Review Article

Diaphragm pacing: the state of the art

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Abstract: Diaphragm pacing (DP) is an orphan surgical procedure that may be proposed in strictly selected ventilator-dependent patients to get an active diaphragm contraction. The goal is to wean from mechanical ventilation (MV) and restore permanent efficient breathing. The two validated indications, despite the lack of randomised control trials, concern patients with high-level spinal cord injuries (SCI) and central hypoventilation syndromes (CHS). To date, two different techniques exist. The first, intrathoracic diaphragm pacing (IT-DP), based on a radiofrequency method, in which the electrodes are directly placed around the phrenic nerve. The second, intraperitoneal diaphragm pacing (IP-DP) uses intradiaphragmatic electrodes implanted through laparoscopy. In both techniques, the phrenic nerves must be intact and diaphragm reconditioning is always required after implantation. No perioperative mortality has been reported and ventilator-weaning rate is about 72% to 96% in both techniques. Improvement of quality of life, by restoring a more physiological breathing, has been almost constant in patients that could be weaned. Failure or delay in recovery of effective diaphragm contractions could be due to irreversible amyotrophy or chest wall damage. Recent works have evaluated the interest of IP-DP in amyotrophic lateral sclerosis (ALS). After some short series were reported in the literature, the only multicentric randomized study including 74 ALS patients was prematurely stopped because of excessive mortality in paced patients. Then, another trial analysed the place of IP-DP in peripheral diaphragm dysfunction but, given the multiple biases, the published results cannot validate that indication. Reviewing all available literature as in our experience, shows that DP is an effective method to wean selected patients dependent on ventilator and improve their daily life. Other potential indications will have to be evaluated by randomised control trials.

Keywords: Diaphragm; diaphragm pacing (DP); phrenic nerve stimulation; spinal cord injury

Submitted Mar 02, 2016. Accepted for publication Mar 17, 2016.
doi: 10.21037/jtd.2016.03.97
View this article at: http://dx.doi.org/10.21037/jtd.2016.03.97

Introduction

Patients dependent on mechanical ventilation (MV) for non-pulmonary diseases represent a limited cohort, most of them suffering from brain or high-level spinal cord injuries (SCI). Other patients suffer from central hypoventilation syndrome (CHS), congenital (Ondine curse disease) or acquired (vascular or infectious diseases). For all these patients, the peripheral effectors, i.e., the lung, the diaphragm and the phrenic nerves are generally intact and functional. It is in these situations that diaphragm pacing (DP) could be proposed to remove positive pressure ventilation and restore more "physiological" breathing obtained by a diaphragm contraction (1-5). The main goal of DP is to improve the daily comfort of the patients (breathing, mobilisation, reduction of infectious lung diseases linked to MV, etc.). However, since this technique initially concerned only tetraplegic patients, DP has remained a little-known technique both for the thoracic surgeon community and also for trauma centres. In fact, it seemed difficult to plan an important surgical procedure in severely injured patients. This was especially true given that an easy cervical approach was initially done but stopped and changed for an intrathoracic procedure because of recurrent cervical local complications. While the thoracic approach was regularly performed with success in a few centres in the world (5-7), a laparoscopic approach was then developed after performing anatomical studies (8,9). Today the two validated indications for DP are restricted to permanent or sleep-related congenital or acquired central hypoventilation, if the diaphragmatic muscle and phrenic nerves are functional. More recent studies have been performed to evaluate the interest of DP in other indications with different objectives. The first was to improve breathing condition of amyotrophic lateral sclerosis (ALS) patients in order to avoid or delay required non-invasive ventilation (NIV) or MV (10). Recently, this technique has also been tested as a temporary tool to avoid diaphragmatic amyotrophy in patients requiring MV for whom spontaneous breathing recovery seemed possible (11).

The goals of our review are to summarise the literature data concerning DP describing the interests and risks for the two techniques available now that are the thoracic approach [intrathoracic diaphragm pacing (IT-DP)] and the abdominal approach [intraperitoneal diaphragm pacing (IP-DP)].

Methods

The Cochrane database and PubMed were searched between 1960 and 2015, using the keywords "diaphragm pacing", "phrenic nerve stimulation", and "phrenic pacing". This research contains a long period of time because very few procedures have been reported around the world. Only the articles published in English language were collected. We only took into account the largest series, over ten patients, to get the widest possible clinical experience. Then we divided the analysis into two parts according to the current available techniques to describe the surgical aspects and give the results.

