Evaluation of Auto-Regulated Inspiratory Support During Rebreathing and Acute Lung Injury in Pigs

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BACKGROUND: Auto-regulated inspiratory support mode (ARIS) is an original closed-loop pressure-support system that regulates the slope (“A”) and the initial level (“B”) of the applied inspiratory pressure, in order to achieve an optimal minute ventilation under constrained respiratory frequency, tidal volume, and maximum inspiratory airway pressure. The servo-controlled design results in a more or less decreasing applied pressure. OBJECTIVE: The aim of this study was to evaluate the ARIS behavior, compared with pressure-support ventilation at a constant applied pressure. METHODS: ARIS and pressure-support ventilation were randomly applied to 2 pig models of increasing ventilatory demand induced by a rebreathing test (n = 6), and of altered lung compliance induced by bronchoalveolar lavage (n = 6). The breathing pattern, work of breathing, and blood gas values were compared. ARIS automatically increased the mean inspiratory airway pressure in both groups. This increase was obtained in the rebreathing group by increasing “B” (35 ± 3.5 cm H₂O vs 42.8 ± 2.5 cm H₂O) and in the lung-injury group by decreasing the absolute value of “A” (25 ± 5.5 cm H₂O/s vs 14.7 ± 8.6 cm H₂O/s). RESULTS: There were significant differences (p < 0.05) between ARIS and pressure-support ventilation. In the rebreathing group, tidal volume was 692 ± 63 mL versus 606 ± 96 mL, work of breathing was 1.17 ± 0.45 J/L versus 1.44 ± 0.27 J/L, and P_{aco₂} was 54 ± 9 mm Hg versus 63 ± 7 mm Hg. In the lung-injury group, respiratory frequency was 25 ± 4 breaths/min versus 42 ± 10 breaths/min, tidal volume was 477 ± 67 mL versus 300 ± 63 mL, work of breathing was 0.54 ± 0.3 J/L versus 0.99 ± 0.45 J/L, and P_{aco₂} was 36 ± 8 mm Hg versus 53 ± 15 mm Hg. CONCLUSIONS: The ARIS servo control operates correctly, maintaining efficient ventilation facing an increase in respiratory demand or a decrease in respiratory system compliance. Key words: mechanical ventilation, closed-loop, pressure-support ventilation. [Respir Care 2005;50(8):1050–1061. © 2005 Daedalus Enterprises]
closed-loop controllers of PSV have been previously designed.1–3 We previously described an original mode of ventilation that we called auto-regulated inspiratory support (ARIS).4 ARIS has the following main characteristics:

1. It is basically a PSV with nonconstant preset pressure (Ppreset).
2. The pressure waveform can be modified from a decreasing to a square one.
3. The ventilatory mode automatically evolves from spontaneous ventilation to PSV (pressure preset, pressure-triggered or flow-triggered, flow-cycled) and to pressure-control ventilation (pressure preset, time-triggered, time-cycled) and returns to spontaneous ventilation, depending on the patient’s performance. The aim of this study was to evaluate the ARIS regulation and behavior in comparison with conventional PSV at a constant level, in 2 pig models of increasing ventilatory demand and of altered lung compliance.

Methods

ARIS Closed-Loop Controller

Basically, ARIS is a nonconstant pressure-preset, pressure-triggered or flow-triggered, flow-cycled mode.4 The inspiration ends when inspiratory flow (V˙I) reaches 0.05 L/s. The expiration is free and ends when the expiratory flow reaches zero minus an adaptable value δ. The sensitivity of the flow-triggering system is automatically adjusted by change of δ, depending on the respiratory frequency (f) and airway occlusion pressure at 0.1 s after the onset of inspiratory effort (P0.1).

A closed-loop controller can be described by controlled and regulated parameters. In ARIS the controlled parameters are the optimal level of minute ventilation (VE,opt), the minimum tidal volume (VT,min), the maximum VT (VT,max), and the maximum inspiratory pressure (PI,max), and the maximum respiratory rate (fmax = VE,opt/VT,min). The minimum respiratory rate (fmin) was preset at 10 breaths/min. VT,max, VT,min, fmax, fmin, and PI,max (the constraints) are strictly constrained and have priority over VE,opt. The regulated parameter is the preset pressure waveform (Ppreset). Instead, to be constant, as in the classical PSV, the ARIS preset pressure waveform is decreasing. Ppreset obeys a first-order equation Ppreset = –At + B, in which t stands for time. “B” determines the peak airway pressure (Paw,insp,max) and thereby the initial level of inspiratory flow (V1). “A” determines the slope of the pressure signal (Fig. 1). The slope can only be negative or null.

