Central Hypoventilation; Long-term Ventilatory Assistance by Radiofrequency Electrophrenic Respiration

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An early report of rhythmic electrical stimulation of phrenic nerves to effect respiration was by Waud in 1937, who used the technic in rabbits to avoid the effects of positive pressure insufflation on the pulmonary circulation. Sarnoff et al.24, 25, 26 between 1948 and 1950 experimented extensively with electrical stimulation of the phrenic nerve and demonstrated that submaximal electrical stimulation of only one phrenic nerve could effect normal oxygen and carbon dioxide exchange. They called this method of ventilation "electrophrenic respiration" (EPR). Clinical application of the method at that time was limited by the danger of infection around percutaneous nerve electrodes and because of the primitive state of induction technics for stimulating tissue through the intact skin. Perfection of the technic for electrical stimulation of excitable tissue by radiofrequency (RF) induction and its successful application to patients in 1959 encouraged us to apply RF stimulation to the phrenic nerve.27-29, 30 Our first clinical application of this technic to obtain ventilatory assistance was reported in 1964. It was short term application in the immediate postoperative period. Since then, EPR using radiofrequency induction has been further developed and applied for prolonged periods to four patients with hypoventilation of central origin.

Selection of Patients for EPR

For the initial clinical application of long-term electrophrenic respiration we sought patients who had unequivocal need for chronic ventilatory assistance, whose phrenic nerves and diaphragm responded normally to electrical stimulation, and whose lungs were normal. In only the first patient, Case 1, were these criteria not met completely. In this patient obstructive disease of the lungs, probably secondary to longstanding severe pulmonary hypertension and polycythemia, was demonstrated by pulmonary function tests. Ventilatory insufficiency, as evidenced by a diminished arterial P O2 and elevated arterial P CO2, particularly during sleep (Ondine's curse), and diminished responsiveness of the respiratory center to 5% carbon dioxide, was present in all four patients (Fig. 1). A number of other patients were evaluated as suitable candidates for EPR but rejected by not meeting the above mentioned criteria.

Operative Procedure

In these patients the phrenic nerve was isolated on one side only because we were uncertain how much damage to the nerves might result from long-term EPR and it had been demonstrated that normal ventilation could be duplicated through electrical stimulation of a single phrenic nerve by radiofrequency electrophrenic respiration. Further developed...
nerve. We selected the left phrenic nerve as we believed there would be less interference with pulmonary function if the left instead of the right became paralyzed.

All operations are performed under local infiltrative anesthesia (1% lidocaine without adrenalin). Preoperative sedation is omitted to avoid respiratory depression. Antibiotics (dicloxacillin or cephaloridine) are administered preoperatively and for about 3 weeks postoperatively.

Two separate incisions are required. A two-inch transverse incision is made one inch above the midportion of the left clavicle, and without removal of the pre-scalene fat pad the phrenic nerve is exposed lying over the scalenus anticus muscle. Very carefully the nerve is gently freed from the anterior surface of the muscle, with particular emphasis on preserving intact the 2 to 3 mm. of perineural tissue on either side of the nerve which invariably contains several small blood vessels. The nerve is then stimulated electrically to ascertain, by demonstration of vigorous contractions of the ipsilateral diaphragm, its suitability for EPR. With the present unit, because the electrodes and electrode cuff (Fig. 4B) are permanently attached to the receiver unit,
dissection of the nerve is discontinued at this point and the receiver pocket made.

To form this pocket, a two-inch transverse incision is made just above the costal margin in the midaxillary line, carried down to the deep fascia. Using sharp and blunt dissection with meticulous care to secure hemostasis, a 3-4-inch tunnel is made cephalad to about the level of the sixth rib, at which level the receiver capsule will be placed. A long tunnel is required to keep the incision from being over any part of the receiver. The midaxillary area has been found most satisfactory for the coupling of the antenna as the skin surface is relatively flat, hairless and motionless. After completion of the receiver pocket, a smaller tunnel is created from this pocket over the front of the chest and left clavicle to the neck incision. This tunnel can be made with a vein graft tunneler inserted into a section of tygon tubing. The tubing is left in place temporarily to aid insertion of the electrodes and electrode cuff.

The nerve and perineural tissues are carefully placed within the electrode cuff. The lips of the cuff are sutured together. The silastic horns of the cuff are fixed to the surrounding tissue with plastic suture material to prevent displacement of the cuff that may cause kinking of or injury to the nerve or its blood vessels.

The response of the phrenic nerve to stimulation is tested with the EPR transmitter and a sterile antenna prior to closure of the incisions. Chronic EPR (8 to 12 hours per night) is usually not begun until the incisions are well healed, about 10 to 14 days after operation.

Case Reports

Case 1 (88-41-18). A 38-year-old man was admitted to the medical service of Yale-New Haven Hospital on February 17, 1966, for in-
tense cyanosis, leukocytosis, polycythemia, pneumonia of the right lower lobe, cor pulmonale and a 2-year history of increasing lethargy. He was one of twins said to be normal at birth. At 2 weeks of age he was afflicted with a severe febrile illness, of unknown etiology, and afterwards failed to develop normally mentally and was, according to his mother, drowsy and lethargic. Because of mental retardation little attention was paid to his increasing cyanosis and limitation of

