Fundamental Considerations in Pacing of the Diaphragm for Chronic Ventilatory Insufficiency: A Multi-Center Study

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GLENN W. ET AL.: Fundamental Considerations in Pacing of the Diaphragm for Chronic Ventilatory Insufficiency: A Multi-Center Study *Records were reviewed of 477 patients who had diaphragm pacemakers implanted for treatment of chronic hypoventilation. Three groups were established for comparison. (1) Center group: 165 patients operated on in six medical centers participating in a cooperative study; (2) Noncenter group, sufficient data available: 203 patients operated on by surgeons with experience limited to a few cases; (3) Nonstudy group, minimal data available: 109 palients operated on as in group 2; vital statistics only were contributed. The protocol for data gathering was comprised of 154 major variables. Basic data on age, sex, diagnosis and etiology were analyzed for homogenicity of data among the groups. A comprehensive analysis of the pacing methods, complication and results fom the Center group yielded information on the early experience with diaphragm pacing important to its future application. (PACE, Vol. 11, November Part II 1988)*

diaphragm, diaphragm pacing, electrical stimulation, hypoventilation, phrenic nerve, ventilatory insufficiency

Introduction

Six centers performing operations to implant diaphragm pacemakers to treat chronic ventilatory insufficiency agreed to pool their experience with the early application of this new therapeutic modality for purposes of this report. The Centers are Yale-New Haven Medical Center, Children's Memorial Hospital (Chicago), Toronto Western Hospital, Umea University Hospital, Mayo Clinic, and Childrens Hospital of Los Angeles. These are referred to, collectively, as Center.

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Data Base

The first of the patients reported received a pacemaker in 1966 and the last was included in the series in 1986. Virtually all patients who received diaphragm pacemakers in these centers were included at least up to about the middle of 1985. There are 165 patients in the Center group. From records maintained in the registry of patients who had diaphragm pacemakers implanted, 312 additional records were examined and some information on 203, referred to as the Noncenter, was incorporated, though minimally, in part of this report: verification of data was difficult, if not impossible. In general, the results of the analysis of the Noncenter patients correspond in principle to the findings in the Center cases.

Information regarding the remaining 109 non-study cases was too sparse for analysis.

Because of the complexity of this many faceted project of data accumulated over a period of years, no meaningful statistical analysis was feasible and would not have served a useful purpose. The basic data on patient population demonstrates reasonable homogenicity among the three groups (Table I).

Patients with ventilatory insufficiency fall into five basic diagnostic groups which here are arranged according to the number of patients in each group: cervical cord lesions, brain stem lesions, idiopathic central alveolar hypoventilation, congenital hypoventilation and hypoventilation secondary to peripheral lesions. The number of Center and Noncenter patients in each diagnostic group is similar, except then was a larger number of cases of congenital lesions from the Center group, which had cases from two children's hospitals, and a larger number of cervical cord lesions from the Noncenter group, predominently traumatic in origin, which are lesions preferentially referred to hospital qualified in the tertiary care of trauma rather than to centers with special care facilities for the treatment of chronic respiratory diseases.

The etiology of ventilatory insufficiency is divided into 17 categories. Trauma was the most common cause of cervical cord lesions. Vascular disease accounted for most of the identifiable brain stem and central lesions. Central alveolar hypoventilation of congenital origin without an identifiable lesion or unexplained hypoventilation of central origin accounted for most of the idiopathic cases. Unusual causes were postpoliomyelitis, syrinx, cervical cordotomy, atlanto-occipital deformity, Arnold-Chiari deformity and Shy-Drager's disease.

In the 165 Center patients, the mean time interval between onset of symptoms and implantation of the diaphragm pacemaker was 43.55 months. In the Noncenter group the interval was considerably shorter–14.00 months–and more so

Table I.

