Negative extrathoracic pressure ventilation in central hypoventilation syndrome

H Hartmann, M H Jawad, J Noyes, M P Samuels, D P Southall

Abstract

Nine patients with central hypoventilation syndrome (CHS) were treated with negative extrathoracic pressure ventilation (VNEP). Treatment with VNEP was started between 20 days and 57 months of age, which was two days to 47 months after diagnosis. The equipment to provide VNEP utilised a new system with a latex neck seal and Perspex chamber allowing easy access to the child.

Seven patients are managed with VNEP at home by their parents. They did not have a tracheostomy when VNEP was started at ages of 22, 24, 31, 38, and 75 days, 5 and 57 months. They have continued to be successfully managed with VNEP and without tracheostomy. Short periods of intubation and positive pressure ventilation were required on 10 occasions (median duration 7 days, range 4 to 21 days) in four subjects during respiratory tract infections. Three patients required periods of continuous positive airway pressure (CPAP) via a nasal mask or a nasopharyngeal airway during sleep to overcome upper airway obstruction. In three patients the hypoventilation improved and two of these do not require regular ventilatory support at 1.3 and 3.4 years of age. Six of these seven patients are developing normally.

In two patients with long term tracheostomies, VNEP could not be established at an age of 29 and 52 months because of tracheal obstruction after temporary removal of their tracheostomy cannula.

VNEP is an effective, non-invasive, treatment in infants with CHS if initiated before tracheostomy. It may improve the children's quality of life during the day-time. If upper airway obstruction is a problem in the first year of life, it may be combined with nasal mask CPAP.

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intermittent positive pressure ventilation (IPPV) through a tracheostomy.^{1 4 5} Augmenting ventilation with diaphragmatic pacing has been used, but in most cases still requires a tracheostomy to overcome upper airway obstruction.⁶ Attempts to achieve adequate ventilation using respiratory stimulants have proved ineffective.^{7 8}

Successful use of negative extrathoracic pressure ventilation (VNEP) has rarely been reported in CHS. Oren *et al* mention an attempt to support ventilation in two infants with an iron lung and a cuirass system, respectively.¹ Marcus *et al* recently reviewed the long term outcome of 13 patients with CHS. One of their patients was successfully changed from IPPV to VNEP using a cuirass ventilator and her tracheostomy was decannulated.⁴ Generally, however, the use of VNEP has been limited in CHS because of upper airway obstruction. This is explained by a failure of the normal activity of the pharyngeal musculature that immediately precedes each inspiratory effort, dilating the upper airway and allowing air to enter the trachea and lung.⁹

Having developed a new system for applying VNEP,¹⁰ we report our experience with this non-invasive respiratory support in nine patients with CHS.

Patients and methods

PATIENTS

Clinical details of nine patients with CHS who have been treated with VNEP are summarised in table 1. Patient 7 had received IPPV through a tracheostomy from 9 to 14 months of age before representation at 57 months.

In patients 1-4 and 7-9, the diagnosis of CHS was confirmed by analog tape recordings during sleep and wakefulness of arterial oxygen saturation (SaO₂) from a validated pulse oximeter (Nellcor),¹¹ expired carbon dioxide (Engström Eliza), transcutaneous carbon dioxide levels (TcPCO₂) (Hewlett Packard or Kontron), and chest wall movements (Graseby volumatic capsule and respiratory inductance plethysmography, Studley Data System). Hypoventilation exclusively during sleep resulted in abnormal hypercapnia and hypoxaemia necessitating assisted ventilation in all cases. Abnormal hypercapnia was defined as a TcPCO₂ persistently >8 kPa.⁴ Abnormal hypoxaemia was defined as an inability to maintain baseline SaO₂ >96% when the infant was in quiet sleep or at rest, or the occurrence of a desaturation to <80% for more than 4 seconds.¹¹ The transcutaneously measured blood oxygen and carbon dioxide levels were confirmed as abnormal during sleep by

Central hypoventilation syndrome (CHS) is a rare condition defined as a disturbance of the central control of breathing in the absence of an apparent structural lesion in the central nervous system.¹ Recent work from Marcus *et al* suggests that such patients have an abnormal central integration of the input from central and peripheral chemoreceptors.² Affected infants and children present with hypoventilation resulting in progressive hypercapnia and hypoxaemia during sleep, particularly non-rapid eye movement sleep.³

Conventional treatment of CHS consists of

Academic Department
of Paediatrics,
University of Keele,
North Staffordshire
Hospital, Stoke on
Trent ST4 6QG
H Hartmann
J Noyes
M P Samuels
D P Southall

East Surrey Hospital,
Redhill
M H Jawad

Correspondence to:
Professor Southall.