Intrathoracic diaphragm pacing (IT-DP)

In 1873, Hufeland first reported direct stimulation of the phrenic nerve for neonatal treatment of asphyxia, as published by Schechter (12). The clinical application of phrenic stimulation started only after the *cardiac pacemakers era*. In 1968, the first large cohort to be reported concerned chronic bronchopathic patients (13). Right after, Glenn reported a full weaning from respirator in a completely dependent tetraplegic patient (1). Today the same technique is still used (5,7,14). It is based on a radiofrequency system using bipolar or quadripolar electrodes reaching a certain degree of sophistication.

After the first implantations at cervical level using alternating periods of unilateral stimulations (1), the implantation site changed, moving to the pleural cavity with bilateral synchronous stimulations (15). In fact, at cervical level, wire breakage due to persistent movements of the neck was observed, just like infectious complications due to the nearby tracheostomy.

This technique is still used, identically to the 70s, and the only technology improvement has been the use of video-surgery to make phrenic nerve dissection safer and reduce scars (5). This approach through bilateral small anterior thoracotomy requires general anaesthesia with double-lumen intubation to carefully place the electrodes around the phrenic nerve (5,15). On both sides, the intrapleural electrodes are connected to the subcutaneous receivers. The main point before implantation is the rigorous selection of patients: identifying those who can be weaned from ventilator with this procedure while avoiding patients with possible spontaneous breathing recovery. This selection should always be done using electromyographic testing (16,17).

Results of IT-DP

The largest and oldest multicentric study carried out in

1988 gathered 477 patients who had IT-DP for chronic hypoventilation (6). Only 165 patients implanted in a referent centre were considered for this retrospective study. Implantation was bilateral in 100 patients and unilateral in 65. Full success or significant support was achieved in 81.81% of cases and complete failure in 6.06%. The relevance of the study was limited by the heterogeneity of the cohort: various neurological indications, cervical or thoracic implantations, bipolar or monopolar electrodes and unilateral or bilateral stimulation. However, at the beginning of this programme, phrenic nerve injuries were observed in 19 nerves out of 265 nerves (7.17%) with irreversible damage in 4.90%. Despite this risk, the results were interesting with full-time stimulation achieved in 26.71% of patients or during sleep in 45.96%, and part-time stimulation in 14.90%. In 2.48%, pacing failed or had no real use.

In 1996, Weese-Mayer *et al*. reported an international study of 64 cases—29 adults and 35 children—issued from the Atrotech registry data, all using quadripolar electrodes (Jukka, Atrotech®, Tampere, Finland) (18). Most of the indications concerned tetraplegia (70.3%) or CHS (22%). Ninety-four percent were implanted at thoracic level. Four phrenic nerve injuries in three patients occurred at time of implantation, and were reversible in two of them. Weaning was achieved in 91% of cases. The authors discussed the theoretical interests of quadripolar stimulation. This alternating stimulation on each quarter of the nerve reduces the risk of neuromuscular fatigue. It allows an improvement in programming the breathing modalities according to the physical activity of each patient and the underlying diseases.

In 2008, a prospective clinical study including 64 SCI patients compared two groups of patients: 32 requiring definitive MV because of destroyed phrenic nerves and 32 implanted with IT-DP using quadripolar electrodes (19). After reconditioning, the incidence of respiratory infections was significantly reduced in the stimulated group compared to the group under MV. Obviously, IT-DP improves patients' quality of life giving them a much better quality of speech and allowing them to return to work or school (9 *vs*. 2). The significant initial additional cost when purchasing the device is rapidly offset in less than a year. The reason is that this easy-to-use device reduces the global cost, nursing is simplified and there are fewer respiratory infections compared to MV.

In 2010, Khong reported an Australian experience with a series of 16 documented paced patients using IT-DP (Avery Biomedical Devices; Commack, NY, USA) in 14 for tetraplegia, 1 congenital CHS, 1 brainstem encephalitis diaphragm (14). With long-term follow-up, mean 13 years (from 1 to 21 years), 11 patients had full-time weaning. Eight patients had revision surgeries. Four of them were to replace the original system (which had a 3–5 years life expectancy) with the current system, which is expected to perform electrically for the patient's lifetime.

