CASE REPORT

Treatment of the severe form of hantavirus cardiopulmonary syndrome using continuous positive airway pressure via face mask*

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In 1993, the first cluster of hantavirus cardiopulmonary syndrome (HCPS) cases in Brazil was reported. The cases all appeared in the city of Juquitiba, in the state of São Paulo. Since then, new cases have been reported, particularly in the southern and southeastern states. In our city of São Carlos, which is also in the state of São Paulo, no cases of HCPS were reported until 2002, when three cases were diagnosed. In one of those patients, ventilatory support was sustained with continuous positive airway pressure via face mask. This represents the first successful management of a severe case of Hantavirus-induced acute respiratory failure using this type of respiratory strategy.

Key words: Pulmonary Ventilation, CPAP Ventilation, Hantavirus Pulmonary Syndrome, Respiratory Insufficiency/Acute, Hypoxemia

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INTRODUCTION

Hantavirus cardiopulmonary syndrome (HCPS) was first described in 1993, when several cases were reported in the USA1. In the same year, three cases were reported in Brazil2. The Brazilian cases occurred in the state of São Paulo, in a recently deforested region of the Atlantic Forest, in the city of Juquitiba.

Only recently identified and often fatal, HCPS presents as severe acute respiratory insufficiency1-7. The disease occurs in previously healthy subjects and initially presents as fever, accompanied by symptoms similar to those of the common cold. However, it may rapidly evolve into pulmonary edema, respiratory insufficiency and shock. Initially, mortality was approximately 75% but has declined over the last few years to roughly 35%6-8. Patients who survive usually recover completely within a week or so after the onset of the respiratory symptoms.

The causative agent is a previously unrecognized hantavirus whose natural reservoir is a wild rodent (Muridae, Sigmodontinae). The common mechanism of human infection is inhalation of viral particles present in the excrement of rodents. However, there was a cluster of cases reported in the region of Bariloche, Argentina, where person-to-person transmission of the disease was confirmed5-7.

No specific antiviral treatment for HCPS has yet been established, although the efficacy of ribavirin is currently under study. Intensive care, including mechanical ventilation and invasive hemodynamic monitoring, is required for the more severe presentations of the disease. Hemoconcentration and thrombocytopenia are common features, and the typical radiological finding is bilateral diffuse interstitial infiltrate that evolves to alveolar consolidation in parallel with the worsening of patient condition1-7.

The Fundação Nacional de Saúde (National Health Foundation), which registers cases occurring in Brazil, had reported 226 cases of HCPS as of October 30, 2002. Approximately 34% of these cases resulted in death8. In the initial years, the cases reported came
predominantly from the states of São Paulo and Minas Gerais. Later, there was a significant outbreak in the southern region of the country, especially in the state of Paraná. The state of São Paulo has the second greatest number of reported cases, surpassed only by the state of Paraná. Within the state of São Paulo, higher concentrations of cases are seen in and around the cities of Ribeirão Preto (in the central region) and Franca (in the northern region). The city of São Carlos is located in the central region of the state of São Paulo, approximately 90 km from the city of Ribeirão Preto, and has approximately 180,000 inhabitants. Its economic activities are mainly industry-based. The most relevant agricultural activities are the production of oranges and sugar cane.

Since 1996, cases of HCPS have been reported in cities neighboring São Carlos (Araraquara, Ribeirão Preto, Guariba, Jardimópolis and Sertãozinho). However, no cases were reported within the city of São Carlos itself until 2002, when a total of three cases were reported. In two of these three cases, there was favorable evolution and complete reversal of symptoms.

Notably, one of the patients who presented a favorable clinical evolution received only continuous positive airway pressure (CPAP) as ventilatory support, which is a method never before reported in case studies of severe HCPS.

CASE REPORT

A 30-year-old man, living in the urban area and working on the assembly line in a large-scale compressor factory, sought medical attention from the company nurse in the third week of May, 2002, reporting pain in the dorsal region and fever for the past three days. The patient was examined by a general practitioner, who made a diagnostic hypothesis of flu and prescribed symptomatic medication.

