Neural control of mechanical ventilation in respiratory failure

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Mechanical ventilation is a life-saving intervention for the management of acute respiratory failure. Its objective is to reduce excessive respiratory effort while improving gas exchange. By applying positive pressure to the airway, the mechanical ventilator assumes to a varying extent the work necessary to breathe, thereby unloading the respiratory muscles. In its most basic form, called controlled mechanical ventilation, a pre-set tidal volume is delivered at a fixed rate, irrespective of the patient's own breathing pattern. If the mechanical and natural respiratory cycles are not matched, however, the patient 'fights' the ventilator, causing discomfort, gas exchange deterioration and cardiovascular impairment[1]. To avoid discoordination between the patient and the ventilator, it is often necessary to suppress the patient's intrinsic respiratory drive with the use of hyperventilation, sedation or even muscle paralysis, which increase the risk of complications due to excessive ventilation[2–3], drug-related adverse effects[4] and muscle disuse atrophy[5]. Assisted modes of mechanical ventilation, in which the mechanical breath is triggered by the patient's own inspiratory effort, were developed to address this. These modes enable the patient to influence the machine cycling to a varying extent, depending on the specific mode utilized. Although it is believed that assisted modes can reduce side effects and complications associated with controlled mechanical ventilation, coordination between spontaneous breathing and mechanical assistance is not guaranteed. Poor interaction between the patient and the ventilator remains one of the main problems in the management of patients with acute respiratory failure[6–7].

Current methods to control partial ventilatory support

The ideal approach to coordinate mechanical assistance with patient demand would be to use the neural output of the respiratory center to control the timing and the magnitude of positive pressure applied by the ventilator (Fig. 1*a*). At present, airway pressure, flow or volume is used to initiate and, to a varying extent, regulate the mechanical ventilatory assistance. A fundamental limitation of this technology is that the ability of these signals to control the ventilator effectively can be expected to worsen with increasing respiratory dysfunction[8,9]. Control of ventilatory assistance by these signals is also limited by the additional resistance imposed by the endotracheal tube and the ventilator circuitry[10], or by the presence of air-leaks with uncuffed endotracheal tubes in the pediatric setting[11] and during non-invasive mask ventilation[12]. The ability of the patient to interact with the ventilator in these circumstances is substantially impaired (Fig. 1*b*).

Neural control of ventilatory assist

Direct measurement of the output of the respiratory center is presently not possible. Phrenic nerve activity has been used to regulate a 'servo-controlled' mechanical ventilator in animal preparations[13], but this approach is not feasible in humans. The next step transforming neural drive into ventilatory output (neuro–ventilatory coupling) is neural excitation of the diaphragm (Fig. 1*a*). Electrical activation of the diaphragm, which represents the spatial and temporal summation of both motor unit recruitment and firing frequency, is directly related to phrenic nerve activity[14]. Until recently, diaphragmatic electrical activity was considered unsuitable for clinical application because of the difficulty in providing a stable signal uncontaminated by the electrical activity of the heart and esophageal peristalsis, noise and artifacts related to electrode position or motion. Today's computer technology and newly developed methods for signal acquisition and processing have made it possible to obtain reliably diaphragmatic electrical activity, free of artifacts and noise, and in real time[9,15,16]. However, use of diaphragmatic electrical activity to estimate respiratory center output requires integrity of the phrenic nerve and neuromuscular junction and assumes the diaphragm to be the primary inspiratory muscle.

