Diaphragmatic Pacing in Infants: Techniques and Results
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ABSTRACT Phrenic nerve pacing was employed in 8 infants with central hypoventilation syndrome. Their ages ranged from 2.5 to 8.5 months. Preoperative diagnosis was established by demonstrating inadequate ventilatory response to hypercapnia and hypoxia. Percutaneous measurements of phrenic nerve conduction time and diaphragmatic action potentials were performed prior to operation to assess the feasibility of diaphragmatic pacing. A single anterolateral thoracotomy incision was used for both electrode placement in the chest and receiver implantation in the flank. The stimulating electrode was inserted around a segment of intrathoracic phrenic nerve isolated with pleura and perineural blood supply. Follow-up is available on all patients six months to 8 years postoperatively. There were no complications or deaths related to the procedure. In all patients, bilateral phrenic nerve stimulation allowed either marked decrease in or discontinuation of positive-pressure ventilation.

Phrenic nerve pacing can be performed safely in infants. It provides an effective alternative method for ventilatory support without the drawbacks of positive-pressure ventilation.

Electrical stimulation of the phrenic nerve for long-term pacing of the diaphragm has been successfully employed in the treatment of certain cases of chronic respiratory insufficiency in pediatric patients [1–3]. Its use for the ventilator-dependent infant has helped to overcome some of the drawbacks of positive-pressure ventilation, and has contributed to effective ambulation and rehabilitation. Despite encouraging clinical results, however, controversy still exists as to whether prolonged phrenic nerve stimulation is harmful to the phrenic nerve and diaphragm of these infants, and whether diaphragmatic pacing, begun early in life, leads to notably extended survival [4]. In this report we review our techniques and long-term results of diaphragmatic pacing in infants in an attempt to resolve some of the uncertainties concerning phrenic nerve pacing in this age group.

Material and Method
Eight infants treated for central hypoventilation with diaphragmatic pacing between January, 1977, and July, 1984, constitute the material for this report. They ranged in age from 2.5 months to 8.5 months. Presenting symptoms included apnea, cyanosis, or pallor during sleep. The cause of the central hypoventilation was congenital (Ondine's curse) in 7 patients and traumatic in 1.

Preoperative evaluation consisted of assessment of awake and sleep ventilation, as well as respiratory responses to hypercapnia and hypoxia. This was performed by continuous monitoring, during sleep, of the patient's electrocardiogram, heart rate, electroencephalogram, transcutaneous partial pressure of oxygen (PtpO2), transcutaneous partial pressure of carbon dioxide (PtpCO2) (Radiometer TMC-1), oxygen saturation (Biox 11A ear oximeter), and the depth and frequency of breathing (Fleisch pneumotachograph) (Fig 1). Evaluation of phrenic nerve and diaphragmatic function using percutaneous nerve stimulation was also performed prior to operation as a part of the workup. Diaphragmatic action potentials were recorded using surface electrodes, a preamplifier, and a standard storage oscilloscope [5]. Phrenic nerve conduction time was measured as the time from the onset of the stimulating pulse to the onset of the evoked diaphragmatic action potential. The amplitude of the action potential was measured as the maximal peak-to-peak voltage. Abnormalities in the conduction time imply damage to the phrenic nerve and therefore preclude successful diaphragmatic pacing [5]. Abnormalities in the action potential reflect dysfunction of the diaphragmatic muscle (Fig 2).

The Apparatus
The system for diaphragmatic pacing consists of several components (manufactured by Avery Laboratories, Farmingdale, NY) (Fig 3). The external transmitter supplies the stimulus information to the receiver through a radio frequency electromagnetic coupling by means of an external antenna. The receiver is a hermetically sealed integrated circuit implanted in a subcutaneous pocket. The electrical current produced by the receiver is carried by an electrode to the phrenic nerve. Early in our experience, a bipolar electrode was used. More recently, however, a unipolar electrode was found to produce less nerve damage in experimental animals, and therefore it has replaced the bipolar electrode [2]. An indifferent, or ground, electrode in the form of a disc implanted subcutaneously completes the circuit. Regulation of the tidal volume, respiratory rate, and the threshold can be per-
formed externally by modifying the stimulus delivered from the transmitter to the phrenic nerve.

