore, apnea phenomena [18]. In the case of negative ventilation with other equipment and in particular with the cuirass, this phenomenon is decidedly limited and especially if the patient assumes an elevation of the trunk of at least 30 degrees.

Another advantage of NPV is that patients have their heads completely free, so they can talk, drink, eat, blow their noses, expectorate and, in the case of the cuirass and the "poncho", even have free arms and lower limbs. If it is necessary to enrich the inspired air with oxygen, all medical devices which normally favor a more adequate alveolar oxygenation, including the delivery of high flow oxygen (HNFC), can be used.

Pros and cons of positive mechanical ventilation

This type of ventilation, especially in recent times, has seen the proliferation of small-sized equipment that has also facilitated home use. Excellent results have been seen with the use of CPAP in patients suffering from OSAS [19-22] and, more recently, during the COVID-19 pandemic [23,24]. In the last 20 years, the marketing of masks and helmets more adaptable to the face of the patient has allowed the spread of non-invasive positive pressure mechanical ventilation (NIPPV) [25], even administered for long periods of time in an intermittent manner, especially in chronic hyper-capnic patients [26-28] or in neurological patients [29]. A further advantage of NIPPV is the reduction of infectious complications and mortality related to invasive mechanical ventilation [30].

In addition to the common advantages offered by extra-thoracic negative mechanical ventilation, as already listed above, it is necessary to recognize to positive mechanical ventilation, especially to the invasive one, a greater interaction between ventilator and patient, a greater safety in guaranteeing preset pressures, flows and volumes, due to the scarce possibility of air leaks in intubated or tracheostomized patients and the possibility of ventilating deeply sedated and / or curarized patients. Another advantage is the immediacy of the positive effects caused by the administration of adequate ventilatory support, especially in the invasive modality (IPPV). The non-invasive modality has, among its advantages, the possibility of administering a ventilatory support using equipment of smaller dimensions, easily transportable, well adaptable (especially with the most recent interfaces) and relatively easier to manage.

The major disadvantages of positive pressure ventilation are found during invasive mechanical ventilation and in the case of prolonged periods of ventilatory support. In fact, in these cases, the reduced possibility of clearance of the airways, the insufficiency of the cough mechanism, the reduced participation of the patient in ventilatory mechanics, especially if sedated, may lead to the obstruction of the airways caused by bronchial secretions, to bronchial obstruction phenomena, to an increased onset of pneumonia, but also to increases in airway pressure and even to barotrauma [31,32]. Pulmonary barotrauma is one of the best-known complications of positive pressure mechanical ventilation and can cause pneumothorax, pneumomediastinum, subcutaneous emphysema. The most frequent disadvantages in NIPPV are related to lesions caused by ventilatory prostheses which can affect up to 50% of treated patients [33,34].

The pressure ulcers created by the interface between the patient and the machine are certainly among the most important, not only for the damage per se created on the patient's body, but also because, by reducing tolerance and comfort, they can cause an asynchrony between patient and ventilator, an incorrect delivery of lung flows and volumes up to point of having to suspend the non-

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invasive mechanical ventilation [35-38]. Other disadvantages that can be encountered in positive mechanical ventilation, especially if air mixtures with a high concentration of oxygen are used, are: oxidative damage to the bronchial epithelium, such as a reduction in the motility of the vibrating cilia with a reduction in mucociliary clearance, and alveolar damage [39] with the possibility of pulmonary edema and pulmonary micro-atelectasis [40,41].

Ventilatory mechanics

Ventilatory mechanics differs substantially between the two modes of ventilation: negative extra-thoracic and positive intrathoracic. Therefore, having to apply a combination of these two methods, it is necessary, first, to have some clarification about them and then to analyze the effects derived from their association.

As already indicated, the transairway pressure (P_{TA}), in the inspiratory act determined by the normal subject or by negative pressure ventilation, will result in a lowering of the pleural (P_{pl}) and alveolar (P_A) pressure with aspiration of air from the outside, while in case of positive pressure ventilation, there will be an increase in the pressure on the upper airways (P_{awo}) with insufflation of air from the outside toward the inside of the chest.