![Fig. 3A. Radiofrequency electrophrenic transmitter block diagram.](image-url)
activity. The admitting diagnosis was cyanotic heart disease, but this could not be confirmed by cardiac catheterization which revealed moderately severe pulmonary hypertension (60 mm. Hg). The pneumonia was treated successfully with endotracheal intubation and antibiotics and he was discharged from the hospital. He was re-admitted to the Research Unit in April because of continued lethargy and cyanosis. Phlebotomy of 1,100 cc. reduced the hematocrit level from 62% to 50% packed cells. During sleep arterial gas tensions deteriorated markedly but returned to near normal levels with voluntary hyperventilation on awakening. On May 7, 1966, an RF electrophrenic pacemaker was implanted, and after intermittent pacing of the diaphragm for 4 months to ascertain that the technic was effective as well as innocuous, electrophrenic respiration for 8 to 10 hours nightly was begun. Repeated nocturnal studies of arterial gas tension showed marked improvement in ventilation during EPR. He was re-admitted to the Research Unit on numerous occasions during the next 20 months. On each admission, twice a day blood gases, hematocrit and hemoglobin levels, also spontaneous and induced minute and tidal volumes with the patient supine, were measured; and every few months complete ventilatory function was studied. After 6 months of nocturnal EPR, differential bronchospirometry was performed which showed reversal of the normal relationship of ventilation of the two lungs during stimulation of the left diaphragm. His course during the first 10 months on EPR has been reported previously. Following that report he continued to do well, with excellent response of the left diaphragm to EPR; it descended 4–6 cm. during stimulation, although there was a modest rise in the threshold to stimulation (though the exact amount could not be determined with his receiver unit, without exposing the electrodes) and in the hematocrit level.

On July 1, 1968, he was admitted, through the emergency room, in shock with severe respiratory distress and cyanosis. Blood gas studies showed a pH of 7.2, Pco2 of 67 mm. Hg, and a Po2 of 59 mm. Hg. An EKG revealed evidence of acute myocardial infarction. The electrophrenic unit was found to function normally on admission. The patient's condition progressively deteriorated and he died on July 10, 1968.

At autopsy a large acute myocardial infarction of the anterior wall of the left ventricle and the interventricular septum was demonstrated.

The electrophrenic electrodes were properly positioned around the phrenic nerve but the thin platinum electrode plates in contact with the nerve were fractured in several places; stimulation of the nerve was through the fragment of plate still attached to the coiled platinum-iridium electrode wire. Microscopic sections of the phrenic nerve above, below and at the level of the silastic electrode cuff were made and appropriately stained. Above and below the cuff the nerve was

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**Fig. 3B.** Radiofrequency electrophrenic respiration unit with antenna attached.

**Fig. 4A.** Radiofrequency electrophrenic respiration block diagram.
has continued and capped because of somnolence and he has continued years bed rocking ure, and months later he was discharged salation syndrome.

By June, 1959, treme cyanosis was made. The patient had developed excessive somnolence with periods of apnea and extreme cyanosis during sleep. He was placed on a rocking bed (16 cpm) for sleeping, which he has continued to use for 10 years. During these years he has continued to be moderately handicapped because of somnolence and congestive heart failure. Polycythemia and severe headaches have been common and were partially relieved by phlebotomy. The early details of his case were reported in 1962.\textsuperscript{5} He is presently under the care of Drs. A. D. Renzetti, Jr. and R. E. Kanner.

Physical examination revealed a plethoric, lethargic, moderately obese male who would sleep when undisturbed. Ventilatory function tests were within normal limits except for an increase in residual volume. During sleep arterial gas tension deteriorated markedly, but was somewhat improved when he was on a rocking bed.

On March 11, 1969, an RF electrophrenic receiver unit was implanted on the left side. EPR was attempted at night during sleep but because of a temporary airway obstruction, apparently from collapse of the pharyngeal muscles, it was done only during waking hours for the first 6 months. This evidently was unsatisfactory, as he was constantly turning the EPR unit on and off to talk, smoke, eat, etc. Therefore another try at nocturnal stimulation was planned. At 6 months he was readmitted to the Research Unit for evaluation and found to pace entirely satisfactorily during night sleep with only occasional temporary

\textsuperscript{5} The examination of the histologic section of the phrenic nerve was done by Drs. G. Manuelides and B. Joynier.
obstruction. The diaphragm on EPR descended 6 to 8 cm.

A third admission was required on March 4, 1970, because of jerky movements of the diaphragm during EPR. There had been a rise in the threshold to stimulation. The receiver capsule was found to be defective and a new one was spliced to the nerve electrodes. At present the patient's unit is functioning well and he is being paced 8 to 10 hours nightly.

Case 3 (76-36-24). A 44-year-old man was admitted to Yale-New Haven Hospital October 20, 1969, for evaluation of hypoventilation syndrome of central origin. He was first seen at Emory University Hospital on October 27, 1958, stating that he was perfectly well until 2 weeks prior to admission when he was suddenly seized with a severe headache in the right retro-orbital region. He also became aware of a right-sided weakness. He was taken to a physician but by the time he arrived the pain and weakness had disappeared. During the next 2 weeks he had bouts of intermittent headache and dizziness, and the day before admission to the hospital he was again seized with a severe retro-orbital headache, vertigo and inability to swallow. There was weakness of the right side of the face and diminished sensation to pinprick over the entire left side of the body. Marked respiratory difficulty occurred characterized by prolonged periods of apnea and profound cyanosis. Tracheostomy was performed and respirations were assisted by positive pressure breathing that was abandoned for a tank respirator which was used for 5 to 6 days. He was weaned from this successfully during the day but at night when he fell asleep he would develop a Cheyne Stokes type of breathing with prolonged periods of apnea. In January, 1959, the patient was placed on a rocking bed during sleep where he has remained for the intervening 11 years. The tracheostomy stoma was plugged during the day but opened during sleep. Dysphagia was so severe that gastrostomy was necessary for feeding. This was closed in August, 1959, after surgical removal of a part of the cricopharyngeus muscle, which allowed him to swallow again.