Operative Technique
The patient is placed in the supine position. Bilateral symmetrical anterolateral inframammary incisions are made. The thoracic cavity is entered through the third intercostal space. The most proximal portion of the thoracic phrenic nerve is identified. Adjacent mediastinal pleura and soft tissue are isolated with a segment of the nerve (Fig 4A). The electrode is then passed around the nerve and secured in place (Fig 4B). A subcutaneous pocket is created and extended to the flank, using the same thoracotomy incision (Fig 4C). The receiver is connected to the electrodes and inserted into the pocket (Fig 4D). No chest tube is left in the pleural cavity at the end of the procedure.

Postoperative Adjustments
Phrenic nerve stimulation is started ten days to two weeks after operation. The threshold, the tidal volume, and the respiratory rate are adjusted separately to achieve optimal function. The threshold, which is reflected by the first stimulating pulse within an inspiration, is adjusted to stimulate just a few phrenic motor neurons and to produce minimally perceptible diaphragmatic contractions. The tidal volume, which is determined by the subsequent pulses within a breath, is adjusted so that the lowest current that produces near-normal diaphragmatic contractions is used (Fig 5). Evaluation of the diaphragmatic action potential produced by a pacemaker stimulus is particularly helpful in obtaining the proper tidal volume setting. The current is set so that the action potential amplitudes within a breath are increased gradually and the last amplitude is near maximal value [6, 7]. Finally, the adequacy of pacing is assessed by monitoring the end-tidal PCO₂ and transcutaneous PO₂, and the respiratory rate is varied to achieve the desired PCO₂.

Results
Preoperative evaluation revealed progressive hypercapnia and hypoxemia during sleep without arousal or increase in frequency of breathing or depth of tidal volume in all 8 infants. These abnormal responses were present only during sleep in 7 patients, and during both the sleep and awake states in the remaining 1. Phrenic nerve conduction and diaphragmatic action potentials were normal in all patients.

Postoperative follow-up is available on all patients six months to 8 years postoperatively (Table). Initially, all the patients with congenital central hypoventilation needed pacing during sleep only and had adequate

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**Fig 1.** Polygraphic tracing demonstrates breathing abnormalities during sleep in a patient with central hypoventilation. Note the marked hypoxemia and hypercapnia. Tidal volumes (V₁) of approximately 3 cc per kilogram of body weight are only slightly above anatomical dead space. The large breath at the end of the trace accompanied an arousal from sleep. (T, PO₂ = transcutaneous partial pressure of oxygen; PA CO₂ = end-tidal partial pressure of carbon dioxide; EEG = electroencephalogram; IN = inspiration.)

**Fig 2.** Oscilloscope pictures demonstrating (A) normal biphasic diaphragmatic action in response to percutaneous phrenic nerve stimulation and (B) absent diaphragmatic response to the nerve stimulation indicating phrenic nerve injury. (S = stimulus; AP = diaphragmatic action potential; ct = nerve conduction time.)
Several factors are responsible for the improved outcome of phrenic nerve pacing in this series; among these is detailed preoperative evaluation. Percutaneous measurements of phrenic nerve conduction time and diaphragmatic action potentials have helped greatly in selecting the appropriate candidates for pacing and avoiding the need for intraoperative testing and manipulation of the nerve.

Another factor that has contributed to our good long-term results with diaphragmatic pacing is modification of the operative technique. The changes in technique have reduced the surgical complications responsible for many of the acute and chronic failures in the past. The use of the intrathoracic phrenic nerve in infants avoids the proximity of the cervical portion to the tracheostomy site [11] and ensures stimulation of all branches of the nerve [3]. It also helps in proper fixation of the electrode in place and prevents its continued mobility, which may result in loss of contact with or long-term damage to the nerve. We have found that isolating a piece of mediastinal pleura and fat with the nerve is essential to preserve the perineural blood supply and to prevent ischemic damage to it [12]. The use of a single incision for both electrode and receiver implantation avoids erosion of the latter through the infant's thin skin, and decreases the incidence of infection [11].