Now let's see what happens in the analysis of a normal respiratory act. To carry out this act, a normal subject, based on his own muscular activity, must oppose a force or pressure (P_{rs}) which must overcome those present inside the lungs (P_L) and the rib cage (P_{cw}) according to the formula:

$$P_{rs} = P_L + P_{cw} \tag{1}$$

The same forces that oppose the movement can also be expressed as resistances which consist of:

- elastic resistances of the thoraco-pulmonary system (P_{el}), which depend on the elastance of the entire system (E_{rs}) and which increase with the increase of the volume of the lung;
- resistances resulting from the production of an air flow (P_{res}), which are influenced by the air resistances present within the bronchial tree;
- inertial resistances (P_{in}), which increase with the acceleration of the thoraco-pulmonary movement or with the variation of the air flow in the unit of time. The inertial resistances are, however, negligible;
- possible pressure resistances, present at the end of expiration (intrinsic PEEP), which we currently do not consider, since they are null in a healthy subject.

Hence, the formula (1) can also be written as:

$$P_{rs} = P_{el} + P_{res} + P_{in} = (E_{rs} \cdot \Delta V) + (R_{aw} \cdot V') + P_{in} \tag{2}$$

This second formula is commonly called the Equation of Motion of the Respiratory System.

We also know that the total elastance (E_{rs}) is the sum of the lung elastance (E_L) and the elastance of the chest wall (E_{cw}), that is:

$$E_{rs} = E_L + E_{cw} \tag{3}$$

So, we can rewrite formula (2) as follows:

$$P_{rs} = P_L + P_{cw} = ((E_L + E_{cw}) \cdot \Delta V) + (R_{aw} \cdot V') + P_{in} \tag{4}$$

To mobilize the entire thoraco-pulmonary system and generate an inhalation or an exhalation requires a force, i.e., the P_{TA}, which will determine a pressure difference between the external airways (P_{awo}), and the alveoli (P_A), and changes sign depending on whether one is inhaling or exhaling, or an equivalent force, the transpulmonary pressure (P_L), which will create a pressure difference between the alveolar pressure (P_A) and the pleural pressure (P_{pl}).

To obtain an inspiratory act one can intervene in two distinct and opposite ways:

- increasing the pressure in the upper airways and pushing air from the outside to the inside of the chest (positive pressure ventilation or PPV).
- reducing the pressure at the level of the alveoli and sucking air from the external environment towards the alveoli (negative pressure ventilation or NPV).

The expiration begins with the suspension of the mechanical activity of the ventilator and, generally, it is a passive act linked to the force of the elastic return of the thoraco-pulmonary system.

In the case of "positive + negative synchronized ventilation", we can assume that the two machines, in a synchronous way, place their force of action on the two diametrically opposite parts of the chest: the first machine acts on the airways, then on the lung parenchyma and on the pleural space (PPV); and the second acts on the thoracic cage, then on the pleural space and on the lung parenchyma (NPV), with both facing and overcoming, in a prevalent manner, the first the lung elastance (E_L) and the second the rib

	End of expiration				Inspiration				End of inspiration				Expiration			
	H	P	N	**P+N**	H	P	N	**P+N**	H	P	N	**P+N**	H	P	N	**P+N**
$P_{TA}= P_{awo} - P_A$	0	0	0	**0**	-5	-5	-5	**-10**	0	0	0	**0**	2	2	2	**4**
P_{awo}	0	0	0	**0**	0	10	0	**10**	0	10	0	**10**	0	4	0	**4**
$P_A= P_L + P_{pl}$	0	0	0	**0**	-5	5	-5	**0**	0	10	0	**10**	2	6	2	**8**
$P_L= P_A - P_{pl}$	5	5	5	**10**	7	7	7	**14**	10	10	10	**20**	8	8	8	**16**
$P_{pl}= P_A - P_L$	-5	-5	-5	**-10**	-12	-2	-12	**-14**	-10	0	-10	**-10**	-6	-2	-6	**-8**
P_{cw}	-5	-5	-5	**-10**	-2	-2	-2	**-4**	0	0	0	**0**	-2	-2	-2	**-4**
P_{mus}	0	0	0	**0**	-10	0	0	**0**	-10	0	0	**0**	0	0	0	**0**
P_{neg}	0	0	0	**0**	0	0	-10	**-10**	0	0	-10	**-10**	0	0	-6	**-6**
$P_{rs}= P_L + P_{cw}$	0	0	0	**0**	5	5	5	**10**	10	10	10	**20**	6	6	6	**12**
P_{bs}	0	0	0	**0**	0	0	-10	**-10**	0	0	-10	**-10**	0	0	-6	**-6**

Table 1. Example of pressures inside the chest, during the single moments of a complete ventilatory act, found in the course of a normal breath of a healthy subject (H), in the course of positive pressure ventilation delivered in the airways (P), of negative extrathoracic ventilation (N) and ventilation corresponding to the sum of the positive and negative pressure (P + N) administered simultaneously.

