Editorial

Short-term phrenic nerve stimulation; no longer a therapy in search of a disease

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We read with interest the article published by Etienne *et al.* describing the use of surgically placed temporary phrenic pacing leads in an ovine model of cardiothoracic surgery (1).

Mechanical ventilation is life-saving, but there is a point at which mandatory modes of ventilation cease to be of benefit. While unloading the respiratory muscles during periods of stress, recovery will be impeded where support is continued for longer than necessary. The onset and severity of ventilator induced diaphragmatic dysfunction are well characterised; increased proteolysis, rapid disuse atrophy and thinning of this muscle are perhaps most severe because it is such a metabolically active muscle (2-10).

Spontaneous awakening and breathing trials when combined with the judicious use of sedation has proven a life-saving strategy in ICU patients [number needed to treat (NNT) =7]; a significant component of this success must be attributed to a reduction in diaphragmatic atrophy (11).

The situation in cardiothoracic surgery is complicated, sedation and mandatory ventilation may be prolonged by cardiac or pulmonary instability. Pain management may be challenging, and while epidural analgesia decreases the risk of postoperative pneumonia in patients undergoing abdominal or thoracic surgery, coagulopathy may preclude its use. Pulmonary oedema is a frequent diagnosis following cardiac surgery, direct compression of lung tissue from retraction, lung injury from resection, or changes in intravascular lung water will adversely affect compliance (12). Atelectasis is more prominent after cardiac surgery with CPB than in other forms of surgery (13).

The premise of this study is: where postoperative weaning is predicted to be difficult, placing leads in close proximity to each phrenic nerve at the time of open surgery may subsequently allow effective diaphragmatic pacing. The effects of diaphragmatic pacing in maintaining diaphragmatic strength and decreasing the extent of atelectasis should then lead to a more rapid liberation from mechanical ventilation.

Long term phrenic ventilation is a proven concept; the phrenic nerves may be paced for upwards of 20 years without injury to the nerve. Many patients who have suffered high spinal injuries or who have central hypoventilation syndrome are ventilator independent as a consequence. Phrenic ventilation mimics human physiology, by generating a negative intrathoracic pressure, it reduces basal atelectasis and has been proven to reduce infectious complications over time (14).

While temporary phrenic stimulation leads are smooth with in-line sequential stimulation points, permanent leads are wide plates wrapped around the phrenic nerves. Two designs are commonly used; a mono or bipolar platinum electrode coated in silicon from Avery Biomedical Devices (USA) or a quadripole termed a "double bipolar electrode" in the case of Atrotech (Tampere, Finland) (15,16). Where leads are placed in close proximity to the phrenic nerve, and the current used to capture the nerve limited to less than 2 mAmps, then the safety of this approach should

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be assured as this is typical of currents used in long-term pacing. In this study the pacing wires provided sequential multipolar stimulation through a quadripole electrode, therefore no single point of the nerve received all of the current. Developments in lead design ensure excellent biocompatibility and the low stimulation currents used in this study were similar to those used in humans for chronic phrenic ventilation. One noteworthy point was the presence of a fibrotic reaction to the presence of the stimulating lead noted in the first two animals at 15 days but which was not evident on post-mortem analysis in the second two animals 30 days post implantation.

There is an undoubted benefit for patients where their diaphragms contract, whether by volition or not, in terms of the pressure cost of mechanical ventilation. One should expect a lesser degree of ventilator induced lung injury or barotrauma where phrenic ventilation is used. This may be particularly important in the context of lung surgery where air leaks are commonplace and bronchial stumps may be particularly susceptible to injury. In cardiac surgery a negative intrathoracic pressure may augment venous return. Maintaining diaphragmatic work of breathing will maintain diaphragmatic strength and possibly lead to earlier extubation. Cardiothoracic surgery is also associated with a significant risk of phrenic injury whether via manipulation of the mammary arteries or hypothermia related via cold slushes. Short term pacing carries the theoretic benefit of maintaining diaphragmatic strength until function returns, in doing this it may ameliorate the detrimental effects of a short-term neuropraxia (17,18).