On the following day, the patient sought further medical attention, complaining of general malaise, cough and breathing difficulty at the slightest effort. The initial physical exam revealed tachypnea and bilateral thin breath sounds in the lung bases.

A chest X-ray revealed discrete interstitial infiltrate in the lung bases. The patient was then hospitalized for respiratory distress and was examined further. Antibiotic therapy with levofloxacin (500 mg/day iv) was started, and oxygen was administered by nasal cannula. Initially, respiratory rate improved. However, on the following day, respiratory function worsened, and a radiograph showed (predominantly interstitial) infiltrate in the lower two-thirds of both lungs.

The patient was transferred to an intensive care unit (ICU). On the day of the transfer, his blood work showed hemoglobin of 15 g/dl, hematocrit of 44.6%, 9,900 leukocytes (1% metamyelocytes, 11% rod-shaped, 63% segmented, 18% lymphocytes and 7% monocytes) and 58,000 platelets/ml. Initially, a Venturi mask was employed as a means of oxygen supplementation. However, when gasometric readings did not improve, CPAP (at 15 cm H₂O) was started. We achieved continuous flow ventilation using a Bird Mark 7® device, limiting inspiratory pressure and increasing inspiratory time to the maximum in order to avoid cycling of the device. The interface used for the application of noninvasive ventilation (NIV) was a Respironics® adult face mask, and there was a rapid improvement in ease of respiration and gas exchange. The chest X-ray taken immediately prior to CPAP application showed diffuse alveolar interstitial infiltrate in both lungs (Figure 1B).

With the application of CPAP, we managed to reduce FiO₂ and maintain it below 60% while maintaining SaO₂ ≥ 93%. The chest X-ray taken a few hours after the initiation of CPAP showed that aeration had already begun to improve in the upper lobes of the lungs (Figure 1C). Over the following days, there was progressive improvement in oxygenation and it was possible to gradually decrease, and eventually discontinue, CPAP, seven days after it was initiated (Figure 1D).

The patient was discharged from the ICU on the ninth day of hospitalization and presented favorable evolution, with full recovery from respiratory symptoms, normalization
of arterial gases and reduced pulmonary infiltrate. Radiography and tomography performed one week after ICU discharge confirmed this positive outcome (Figure 2).

Since the patient was in contact with rodents in his work environment, HCPS was suspected and later confirmed by serology using ELISA to detect the specific antibodies IgM and IgG. Laboratory testing was conducted at the Adolfo Lutz Institute, located in the city of São Paulo and recognized by the World Health Organization (WHO) as one of only two accredited viral research reference laboratories in Brazil.

DISCUSSION

Classified as a zoonotic disease, HCPS may develop very rapidly in human beings, presenting a clinical profile of respiratory insufficiency due to noncardiogenic pulmonary edema and shock, with low cardiac deficiency and high peripheral vascular resistance 5-7.

Since we lack laboratories with respiratory security systems for viruses, viral culture for hantavirus is not conducted in Brazil. Such testing would confirm the diagnosis by identifying hantavirus-specific IgM, which is always present after the onset of HCPS symptoms 4,6,7.

The pathogenesis of HCPS seems to be determined by connections between the viral particles and \( \beta_3 \) integrins, which are components of the tight junctions of the endothelium. It is believed that this interaction alters the integrity of the intercellular junctions, with a resulting increase in endothelial permeability and loss of fluids from the alveolar space, but no cell damage. There also seems to be local infiltration by immunoblasts (T-activated lymphocytes), which could induce significant cytokine liberation. This would be combined with a decrease in the cardiac and circulatory function. Since no cell damage or cell death occurs, complete recovery is typically achieved once the acute inflammatory phase has passed 3,6.