To facilitate the explanation, we consider the absolute value of “A”. Accordingly, an increase of “A” corresponds to an increase of the slope, and a decrease of “A” to a decrease of the slope. The variation of “B”
Fig. 2. Flowchart of auto-regulated inspiratory support (ARIS) controller. The values of tidal volume (VT), respiratory frequency (f), and minute volume (VE) are the mean value of 5 consecutive cycles. According to these current values, “A”, “B” (which characterize the shape of the applied pressure according to the preset pressure [P preset], P preset / HT1001 – At / HT1005 B), and sensitivity of flow trigger values are modified. Paw,insp,max / HT1005 maximum inspiratory airway pressure. P I,max / HT1005 maximum value of the inspiratory pressure. VT,min / HT1005 minimum tidal volume. TE / HT1005 expiratory time. VE,opt / HT1005 optimal minute volume.
ranges from 3 cm H₂O to 60 cm H₂O and the variation of “A” from 0 to 40 cm H₂O/s. After input of the settings (ie, the values of controlled parameters), the system starts with arbitrary preset values of “B” and “A”, respectively, at 12 cm H₂O and 20 cm H₂O/s. Then the system evolves, modifying “A” and “B” every 5 cycles, according to the flowchart of the ARIS controller (Fig. 2). The mean value of the 5 cycles was taken as the actual value of each ventilatory parameter. VT,max, VT,min, f_max, f_min, and P₁,max determine an authorized area inside of which V˙E,opt determinates an optimal area of ventilation (Fig. 3). As soon as the representative point of the patient is in the optimal area, a weaning procedure is initiated. This representation does not include the maximum value of the inspiratory pressure (P₁,max).

Preparation of the Animals

The experimental procedure was conducted according to the French law related to animal protection. Twelve healthy female pigs of the race large white, weighing 25–28 kg, were anesthetized intramuscularly with 100 mg of chlorhydrate of ketamine, followed by 25 mg of pancuronium bromide given via an ear vein. The animals were placed supine. The trachea was intubated with an 8-mm inner diameter cuffed tracheal tube (Mallinckrodt, Argyle, New York). The animals were first ventilated using controlled mechanical ventilation (CMV, volume preset, time-triggered, time-cycled). A 20-gauge catheter (model RA-04220-W, Arrow International, Reading, Pennsylvania) was inserted into the right carotid artery for measuring arterial blood pressure and sampling arterial blood. A second catheter was inserted into the right external jugular vein for administration of drugs. A balloon catheter (Mallinckrodt, Phillipsburg, New Jersey) was placed at the inferior third of the esophagus. After intubation and instrumentation, pigs were placed in ventral recumbent position. Body temperature was kept at 38°C. Adequate volume filling and energy supply was ensured with a continuous infusion of 5% dextrose. After elimination of the curare, an infusion of chlorhydrate of ketamine (30 mg/kg/h) maintained the anesthesia and analgesia. Ade-
quacy of anesthesia and analgesia was evaluated every 15 min by the clinical status and the lack of increase in heart rate and blood pressure in response to strong nociceptive stimulations. At the end of the procedure, the animals were sacrificed by an overdose of thiopental and potassium chloride.

Measurements

Cardiovascular Measurements. Intra-arterial pressure and heart rate were monitored by a cardio-monitor (PC Express 90308, SpaceLabs Medical, Issaquah, Washington).

Ventilatory and Pulmonary Mechanics Measurements. Gas flow was measured between the tracheal tube and the Y-piece of the ventilator circuit with a No. 2 Fleisch pneumotachometer connected to a differential pressure transducer (DP45, Validyne, Northridge, California). The response of the pneumotachometer was verified as linear in the full range of flow rates observed in the study. From the flow signal analysis, the total breath duration (T\text{tot}), f (60/T\text{tot}), inspiratory time (T\text{I}), expiratory time, and T\text{I}/T\text{tot} were measured. V\text{T} was calculated by numerical integration of flow and V\dot{\text{T}}, as the product of V\text{T} and f/10.

