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Identification of unexpected respiratory abnormalities in patients with amyotrophic lateral sclerosis through electromyographic analysis using intramuscular electrodes implanted for therapeutic diaphragmatic pacing

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Abstract

BACKGROUND: Amyotrophic lateral sclerosis patients have significant respiratory abnormalities with incomplete understanding of respiratory control. This study analyzes electromyography (EMG) of the diaphragm (dEMG) using implanted diaphragm pacing (DP) electrodes.

METHODS: Retrospective analysis of dEMG data were obtained during Institutional Review Board and US Food and Drug Administration approved trials. The electrodes were used to analyze epochs of dEMG during multiple respiratory cycles.

RESULTS: Fifty-three patients were implanted. Thirty-six had bilateral dEMG assessments, 18 had continuous overnight readings with pulse oximetry, and 19 had serial analysis. Several findings revealed an alteration in the central respiratory drive including central apnea, hypoventilation, and hypercarbia. The electrodes showed unilateral dysfunction and demonstrated noninvasive ventilation suppression of diaphragm activity. DP can be used for serial monitoring, to decrease hypercarbia, improve sleep, and decrease atrophy.

CONCLUSIONS: Multiple abnormalities of respiratory control can be seen in amyotrophic lateral sclerosis patients using dEMG through therapeutic DP electrodes. DP is used to overcome instability of respiratory control when there are intact diaphragm motor units leading to improved survival.

Dr Raymond Onders, University Hospitals of Cleveland and Case Western Reserve University School of Medicine, has intellectual property rights involved with the diaphragm pacing system and equity in Synapse Biomedical, who manufactures the device. The remaining authors declare no conflicts of interest.

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Ventilatory control through diaphragm contraction is incompletely understood. Important structures likely include the special somatic respiratory nuclei of the brainstem, the cerebral cortex, and the carotid body among others. Output from these centers is transmitted through the phrenic nerve to the diaphragm. Single measurements of diaphragmatic muscle electrical activity are difficult, thereby further limiting investigations of neuromuscular control of breathing. Electromyography (EMG) of the diaphragm (dEMG) is a relatively uncommon test but it has been employed to study the peripheral electrophysiology of the diaphragm in various conditions. The usual method of studying dEMG involves transcutaneous surface measurements, which are inconsistent or needles directly into the diaphragm, which is technically difficult, has risks of pneumothorax, uncomfortable, and cannot be used for extended periods of time. Theoretically, directly implanted diaphragmatic electrodes to obtain recordings would be an ideal system to study respiratory control and diaphragmatic activation. This approach using temporarily implanted diaphragm electrodes has been used in the postoperative setting after laparoscopic cholecystectomy to evaluate diaphragmatic muscle function.[1]

The secondary fortuitous ability to analyze long-term respiratory control of the diaphragm through dEMG became possible with the use of therapeutic diaphragm pacing (DP) using the NeuRx system (Synapse Biomedical, Oberlin, OH). This system uses percutaneously placed electrodes, where 2 electrodes are placed laparoscopically into each hemidiaphragm at the point of maximal contraction identified through mapping. DP is a proven therapy to replace mechanical ventilators for spinal cord injured (SCI) patients who had lost control of their diaphragm.[2] It can also delay the need for mechanical ventilators and death in patients with amyotrophic lateral sclerosis (ALS or Lou Gehrig's disease).[3] The ability to use implanted electrodes to analyze dEMG has previously been reported by our group and has demonstrated recovery of natural control of breathing in SCI patients.[4] DP electrodes have also been used for both therapy and monitoring in patients who have diaphragm dysfunction with phrenic nerve abnormalities and allow for ongoing serial assessment of dEMG activity.[5]

ALS is a progressive and fatal neurodegenerative disease caused by degeneration in upper and lower (spinal) motor neurons. Patients with ALS have significant respiratory abnormalities that ultimately lead to death. Control of respiration is incompletely understood in normal subjects and even less in ALS.[6] This report describes observational analysis of dEMG activity through the use of therapeutically implanted DP electrodes in ALS patients to increase the understanding of respiratory control abnormalities in ALS and help extend the duration and quality of ventilator free life.