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cage elastance (E_{cw}). Needless to say, we must bear in mind that it is the set of all the forces, pressures and resistances that must be overcome by the ventilators in order to perform a mechanical act. In this act, it is essential to always remember that PPV increases the pressure inside the airways and at the alveolar level, while NPV, being a negative pressure, lowers the same pressures. With the combined use of both ventilators the increased pressure in airways created by the PPV is counterbalanced by the action of the NPV. The forces present within the thorax are represented in Figure 1.

Now, if we take into consideration Table 1, in which numbers are expressed in cmH_2O, and we observe the ventilatory mechanics generated by the muscular activity of a normal subject (H), compared to one resulting from the application of a positive pressure ventilator (P) and one relative to a negative pressure ventilator (N), it is easy to find that, respectively, the transairway pressure, the transpulmonary pressure and the pressure relative to the entire respiratory system (P_{rs}) are always the same in every single phase. In other words, applying equal forces to the thoraco-pulmonary system with the three methods (H, P, N), the pressures referred to the P_{TA}, P_L and P_{rs}, at each moment of the ventilatory cycle (end of expiration, inspiration, end of inspiration, expiration), are always identical to each other. However, it must be considered that PPV, having a different physiological mechanism from muscular respiration and from that of a negative pressure ventilator, increases the pressure inside the airways and at the alveolar level, while the other two ventilation modes, being both negative pressures, tend to lower the same pressures.

Looking at Table 1 it is easy to see that, except for the moment of rest at the end of the expiration, with positive pressure mechanical ventilation (P) there are always positive pressures in the airways and alveoli, while with muscular and negative ventilation (N), especially during the inspiratory act, there are negative pressures. In the same Table, the columns relating to this new "positive + negative synchronized ventilation" (P + N) have also been inserted, in which the sums of the relative pressures delivered are expressed. It is easy to find that the total forces necessary for the mobilization of the thoraco-pulmonary system (P_{TA}, P_L, P_{rs}), in this case, are doubled and corresponding to the respective sums of the pressures delivered with the positive pressure ventilator and the negative pressure ventilator. However, what emerges mostly is that the P_A is always equal to zero ($P_A = 0$) throughout the inspiratory act, despite the fact that a doubled force is being applied by the two machines at the same time. This is due to the fact that the positive pressures, delivered by the positive pressure ventilator, are counterbalanced by the negative pressures produced by the second negative pressure ventilator. The importance of this finding is confirmed by the fact that it is precisely in the inspiratory phase that the greatest damage from the ventilator can occur, since, in this period, the ventilator delivers all its power, while expiration is normally an act in which this force is interrupted and the pulmonary elastic return is exploited. So, zeroing the pressures inside the airways and alveoli becomes a fundamental fact. We also know that the duration of the inspiration, which is generally always shorter than the expiration, is the moment in which increased risks of pressure peaks can occur.

The idea of combining the two mechanical ventilation techniques, *i.e.*, positive pressure ventilation with negative pressure ventilation, came precisely while taking into account these physiological considerations. Furthermore, since the single forces delivered by the two ventilators act in a diametrically opposite direction with respect to the lungs and the thorax, no side effects, due to the simple doubling of a force delivered in one direction, should be encountered.

Equipment used

In the application of this concept and in its development from an operational point of view, that is creating a "positive + negative ventilation", it was necessary to synchronize both machines with each other, so that there was no delay in the application and modulation of the individual forces. This was possible with the collaboration of all the technical and engineering staff of the Company

