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Clinical study

Phrenic nerve stimulation experiences. A single centre, controlled, prospective study

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ABSTRACT

Patients with central apnoea may use electro ventilation, provided their phrenic nerves and diaphragm muscles are normal. A tendency towards better survival has been found, and both an improved quality of life and facilitated nursing have been claimed with electro ventilation compared to mechanical ventilation. The high investment for the device may form a hurdle for fund providers like our hospital administration board. We, therefore, from our first patient onwards, collected clinically meaningful data in a special register of all patients using electro ventilation and their controls on mechanical ventilation. Since 1988 172 patients left our institution dependent on a respiratory device. Of these, all 48 patients with preserved phrenic nerves chose phrenic nerve stimulation. A patient on mechanical ventilation who agreed to participate was chosen as a control ($n = 44$). All patients were seen at least once a year. 90 patients suffered high tetraplegia, and 2 suffered central apnoea for other reasons. There is a tendency towards better survival, and there is a lower frequency of decubital ulcers (0.02) and respiratory tract infections (p0.000) with electro than with mechanical ventilation. The frequency of respiratory infections turned out to be a better measure of the quality of respiratory care than survival. The resulting decrease in the need for airway nursing, and the reduced incidence of respiratory infections repaid the high investment in electro ventilation within one year in our setting. Informed patients prefer electro to mechanical ventilation; fund providers might also agree with this preference.

1. Introduction

In cases of a lost connection between the respiratory centre and the peripheral phrenic nerves, i.e., high tetraplegia (C2-tetraplegia) due to cervical spinal cord injury (SCI), or a failing centre, i.e., brain stem lesions or central hypoventilation syndrome (CHS), rhythmic electrical stimulation of the phrenic nerves can compensate for the failing functions. Normal phrenic nerves and diaphragm muscles are prerequisites for successful electro ventilation (EV) [1].

EV, today provided as diaphragm pacing (DP) [1] or phrenic nerve stimulation (PNS) [2], provides an artificial respiratory centre. The mechanical energy for ventilation with EV is provided by the patient's diaphragm. The huge energy supply for mechanical ventilation (MV), the ventilating tubes and filters, and even the almost invariably used tracheostomy tube may become unnecessary. The nose and larynx then become the natural filters and airways once again.

During implantation electrodes are attached to the nerves, preferably aside the upper mediastinum [3], a location without movement between the electrodes and the nerves. The small electrical fields of the PNS four-pole electrode [4] do not interfere with other devices or excitable tissues.

In contrast to cardiac pacing, each contraction of the diaphragm necessitates a series of at least 200 pulses instead of one pace [2]. Therefore, the inductive feed of electric current to the implanted stimulator is still necessary, which was originally intended to avoid bulky batteries and possible pain, burns, the dislocation of surface electrodes, and skin penetrating wires [5].

To avoid electrically induced fatigue [6] all participating muscle

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fibres have to be transformed into fatigue-free fibres [7] during a conditioning period [8].

The type of a muscle fibre depends on the firing frequency of its axon. Slow twitch fatigue resistant (type 1) fibres receive frequencies below 8 Hz [7]. Experimentally, the fibre type can be changed using continuous stimulation with an appropriate frequency [7]. Patients cannot tolerate continuous trembling of their diaphragm. Lowering the stimulation frequency of the phrenic nerve from 40 Hz – the diaphragm fusion frequency – in weekly steps of 2 Hz to below 8 Hz is tolerable; with diaphragm pacing (DP) due to its unipolar stimulation conditioning takes five months [8].

Using 4-pole sequential stimulation, changing the frequency of the whole nerve to 36 Hz means stimulating a single pole and its muscle fibres with 8 Hz. Compared to DP, the conditioning period with PNS shrinks remarkably [9].

The superiority of diaphragm pacing over MV was self-evident for the pioneers [1]. However, the high investment and necessary secure social environment seemed to restrict its use to privileged patients. To convince the administration of our insurance-company-run trauma hospital, controlled data were necessary. Therefore, we recorded clinical meaningful data of all patients who used PNS and their controls on MV in a special register. Since 1996 the register is kept by SH.

We started to use the 4-pole sequential phrenic nerve stimulator [2] (PNS) (Atrostim PNS, Atrotech Ltd., Tampere, Finland. https://www.Atrotech.com) in 1988 for patients with traumatic C2-tetraplegia. In 1996 the regulations changed, also permitting the care of non-traumatic high tetraplegia patients. Today, our department for respiratory care applies PNS to all kinds of central apnoea.