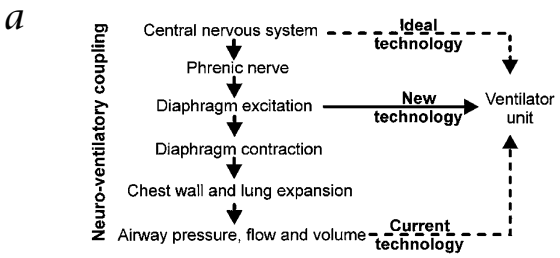
Neural triggering

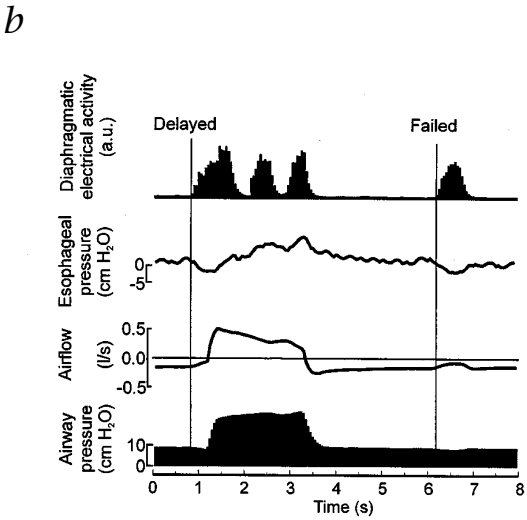
Current methods can fail to detect the onset of inspiratory effort accurately because of the delay introduced by the various steps in the neuro–ventilatory coupling process, particularly with respiratory dysfunction (Fig. 2*a*). In a patient with severe chronic obstructive pulmonary disease (Fig. 2), the expiratory flow limitation is associated with gas trapping and an increase in intrathoracic pressure referred to as auto or intrinsic positive end-expiratory pressure[17] (PEEP). Intrinsic PEEP must be overcome before airway pressure can be lowered or flow generated to trigger the ventilator, and therefore imposes an additional load on the respiratory muscles. As indicated by the negative deflection in esophageal pressure, most of the patient's inspiratory effort has been generated before positive pressure is provided by the ventilator. Intrinsic PEEP can be counterbalanced, at least in part, by applying PEEP externally

Methods

The following describes an automated method for on-line acquisition and processing of diaphragmatic electrical signals that represent neural drive to the diaphragm[9,15,16]. Diaphragmatic electrical activity is recorded from an array of bipolar electrodes (Fig. 1*c*, i) positioned in the lower esophagus (Fig. 1*c*, ii). Signals from each electrode pair are differentially amplified (Fig. 1*c*, iii), digitized and processed (Fig. 1*c*, iv). Filters that give the highest possible signal-to-disturbance ratio were determined from experimental data using Wiener filtering, implemented with individual filter links of low-pass, band-pass, high-pass and notch filter characteristics, and transformed into recursive time domain filters. The position of the electrically active region of the activated diaphragm (EARdi) is determined by cross-correlating signals obtained along the electrode array[16]. With the perpendicular electrode array arrangement, all simultaneously obtained signals are in phase. Signals on opposite sides of the EARdi correlate with extreme negative values, whereas signals on the same side of the EARdi correlate with extreme positive values[16]. The electrode pairs with the most negative correlation value span the EARdi. Subtracting these signals minimizes diaphragm-to-electrode position filtering and enhances signal-to-noise ratio[15]. Signal segments with residual disturbances due to cardiac electrical activity or common mode signals are evaluated via specific detectors, and can be replaced by a predicted value (for example, the previously accepted value)[9]. The processed signal is then transferred to the ventilator unit (Fig. 1*c*, v) for monitoring and regulating ventilatory assist.

