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ORIGINAL ARTICLES

Long-term ventilation of patients with Duchenne muscular dystrophy: experiences at the Neuromuscular Centre Ulm

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The various measures used to treat the symptoms of Duchenne muscular dystrophy (DMD), i.e. medication with steroids, early operation on contractures and spine deformities as well as cardiac diagnostics and therapy, should always be accompanied by careful monitoring of the patient's respiratory status. Therapy for respiratory failure, in particular long-term ventilation, is now generally accepted as essential for DMD patients. The provision of assisted ventilation has made a decisive contribution to the quality of life for older patients and the stigma hitherto attached to it as being merely a means of keeping a patient comfortable towards the end of life has now been dispelled. Even outside the hospital, assisted ventilation has become routine. These days it is not uncommon for patients on assisted ventilation to have their life extended by 10 years or more.

Non-invasive ventilation is sufficient if used concomitantly with coughing aids. Before undergoing orthopaedic surgery the patient's respiratory status has to be carefully assessed in order to minimize the risk of perioperative complications. Feeding and swallowing problems may develop if the patient has a scoliosis of the cervical spine region, even if he has had thoraco-lumbar spine surgery. There is still insufficient awareness of this potential problem in relation to respiratory care.

Interdisciplinary collaboration between hospitals, general practitioners, muscle and respiratory centres, as well as advocacies and self-help groups is vital. The administration of aids to support DMD patients is now facilitated by guidelines drawn up by several centres of excellence. Here we mainly describe the historic development of respiratory care at the Ulm Neuromuscular Centre.

Key words: Duchenne muscular dystrophy, respiratory failure, non-invasive ventilation, increased survival

Historical review

Immediately after the Rehabilitationskrankenhaus (rehabilitation hospital) Ulm (RKU) had opened in 1984 comprising clinics for orthopaedic surgery (including a centre for spinal cord injuries), neurology and anaesthesia, we were confronted with patients having severe chronic insufficiency of breathing. Within a few years we had to treat three children at the age of 3-4 years with high cervical lesions of the spinal cord in our intensive care unit. We wanted to give them – by means of assisted ventilation – the opportunity to enjoy a long-term, dignified quality of life at home. This contrasted with their expectations in other German hospitals where such patients were generally provided with a tracheostomy and sometimes kept for years in the intensive care unit with no prospect of returning home.

There were, however, a few exceptional centres in Germany, such as the Pfennigparade (March of Dimes) foundation in Munich, where Dr Angelika Bockelbrink had a special intensive care unit for children with tetraplegia or muscle disease and who were dependent on assisted ventilation. The foundation also provided housing and classrooms, opening doors for the children to return to a world with their able-bodied peers. We visited the institution and were convinced that life for a patient with a spinal lesion high up can still be worth living as long as there are adequate facilities to cater for their needs, improving their long-term prospects (1).

At that time invasive ventilation by means of a tracheostomy was state-of-the-art. Ventilation was performed using the Lifecare respirator PLV 100®. This device had few individual adjustments: there was just a presetting for respiratory volume by tidal volume and frequency, and a trigger. Only a few alarms were provided, monitoring such things as air pressure or battery energy levels. The gadget weighed about 17 kg and needed nothing more than a 220-V outlet. An internal battery would sustain respiration for an hour in the event of a power failure. With appropriate adaptors the gadget could also be used in the car, or on the back of an electric wheelchair, powered by

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Figure 1. A Duchenne patient using the Dräger EV 801® respirator.

the wheelchair's battery. Artificial ventilation could be implemented for children weighing 12 kg or more. For smaller children one had to use leakage valves to reduce the tidal volume. The German manufacturer was Draeger who produced its EV 800/801® (Fig. 1) under license of the American PL6 ® model of Aequitron Medical.

At that time, there was also a renaissance of smaller type iron lungs for travelling. A small workshop affiliated to the Pfennigparade facilities produced them as one-off prototypes. We have supplied these travel lungs to adults and children. However, equipment such as this could not normally be used for children and adolescents with muscle disease, in view of their physical condition which includes scoliosis, contractures, often with severe pain; or sometimes there was simply no space. Consequently there are few reports on iron lung ventilation in Duchenne dystrophy (2).