Work of breathing (WOB) and its respiratory parameters. PE\text{EPi}, C\text{RS}, and R\text{aw} were measured only during CMV and in paralyzed animals.

Blood-Gas Analysis. P\text{\textsubscript{aO2}}, P\text{\textsubscript{aCO2}}, and pH were measured immediately after sampling, with standard blood gas electrodes (ABL 520, Radiometer Medical, Copenhagen, Denmark). Arterial saturation was measured with a co-oximeter (OSM3, Radiometer, Copenhagen, Denmark) programmed for pig hemoglobin.

Experimental Models

Rebreathing Test. The rebreathing test consisted of an additional dead space of 300 mL fitted to the T-piece to increase the inspired CO2 concentration. The duration of the test was 20 minutes.

Acute Lung Injury. The experimental ALI was induced by instillation of 10 mg/kg of isotonic saline serum through the tracheal tube within 10 min and repeated every 20 min until adequate lung injury was evident. We considered ALI evident when C\text{RS} decreased by at least 30% and P\text{\textsubscript{aO2}} was inferior to 300 mm Hg with pure oxygen, both remaining stable. A mean of 6 lavages per animal was realized. The protocol started 30 min after the last lavage.

Experimental Protocol

Initial Phase. The 12 animals, still paralyzed, were ventilated on CMV, with T\text{I}/T\text{tot} of 0.35, fraction of inspired oxygen (F\text{\textsubscript{IO2}}) of 0.3, and zero P\text{EEP}. V\text{T} and f were adjusted to obtain a P\text{\textsubscript{aCO2}} close to 40 mm Hg. C\text{RS}, R\text{aw}, and PE\text{EPi} were calculated. Then a 30–40 min period was necessary to allow the elimination of curare, and the animals, breathing spontaneously, were submitted to volume-assist control mode (VAC, which is volumepreset, flow-triggered or pressure-triggered, and time-cycled).

Baseline. The normal-lung animals underwent, successively, during 20 min, VAC, ARIS, and PSV modes. V\text{T} determined in CMV served as the reference to V\text{T} in VAC. V\text{E} obtained in VAC, after stabilization of arterial blood gas, served as the reference to V\text{E,OPT} in ARIS and P\text{aw,insp,mean} obtained in ARIS, after 20 minutes for stabilization, as the reference to P\text{preset} in PSV. In ARIS, V\text{T,min} was arbitrarily chosen as 80% of V\text{T} in VAC, and P\text{L,max} was set at 50 cm H2O.

Tests. The animals were divided into 2 groups of 6. The first group was submitted to a rebreathing test and the second to acute lung injury (ALI group). First, all the animals were ventilated in VAC. Then the order of PSV and ARIS tests was randomly determined and the animals underwent each mode during 20 min, a duration observed sufficient for stabilization of respiratory and hemodynamic variables. Between each step, a 20-min period in VAC allowed the animal to recover its previous state.
EVALUATION OF AUTO-REGULATED INSPIRATORY SUPPORT