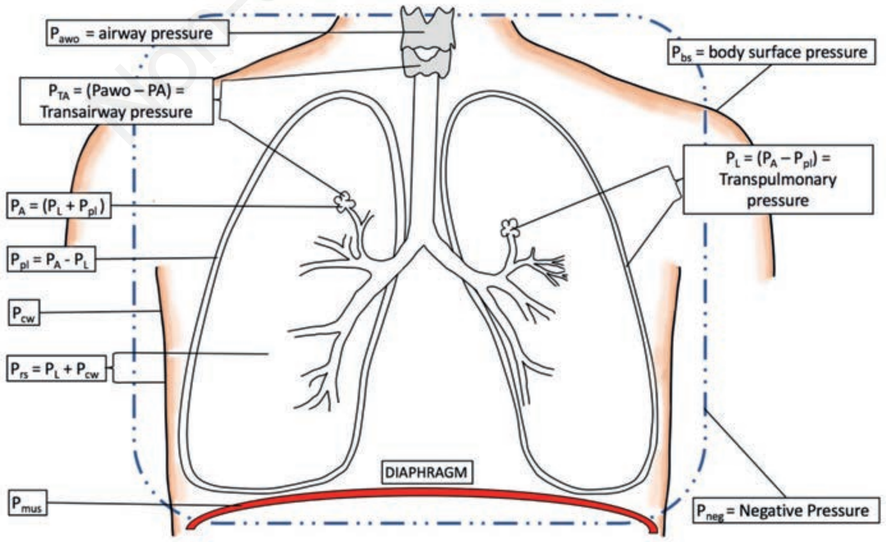

Figure 1. Pressures detectable inside the chest. P_{awo}, airway pressure (in contact with the external environment); P_{TA}, transairway pressure; P_A, alveolar pressure; P_{pl}, pleural pressure; P_{cw}, chest wall pressure; P_{rs}, pressure of the entire respiratory system; P_{musc}, muscle pressure; P_{bs}, body surface pressure; P_L, transpulmonary pressure; P_{neg}, negative pressure.

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DIMA Italy from Bologna that, by embracing the idea, made possible the realization of this innovative project. An essential point in the study of this new mechanical ventilation was the choice of identifying which was the "master" machine and which was the "server". In other words, it was necessary to try to give maximum sensitivity on the part of the sensors that acted, above all, as triggers for the start and stop of the inspiratory act. Given the greater sensitivity of the flow triggers, placed in the patient circuit of positive pressure ventilators and also in consideration of the greater possibility of measuring, moment by moment, the entity of flows, volumes and pressures during the entire duration of the ventilatory cycle, it was easier to assign the master function to the positive pressure ventilator rather than to the negative pressure ventilator. The energy delivered by the negative pressure ventilator (NPV) synchronously accompanied the positive pressure ventilator (PPV) and enhanced its strength.

From a technological point of view, this new ventilation has been designed to work both in a completely non-invasive way (Figure 2) and in an invasive way (Figure 3).

The machines used, both by DIMA Italy, were: "Luna Ventilator", a positive pressure ventilator, and "Pegaso Ventilator", a negative pressure ventilator.

The first machine, set in Pressure Support (PS), delivered the air mixture into the upper airways through a circuit connected to a full face or oral mask (in non-invasive mode), or it was connected to a tracheal tube or a tracheostomy tube (in invasive mode). The patient had a high degree of control over the ventilator: inspiratory initiation, ventilatory rate, delivered tidal volume. The second ventilator, always acting in a non-invasive way, delivered negative extrathoracic pressures through the use of a shell, of different sizes depending on the body of the patient to be treated, placed in front of the chest and fastened by elastic straps. The pressures delivered were preset by the intensivist pulmonologist and were identical for both the first and second ventilator.

Clinical applications

Methods

This new mode of ventilation was applied, in a completely non-invasive way, for short periods of time (1 hour), on patients suffering from exacerbated COPD and hospitalized in the Respiratory Intensive Care Unit of the "Colonnello D'Avanzo" Hospital, part of "Ospedali Riuniti di Foggia" (Foggia General Hospital) in Foggia, Italy. The application of all three ventilation modes, namely NIPPV, NPV, NIPPV + NPV, took place randomly and on different days, on 8 patients. Anthropometric, physiological, clinical and blood gas analytical data were collected on these patients to evaluate their effects and possible complications.

The study was based on the need to treat elderly patients, suffering from COPD and severe acute respiratory failure, with a mode of mechanical ventilation that maintained its characteristics of non-invasiveness, which had to be more effective without increasing the risks for the patients. The treated patients (6 males and 2 females), all suffering from severe acute hypoxemic-hypercapnic respiratory failure (ARF), were decidedly elderly (mean age of patients = 74±8.6 years). The initial mean values of pH (= 7.31±0.05) and $PaCO_2$ (= 85.01±12.25) indicated the severity of their respiratory insufficiency and clinical status. Furthermore, their functional deficits were evident. Mean FEV_1 values were = 50%±5% than theoretical; the average values of the FVC = 73% ± 6% than theoretical; the mean values of the FEV_1/FVC ratio = 67.5±3 than theoretical. The pressures set on the ventilators were the same as those used with non-invasive mechanical ventilation (positive or negative) previously used on each individual patient, prior to the study.

The study involved measuring blood gas analytical and clinical changes at the beginning and after one hour of treatment with the three modes of mechanical ventilation or with NIPPV and NPV alone and with combined ventilation NIPPV + NPV. Possible side effects were also to be recorded, but none was present in any patient and with any type of mechanical ventilation applied. There were no changes in blood pressure, heart rate and ECG values in the course of the three methods used.

