Continuous Negative Chest-wall Pressure as Therapy for Severe Respiratory Distress in Older Children*

Shyamal K. Sangal, M.B.B.S.; Charles Mitchell, M.D.; Walter T. Hughes, M.D.; Sandor Feldman, M.D.; and Josefina Caces, M.D.

with technical assistance of Scott Harris

Continuous negative chest-wall pressure (CNP) was used to treat five children, 4 to 11 years of age, who had progressively severe respiratory distress caused by Pneumocystis carinii pneumonitis. After initial improvement, two patients developed progressive increases in respiratory rate, alveolar-arterial oxygen gradient, intrapulmonary right-to-left shunt, and hypoxia. The disease ended fatally in both. The remaining three patients continued to improve and recovered from their pulmonary disease. These results show that CNP therapy provides an effective means of improving arterial oxygenation in spontaneously breathing older children, just as in neonates, without the need for endotracheal intubation, prolonged sedation, and muscle relaxants.

Maintenance of increased transpulmonary pressure by application of continuous negative pressure (CNP) around the chest wall is now a well-recognized means of improving arterial oxygenation in patients with spontaneous ventilation.1 To date, however, this mode of therapy has been limited to management of progressive hypoxia in newborn infants with severe respiratory distress syndrome.2-7 In a recent preliminary report,8 we described for the first time the successful use of CNP therapy in management of an older child with respiratory insufficiency characterized by progressive tachypnea, an increase in alveolar-arterial gradient and intrapulmonary right-to-left shunt with a concomitant fall in arterial oxygen tension. The purpose of this communication is to report a more extensive study of CNP therapy in management of severe hypoxia in older children with diffuse bilateral alveolar disease.

MATERIALS AND METHODS

Patients and Laboratory Data

This study includes five children, 4 to 11 years of age, who were admitted to St. Jude Children's Research Hospital with chief complaints of fever, weight loss, cough, and progressive respiratory distress of 4 to 16 days' duration. Three of these children (cases 1, 2, and 5) had acute lymphocytic leukemia and were in complete hematologic remission.9 The other two patients had acute myelocytic leukemia, one in relapse (case 3) and the other in remission (case 4).

Physical examination on admission showed moderate-to-severe respiratory distress in all but one patient. Temperature ranged from 38.7° to 39.7°C, and heart rate from 110 to 160 per minute. Respiratory rate was 70 per minute or above in all but one patient, whom it was 36 per minute (Table 1). None of the patients had clinical evidence of cyanosis, and lungs were clear to percussion and auscultation.

Initial laboratory data showed hemoglobin ranging from 8.2 to 10.5 gm percent and total white blood cell count from 6,800 to 8,200/mm3 with a predominance of neutrophils. In each patient, blood cultures were sterile, and urine and throat cultures did not grow any pathogens. Skin tests for histoplasmosis and tuberculosis were nonreactive. Complement fixation titers for influenza viruses A, B, and C, parainfluenza viruses, toxoplasma, and mycoplasma were all less than 1:8. In each patient roentgenograms of the chest showed bilateral pulmonary densities compatible with diffuse alveolar disease.

Initial Acid-Base and Blood-Gas Studies

Blood-gas patterns were determined in blood samples obtained from the radial artery under anaerobic conditions while the patients were breathing room air. In one patient (case 1), pH was 7.44; arterial carbon dioxide tension (PaCO₂), 37.8 mm Hg, and arterial oxygen tension (PaO₂) 86 mm Hg. In the remaining four patients, pH was above 7.45 and PaCO₂ was less than 30 mm Hg. Arterial oxygen tension in these four patients ranged from 32 to 48 mm Hg (Table 1). Blood gas measurements were repeated after the patients had breathed 100 percent oxygen for 15 minutes; these determinations showed PaO₂ ranging from 435 to 117 mm Hg, alveolar-arterial oxygen gradient (A-aDO₂) from 232 to 539 mm Hg, and intrapulmonary right-to-left shunt from 17.1 to 28.4 percent.