Methods

This is a single institution retrospective analysis of dEMG data obtained during ALS patients' postoperative evaluations throughout an initial pilot trial and subsequent multicenter trial. This was performed under US Food and Drug Administration Investigational Device Exemption G040142 and Institutional Review Board approved the investigations. The study was registered at www.clinicaltrials.gov with the specific identifiers NCT00420719. All patients gave informed consent and health insurance portability and accountability act compliance was met. The implantation of the electrodes has been well described during the initial operation.[2–5]

During the initial programing, the implanted electrodes were directed into a portable EMG machine and epochs of dEMG during normal respiration and during maximal inspiration were recorded. Because of the characteristics of the implanted electrodes, the measurements assess the spatial summation between 9 mm of exposed intramuscular electrodes in each hemidiaphragm using the implanted remote subcutaneous electrode as a reference. These electrodes were able to be used with a home polysomnography unit (Crystal PSG; CleveMed, Cleveland, OH) by using the implanted electrodes and then relabeling the chin and leg EMG recording as the right and left diaphragm recordings. This unit allowed continuous evaluation of epochs of diaphragm burst activity during sleep or noninvasive ventilation (NIV) use. The implanted electrodes secured consistent reliable serial measurements because it has been shown through consistent impedance measurements in the SCI trial of DP that the implanted electrodes do not migrate over time. The implanted electrodes can also identify control problems of each hemidiaphragm separately.

The dEMG was compared with available chest radiographs, diaphragm fluoroscopy, pulmonary function tests, phrenic nerve conduction tests, sleep studies, and arterial blood gases. Patterns of respiratory control abnormalities were then categorized.

Results

A total of 53 patients were implanted with DP electrodes during this time period of 2004 to 2008. Of this group, 36 patients had bilateral dEMG assessments, 18 had continuous overnight dEMG analysis with pulse oximetry, and 19 had serial dEMG analysis. Not all patients were able to have complete dEMG evaluations overnight or in follow-up. The review of this group of patients' dEMG results formed the basis for the following observations.

dEMG was evaluated to confirm that it could provide clinically relevant information, specifically that dEMG burst activity size correlates with the amount of diaphragm contraction. The initial correlation was to operative findings. In patients who retained respiratory control of their phrenic motor neurons, dEMG burst activity corresponded with the degree of diaphragm movement visualized during surgery. This was verified under fluoroscopy where the maximum dEMG correlated with the most diaphragm movement the patient could volitionally illicit and to a

standard polysomnography unit that records the chest and abdominal excursions when simultaneous outward movement with air flow correlates with diaphragm excursion. Some patients had minimal or absent dEMG activity but strong diaphragm contraction when the electrodes were stimulated. This was consistent with significant upper motor neuron loss of respiratory control, similar to that of an SCI patient. An SCI patient who has lost complete upper motor neuron control of the diaphragm has no measurable dEMG activity but can have a stimulable diaphragm excursion and can be ventilated with DP. This is the first finding of dEMG, the central or brainstem loss of control of intact diaphragm motor units. With disuse, the intact motor units of the diaphragm will rapidly convert to Type IIb fast-twitch muscle fibers.[7]