Chronic Ventilatory Insufficiency Treated by Diaphragm Pacing: Age, Sex, Diagnosis and Number of Years Paced Total Registry—475 patients

	Center	Non-Center	Non-Study
Number patients	165	203	109
Age (in years)			
Mean	32.66	35.92	39.23
Range	0–83.00	0–79.00	0.5–80.00
SD	24.74	23.06	
Sex (percent)			
Male	60 (36.36)	80 (39.41)	39 (36.79)
Female	105 (63.64)	123 (61.58)	67 (63.21)
Diagnosis			
Cervical cord	55 (33.33)	114 (56.16)	
Brain stem	50 (30.30)	54 (26.60)	
Idiopathic	31 (18.79)	17 (8.37)	
Congenital	27 (16.36)	8 (3.94)	
Peripheral lesions	2 (1.21)	10 (4.93)	
Patients	165	203	
Number of years paced			
Up to 5	108 (67.9)	155 (86.1)	
5 to 10	31 (19.5)	24 (13.3)	
10 to 15	16 (10.1)	1 (0.6)	
15 to 20	4 (2.5)		
Patients	159	180	

for brain stem lesions. This was probably because Noncenter physicians started using diaphragm pacing later than the Center group, after a surge of enthusiasm for the treatment, following reports of success from the Center, sparked earlier case referrals. Only in the congenital cases were the two groups' intervals alike. Earlier operation in the Noncenter cases may account for the apparently higher rate of complete return of normal ventilatory control where loss of control had been presumed to be permanent.

The analysis of data from this point on will refer only to Center group's patients. Occasionally, for convenience, percentages will be rounded.

Analysis of Center Patients

Pacing Methods

Viability of the phrenic nerves was assessed prior to pacemaker implantation in 92 percent of patients. A false negative response was elicited in only two patients, one in whom pacing was later successful and one to whom it gave minimal support. Transcutaneous phrenic nerve stimulation in the neck preoperatively thus proved to be a reliable predictor of phrenic nerve viability. Intraoperatively, three nerves were unresponsive to stimulation and remained so postoperatively. Two of these had responded to preoperative testing positively, one negatively, and one had not been tested. One additional nerve that responded positively beforeoperation could not be found (severe scoliosis) at operation. Postoperatively, early and late, 13 additional nerves failed to respond to stimulation.

There were 265 nerves at risk (NAR) of injury from operations to implant the receiver-electrode assemblies, 65 from unilateral procedures, 100 bilateral. Of the 100 bilateral implantations, 43 were done on the same day and 57 on separate days. The data covers a period when both types of electrode, bipolar and monopolar, and both sites of application to the nerve, neck and thorax, were being employed: 85 bipolar and 68 monopolar electrodes were implanted in the neck and 30 and 54 respectively in the thorax; 24 were mixed as regards type and site. The data on four nerves was unavailable.

Diaphragm pacing was not carried out in five patients in whom it was indicated and planned. Three were classified as never paced: In one patient the nerve could not be found at operation. Of two others, one died at operation before pacing had started and one recovered breathing spontaneously. Two other patients, one with a wound infection requiring removal of the components, and the other where the cause was unknown, were classified as failures.

Spontaneous complete recovery of respiration occurred in two patients who were operated on; a quadriplegic after unilateral implantation and a patient in whom nocturnal hypoventilation that was due to myasthenia gravis lessened upon specific treatment for the latter. Twenty-hour patients, 19 (78.15%) of whom had cervical cord or brain stem lesions, partially recovered respiration though all but three continued to require ventilatory support.

The most common pacing mode in this study was the unilateral. In all infants and young children and some adults, both hemidiaphragms were paced, simultaneously and part-time. Full-time simultaneous bilateral pacing was used in those quadriplegic in whom such application became possible after the diaphragm had been conditioned; previously, before diaphragm conditioning was practiced, full-time support usually was achieved by pacing the sides alternately for 8 to 12 hour periods.

Pacing was applied for support during sleep in 45.96% of the patients, all the time in 26.71%, and part of the time, night and/or day, in 14.90%. About 9.94% of patients were unable to be paced for significant periods, and 2.48% were paced on special occasions only.