2. Material and methods

2.1. Inclusion criteria

We included all suitable patients who wanted a PNS instead of MV. Suitable patients were those with normal phrenic nerves, i.e. a latency below 0.9 ms [10] and a descent of the diaphragm of at least 4 cm at supramaximal stimulation of the phrenic nerve in the neck [1]. We chose as a control a patient on MV as close as possible timely to the patient on PNS. Exclusion criteria were, as established by Glenn et al. [1], neuromuscular diseases, malfunction of the phrenic nerves, and insufficient muscle mass.

2.2. Implantation

The thorax is opened aside the sternum through the second, third or fourth intercostal space; skin incision is 8–10 cm. The electrodes are attached to the phrenic nerves aside the upper mediastinum [1]. To avoid sutures near the nerve we created a snuggly fitting pouch behind the nerve for the back stripe [11] since 1998 and used tissue glue (TachoSil®) since 2014 to affix the front stripe of the two-stripe, four pole electrode [4]. We place the receivers (stimulators) subcutaneously on to the front of the ribcage or abdomen. Subcutaneously tunnelled wires connect the electrodes and receivers.

2.3. Ventilation

Stimulation parameters are set to cause tidal volumes of 700 to 1300 ml at respiratory frequencies of 8–12/min. All participating patients are seen once a year.

2.4. Statistics

Due to the skew distributions, the values of continuous variables are expressed as median with quartiles or range. The differences between devices were tested by the Mann–Whitney test. The differences between time periods were tested by the Wilcoxon signed-rank test. The categorical variables were tested by the chi-square test or Fisher's exact test. Other tests are presented with the appropriate results. Statistical analyses were performed using SPSS 26 (Armonk, NY: IBM Corp). A p-value less than 0.05 was considered statistically significant.

3. Results

By 31 March 2019, our department had treated 172 respiratory device dependent (RDD) patients. During the previous 31 years PNS was implanted in 48 patients; 30 patients used PNS "full-time long-term" [12], two of them because of central apnoea. 18 used PNS intermittently; 16 of them used MV during sleep "for safety reasons" (see Discussion). Two had recovered spontaneous respiration during daytime but still needed PNS during sleep. The latter two were 9 years of age at insult; their survival is six years today. 44 patients on continuous MV had been recruited as controls. Of the patients on PNS, 36 continued to use a tracheal cannula (speaking valve), nine had their tracheostoma plugged, and three had the tracheostoma closed. All patients on MV used speaking valves. No patient stopped PNS voluntarily. Table 1 depicts the mean values of groups MV and PNS.

75 of our 92 study patients suffer from traumatic, 15 from non-traumatic high tetraplegia, and two from a failing respiratory centre. Traffic and work accidents, nine cases each, were the reason for traumatic SCI; all kinds of leisure activities were responsible for the remainder. The aetiologies of non-traumatic SCI were inflammation in nine cases, medullar infarction and spinal tumour, two cases each, one case of spinal stenosis and one of spinal degeneration, and two cases of spinal surgery complications. Central apnoea was congenital in one case (cCHS) and acquired due to brain stem surgery in a second case (aCHS).

The differences between MV and PNS for gender, type of insult, and state and location after stay at our institution are insignificant. The differences are significant for age at insult, first year mortality, and the duration of stay at our hospital.

A complete SCI, American Spinal Injury Association Impairment Scale (ASAI) Type A, was present in 76%; distribution of scale types was equal in groups MV and PNS and did not influence the duration of stay at

Table 1
Demographics.

	PNS n = 48		MV n = 44		p-value
	n/ median	%/ range	n/ median	%/ range	
Gender					
Female	17	35.4	10	22.7	
Male	31	64.6	34	77.3	
Age at Insult (years)	21	0 – 70.6	27	0 – 64.9	0.001
Type of Insult					
tSCI	40	87.5	33	75.0	
ntSCI	6	8.3	11	25.0	
CHS	2	4.2			
Stay at Inst. (months)	6.5	0–47.2	9.5	0.07–23.73	0.05
for PNS only (days) n = 26	26.3	0–84			
Insult-Implantation (yrs)	1.47	0.38–15	n.a.	n.a.	
First year Mortality	2	4.4	5	11.4	0.001
Location after Rehab.					
Nursery	3	6.3	1	2.3	
Home	45	93.7	43	97.7	
State after rehabilitation					
retired	40	83.3	41	93.2	
student	8	16.6	3	4.5	

Explanations: tSCI: traumatic spinal cord injury; ntSCI: non-traumatic spinal cord injury. CHS: central hypoventilation syndrome; Inst.: Institution.

our hospital.