A second finding in the analysis of dEMG was in helping to explain hypoventilation leading to hypercarbia. The medulla pre-Botzinger complex should drive ventilation when CO_2 levels elevate. Several patients had elevated CO_2 levels and dEMG can be used to analyze the cause. If a diaphragm is extremely weak with areas of denervation at surgery, the cause of hypercarbia is from natural progression of lower motor neuron loss and diaphragm death. If the diaphragm is strong at surgery but the patient is hypercarbic, a central mechanism needs to be evaluated. Pivotal patient 01-11 was evaluated for increasing daytime somnolence and was found to have an elevated pCO_2 with normal oxygen levels. On dEMG, he was found to have significant respiratory instability, centrally mediated, where his respiratory rate was only 4 breaths/minute. He could, however, generate a large tidal volume. This suggests a defect in either central CO_2 sensing or in a central respiratory pacemaker leading to frequent apneic episodes. The patient did have excellent diaphragm burst activity and preserved lower motor neuron innervation of the diaphragm. Continuous diaphragmatic pacing in this patient lead to normalization of pCO_2 levels (pCO_2 decreased from 53 to 39 mm Hg).

A third observation from dEMG arose from the analysis during sleep and the use of NIV. There is growing evidence that ALS patients have sleep-disordered breathing that is most often because of central mechanisms. This phenomena was further confirmed in a group of our patients by recording overnight measurement of dEMG. We found suppression of dEMG activity during the use of NIV. Although NIV can improve sleep and subsequent quality of life, in certain ALS patients, NIV may have the potential to weaken the diaphragm by conversion to Type IIb muscle fibers with disuse atrophy when diaphragm activity is suppressed.

A fourth observation was the demonstration of significant asymmetry in hemidiaphragm response arising from the ability of dEMG to analyze each diaphragm separately. Many ALS patients can have an elevated diaphragm seen on a simple chest X-ray. A diaphragm can become elevated when there is paradoxical movement during breathing. The diaphragm muscles atrophies and becomes elongated with sarcomere damage. At surgery, some of these elevated diaphragms can have strong contractions with stimulation, yet, postoperatively, during automatic breathing there will be no dEMG activity in the elevated diaphragm. In this same group of patients, volitional breaths that would involve the cerebral cortex, bilateral dEMG activity can be seen. This highlights the complexity of respiration and our incomplete understanding of it.

A fifth observation was that dEMG burst activity improved for some patients after DP conditioning or a rhythmic breathing pattern would continue when DP was not being used. Fig. 1 highlights the dEMG improvement in burst activity. This subject was becoming more dependent on NIV with hypercarbia; however, at surgery, he had significant stimulable diaphragm. In the immediate postoperative time period, dEMG during NIV showed suppression of burst activity and when NIV was removed there was only minimal automatic and volitional breaths. After therapeutic DP, there was a significant improvement in diaphragm burst activity correlating to improved strength and the subject was able to decrease NIV use. In other patients with instability of respiratory control who used DP for long-term ventilation, dEMG showed a return of rhythmic consistent breaths. These data suggest that DP may improve automatic respiratory control. Several patients used DP as their sole ventilatory support until all therapy including DP was withdrawn (25% of pilot trial patients[3]). Death can occur within hours of DP withdrawal indicating that there can be a rapid loss of control leading to respiratory failure with DP cessation.

Comments

This report confirms that the DP electrodes allow reproducible dEMG recordings that may have significant clinical utility in evaluating ALS patients. The dEMG burst amplitudes correlate with movement on fluoroscopy, with strength identified during abdominal/chest excursions and intraoperative diaphragm measurements. The ability to monitor diaphragm physiology with dEMG using DP electrodes allowed the identification of previously unknown abnormalities of ALS respiration. Several important new findings were identified through dEMG analysis: (1) intact diaphragm motor units with loss of respiratory control; (2) instability of ventilator drive causing hypoventilation with increasing hypercarbia; (3) evidence of acquired central sleep apnea and NIV causing diaphragm activity suppression; (4) identification of unilateral abnormalities with a loss of control of the diaphragm from respiratory control centers in the brainstem; and (5) DP improves diaphragm burst activity and helps in maintaining the respiratory pacemaker.