A tracheostomy, which was necessary to maintain a patent airway for positive pressure ventilation if required and to prevent onset of upper airway obstruction during sleep, was performed in over 90% of Center patients. The stoma was retained in 119 patients (72.12%). It was allowed to close in 32 (19.39 %) but in 24 of these (75.00%) was reopened. No tracheostomy was done in 14 (8.48%). The necessity of reopening 11 of the 12 stomas in patients with brain stem lesions was related to the high incidence of aspiration in this condition, a major problem which sometimes required closure of the larynx.

Most patients, or about 64% of 157 on whom data was available, were living at home at the time they died or when this survey was made: of these who were still pacing, 82% required no or minimal supplemental support. About 23% were in a hospital, about 13% in a rehabilitation unit and less than 5% were in a nursing home. Concerning their activity level, before death or at the termination of this study, about 42% were working, were in school or were normally or moderately active; about 16% had retired and about 39% were inactive.

Complications

Complications of diaphragm pacing were related to the surgical procedure, the conduct of pacing and the pacemaker components. The patient's response to pacing was affected also by the status of the underlying disease (Table II).

Malfunction of the phrenic nerve that occurs incidental to the surgical procedure of implanting of the electrode–from manipulation, contact with the electrode, compression by the electrode cuff and scar tissue–is manifested by failure to pace.

Analysis was made of suspected or proved electrode-related phrenic nerve injuries to determine their association with the type of electrode implanted (monopolar or bipolar) and the site of implantation (neck or thorax), taking into account the postoperative complications of acute or chronic inflammation, pressure on the nerve from the neural cuff, and constriction by scar tissue. (Diaphragm fatigue secondary to the pacing schedule employed is not included in this category).

Where compromised function of the nerve is judged as possibly and probably electrode-related, the bipolar electrode, in either the neck or thorax, was associated with 15.65% of NAR (18/115) and the monopolar electrode with 6.56% (8/122). If only probable cause of malfunction is considered, the bipolar was associated in 7.83% of NAR (9/115) and the monopolar in 5.74% of NAR (7/122). The lowest risk of injury to the nerve existed with the monopolar application in the thorax, in which 3.70% of NAR (2/54) were compromised.

Infection, or dehiscence, a complication common to all surgical procedures, was detected in 11 wounds (4.50% of implantation procedures). It cleared spontaneously in some, but in seven cases necessitated removal of pacemaker components. When new components were implanted in a fresh site, pacing was reinstituted, though interim recuperation sometimes took many months.

Table II.

Complications Center Group—165 patients, 265 NAR

Complication		Cause		
		Surgically related	Patient's disease	Unknown
Failure to pace				
Intraoperative	4		2	2
Postoperative	13	7*	3	3
Infection				
Perioperative	9	9**		
Delayed	2			2
Pacing inadequate				
Constricting scar tissue	3	3		
		19***	5	7

* In 2 patients infection and failure to pace coexisted; cases classified as failure to pace.
** Pacemaker components removed in 7 for control of infection (2 in 1 patient).
*** Pacing was restored in 6 nerves by operative intervention.

Where pacing was unilateral a second unit was implanted on the contralateral nerve; where bilateral, other ventilatory support was substituted for as long as necessary. Infection was unrelated to electrode type; cervical implantation had a higher infection rate than thoracic (more cervical cases were done in this early experience). Where it could be controlled, infection did not prevent successful pacing.

The complications of diaphragm pacing are summarized in Table II. As mentioned above, there were 265 nerves at risk (NAR). In the category of sustaining probable surgically-related injury, there were 19 nerves (7.17%). Six of these had function restored to normal or near normal by surgical removal of the cause of injury, thus probable injury at termination of this study pertains to 13 (4.90%).

