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Association between ventilation index and time on mechanical ventilation in infants with acute viral bronchiolitis

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Abstract

Objective: To evaluate the association between time on mechanical ventilation and anthropometric, clinical and pulmonary function variables, measured early, in infants on invasive mechanical ventilation with acute respiratory failure due to viral bronchiolitis, and the temporal progression of variables with significant correlations.

Methods: Twenty-nine infants admitted to the pediatric intensive care unit of UNICAMP university hospital were studied. Acute viral bronchiolitis was defined according to clinical and radiological criteria. Children with chronic diseases and those that were hemodynamically unstable were excluded. All measurements were taken after 24 to 72 hours' mechanical ventilation, using volumetric capnography and blood gas analysis. Mechanical ventilation time was divided into: $\leq$ 7 days and > 7 days. Association between time on mechanical ventilation and the variables analyzed was determined by Spearman's Correlation Coefficient (r_s).

Results: Time on mechanical ventilation showed a significant positive correlation with $PaCO_2$ ($r_s = 0.45$, $p = 0.01$) and ventilation index ($r_s = 0.51$, $p = 0.005$), and a negative correlation with pH ($r_s = -0.40$, $p = 0.03$). Ventilation indices of 37, measured between day one and day five, was associated with a progressively increased risk of more than 7 days on mechanical ventilation (OR = 4.2 on the first day to 15.71 on the fourth day).

Conclusions: Ventilation index, $PaCO_2$ and pH, measured early, were associated with prolonged mechanical ventilation, reflecting the severity of ventilatory disturbance and the need for support.

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Introduction

Acute viral bronchiolitis (AVB) is one of the principal causes of acute respiratory failure (ARF), leading to invasive mechanical ventilation (IMV) among infants in pediatric intensive care units (PICU).[1] Prolonged periods on IMV increase the incidence of complications, such as intra-hospital infections, upper airway trauma, stress to the patient and increased costs.[2,3] An assessment of the factors associated with length of period on IMV may provide important foundations for improvement of the care given to these patients.

There are few published studies that have analyzed factors linked to the time infants with AVB spend on IMV. In 2000, Bont et al., studied 30 infants with AVB due to respiratory syncytial virus (RSV) and found an association between ventilation index (VI) during the first 24 hours,

interleukin 12 production by mononuclear peripheral blood cells and time on IMV.[4] Tasker et al., in 2000, identified an association between prolonged periods on IMV and severity of radiological findings, arterial oxygenation disorders higher mean airway pressure requirements, measured during the first 24 hours, in a group of 45 infants with AVB due to RSV.[5]

This study took as its initial objective the identification of pulmonary function variables associated with time on IMV with AVB. Once an association between pH, $PaCO_2$ and VI with time on IMV had been identified, the evolution over time of these variables was evaluated with the aim of identifying cutoff values that could define the risk of prolonged IMV.

Methods

This was an observational study of a historic prospective cohort, undertaken at a PICU in the *Hospital de Clínicas* at UNICAMP. All patients aged 28 days to 12 months, irrespective of sex, with clinical and radiological diagnoses of AVB, on IMV in the PICU during the period April 2001 to September 2003, were included in the study. No etiological classification was performed because of the lack of viral identification tests at the service. Clinical diagnosis took account of the following criteria: history of coughing; wheezing; at least two signs of respiratory distress (nostril flaring, tachypnea, dyspnea, subcostal retraction, suprasternal retraction, accessory musculature involvement; pulmonary auscultation with a predominance of wheezing or prolonged expiration); chest x-ray with hyperinflation pulmonary; and absence of condensation in more than 1/3 of the image of one of the lungs. Data were collected between 24 and 72 hours of IMV. This time range was chosen in order to avoid the phase during which patients are least stable, the first 24 hours on IMV, and to guarantee that their clinical conditions were predominantly obstructive, avoiding the complications of prolonged IMV and possible progression to acute respiratory distress syndrome. All patients were put on conventional ventilation, aiming to maintain target values for gaseous exchange and pH within physiological limits. The modes employed were synchronized intermittent mandatory ventilation (SIMV) or IMV. Neither corticosteroids nor bronchodilators were employed. To avoid possible interference with monitoring, all patients were sedated with midazolam and/or fentanyl during data collection.

Patients were excluded if they had any of the following: upper airway obstruction, air leakage around the endotracheal tube of more than 20%; hemodynamic instability; neuromuscular disease; heart disease; post-op; use of muscle relaxants; chronic respiratory disease. The study was approved by the Committee for Ethics in Research at FCM-UNICAMP. Informed consent was obtained in writing from one parent or legal guardian of each child before enrollment on the study.