With increasing age at insult, the duration of stay at our hospital increases, p 0.05 (Spearman's rho). Age at insult increases from motor lesion below C0 to below C3, p 0.009. Increasing age at insult correlated with decreasing survival, p 0.009. Age at insult had no influence on ASIA type.

We found significant differences between MV and PNS for Quality of Speech (personal score, [13], p 0.001), but not for spasticity (Ashworth score). Frequencies differed for decubital ulcers (PNS 5, MV 18), p 0.009, and urological complications (PNS 13, MV 27), p 0.037. No significances were found for gastrointestinal complications (PNS 6, MV 8).

3.1. Respiratory tract infections (RI)

We recorded RI when the patient presented with fever, leucocytosis, increased production of secretions and the doctor in charge diagnosed the reason to be RI with antimicrobic therapy being necessary. We present the incidence of RI after discharge as RI per 100 days (RI/100d). 0.274 equals one RI per year. The difference between MV and PNS is highly significant, p less than 0.000, see Table 2.

3.2. Survival and mortality reasons

For the whole study population, survival is 92.39% after 1 year, 63% after 10 years, and 60.9% after twenty years. A difference in favour of PNS is visible, see Fig. 1.

37 patients (40.2%) died during the observation period. First-year mortality is 7.6%, two cases with PNS and five with MV; for the following 32 years there are 30 cases, i.e., 1.14 cases (1.24%) per year.

The leading cause was pneumonia (10 in the MV group, 4 in the PNS/MV group and 1 in the PNS group 24 h). The other reasons were nonspecific SCI-induced (3 MV), intestinal occlusion (2 MV, 2 PNS), decubital sepsis (1 MV, 1 PNS), urosepsis (MV), tumour, and myelitis (PNS). Heart failure caused 4 fatalities in the PNS group and 1 in the MV group, suicide 1 in MV and 2 in PNS, and seizures (PNS) and bleeding (PNS) one case each.

3.3. Conditioning

Our average duration of conditioning was shorter than two months (50.1 (30.7) days).

3.4. Complications

We registered 15 complications in 13 patients due to the implantation of 48 bilateral PNS. Within three weeks from implantation, two failing electrode sites and five times a haemo- or pneumothorax needed revision.

Between seven weeks and five years after implantation, three electrode sites needed revision, one of them three times; the latter nerve was lost. One dislocated stimulator and one failing stimulator caused surgical intervention.

47% of all our patients suffered from granulomas in the tracheostoma; 22% needed surgical intervention, one patient because of acquired tracheomalacia.

Table 2
Respiratory Infections (RI/100d) after discharge.

	n	RI/100d	SD	range
MV	44	0.2	0.15	0–0.78
PNS 24 h	30	0.07	0.17	0–0.9
PNS intermittently	18	0.08	0.08	0–0.25

Explanations: MV: Mechanical Ventilation; PNS 24 h: Full-time use of phrenic nerve stimulation; PNS intermittently: 14 used MV during sleep; four had recovered spontaneous respiration at daytime but needed PNS during sleep. MV vs. PNS24h and MV vs. PNS intermittently: P = 0.000; PNS 24H vs. PNS intermittently: ns (Mann-Whitney *U* test).

3.5. Costs

The costs for treatment mainly result from the salaries paid to five persons, the single use equipment for airway nursing, the treatment of respiratory infections, and the amortisation of the respiratory device. In hospital, four persons' salaries are necessary with PNS, but salaries for five are required with MV [14,15]. Out of hospital, one nurse and four helpers are recommended for PNS, two nurses and three helpers with MV [14,15]. Salaries are higher in hospital than out of hospital, a nurse costs about 5,250/month, a helper 1,750/month [16]. Single use equipment is yearly about 5,000€ for PNS and 15,000€ for MV [16]. The treatment of one RI costs 19,600€ [17]. We used German market prices for the respiratory devices, 75,000€ for PNS and 12,000€ for MV, amortising within 14 (PNS) or 11 (MV) years (mean survival). Of the first year, in hospital stay (rehabilitation) with PNS is 6.5 months, with MV 9.5 months.

First year costs are 231,302€ with PNS and 343,924€ with MV; the difference is 112,621€. Investment for PNS is 75,000€, for MV 12,000€; the difference is 63,000€. In our setting, the higher investment with PNS is repaid within the first year.