Diaphragm muscle fatigue is the principal manifestation of overstimulation. Muscle fatigue was probably the most common complication of the early application of diaphragm pacing, before the electrical parameters for stimulation and schedules for pacing had been declined. Without physiological or pathological evidence the exact incidence and extent of muscle fatigue could not be assessed by the analysis of the data presented.

In regards to the rf stimulator: all four major components were reported to have had failures, with, usually, a temporary loss of pacing. For certain components, such as the power source, failure was inevitable and prophylactic replacement was routine. The three most common component failures, other than battery exhaustion, were breakage of the wire from the 9-volt battery to the portable transmitter, breakage of the silastic-insulated antenna wire and loop, and failure of the epoxy-encapsulated receiver. Less common were malfunction of the transmitter and breakage of the electrode lead wire. Details of pacemaker performance from some of the Centers is available for review (Summary of Safety and Effectiveness Data for Avery Laboratories' Diaphragm Pacer, Docket No. 87M-0022, Food and Drug Administration Dockets Management Branch (HFA-305), Rockville, Maryland).

Autopsy data was available on 25 patients. The phrenic nerve was examined in 13, in seven of whom abnormalities were seen. Seven diaphragms were examined, five of which were abnormal. Because of the paucity of pathological studies on phrenic nerves and diaphragms of patients who died during or following pacing, an accurate assessment of the efects of long-term electrical stimulation on these structures is not possible.

Results

Classification

Criteria taken into consideration for classifying the results of pacing in each patient are as follows: Were ventilatory needs satisfied by pacing alone? Was additional respiratory support supplied? What was the maximum pacing period? How effective was diaphragm pacing? What is the assessment of overall results? Patients were placed according to these criteria in one of five categories:

1. Success. Ventilatory needs satisfied by diaphragm pacing only with no additional ventilatory support, except rarely for a brief period.

2a. Significant support: Ventilatory condition significantly improved with no additional ventilatory support. 2b. Significant support with addition of mechanical ventilatory support; active or inactive state.

3. Minimal support. Pacing used for special circumstances, not maintained for significant length of time.
4. Failure. Pacing not maintained for significant length of time, or ventilation not improved, or worsened with pacing.
5. Never paced. Unable to establish pacing schedule.

The number of patients in each category is given: success, 78 (47.27%); significant ventilatory support, 57 (35.54%); failure or minimal support, 26 (15.76%); never paced, three (1.82%); data missing, one (0.61%). How these results apply to the diagnostic categories is tabulated in Table III.

The number of patients classified as "success" or "failure" is lower and higher respectively than when these patients were classilied on the basis of the single question "overall result." Since the termination of the major portion of this study,

Table III.

Results of Diaphragm Pacing by Diagnosis Center Group—165 patients

Results	Diagnosis: Cervical cord	Brain stem	Idiopathic	Congenital	Peripheral	Results total
	number (percent)					
Success	24	29	15	10	0	78 (47.27)
Significant support	19	14	11	12	1	57 (34.54)
Failure or minimal support	10	7	4	4	1	26 (15.76)
Never paced	1	0	1	1	0	3 (1.82)
Lost to followup	1	0	0	0	0	1 (0.61)
Diagnosis total	55 (33.33)	50 (30.30)	31 (18.79)	27 (16.36)	2 (1.21)	165

about 3 years ago, the classification of the results of pacing has been downgraded in some of the patients and others have died. Many continue to benefit significantly from pacing. Several patients (it is not possible to determine how many, but it is estimated between 10 and 15) have discontinued pacing voluntarily, some because they did not believe it was of help. Others found the maintenance of the rf equipment too complicated; suicide was the motive in at least one patient.

With respect to unilateral and bilateral stimulators, pacing with unilateral units was successful or gave significant support in 50 cases (79.82%), with bilateral units implanted at the same operati on 33 (76.75%) and with bilateral units implanted at separate operations 52 (91.23%). Failure or minimal support was reported in 12 cases (18.46%), nine cases (20.93%) and five cases (8.77%) respectively. Thus, comparing bilateral implantation done on the same day versus on separate days, there are more successes and less failures with the latter. The reason for this difierence in results was not revealed from an analysis of several possible influential factors.