Arterial blood gas analysis was performed at the same time that pulmonary mechanics were monitored and volumetric capnography performed. The monitor used was a CO_2SMO-Plus®, (DIXTAL, São Paulo, Brazil). This is a noninvasive monitor that consists of a capnograph, a pulse oximeter and a pneumotachograph. Capnography and pneumotachography measurements are provided in real time, by means of analysis of inspired and expired gasses, by sensors placed between the endotracheal tube and the mechanical ventilator connection. Based on the $PaCO_2$ provided, the monitor calculates measurements for airway, alveolar and physiological dead spaces. This instrument was chosen because its measurements have been validated in prospective studies with animals and with pediatric patients on IMV.[6,7] The monitor was recently used in pediatric studies aimed at assessing the prognostic value of VD/VT for extubation[8] and for Assessing the effects respiratory physiotherapy on pulmonary function.[9]

Data were collected on: weight, sex, age in months, total and mechanical respiratory frequency (RF), peak inspiratory pressure (PIP), positive end expiratory pressure (PEEP), fraction of inspired oxygen (FiO_2), PaO_2, $PaCO_2$, pH, PaO_2/FiO ratio, alveolar-arterial oxygen difference [$P(A\text{-}a)O_2$], PAO_2/PaO_2 ratio, $P(A\text{-}a)O_2/PaO_2$ratio, oxygenation index ($IO = FiO_2 \times MAP \times 100/PaO_2$), ventilation index ($VI = PIP \times FRmec \times PaCO_2/1000$), expired tidal volume ($V_T$exp), alveolar minute-volume (MValv), total minute-volume (MVtotal), VCO_2, dynamic airway resistance (Raw), dynamic complacency (Cdyn), alveolar dead space ($V_D$alv), physiological dead space ($V_D$phys), dead space volume/tidal volume ratio (V_D/V_T). Correlations between these variables and time on IMV were then explored.

Once statistically significant associations had been identified between VI, $PaCO_2$ and pH and time on IMV (Table 1), a retrospective analysis was made of the behavior of these variables over the first 5 days of IMV. Patient records were reviewed and daily values for $PaCO_2$, PIP and FRmec were noted. When calculating VI the highest readings were used if there were more than one measurement for any given variable on a given day. Patients were split into two groups according to time on IMV, less than or equal to 7 days or more than 7 days.

The database and statistical analysis were produced using SPSS for Windows 7.5.1 (SPSS Inc., Chicago, IL, USA). Associations between numerical and categorical variables were analyzed using the Mann-Whitney non-parametric test. Associations between two continuous variables were analyzed with the Spearman Correlation Coefficient (r_s). Statistically significance was defined as $p \leq 0.05$.

Estimates of the risk of prolonged IMV were calculated using odds ratios, sensitivity, specificity and positive and negative predictive values. Cutoff values for VI against time on ventilation were calculated by taking the value between the 75th percentile of the $\leq$ 7 days group and the 25th percentile for the > 7 days group, on the second day (when statistically significant differences began to appear between the groups).

Results

Twenty-nine infants were enrolled: 23 were male and 6 female; median age of 2.8 months (1.1 to 11.9 months); median weight of 6 kg (3.6 to 8.9 kg). The median time on mechanical ventilation was 8.2 days (from 3.9 to 22 days). Eleven patients remained on IMV for a period less than or equal to 7 days, and 18 for more than 7 days. There were no deaths in the group studied.

Table 1 shows the correlations between the values of the study variables and time on IMV. Observe the statistically significant, positive correlation between time on IMV, VI and $PaCO_2$ and the negative correlation with pH.

Analyzing the distribution of the values for VI (between 24 and 48 hours), a median score of 29.2 was observed (min. 12.1; max. 73.6), in the study population. The analysis by categories (time on IMV $\leq$ 7 days and > 7 days) demonstrated a statistically significant association between VI and time on IMV from the second day onwards. The association was maintained until the fifth day (Figure 1). The VI cutoff point of 37 presents a progressive increase in odds ratio, specificity and positive predictive value from the second to the fifth day (Table 2). There was only a statistically significant association between $PaCO_2$ and time on IMV on the second and fifth days (Table 3). No statistically significant association was observed between pH values and time on IMV categories during the first 5 days.

Discussion

This is the first report to analyze pulmonary function and gaseous exchange parameters and their association with time on IMV in Brazilian infants with AVB.