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Table 1 Clinical details of patients

Patient No	Sex	Birth weight (g)	Family history	Additional disease	Age at presentation	Age at diagnosis	Duration of IPPV before VNEP
1	F	3680	Parents are first cousins, sister died with major neurological disorder	Severe learning difficulties, deafness, blindness, epilepsy	10 Days	10 Days	21 Days
2	M	3600	None	Epilepsy	Birth	14 Days	23 Days
3	M	3080	None	None	Birth	20 Days	30 Days
4	F	2780	None	None	Birth	49 Days	20 Days
5	F	3440	None	None	Birth	21 Days	38 Days
6	M	3670	Brother has cleft lip and palate	None	2 Days	36 Days	5 Months
7	F	2960	Father died of cerebral tumour, sister had thoracic rhabdomyosarcoma	Hypogammaglobulinaemia	9 Months	10 Months	4 Months
8	F	4000	None	None	Birth	20 Days	29 Months
9	F	3000	None	None	Birth	23 Days	52 Months

direct arterial line or capillary blood samples.

Patients 5 and 6 were treated in local hospitals in Germany and the diagnosis of CHS was established by clinical measurements before the initiation of VNEP. This demonstrated their inability to maintain a $TcPCO_2 \leq 8$ kPa, and transcutaneous $SO_2 > 96\%$ (Nellcor N200), confirmed by arterial blood gas samples, when in quiet sleep. Physiological recordings had previously been performed by another laboratory. These had demonstrated hypoventilation during sleep and diminished response to hypercapnic challenges in both patients.

Patients underwent the following investigations which in all showed normal values: serum glucose, calcium, liver function tests, thyroid function tests, plasma and urinary amino acids, blood lactate, pyruvate and ammonia, electrocardiography, and chest radiography. Diagnostic imaging techniques (cranial ultrasound, computed tomography, and magnetic resonance imaging) were used in all to exclude underlying structural abnormalities.

METHODS

Negative extrathoracic pressure ventilation

The system for applying VNEP has been described in detail elsewhere.^{10 12} In brief, it consists of a Perspex chamber (Horner and Wells Ltd), which encloses the patient from below the neck (figure). The chamber is made virtually airtight by a latex neck seal (350 micrometer thickness) (Pentonville Rubber Products) which is placed over a polo necked stockinette vest (Eesiban, E Sallis). Silicone gel (Spenco UK Ltd) is used around the neck to protect the skin. Routine access for care occurs via two portholes on each side of the chamber. Each has an elasticated sleeve that forms a seal around the arms and enables the negative pressure to be maintained during care. Emergency access is gained by undoing two quick release catches at the side of the chamber thus allowing chamber lid to open. Negative pressure within the chamber is generated by an electric fan suction unit (DHB Tools) and monitored by a pressure monitor with an alarm system (March Designs). The chamber is rested on a standard bed base or supplied with a purpose built stand which is able to provide up to 20° head up tilt. The patient can rotate within the neck seal and adopt any posture that he/she finds most comfortable.

Patient 5 was initially weaned off IPPV to VNEP at an age of 38 days using a different system which encompasses the patient from below the axilla (Stephan Respirator CNPV). She was transferred to the system described above at an age of 78 days because patient access was thought to be better and because of sores she had developed underneath her axilla.