through the ventilator circuit[17–19]. However, determining intrinsic PEEP in the clinical setting is not easy[17–22]. When the inspiratory muscles are active, as with assisted modes of mechanical ventilation, correct assessment of intrinsic PEEP requires measurement of the intrathoracic pressure and a relaxed expiration. If the expiratory muscles are active, which raises intrathoracic pressure during expiration, the measurement of intrinsic PEEP can be considerably overestimated[19,21,23,24]. Active expiration is common in mechanically ventilated patients with intrinsic PEEP, but there are no means available to account routinely for its influence in the clinical setting[19,21,24]. If excessive or undue[23], external PEEP can produce further hyperinflation[25], with an additional mechanical disadvantage for the diaphragm[26–27], impaired hemodynamics[25,28] and gas exchange[25], and increased risk of barotrauma[25]. The use of diaphragmatic electrical activity to trigger the ventilator can correct this problem. Different from the technology now used to trigger the ventilator, the neural trigger is not affected by intrinsic PEEP and therefore does not require application of external PEEP for triggering purposes. When positive pressure is applied at the onset of diaphragmatic activity, the delay from the onset of inspiratory effort and mechanical assistance is shortened, the esophageal pressure deflection is reduced at a maintained tidal volume, and the actual work of breathing by the patient is thus decreased (Fig. 2*b*). In situations in which conventional triggering cannot provide ventilatory support in synchrony with the patient's neural inspiratory drive (Fig. 2*c*), implementation of neural triggering can greatly improve patient–ventilator interaction (Fig. 2*d*).





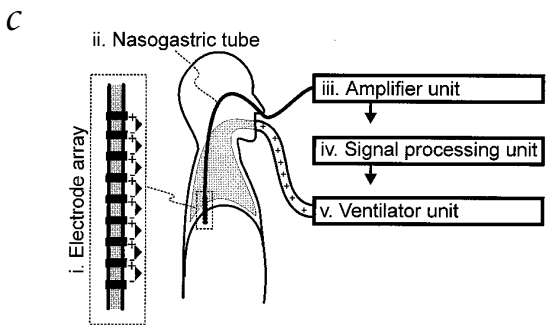


Fig. 1 Description of the new technology in perspective to current technology. ***a***, Steps necessary to transform central respiratory drive into an inspiration (that is, the neuro–ventilatory coupling; left), with indications for the levels (right) at which technology able to control a mechanical ventilator could be implemented. ***b***, Impaired patient–ventilator interaction during airway pressure triggered ventilatory assist. Left, delay from the onset of inspiratory effort, indicated by the beginning of diaphragmatic electrical activity (vertical lines) and the negative deflection in esophageal pressure, to the start of ventilatory mechanical assistance (reflected by the rise in airway pressure). Multiple inspiratory efforts, an extreme form of patient–ventilator asynchrony, are also shown. Right, a completely wasted inspiratory effort where the patient effort failed to trigger the ventilator, another form of severe patient–ventilator incoordination. ***c***, Electrode array arrangement (i), attached to a nasogastric tube (ii) normally used for feeding or other purposes. The electrode array is positioned in the esophagus at the level of and perpendicular to the crural diaphragm such that the active muscle creates an electrically active region around the electrode. Signals from each electrode pair on the array are differentially amplified (iii) and digitized into a personal computer, and filtered (iv) to minimize the influence of cardiac electric activity, electrode motion artifacts, and common noise, as well as other sources of electrical interference. The processed signal's intensity value is displayed for monitoring purposes or fed to the ventilator (v) to control the timing and/or levels of the ventilatory assist.