It was the opinion of the neurological consultant, Dr. Herbert Karp, who saw him at that time, and has followed him since, that the lesion was located in the right brain stem at a midpontine level and was most likely vascular in origin. A muscle biopsy, which was repeated, showed arteritis. Over the years he has gradually become rehabilitated and now works productively at a desk job. Sleep is still not possible except on the rocking bed.

On admission to Yale-New Haven Hospital he was ambulatory and in no distress. The tracheostomy stoma was well epithelialized and plugged with a removable Teflon button. Neurological examination revealed absent pinprick and temperature sensation over the distribution of the right trigeminal nerve except for the cheek.

There was a mild residual hemiparesis on the left with diminished sensation to pinprick and temperature on the left. Slight ataxia on the left side was also noted. His inability to sleep except on a rocking bed (16 cpm.) was confirmed.

Laboratory studies showed a hematocrit of 41%. Mild pulmonary insufficiency was characterized by a decrease in FEV-1 and increase in RV. On October 11, 1969, the left phrenic nerve was exposed and stimulated electrically. There was vigorous contraction of the diaphragm. Therefore, an RF electrophrenic pacemaker was implanted. Overnight pacing was begun 7 days after implantation of the pacemaker. During EPR, there was found to be marked improvement of the blood gas tension. The left diaphragm descended 4.5 cm. on stimulation. At the present time, 6 months after operation, the patient is pacing regu-
larly for 8 to 10 hours each night and is sleeping on an ordinary bed.

Case 4 (76-97-46). A 47-year-old man was admitted to Yale-New Haven Hospital on January 2, 1970, for evaluation of primary hypoventilation syndrome. Three months prior to admission he had febrile upper respiratory tract infection complicated by a unilateral facial palsy, from which he made complete recovery. One month later he again developed an upper respiratory tract infection with a febrile course and progressively lapsed into coma with severe respiratory insufficiency. Tracheostomy was performed and ventilation was assisted mechanically. He was transferred to Dallas Methodist Hospital where he was under the care of Dr. William Miller. A diagnosis of encephalitis was made and supporting ventilatory and general treatment was given. His ventilatory drive was noted to be markedly decreased during sleep. In an attempt to maintain the drive, Dextroamphetamine and Emivan* were used in large doses, but as this treatment was ineffective he was transferred to Yale-New Haven Hospital for evaluation for ERP. Previously the patient had a subtotal gastrectomy because of an ulcer.

At the time of admission the patient was extremely lethargic, requiring constant external stimulation to keep him awake. He was unable to speak coherently and was not oriented as to time or place. His breathing was shallow and slow; while sleeping he showed constant generalized twitching.

From an arterial blood sample the pH was 7.26, P02 73% and P2 52%. Spinal fluid from lumbar puncture showed normal pressure, protein 80 mg./100 ml., glucose 96 mg./100 ml., and 24 lymphocytes per high powered field. A brain scan showed no defect and the EEG though grossly abnormal was not consistent with any localized lesion. After the patient was placed on a rocking bed at 16 cpm., his sensorium gradually improved, coincident with improved ventilation. On January 7, 1970, the left phrenic nerve was explored and stimulated electrically, and since the left diaphragm responded to this with vigorous contractions an RF EPR electrode receiver unit was implanted. The stimulant drugs were discontinued. Five days after admission RF EPR was begun. However, the nerve was found to be extremely sensitive and the rocking bed had again to be employed. Pacing was discontinued until the 10th postoperative day when it was begun again and used each night for 10 hours. The rocking bed was then discontinued and has not had to be used again. On fluoroscopy the left dia-

* Dextroamphetamine sulfate and ethamivan.

phragm descended 6 cm. during EPR. The patient's sensorium returned to normal, he became ambulatory and he was discharged in full command of his activities and no medication.

Materials

Electronic Apparatus

Transmitter (External Unit). The first patient (Case 1) was stimulated with an amplitude modulated radiofrequency (RF) transmitter tuned to 2 MHz. Square-wave pulses 200 μ seconds in duration were employed to simultaneously turn on and control the amplitude of the RF carrier voltage applied to the patient's antenna. The 200 μ second wide stimulating pulses occurred at a 60 Hz rate and lasted 2.0 seconds. The initial 0.5 second amplitude modulated the transmitter so that a treppe (staircase) pulse train resulted. The 2.0 second inspiration pulse groups were typically set at a 4.0 second spacing to provide 15 breaths per minute. This modulation technic is similar to that reported for the RF cardiac pacemaker.7,12

Our three most recent patients (Cases 2, 3 and 4) were provided with a pulse-width modulated (PWM) RF transmitter. A block diagram (Fig. 3A) illustrates the principles of operation of this unit. The top three blocks, the Respiration Rate Oscillator, the Inspiration Duration Timer, and the Inspiration-Onset Shaper, serve to generate the required voltage analogue of the desired diaphragm motion. The Respiration Rate Oscillator generates, at an adjustable rate, a series of 5 μ second pulses, usually at a rate of 15 per minute. These pulses are fed to the Inspiration Duration Timer which is adjusted to provide a 1.4 to 1.5 second inspiration duration time pulse. The inspiration-time pulses are shaped in the Inspiration-Onset Shaper so that a rounded-edge pulse results. This pulse shape approximates normal diaphragm motion recorded on the oscillograph.30 At this point the Inspiration Depth Control is interposed in the circuit.
The Stimulus Rate Oscillator generates a continuous train of 5 millisecond duration square waves at a 25-hertz frequency, during each inspiration period. The Ramp Generator transforms each of these square wave pulses into a ramp or saw-tooth shaped voltage. The Pulse Width Modulator receives the conditioned inspiration pulse via the depth control and the train of ramp pulses spaced at 40 milliseconds. Electronic circuitry in the Pulse Width Modulator effectively combines the two inputs in order to create a new digital coded pulse train. This resulting pulse train appears as a square wave train at the same frequency (25 hertz) as the Stimulus Rate Oscillator. Each individual pulse is width coded to reflect the amplitude of the desired inspiration analogue. This pulse train will be decoded by the surgically implanted internal (receiver) unit.