The statistical elaborations, carried out with the Student's *t*-test, have shown very interesting results. After 1 hour of ventilatory treatment, with the new ventilation (NIPPV + NPV) it was seen that the pH had undergone an important and evident change for betterment (pH from = 7.31 had risen to = 7.42) with a very high significance (p=0.0008), while NIPPV and NPV applied separately were not significant. Carbon dioxide values underwent a marked

Figure 2. Woman subjected to positive + negative synchronized ventilation (PNSV) administered non-invasively.

Figure 3. Woman subjected to positive + negative synchronized ventilation (PNSV) administered invasively while being intubated.

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improvement with NIPPV + NPV ($PaCO_2$ reduced from 85.01 mmHg to 61.93 mmHg), with high significance (p=0.002), while significance was lower (p=0.02) with only NIPPV or absent with only NPV. There were no statistically significant changes in the PaO_2/FiO_2 ratio with the three ventilatory modes. All these data are summarized and graphed in Figure 4.

These encouraging data, despite the small number of patients studied, showed how, after only one hour of application of the non-invasive positive + negative ventilation, important ventilatory and clinical benefits were obtained without any side effects.

Indeed, these results of NIPPV + NPV, which we can consider excellent when compared with the other two conventional ventilation modes applied separately, were due to the application of doubled forces on the thoraco-pulmonary system. Therefore, it was logical to expect such an obvious result. But what was more important, in this case, was the verification of the operational feasibility of this new mode of ventilation and, in particular, that there were no complications or side effects. In reality these were not expected, since the alveolar pressures, as previously explained, were counterbalanced by the two ventilatory modes, but neither could they be excluded a priori with certainty. In the same period of study [1] we also applied the positive + negative synchronized mechanical ventilation to some patients already intubated or tracheostomized, that is, invasively ventilated (IPPV + NPV).

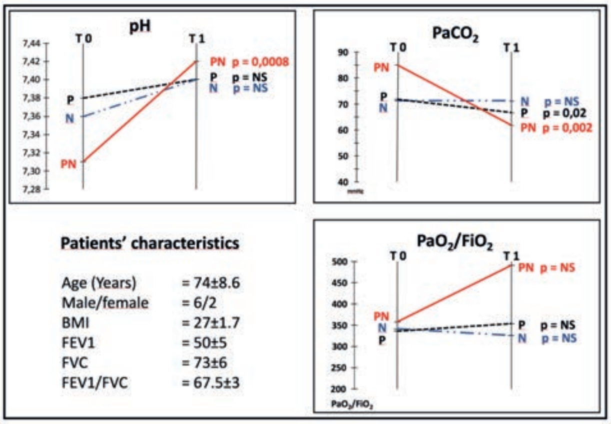
Patients were not sedated and ventilation was assisted and uncontrolled. The mode set on the positive pressure ventilator was "pressure support" (PS) and the one set on the negative pressure ventilator, being synchronized, followed exactly the cyclical trend of the first ventilator. The pressures set in the IPPV (both of the PS and of the eventual PEEP) were those previously used on the ventilator of the ICU before the application of the new ventilation, while the negative pressures set in the NPV were the same value as those set in the "pressure support", with the exclusion of PEEP. An additional negative pressure equivalent to PEEP could be added by making the agent ventilator cycle externally on two levels of negative pressure, but this was not used in the study.

Patients, awake and cooperating and without any level of sedation, with their muscle strength, activated the inspiratory trigger of the positive pressure ventilator and initiated the inspiratory act. Exhalation began when the positive pressure ventilator reached the expiratory trigger level set in the machine or, voluntarily, by the patient. Even in this case, the application of the positive + negative synchronized ventilation took place for 1 hour.

The physiological principle, on which the application of the two machines was based, was the same as that studied in a completely non-invasive way and the results were equally encouraging, but, due to the onset of the COVID-19 pandemic that interrupted the study, at the moment it is not possible to process statistical data. At any rate, it is possible to state that "positive + negative synchronized mechanical ventilation" (PNSV) is also applicable to patients already in invasive mechanical ventilation as it can be seen in Figure 3. In some patients, moreover, an attempt was made to evaluate other aspects related to ventilatory mechanics. Therefore, pulmonary mechanical function monitoring was performed by electrical impedance tomography (EIT) using a Draeger Pulmo Vista® 500 device.

Figure 5 concerns a patient intubated and ventilated under pressure support only in invasive mode, while Figure 6 concerns the same patient to whom the double synchronized mechanical ventilation was applied. The same argumentation concerns another patient represented respectively in Figures 7 and 8.