In the mid 1980s, Dr Reinhardt Rüdel, founder of the Ulm Neuromuscular Centre, pointed out to the heads of our clinics that the combination of therapeutic facilities available within our hospital was ideal for helping DMD patients manage their respiratory problems (3). He reported with enthusiasm Prof Yves Rideau's comprehensive concept for treating Duchenne boys in Poitiers, France, which consisted of releasing contractures by surgery (4), stabilization of the spine (5) and assisted ventilation (6) through nasal masks using light-weight respirators that could be run at home. Our hospital would be able to supply all these services as well, he argued. Without such treatment the children would die between the ages of 14 - 18 years as a result of severe respiratory complications such as pneumonia. With their respiratory problems resolved, however, the patients could enjoy a life extended by a number of years, with cardiomyopathies then becoming the life-limiting factor (7).

We were much impressed by these accounts, but as anaesthetists we had some doubts as regards the safety and the practicability of the procedure, for at that time we had no experience with ventilation through masks without leakages through mouth and nose – except in their application in the operating theatre. For example, patients who had been fasting prior to surgery and had been administered anaesthetic drugs were ventilated for short periods of 10 to 30 min through a mask. But like most anaesthetists at that time we were greatly concerned about the possible aspiration of food and – as a consequence – the development of acute pneumonia. Of course, when patients without reflexes were resuscitated, they were ventilated immediately before intubation – but through a mask via the nose only and with a mobile ventilator, without anaesthesia or monitoring: that is to say, only non-anaesthetized patients would have been allowed to control their own ventilation.

Sullivan and his group (8) were the first to use masks that would work only through the nose, with turbines from vacuum cleaners to avoid patients with severe sleep apnoea having to undergo a tracheostomy – and it worked! Within a few years this method led to the development of the techniques of CPAP (Continuous Positive Airway Pressure) and BIPAP (Bi-level Positive Airway Pressure). By means of these techniques, then, the airway could be kept open by the application of continuous positive pressure (e.g. +5 to +10 mbar) or even by varying the pressure levels, with the aim of preventing any snoring that might arise from obstructions in the airway.

However, it transpired that supplying a simple CPAP device to DMD boys with exhausted respiratory muscles was unsatisfactory for long-term ventilation (9). Top priority for these patients is to relieve their fatigued respiratory muscles. This is much more important than keeping the airway open. Certainly, in some Duchenne patients obstruction of the airway does play an additional role, but in most of the cases this is not a crucial factor in their ventilatory inefficiency. The first reports on effective nasal ventilation combined with a portable volume ventilator were published by Bach (10) and Curran (11).

Respiratory exercises

In the mid-1990s we started to provide perioperative care and anaesthesia for Duchenne boys who underwent operations to relieve contractures of the lower extremities prior to showing signs of scoliosis. The age of these boys was under 14 years (12, 13). Although lung function was slightly restricted, prophylactic ventilation was not indicated. But rather than waiting passively for a further deterioration of their muscle strength, we introduced equipment to exercise the diaphragm and the small inspiratory muscles 2-3 times per day by means of IPPB

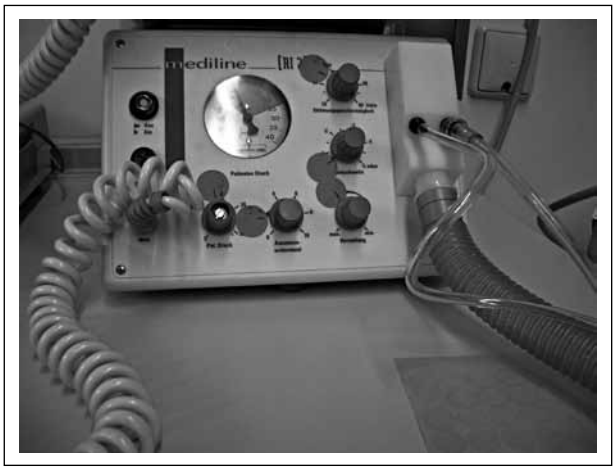

Figure 2. The Mediline Ri2® device for IPPB intermittent positive pressure breathing.