Neurally adjusted ventilatory assist

A challenging approach to improve patient–ventilator interac-

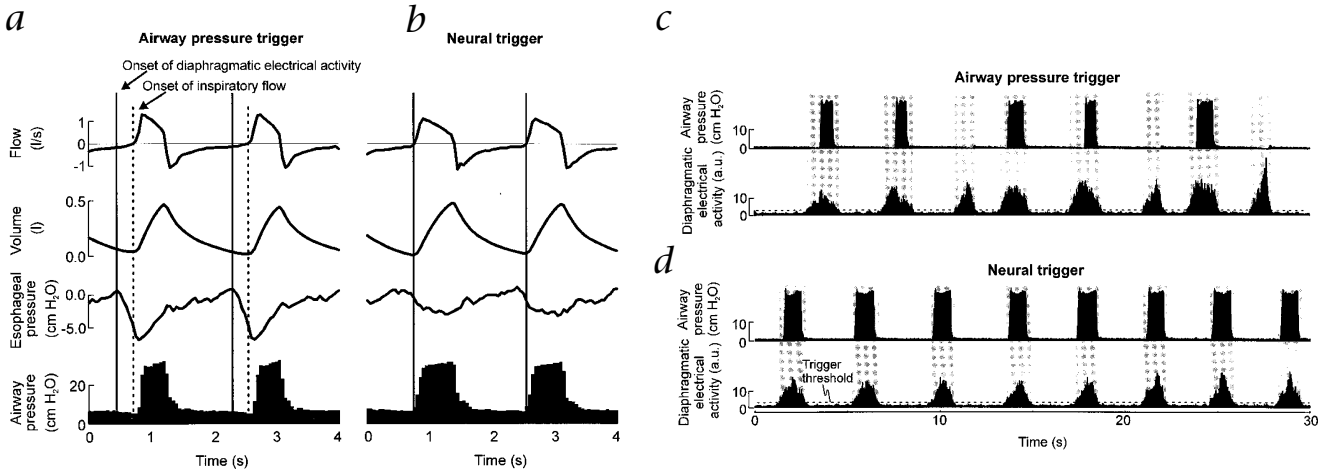


Fig. 2 Partial ventilatory support in two subjects with severe chronic obstructive pulmonary disease and acute respiratory failure. ***a***, Conventional pressure trigger: Mechanical ventilatory assistance starts when airway pressure decreases by a preset amount. The beginning of inspiratory effort (solid vertical line) precedes inspiratory flow by several hundred milliseconds. This delay is due to intrinsic PEEP and occurs despite externally applied PEEP. A further delay from the onset of inspiratory flow (vertical dashed line) to the rise in positive airway pressure is present, due to the mechanical limitation of the ventilator trigger. ***b***, Neural triggering. The ventilator provides support as soon as diaphragmatic electrical activity exceeds a threshold level. The delay to onset of inspiratory flow and increase in airway pressure is almost eliminated. ***c***, Poor patient–ventilator interaction with conventional pressure triggering. Diaphragmatic electrical activity (shaded areas) is poorly coordinated with the ventilatory support (indicated by increased airway pressure) and often results in completely wasted inspiratory efforts. ***d***, Implementation of the neural trigger (same patient and identical ventilatory settings, except for the trigger system, as in *c*) can restore the interaction between the patient's neural drive and the ventilatory support. a.u., arbitrary units (*c* and *d*).

tion is to match ventilatory support with patient demand[13]. Recently, this has been attempted by adjusting the level of machine support in proportion to the estimated patient's effort, the latter derived from flow, volume and knowledge of respiratory mechanics[29]. The use of this mode may be limited, however, by the fact that reliable determination of respiratory mechanics can be difficult and time consuming to obtain. In addition, its efficacy is adversely affected by variation in respiratory muscle function. Diaphragmatic electrical activity can also provide a means to give continuously ventilatory assist in proportion to the neural drive, both within a given breath (Fig. 3*a*) and between breaths (Fig. 3*b*), and will subsequently be referred to as neurally adjusted ventilatory assist. With neurally adjusted ventilatory assist, the magnitude of the mechanical support will vary on a moment-by-moment basis according to a mathematical function that represents diaphragmatic electrical activity times a gain factor selected on the machine. This allows the patient's respiratory center to be in direct control of the mechanical support provided throughout the course of each breath, allowing any variation in neural respiratory output to be matched by a corresponding change in ventilatory assistance (Fig. 3*a*). The level of assistance is automatically adjusted in response to changes in neural drive, respiratory system mechanics, inspiratory muscle function, and behavioral influences (Fig. 3*b*). Because of the coordination between diaphragmatic activation and ventilatory support throughout the breathing cycle, undue prolongation or premature interruption of mechanical assistance in relation to patient effort should be avoided.