Table 1. Respiratory and Hemodynamic Variables in the Rebreathing Group (n = 6)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Baseline (mean ± SD)</th>
<th>Rebreathing Test (mean ± SD)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>VAC</td>
<td>ARIS</td>
<td>PSV</td>
</tr>
<tr>
<td>f (breaths/min)</td>
<td>18 ± 1</td>
<td>18 ± 3</td>
<td>20 ± 8</td>
</tr>
<tr>
<td>VT (mL)</td>
<td>490 ± 51</td>
<td>557 ± 85</td>
<td>550 ± 112</td>
</tr>
<tr>
<td>V̇E (L/min)</td>
<td>8.9 ± 1.2</td>
<td>9.5 ± 0.8</td>
<td>10.2 ± 2.2</td>
</tr>
<tr>
<td>TІ/TITot</td>
<td>0.41 ± 0.04</td>
<td>0.23 ± 0.06</td>
<td>0.35 ± 0.10</td>
</tr>
<tr>
<td>TІ (s)</td>
<td>1.34 ± 0.12</td>
<td>0.78 ± 0.10</td>
<td>1.10 ± 0.18</td>
</tr>
<tr>
<td>PIF (L/s)</td>
<td>0.74 ± 0.02</td>
<td>1.77 ± 0.22</td>
<td>1.17 ± 0.21</td>
</tr>
<tr>
<td>Paw,insp,mean (cm H₂O)</td>
<td>16.2 ± 1.6</td>
<td>29 ± 5</td>
<td>19.6 ± 1.7</td>
</tr>
<tr>
<td>WOB (J/L)</td>
<td>NM</td>
<td>0.35 ± 0.14</td>
<td>0.64 ± 0.48</td>
</tr>
<tr>
<td>WOBres (J/L)</td>
<td>NM</td>
<td>NM</td>
<td>NM</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>130 ± 22</td>
<td>125 ± 17</td>
<td>115 ± 14</td>
</tr>
<tr>
<td>Mean arterial pressure</td>
<td>102 ± 15</td>
<td>105 ± 15</td>
<td>107 ± 12</td>
</tr>
<tr>
<td>pH</td>
<td>7.46 ± 0.04</td>
<td>7.48 ± 0.04</td>
<td>7.46 ± 0.02</td>
</tr>
<tr>
<td>PaCO₂ (mm Hg)</td>
<td>40 ± 3</td>
<td>39 ± 4</td>
<td>40 ± 4</td>
</tr>
<tr>
<td>PaCO₂/PaO₂</td>
<td>507 ± 50</td>
<td>574 ± 152</td>
<td>479 ± 42</td>
</tr>
<tr>
<td>A (cm H₂O/s)</td>
<td>NA</td>
<td>25.3 ± 5.3</td>
<td>NA</td>
</tr>
<tr>
<td>B (cm H₂O)</td>
<td>NA</td>
<td>35 ± 3.5</td>
<td>NA</td>
</tr>
</tbody>
</table>

* p-values were calculated with Wilcoxon’s signed rank test.
† p < 0.05 VAC vs ARIS
‡ p < 0.05 ARIS vs PSV
§ p < 0.05 VAC vs PSV
V̇E = minute ventilation
TІ/TITot = inspiratory time divided by total respiratory cycle time
PIF = peak inspiratory flow
Paw,insp,mean = maximum inspiratory airway pressure
WOB = work of breathing
WOBres = resistive component of WOB
A = absolute value of slope of the applied pressure, B = initial level of pressure
NM = not measured, NA = not applicable
RT = rebreathing test

Values for respiratory and blood-gas variables obtained on VAC during lung injury are given as reference for the effectiveness and severity of the tests, but were not used for comparison with ARIS or PSV.

Statistical Analysis

The results are expressed as mean ± SD. The data obtained during VAC, PSV, and ARIS were compared using Wilcoxon’s signed rank test. p < 0.05 was considered statistically significant.

Results

Rebreathing Group

The mean ± SD values of the main variables obtained with the 3 ventilatory modes at baseline and at the end of the test are listed in Table 1. According to the protocol, the values of the constraints in ARIS were V̇E,opt = 8.9 ± 1.2 L/min, V̇T,min = 373 ± 53 mL, fₘₐₓ = 24 ± 1 breaths/min. In ARIS at baseline, Paw,insp,mean (19.5 ± 2.8 cm H₂O) corresponded to the value of the inspiratory pressure applied with PSV (19.6 ± 1.7 cm H₂O).

Baseline. At baseline, f and V̇E were not different during VAC, ARIS, and PSV. The peak inspiratory flow (PIF) was more elevated in ARIS, compared to PSV. The values of TІ and TІ/TITot ratio were lower with ARIS, compared to VAC and PSV. ARIS regulated “A” at 25 cm H₂O/s and “B” at 35 cm H₂O. PaCO₂ was maintained around 40 mm Hg, with a moderate metabolic alkalosis observed with the 3 modes.

Rebreathing Test. In VAC, V̇E increased by only 16%, compared to VAC at baseline (not significant), with a significant increase in f. A respiratory acidosis and a decrease in PaCO₂/FIO₂ were observed.
ARIS regulated “B” from 35 ± 3.5 cm H₂O to 42.8 ± 2.5 cm H₂O (p < 0.05). “A” remained constant. In other words, the waveform of the applied pressure became sharper. By result, P_{aw,insp,mean} increased from 20.3 ± 1.4 cm H₂O to 26.2 ± 2.2 cm H₂O (p < 0.05).