With a positive + negative mechanical ventilation there is an evident greater surface area of lung being ventilated, that is, a greater alveolar recruitment. This can also be verified visually by



Patients' characteristics

Age (Years) = 74±8.6
Male/female = 6/2
BMI = 27±1.7
FEV1 = 50±5
FVC = 73±6
FEV1/FVC = 67.5±3

Figure 4. Patient characteristics and changes in pH, $PaCO_2$ and PaO_2/FiO_2 ratio after 1 hour of treatment with positive ventilation (P), negative extrathoracic ventilation (N) and synchronized positive + negative ventilation (PN), as detected in the indicated study [1].

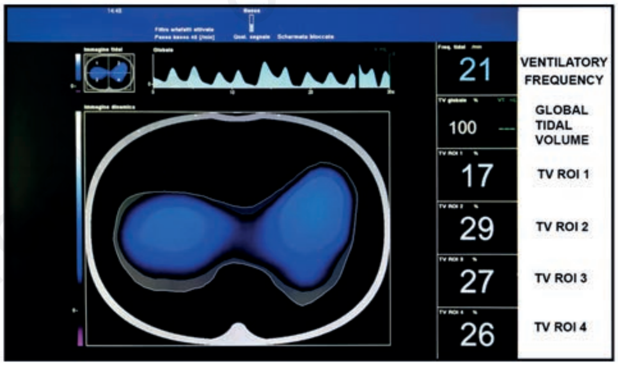


Figure 5. Electrical impedance tomography detected in a patient receiving positive pressure ventilation only. The values found in the ROI boxes, to the right of the figure, indicate the percentage of tidal volume of interest for each quadrant. The ROI 1 quadrant corresponds to the left anterior thoracic portion, the ROI 2 to the right anterior, the ROI 3 to the left posterior, and the ROI 4 to the right posterior.

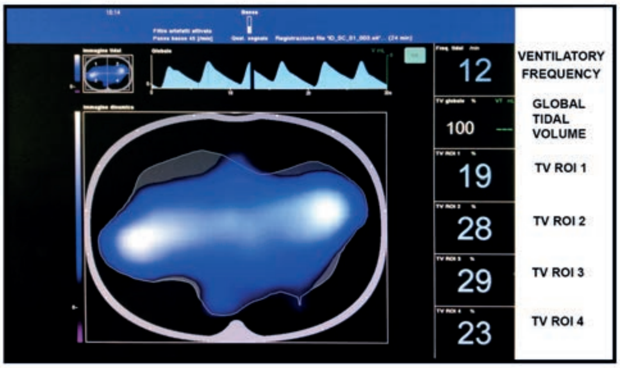


Figure 6. Electrical impedance tomography detected in the same patient as Figure 5 receiving positive + negative synchronized ventilation. The percentage of values shown in the ROI quadrants is no different from that shown in Figure 5, but the ventilatory rate has significantly decreased. There is also visually a greater pulmonary alveolar recruitment.

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comparing the respective central areas of the images, colored blue and white. In the case represented in Figures 5 and 6, looking at the quadrants shown on the right as ROI (ROI 1 and ROI 2 for the anterior quadrants, ROI 3 and ROI 4 for the posterior quadrants of the thorax), the percentages are similar. This explains why the increase in the ventilated lung area occurred homogeneously throughout the chest. In the case, instead, represented in Figures 7 and 8, this greater recruitment took place in the posterior areas of the thorax, confirmed by a corresponding percentage increase in the ROI 3 and ROI 4 quadrants which, respectively, went from values of 23% and 25% to values of 33% and 27%.

A greater area affected by pulmonary ventilation is certainly a positive fact, and if this occurs in the posterior areas of the thorax, it represents an additional advantage. In fact, these are the most difficult areas to recover when trying to recruit more lung tissue [42]. This, of course, occurs if the patient is not ventilated in a prone position.

We find a clear difference in the ventilatory rate compared to the single positive pressure ventilation (IPPV). In fact, from the respective values of ventilatory rate of 20 and 21 acts/min with single positive pressure ventilation, we passed to a frequency of 11 and 12 acts/min with the PNSV. This evident reduction of the ventilatory rate has been a fairly frequent finding in patients undergoing IPPV + NPV and can be explained by the fact that this method determines a ventilation with forces doubled in themselves, which, inevitably, lead not only to a greater alveolar recruitment, but also to a greater quantity of ventilated air. In fact, the patients, being ventilated in "pressure support mode" (PS) set on the positive pressure ventilator, had full control of the ventilatory rate which they modulated according to their metabolic respiratory needs. In this case, being faced with an improvement in gas exchange or an increase in oxygenation and an improvement in respiratory insufficiency, they instinctively slowed down their ventilatory rate.