4. Discussion

The first study comparing MV to EV in spinal cord injured (SCI) patients proposed a trend towards longer survival with EV compared to MV [18]. A difference in survival was sought in successive studies as a measure of the quality of different modes of artificial ventilation in SCI centres [13,19–21], and was verified once [20]. In quantifying the quality of respiratory care, the frequency of RI is obviously more appropriate than survival [13].

There are more than 420 publications on electro ventilation (EV) [22], but few studies compare EV to MV. Controls have been all patients on MV of the same study period [18–21] or the next patient on MV [13]. Randomisation is impossible because informed patients prefer EV [13].

When starting our register, quality of life (QOL) of tetraplegic patients was below the scores for QOL [23]. All recent scores ask the patient's opinion. Therefore, we cannot report on QOL. High tetraplegic patients on MV receive three points, those on PNS 11 points on the independence score for spinal cord injured [24]. Restored olfaction with PNS improved QOL [25]. Well-informed patients showed a preference for PNS over MV [13], which may be taken as proof of a higher QOL with PNS.

4.1. Delay

The large variation in reasons for the delay from insult to implantation is due to the different approaches to implantation. A long delay, however, is no hurdle to the use of PNS. The structure of an unused healthy moto unit remains, but muscle mass is lost [7]. Thus, the longer the delay, the longer the conditioning period to restore the necessary muscle mass.

Patients using MV are significantly older than those using PNS; this has also been found previously [13,18–21]. Additionally, we found a decreasing level of motor lesion correlating with increasing age, which means, with increasing age at insult, the risk of the destruction of the motor cells of the phrenic nerves is increased. We speculate at different trauma mechanisms in different age groups.

When starting 33 years ago we decided to ask as a control a patient on MV after the implantation of a PNS. Therefore, some of the controls stayed at our hospital for some days only for their evaluation as candidates for PNS, or for their yearly check-up because of SCI. In the PNS group, short stays are caused by patients who come from outside our hospital area for implantation only.

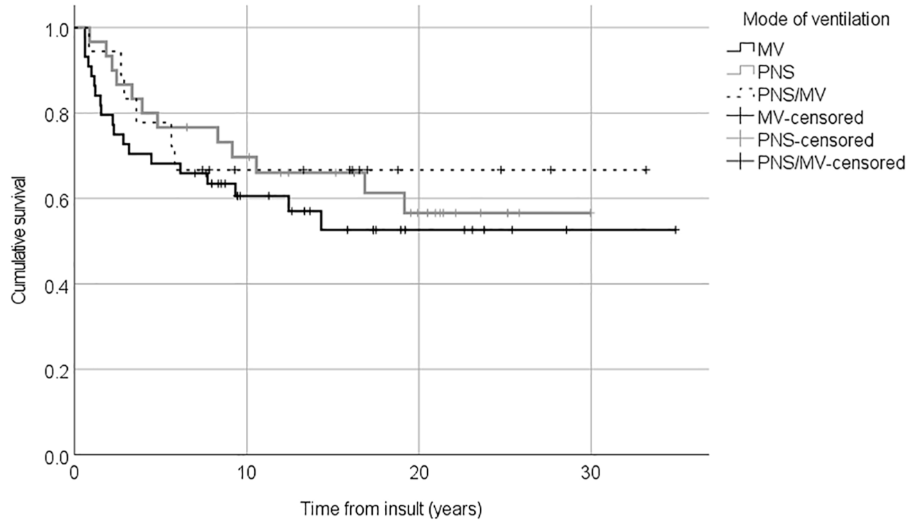

Fig. 1. Survival from Date of Insult to Today or Death. Explanations. mode vent: Mode of ventilation; MV: mechanical ventilation; PNS: Phrenic nerve stimulation 24 h; PNS/MV: PNS 18 h, MV 8 h (sleep). Log Rank (Mantel-Cox) 0.962.

Undue long stays in both groups, but especially in the PNS group, were caused by the refusal of the admitting institution to re-accept the rehabilitated patient because of the difficulty to comply with the necessary higher level of care; the appropriate regulations were changed in 1996. Such a wide range in the length of stay is similar in similarly working institutions [21].

Younger patients continued studying after their re-socialisation and regained mobility; seven of them belonged to PNS, two to MV. Three started to work after their successful studies.