In ARIS, when compared to PSV, V_E increased to approximately twice the baseline value in both modes (p < 0.05). The increases in V_E, PIF, and P_{aw,insp,max} were significantly higher with ARIS. The T_I/T_{tot} was not different in the 2 modes. WOB and the resistive component of WOB were significantly lower in ARIS. The P_{aO2}/FIO₂ ratio and P_{aCO2} were significantly less altered in ARIS. No difference was observed in hemodynamic variables.

Lung-Injury Group

The mean ± SD values of the main variables with the 3 ventilatory modes and characteristics of the applied pressure on ARIS (“A” and “B”) are listed in Table 2. According to the protocol, the values of constraints in ARIS were V_{E,opt} = 8.4 ± 1.2 L/min, V_{E,min} = 337 ± 34 mL, and f_{max} = 24 ± 2 breaths/min. In ARIS at baseline, P_{aw,insp,mean} (18.4 ± 4.4 cm H₂O) corresponded to the value of the inspiratory pressure applied with PSV (18.4 ± 3.9 cm H₂O).

Baseline. At baseline f, V_E, and V_T were not different on VAC, ARIS, and PSV. The PIF was not significantly higher during ARIS than during PSV. The T_I/T_{tot} was significantly lower during ARIS than during VAC. P_{aCO2} was maintained around 40 mm Hg, with a moderate metabolic alkalosis observed in the 3 modes.

Acute Lung Injury Test. During VAC, the lung injury produced a 42% decrease in C_RS (from 33 ± 7 mL/cm H₂O to 19 ± 4 mL/cm H₂O) (p < 0.05). The inspiratory R_{aw} increased by 26% (from 10.9 ± 1.4 cm H₂O/L/s to 13.7 ± 2.8 cm H₂O/L/s) (p < 0.05). P_{aO2}/FIO₂ decreased by about 50% (p < 0.05).

ARIS regulated “A” from 25 ± 5.5 cm H₂O/s to 14.7 ± 8.6 cm H₂O/s (p < 0.05), with a moderate increase of “B” (from 35.8 ± 7.3 cm H₂O to 37.3 ± 7.9 cm H₂O) (not significant). In other words, the shape of the applied pressure was changed, with an important decrease of the slope. By result, P_{aw,insp,mean} increased from 18.4 ± 4.4 cm H₂O to 25.1 ± 5 cm H₂O (p < 0.05).

In ARIS, when compared to PSV, f was significantly lower and V_T was maintained, whereas it was significantly reduced in PSV. The T_I/T_{tot} was not different, but PIF was significantly higher in ARIS. WOB and the resistive component of WOB were lower in ARIS. ARIS regulation induced hypocapnia and alkalosis. Yet P_{aCO2} and pH were maintained at baseline levels with ARIS, and were significantly more impaired in PSV. The decrease in P_{aO2}/FIO₂ ratio was not different. No differences were observed in the hemodynamic variables.

Discussion

The results of this experimental study demonstrate that the ARIS regulation operates correctly in 2 experimental models of increasing ventilatory demand and ALI in pigs. ARIS mode was efficient in maintaining within acceptable ranges the breathing pattern, WOB, and blood-gas values. The discussion will focus on the relevance of animal models, a comparison between ARIS and other previously described closed loops, and on the potential for ARIS to induce pulmonary injury.

Animal Models and Procedure

Two basic conditions were required for this evaluation and comparison of ARIS with PSV: (1) the necessity to keep the animals breathing spontaneously and (2) the stability of the model. In order to determine the choice and dose of the anesthetic and analgesic drugs and the quality of spontaneous ventilation in response to carbon dioxide after the elimination of the curare, the experimental protocol was designed after a preliminary study of 2 animals. The stability of the ALI experimental model was also verified by measuring C_RS and P_{aO2}/FIO₂ within the 3 hours following the last instillation of serum saline.

Chlorhydrate of ketamine was continuously infused at the rate of 30 mg/kg/h. This drug produces a state of dissociative anesthesia, with unconsciousness and deep analgesia. It does not induce respiratory depression or modify the response of the respiratory centers. Several tracheal suctionings were regularly performed. We carefully monitored the quality of spontaneous breathing and the response to nociceptive stimulation by pinching the pig’s tail, as recommended. Nevertheless, PSV and ARIS modes were randomly applied, to exclude a possible bias due to different depths of anesthesia from one animal to another.