Initial management

Patients were initially placed into the chamber while receiving IPPV via a nasotracheal tube or tracheostomy cannula. Patient 7 was awake and spontaneously breathing when VNEP was started. In patients receiving IPPV, constant negative extrathoracic pressure (CNEP), of -6 cm H₂O was administered. The positive end expiratory pressure was simultaneously reduced to as near to zero as possible and the peak inspiratory pressure was reduced by 6 cm H₂O. Patients were subsequently extubated and intermittent negative pressure ventilation (INEP) was initiated with a rate of 20–22 breaths/minute, an inspiratory time of 1–1.5 seconds and an inspiratory peak pressure of -30 to -35 cm H₂O. CNEP of -6 cm H₂O was maintained throughout expiration to minimise the risk of airway closure or falls in lung volume. Peak pressure and rate were then adjusted to maintain SO_2 97–100% and $TcPCO_2$ 5–9 kPa. This required peak pressures between -25 and -40 cm H₂O, with the greatest negative pressures required in the oldest patient (patient 7).

Patient 3 receiving nasal mask CPAP to overcome upper airway obstruction while being ventilated with INEP during sleep. Although there is a large dead space the high flow of gas through the system (12 l/min), escaping through the mouth and around the mask during expiration, avoids rebreathing. $TcPCO_2$ was monitored continuously when CPAP was administered.

Table 2 Ventilatory outcome of patients

Patient No	Age at initiation of INEP	Age at home discharge	INEP required (cm H ₂ O)	IPPV for respiratory tract infections	Age at last follow up (years)	Present respiratory support
1	22 Days	66 Days	-20/-6	Six occasions, 4-14 days	5.2	INEP every second night
2	24 Days	9 Months	-30/-6	Two occasions, 14 and 16 days	4.7	INEP when asleep†
3	31 Days	17 Months	-35/-6	None	2.0	INEP and CPAP when asleep, additional inspired oxygen when awake
4	75 Days	7 Months	-30/-7	One occasion, 21 days	1.3	None
5	38 Days	7 Months	-30/-6	None	0.8	INEP when asleep
6	5 Months	7 Months	-35/-6	One occasion, 7 days	3.4	None
7	57 Months*	59 Months	-40/-8	None	8.6	INEP when asleep†
8	29 Months (failed)	20 Months		(Three hospital admissions for infections)	6.3	IPPV when asleep
9	52 Months (failed)	25 Months		(Two hospital admissions for infections)	7.1	IPPV when asleep

*Representation at this age. †Since transferred to nasal mask IPPV.

Nasal continuous positive airway pressure (CPAP) to overcome upper airway obstruction following extubation was administered via a nasal mask (figure) or nasopharyngeal airway to patients 2, 3, and 4. A pressure of +10 cm H₂O was used, generated by a standard time cycled pressure limited ventilator (SLE 250). The fractional inspiratory oxygen (FiO₂) was adjusted to the requirement of the patient, the gas mixture was humidified and heated to 35-37°C. Patients 1-6 needed additional inspired oxygen via nasal cannulas when asleep in INEP and when awake in order to maintain SaO₂ within the normal range of 97-100% (Nellcor N200).¹¹

Patients 8 and 9, at 29 and 52 months of age, were ventilated adequately using INEP with the tracheostomy tube in place and open. Temporary removal of the cannula and occlusion of the tracheostomy stoma led to severe airway obstruction. An attempt to overcome tracheal obstruction with nasal mask CPAP failed. Neither of these patients had become accustomed to the mask before. Patients were woken, the tracheal cannula was replaced, and IPPV given as before.

Long term management

After stabilisation with VNEP, arrangements were made for patients 1-7 to be discharged home on VNEP. Parents were encouraged as early as possible to participate in their child's care. A competency based individual parental education programme was written and co-ordinated by a clinical nurse specialist.¹² This programme included management of VNEP, monitoring, and interpretation of SaO₂, TcPCO₂, and transcutaneous oxygen tension (TcPO₂), administration of additional inspired oxygen via nasal cannulas, and bag and mask resuscitation techniques using infant manikins that demonstrate chest expansion (Laerdal). Parents and care givers were taught to recognise and manage complications, for example transient upper airway obstruction. Care givers also received advice on appropriate play and physiotherapy techniques to advance head control and developmental potential. The home environment required adapting before discharge to accommodate the equipment. If possible the infants had a staged discharge via

the local hospital in order to acquaint staff in all aspects of management.