Duration of Survival

A graph of survival function for 161 patients (one missing data and three not paced) in the four

Table IV.

Results by "Indicated in Hindsight" Center Group—165 patients

Results	Indicated in hindsight: yes	no	questionable
		number (percent)	
Success or significant support	135 (81.81)	1 (0.61)	3 (1.81)
Failure or minimal support	10 (6.06)	14 (8.48)	2 (1.21)
Never paced	1 (0.61)	2 (1.21)	
Lost to followup	1 (0.61)		

major diagnostic categories showed maximum months paced to be 205.1 (17.08 years) up to the end of this study which for most cases concluded with the submission of data by the middle of 1985. (A few cases were added to mid 1986). The median survival time for this data is 106.4 months.

Up to the writing up of this study, in April 1988, the longest time any patient had paced, is 220 months (18.33 years). The patient in this case 62 years old, developed ventilatory insufficiency after a brain stem lesion at age 33. Nocturnal pacing of the left hemidiaphragm was started in November 1969 and continued until his sudden death in February 1988. The longest duration of full-time pacing is 187 months (15.58 years): a total quadriplegic, who continues on pacing, had bilateral diaphragm pacemakers implanted, the first in 1970 and the second in 1971, at age 19, three years afer a cord injury at Cl-C2 level; unilateral pacing was begun in 1970 while full-time bilateral pacing was delayed until 1972.

Sixty-eight of the Center group patients, including two who never paced, were dead at the time of this study, 97 were living and 1 never paced. In those who had died pacing was successful or provided significant supportd to 54 (79.41%), and gave minimal support or no benefit to 13 (19.12%). Primary causes of death were respiratory or cardiac failure and systemic infection (unrelated to the implantation). Seventy-five percent who died had brain stem or cervical cord lesions. Progression of disease related or unrelated to the cause of ventilatory insufficiency was the cause of death in 46 patients. Death probably was related to an inappropriate pacing schedule in 10 patients, possibly in 10 others. Eighteen of these patients were underpaccd, or overpaced, which caused fatigue of the diaphragm and hypoventilation.

Factors responsible for less than ideal results were poor selection of patients, complications of the treatment related either to the implantation or an inappropriate pacing schedule, inadequate follow-up, lack of patient or family support, progoression of or complications due to the underlying cause of hypoventilation, equipment problems, use of unilateral rather than bilateral pacing in cases needing additional pacing support, or no provision of supplementary mechanical ventilation where needed.

Observations in Hindsight

In hindsight, when was diaphragm pacing not indicated? The available data on each of the 165 patients in the Center group was reviewed and an "in hindsight" judgment was made of the indication for diaphragm pacing. In 17 (10.30%) pacing was believed not to have been indicated and in 14 of these (82.36%) pacing was classified as failure. From data available from the Center group, it appears that with the present knowledge of diaphragm pacing, at least 50 percent of the problems that were encountered in their initial limited experience with pacing could now be prevented.

Future Needs

If future results of diaphragm pacing are to be optimum, our recommendations are:

1. Designation of centers for evaluating and caring for patients needing and undergoing pacing;
2. A program to assure long-term follow-up of patients by physicians and paramedical personnel knowledgeable in pacing;
3. Facilities for regular monitoring of pacemaker performance and patient response to pacing;
4. Improved techniques of pacing the diaphragm, particularly the development of state of the art neural stimulators;
5. Strict adherence to previously published caveats;
6. Autopsy examination of all deceased patients who have had a diaphragm pacemaker implanted, with detailed study of the phrenic nerve and diaphragm muscle to determine the effects of electrical stimulation on these vital structures: Pathological studies will provide definitive factual information required to determine the future role of diaphragm pacing in the treatment of chronic ventilatory insufficiency and which will be applicable to other neuromuscular stimulation

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