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Table 1—Effect of CNP Therapy on Blood-Gas Profile, FIO₂ and Respiratory Frequency in Children with P carinii Pneumonitis

<table>
<thead>
<tr>
<th>Case No (age)</th>
<th>Parameters*</th>
<th>Duration of CNP</th>
</tr>
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<tbody>
<tr>
<td>1 36 (5 yrs)</td>
<td>FIO₂ RA* PaO₂</td>
<td>Survivors</td>
</tr>
<tr>
<td>1 36 (5 yrs)</td>
<td>36 107 98 91 71 78 50 33 30</td>
<td>27 24</td>
</tr>
<tr>
<td>1 36 (5 yrs)</td>
<td>PaO₂ 86 44 55 64 155 82 77 85 106</td>
<td>No CNP</td>
</tr>
<tr>
<td>1 36 (5 yrs)</td>
<td>A-aDO₂ 287 582 — 418 394 391 394 355 320</td>
<td>199 248</td>
</tr>
<tr>
<td>1 36 (5 yrs)</td>
<td>CNP — — — 10 12 9 12 13 7 0 —</td>
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<tr>
<td>1 36 (5 yrs)</td>
<td>FIO₂ 70 100 96 82 72 54 60 71 60 38</td>
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<tr>
<td>1 36 (5 yrs)</td>
<td>PaO₂ 48 45 70 87 72 88 75 67 75 75</td>
<td></td>
</tr>
<tr>
<td>1 36 (5 yrs)</td>
<td>A-aDO₂ 232 528 486 469 394 467 381 515 185 27</td>
<td></td>
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<tr>
<td>1 36 (5 yrs)</td>
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<tr>
<td>1 36 (5 yrs)</td>
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<tr>
<td>1 36 (5 yrs)</td>
<td>PaO₂ 32 29.5 46 137 62 70 73 64 45 57 62 76 78 89</td>
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<tr>
<td>1 36 (5 yrs)</td>
<td>A-aDO₂ — — — 487 498 604 599 630 640 625 405 479 194 139</td>
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<tr>
<td>1 36 (5 yrs)</td>
<td>FIO₂ 80 73 49 51 41 45 40 43 37 36 42</td>
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<tr>
<td>1 36 (5 yrs)</td>
<td>PaO₂ 32 49 55 76 78 48 49 38 60 39 24</td>
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<tr>
<td>1 36 (5 yrs)</td>
<td>A-aDO₂ 541 595 — 554 516 553 586 591 627 621 631</td>
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<tr>
<td>1 36 (5 yrs)</td>
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<tr>
<td>1 36 (5 yrs)</td>
<td>PaO₂ 36 35 70 61 42 40 52 60 55 60 92 100</td>
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<td>1 36 (5 yrs)</td>
<td>A-aDO₂ 497 627 — 606 595 590 536 498 531 544 630 634</td>
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'C', respiratory frequency per minute; FIO₂, fractional concentration of oxygen in inspired air (percent); RA, room air; PaO₂, partial pressure of oxygen in arterial blood (mm Hg); A-aDO₂, alveolar-arterial oxygen difference (mm Hg); CNP, continuous negative pressure (cm H₂O); RA, room air; pH and PaCO₂ are not reported here, as they did not change significantly during CNP therapy. †This patient developed pneumothorax at CNP of —5 cm H₂O. Since the patient was able to maintain PaO₂ at 65 mm Hg without CNP (FIO₂ 40 percent), therapy was discontinued. ‡Values obtained on ninth day of CNP therapy shortly before fatal termination of the disease.

Lung Aspiration

Lung specimens were obtained from each patient by percutaneous transthoracic needle aspiration. These were stained with polyethylene naphthyl blue and methylene silver nitrate and showed P carinii organisms. Cultures of the aspirates were sterile for bacteria and fungi.

Hospital Course

Once the diagnosis of P carinii pneumonia was confirmed, patients were given pentamidine isethionate (150 mg/M²/24 hour), intravenous fluids, antibiotics, and oxygen. The initial oxygen concentration in inspired air (FIO₂) ranged from 28 to 40 percent. During the next 48 hours there was an increase in tachypnea in all patients and a drop in arterial oxygen tension despite an increase in FIO₂. Serial values for A-aDO₂ and intrapulmonary right-to-left shunt were determined in three patients after they had breathed 100 percent oxygen for 15 minutes, and showed an increase in each. Because of progressive respiratory distress and hypoxia, and an increase in FIO₂, CNP therapy was started in all five patients.
for two hours without CNP, the patients were removed from the respirator and the oxygen concentration in inspired air was decreased as tolerated.

RESULTS during CNP Therapy

Survivors

Three patients survived. Within 24 hours after the start of CNP therapy, respiratory frequency, A-aDO₂ gradient, and intrapulmonary right-to-left shunt decreased sharply in two of the survivors (Fig 1, Table 1). These decreases were associated with a concomitant rise in PaO₂ that permitted a subsequent decrease in FIO₂ to 40 percent. In the third patient, a negative pressure of −18 H₂O was required to maintain PaO₂ >50 mm Hg at FIO₂ of 60 percent. At this point, the patient developed bilateral pneumothorax that resulted in a precipitous drop of PaO₂ and an increase in FIO₂ to 1 atm (100 percent). Pneumothorax on both sides was successfully decompressed. FIO₂ was maintained at 100 percent for 72 hours to keep PaO₂ at >60 mm Hg. During the next 48 hours, because of a persistent rise in PaO₂, FIO₂ was gradually decreased to 65 percent. The continuous negative pressure and FIO₂ were then gradually reduced over the next nine days to 0 and 40 percent, respectively.