The last three blocks of the transmitter, the Keyer, the Radiofrequency Oscillator and the output Power Amplifier, are the same as those in the RF cardiac pace-maker except that the output level control has been eliminated. The antenna is driven with a series of constant amplitude 2 megahertz RF bursts, of modulated width. Each burst provides instructions for one stimulating pulse to the phrenic nerve bundle, when decoded by the receiver. RF pulse amplitude must only be sufficient to drive the internal implant above a minimum threshold. The physical and electrical characteristics of the pulse-width modulated transmitter are as follows:

Type: Pulse-width modulated
Pulse characteristic: 25-hertz pulse train lasting 1.4 to 1.5 seconds (inspiration); repeating every 4.0 seconds (respiration); pulses 0.4 msecs. to 2.5 msecs. duration.
Pulse amplitude: 6 to 8 volts dc *
Size: Width 7.4 cm., length 14 cm., depth 2.6 cm.

Receiver (Internal Unit). In our first patient (Case 1) the receiver consisted of a parallel resonant circuit, an impedance matching winding and a resistor-capacitor network to provide a biphasic output network. The assembled receiver was encapsulated in epoxy resin and coated with medical grade silastic. Patients 2, 3 and 4 were supplied with controllable constant current receivers.

A block diagram (Fig. 4A) illustrates the principles of operation of the receiver. Power for the unit is derived from the externally supplied pulsed RF field through the antenna applied to the skin and transmitted to the inductance L1. This 2 MHz pulse burst is full-wave rectified in the Rectifier to form a rectangular pulse. An Energy Storage and Regulator maintains an output of 10 volts dc, even without external excitation, for brief periods. During the time that the external transmitter is ON, the Ramp Generator integrates the applied rectangular pulses to form a linear ramp-shaped voltage, \( e_1, e_2, e_3 \), etc., as illustrated. The Switch and Amplifier module completes a circuit to the Constant Current Generator stage. This stage transforms each ramp voltage to a predetermined stimulating current. Since the voltage to current transformation is linear (Fig. 5), and the voltage is a function of applied pulse-width, the amount of current to the tissue can be accurately programmed. For instance, a change of 200 \( \mu \) amperes in the stimulating current was typically obtained.

Weight: 295 Gm.
Frequency: 2.0 MHz (\(-0.1\) MHz + 2 MHz)
Power: 1 NEDA 1604 (Burgess 2U6) 9 volt battery
Battery Life: 40 to 60 hours
Components: transistors 19
diodes 6
resistors 44
capacitors 20
inductances 3

* Refer to Yale standard cardiac receiver.
with a change in pulse width of 100 microseconds. The circuitry of the Constant Current Generator will supply a constant current for any tissue resistance within the compliance of the power supply and Ohm's law, i.e., for a 2 milliampere nerve current:

\[ i = \frac{e}{r} = 2 \times 10^{-4} = \frac{10}{r} \]

\[ r = 5 \times 10^3 = 5000 \Omega \]

This value exceeds what we have observed as typical peripheral nerve load resistance values (500 to 1,000 Ω). Inductance L2 drives an electronic circuit which senses the end of the input pulse burst. The output from this stage excites the 150 μ sec. Pulse Generator almost instantaneously. During the time the 150 μ sec. Pulse Generator output is ON (0 VDC), the Switch closes and the tissue receives a stimulating current. The trailing edge of the 150 μ sec. pulse is also employed to discharge the Ramp Generator output to the low state.

The components are assembled on a two-sided printed circuit board 41 mm. in diameter. All components are protected by a covering of silastic rubber (Dow 3145) before encapsulation in the epoxy resin system. The physical and electronic characteristics of this receiver are as follows:

Circuit: Pulse width to amplitude converter which receives energy from the "instruction" pulse. Output current is constant for varying tissue load resistance.

Size: 50 mm. width; 14 mm. depth

Weight: 37 Gm.

Frequency: 2 MHz (±.1 MHz)

Power: Inductively coupled from transmitter during instruction pulse

Sterilization: Ethylene oxide gas 145° F. maximum

Pulse duration: 150 μ seconds (fixed)

Pulse current: 100 μ amps to 10,000 μ amps (adjustable)

Pulse shape: Biphasic

Components: transistors 13
diodes 16
resistors 23

Nerve Electrode. All four patients were supplied with longitudinal bipolar platinum strap assemblies enclosed in a silastic rubber (Dow 372) cuff. In Case 1 the electrode assembly which was used was that previously described \(^\text{15}\) with two 17-inch lengths of coiled platinum-iridium (90%–10%) helical electrode lead wires. Pure platinum (99.93%) straps, 2.5 mm. wide, .002 inch thickness, were electrically welded to the electrodes. The straps were placed both on the same side as illustrated (9 mm. between centers). The inside diameter of the cuff was 5 mm.