In 2011, we reported our homogenous series of IT-DP using quadripolar electrodes (Jukka, Atrotech®, Tampere, Finland) implanted through video-assisted anterior mini thoracotomy (5). All patients, 19 with posttraumatic tetraplegia and one with congenital CHS, had preoperative tests to validate the indication. No Neuromuscular blocking agents were used during the anaesthesia in order to do peroperative stimulation tests. No peroperative morbidity, mainly phrenic nerve injury, was observed. Stimulation thresholds measured intra-operatively ranged from 0.05 to 2.2 mA. The only failure concerned a compassionate indication that was a wrong indication because preoperative tests did not detect any phrenic nerve conduction. All other patients achieved full (n=16) or partial (n=2) weaning from MV after a mean reconditioning time of 6 weeks (2–11 months). All weaned patients reported a real improvement of the quality of life particularly because of more natural breathing, independency from mechanical ventilator and return to social or professional life.

In 2012, Romero reported a retrospective study using prospectively collected data comparing 88 high SCI tetraplegic patients under MV with 38 patients who sustained IT-DP (7). It was a homogeneous cohort as all patients had high cervical SCI. Initially, the bipolar electrodes had been implanted through thoracotomy and after, all patients were implanted using four-pole electrodes. Seven patients were operated on thoracoscopically. By a univariate analysis, a greater survival expectency in years was observed in the IT-DP group (mean 21.78; from 17.95 to 25.61 years) compared with the MV group (mean 8.69; from 6.37 to 11.02 years) $P<0.001$. Because the patients in the IT-DP group were younger, the analysis was done after the age adjustment. The multivariate Cox regression analysis confirmed the longest survival in patients in the IT-DP group ($P=0.04$).

All those studies reported lower rates of phrenic nerve iatrogenic trauma (from 0% to 4.9%), electrodes dysfunction (around 3%) and external receptor dysfunction that was easy to change (5.9%) (5,6,18). In the end, effective stimulation was achieved in 82% to 90% of cases with constant comfort improvement in breathing and daily life (5-7,14,18,19).

Intraperitoneal diaphragm pacing (IP-DP)

This more recent technique, developed since the early 2000s, consists in implanting a hook electrode via a laparoscopic surgical procedure, directly within each hemidiaphragm close to the phrenic nerve ending (4). The first step of the technique is to identify the motor point of the phrenic nerve, not directly seen by this way but using a mapping technique (9). Each implanted intramuscular diaphragm electrode is directly connected to a four-channel external stimulator at a percutaneous exit site (through the abdominal wall). This stimulator box delivers the stimulus pulses and provides respiratory timing. Stimulating currents typically range between 5–20 mA. Only one device is currently available (NeuRx, Synapse Biomedical, Oberlin, OH, USA). The first short series of 5 tetraplegic patients paced with this technique was reported by DiMarco (20). The main goal was to validate the technique on a restricted homogeneous cohort of patients. All patients had a preoperative phrenic nerve stimulation evaluation. IP-DP was done on outpatients and the resulting inspired volumes generated by IP-DP were comparable to those achieved with IT-DP. Four out of five patients achieved full-time ventilatory support by IP-DP. Similar benefits were reported concerning more comfortable breathing, easier mobilization, etc., which led the authors to conclude that this technique was less invasive and gave the same results in tetraplegic patients. The mapping to determine the motor point before implantation was time consuming and sometimes incomplete mainly on the right hemidiaphragm. After this first step of evaluation, other larger series were then reported.

Results of IP-DP to wean patients from the ventilator

A complete evaluation of this technique was done in prospective Food and Drug Administration (FDA) trials gathering 50 patients with SCI and 38 with ALS (10). For spinal-cord-injured patients, this study was undertaken under FDA Investigational Device Exemption (IDE) G920162. Ten patients in that cohort had been analyzed in a previous published study. The elapse time from the injury was 3 months to 27 years. Only one patient had mapping failure corresponding to a false positive. There was no peroperative mortality and 96% of patients were weaned from their MV. No postoperative morbidity was observed: no electrode migrations or late change in electrode impedance and no organ erosions due to the electrode. Only one superficial wound infection was observed without any consequences. A capnothorax was observed in 42% of patients with no hemodynamic or respiratory consequences.

In 2014 Posluszny reported a multicentric study of IP-DP, early implanted after trauma—mean 40 days, range 3–112 days—in 22 ventilator-dependent patients with SCI (21). Sixteen patients (72% implanted patients) were completely weaned from MV after mean time of 10.2 days from implantation (range, 1–45). For two other patients implanted at day 16 and day 26 respectively, delayed weaning was observed (180 days). Out of all these 18 weaned patients, 8 had pacing wires removed (44%). The authors did not specify the time from MV weaning to DP removal, i.e., the date for spontaneous breathing recovery. In their manuscript the authors admitted that the long-term MV outcomes of the patients were unclear. It was then impossible to know how many patients weaned from MV would be weaned without IP-DP. In conclusion, the potential place of the technique as a bridge to independent breathing was mentioned but not formally validated.

