Manual hyperinflation combined with expiratory rib cage compression for reduction of length of ICU stay in critically ill patients on mechanical ventilation*

Hiperinsuflação manual combinada com compressão torácica expiratória para redução do período de internação em UTI em pacientes críticos sob ventilação mecânica

Juliana Savini Wey Berti, Elisiane Tonon, Carlos Fernando Ronchi, Heloisa Wey Berti, Laércio Martins de Stefano, Ana Lúcia Gut, Carlos Roberto Padovani, Ana Lucia Anjos Ferreira

Abstract

Objective: Although manual hyperinflation (MH) is widely used for pulmonary secretion clearance, there is no evidence to support its routine use in clinical practice. Our objective was to evaluate the effect that MH combined with expiratory rib cage compression (ERCC) has on the length of ICU stay and duration of mechanical ventilation (MV).

Methods: This was a prospective randomized controlled clinical trial involving ICU patients on MV at a tertiary care teaching hospital between January of 2004 and January of 2005. Among the 49 patients who met the study criteria, 24 and 25 were randomly assigned to the respiratory physiotherapy (RP) and control groups, respectively. Of those same patients, 6 and 8, respectively, were later withdrawn from the study. During the 5-day observation period, the RP patients received MH combined with ERCC, whereas the control patients received standard nursing care.

Results: The two groups were similar in terms of the baseline characteristics. The intervention had a positive effect on the duration of MV, as well as on the ICU discharge rate and Murray score. There were significant differences between the control and RP groups regarding the weaning success rate on days 2 (0.0% vs. 37.5%), 3 (0.0% vs. 37.5%), 4 (5.3% vs. 37.5%), and 5 (15.9% vs. 37.5%), as well as regarding the ICU discharge rate on days 3 (0% vs. 25%), 4 (0% vs. 31%), and 5 (0% vs. 31%). In the RP group, there was a significant improvement in the Murray score on day 5.

Conclusions: Our results show that the use of MH combined with ERCC for 5 days accelerated the weaning process and ICU discharge.

Keywords: Physical therapy modalities; Ventilator weaning; Length of stay.

Resumo

Objetivo: Embora a hiperinsuflação manual (HM) seja largamente usada para a remoção de secreções pulmonares, não há evidências para sua recomendação como rotina na prática clínica. O objetivo do estudo foi avaliar o efeito da HM combinada com compressão torácica expiratória (CTE) na duração de internação em UTI e no tempo de ventilação mecânica (VM) em pacientes sob VM. Métodos: Ensaios clínicos prospectivos, randomizados e controlados com pacientes de UTI sob VM em um hospital acadêmico terciário entre janeiro de 2004 e janeiro de 2005. Dentre os 49 pacientes que preencheram os critérios do estudo, 24 e 25 foram randomicamente alocados nos grupos fisioterapia respiratória (FR) e controle, respectivamente, sendo que 6 e 8 foram retirados do estudo. Durante o período de observação de 5 dias, os pacientes do grupo FR receberam HM combinada com CTE, enquanto os controles receberam o tratamento padrão de enfermagem. Resultados: Os dois grupos apresentaram características basais semelhantes. A intervenção teve efeito positivo na duração de VM, alta da UTI e escore de Murray. Houve diferenças significativas entre os grupos controle e FR em relação à taxa de sucesso no desmame nos dias 2 (0,0% vs. 37,5%), 3 (0,0% vs. 37,5%), 4 (5,3% vs. 37,5%) e 5 (15,9% vs. 37,5%), assim como à taxa de alta da UTI nos dias 3 (0% vs. 25%), 4 (0% vs. 31%) e 5 (0% vs. 31%). No grupo FR, houve uma melhora significante no escore de Murray no dia 5. Conclusões: Nossos resultados mostraram que o uso combinado de HM e CTE por 5 dias acelerou o processo de desmame e de alta da UTI.

Descritores: Modalidades de fisioterapia; Desmame do respirador; Tempo de internação.

