Respiratory Physiology & Neurobiology 228 (2016) 69–75

Contents lists available at ScienceDirect

Respiratory Physiology & Neurobiology

journal homepage: www.elsevier.com/locate/resphysiol

Driving pressure during assisted mechanical ventilation
Is it controlled by patient brain?

Dimitris Georgopoulos[a,b,*], Nectaria Xirouchaki[a], Nikolaos Tzanakis[b], Magdy Younes[c]

[a] Intensive Care Medicine, University Hospital of Heraklion, Medical School, University of Crete, Heraklion, Crete, Greece
[b] Pulmonary Department, University Hospital of Heraklion, Medical School, University of Crete, Heraklion, Crete, Greece
[c] Sleep Disorders Centre, Misericordia Health Centre, Winnipeg, Manitoba, Canada

ARTICLE INFO

Article history:
Received 17 January 2016
Received in revised form 3 March 2016
Accepted 15 March 2016
Available online 17 March 2016

Keywords:
Proportional assist ventilation
Reflex feedback
Chemical feedback
Respiratory system compliance
Tidal volume

ABSTRACT

Tidal volume (V_T) is the controlled variable during passive mechanical ventilation (CMV) in order to avoid ventilator-induced-lung-injury. However, recent data indicate that the driving pressure [ΔP; V_T to respiratory system compliance (Crs) ratio] is the parameter that best stratifies the risk of death. In order to study which variable (V_T or ΔP) is controlled by critically ill patients, 108 previously studied patients were assigned to receive PAV+ (a mode that estimates Crs and permits the patients to select their own breathing pattern) after CMV, were re-analyzed. When patients were switched from CMV to PAV+ they controlled ΔP without constraining V_T to narrow limits. V_T was increased when the resumption of spontaneous breathing was associated with an increase in Crs. When ΔP was high during CMV, the patients (n = 12) decreased it in 58 out of 67 measurements. We conclude that critically ill patients control the driving pressure by sizing the tidal volume to individual respiratory system compliance using appropriate feedback mechanisms aimed at limiting the degree of lung stress.

1. Introduction

T

idal volume (V_T) has been recognized as the variable that should be controlled during mechanical ventilation in order to avoid ventilator-induced lung injury (VILI) (Amato et al., 1998; The ARDSnet, 2000; Malhotra, 2007; Mascia et al., 2010; Serpa Neto et al., 2012; Futier et al., 2013). However, in a recent study on 3562 patients with acute respiratory distress syndrome (ARDS) enrolled in previously reported randomized trials and ventilated passively, Amato et al. (2015) showed that reductions in V_T or increases in external positive end-expiratory pressure (PEEP) increased survival only if associated with decreases in driving pressure [ΔP; static end-inspiratory plateau pressure (P_{plat}) minus PEEP, or V_T to respiratory system compliance (Crs) ratio]. Increases in ΔP were strongly associated with decreased survival, particularly at ΔP values above 15 cmH_2O.

ΔP essentially reflects the extent of lung stretch during tidal breathing. The respiratory system is endowed with mechanoreceptors that sense the degree of lung stretch. These tend to naturally protect the lung from over-distension. The most relevant responses here are (a) the Hering-Breuer inspiratory-inhibitory reflex, which inhibits the increase in inspiratory activity, and associated increase in lung volume, when a threshold lung stretch is reached during inspiration (von Euler, 1986; Clark and von Euler, 1972; Grunstein et al., 1973) and, (b) recruitment of expiratory muscle activity in the presence of increased respiratory drive and/or PEEP, which in the absence of expiratory flow limitation, reduces end-expiratory volume below passive FRC with the result that a larger tidal volume is obtained at the same end-inspiratory lung stretch (Younes and Remmers, 1981; Iscoe, 1998). Obviously, these reflexes cannot operate to protect the lung during passive ventilation.

With proportional modes of assisted mechanical ventilation [neurally adjusted ventilatory assist (NAVA) and proportional assist ventilation (PAV+)] the ventilator responds directly to instantaneous muscle activity (Younes, 1992; Sinderby et al., 1999). As a result, the operation of these native reflexes is restored. Studies in anesthetized animal models of ARDS have shown that allowing the animals to control their breathing pattern is at least as protective as the low V_T strategy (Brander et al., 2009; Mirabella et al., 2014). However, these stretch reflexes are considerably weaker in humans and influenced by anesthesia (Widdicombe, 1961; Clark and von Euler, 1972; Younes and Youssef, 1978) so that these animal results cannot be directly extended to unanaesthetized humans.