Closed-Loop Control System in Mechanical Ventilation

An excellent review from Branson et al reports all the available closed-loop controllers to date. Two important notions about feedback control in mechanical ventilation were underlined by Brunner. The first one was relative to positive and negative feedback control and the second to breath-to-breath and intra-breath control.

A positive feedback control aims to create a difference between the target and the measured value, acting as an intra-breath amplifier of the patient’s inspiratory activity. Proportional-assist ventilation (PAV) is the best example of intra-breath positive feedback. Like an additional in-
Evaluation of Auto-Regulated Inspiratory Support

Table 2. Respiratory and Hemodynamic Variables in the Lung-Injury Group (n = 6)

<table>
<thead>
<tr>
<th>Baseline (mean ± SD)</th>
<th>Lung Injury Test (mean ± SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>VAC</td>
</tr>
<tr>
<td>f (breaths/min)</td>
<td>18 ± 2</td>
</tr>
<tr>
<td>V T (mL)</td>
<td>463 ± 29</td>
</tr>
<tr>
<td>V E (L/min)</td>
<td>8.4 ± 1.2</td>
</tr>
<tr>
<td>T I/T tot</td>
<td>0.36 ± 0.01</td>
</tr>
<tr>
<td>T I (s)</td>
<td>1.20 ± 0.16</td>
</tr>
<tr>
<td>PIF (L/s)</td>
<td>0.78 ± 0.06</td>
</tr>
<tr>
<td>Pwv,insp,max (cm H2O)</td>
<td>16.8 ± 2</td>
</tr>
<tr>
<td>WOB (J/L)</td>
<td>NM</td>
</tr>
<tr>
<td>WOBres (J/L)</td>
<td>NM</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>118 ± 20</td>
</tr>
<tr>
<td>Mean arterial pressure (mm Hg)</td>
<td>95 ± 8</td>
</tr>
<tr>
<td>pH</td>
<td>7.44 ± 0.04</td>
</tr>
<tr>
<td>P acO2 (mm Hg)</td>
<td>41 ± 3</td>
</tr>
<tr>
<td>P aO2/P FiO2</td>
<td>474 ± 72</td>
</tr>
<tr>
<td>A (cm H2O/s)</td>
<td>NA</td>
</tr>
<tr>
<td>B (cm H2O)</td>
<td>NA</td>
</tr>
</tbody>
</table>

*p values were calculated with Wilcoxon’s signed rank test.

‡p < 0.05 VAC vs ARIS

†p < 0.05 ARIS vs PSV

‡p < 0.05 VAC vs PSV

VAC = volume-assist control

ARIS = auto-regulated inspiratory support

PSV = pressure-support ventilation

NS = not significant

f = respiratory frequency

V E = tidal volume

Values for respiratory and blood-gas variables obtained on VAC during lung injury are given as reference for the effectiveness and severity of the tests, but were not used for comparison with ARIS nor PSV.

spiration muscle, PAV amplifies the patient’s inspiratory effort without any pre-selected target. Positive feedback systems are inherently unstable, potentially dangerous in case of ventilatory weakness, and susceptible to runaway. The few previous clinical studies comparing PSV and PAV failed to demonstrate any significant superiority of PAV over PSV. Interestingly, in these studies the design of PAV was efficient during increasing ventilatory demand, increasing flow and delivered volume, and allowing a great variability in V T and f.

A negative-feedback control aims to reduce the difference between the target and the controlled value. The target can be achieved precisely or within predetermined limits, even if the impedance of the respiratory system acutely changes. Most of the available closed-loops control systems are negative inter-breath feedback control systems. They have been proposed to guarantee a given V E (extended mandatory minute ventilation, Veolar, Hamilton, Switzerland), a given f (minute mandatory frequency, Cesar, Air Liquide, France), or a minimum V T (pressure-regulated volume control, Servo 300, Siemens, Sweden). Their real clinical interest remains to be proven. Nevertheless, the first clinical trials pointed to the potential disadvantage of “rigid” control with a preset value achieved at any cost. A demonstrative example is minute mandatory frequency, in which the level of PSV (and V T as a result) may reach very high levels in an attempt to achieve the desired f. Such failure of “rigid” control of a single parameter stresses the need of more complex multi-parametric closed loops that include limits to increase the safety. The adaptive lung ventilation mode is a good example of a complex closed-loop control system. In adaptive lung ventilation, automatic adjustments of f and inspiratory pressure support are based on measurements of the patient’s lung mechanics and serial dead space, with the goals of achieving alveolar ventilation at the lowest possible WOB and avoiding in-
trinsic PEEP. Dojat et al designed a computerized system that sets the lowest level of PSV that maintains f, VT, and end-expiratory carbon dioxide concentration within predetermined ranges.