The blood gas values, measured in patients with positive + negative invasive mechanical ventilation (IPPV + NPV), as well as those found in patients undergoing positive + negative non-invasive ventilation (NIPPV + NPV) showed a clear overall improvement.

Discussion

The positive + negative synchronized ventilation is a new mode of ventilation that paves the way to new studies on ventilatory mechanics and on how to deal with respiratory insufficiencies. The simultaneous use of two ventilators, one acting with pressures and flows administered internally to the chest (PPV), the other with negative pressures administered externally to the chest (NPV), has allowed us to better understand some physiological mechanisms and has given us the possibility of new therapeutic pathways in an intensive care setting. Both machines must always face and overcome all the forces present in the chest which, in this case, are halved for each machine. A very important point is that the pressures in the airways, and in particular in the alveoli, remain at zero throughout the inspiratory act, even when the doubled forces are being used. Quite another thing would have been if an increase or doubling of the power of the positive pressure ventilator had been used, which would have seen a parallel increase in pressure within the airways and alveoli, with the danger of barotrauma and/or cardio-circulatory complications. The clinical, functional and blood gas analytical results, as we have seen, were very positive and without side effects. Nothing would prohibit the use of halved or lower pressures to lighten the power applied to the lungs and have forces which, though added together, are equivalent to those of a single ventilator being normally used. The ability, then, to act on the control panel of both machines and, therefore, to modulate their power, offers the intensivist doctor more weapons in the fight against respiratory failure.

An undoubted advantage is the greater pulmonary recruitment with the possibility of opening some lung areas, in particular the posterior areas, previously hard to recruit by positive pressure ventilation, which was also encountering a greater difficulty in finding a correct driving-pressure. In this new ventilatory mode, regarding the use of negative pressure, only the cuirass was used. It would also be interesting to study the effects of a more powerful and larger ventilator, such as the iron-lung, in its more modern and lighter versions. This is because the iron-lung effects also an action on the abdominal part of the patient which directly mobilizes the diaphragm, resulting in enhancement of the ventilatory act. In addition, better than any other negative pressure ventilators, the iron-lung can exert its power even during exhalation, creating a positive pressure inside the body (biphasic ventilation).

A new field yet to be explored concerns the cardio-circulatory hemo-dynamics and heart-lung interaction in the course of this new ventilatory modality. The negative effects of positive pressure ventilation on cardiac hemo-dynamics have long been known.

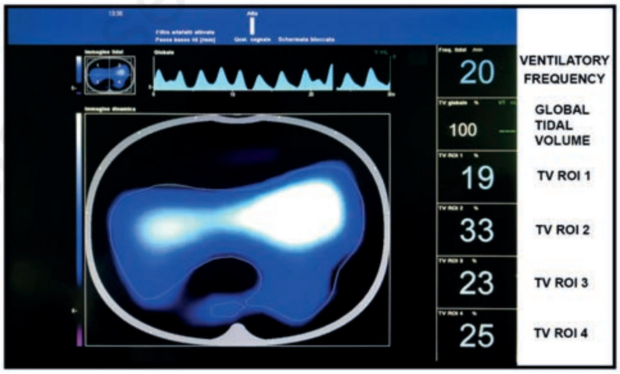

Figure 7. **Electrical impedance tomography corresponding to another patient undergoing positive pressure ventilation only. The percentage of tidal volume detected in the anterior quadrants (ROI 1 and ROI 2) is slightly higher than that detected in the posterior quadrants (ROI 3 and ROI 4).**

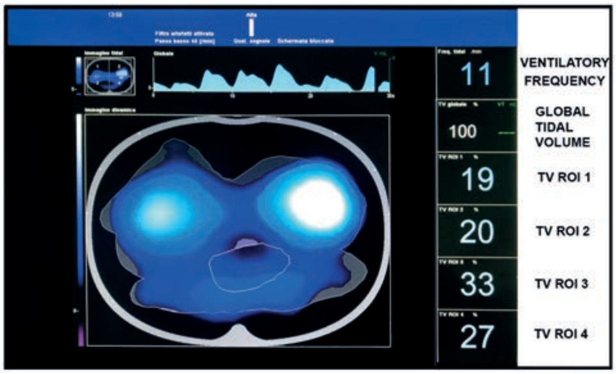

Figure 8. **The same patient as in Figure 7, undergoing positive + negative synchronized ventilation. Note the greater pulmonary alveolar recruitment, mainly involving the posterior parts of the thorax (ROI 3 and ROI 4 increased in percentage). Also in this case the reduction in respiratory rate is evident.**