* Corresponding author at: Intensive Care Medicine, University Hospital of Heraklion, Medical School University of Crete, Heraklion, Crete, Greece.
E-mail address: georgop@med.uoc.gr (D. Georgopoulos).

http://dx.doi.org/10.1016/j.resp.2016.03.009
1569-9048/

We previously reported (Xirouchaki et al., 2008) on breathing pattern and respiratory mechanics in 108 critically ill patients ventilated with PAV+ for 48 h. The majority of patients (59.3%) met ARDS definition (Force et al., 2012) at study entry. P_{plat} averaged 17 cmH_2O while PEEP averaged 7 cmH_2O, giving an average ΔP of 10 cmH_2O, well below the values found by Amato et al. (2015) to adversely affect survival. Although these results indicate that, on average, the protective reflexes are effective, we did not examine the range of ΔP in individual patients. This is of importance since the potency of these reflexes is highly variable among mechanically-ventilated patients (Kondili et al., 2001; Younes et al., 2002). Accordingly, in the current study, we determined individual ΔP in these patients and examined how it related to ΔP when the same patients were ventilated with CMV using the currently accepted lung-protective strategy (The ARDSnet, 2000; Malhotra, 2007). We hypothesized that the patients' control of breathing system is adept at protecting the lungs by preventing high ΔP using appropriate feedback mechanisms, while not unnecessarily restricting tidal volume when this has no protective value.

2. Methods

One hundred and eight patients who were randomized in our previous study (Xirouchaki et al., 2008) to receive PAV+ [Puritan-Bennett 840 ventilator (Covidien, Boulder, CO)] were re-analyzed. Before switching to PAV+, the patients were on mechanical ventilation for at least 36 h and ventilated passively with a CMV mode (volume or pressure control) [see Ref. Georgopoulos et al., 2016]. Criteria for switching to PAV+ were (Xirouchaki et al., 2008): ability to trigger the ventilator at >10 breaths/min; PaO_2 > 60 mmHg, with fractional concentration of inspired O_2 (FIO_2) <65%; total [PEEP and intrinsic PEEP (PEEPi)] positive end-expiratory airway pressure <15 cmH_2O; pH > 7.30; no severe hemodynamic instability; no severe bronchospasm; and a stable neurological status. Initially, PEEP and F_IO_2 were set to values similar to those during CMV immediately before the randomization. The PAV+ assist was set relatively high [70% (70–70), median (interquartile range)]. Subsequently, specific pre-defined written algorithms were used to adjust the ventilator settings (Xirouchaki et al., 2008). PAV+ was continued for 48 h unless the patient met pre-defined criteria either for switching to CMV, or for breathing without ventilator assistance (Xirouchaki et al., 2008).

During CMV respiratory system mechanics were assessed within 8 h before switching to PAV+ (passive mechanical ventilation), using the 3-s occlusion technique on volume control mode with square-wave inspiratory flow-time profile (Bates et al., 1985; Gottfried et al., 1985). P_1 (the pressure level at which airway pressure drops immediately after end-inspiratory occlusion), P_{plat} ($P_{platCMV}$) and PEEPi were measured. During PAV+ V_T, P_{plat}, PEEP and $PEEP_i$ were measured approximately 5–10 min after switching to PAV+ and at 1, 4, 8, 12, 24, 28, 32, 36 and 48 h later (if the patient continued to be on PAV+). P_{plat} during PAV+ ($P_{platPAV+}$) was measured using a modification of end-inspiratory occlusion technique (Younes et al., 2001), and PEEPi by calculating the time course of elastic recoil pressure during expiration, assuming that expiration is passive [see Ref. Georgopoulos et al., 2016].

During CMV, the primary physician, who was not involved in the study, was responsible for ventilator settings based on the principles of lung protective strategy (V_T 4–7 ml/Kg, P_{plat} < 30 cmH_2O) (The ARDSnet, 2000). To follow the methods used in patients of the Amato et al. (2015) study, respiratory system compliance (Crs_{CMV}) was measured as $V_T/(P_{platCMV} - PEEP)$ and driving pressure (ΔP_{CMV}) was calculated as V_T/Crs_{CMV} ratio. Crs and ΔP during PAV+ (Crs_{PAV+}, ΔP_{PAV+}) were similarly calculated from average V_T (V_{TPAV+}), PEEP and average $P_{platPAV+}$ in the occluded breaths. Arterial blood gasses were measured during CMV and after switching to PAV+ at 1, 4, 8, 12, 24, 28, 32, 36 and 48 h later.