4.2. Respiratory Tract Infections (RI)

We report about RI after discharge only. The significant difference between MV and PNS found in 2008 [13] remained. Our result of 0.2 RI/100 days with MV is similar to that of 0.174/100 days of ventilator-associated pneumonias in 100 long-term mechanically ventilated SCI patients [26].

Long-term MV involves the need for a tracheostoma, tracheal suction, and ventilator tube manipulation: thus, there are infection port and infection-prone manipulations. This may explain the high frequency of RI with MV. Patients on PNS/MV mostly used MV during sleep only, namely when being socially isolated, which may explain the negligible difference of RI between PNS 24 h and PNS intermittently, see Table 2.

Patients on PNS may produce a weak cough using their accessory respiratory muscles in the neck to cause a breath [27] (neck breathing) on top of the sigh of the stimulator. This ability depends on a closed tracheostoma, mostly closed using a tracheal button or, rarely, by omission. Most of our patients kept the tracheostoma for safety reasons and use an expelling machine. Both coughing methods make airway suctioning unnecessary for long periods.

The first comparative study proposed a trend to longer survival with EV compared to MV [18]. A difference in survival, a familiar measure in the field of SCI rehabilitation, was sought in successive studies as a measure of the quality of different modes of artificial ventilation [13,18–21] and was verified once [20]. A diminished need for airway single use equipment and nursing was stated but was not really quantified [13,19]. The frequency of RI is obviously more appropriate than survival in quantifying the differences between the modes of ventilation.

4.3. Survival and mortality reasons

A better survival with EV compared to MV had been surmised in the first controlled study, but patients on EV had been significantly younger than those on MV [18]. Similar tendencies have been published thereafter [13,18–21]. Statistical significance in favour of EV has only once been published [20]. We mention once again a tendency in favour of PNS.

Our total mortality is 40.2% (18 MV, 19 PNS). In comparable cohorts, total mortality was between 22.7% of 22 (4MV,1EV) [19] and 46.8% of 126 (41MV, 6EV) [20].

Pneumonia is the leading cause of death in patients with cervical SCI. RI is the reason for death in 15 cases (40%) of all our deceased, 14 appearing in patients using MV. In comparable mixed groups, RI is the reason for death in 66% [19] and 80% [21].

The setting of the stimulation frequency of the stimulator is restricted to authorised personnel. Changes cannot happen inadvertently. Manipulation by unqualified personnel in two cases led to "over pacing", resulting in permanent muscle failure. This forced to use MV again with a subsequent steep loss of QOL. The two patients subsequently committed suicide. One case of fatal over pacing has been published previously [28].

Watt et al. double checked the death certificates of their patients and found two wrongly recorded fatal disconnections with MV. This would mean one case per 2810 man-ventilator years [21]. The estimated number of unreported cases in anaesthesia and ICU is of concern and may be higher with home ventilation [29]. No fatal disconnection or failure of an electro ventilator has been reported so far.

The intermittent use of MV and PNS is strongly recommended in growing patients to avoid kyphosis [30]. Only 10 of our 22 patients younger than 25 years of age kept to that rule. Fortunately, no kyphosis has been diagnosed so far.

In adult patients, the intermittent use of PNS and MV "in most cases is due to ignorance" [31] about three facts:

- With PNS, there is no "electrically induced diaphragm fatigue" [8];
- a pneumatic device (MV) is not safer than an electronic device (EV);
- a tracheostoma is not essential to avoid possible obstructive sleep apnoea.

Fatigue was eliminated from EV in 1984 [8], see Conditioning, below.

Another reason to use MV instead of EV during sleep is for "safety reasons"; four fatal disconnections happened during such use [12,32]. A pneumatic ventilator full of moving parts and connected to the patient via continuously moving tubes is generally more prone to failure than an electronic device with wire connections attached to the skin by adhesives.

The suggestion to keep the tracheostoma when using EV because of possibly arising obstructive sleep apnoea (OSA) is from 1978 [33]. The tracheostoma can be omitted in patients with CHS without OSA [34]. Today, OSA in patients on EV would be primarily treated by CPAP.

4.4. Conditioning

The human diaphragm contains about 40% of fatigue resistant fibres. Their low force suffices for life-long breathing during sleep. At 20 Hz stimulation, these fibres fatigue [6,7]. For full-time long-term EV all fibres within the stimulation field must be changed into fatigue-resistant fibres to compensate for their low force [7].