Table 1 - Analysis of the correlation between anthropometric and pulmonary function variables and time of invasive mechanical ventilation in 29 infants

Variable	Median (Minimum and Maximum)	Spearman's Correlation Coefficient (rs)	p
Weight (kg)	6.0 (3.6-8.9)	-0.2	0.92
Age (months)	2.8 (1.1-11.9)	0.21	0.27
pH	7.4 (7.2-7.5)	-0.40	0.03*
PaO_2 (mmHg)	99.2 (58.5-181.9)	-0.06	0.76
$PaCO_2$ (mmHg)	42.3 (24.2-62.6)	0.45	0.01*
$SatO_2$ (%)	98.0 (88.6-100.0)	0.11	0.58
PaO_2/FiO_2	251.2 (134.8-519.7)	-0.18	0.35
$P(A-a)O_2/PaO_2$	1.2 (0.1-3.1)	0.10	0.62
PaO_2/PaO_2	0.5 (0.2-0.9)	-0.10	0.62
PIP (cmH_2O)	29.0 (22.0-50.0)	-0.89	0.65
PEEP (cmH_2O)	4.0 (2.0-7.0)	-0.03	0.88
Total Rf (rpm)	30.0 (24.0-79.0)	-0.02	0.90
FiO_2	0.4 (0.2-0.5)	-0.20	0.30
VTexp mec (ml)	6.9 (2.6-11.4)	-0.27	0.16
VT Alv (ml)	30.0 (10.0-65.0)	-0.09	0.66
VE (l/min)	1.1 (0.5-2.5)	-0.21	0.26
MValv (l/min)	0.8 (0.2-1.8)	-0.33	0.08
IV	29.2 (12.1-73.6)	0.51	0.005*
OI	3.7 (1.8-7.9)	0.23	0.23
VCO_2 (ml/min)	25.1 (11.2-62.6)	-0.01	0.97
VDphys (ml)	16.0 (8.0-25.0)	-0.15	0.42
VDalv (ml)	9.0 (3.0-17.0)	-0.20	0.29
VD/VT	0.5 (0.3-0.7)	0.29	0.13
Rexp (cmH_2O/l/s)	128.5 (39.3-282.9)	0.29	0.12
Cdin (ml/cmH_2O)	2.7 (1.2-7.0)	-0.20	0.31

* p value = 0.05.

PIP = peak inspiratory pressure; PEEP = positive end expiratory pressure; Total Rf= total respiratory frequency; VTexp mec = expired tidal volume; VT Alv = current alveolar volume; VE = total minute volume; MValv = alveolar minute volume; VI = ventilation index; OI = oxigenation index; VDphys = physiological dead space; VDalv = alveolar dead space; VD/VT = dead space volume/tidal volume ratio; Raw = dynamic airway resistance; Cdyn = dynamic complacency.

Table 2 - Epidemiological risk markers of IMV (invasive mechanical ventilation) with VI of 37

Days	VI (%)	Sensitivity (%)	Especificit (%)	PPV (%)	NPV (CI95%)	Odds Ratio
1	37	78	55	74	60	4.2 (0.8-21.3)
2	37	72	73	81	62	6.6 (1.3-37.2)
3	37	44	91	89	50	8.00 (0.8-76.4)
4	37	61	91	92	59	15.71 (1.6-151.1)
5	37	56	100	100	58	NC

VI = ventilation index; PPV = positive predictive value; NPV = negative predictive value; CI 95% = 95% confidence interval.

Table 3 - Median, minimum, maximum and significance level of $PaCO_2$ values on the fifth day of IMV (invasive mechanical ventilation) in 29 infants divided into two groups: less than or equal to 7 days and more than 7 days in IMV

IMV Days	$PaCO_2$ (median, minimum, maximum)		p (Mann-Whitney)
	≤ 7 days (n = 11)	> 7 days (n = 18)	
1	43.6 (26.1 – 122.0)	48.5 (33.7 – 109.0)	0.122
2	40.2 (29.2 – 49.4)	44.7 (36.2 – 89.5)	0.003*
3	42.7 (27.6 – 55.8)	44.2 (32.7 – 72.4)	0.134
4	41.6 (30.6 – 59.0)	52.9 (29.2 – 75.9)	0.188
5	41.9 (25.6 – 62.9)	48.2 (26.6 – 68.9)	0.006*

* $p < 0.05$

The study population included a predominance of the male sex and of patients less than 6 months old, which is compatible with published data on AVB.[10] Based on epidemiological and clinical data, although without having performed viral identification tests, we consider that all these patients fulfilled the clinical criteria for AVB diagnosis. At our service viral identification is not a routine diagnostic tool in AVB cases. Tests for the most common agent, respiratory syncytial virus, have recently been introduced as an exercise in clinical research. We believe that knowledge of the etiologic agent, in this study population, would significantly increase the consistency of the study, but would not invalidate its results since AVB is a well-defined clinical syndrome.