* Study carried out at the Botucatu Hospital das Clínicas, Botucatu School of Medicine, São Paulo State University, Botucatu, Brazil. Correspondence to: Carlos Fernando Ronchi. Departamento de Clínica Médica, Faculdade de Medicina de Botucatu, Universidade Estadual Paulista Júlio de Mesquita Filho, CEP 18618-970, Botucatu, SP, Brasil. Tel. 55 14 3880-1171; Fax: 55 14 3882-2238. E-mail: fernando.ronchi@yahoo.com.br

Financial support: This study received financial support from the Fundação para o Desenvolvimento da Universidade Estadual Paulista (FUNDUNESP, Foundation for the Development of the São Paulo State University, Process no. 884/03-DFP) and the Coordenação de Aperfeiçoamento de Pessoal de Nível Superior (CAPES, Office for the Advancement of Higher Education).

Submitted: 3 November 2011. Accepted, after review: 10 May 2012.

**A versão completa em português deste artigo está disponível em www.jornaldepneumologia.com.br
Introduction

Mechanical ventilation (MV) and the consequent pulmonary secretion retention[1] are major risk factors associated with prolonged ICU stay and mortality in critically ill patients. Certain strategies, such as chest physiotherapy, can improve secretion clearance and prevent pulmonary complications,[2] therefore potentially reducing the length of ICU stay. Early ICU discharge is particularly relevant in public hospitals in developing countries, where there are financial restraints.

Various respiratory physiotherapy techniques, such as mobilization, manual hyperinflation (MH), percussion, and vibrations, are used in patients on MV. It has been shown that the use of respiratory physiotherapy techniques can reduce pulmonary secretion retention,[1,3] as well as improving dynamic compliance[4] and static compliance.[5,6] One of a number of respiratory physiotherapy techniques, MH is commonly used by physiotherapists in patients receiving MV.[5]

Originally called “bag squeezing”, MH consists of a series of deep breaths with a three-second inspiratory pause combined with expiratory rib cage compression (ERCC) and suctioning.[5] Although MH has been shown to have a positive effect on airway secretion clearance,[2,5,8] atelectasis,[8] and alveolar recruitment,[7] there is moderate evidence that MH has a short-lived beneficial effect on respiratory function.[10] The absence of more convincing evidence might be due to the lack of studies evaluating the effectiveness of MH in terms of the abovementioned variables[2,11,12] or to inconsistent definitions of MH across studies. Procedures either including or excluding the ERCC step are equally referred to as MH. In fact, some studies[5,9,13] do not clearly state whether the ERCC step was included in the MH procedure.

Although chest physiotherapy plays an important role in the multidisciplinary approach to patients in most ICUs, there is very limited or no evidence that chest physiotherapy facilitates weaning from MV, reduces the length of ICU stay, and reduces mortality.[10] There is only one study examining the effectiveness of MH (without the ERCC step) and taking those variables into consideration.[13] Because there is a lack of evidence to support the use of MH in clinical practice, we aimed to investigate whether MH, combined with ERCC after percussion and applied twice a day for five days, could shorten the length of ICU stay and the duration of MV in patients on MV.

Other outcomes assessed included the extent of lung damage and disease severity.

Methods

This was a prospective randomized controlled clinical trial conducted between January of 2004 and January of 2005 and involving patients admitted to the 9-bed ICU of the emergency room (ER) of a 450-bed tertiary care teaching hospital. The study project was approved by the local research ethics committee (Protocol no. 448/2002).

All of the patients or their legal guardians gave written informed consent, in compliance with the Helsinki Declaration. Consecutive adult patients in the ER were eligible for inclusion in the study if they had been endotracheally intubated and mechanically ventilated for 24-72 h.

Exclusion criteria were as follows: age < 18 years; length of ICU/ER stay ≤ 24 h; referral to another ICU; positive end-expiratory pressure (PEEP) > 8 cmH2O; severe asthma; ARDS; invasive bronchoscopic procedure; pneumothorax or a history of pneumothorax; chest tube drainage; chest trauma; brain swelling, raised intracranial pressure, or the potential to develop pathologically raised intracranial pressure; unstable cardiovascular status (defined as systolic blood pressure < 100 mmHg or > 180 mmHg, mean arterial pressure < 70 mmHg or > 110 mmHg, or HR < 70 bpm or > 120 bpm) on inotropic support; obesity; spinal cord injury; and do-not-resuscitate status.