In all patients, the TcPO₂ was monitored continuously when asleep in order to allow early detection of sudden unexpected hypoxaemic episodes.¹³ In infants <1 year of age, SaO₂ and TcPCO₂ were also monitored whenever asleep. In the older patients, SaO₂ and TcPCO₂ monitors were used only when the patient appeared to be unwell or were noted to have TcPO₂ levels below 6.7 kPa (50 mm Hg). They were always used when the patient was receiving nasal mask CPAP.

Developmental progress of patients was assessed regularly by the local paediatricians. In order to assess acceptance of treatment by the families parents of all patients treated at home in May 1993 were sent a questionnaire and asked to comment on questions relating to the following issues: (i) quality of training they received, (ii) the effort related to the treatment and additional support they had received, (iii) the development of their child, and (iv) the influence of the treatment on the child's and family's quality of life. As far as possible scales were used to provide an objective analysis of the answers.

Results

Results of treatment with VNEP are outlined in table 2. VNEP was successfully initiated in seven out of nine patients. In these it was attempted after a period on IPPV of 0-152 days, median 23 days. None of these patients had a tracheostomy at the time VNEP was started, although patient 7 had had a temporary tracheostomy for a four month period three years beforehand.

Additional inspired oxygen was initially required in all but patients 7 and 8 during sleep and wakefulness until ages 2-12 months, median 4 months, and during sleep thereafter in three patients until ages of 12, 12, and 18 months. Patient 3 is currently on continuous additional inspired oxygen. All patients required additional inspired oxygen during subsequent respiratory tract infections and this was given in sufficient amounts to produce normal SaO₂ levels.¹¹ Three patients required nasal CPAP for upper airway obstruction after extubation: patient 2 needed nasal mask CPAP

Table 3 Development of patients

Patient No	Method of home ventilation	Motor development	Learning ability	Emotional binding	Speech development	Parental view on developmental progress
1	VNEP	Severely delayed	Severely delayed	'Content child'	Severely delayed	Poor progress
2	VNEP	Normal	Poor concentration span	Good	Delayed	Normal progress, speech improved after grommet insertion (No questionnaire sent)
3	VNEP	Normal	Normal	Good	Normal	(No questionnaire sent)
4	VNEP (none now)	Normal	Normal	Good	Not relevant	(No questionnaire sent)
5	VNEP	Normal	Normal	Good	Not relevant	(No questionnaire sent)
6	VNEP (none now)	Unsteady when running	Normal	Good	Normal	Unsteadiness felt to be related to long stay in hospital
7	VNEP	Normal	Initially poor, now better concentration span	Good	Initially delayed, now normal	Delay related to tracheostomy, rapid progress since VNEP was started
8	IPPV	Normal	Poor concentration span	Shy	Delayed	Delay related to tracheostomy and long stay in hospital
9	IPPV	Normal	Normal	Normal	Delayed	Delay related to tracheostomy

intermittently for the first two weeks of treatment, patient 3 required CPAP via a nasopharyngeal airway and currently via nasal mask when asleep, and patient 8 received nasal mask CPAP for seven days.

Six patients are receiving VNEP at home and were discharged from hospital after periods of 46, 48, and 61 days, 6, 9, and 17 months during which their condition stabilised and parents and care givers could be trained in the necessary skills.

In three patients, hypoventilation improved with time: patient 6 was weaned off VNEP at 21 months. During self ventilation, TcPCO₂ readings were obtained for a period of six nights at intervals of 15 minutes. The TcPCO₂ monitor was validated with a capillary blood gas sample each evening. Mean readings per night were between 6.7 and 7.7 kPa, with minimum readings between 4.9 and 5.7 and maximum readings between 8 and 9.5 kPa. SaO₂ and TcPO₂ were normal throughout this period while he was receiving no respiratory support. It was decided to discontinue VNEP and continue the home monitoring with a TcPO₂ monitor, with the option of using a TcPCO₂ monitor and, if necessary, VNEP during respiratory tract infections. At 27 months, a sudden respiratory collapse occurred during a holiday in Spain. The patient was intubated and IPPV was given for seven days. He was again successfully weaned from IPPV to VNEP and is now breathing spontaneously when asleep. Since the age of 38 months patient 1 has required VNEP every second night only. Patient 4 was fully weaned off VNEP at age 5 months. Subsequent physiological recordings showed normal ventilation and oxygenation during sleep. She was discharged home without respiratory support and is closely monitored during sleep, using TcPO₂ and TcPCO₂ monitors.