By maintaining diaphragmatic activity, even short-term phrenic stimulation has been proven to maintain diaphragmatic thickness and Maximum Inspiratory Pressures (MIP) as surrogates for diaphragmatic strength. This was demonstrated in two trials of temporary phrenic pacing: the PEPNS and the RESCUE 2 (19,20). In the Percutaneous Electrical Phrenic Nerve Stimulation trial leads were inserted in the cervical region on the surface of scalenus anterior. Although a small trial (N=12) PEPNS demonstrated a 15% increase in diaphragmatic thickness at 48 hours and all patients were successfully paced. In RESCUE 2, the "Livecatheter" system provided transvenous stimulation of the phrenic nerves within the chest. In Lungpacer's RESCUE 2 trial, although only 75% of the treatment arm received the device, diaphragmatic strength as measured by the MIP increased at all timepoints from day 8 in the treatment group.

The phrenic nerves may also by stimulated from the abdominal side of the diaphragm. Leads are placed following the laparoscopic mapping of the motor endplates of the phrenic nerves within the diaphragm muscle. In 2014, a multicentre review of 29 patients who had suffered high spinal injuries demonstrated the benefits of early prophylactic diaphragmatic pacing. Of 29 patients, 22 had stimulatable diaphragms and were implanted. Sixteen of this group were ventilator free after 10 days of therapy and eight patients had their diaphragmatic leads subsequently removed following successful weaning (21).

The authors of this study have considerable experience and expertise in this field and must be complemented for considering this application. This study represents a preliminary examination of short term leads in an ovine model. While it has several merits, early stimulation failure in the first animal suggests a learning curve and overall a limited number of animals were used, as such the results may limit a broader generalisation. The authors examined the animals "phrenic stimulated" minute ventilation at day 1, immediately following implantation and then later after either 15 or 30 days. Despite difficulties with electrode placement in their first animal and subsequent difficulties with stimulation on the right side in a further two animals, six of the 8 attempted placements proved successful. In addition, no damage was noted to the phrenic nerves on post-mortem examination, certainly no damage would be expected from leads placed in close proximity to the nerves with direct visualisation and without mobilisation of the nerves, however the fibrotic reaction and its evolution over time is noteworthy. One could potentially conceive that stimulation at high amplitudes could cause damage, however current amplitudes used were in the low-normal ranges and charge density would have been distributed by sequential multipolar stimulation.

There are difficulties with end-points chosen in animal studies where diaphragmatic pacing is concerned. Ultimately if our goal is to shorten the weaning phase for patients, studies which will measure clinically important endpoints such as time to extubation or ventilator independence are the goal.

Surrogates which measure diaphragmatic strength may require a calm cooperative patient, one example, the Maximal Inspiratory Pressure (MIP) generated is heavily dependent upon patient cooperation (22-24). Transdiaphragmatic pressure measures inspiration against a closed glottis and requires gastric and oesophageal balloon catheters, this additional catheter may be uncomfortable for patients. The "Twitch Pressure" or Stimulated

Transdiaphragmatic Pressure" (PdiStim) does not require cooperation, may be performed in deeply sedated patients and does correlate well with outcomes. Measuring the PdiStim also requires a gastric and oesophageal balloon catheter, however, rather than a volitional inspiratory effort, bilateral magnetic or electrical stimulation of the phrenic nerves creates the inspiratory force, it is reproducible and easy to perform (25,26). Diaphragmatic ultrasound has a learning curve and its reliability depend upon the skill of the operators, however despite this it has broad applicability, is non-invasive and painless.

Perhaps the greatest challenge going forward might be to identify the population who will benefit most from this emerging technology. It is estimated by consensus that approximately 15% of mechanically ventilated patients fall within the difficult to wean group i.e., this would include patients who require more than three Spontaneous Breathing Trials (SBT) or greater than 7 days of weaning after the first SBT (27). Perhaps the model of cardiothoracic surgery with its attendant pain, atelectasis, and immobility may prove an ideal model for this therapy.

In conclusion, the outcomes of this animal study add to an emerging consensus that short-term phrenic stimulation will ameliorate the damaging effects of diaphragmatic immobility and carries the potential to improve outcomes in several patients groups.

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