All of the patients were placed on a mechanical ventilator (Monterey model; Takaoka, São Paulo, Brazil) set to a tidal volume of 7 mL/kg of body weight and assist-control ventilation or synchronized intermittent mandatory ventilation. All ventilatory parameters were routinely audited and adjusted as needed (FiO2, tidal volume, and PEEP). The patients who were successfully discharged from the ER/ICU were followed until postadmission day 30.

The patients were randomly assigned either to the usual treatment (control) group or to the respiratory physiotherapy (RP) group. The randomization process was performed daily for 13 consecutive months by means of a computer-generated random sequence. Allocation concealment was successful. The physicians who treated the patients had no influence on patient eligibility or allocation. The participants
were analyzed in the groups to which they were randomly assigned. The patients assigned to the control group received standard nursing care, which consisted of positioning (i.e., changing the body position every two hours throughout the day) and airway suctioning. Airway suctioning included disconnecting the patient from the ventilator, followed by tracheal instillation of 1 mL of saline solution.\[13,14\] four sets of six cycles being performed with a manual resuscitation bag (Adult Lifesaver Manual Resuscitator; Hudson RCI, Temecula, CA, USA) in order to ventilate patients with 100% oxygen (flow rate = 15 L/min and airway suctioning being performed for 15 s in order to remove secretions. This procedure was performed six times a day. The patients assigned to the RP group received the same treatment as did those in the control group, although they did so only four times a day. They also received respiratory physiotherapy twice a day, i.e., percussion in alternate side-lying positions (10 min each), followed by MH combined with ERCC. Initially, percussion was performed manually by clapping the chest wall, the head of the bed being in a horizontal position. The patients were returned to the supine position and received 1 mL of saline solution (via the endotracheal tube), MH being subsequently performed. The first step of MH consisted of a three-second pause at the end of the inspiratory phase,\[11\] followed by a quick release; as soon as the expiratory phase started, ERCC was manually applied (without vibration) to both hemithoraces. This step consisted of four sets of six MH breaths combined with six ERCC maneuvers (using the palms of both hands toward the sternum).\[7\] The MH technique involved disconnecting the patients from the ventilator and was performed with a 2.0-L reusable manual resuscitation bag (Hudson RCI) connected to a flow of 100% oxygen at 15 L/min (calibrated with an oxygen analyzer). In order to maximize lung volume, a pressure manometer (Child Lifesaver Manual Resuscitator; Hudson RCI) was connected to the manual resuscitation bag, and each inflation was delivered to a peak airway pressure of 40 cmH\(_2\)O.\[6,11,15\] Finally, tracheal suctioning was applied for 15 s after each set of MH breaths. Exhaled and inhaled tidal volumes were not measured. Percussion and ERCC were performed by a physiotherapist, whereas MH and suctioning were performed by a nurse. The same nurse and the same physiotherapist, who were not blinded to the intervention allocation, performed the maneuvers in all of the patients in the RP group.

The study was conducted during the routine treatment of other patients in the ER/ICU, where the enrolled patients were followed for 5 days. No adverse events occurred during or after each physiotherapy intervention in any of the participants. No hemodynamic, respiratory, or neurological changes were observed during the observation period. Weaning from MV was initiated after the patients had achieved general, hemodynamic, neurological, and respiratory stability (temperature < 38°C; pH < 7.6 or > 7.3; mean arterial pressure > 70 mmHg or < 110 mmHg; no hemodynamic support; HR > 70 bpm or < 130 bpm; Glasgow coma scale score > 8; PaO\(_2\)/FiO\(_2\) > 200; and RR < 25 breaths/min). The weaning process involved the use of a T-piece with an FiO\(_2\) ≤ 50%. It started with 15 min/h, and the frequency was increased until patients had been completely weaned from MV on the basis of their hemodynamic, neurological, and respiratory status. The respiratory physiotherapy interventions were monitored by Sp\(_2\)O, HR, and electrocardiography immediately before, during, and after each intervention.

After all of the patients had been weaned from MV and disconnected from the endotracheal tube, they received respiratory physiotherapy consisting of percussion followed by airway clearance—either by coughing (if the patient was able to) or by suctioning—until the fifth day of treatment.

The patients who were excluded or withdrawn from the study received standard nursing care, which consisted of positioning (i.e., changing the body position every two hours throughout the day) and airway suctioning.