In two other patients VNEP has failed. These had both undergone long term IPPV via tracheostomy for 29 and 52 months respec-

tively and were nursed at home with IPPV when asleep (home discharges after 20 and 25 months). Play therapy has begun to help these patients to accept a nasal mask and when they are able, attempts will be made to use nasal mask IPPV.

During the first year of life, all patients showed increased requirements for ventilation during respiratory tract infections. VNEP during both sleep and wakefulness became necessary in patient 6 for two periods at 8 and 12 months, and four patients required periods of nasotracheal intubation and IPPV for 4–21 (median 7) days.

Details of the patients' development are summarised in table 3. Speech development was delayed in both patients treated with IPPV, and in patient 2 (due to conductive hearing loss which improved after grommets were inserted). Patient 1 is severely handicapped. The cause of this remains unknown but may be related to the previous sibling's neurological disease. Currently, three children attend a day time nursery, two an infant school, and case 1 a special needs school. Two patients have epilepsy, including the child with severe developmental delay. In patient 2, no cause for his seizures has been found. Patient 9 experienced a convulsion after the administration of doxapram during the neonatal period.

Our questionnaire survey on the six patients treated at home in May 1993 with either VNEP or IPPV yielded additional information on the patients' and families' quality of life (table 4). Training before discharge was considered 'very good' or 'good' by all parents. There was no apparent difference between patients treated with VNEP or IPPV with regards to the amount of time each day parents were primarily involved in their care (4–24 hours, median 13), or with regard to additional nursing support. Support was considered good or very good in three cases, adequate in one, and insufficient in two.

Table 4 Parental views on the family's quality of life

Patient No	Methods of home ventilation	Amount of time parents are primarily involved in care (hours/day)	Initial domiciliary nursing support (hours/day)	Domiciliary nursing support now (hours/day)	Support judged by parents	Holidays (occasions, duration)
1	VNEP	24	None	None	Insufficient	1, 1 week
2	VNEP	4	10	10	Good	No
6	VNEP (none now)	7	12	None	Adequate	None while on VNEP
7	VNEP	10	2 (1 night/week)	7 (4 nights/week)	Very good	2, 2 weeks
8	IPPV	16	6	10	Very good	2, 2 weeks
9	IPPV	18	None	None	Insufficient	6, 6 weeks

Four families went on holidays with their ventilator dependent children. Whereas the two families with children treated with IPPV went on holidays on two and six occasions and reported no problems during the holiday, only patients 1 and 7 took part in a family holiday while being treated with VNEP on one and two occasions respectively. The parents of patient 7 reported difficulties organising transport of equipment and local care.

Parents of three patients treated with VNEP mentioned the ability to treat their children normally during the day time as the biggest advantage of this treatment in comparison to those receiving IPPV in whom a tracheostomy continues to require attention and prohibits activities such as swimming. Parents of patient 2 were worried about the lack of knowledge of local care givers about their child's treatment. Parents of both patients treated with IPPV said that they wanted attempts to wean their children from IPPV and tracheostomy to continue. They mentioned the easier mobility as an advantage of treatment with IPPV. The parents of patient 8 also mentioned the ability to give their child additional ventilatory support by bag ventilation as an advantage of tracheostomy. Both parents utilising IPPV and tracheostomy were worried about increased occurrence of chest infections and their severity.

Discussion

Our patients with CHS present with a varying degree of respiratory failure. By definition, however, they have all demonstrated hypoventilation when asleep. When awake, they show impaired responses to hypercapnia and to hypoxaemia.³ A degree of hypoventilation during wakefulness has recently been reported as a feature in most patients with CHS, especially during the first year of life.¹¹ In our patients, this was particularly noticeable during and after feeding. Hypoventilation also worsens during respiratory tract infections later in life and when children sit still and concentrate.⁴ Some patients with the most severe forms of CHS require continuous respiratory support. Treatment of CHS must therefore be adapted to the requirement of the individual patient in order to allow a good quality of life, the least level of dependence, and near normal development. It has recently been shown that this can be achieved with adequate respiratory support and that mortality can be low.^{1,4}