The first 4 findings could be addressed by DP through the simple act that DP overcomes loss of upper motor neuron control in the brainstem or cerebral cortex. This loss of control of diaphragm motor units has important clinical implications. Diaphragm muscle that is not used converts to Type IIb glycolytic fast-twitch muscle fibers.[7] DP converts stimulated diaphragm muscle into the slow-twitch fatigue-resistant Type I muscle fiber.[8] In animal models,

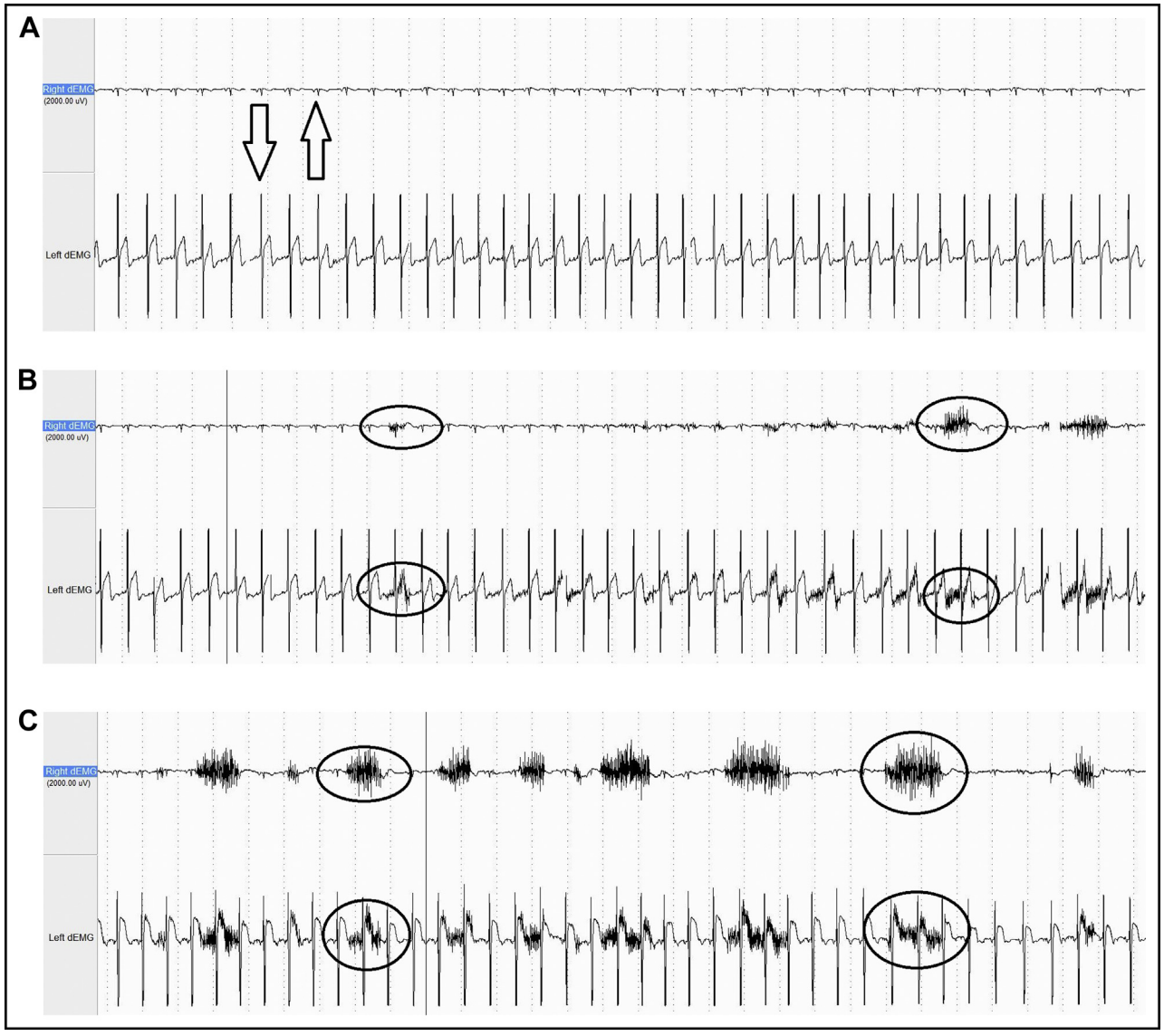

Figure 1 Postoperative dEMG analysis in an ALS subject with NIV dependence and hypercarbia. Both the right and left hemidiaphragm electrodes are displayed. The electrocardiogram tracing artifact is marked with an arrow and is visualized as larger on the left because the electrodes are closer to the heart. Representative diaphragm burst activities are circled in which the size correlates with the strength of diaphragm contraction and ventilation. (A) This 30-second recording of dEMG when the subject is on NIV shows complete suppression of diaphragm activity. (B) When the patient is removed from NIV, there is small burst of dEMG activity. (C) After the subject has conditioned his diaphragm by using diaphragm pacing whenever he is on NIV, there is significant improvement in the burst activity. The patient is also less dependent on NIV. (For interpretation of the references to color in this Figure, the reader is referred to the Web version of this article.)

Type IIb muscle fibers and their associated motor neurons degenerate before the Type 1 muscle fibers and their associated motor neurons.[6] Maintaining the functional Type I muscle fibers with DP not only improves diaphragm movement, which improves ventilation, but could also delay the death of those motor neurons. This explains why patients using DP late in their disease can maintain normocarbic ventilation but have very low recorded pulmonary function tests. The tests require the recruitment of the fast fatigable Type IIb muscle fibers to get the more explosive flow for measurement of maximal force or pressure measurements that have been historically used to assess patient function. DP converts all the diaphragm to Type I muscle, which is more important for long-term minute ventilation, particularly because ALS patients become increasingly sedentary with the progression of the disease.