Results of IP-DP in ALS patients

Probably because IP-DP was considered a less invasive procedure, it has been tested in ALS (10,22). In this neurodegenerative disease, there is a degeneration of anterior horn cells of the spinal cord leading to an axonal degeneration with amyotrophy of the diaphragm (23). The goal of IP-DP was to get a potential benefit of muscular stimulation like in Duchenne myopathy. However, the physiopathology of ALS is complex with a major heterogeneity of axonal degeneration level (23). Theoretically, the best candidates for IP-DP are patients with preserved inferior motor neurons. The initial pilot group of 16 ALS patients implanted between March 2003 and March 2007 were reported in a multicentric study (24). The main goal was to reduce the decline of vital capacity (VC) of ALS patients by musculature conditioning using daily session of stimulation (3 to 5 sessions of 30 min). The median time between diagnosis of ALS in the patients and enrolment in the study was 19.6 months. Before surgery, all the patients had a phrenic nerve conduction evaluation, a diaphragm thickness measure using ultrasound, and fluoroscopic analysis. The average stimulator output value was 13 mA. In the post implantation period, there were no failure due to the electrodes but seven external devices had to be repaired. A significant increase of the diaphragm thickness was observed (22). The long-term analysis showed no safety issues and DP can improve respiratory functions in ALS by artificially replacing or supporting the affected pathways.

The preliminary results seemed to be negative because no reduction of VC was observed in 25% of patients during observational the preimplantation period. Therefore, for 75% of patients with VC reduction during the preimplantation period, the slope of decline was reduced. Because of the reduced mortality for ALS patients with DP compared to those with NIV (25), a compassionate authorisation was accepted in the US for patients with alveolar hypoventilation criteria.

In 2015, a multicentric, open-label, randomised controlled trial evaluated the safety and efficacy of IP-DP in ALS patients with respiratory insufficiency in seven specialist centres in the UK (26). Its aim was to evaluate if IP-DP with early low intensity could reduce the progression of ALS-related respiratory insufficiency and potentially delay the need of ventilatory assistance. Patients were randomised in two groups: NIV plus IP-DP (NeuRx) or NIV alone. The modalities of the real treatment were unknown to patients and the investigators. Seventy-four patients were enrolled in the trial, 37 in each group, from December 2011 to December 2013. The total duration of the study had been planned for 6 years. But the Data Monitoring and Ethics Committee decided to prematurely stop the trial and recommended a suspension of recruitment on the basis of overall survival figures. The causes were the absence of benefits and a statistically significant excessive mortality in the group of patients receiving active stimulation. Indeed, 162 adverse events occurred (5.9 events per person-year) in the pacing group, of which 46 events were serious, compared with 81 events (2.5 events per person-year) in the group with NIV alone, of which 31 events were serious.

Recent extension of the indication of IP-DP

In 2014, Onders reported a new way to use IP-DP for patients who did not have SCI or ALS but for patients with unilateral or bilateral diaphragm dysfunction. The single-institution non-randomised retrospective study concerned 27 patients with symptomatic hypoventilation from different origins (11). The causes were idiopathic or due to chest or shoulder surgery, traumatism and others causes. The global care was identical to previous studies (preimplantation tests and peroperative mapping via laparoscopy). Twenty-one patients with stimulable diaphragm were implanted (17 bilateral and 4 unilateral involvements) and half of the 6 not stimulable patients had diaphragm plication. After DP, 62% of patients had improved condition and 7 had little or no improvement. Among the 21 implanted patients, 7 had device removal because of full breathing recovery. The authors reported different study limitations: the retrospective study, the lack of control group, the non-uniform data collection, and selection bias based on a single-site analysis. The authors could not exclude breathing recovery without IP-DP. They mentioned that the removal of the electrodes was not a problem because it was performed for epicardial electrodes.