Four modifications were made to the nerve electrode assembly used in Cases 2, 3 and 4. First, the straps were repositioned within the cuff so that the current pathway between electrodes would be on a diagonal line through the nerve. Second, the stimulating straps were increased in thickness to .004 ± .001 inches. Third, the electrode lead wires were changed to lightweight multifilament (365 × 8 microns) stainless steel material. In Cases 2 and 4, a 5 mm. internal diameter cuff was used but in Case 3, a 4 mm. one. Fourth, the silastic cuff mold was modified to provide a small pair of inline flaps or fins (Fig. 6) for handling purposes. The platinum area in contact with tissue is 17.5 mm². The maximum electrode current density we have employed to date was used in Case 2. The values for this electrode were determined as follows:

\[ i = \frac{I_m}{A} = \frac{1.7 \times 10^{-3}}{17.5 \text{ mm}^2} = 9.7 \text{ mA/cm}^2 \]
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where, \( i = \) electrode current density
\[ I_m = \text{current stimulus (for Case 2)} \]
\[ A = \text{electrode area} \]

In the last three patients care was taken that the caudal electrode was the cathode.
Postoperative non-destructive evaluation of the implanted receiver was accomplished by placing on the skin a pair of silver-silver chloride ECG electrodes (Electrodyne Dispos-E1) immediately caudal and cephalad to the implanted nerve electrode assembly in the neck. A high gain oscilloscope (Tektronix 502), equipped with shielded leads, is used to detect function of the implanted receiver during EPR (Fig. 7).*

Methods

Fluoroscopy, cinefluoroscopy, and double exposure films were used to investigate motion of the diaphragm off and on EPR. Diaphragm motion prior to beginning EPR was evaluated during voluntary hyperventilation and during electrical stimulation of the phrenic nerve. Stimulation by transcutaneous conduction of electrical impulses was attempted using the thimble technic of Sarnoff or by transvenous conduction using an electrode catheter. Direct stimulation of the exposed nerve was done at operation.

To demonstrate the effect of EPR on pulmonary function and pulmonary circulation the following studies were carried out, on and off EPR:

1. Tidal volume and instantaneous flow rate
2. Regional gas distribution
3. Ventilation during sleep
4. Diaphragm motion
5. Diaphragm fatigue
6. Blood pressure

Results

1. Tidal volume and instantaneous flow during submaximal EPR demonstrated ventilation in excess of resting normal (awake) state (Fig. 8). Almost immediately after EPR was begun, the natural respiratory rhythm was superseded by EPR rhythm. The flow and volume tracings during EPR were similar in contour to those of spontaneous respiration and did not show a biphasic response, suggesting that stimulation of the left diaphragm by EPR is associated with reasonable preservation of the normally well-integrated operation of all respiratory muscles.

2. Regional gas distribution was measured by the use of xenon 133.† Xenon 133 gas was administered by inhalation in Case 2 until the gas distribution in the lungs reached a steady state.* The washout pattern on EPR (15/min.) was studied. When compared with normal values, the washout was faster in all parts of the lung except the right lower lobe (Fig. 9). Xenon 133 gas was dissolved in saline and administered by vein in patients 2 and 3.** Again the washout of gas from the left lung during EPR was more rapid than from the right side.

3. Ventilation during sleep off and on EPR demonstrated in patients 1, 2 and 4 a marked rise in \( P_{\text{aw}} \), during sleep that was promptly reversed by EPR (Figs. 10, 11). We were never able to obtain a sleeping sample in patient 3, nor were others who had studied this patient, as he invariably developed apnea and awoke when respiratory assistance was discontinued. The values given for him are after 3 hours of "resting" at night followed by 3 hours asleep on EPR.

Alveolar ventilation \( (V_A) \) was measured in patients 2 and 3 with the patients awake

* The EPR unit was assembled by Avery Laboratories.

† Study performed by Drs. R. E. Kanner and A. D. Renzetti, Jr.

** Study performed by Dr. Gerald S. Freedman.
and in patient 4 during sleep. Increased ventilation during EPR was demonstrated in each instance.

The effects of EPR on gas exchange have been generally indicated by the reversal of hypercapnia and hypoxemia. Since EPR is necessarily primarily unilateral stimulation, the possibility exists that such unilaterality may cause ventilatory maldistribution, and the xenon studies do indicate increased ventilation to the left lung. However, evidence indicating this problem to be a quantitatively minor one has been obtained by measurements of respiratory gas exchange.

In patient 4, during sleep, EPR caused a twofold increase in both total and alveolar ventilation and a partial reversal in both hypoxemia and hypercapnia (Table 1). More specifically, EPR, at the most, causes small changes in wasted ventilation as measured by \( V_D/V_T \) ratio. This is confirmed by the demonstration that \( A-a_O_2 \) gradients are likewise little affected by EPR. Thus the effect of EPR, at least in this sleeping subject, was to increase \( V_A \) with but only minor changes in relative distribution of ventilation to perfusion.

4. The diaphragm on both sides in all four patients preoperatively showed limited excursion during resting (normal) breathing but wide excursions during forced hyperventilation. Trans-caval stimulation of the right phrenic nerve was carried out in two of the patients using a cardiac pacemaker.4,9 A hiccup-like contraction of the right diaphragm was seen when the nerve was stimulated but a consistent response to stimulation was not possible due to motion of the catheter tip in the vein. Also, we experienced great difficulty in locating and stimulating the phrenic nerve in the neck using a transcutaneous electrode. Direct stimulation of the nerve at operation resulted in forceful contraction of the ipsilateral diaphragm in all four patients.