The outcome measures were assessed daily by the same physiotherapist. The patients were evaluated in the supine position, in which ventilatory parameters, SaO\(_2\), arterial blood pressure, temperature, HR, pulmonary auscultation findings, chest expansion, and chest X-ray findings were recorded.

The primary outcome measures were ICU/ER discharge and weaning success. Endpoints related to ICU/ER discharge and weaning success were assessed daily throughout the 5-day observation period. Secondary outcome measures included
Results

Of the 472 enrolled patients, 397 (84%) were hospitalized for respiratory failure, and 235 were intubated and kept on MV. Of the 235 patients, 186 were excluded on the basis of the study criteria. Of the 49 remaining patients, 24 and 25 were randomly assigned to the RP and control groups, respectively. During the study period, 6 and 8 patients in the RP and control groups, respectively, were withdrawn from the study for several reasons, and 19 patients having therefore completed the study in their respective groups (Figure 1).

The use of MV was based on two or more indications in 15 (79%) and 12 (75%) of the patients in the control and RP groups, respectively, and pulmonary disease associated with another event (or disease) was found in 10 (53%) and 11 (69%) of the patients (Table 1).

There were no significant differences between the groups regarding age, gender, Murray score, APACHE II score, and CCI. As for MV parameters, no significant differences were found between the RP and control groups regarding the need for synchronized intermittent mandatory ventilation (21% vs. 50%) or PEEP $\leq 5$ cmH$_2$O (89% vs. 94%). However, the use of FiO$_2 < 50\%$ was more common in the RP group than in the control group (88% vs. 58%; Table 2).

The duration of MV was shorter in the RP group than in the control group from day 2 on, when 37.5% of the RP patients had already been weaned and disconnected from the endotracheal tube. Statistical analyses identified differences between the groups on days 2 and 3 ($p < 0.01$ for both), as well as on days 4 and 5 ($p < 0.05$ for both). Similarly, the length of ICU stay was shorter in the RP group than in the control group from day 3 on, when 25% of the RP individuals ($p < 0.05$) had already been discharged from the ICU. This proportion increased to 31% on days 4 and 5 ($p < 0.01$). It must be emphasized that none of the patients in the control group were discharged from the ICU before day 5. After the removal of the endotracheal tube, all of the patients were submitted to FiO$_2 \leq 30\%$ via a Venturi mask. In either group, none of the patients needed reintubation. Chest physiotherapy had no effect on the evolution of APACHE II scores. Murray scores were lower on day 5 than on day 1 in both groups, the scores on day 5 being significantly lower in the RP group than in the control group ($p < 0.01$; Table 3). Between days 1 and 5, there were no deaths in either group. There was no significant difference between the
Manual hyperinflation combined with expiratory rib cage compression for reduction of length of ICU stay in critically ill patients on mechanical ventilation

Discussion

The present randomized controlled trial showed that the use of simple techniques, performed twice a day for 5 days, improved weaning from MV, as well as reducing the duration of ICU stay and the extent of lung injury in ICU patients. We used a combination of percussion, clearance, MH (combined with ERCC), and suctioning, the technique being performed twice a day. Few studies have examined the effect of percussion on intubated patients, having shown improvement or no significant pulmonary function changes. However, uncontrolled studies have reported that percussion is ineffective. Although MH is widely used in order to remove pulmonary secretions and treat atelectasis, there is no evidence to support its routine use in clinical practice. This lack of evidence is due, in part, to the scarcity of studies examining the clinical relevance and efficacy of MH and to the maneuver itself. Procedures either including or excluding the ERCC step are equally referred to as MH. In addition, some studies do not clearly state whether the ERCC step was included in the MH procedure. We included the ERCC step because we decided to use the maneuver as it was originally described and because the ERCC step has proven effective in improving secretion clearance, alveolar recruitment, atelectasis, and alveolar ventilation.