Most patients have been managed previously with IPPV via a tracheostomy during sleep. This offers reliable long term ventilatory support with immediate access to the airways for resuscitation and an ability to gradually increase ventilatory support during respiratory tract infections. This invasive technique is, however, associated with a number of problems. Frequency and severity of respiratory tract infections are increased and IPPV may lead to progressive lung damage.^{14,15} Pulmonary function tests have shown signs of airway obstruction and hyperinflation in some patients with CHS and tracheostomies.⁴ These

may be related to both chronic infections and to barotrauma. Speech development is almost always impaired. The overall risk of sudden unexpected death in patients with tracheostomies and without disturbances in the control of breathing is greatly increased, with rates between 0.8 and 2%.¹⁶⁻¹⁸

Diaphragmatic pacing has become an alternative treatment for respiratory failure in infants with CHS. In contrast to older patients or adults with hypoventilation, bilateral phrenic nerve pacing is usually required to achieve adequate ventilation.¹⁵ Upper airway obstruction during electrically stimulated inspiration usually necessitates a tracheostomy. In a recent report, the tracheostomy could only be closed in one out of six patients who receive diaphragmatic pacing.⁴ Weese-Mayer *et al* do not recommend its use before the age of 6 to 12 months when the severity of the CHS has become apparent and the infant's condition is stable.¹⁹ They recommend diaphragmatic pacing particularly for the most severely affected patients who require respiratory support during both wakefulness and sleep. Mobility of these patients can be greatly improved by diaphragmatic pacing during the daytime in combination with IPPV when asleep. It may also offer respiratory support to the older child or adult with CHS. Potentially, these patients may be treated with unilateral pacing at low frequency, a situation that may not require a tracheostomy.¹⁹

The experience with non-invasive forms of positive airway pressure ventilation in CHS is limited. Successful management with nasal mask ventilation was described in a 12 year old girl.²⁰

VNEP offers a non-invasive form of ventilation. Its previous application in CHS has been limited mainly because of upper airway obstruction. All nine patients in this study were able to maintain ventilation when awake after an initial period of stabilisation. We established VNEP in all seven patients who did not currently have a tracheostomy, and any upper airway obstruction was successfully managed with nasal CPAP in addition to VNEP. Hospitalisation was not prolonged in comparison to positive airway pressure ventilation¹⁹ and respiratory failure requiring renewed hospital admission and ventilation was infrequent. As with the patients described by Marcus *et al*,⁴ respiratory failure during respiratory tract infections was mainly confined to the first year of life in our patients. It was extremely interesting to note that the hypoventilation during sleep improved in three of our patients (1, 4, and 6). There was no doubt about diagnosis of CHS in these patients. Oren *et al* also reported a patient with CHS who was self ventilating at 2 years of age.¹ In our patients, avoidance of additional lung damage by IPPV and/or an alteration of respiratory control through the avoidance of tracheostomy may have contributed to the improvement of the hypoventilation, but these hypotheses require further study.

Monitoring of TcPO₂ during sleep to provide an early warning of baseline or sudden

hypoxaemia is an essential part of our management.¹³ Initially, monitoring of SaO_2 and TcPCO_2 in the home is also necessary in order to enable respiratory failure to be diagnosed immediately by the parents and the necessary measures initiated. Some groups advocate hyperventilation when asleep to compensate for hypoventilation when awake and to provide physiological leeway.^{4,19} With adequate oxygenation and monitoring we do not consider hyperventilation to be appropriate.

In conclusion, VNEP provides a non-invasive and safe respiratory support for infants and children with CHS. It is an alternative to IPPV or phrenic nerve pacing for patients who require ventilation when asleep. The results of our questionnaire study indicate that it was well accepted by patients and families. Development was not hindered by VNEP, on the contrary parents said that their children's development improved after the initiation of VNEP. The immobility of the equipment was regarded as a major problem. Further developments of negative pressure ventilators, especially cuirass ventilators, need to take this into account. Finally, the parents' responses indicate that regardless of the type of ventilatory support these patients and their families receive, care does not end with discharge from hospital and that support in the home environment was not always satisfactory.

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Since the manuscript was accepted patients 2 and 7 have been successfully transferred from INEP onto nasal mask IPPV for two and six months respectively.

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