Postoperatively, diaphragm motion was observed by fluoroscope off and on EPR. The minimum current (threshold) required to cause movement of the diaphragm was accurately determined except in patient 1 in whom the amount of current flowing to the tissue could not be measured without exposure of the electrode wires. These studies were repeated frequently and a
rise in the threshold to stimulation was observed in patients 2 and 4. Patient 3 has maintained a very low threshold without a measurable rise for the 6 months he has been observed (Table 2). Usually nocturnal pacing was not begun for 10 to 14 days postoperatively but in patient 4 it was started on the day of operation. The nerve was found to be exceedingly sensitive to stimulation: for forceful contractions of the diaphragm less than 100 microamperes of current was required. Stimulation was discontinued and after a few days the threshold to stimulation rose to approximately 700 microamperes where it remained until the patient’s discharge.

During EPR the contralateral diaphragm showed paradoxical motion in all patients. In patient 2, after 1 year of EPR, there was slight positive contraction of the medial side of the contralateral diaphragm just at the end of the stimulating interval.

5. To elicit the time of onset of fatigue of the diaphragm due to EPR, continuous EPR was carried out for 20 to 25 hours in patients 1, 2 and 3. In patient 1, motion of the diaphragm was watched under the fluoroscope. After 8 hours of stimulation there was a definite decrease in motion which was progressive to 20 hours, when EPR was stopped. Approximately 24 hours without EPR was required for full recovery of diaphragm motion. In patients 2 and 3, in whom the units were designed to provide a wave form that caused less fatigue of the nerve in the experimental animal, EPR was continued for 18 hours with no sign of fatigue and 24 hours with only a moderate decrease in function. Fatigue in these patients was determined with double exposure films made during EPR* (Fig. 12).

* The first exposure of the film was at maximum inspiration and the second at maximum expiration. These exposures were made by using a timing device coordinating the transmitter signal with the film exposure switch.

| TABLE 1. (Case 4) Alveolar Ventilation during Sleep on and off EPR |
|---------------|--------|--------|
|               | Off EPR | On EPR |
| \( V \)       | l/min.  | 3.03   | 6.34   |
| \( V_{A} \)   | l/min.  | 1.47   | 3.40   |
| \( V_{D} \)   | l       | 0.14   | 0.21   |
| \( V_{T} \)   | l       | 0.20   | 0.45   |
| \( V_{D}/V_{T} \) |       | 51     | 46     |
| \( V_{CO_2} \) | ml./min.| 0.19   | 0.22   |
| \( V_{O_2} \) | ml./min.| 0.26   | 0.27   |
| \( R \)       |         | 0.74   | 0.80   |
| \( P_{A_{CO_2}} \) | mm. Hg | 69     | 82     |
| \( P_{A_{O_2}} \) | mm. Hg | 51     | 59     |
| \( A_{-a_{CO_2}} \) | mm. Hg | 18     | 23     |
| \( P_{a_{CO_2}} \) | mm. Hg | 64     | 55     |

\( \dot{V} \) = total ventilation  
\( V_{A} \) = alveolar ventilation  
\( V_{D} \) = dead space, \( V_{T} \) = tidal volume  
\( V_{CO_2} \) & \( V_{O_2} \) = CO₂ production and O₂ consumption  
\( R \) = respiratory exchange ratio
TABLE 2. Phrenic Nerve: Electrical Threshold to Stimulation

<table>
<thead>
<tr>
<th>Case</th>
<th>Operation</th>
<th>1 Month</th>
<th>6 Months</th>
<th>1 Year</th>
<th>Current (μA)</th>
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<td></td>
<td>&lt;500</td>
<td>720</td>
<td>1,050</td>
<td>1,300</td>
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6. Direct arterial blood pressure measured in patients 2, 3 and 4 demonstrated a fall in systolic pressure within 30 seconds of onset of EPR (Fig. 13). The systolic pressure decreased 15 to 20% within 10 minutes and remained at the new level until EPR was discontinued. Diastolic pressure decreased less than systolic (Table 3). The most striking effect was observed in the patient who was mildly hypertensive (Case 4). Similar changes, unaffected by the inhalation of oxygen, occurred in pulmonary artery pressure during EPR; here the most marked change was in the patient whose pulmonary artery pressure was elevated (Case 2) (Fig. 14).

Discussion

Studies on animals and on man have shown that electrical stimulation of the phrenic nerve in a manner mimicking normal diaphragm movement effects an exchange in respiratory gases adequate to maintain arterial oxygen and carbon dioxide tensions at or near normal levels. EPR, despite its obvious value for ventilatory assistance in cases with normal phrenic nerves, diaphragm and lungs is not a method without danger because of possible

![Fig. 12. Fatigue on EPR. Double exposure films of left diaphragm at maximum inspiration and maximum expiration during 25 hours of continuous EPR. There is no evidence of fatigue for 18 hours, but the contraction of the left diaphragm has decreased 30% at the end of 25 hours (Case 2).](image-url)
injury to the phrenic nerve, and consequent paralysis of the diaphragm. In patients with abnormal ventilation such impairment could be disastrous. Further, it should be obvious that if nerves, diaphragm or lungs are not normal, EPR probably will not improve ventilation. Thus, until it is proved that the method will not cause injury to the phrenic nerve, EPR should be applied only in instances of hypoventilation, where sufficient respiratory reserve will prevent serious crippling in the event of nerve injury. Patients in this category are those with hypoventilation of central origin, such as the four cases reported herein, and patients with high cervical cord lesions where the phrenic nerve cell bodies are unaffected.