Modification in the postoperative management of patients with the diaphragmatic pacers also has been a factor in improving long-term results. Limiting the nerve stimulation to 12 continuous hours at one time and a total of 16 to 18 hours per day has reduced markedly the incidence of phrenic nerve damage and neuromuscular function changes observed following prolonged stimulation [8, 13]. Moreover, monitoring the threshold and the amplitude of the electrical stimulus, using the diaphragmatic action potentials as a guide, helps in avoiding high-frequency impulses or excessive stimulation that have been shown experimentally to produce severe injury to the diaphragm [6, 7, 14].

In spite of the advances in phrenic nerve stimulation in infants, a few limitations still exist. Pacing-related upper airway obstruction is consistently observed and requires a tracheostomy. It is caused by failure to activate laryngeal and upper airway muscles in synchrony with diaphragmatic contraction [15–17]. Such activation is necessary to counteract the negative pharyngeal pressure generated during inspiration [18]. Synchronization of diaphragmatic stimulation with a nasopharyngeal muscle electromyogram has eliminated airway obstruction in experimental animals [19]. Future clinical application of this principle would result in more physiological pacing in infants.

In infants with adequate awake ventilation, bilateral pacing during spontaneous breathing during the awake state (Fig 6). In 1 patient, however, awake hypoventilation subsequently developed, and he now requires respiratory support at all times. Similarly, the patient with acquired central hypoventilation had inadequate awake ventilation. At present, these 2 patients are paced during the day and placed on the respirator at night, since continuous diaphragmatic pacing is harmful to the phrenic nerve if extended for more than 12 continuous hours or used for more than 16 to 18 hours in a 24-hour period.

There was one receiver failure 4.8 years after initial placement. It was manifested by pacing-related neck and chest pain during pacing. Malfunction of the phrenic nerve electrode occurred in another patient six months postoperatively and resulted in loss of pacing. Three deaths occurred following discharge from the hospital. One patient died of meningitis, 1 of aspiration, and 1 because of maternal neglect.

Comment
Concerns over the effectiveness and long-term results of phrenic nerve pacing have dampened enthusiasm for its use in infants who need ventilatory support. Complications such as pathological changes in the phrenic nerve or progressive diaphragmatic fatigue were cited as evidence against the therapeutic value of diaphragmatic pacing in children [8–10]. Our experience, however, does not substantiate these concerns. Diaphragmatic pacing resulted in discontinuation of the respirator, or a substantial decrease in its use, and contributed to effective ambulation and rehabilitation in all patients. Phrenic nerve conduction time and diaphragmatic action potentials revealed no evidence of nerve injury or muscle dysfunction following 8 years of pacing.
sleep would completely eliminate the need for positive-pressure ventilation. In contrast, patients with awake hypoventilation could use the diaphragmatic pacers during the day for 12 hours, but would have to use the respirator during the night. Recently, a specially designed electrode that stimulates different portions of the circumference of the nerve in a rotating fashion, so that only a few neurons are activated at a time, has been tested clinically with encouraging results [21]. Such a technique would allow continuous stimulation without damage to the nerve and could replace positive-pressure ventilation in infants with central hypoventilation.

Development of inadequate awake breathing has been observed in a considerable number of infants with congenital central hypoventilation syndrome, including 2 of 7 in this series. Awake breathing has been normal in early infancy in almost all instances, with loss of adequate awake ventilation generally becoming evident at 6 to 12 months of age. This awake loss has thus followed the institution of phrenic nerve pacing when pacemaker implantation occurred in early infancy and has preceded pacemaker implantation when pacing was not begun until at least late infancy. A theoretical pacemaker-

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Fig 4. Operative technique for insertion of diaphragmatic pacemaker in infants. (A) Anterolateral thoracotomy is made, and the phrenic nerve with a piece of surrounding pleura is isolated. (B) The electrode is passed around the nerve and secured in place. (C) A subcutaneous pocket is created and extended to the flank. (D) The receiver is inserted in place.
Fig 5. A train of pacemaker impulses that produces an inspiration. Note the relationship between the transmitter and receiver waveforms. The width of each transmitter pulse determines the amplitude of the pulse current delivered to the nerve. The radio frequency energy is increased progressively until the optimal amplitude (3.6 mA) is reached at the end of the inspiration. Arrows outline the pulse interval and the duration.

related explanation for loss of awake spontaneous ventilation is that the sustained diaphragmatic contractions and prolonged inspiratory time produced by the pacer stimulus might impair blood flow to the diaphragm, thereby resulting in fatigue and degeneration [22].