Discussion

Though no randomised study has been conducted up to now, to formally validate the interest of DP in selected ventilator-dependent patients, it seems difficult now not to propose such a device to these patients, given the improvement of quality of life they can get from it (5,7,10,18,19,27). Indeed, nowadays, IP-DP or IT-DP performed in expert teams gives the opportunity to restore or improve breathing for strictly selected patients. Even if IT-DP is the oldest technique, there are few publications all concluding on its feasibility and main interest. This technique has evolved using minimally invasive approach showing its safety in expert hands (5). IP-DP has recently been the subject of more publications by the same authors who developed it initially. However, several publications report on the same patients, which prove that it is still an "orphan" operation with few patients concerned. In both techniques, implantation is feasible and enables an efficient contraction of the diaphragm only on condition of a rigorous selection upfront. For tetraplegic patients, the key point is to validate the definitive interruption of spontaneous breathing with a persistent phrenic nerve vitality using cervical and transcranial magnetic stimulation (28). Under these conditions of stringent electrophysiologic criteria to select the candidates, the "diaphragm stimulation" in the broad sense, through thoracic or abdominal approach, gives tetraplegic patients a real improvement in their daily life (5-7,14,18,19). It allows more comfort with physiological breathing, better speech, restored olfaction, and better "mobilisation" for themselves and their caregivers. In this selection, more general aspects like patients' major denutrition must be considered before proposing such a procedure as it might be the cause of longer reconditioning, delay in ventilator weaning or even weaning failure (5). Moreover, the absence of any diaphragmatic contraction during the tests, even in case of a functional nerve, is evidence of a major irreversible

amyotrophy, contraindicating implantation of stimulation devices regardless of the type (5).

For patients with CHS, even fewer cases are reported in the literature, calling for extreme caution regarding the indications and the choice of stimulation mode. The few reported cases of implantation with IT-DP showed a benefit of the technique for ventilator independence. Indeed, while ventilator dependency mainly concerns nighttime, deterioration is often observed with adolescence, resulting into a poorer daytime breathing. This more permanent dependency on MV can then be improved with phrenic stimulation.

To date, IP-DP is not recommended in ALS patients with respiratory failure because the recently published multicentre randomised study shows no clinical improvement and a decreasing survival (26).

Nevertheless, several interesting points have previously been shown using IP-DP for these patients. Thus a significant sleep efficiency improvement was shown after DP conditioning in ALS patients with a reduction in the arousal index driving a decrease in awakenings after sleep onset (29). Moreover, the analysis of the electromyogram using intramuscular electrodes implanted in ALS patients for therapeutic goal even allowed detection of breathing control abnormalities in the cohort of patients (30). Isolated central apnea was identified with intact diaphragm motor units but also some instability of central control causing hypoventilation and hypercapnia. Cases of unilateral abnormalities arising from control centres in the brainstem also showed a more complex process in addition to the diaphragm denervation. Some results in patients suggested that IP-DP may also improve automatic respiratory control. All those results were interesting and promising but the only randomized control study definitively stopped the use of IP-DP in ALS patients because of the increasing risk of death in association with usual cares (26). Besides the indications validated by strong results with hindsight, like in cases of SCI or central hypoventilation, recent tests have assessed the interest of IP-DP in unilateral or bilateral peripheral dysfunctions (11). In his recent series, Onders collected bilateral or unilateral dysfunctions in extremely heterogeneous situations like the peroperative phrenic nerve reversible crush procedure, Charcot-Marie-tooth disease, spinal muscle atrophy syndrome. Given these first results of limited and inhomogeneous cohorts, such indications for implantation seem impossible to be validated now.

To date, there is no consensus concerning the date of implantation and evidence about an ideal time for implanting the stimulation devices. In fact, proposing implantation very soon after injury is probably not recommended because spontaneous recovery of breathing may occur. In that case, implanting a stimulator when a patient requires only temporary MV cannot be considered a reasonable indication. In fact, implanting such a device has a financial cost, and it is a surgical procedure done under general anaesthesia with a potential risk of phrenic nerve injury, even with an implantation via laparoscopic approach. Indeed, inserting hook electrodes in the muscle close to the phrenic nerve ending often causes a hematoma in the neighbouring structures and it may also affect one or several nerve endings arising from the phrenic nerve itself. The strategy that aims at reducing the period before implantation for SCI patients represents, in our view, a divergence that cannot be justified to date, even if the laparoscopic approach is less invasive and has a lower cost, 38% discount compared to the radiofrequency system. If this mode of intervention in the very short term had to be considered a prospective randomized study should be anticipated to validate the legitimacy of the procedure. To date, no study can validate this strategy.