No pharmacological treatment was given with either corticosteroids or bronchodilators, due to the controversies surrounding such medications in AVB.[11] The median weight and age illustrate the uniformity of the group studied, making possible better data comparison.

The median length of time on IMV of 8.2 days; observed in the study population, is comparable with what has been described in other clinical series of AVB sufferers.[11-13]

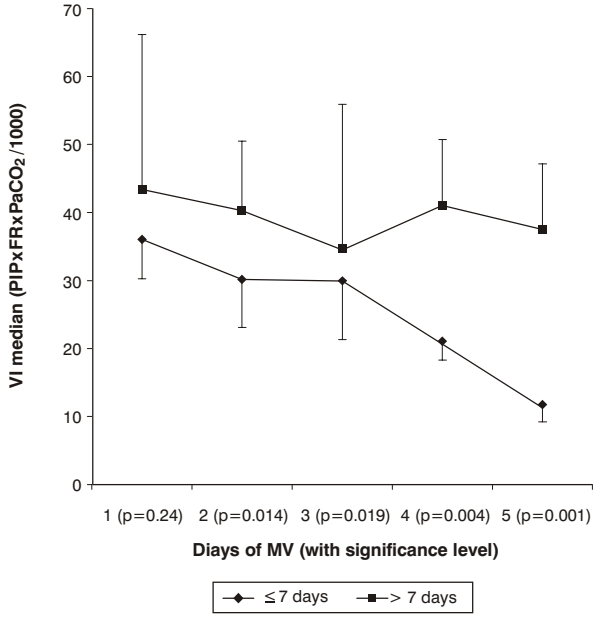

Figure 1 - Ventilatory index curves tendency at the first 5 days in IMV (invasive mechanical ventilation) in both study groups: less or equal to 7 days and more than 7 days in IMV

The principal finding of this study was the correlation between VI, measured between 24 and 48 hours of IMV and the duration of IMV. Bont et al. report similar results in patients with AVB, although those results were obtained by the analysis of the arithmetic means of three measurements at 8-hour intervals, during the first 24 hours of IMV.[4] This is different from the method used in our study to calculate VI. As a result of the historic prospective nature of our study, the study protocol did not include serial blood gas measurements at short intervals. Additionally, we chose not to use data from the first 24 hours on IMV because this is an initial period of clinical stabilization and of IMV parameter adjustment, which significantly influences the VI calculation.

The association between VI and time on IMV categories was strengthened by the retrospective analysis of the progress of VI over time (Figure 1) and of the epidemiological risk markers (Table 2). The potential use of VI as a risk marker was also analyzed by Paret et al., who observed that the indices of children with acute respiratory distress syndrome were associated with mortality from the disease.[14] Despite the different clinical outcomes of the study populations, it is worth pointing out that in both studies an association was observed between VI and markers of severity.

Although they had been significant in the preliminary analysis, the associations between pH, $PaCO_2$ and time on IMV did not exhibit the same consistency observed in the analysis of VI. It is apt to note that, even during one of the periods during which differences of $PaCO_2$ with relation to time on IMV (second day) were statistically significant, median values (40.2 mmHg versus 44.7 mmHg) did not suggest clinical abnormality. This finding reiterates the priority given to the analysis of VI, since its calculation provides a more complete measure of clinical and physiological alterations. The VI therefore represents a measurement of ventilatory disorder that takes account of the variations in intensity of ventilation management, incorporating both variables linked with the intensity of therapeutic support and its results.

The results suggest that lower pH values and higher $PaCO_2$ and VI values, measured early on, were associated with longer time on IMV in infants with obstructive ARF. We emphasize that these associations are clinical findings from the study cohort and do not constitute proposal for therapeutic objectives to be achieved.

The clinical and epidemiological analysis of VI demonstrated that VI values above 37 are associated with risk of prolonged IMV in this population, reflecting the severity of the ventilatory disorder and the need for support. Calculating VI can be of use to intensive care specialists, calling attention to deviations that can take place with relation to the outcome hoped for. Nevertheless, prospective studies dealing with the prognostic value of VI are necessary to validate it for this use.

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