The fifth finding is a growing area of research in respiratory physiology. There is evidence that the respiratory system is able to "fight back" and trigger spontaneous compensatory plasticity that can maintain respiration in the face of motor neuron loss.[6] This plasticity has been demonstrated in other disease states with stimuli such as intermittent hypoxia.[6] The improvement and control of dEMG and respiration in certain ALS patients means that DP through

neuroplasticity may improve the respiratory control through improvement in the upper motor neuron control of the diaphragm. This plasticity although somewhat persistent was shown to wane when DP is discontinued. For example, in one case a patient with DP became intubated secondary to aspiration pneumonia and DP was stopped for several days at an outside hospital. Prior to the event the patient had large dEMG burst activity and was using DP as the primary mode of ventilation even though he was late in his disease. When re-evaluated, the patient had no dEMG volitional burst activity and DP could no longer maintain ventilation. The plasticity seen from DP may rapidly degenerate when DP is stopped in ALS patients. This has not been seen in SCI patients or in patients with isolated diaphragm dysfunction.[4,5]

The use of dEMG has influenced the clinical practice of DP in ALS patients in several other important ways. With the knowledge that NIV can suppress diaphragm activity, all patients use DP whenever they are on NIV. Many patients need to use both NIV and DP together especially when there is a continued loss of diaphragm motor units. Because DP prevents diaphragm atrophy from NIV suppression, DP can decrease the need for NIV during the day.

ALS patients should have routine chest X-rays to assess for diaphragm elevation. DP should be initiated before significant elevation with associated diaphragm elongation with sarcomere changes. If dEMG shows no burst activity but the diaphragm was stimulable then the patient requires 24 hours pacing to maintain diaphragm function.

dEMG can also show that DP may have little clinical benefit in patients. Unfortunately, this, presently, can sometimes only be identified postoperatively, for example, a patient may be maintaining ventilation with accessory muscles. If at surgery, the diaphragm is extremely weak and postoperatively dEMG measures small burst activity with both volitionally and automatic breathing; then this patient has few diaphragm motor units available and DP cannot help maintain muscle or add to ventilation. DP therapy is optimum when the patient has unused motor units that DP can drive and dEMG shows the patient has instability of control of those motor units.