In the multicentric study by Posluszny, the largest cohort of IP-DP for SCI with early implantation, the mean time was 40 days after traumatism, which means that some patients were implanted in the days following the accident (21). It was normal for the delay of MV weaning to be short because the phrenic nerves and diaphragm were immediately functional. It is indeed surprising that two patients had 3 months of reconditioning before weaning. Maybe some lung or pleural diseases occurred after traumatism rather than diaphragm problems, complicating weaning. The major risk due to this short delay is to implant patients with a potential unstable neurological state and then to perform excessive and unnecessary implantations on patients because of spontaneous breathing recovery. So Pacing removal in almost half the cases (44.4% of full weaned patients) can though raise the question whether some implantations are well indicated or not. The essential point that is missing in the article is the actual duration of pacing as the only mode of ventilation, given that the patients had been implanted at a very early stage. Is it legitimate to propose such a surgical procedure, even when described as minimally invasive, for mechanical ventilator dependency that proved to be temporary in almost half the cases? In these patients, isn't IP-DP removal risk taking with local complications such as local infection, hematomas, or traumatism of phrenic nerve ending? In such a situation, it would be prejudicial to

have a definitive phrenic paralysis whereas the indication was still marginal in a patient temporarily dependent on positive pressure ventilation. This early implantation was justified based on the amyotrophy that can occur soon after diaphragmatic contractions have stopped after trauma (31). Intensive care specialists are well aware of this situation of neuropathy and muscle loss while providing the patients with more or less prolonged ventilation. Besides, a deliberate early implantation as a bridge for recovery of spontaneous breathing to avoid amyotrophy, in our view, is not risk free for the patients. According to our experience, we have always waited for neurological stabilisation to avoid any unnecessary implantation, or any undue risk taking for the patient. On the contrary, the patients for whom the stimulation tests showed a lack of initial conduction were all retested 6 months and 1 year after the initial assessment. In some cases, the recovery of phrenic nerve conduction without recovery of spontaneous breathing led us to perform a deferred implantation in the patients, with success. Only a randomised study would allow us to clarify whether it is interesting to perform an early implanting in SCI patients, organising larger cohorts and randomising the medical care. Identifying whether the lesions stopping ventilation are reversible or not is a key element in medical care.

Surgical technique and postoperative complications

One of the criticisms against IT-DP is that it still requires the manipulation of the phrenic nerves and is technically quite challenging. It is true that this technique requires a real competence in thoracic surgery but done by expert thoracic surgeons, the risk of nerve injury is almost inexistent. Since the first experiences reported by Glenn showing 4.9% irreversible injury, this rate has come down to 0 in the recent series (5-7,14).

However, the decision to simplify the diaphragmatic electrode implantation method led to propose a laparoscopic implantation. The hook placement inside the diaphragmatic muscle, after mapping, requires a usual laparoscopic technique. No incidental displacement of electrodes has been reported up to now but that cannot be certified in the absence of a very precise duration for the follow up after implantation (24). Yet, this surgical technique is very simple because direct dissection of the phrenic nerve is not necessary, but the risk of injury of a phrenic nerve ending can be questioned, as it is a blind insertion of the hook. Another expected complication was an infection of the device given the simple transparietal crossing of the cable connecting the electrode to the internal device. The only reported case did not require an equipment removal and was solved by treating with antibiotherapy. To reduce the invasiveness of mini-thoracotomy, video assistance has been developed. It is what we have done since the beginning combining safety, efficiency and minimally invasive approach. An endoscopic approach with robotic assistance has also been used in six adult patients, without complications (32). Sometimes, a replacement of the internal device is required because of failure without the possibility of defining the exact cause of failure (14). Sometimes only a change of subcutaneous receiver is required, which happened to us once (recent not published). We could also successfully reimplant an external device after a trauma. Our team reported cases of bilateral shoulder pains after IP-DP that had never been observed using IT-DP (33). Five patients implanted with IT-DP (four CHS and one post-neurosurgery) were compared with four patients implanted with IP-DP (three post-neurosurgery and one CHS) after similar preimplantation procedures. The follow-up procedures were similar and standardised in the same centre. The shoulder pains were so intense that reduction of the stimulation thresholds was required in all cases. This situation led to an interruption of stimulation in half of the painful cases with persistent hypoventilation. The possible explanation is the high level of stimulation required for IP-DP (5 to 25 mA) to obtain a diaphragm contraction. This level is higher than for IT-DP (0.5 to 2.2 mA). The difference is due to the distance between the nerve and the electrode which is higher in IP-DP than in IT-DP, where the electrodes are directly in contact with the nerve. Because the phrenic nerve is a mixed nerve, using higher stimulation intensity is sufficient to depolarise C-fibres in the vicinity of the electrodes and thus induce pain. This aspect is important when choosing the technique to implant DP.