Data are given as median (25–75th interquartile range), unless stated otherwise. Proportions were compared using the Fisher exact test. Continuous variables were compared with Wilcoxon and Man-Whitney tests, as appropriate. Regression analysis was performed using the least square method. Linear mixed effect models on parameters of repeated measurements were used to investigate changes in various variables over time during PAV+. The values of the first four serial measurements, corresponding to an 8-h PAV+ period, were included in the model in order to compare with the corresponding variables obtained within the 8-h CMV period. $P < 0.05$ was considered as significant.

Table 1
P_1 and $P_{platCMV}$ during CMV and $P_{platPAV+}$ measured during the first 8 h on PAV+.

P_1 (cmH_2O)	20.5 (18.0–23.0)
$P_{platCMV}$ (cmH_2O)	17.8 (15.3–20.1)
$P_{platPAV+}$ (cmH_2O)	
0 h	17.2 (14.7–20.5)
1 h	16.5 (14.7–20.3)
4 h	16.4 (14.5–19.1)
8 h	16.5 (14.5–20.0)

Values are medians (interquartile range). P_1; the pressure level at which airway pressure drops immediately after end-inspiratory occlusion during controlled mechanical ventilation (CMV). $P_{platCMV}$; airway pressure measured at the end of the 3 s end-inspiratory occlusion maneuver during CMV. $P_{platPAV+}$; airway pressure measured 0.3 s after the end-inspiratory pause maneuver at the end of selected inspirations at 0, 1, 4 and 8 h on PAV+. For clarity of presentation, $P_{platPAV+}$ values after 8 h on PAV+ are not shown.

3. Results

Since the results were similar when patients with (n = 64) and without ARDS (n = 44) were analyzed separately [see Fig. 1, 2, 4, 5, 7–9 in Ref. Georgopoulos et al., 2016] we present data pertaining to all patients (n = 108). Also, the results were not modified if PEEPi was taken into consideration in calculating Crs (and thus ΔP), due to very low PEEPi in these patients (median PEEPi was <0.5 cmH_2O both during CMV and PAV +) (Xirouchaki et al., 2008).

Median and interquartile range of V_{TPAV+}, Crs_{PAV+} and ΔP_{PAV+} are shown in Fig. 1 and P_1, $P_{platCMV}$ and $P_{platPAV+}$ are reported in Table 1. VT_{PAV+}, Crs_{PAV+} and ΔP_{PAV+} during the initial 8-h PAV+ period did not differ as a function of time (linear effect model, $p > 0.05$). Therefore, the values of each variable during this 8-h period were averaged ($VT_{PAV+aver}$, $Crs_{PAV+aver}$ and $\Delta P_{PAV+aver}$) and compared to the corresponding values (VT_{CMV}, Crs_{CMV}, ΔP_{CMV}) obtained during CMV within 8 h before switching to PAV+. $\Delta P_{PAV+aver}$ did not differ from ΔP_{CMV} [10.2 cmH_2O (8.1–12.4) vs. 10.7 cmH_2O (9.0–12.9), respectively], while $VT_{PAV+aver}$ and $Crs_{PAV+aver}$ were significantly higher than VT_{CMV} and Crs_{CMV}, respectively (Fig. 1). During PAV+ a total of 744 measurements of VT_{PAV+}, Crs_{PAV+} and ΔP_{PAV+} were performed [median 8 (4–10) measurements per patient]. During CMV, V_T was relatively tightly controlled as dictated by the principle of lung protective strategy, and as a result ΔP_{CMV} was less than 15 cmH_2O in the majority of the patients (Fig. 2). When the patients were switched to PAV+, ΔP_{PAV+} (but not V_T) was tightly controlled by the patients (Fig. 2). Compared to CMV, in 83 out of 108 patients (76.9%) $VT_{PAV+aver}$ was higher, and in 70 of them (84.3%) this increase was associated with an increase in $Crs_{PAV+aver}$ (Fig. 3), [see also Fig. 3 in Ref. Georgopoulos et al., 2016]. When $Crs_{PAV+aver}$ was lower than Crs_{CMV} (n = 10), the increase in V_T was minimal [0.74 (0.62–0.79) ml/kg].

Fig. 4 shows individual differences between ΔP_{PAV+} and ΔP_{CMV} as a function of ΔP_{CMV}. Data are given for ΔP_{PAV+} measured at 5–10 min (Fig. 4A) and at 1 h (Fig. 4B) after switching to PAV+. At both times, a significant negative relationship was observed