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These effects are reflected proportionally to the levels of positive pressure administered, with or without PEEP, to a reduction in venous return (VR), stroke volume (SV) and cardiac output (CO) up to a reduction of the systemic arterial pressure [43,44]. Less known are the effects on hemo-dynamics during negative mechanical ventilation (NPV). Some studies, carried out in the surgical field, have shown that, with the application of negative extrathoracic pressure, the stroke volume index (SVI) and cardiac index (CI) were significantly increased [45,46]. Other authors have shown that the use of Biphasic Cuirass Ventilation allowed a reduction in mean pulmonary arterial pressure (mPAP), and an improvement in pulmonary artery occlusion pressure (PAOP), the cardiac index (CI) and serum NT-proBNP levels compared with baseline [47]. At this point, it can be assumed that the "positive + negative synchronized ventilation" would allow a greater balance in the pressures that affect cardio-pulmonary hemo-dynamics, since the possible negative effects of one mode can be compensated by the other ventilatory mode. From the foregoing it is clear that the studies on this new ventilatory modality are still in their infancy and this PNSV does not exclude, *a priori*, any pathological situation to be treated. ARDS could also be treated, considering that, in this disease, the ventilable parenchyma could be greatly reduced (the so-called "baby lung") and inhomogeneous [48], resulting in significant local stress and pulmonary tension [49]. Precisely this reduction in ventilable lung volume would require great care in setting the driving pressure or in the delivery of pressures, flows, volumes and frequencies to be used as well as in setting a PEEP based on the measurement of the so-called stress-index [50]. It should also be kept in mind that the danger of barotrauma is higher in the treatment of patients suffering from ARDS due to COVID-19 [51] and that the difficulty in obtaining sufficient lung recruitability is further increased [52].

The goal of proper ventilation is to improve alveolar recruitment, to slow down the ventilatory rate, to counterbalance alveolar edema and to reduce hyperventilated areas and relative pressure increases [53]. The danger of creating local stress and sectorial pressure peaks is always possible when only a positive pressure ventilator is used, while, in our opinion, in the case of the PNSV, the possibility of lowering or zeroing the alveolar and airway pressures, of recruiting previously unventilated areas and slowing the ventilatory rate, paying always attention to carefully modulate the forces delivered by the two machines, could offer an additional weapon in the treatment of this pathology. This would also affect the different pressure ratio between well ventilated and poorly ventilated lung units with an overall reduction in respiratory stress.

It is logical that, in the case of ARDS, the total pressure to be applied to the chest, albeit divided between the two machines, should be close to that applicable to the single positive pressure ventilator. But, if, with a PNSV, the pressures at the alveolar level and in the airways are lowered, it should be easier to reach the optimal pressure balance to avoid the onset of acute lung injury and, therefore, of volutrauma and barotrauma. A case report concerning an intubated patient suffering from ARDS, treated with a combination of continuous negative pressure ventilator (CENPV) and a positive pressure ventilator in pressure-controlled mode with PEEP, was reported by Raymondos and collaborators [54]. These authors have demonstrated a first possibility of a combined approach of the two ventilatory methods in a field as difficult as the treatment of patients with ARDS, noting, as well, a progressive improvement of the patient. In this case, however, inside the self-built chamber, a continuous and unsynchronized negative pressure was delivered by the two machines, while, instead, it would have been possible to use the method just outlined.

Conclusions

The synchronization and the possibility to intervene separately on the controls of the two machines, allows to modulate, in each single ventilator, the flows, volumes and pressures to be delivered.

Therefore, any ventilatory mode (both volumetric and pressumetric, with or without PEEP) is always allowed with the positive pressure device and the same amount of ventilatory freedom (continuous negative, synchronized negative, double level of synchronized negative pressure, negative in the inspiratory and positive phase in the synchronized expiratory phase) is available with the device acting externally, having, in addition, the indisputable advantage of being able to act on the entire thoraco-pulmonary system on two diametrically opposite fronts.

Therefore, in the near future, it will always be possible to use the "double positive + negative synchronized ventilation" by combining an external negative pressure ventilator with a positive pressure machine that uses the Neurally Adjusted Ventilatory Assist (NAVA) [55], since the latter is essentially based on the neuronal identification of inspiratory and expiratory triggers and on the ability to detect early PEEPi level. This integration would involve a rapid synchronization between the patient and the machines and an earlier and better adaptation of the patient to the ventilatory treatment.

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