We do not think this is an adequate explanation for the clinical situation, however, for three major reasons. First, the primary relationship of the awake loss is to chronological age rather than age at onset of pacing. Second, pacing ventilation remains normal, as does phrenic nerve and diaphragmatic function. Finally,

Clinical Experience with Phrenic Nerve Pacing

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Age at Onset of Symptoms</th>
<th>Age at Pacing (yr)</th>
<th>Follow-up (yr)</th>
<th>Pacer-Related Problems</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>CONGENITAL CENTRAL HYPOVENTILATION</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 Neonatal</td>
<td>0.7</td>
<td>8.0</td>
<td>Receiver failure</td>
<td>Home; normal awake ventilation, alternate pacing asleep</td>
<td></td>
</tr>
<tr>
<td>2 Birth</td>
<td>0.4</td>
<td>1.8*</td>
<td>None</td>
<td>Home; normal awake ventilation, bilateral pacing asleep; fatal meningitis</td>
<td></td>
</tr>
<tr>
<td>3 Neonatal</td>
<td>0.2</td>
<td>0.7*</td>
<td>None</td>
<td>Home; normal awake ventilation, bilateral pacing asleep; fatal aspiration</td>
<td></td>
</tr>
<tr>
<td>4 Birth</td>
<td>0.5</td>
<td>2.5*</td>
<td>None</td>
<td>Home; normal awake ventilation, bilateral pacing asleep; died of maternal neglect</td>
<td></td>
</tr>
<tr>
<td>5 Birth</td>
<td>0.2</td>
<td>1.0</td>
<td>None</td>
<td>Home; abnormal awake ventilation: pacing awake, ventilator asleep</td>
<td></td>
</tr>
<tr>
<td>6 Neonatal</td>
<td>0.3</td>
<td>0.5</td>
<td>None</td>
<td>Home; normal awake ventilation, bilateral pacing asleep</td>
<td></td>
</tr>
<tr>
<td>7 Neonatal</td>
<td>0.3</td>
<td>1.5</td>
<td>Electrode failure</td>
<td>Home; marginal awake spontaneous breathing: pacing awake, ventilator asleep</td>
<td></td>
</tr>
<tr>
<td>ACQUIRED CENTRAL HYPOVENTILATION</td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>0.3 yr</td>
<td>0.7</td>
<td>3.5</td>
<td>None</td>
<td>Home; pacing awake, ventilator asleep</td>
</tr>
</tbody>
</table>

*Patient died late.
there is the invariable observation that voluntary ventilation remains intact even with the total loss of spontaneous (involuntary) awake ventilation. It seems more likely that development of awake hypoventilation is related to the natural progression of the disease in the respiratory centers [4] or could be secondary to ongoing parenchymal changes in the lung.

Our experience suggests that diaphragmatic pacing in infants is safe and lacks major side effects. In spite of a few limitations, it offers several advantages over positive-pressure ventilation, which make it the therapeutic method of choice in the management of central hypoventilation syndrome in this age group.

References


Discussion

DR. ROBERT M. SADE (Charleston, SC): I congratulate the authors for their work, which extends over the past 7 years and enables them to present this substantial series of infants with central hypoventilation managed with diaphragmatic pacing.

As was pointed out by the authors, there are two major controversies surrounding the use of phrenic nerve pacing in infants. First is the question of whether prolonged pacing is harmful to the phrenic nerve and diaphragm. The authors say that it is not, but their data are not entirely convincing. Were autopsies done on 2 of the children who died? If so, was there morphological evidence of damage to the phrenic nerves that might portend future difficulties for children having phrenic nerve pacing?