Fatal Cases

Two patients died. Both showed initial improvement during CNP therapy, characterized by a decrease in respiratory frequency and severity of hypoxia, but this was followed by a progressive increase in tachypnea, A-aDO₂ difference, intrapulmonary right-to-left shunt, and a drop in PaO₂ despite an increase in FIO₂ to 1 atm (100 percent). One died on the ninth day of CNP therapy and the other on the sixteenth. None of the five patients showed significant changes in pH, PaCO₂, or blood pressure during CNP therapy.

Autopsy Data

Sections of lung tissue from both fatal cases showed diffuse and confluent alveolopathy of varying severity. These changes consisted of a reduction in alveolar space due to proliferation of hyperplastic epithelial cells lining the alveoli, proteinaceous eosinophilic exudate containing macrophages and a widening of interalveolar septae (Fig 2). This widening was due to fibrosis (increase in collagen tissue), mononuclear cellular infiltrate and proliferation of congested capillaries. Electron microscopic studies showed proliferating granular pneumocytes. Septal fibrosis and widening of the air-blood barrier were more pronounced in Case 5 (Fig 3).

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cystis carinii pneumonitis can produce significant alterations in acid-base profile and blood-gas composition is being recognized with increasing frequency.\(^\text{14,15}\) These alterations, which most probably are related to various degrees of atelectasis and intrapulmonary right-to-left shunt, are similar to those reported in patients with respiratory distress syndrome (RDS) and other forms of pneumonia.\(^\text{16-19}\) Since Harrison et al\(^\text{20}\) pointed out that an inability to grunt lowers arterial oxygen tension in neonates with RDS, the application of a continuous distending pressure across the lungs during both artificial and spontaneous ventilation has been shown to alter significantly the arterial oxygenation in these patients.\(^\text{1-7,19}\)

The mechanisms(s) through which CNP therapy produces its beneficial effects, however, is not entirely clear. Thibeault et al\(^\text{21}\) have shown that application of constant negative pressure around the chest wall in healthy premature infants resulted in an increase in functional residual capacity (FRC). Bancalari et al\(^\text{22}\) recently reported a similar increase in FRC following CNP therapy in neonates with severe hyaline membrane disease. The authors attributed this increase to an expansion of collapsed alveoli and/or overexpansion of ventilated units. Since the pressure required to expand a ventilated unit is less than that required to open a collapsed alveolus, the second possibility appears more likely. Concomitant with an increase in FRC, Bancalari et al\(^\text{22}\) observed a fall in dynamic compliance during CNP therapy. On the basis of these results, the authors suggested that the increase in lung volume associated with CNP therapy is not only due to expansion of collapsed alveoli, but also to an over-expansion of ventilated units, bringing these units to the flattened portion of their pressure volume curve.\(^\text{20}\) However, no significant linear correlation was found between the increase in FRC and improvement in arterial oxygenation. These observations, therefore, suggest that factors other than an overall increase in alveolar ventilation are responsible for the beneficial effects of CNP therapy on arterial oxygenation. The fact that pH and PaCO\(_2\) remained relatively stable in our patients, as well as in others,\(^\text{24,6}\) adds further support to this contention.

That hypoxia can cause pulmonary vasoconstriction, an increase in pulmonary vascular resistance and hence a reduction in pulmonary blood flow is well known.\(^\text{23}\) Since application of CNP around the chest wall increases thoracic gas volume and FRC, it might permit a longer time for gas exchange with subsequent improvement in arterial oxygenation. An increase in PaO\(_2\) will ultimately decrease pulmonary

### Complications

Three patients developed pneumothorax while receiving CNP therapy. In two patients the complication was bilateral and occurred at \(-16\) and \(-18\) cm H\(_2\)O, whereas in the third it occurred when CNP had been reduced to \(-5\) cm H\(_2\)O. It is of interest that mild pneumothorax developed in two of these patients after transthoracic percutaneous lung aspiration, but it absorbed spontaneously prior to initiation of CNP therapy. In each patient who developed pneumothorax while receiving CNP therapy, the complication was successfully decompressed by the use of chest tubes. Moderate-to-severe neck abrasions were noted in two of the youngest patients. Excessive cooling of the body did not occur.