To our knowledge, the only study in which MH was reported to have a positive effect on weaning from MV, length of ICU stay, and mortality in patients on MV was a study by Ntoumenopoulos et al., who conducted a similar study using postural drainage, MH (without ERCC), and suctioning twice a day throughout the ICU stay of the patients. No
significant differences were found between the control and study groups regarding the length of ICU stay (6.8 days vs. 7.4 days), duration of MV (5.2 days vs. 6.1 days), or ICU mortality (0% for both) in trauma patients.\(^{(11)}\) The replacement of MH by a vibration step did not improve these variables in a nonrandomized study involving patients with ventilator-associated pneumonia.\(^{(2)}\) Although these studies\(^{(2,11)}\) did not compare the techniques in the same population, their results indicate that neither MH nor vibration was effective in patients on MV when individually applied. In a previous study involving patients in whom MH was used in combination with

<table>
<thead>
<tr>
<th>Table 1 - Characteristics of the patients included in the groups studied.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ID/age, years/gender</strong></td>
</tr>
<tr>
<td>1/53/M</td>
</tr>
<tr>
<td>2/54/M</td>
</tr>
<tr>
<td>3/67/M</td>
</tr>
<tr>
<td>4/19/M</td>
</tr>
<tr>
<td>5/50/M</td>
</tr>
<tr>
<td>6/55/M</td>
</tr>
<tr>
<td>7/66/M</td>
</tr>
<tr>
<td>8/56/F</td>
</tr>
<tr>
<td>9/80/F</td>
</tr>
<tr>
<td>10/83/F</td>
</tr>
<tr>
<td>11/49/M</td>
</tr>
<tr>
<td>12/78/F</td>
</tr>
<tr>
<td>13/58/F</td>
</tr>
<tr>
<td>14/44/M</td>
</tr>
<tr>
<td>15/47/M</td>
</tr>
<tr>
<td>16/23/M</td>
</tr>
<tr>
<td>17/73/M</td>
</tr>
<tr>
<td>18/46/F</td>
</tr>
<tr>
<td>19/52/M</td>
</tr>
</tbody>
</table>

RP: respiratory physiotherapy; ID: patient identification; M: male; F: female; pp: postoperative period; BT: brain tumor; CIS: cerebral ischemic stroke; TCE: traumatic cerebral edema; SAH: subarachnoid hemorrhage; CAC: cerebral aneurysm clipping; CPE: cardiogenic pulmonary edema; and GI: gastrointestinal surgery.

<table>
<thead>
<tr>
<th>Table 2 - Baseline demographic characteristics of the participants in the groups studied.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Variables</strong></td>
</tr>
<tr>
<td>Age, years(^a)</td>
</tr>
<tr>
<td>Gender, M/F(^b)</td>
</tr>
<tr>
<td>Comorbidity(^b)</td>
</tr>
<tr>
<td>APACHE II score(^a)</td>
</tr>
<tr>
<td>CCI(^b)</td>
</tr>
<tr>
<td>Murray score(^a)</td>
</tr>
<tr>
<td>SIMV mode(^b)</td>
</tr>
<tr>
<td>PEEP ≤ 5 cmH(_2)O(^b)</td>
</tr>
<tr>
<td>FiO(_2) &lt; 50%(^b)</td>
</tr>
</tbody>
</table>

RP: respiratory physiotherapy group; M: male; F: female; Comorbidity: pulmonary disease (pneumonia, pulmonary embolism, or cardiogenic pulmonary edema) associated with another disease or event; APACHE II: Acute Physiology and Chronic Health Evaluation II; CCI: Charlson comorbidity index; SIMV: synchronized intermittent mandatory ventilation; and PEEP: positive end-expiratory pressure. Values expressed as mean ± SD. *Values expressed as % of patients. *Student’s t-test. **Goodman test.
Table 3 - Effect of the 5-day respiratory physiotherapy on weaning from mechanical ventilation, ICU discharge, and disease severity scores.

<table>
<thead>
<tr>
<th>Variable</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>RP (n = 16)</td>
<td>C (n = 19)</td>
<td>RP (n = 16)</td>
<td>C (n = 19)</td>
<td>RP (n = 16)</td>
</tr>
<tr>
<td>Weaning(^a)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>6 (37.5)</td>
<td>0 (0.0)</td>
<td>6 (37.5)</td>
</tr>
<tr>
<td>Discharge(^b)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>4 (25.0)</td>
<td>0 (0.0)</td>
<td>5 (31.0)</td>
</tr>
<tr>
<td>Murray score(^b)</td>
<td>1.00 [0.75-1.25]***</td>
<td>1.25 [1.00-1.50]*</td>
<td>0.00 [0.00-0.00]</td>
<td>1.00 [1.00-1.00]****</td>
<td></td>
</tr>
</tbody>
</table>