Patients with obesity and hypoventilation (Pickwickian syndrome) could benefit from EPR but because a simple reduction in body weight improves most of these individuals it should be tried first. In bulbar poliomyelitis, where there is asynchronous firing of the respiratory center, EPR should be beneficial by suppressing the respiratory center and setting up a stable respiratory rate. As many polio patients tend to correct themselves and as the disease is now uncommon, EPR will have little application here. It is, of course, of no value where the cell bodies of the phrenic nerve are destroyed. Lesions affecting conduction in peripheral nerves, myotonia and other primary muscle disorders involving the diaphragm and obstructive lung disease may all cause hypoventilation, but the patients would benefit little from electrical stimulation. Application of EPR in these instances should be made only if, after careful evaluation, sufficient improvement in pulmonary function is expected, which would outweigh the risk of damage to the phrenic nerve.

We tried transcaval stimulation of the right phrenic nerve to assess its viability but found this unsatisfactory as we could never be certain that the exploring electrode was in the optimal position in patients with little or no diaphragm reactivity. In the transcutaneous method of Sarnoff the same objection was found. The best way to assess nerve viability is to expose the nerve and stimulate it directly. One must, of course, be prepared to implant a permanent electrode at the same time.

Short-term EPR has been recommended for patients undergoing thoracotomy to avoid the respiratory tract complications and the interference with pulmonary blood flow caused by positive pressure breathing. Although our first clinical application of EPR in 1964 was to patients with thoracotomy, we do not now recommend such use in the early postoperative period. First, because ventilatory insufficiency is often the result of intrapulmonary airway ob-

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<th>Arterial Blood Pressure During EPR</th>
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<td>2</td>
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Fig. 13. Arterial blood pressure and blood gases during EPR (Case 4).
struction; secondly, unless phrenic stimulation is done bilaterally the uneven distribution of air, shown by xenon gas studies to result from unilateral stimulation, would favor some areas of the lungs but would aggravate the debility of others; thirdly, because injury of a phrenic nerve from application of EPR would cause paralysis of the diaphragm which in the critically ill postoperative chest patient would be dangerous. In cases of poisoning with short-term reversible respiratory depression the difficulty of applying transvenous or transcutaneous EPR precludes their selection over conventional methods.

More sophisticated design is responsible for the efficiency and safety of our present EPR unit. Accurate control of the amount and constancy of current flow to the nerve to avoid overstimulation is achievable in the present EPR unit due to replacement in the circuit of pulse-amplitude modulation. In earlier models, this is achieved by pulse-width modulation which permits wide displacement of the antenna and receiver without an appreciable change in current flow to the nerve, and by the constant current feature which permits changes in tissue resistance without current changes. In the present unit the current remains steady until the antenna is moved at least two inches off the center of the receiver, when it abruptly falls to zero. The large diameter antenna, recently adapted, also favors more consistent stimulation.

The most critical feature of the operative procedure is isolation of the phrenic nerve and fixation of the cuff electrode around it. Particular emphasis is placed on preservation of the perineural blood vessels. Our one autopsy specimen, 22 months after implantation of the nerve electrode, showed a number of small patent vessels accompanying the nerve through the cuff. These vessels must be preserved since the nerve is otherwise isolated from tissue providing a blood supply as it passes through the cuff for a distance of 12 mm. Further, to avoid injury to the nerve itself or the small vessels supplying it, the dissection must be done meticulously. The phrenic nerve fascicles, in the cat at least, are not abundantly supplied with blood vessels and preservation of these latter may be critical to the vitality of the nerve. The cuff must be firmly fixed to the adjacent tissues to prevent displacement and kinking of the nerve. Leakage of current to the brachial plexus has fortunately not been a problem except where high currents were used momentarily to test the circuit in the early postoperative period. In the design of the cuff electrode we provided an ample internal diameter in which nerve and perineural vessels could swell in the early postoperative period without compressing the nerve; also, in which the fibrous tissue sheath could develop, invariably the reaction of tissue in contact with silastic rubber. A 4 or 5 mm. internal diameter cuff is satisfactory. To assure the passage of current across the entire nerve bundle, the platinum electrode strips were set at 180 degrees to each other (Fig. 6). Care must be taken in placing the nerve in the cuff not to impale tissue on the leading edge of an electrode.

Direct injury to the nerve at the site of electrode attachment has been a concern of investigators for many years. Until induction techniques were perfected

Fig. 14. Pulmonary artery blood pressure during EPR (Case 2).
one of the principal causes of nerve injury was infection of the nerve from percutaneous wires. In recent years with the widespread application of the cardiac pacemaker electrochemical changes occurring at the tissue-metal interface have received a great deal of attention. Metal-free electrodes have been developed by several investigators but it is not certain they will have application to nerve stimulation.

In patients with hypoventilation of central origin nocturnal stimulation is preferred. At night hypoventilation is most severe, and if EPR is carried out during the day when the subject is awake, it must be temporarily discontinued for eating or drinking to avoid possible aspiration during inspiration. The only justification for the use of bilateral phrenic nerve stimulation is an irreversible lesion of the upper cervical cord or respiratory center with viable phrenic nerves in a patient wholly dependent on a mechanical respirator.

Treatment by continuous EPR using stimulation of a single phrenic nerve is not possible at the present time due to the development of fatigue. The site of fatigue is the neuromuscular junction and its onset is influenced by the type and form of the electrical stimulus. Stimulation before fatigue has been as long as 18 hours when the pulses had wide intervals, and anodal block at the site of the electrode implantation was avoided by placing the cathode electrode caudad on the nerve. It may be possible to achieve even longer periods of fatigue-free stimulation by using bidirectional alternating pulses. This mode of phrenic nerve stimulation has been investigated in our laboratory with encouraging results.