In conclusion, these dEMG findings demonstrate that ventilatory dysfunction in ALS is likely much more complex than just denervation atrophy of the diaphragm. Significant areas of central dysregulation were seen along with interesting observations of apparent asymmetric central dysfunction. This knowledge has benefited ALS patients and has helped identify the correct role of DP in ALS patient management.

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Discussion

Dr G. Paul Wright (Grand Rapids, MI). How consistent were these abnormalities identified between patients? In other words, is the nature or progression of dysfunction at all predictable, or is there significant degree of individual variation? From the data you collected, how frequently and in what way did the results of the EMG impact clinical management. And, finally, as the outcomes from your study have been positive, in your opinion, is diaphragm pacing now indicated in all patients with ALS? And along that line, should all patients receive EMG testing, and, if so, with what frequency should the testing be conducted?

Dr Onders: ALS has a wide variety of presentations. Some patients may die within 18 months. Some patients in four years. Some patients will have no respiratory abnormalities. We know that if you have this instability of respiratory control, if we've identified that in you, pacing will probably work the best. If you don't have the instability and you're just losing lower motor neurons, diaphragm pacing will not help you. And so it's an interesting finding, where we don't really know if diaphragm pacing will work in ALS patients until after surgery, which for most patients that are faced with a fatal disease, they may be accepting of this.

Again, this is a surgical procedure in an ALS patient that's at high risk because they're declining. Not all ALS patients want to have any therapeutic interventions. Diaphragm Pacing is prolonging their life by about 18 months in our trial. So what's the utilization of dEMG? Presently, we are one of the only sites that can read the electrodes. It's not a commercially available device to read the electrodes. Diaphragm pacing is commercially available, but dEMG is still under the research. But what we found is that we have now changed the way that ALS patients are managed when they're on BiPAP. If you're on BiPAP, which may suppress your respiratory control and cause diaphragm atrophy, we then recommend that you should be on pacing whenever you're on BiPAP.

ALS is a disease that more commonly effects the Type IIb fast twitch muscle fibers. Our diaphragm is mostly Type I. When you are not using your diaphragm, it converts to Type IIb. So diaphragm pacing will always make your diaphragm Type I muscle fibers, which may allow those motor neurons involved with the muscle fibers to live longer. That may be one reason we're seeing this improvement in survival.

Dr Samir Gupta (Peoria, IL). I have been reading these papers with interest. Is this a novel diaphragmatic pacer, then, versus what we're seeing in the literature, other pacing devices? And the reason I ask is that you're looking at the subset of patients with ALS. In our practice, of course, is the quadriplegics that are injured by trauma of various sorts. And the question has always been those patients that require long-term ventilation. It would be nice to have another option for them. And some of the literature suggested that there was improvement in diaphragmatic function in those patients when you started stimulating them.

Dr Onders: Diaphragm pacing initially began for spinal cord injured patients. The Journal of Trauma just published our multi-center use of early implantation. So in our multi-center analysis is that every spinal cord injured patient should be offered this. There is no downside. The neuroplasticity effects were at 30 percent of the patients that we implant this in, recover their breathing because of the changes in their respiratory control. We've now realized that just being on the ventilator in your intensive care unit, if you get a pneumonia, actually changes your brain stem control of respiration. There's actually adverse effects in your pre-Botzinger complex. And this is the future of how we're going to manage ventilator patients is overcoming brainstem abnormalities that were previously undescribed.

So in spinal cord injury both the direct phrenic nerve pacing, which has been around since the group out of Yale developed this in the 1960s or intramuscular diaphragm pacings are available for ventilator dependent spinal cord injured patients. The main difference is that you can remove intramuscular pacings. Unfortunately these technique are very rarely used for spinal cord injury for reasons that are unknown.