ARIS Specificity

ARIS can be classified in the group of complex negative-feedback control. Like adaptive lung ventilation, the targets are not fixed values but a running zone that allows a great variability of the breathing pattern within the limits imposed by the constraints. This has been presented as an advantage. Arold et al have compared CMV to variable ventilation (VT and f varied by 10, 20, 40, and 60%). Variable ventilation significantly improved lung elastance and blood oxygenation.

The feature that makes ARIS original is the regulation of both initial level and slope of the applied pressure, which results in a manipulation of the flow. Modifications of “A” and “B” have effects on VT, TI, f, and P_{aw,insp,max}. An increase of “B” leads to an increase in VT, to a decrease in f (by increasing TI), and to an increase in P_{aw,insp,max}. A decrease of “B” has the inverse effect. A decrease in “A” (absolute value) leads to an increase in VT and to a decrease in f (by increasing TI) without an increase in P_{aw,insp,max}. An increase of trigger sensitivity leads to an increase in f, and in turn, a decrease of trigger sensitivity leads to a decrease in f. The effects of manipulation of “A” and “B” obtained with a lung mathematical model are illustrated in Figure 4.

Such a pressure pattern and the resulting high initial inspiratory flow have demonstrated some beneficial effects. In most of the recent ventilators the speed of pressurization is adjustable, to modify the initial pressure ramp profile and increase the PIF. Previous studies demonstrated that PIF interferes with breathing pattern and WOB and that inspiratory flow rate has an important impact on patient-ventilator synchrony and comfort. Maclntyre et al underlined that, in PSV, low insufficient PIF value was associated with marked deleterious consequences, while high PIF had minor undesirable effects and was beneficial in most patients. During pressure support, high PIF is associated with the shortest inspiration time and the lowest WOB. In ARIS, according with the pressure waveform, the PIF could be very much higher than the highest PIF delivered by traditional PSV. As a result, during the initial part of the inspiratory time, the machine supports most of the WOB, decreasing mainly the resistive component of WOB. Then the steep slope of the applied pressure may facilitate the patient’s own inspiration at the end of inspiratory time.

ARIS Behavior and Ventilator-Induced Lung Injury

One could suppose that such a pattern of unusual high flow and pressure could have some potential barometric and volumetric deleterious effects, especially in heterogeneous lung diseases. Ventilator-induced lung injury (VILI) is generally attributed to cyclic opening and closing of small airways, and a high acceleration of the flow rate applied just at the point of alveolar collapse could induce or increase lung injury related to shear stress. Few experimental studies in normal sheep and rabbits have reported detrimental pulmonary effects, assessed by lung mechanics and morphometry, of high inspiratory flow rate. In a sheep model, Rich et al compared 2 levels of applied pressure, 20 cm H_2O and 45 cm H_2O, in a P_{preset}, time-triggered, time-cycled mode (pressure-controlled ventilation, f = 5 breaths/min and 15 breaths/min, mean inspiratory flow = 60 L/min [40 mL/kg/s]) with CMV mode (f = 5 breaths/min, VT = 15 L/min [10 mL/kg/s]). CMV induced the least damage, even at high P_{aw,insp,max}. They concluded that low inspiratory flow at similar P_{aw,insp,max} protects against VILI. However, in this study the VT was not controlled and the lung injury appeared to be marked when high PIF and injurious VT (higher than 30 mL/kg) were simultaneously delivered.

Maeda et al used the pressure-regulated volume-control mode (Siemens Servo 300 ventilator) to investigate the effects of PIF on VILI in rabbits at constant high VT.
(30 mL/kg). Pressure-controlled ventilation (PIF 28.8 L/min [171 mL/kg/s]) was compared to CMV with 2 settings (T\textsubscript{I}/T\textsubscript{tot} 25%, PIF 7.5 L/min [44 mL/kg/s], and T\textsubscript{I}/T\textsubscript{tot} 50%, PIF 2.6 L/min [15 mL/kg/s]). The reduction of inspiratory flow provided pulmonary protection against high inspiratory pressure and VT. Interpretation of these findings is difficult. Interestingly, in a recent study by D’Angelo et al., high flow (44 mL/kg/s and VT/H\textsubscript{11005} 11 mL/kg) had no effect on lung mechanics, gas exchange, lung morphometry, or wet-to-dry ratios, in an open-chest rabbit model, when PEEP (2.5 cm H\textsubscript{2}O) was applied.