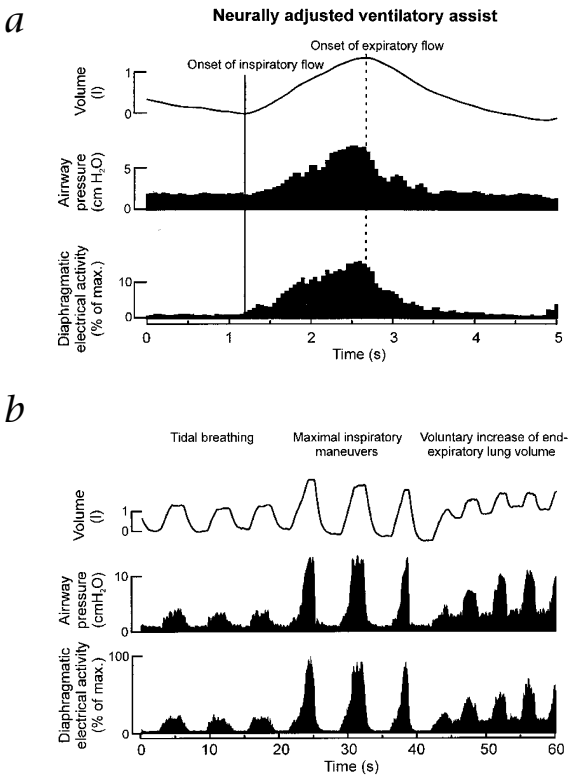


Fig. 3 Neurally adjusted ventilatory assist during a single breath (***a***) and during various breathing maneuvers (***b***). There is continuous proportional adjustments of airway pressure (reflecting ventilatory assist) with changes in diaphragmatic electrical activity (reflecting neural drive) during changes in tidal and end-expiratory lung volumes.

Clinical effect

By overcoming the problems associated with the current technology for triggering, neural triggering has the potential to improve patient–ventilator interaction and patient comfort

during assisted mechanical ventilation. Moreover, neurally adjusted ventilatory assist introduces a new dimension to mechanical ventilation. In fact, this represents the first form, to our knowledge, of assisted ventilation in which the patient's respiratory center can assume full control of the magnitude and timing of the mechanical support provided, regardless of changes in respiratory drive, mechanics and muscle function. Taking advantage of the intrinsic respiratory control reflexes, this technology may serve to reduce the risk of iatrogenic hyperinflation[25–27], respiratory alkalosis[2–3] and hemodynamic impairment[28,30,31]. Many patient groups should benefit from the use of neural triggering and neurally adjusted ventilatory assist, as long as the respiratory center, phrenic nerve and neuromuscular junction are functionally intact and there is no contraindication or limitation to electrode catheter placement. As the diaphragmatic electrical activity necessary to obtain a given airway pressure, flow and volume increases with the extent of respiratory dysfunction[8,9], the improvement with neural triggering and neurally adjusted ventilatory assist, relative to the current technology, will be particularly apparent in patients with the most severe respiratory impairment. Severe airflow obstruction with impaired and varying neuro–ventilatory coupling because of dynamic hyperinflation and intrinsic PEEP exemplifies this well[6,7]. Many of the concerns described above are exaggerated in the pediatric setting because of the high breathing frequencies, small tidal volumes, and use of uncuffed, small-bore endotracheal tubes (which result in high system impedance, air leaks and difficulty in reliably measuring flow and volume)[11]. Establishing patient–ventilator synchrony in infants also has the potential to improve oxygenation and to reduce the incidence of pneumothorax, the latter associated with an increased incidence of cerebral hemorrhage[32]. The use of diaphragmatic electrical activity to regulate ventilator operation would also be applicable to noninvasive forms of mechanical ventilation attained using either masks[19] with positive-pressure ventilators or machines that apply sub-atmospheric pressure around the thorax[33]. By improving patient–ventilator coordination, the new technology for neural control of mechanical ventilators has the potential to reduce ventilator-related complications substantially, to facilitate weaning from mechanical ventilation, and to decrease the duration of the stay in the intensive-care unit and overall hospitalization.

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