Over the last two decades, NIV has received special attention for its proven efficiency, with a 1A level of evidence for ventilation of patients presenting chronic hypercapnic respiratory insufficiency or acute exacerbations related to chronic pulmonary obstructive disease 9,10. In comparison with invasive mechanical ventilation, NIV has been shown to shorten ICU and overall hospital stays, as well as lowering mortality rates 9,10,11,12. The same comparison revealed that NIV has also been associated with fewer cases of hospital-acquired pneumonia, as well as lower numbers of tracheal lesions, since tracheal prostheses are not required for NIV 9-2.

In patients presenting acute respiratory insufficiency, CPAP is employed in order to correct hypoxemia. The technique and benefits of the use of positive airway pressure via face mask were described in the 1930s by Barach et al 13, who pointed out the utility of CPAP in the treatment of acute pulmonary edema.

In 1991, Bersten et al.14 published a prospective study comparing NIV using CPAP to routine clinical treatment for patients with acute pulmonary edema. A total of 39 patients were studied, and orotracheal intubation (OTI) was recommended for seven patients in the group submitted to clinical treatment alone.

Some studies indicated that NIV is effective in decreasing respiratory effort, improving patient comfort and avoiding OTI, as well as improving median survival of patients with acute respiratory insufficiency 10,11,15-18.

In type 1 or hypoxic respiratory failure, NIV presents a higher potential effectiveness in rapidly reversible pathological processes such as acute pulmonary edema and postoperative atelectasis 11,12. The method increases mean airway pressure, improving ventilation in collapsed areas of the lungs and may also reduce and redistribute alveolar edema 19,20.

Use of CPAP or NIV, together with ventilatory support, is theoretically and pathologically justified in HCPS patients presenting signs of a significant increase in respiratory effort or respiratory muscular fatigue.

In this case, since the Bird Mark 7 was the only respirator available, we opted for trying to increase the average alveolar pressure and oxygenation through CPAP, despite the fact
that evaluation of the respiratory rate provided no evidence of either use of accessory muscles or respiratory patterns that would indicate muscular fatigue. As it was started early (at the beginning of the cardiopulmonary phase of HCPS), we successfully managed to avoid tracheal intubation and invasive mechanical ventilation.

Another important aspect in the treatment of these patients is avoiding positive fluid balance through careful fluid replacement, which has been correlated with better prognoses in cases of HCPS.

Subsequent to our case study, in April and May of 2003, Asia and North America were caught unawares by a coronavirus, namely severe acute respiratory syndrome (SARS), which has the potential of causing acute respiratory symptoms similar to those of HCPS. The NIV technique has also proven useful in early ventilatory support of SARS patients.

We concluded that CPAP was beneficial in this case of HCPS-related severe acute respiratory insufficiency, avoiding OTI, invasive ventilation and the progression to acute respiratory failure. This procedure may have facilitated the favorable evolution of the patient.

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Figure 1C. Chest radiograph showing improved ventilation in the upper lobes of the lungs after CPAP at 16 cm H₂O.

Figure 1D. Chest radiograph after discontinuation of CPAP.

Figure 2. Chest computed tomography seven days after discharge from the intensive care unit showing normality of the lung parenchyma.
<table>
<thead>
<tr>
<th>Day of admission</th>
<th>INF</th>
<th>ICU day 1</th>
<th>ICU day 2</th>
<th>ICU day 3</th>
<th>ICU day 4</th>
<th>ICU day 5</th>
<th>ICU day 6</th>
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<td>71.4</td>
<td>103.4</td>
<td>132.4</td>
<td>92.1</td>
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<td>230</td>
<td>264</td>
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<td>21%</td>
<td>Mask</td>
<td>40%</td>
<td>40%</td>
<td>21%</td>
<td>21%</td>
<td>Mask</td>
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<td>O₂ 5 L/min</td>
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<td>Fig 1c</td>
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<td>Fig 1d</td>
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</table>

INF: infirmary; ICU: intensive care unit; PaO₂: arterial oxygen tension; PaCO₂: arterial carbon dioxide tension; SaO₂: arterial oxygen saturation; FiO₂: fraction of inspired oxygen; RR: respiratory rate; HR: heart rate; AP: arterial pressure