Interests and limits of each technique

The main advantages of IP-DP are an easy laparoscopic approach, no selective intubation and no phrenic nerve dissection. However, placing a hook inside the diaphragm muscle near the ending part of the phrenic nerve may potentially lead to local hematoma causing nerve dysfunction. Without a direct view of the nerve, any surgeon would have problem to avoid it. Moreover as previously described the stimulation thresholds by IP-DP are higher than with DPNP because of the site of insertion of electrodes is not in direct contact with the nerve. Finally, the rustic character of the device in IP-DP, with the wire

going through the abdominal wall, is the main critical point because local infectious complications main occur. This aspect may improve in the future with the development of a fully implantable device. Then, there may be an increase in the cost of the new NeurX model, whereas the current price is a strong commercial argument.

Regarding IT-DP, it is a more invasive procedure compared to laparoscopy but a more sophisticated device is implanted, requiring a short dissection of the phrenic nerve, easily performed by a thoracic surgeon through small anterior thoracotomy. In the literature it is often described as a risky procedure, but in experienced centers it is now a safe procedure (5,7,14,34). By this intrapleural approach and the possibility of a complete view of the phrenic nerve, local observations will determine the best implantation site for each patient. This quadripolar device, stimulating different points of the nerve, probably prevents the nervous tiredness and suffering. Nowadays this technique remains extremely safe in expert hands and the intrapleural approach allows a possible simultaneous lung or mediastinal procedure. Thus, our team reported a successful concomitant lobectomy for post-infectious destroyed lobe and IT-DP (35). Theoretically, in case of major diaphragmatic eventration, the intrapleural approach could also allow a concomitant partial diaphragm plication to improve the diaphragmatic contraction strength during the stimulation.

The first implantation of IT-DP under robotic assistance using the Da Vinci robotic system (Intuitive Surgical, Mountain View, Calif) was reported by Morgan in 2003 (32). Bipolar electrodes were used (Avery Laboratories, Dobelle Institute, Commack, New York, NY, USA) in six patients for several indications: two tetraplegia, two CHS and two intractable hiccups. There were no intraoperative complications or conversions to open surgery and all stimulators were functional. It was considered as a less invasive operative approach but no long-term follow-up results were reported.

To sum up, IT-DP is the technique with more hindsight and a homogeneous cohort compared with IP-DP. The lack of control groups in all these studies makes it difficult to strictly validate the techniques (IP-DP and IT-DP). However, ventilator-dependent patients' opinion is interesting. When weaning from mechanical ventilator is achieved, their general condition and mobility improve. Different senses are also improved: olfaction (36), taste and hearing because there is no more ventilator noise. It is also considered to decrease healthcare cost, thanks to earlier home discharge, reduced infection pulmonary complications and potentially increases survival (7).

For the future: is tracheostomy removal possible?

The synchronisation between activation of upper airway abductor muscles and the active contraction of the diaphragm is required to assume correct breathing. Theoretically if there is a correct synchronisation, a tracheostomy closure is possible after IP-DP or IT-DP and occasionally done in some centres in the USA mainly for congenital CHS (37). Apart from the mechanical risk of upper airway obstruction, other safety considerations must be anticipated when tracheostomy closure is proposed in tetraplegic patients or CHS. Indeed, tracheostomy is regularly used for tracheal secretion suctions, or in sudden reinstatement of the MV for stimulator failure or in vital emergency like severe pneumonia. For all these reasons, some teams prefer to maintain a permanent closed safety tracheostomy. In the old series by Glenn, tracheostomy was closed in 19.39% of patients. It was necessary to reopen it in 70% of them because of high incidence of required aspiration (6).

In a recent study concerning 18 Congenital CHS patients, IP-DP was only used during sleep (37). Among the 15 patients with tracheostomy prior to IP-DP, 11 (73%) were decannulated and kept that way on a long follow up (CCC). Two patients, one with obesity and one with upper airway obstruction, could not have IP-DP without tracheostomy.

In our team, for safety reasons, we have always preferred to maintain tracheostomy, generally closed during the day. We acknowledge that our attitude may correspond to some amount of "safety over-kill", but it did not prevent benefits. Future studies are needed to determine the actual best management of this issue. Of note, the maintenance of a tracheostomy should not have a major impact on the cost-effectiveness of the technique, which is mostly driven by home discharge and infection risks.

What to do in case of concomitant phrenic nerve injury?

Currently, no DP is indicated but some trials of phrenic nerve re-innervation were reported with interesting results. However, an intercostal transfer to supply the phrenic nerve is technically difficult but feasible, as shown in the short series reported by Krieger (38). A response to electrical stimulation was detected in a mean time of 9 months allowing successful DP.