Because of the five-months' duration with unipolar stimulation [8], conditioning has been blamed for prolonging rehabilitation. With PNS, due to its four-pole sequential stimulation, a new low fusion frequency of the diaphragm muscle can be reached within two weeks [9]; a longer period of interval training, however, is necessary to restore muscle force. In 38 patients on PNS, conditioning lasted 47.3(19.6) days [20]. Our conditioning took 50.1(30.7) days and even the longest duration (196 days) remained within the average time of stay for rehabilitation.

4.5. Implantation

Glenn carefully explored the optimum approaches to the phrenic nerves [1]. The tissue trauma is almost equal to the cervical and the thoracic approach. In C2-tetraplegia, the neck is the lowest area with skin sensibility and the only moving one. Additionally, nerves close to the phrenic nerves may be stimulated, too. The complication frequency is significantly higher with the cervical approach than with the thoracic approach [3]. The thoracic skin incision is about 10 cm; thus, mini thoracotomy would be the right term for Glenn's thoracic approach. Thoracoscopy has been used for implantation with good results [35,36], but the duration of the procedure increases. With robot-assisted implantation [37] costs increase additionally many-fold [38].

4.6. Complications

Long-term EV depends on the reliability of the electrode nerve interface. Of the possible acute surgical complications like haemo- and pneumothorax and surgical nerve damage, only the latter will impair long-term success. In a multicentre study of more than 400 cases, surgical nerve complications appeared in 7.4% of 265 nerves at risk (NAR) of 165 patients of experienced centres, 4.9% remained damaged. Complications were seen mostly in inexperienced hands and with cuff-type electrodes. "The lowest risk of injury to the nerve existed with the monopolar application in the thorax, in which 2,7% of NAR (2/54) were compromised." [3].

This caused Glenn to re-introduce the easy-to-apply unipolar electrode [3]. Garrido-Garcia et al. reported 8.6% of NAR damaged and 1 (2.9%) lost [32]. Weese-Mayer registered surgical damage in 3.8% of 128 NAR, one nerve (0.8%) was lost [39]. Our percentage is 7.3 of 184 NAR, one nerve (0.5%) was lost.

Late nerve complications are possibly caused by infection, biofilm, scar formation, foreign body reaction, the electrode configuration and/or by the electrode location. The unipolar and the four-pole PNS electrode matrix do not encircle the nerve [3,4]. Late nerve problems are seen more often in the moving neck [3] than in the thorax and more often with nerve-encircling cuff type electrodes than with electrodes allowing the nerve to escape scar pressure [2,3]. We implanted only at the parietal pleura beside the upper mediastinum.

Of 70 NAR in 35 patients, surgical nerve damage appeared and was resolved in 3 (4.3%) NAR. Assumed from the development of the threshold currents, foreign body reaction impaired the nerve-electrode interface in 3 (8.6%) patients. In 2 (5.7%) patients, obviously biofilm on the electrode surfaces caused interface problems when the patients' immune system was impaired (i.e., common cold) [4].

A recent prospective study revealed frequent complications with tracheostomy tube changing in experienced settings [40], which may explain the high frequency of granulomas at the tracheostoma we saw.

4.7. Costs

The diminished need for airway single use equipment and nursing was stated but was not really quantified [13,19]. We now provide sources for salaries [14–16], the treatment of RI, the costs of single use equipment for airway nursing, and the amortisation of respiratory devices [17].

4.8. Strengths and limitations

This is the first prospective study comparing electro ventilation to mechanical ventilation in patients with central apnoea. Like all studies on the ventilation of RDD tetraplegic patients, our study lacks blinding and randomisation. Its statistical power might have been higher if we had included all RDD tetraplegic patients treated at our institution. - Economic conclusions must be adjusted for each setting because prices, regulations and salaries vary.

5. Conclusions

Modern EV, diaphragm pacing, and phrenic nerve stimulation (PNS) provide reliable full-time long-term artificial ventilation for some of the patients suffering central apnoea. With PNS, we found a tendency towards better survival compared to MV. The frequency of decubital ulcers and urological complications appear significantly more with MV than with PNS, proving enhanced mobility and facilitation of nursing with PNS. Patients prefer PNS and refuse randomisation, which may be taken as their opinion of the improved quality of life with PNS. The frequency of respiratory infections differed highly significantly in favour of PNS. Large savings are subsequently obvious.

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Author contributions

GB initiated the study (1987) and wrote the primary draft. SH and RT recruited patients, implanted devices and performed yearly check-ups. SH kept the register and provided data. HH analysed data and performed the statistics. All authors edited the draft. GB wrote the final version, which all authors accepted.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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