The second controversy is whether pacing truly extends survival in these patients. Although the authors say that it does, the answer is really not clear from their data. Two children died because of a medical condition, 1 of aspiration and 1 of meningitis. Could the aspiration have been related to the known asynchrony of laryngeal reflexes and phrenic nerve pacing? Was the meningitis caused by a respiratory infection associated with a tracheostomy?

Reported complications in children with chronic mechanical assisted ventilation include pulmonary hypertension with cor pulmonale, growth and developmental abnormalities, and respiratory infections leading to frequent hospitalizations. Did the 5 survivors in the current study have any of these problems? How did they handle the respiratory infections of childhood? How often were they hospitalized?
I have two additional questions. First, is there any hope for using phrenic nerve pacing in peripheral phrenic nerve injuries, which are much more common than central hypoventilation? Second, central hypoventilation is very uncommon. Should phrenic nerve pacing be attempted in centers that see such a patient only once in 2 or 3 years, which I suspect describes most of us, provided that a sophisticated pulmonary laboratory and experienced pediatric thoracic surgeons are available, or are the techniques so demanding that we all should send our patients to Chicago?

Despite this critique, I offer my sincere congratulations and admiration to the authors for refining the operative techniques and postoperative management needed to successfully treat these infants with an uncommon disease that would otherwise be lethal.

DR. ERNST WOLNER (Vienna, Austria): I also congratulate the authors on their fine results. My colleagues and I in Vienna are interested in phrenic nerve stimulation. In fact, we have used phrenic nerve stimulation for many years, especially in paralyzed patients with high spinal cord injuries. In addition, we have seen 4 paraplegic patients. We stimulated the femoral and ischiadic nerves in these patients, and they now can walk short distances.

In all these patients we found a particular problem—nerve fatigue. After a long period of stimulation, the well-known reaction of the phrenic nerve (at the level of the neuromuscular junction) to the electrical stimulus decreases, and the electrical current must be increased.

To overcome this problem, we developed a special stimulation mode. Using microsurgical techniques, we attach four small electrodes on each nerve with 8-0 Prolene sutures. The electrodes are within a 1-cm length. As a result, we can obtain a variation in intensity of the local electrical field by different polarizations of the electrodes. An automatic switching logic causes a rotating electrical field around the nerve cross section. This approach gives us the opportunity to stimulate patients for a longer period. One patient has received such a stimulus for more than 1 year.

Since we do not have experience with very small infants, I wonder if Dr. Ilbawi and his co-workers have observed similar problems in their patients. How long can 1 infant be continuously stimulated?

DR. ILBAWI: I thank the discussants for their remarks. I have a few answers for some of the questions they have raised.

In response to the question of whether phrenic nerve fatigue occurs after a prolonged period of phrenic nerve stimulation, our experience does not substantiate that at all, and I think the reason is the postoperative management guidelines I have already mentioned. The stimulation should be limited to 12 hours every day or 16 to 18 hours intermittently, and the setting of the stimulating current has to be very accurately assessed. Adherence to these principles would dramatically improve the results of phrenic nerve stimulation and avoid the problem with nerve fatigue.

As for the question of whether phrenic nerve injury has occurred in any of our patients, we have followed these patients with serial percutaneous phrenic nerve stimulation, and to date, no patient has manifested any changes that would suggest phrenic nerve damage or diaphragmatic muscle damage.

The development of cor pulmonale in patients with diaphragmatic pacing can be a serious complication. The basis for cor pulmonale in these patients is probably awake hypoventilation. If these patients are followed closely and their ventilation is assessed periodically, there should be no problem with cor pulmonale. Recurrent respiratory tract infections and frequent hospitalizations have not been a major problem in our patients.

Is there any future role for phrenic pacing in infants? I believe diaphragmatic pacing is becoming more and more important as a method of treatment. The indications for its use include not only congenital hypoventilation syndrome, but also acquired hypoventilation secondary to trauma or infection in or around the brain stem. Such improvements as rotating stimulation of the nerve and synchronization of the diaphragmatic contractions with the electromyogram of the upper airway muscles will markedly improve the outcome of diaphragmatic pacing in these young patients.