To summarize, these results have demonstrated deleterious effect of high PIF when associated with high pressure or volume, and the protective effect of low constant flow and PEEP. A deleterious direct effect of high flow rate requires further studies to be documented. Concerning the possible deleterious effect of the high peak pressure delivered by ARIS, a discrepancy exists between the pressure and flow waveforms administered by the ventilator and the effective pressure and flow at the level of the respiratory system. The pressure pattern varies from the T-piece to the carina and from the carina to the small bronchi. At the carina the PSV and ARIS waveforms become, respectively, increasing and square (Fig. 5). This alteration is related to the resistance of both the tubing system and the patient’s airway. These alterations can result in a lack of positive-pressure assistance at the beginning of inspiration, when low P\textsubscript{preset} is used in PSV. The high PIF delivered by ARIS overcomes the resistance.

**ARIS Behavior During the Tests**

During rebreathing, compared with baseline, ARIS regulation led to an increased “B,” with a sharp pressure waveform and steep slope, resulting in a great increase in V\textsubscript{T} and a moderate increase in f. PIF and P\textsubscript{aw,insp,max} increased dramatically. Such an initial inspiratory flow seems suitable in a situation of high ventilatory demand.

During ALI, compared with baseline, ARIS regulation led to a decrease in “A,” with a relatively flat waveform and gentle slope. As a result, PIF increased moderately. In contrast with PSV, V\textsubscript{T} and f were maintained at the values observed in VAC, avoiding rapid shallow breathing. ARIS behavior in ALI group is illustrated in Figure 6.

The V\textsubscript{T} resulting from the regulation seems very high, regarding the weight of the animals. Yet at baseline in CMV, a V\textsubscript{T} of 17.8 mL/kg and a V\textsubscript{E} of 8.4 L/min were necessary to obtain a PaCO\textsubscript{2} close to 40 mm Hg. Nevertheless, in the rebreathing group, compared with baseline, V\textsubscript{T} was increased to 26 mL/kg and remained stable in the ALI group (17 mL/kg). ARIS regulation induced hypocapnia, accompanied by alkalosis, which was mainly metabolic and due to contraction of extra-cellular volume, despite the vascular filling. Such a breathing pattern adopted by ARIS in the ALI group was not in accordance with the actual recommendations for VILI prevention. This observation stresses the fact that the regulation mainly depends on the chosen values of the constraints. The lower the V\textsubscript{T,min} and the P\textsubscript{I,max} are set, the lower the V\textsubscript{T,max} will be and the earlier an action on the slope will be activated. Consequently, in ARIS, as in other closed loops, the values of the constraints have to be carefully chosen, depending on the cause of the respiratory failure and possible complications. An improvement could be to introduce automatic settings of constraints depending on the patient’s airway resistance and compliance. That will imply continuous monitoring of pulmonary mechanics for adaptation during the course of acute respiratory failure, resulting in a more...
complex closed loop and increasing the risk of dysfunction.

Conclusions

The results of this comparison of ARIS versus standard PSV at constant levels of inspiratory pressure were expected. In both the rebreathing group and the ALI group, manual and continuous adjustments of PSV would have surely resulted in a less worsening breathing pattern. Yet the aim of this study was to verify that ARIS operates well, according to its principles, and its clinical interest remains to be documented. Closed-loop controllers will probably never replace a well-trained clinician continuously standing at the bedside. Such an ideal condition is not usual in clinical practice. Closed-loop controllers are generally considered useful in the most complex, unstable cases. On the contrary, our opinion is that they could be more useful in stable patients but susceptible to acute complication. Weaning from mechanical ventilation and post-anesthesia recovery seem to be the best clinical situations for ARIS future clinical experiments. Trying to reduce mechanical support as soon as the patient’s condition is optimal, ARIS could reduce the duration of mechanical ventilation. In turn, it will probably be difficult to document that such a closed loop is able to improve the prognosis of acute respiratory failure.

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