RP: respiratory physiotherapy group; C: control group; and APACHE II: Acute Physiology and Chronic Health Evaluation II. \(^a\)Values expressed as n (%). The Goodman test was used in order to compare the differences between the groups on the same day (*p < 0.05; **p < 0.01). \(^b\)Values expressed as median [interquartile range]. Nonparametric repeated measures ANOVA was used in order to compare the differences between days 1 and 5 in the same group (***p = 0.01; *p < 0.05) and the differences between the groups on the same day (****p = 0.01).
several respiratory physiotherapy techniques, including ERCC,[12] the length of ICU stay and the duration of MV were similar in the study and control groups. However, the proportion of smokers and that of patients with higher disease severity index scores were higher in the study group than in the control group, which might have interfered with the results. Using a different hyperinflation technique (i.e., ventilator-induced hyperinflation), a recent study showed an improvement in secretion clearance and static compliance of the respiratory system in patients on pressure support ventilation.[127]

In the RP group, the improvement in lung injury, as measured by the Murray score, was not followed by an improvement in disease severity, as measured by the APACHE II score. Although previous studies have employed the Murray score[28] and the APACHE II[2,3,29] score, the effect of respiratory physiotherapy interventions on those indexes was not evaluated, further comparisons being therefore impossible. The present study showed that although the Murray scores improved in both groups, the proportion of patients who were successfully weaned from MV and discharged from the ICU on day 5 was higher in the RP group than in the control group (37.5% vs. 15.9% and 31% vs. 0%, respectively).

One cohort study of comorbidities in the ICU found that the mortality rate was lower in study group patients with a CCI of 2 than in control group patients with the same CCI (12.5% vs. 26.0%), although there was no difference between the two groups regarding 30-day mortality.[19]

The randomization process allowed the formation of homogeneous groups regarding most of the baseline characteristics, including age,[30] gender,[1,5,29] and diagnosis.[1,28] In our study, these characteristics represent the common profile of general ICU patients. The median baseline CCI (2 in both groups) and APACHE II scores (16 and 17 in the control and RP groups, respectively) found in the present study were consistent with those reported in previous studies of critically ill patients.[2,29,30] However, the baseline Murray scores (1.25 and 1.00 in the control and RP groups, respectively) were lower in the present study than in another study of patients on MV.[30]

Our study has some limitations, such as the small sample size. Although the number of patients in the present study was small, our data showed that the power of the study was 0.8, the effect size for ICU discharge or successful weaning from MV being greater than 0.45. Another limitation is that the study was not blind. The interventions were performed by the only physiotherapist available. Therefore, it was impossible to conduct a blind study.

In summary, the present study demonstrated that the use of MH in combination with ERCC in patients on MV accelerates the weaning process, as well as reducing the extent of lung injury and the length of ICU stay. Further studies evaluating the effectiveness of chest physiotherapy in ICU patients on MV can provide additional evidence.

References


About the authors

Juliana Savini Wey Berti
Physiotherapist. Botucatu Hospital das Clínicas, Botucatu School of Medicine, São Paulo State University, Botucatu, Brazil.

Elisiane Tonon
Physiotherapist. Botucatu Hospital das Clínicas, Botucatu School of Medicine, São Paulo State University, Botucatu, Brazil.

Carlos Fernando Ronchi
Physiotherapist. Intensive Care Unit, Botucatu Hospital das Clínicas, Botucatu School of Medicine, São Paulo State University, Botucatu, Brazil.

Heloïsa Wey Berti
Assistant Professor. Department of Nursing, Botucatu School of Medicine, São Paulo State University, Botucatu, Brazil.

Laércio Martins de Stefano
Assistant Professor. Department of Internal Medicine, Botucatu School of Medicine, São Paulo State University, Botucatu, Brazil.

Ana Lúcia Gut
Assistant Professor. Department of Internal Medicine, Botucatu School of Medicine, São Paulo State University, Botucatu, Brazil.

Carlos Roberto Padovani
Full Professor. Department of Biostatistics, Institute of Biosciences, São Paulo State University, Botucatu, Brazil.

Ana Lucia Anjos Ferreira
Associate Professor. Department of Internal Medicine, Botucatu School of Medicine, São Paulo State University, Botucatu, Brazil.