In 2015, Kaufman *et al*., reported a series of 14 consecutive patients with concomitant cervical SCI and bilateral phrenic nerve lesions (39). A nerve transfer in addition to DP was done in all patients. Recovery of efficient diaphragm contraction was observed in 13 of 14 patients (93%) allowing 25% of weaning from MV.

Finally, a totally implantable stimulator similar to cardiac pacemakers would be the ideal solution to avoid the local complications and possibility of disconnection of external device. It does not exist yet but we are waiting for future innovation in this area despite the small number of concerned patients.

Personal opinion

Since 1997, we have performed about 30 DPNP implantations and the 20 first ones have been published (5). Given our specialisation in thoracic surgery, all implantations have been done through pleural approach always using quadripolar stimulation, applying the same technique carried out by a single surgeon. Thanks to the development of minimally invasive surgical techniques, like video-assisted minithoracotomy (4 cm), all those procedures have been performed in a very safe way without any surgical complications particularly phrenic nerve injury. The cohort is quite homogeneous as it includes only patients under MV, and all patients have been examined at least once with cervical and transcranial stimulation tests. In addition to these tests, a minimum delay of 1 year has always been required before implantation in order not to implant patients who can recover spontaneous breathing. The indication of implantation has always been decided by a multidisciplinary staff and rigorous long-term follow-up has been possible, sometimes up to 10 years. Improving quality of life in patients weaned from ventilator, whether tetraplegic or not, has constantly been observed for them and their caregivers. The equipment is regularly maintained by annual or biannual control of stimulation quality and thresholds, guaranteeing safety for the patients whose breathing depends on that equipment. Tracheostomy removal was not proposed to our patients. This was driven by safety considerations. In fact, in the event of an acute problem, it is easy to reventilate using tracheostomy. This may happen in case of failure of the external device requiring a mere change of antennas or cable, or in case of transitory hypoxemia due to respiratory infection requiring temporary MV with regular bronchial suction. Moreover, the risk of obstructive apnoea owing to the lack of upper airway dilators–diaphragm synchronization may also require reventilation.

We have recently reimplanted a patient in whom DP was causing pains in the shoulders that made it impossible for him to use his stimulator every day. This patient has been reimplanted using DPNP in thoracic position. The pains have disappeared and the patient can now use his device "full time". We think that precise implantation of the electrodes under visual control at middle mediastinum level is a safe technique when performed in a thoracic surgery environment with an important case volume. This technique is not invasive, in the "critical sense" of the term, as the nerve release is controlled and limited to 2 cm, with precise electrode positioning. Moreover, the thoracic environment allows a better management of postoperative morbidity for these patients as it is not surgical but pneumological. In fact, tracheotomised patients under MV often have bronchial congestion and pneumonias which can easily be taken care of in respiratory intensive care units. Our team has recently been able to compare two groups of patients implanted either by IP-DP or by IT-DP.

Conclusions

Diaphragm stimulation is a technique that has been used for about 40 years, which gives excellent results in rigorously selected patients. The main benefit lies on the restored "physiological" breathing possible with the diaphragm contraction allowing MV weaning. In addition to the reference technique, IT-DP, of which the results have been known for a long time, an easier technique, IP-DP, was developed. It led to broadened indications not all validated to date. Indeed, it was tested for ALS patients, for whom the fatal evolution is sure in the short term, in order to postpone NIV or MV. The indication in this disease is still very controversial because it has been accepted in the USA as compassionate authorisation, but recently stopped in Europe due to an increasing mortality.

Trials of early implantation in patients with SCI have given some results impossible to validate without a rigorous scientific study. Patients with peripheral diaphragmatic dysfunctions have also been proposed for IP-DP, but again, no scientific conclusions can be established given the significant limits of the study. To define the exact role of these techniques of stimulation for all these new potential indications, future studies are required. Selected patients with tetraplegia or CHS still represent excellent validated indications for DP in order to improve breathing comfort and everyday life for these patients.

Acknowledgements

We are grateful to Valérie Mège-Lin for her help with English style and grammar.

Footnote

Conflicts of Interest: The authors and Valérie Mège-Lin have no conflicts of interest to declare.

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Cite this article as: Le Pimpec-Barthes F, Legras A, Arame A, Pricopi C, Boucherie JC, Badia A, Morelot Panzini C. Diaphragm pacing: the state of the art. J Thorac Dis 2016;8(Suppl 4):S376-S386. doi: 10.21037/jtd.2016.03.97