### Discussion

These observations demonstrate that CNP therapy provides an effective means of improving arterial oxygenation in spontaneously breathing older children who have progressively severe hypoxia associated with diffuse bilateral alveolar disease.

That bilateral alveolar disease such as Pneumo-
vascular resistance and hence increase pulmonary blood flow,24 with a consequent improvement in the ventilation-perfusion ratio and a decrease in intrapulmonary venous admixture. The net result of these changes may explain the decrease in alveolar-arterial gradient and intrapulmonary right-to-left shunt, as well as the concomitant increase in arterial oxygen tension with no significant change in pH and PaCO₂ that we observed in our patients following CNP therapy. This improvement in respiratory distress and blood gas composition within 24 hours after initiation of CNP therapy contrasts sharply with the response of five other patients with equally severe bilateral disease due to Pneumocystis carinii pneumonitis. In this latter group of patients who received oxygen, antibiotics, and pentamidine with ventilatory assistance from a preset-volume respirator the disease ended fatally. It is of further interest that a comparison of the mortality rates between patients with Pneumocystis carinii pneumonitis who were treated at our institution during the period when CNP therapy was given, and an equal number of successive patients with the disease who were treated immediately prior to this period, showed a drop in mortality rate from 4 of 11 patients (36 percent) to 2 of 11 (18 percent), respectively.

In the two patients who received CNP therapy but later died of their disease, initial improvement was followed by a gradual deterioration. This was characterized by a progressive increase in both A-aDO₂ gradient and intrapulmonary right-to-left shunt, as well as a decrease in PaO₂ that necessitated an increase in FIO₂ to 1 atm. Histologic and ultrastructural studies of the lung tissue in both patients showed structural changes in the form of patchy atelectasis, capillary congestion, destruction of membranous pneumocytes, proliferative changes of granular pneumocytes, and obliteration of alveolar spaces. In addition, there were changes in alveolar septum that consisted of an increase in septal cells, pools of collagen tissues, and mononuclear cellular infiltrate, all of which caused a widening of interstitial space and air-blood barrier. It is of interest that these changes, which closely simulate those described for pulmonary oxygen toxicity,25-27 were more pronounced in the patient (Case 5) who was exposed to higher oxygen concentrations for longer periods, and in whom CNP therapy was started only after FIO₂ had remained as high as 0.65 atm (65 percent) for 48 hours. These findings strongly suggest the need for early institution of CNP therapy and form the basis of our using FIO₂ of 0.5 atm (50 percent) as an indication to start CNP therapy in patients with progressive hypoxia and intrapulmonary right-to-left shunt.

During CNP therapy three patients developed pneumothorax. In two, mild pneumothorax occurred immediately after transthoracic percutaneous lung aspiration. In both of these patients, pneumothorax resolved spontaneously prior to institution of CNP therapy and then recurred with CNP of −18 cm H₂O. In the third patient, pneumothorax developed at a time when CNP had been reduced to −5 cm H₂O and the patient was able to maintain an adequate PaO₂ with 40 percent FIO₂. The occurrence of pneumothorax at this stage suggests an increased vulnerability of the lungs during improvement in lung mechanics associated with resolution of the underlying pneumatic process. In addition to pneumothorax, limited accessibility to the patient for examination, routine nursing care, or emergency treatment was a major disadvantage of this form of therapy. Neck abrasions developed in two patients because of pressure from the ring that supported the neck. Despite these problems, the ability to increase arterial PaO₂ in spontaneously breathing patients without resorting to endotracheal intubation, muscle relaxants, or prolonged sedation offers a distinct advantage of CNP therapy.

Of greater significance, the benefits of CNP therapy may not be limited to neonates and older children with progressively severe hypoxia, but may also prove an important adjuvant in management of adults with similar forms of disease.

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Blaise Pascal (1623-1662)

In 1640, while helping his father, a tax assessor in Rouen, young Pascal conceived of a machine that would perform the tediously long additions and multiplications by making the figures on paper correspond to the movement of interlocked wheels. In the contemporary state of the practical arts the making of such a machine was enormously difficult. Pascal made fifty models and spent five years before the first calculator was made in 1652. It was this "Pascaline" that inspired the inventor's sister, Gilberte, to say: "He reduced to mechanism a science which is wholly in the human mind." Two hundred years later, Byron's daughter, Lady Lovelace, who, herself mathematical, assisted Babbage, the inventor of a notable computer in 1840, was struck by the same transmigration of intellect.