The mechanism of the decrease in systemic and pulmonary arterial blood pressure during EPR is not clear. It probably is due to several causes. Expansion of the underinflated lung during EPR decreases pulmonary resistance and thus could account for an immediate decrease in effective circulating blood volume and a fall in pressure. This change in blood volume, however, should have only a temporary effect on the pressure. The antidromic stimulation of the respiratory center through afferent fibers in the phrenic nerve may in some way fire the vasomotor center lying nearby. Actually, however, such stimulation of the phrenic nerve usually causes a rise in pressure unless the stimulation is very strong. Hypoxia and hypercarbia may cause hypertension which, during EPR, may be relieved when the blood gas values return towards normal. On this point we found that the blood pressure change occurred before there was a change in $P_{CO_2}$ or $P_{O_2}$. Whatever its cause, the fall in blood pressure, at least in the pulmonary circulation, is probably beneficial, particularly to patients with cor pulmonale with right heart failure, such as patients 1 and 2.

A rapid change in the arterial blood gas level and hydrogen ion concentration may induce cardiac arrhythmias. In patient 2 who had a wide excursion of the diaphragm on EPR and a threefold increase in tidal volume, it was possible to reduce the arterial $P_{CO_2}$ to the low 20 mm range in only a few minutes, occasioning the onset of tetany. This was easily avoided, however, by manually adjusting the current flow from the transmitter. In the other patients hyperventilation to the point of tetany did not occur when the current was set to give first submaximal contraction of the diaphragm. Typically, during the first month after operation it was necessary to increase slightly the current flow to the nerve 30 to 60 minutes after beginning EPR to obtain consistent air volume for the remainder of the night. Later, one setting of the current flow was satisfactory for at least 8 to 10 hours of EPR. It is anticipated that in most instances there will be, with the passage of time, at least some rise in the stimulation threshold as the fibrous tissue envelope inside the nerve cuff increases in depth.
Hopefully, growth of this envelope will be limited to a thin membrane as is the case when silastic is implanted adjacent to tissues elsewhere.

Summary

Radiofrequency electrophrenic respiration has been applied for 4 to 22 months to four patients with hypoventilation of central origin. The left phrenic nerve alone has been stimulated for 8 to 10 hours nightly. Studies have confirmed the effectiveness of long-term EPR in maintaining reasonably normal respiration during sleep. Fatigue at the neuromuscular junction, which is reversible, develops after 18 hours of stimulation and the time of onset has been modified by alterations in the pulse-wave pattern. Nerve fatigue is rapidly reversible, and permanent damage to the nerve has not been seen.

Sophistication in the electronic design enables the unit to deliver controlled current that is constant to the nerve and to be decoupled over a wide latitude without loss of power.

For the present time long-term electrophrenic respiration is recommended only for patients who have an unequivocal need for chronic ventilatory assistance, whose phrenic nerves and diaphragm respond normally to electrical stimulation and whose lungs are normal. This would include patients with lesions involving the respiratory center or the cervical cord above the C3 level. The application of EPR to other patients with hypoventilation should be made only if, after careful evaluation, sufficient improvement in pulmonary function is assured which would outweigh the risk of damage to the phrenic nerve.

Addendum

Since this report was submitted two additional patients with hypoventilation of central origin have had RF EPR units implanted. In one the diaphragm failed to respond to stimulation after two weeks. The nerve was reexplored and found to be edematous at the site of the electrode application. The electrode was replaced with a new one. Injury to the nerve from ethylene oxide used to sterilize the electrodes five days before operation was suspected. The diaphragm of the second patient whose electrode was heat sterilized has responded to stimulation in a manner similar to the four patients reported above: There was dramatic improvement in ventilation and a decrease in systemic and pulmonary blood pressure during EPR.

References

11. Glebovskii, V. D.: Variations in Respiration and Blood Pressure in Response to Stimulations of Varying Intensity of the Dia-


DISCUSSION

Dr. James V. Maloney, Jr. (Los Angeles): We have recently treated a 12-year-old boy with postencephalitic syndrome who had respiratory center damage. He would "forget" to breathe at night after going to sleep and would suffer anoxic convulsions.

With Dr. Glenn's help we obtained one of these units and inserted it. It worked effectively for some days but, due to a technical error on my part, the electrode became displaced from the phrenic nerve.

In the late 1940's when electrophrenic respiration was first developed, Dr. Stan Sarnoff and I applied it to 15 or 20 patients who had polioenye-litis of the bulbar type. Not having Dr. Glenn's radio transmission facilities available, we had to lead the electrode through the patient's skin. The maximum time we could stimulate the nerve was from 4 to 10 days because of nerve fatigue and, perhaps, because of infection which traversed the skin.

Dr. Glenn has significantly eliminated the necessity of having a wire traverse the skin and has improved the type of current so that polarization around the phrenic nerve is minimized, which permits long-term therapy.

Dr. William W. L. Glenn (Closing): Dr. Maloney is one of the pioneers in electrophrenic respiration and it was an inspiration to read the many reports by himself and Dr. Sarnoff. Their work helped a great deal in the development of the present technics.

[Slide] In these days of increasing medical costs, I thought it might be a welcome relief to know that at least in the development of artificial respirators costs are down. The 9-volt battery that is used in this unit, if made in Hong Kong, costs only 19 cents and is good for one week's nightly use of the respirator, approximately 70 to 80 hours. The best U. S. type battery is only slightly more.