(Intermittent Positive Pressure Breathing). The advantage of this method is that no-one is usually required to assist. The boy is able to position the tube of the apparatus via mouthpiece or mask, and also to start or stop it by a push-button, all without assistance (Fig. 2). Inhalation solutions like beta-sympathomimetics or corticosteroids, or just 0.9% to 5.85% sodium chloride solution can be nebulized for mucolysis. Periodic breathing training may continue for up to 5 yrs, until vital capacity values are so low that assisted ventilation becomes necessary.

In a large study, Raphael (14) showed that prophylactic ventilation is ineffective and may even lead to increased mortality rates. But many authors were able to demonstrate a positive effect on lung function by lung insufflation training (15-19). Some hospitals, like ours, used an intermittent positive pressure breathing (16), or a computer-assisted device (17); others employed a positive end-expiratory pressure valve (18). Even with as few as three training sessions per day, the benefits were evident (19). The important thing is to check lung function and blood gas levels regularly to detect any clinical deterioration at an early stage.

Rideau et al. demonstrated quite emphatically that continuously diminishing lung function remains the best negative predictor of survival in DMD patients once vital capacity has fallen below 1 litre (20).

Non-invasive ventilation (NIV)

When patients suffer dyspnoea the loading on the respiratory muscles increases and endurance decreases (21). In the early 1980s, non-invasive ventilatory support was introduced to compensate for the decrease in muscle force necessary for normal breathing. Nocturnal ventilatory support was then shown to be effective in restoring ventilatory function (10).

Interfaces

When non-invasive ventilation was first introduced in Duchenne boys the choice of masks was very small. The nasal masks for CPAP therapy were made only for open one-tube systems with swivel valves for expiration, with additional overflow valves on the mask. To obtain adequate respiration when using the closed systems with expiratory valve, we had to seal the overflow hole in the mask (usually with tape). We also considered the alternatives of a nasal mask and an oralnasal mask. Thus, our first masks were oralnasal masks with a hard plastic shell and a padded rim. They were moulded on individual plaster casts on a machine designed for making orthoses. Although respiration with these masks worked relatively well, we soon abandoned oralnasal respiration because the patients, who were unable to raise their hands to the head, tended to panic when they could not take off the masks unaided, or were unable to cry for help with the mask attached.

Therefore we turned to making a nasal mask made from a hard-cast shell with a soft, smooth interior. This mask was much more readily accepted – our patients were content.

At that time we had to tolerate bruises, cases of redness, skin ulcerations, conjunctivitis and leakages which were complications frequently encountered (20). The respirators were just made to deliver a pre-set tidal volume; whenever there were substantial leakages we simply increased the volume.

As time progressed, the industry delivered custom-made masks with increasing precision, in particular masks with soft rims made of silicone gel, providing greater comfort for the patients. The leakage systems were transferred from the masks to the connecting angle pieces, allowing the patient to be ventilated either in the one-tube mode with the angle piece opened, e.g. the BI-PAP setting, or with a valve at the mask and the angle piece closed.

Nevertheless, two substantial problems of the so-called non-invasive appliance remained: (i) the danger of bruising, in particular if the respiratory apparatus was applied as an emergency, and (ii) the risk of receiving insufficient respiratory pressure caused by high leakages either around the mask or through the opened mouth. A solution was only to be reached with an improved individual mask because patients with muscle disease often suffer significant atrophy to their face as well as having bony upper and lower jaws. We were fortunate to have a dental student working for us who developed a mask with two polymerized layers in one cast, the outer one solid and the inner one extremely soft and kind to skin (22). With this mask (Fig. 3) we could, for the first time, ventilate our Duchenne boys applying relatively little pressure to the

Figure 3. The individual mask type Bemetec®.

nasal area and yet have little leakage. The only leakages still to be resolved were those arising at night when the patient is asleep with his mouth partially open. One advantage of these home-made masks over the commercial ones is that, to accommodate changes as the boys grow, one can simply cut away small sections from the rim of the mask.

Only very rarely do we see dysplasia (23) of the central facial area in our Duchenne boys, and even when it does occur it is only mild. In general the permanent teeth have grown through and pubertal growth is complete by the time nasal respiration is required.

Respirators

At the end of the 1990s respirators appeared on the market with bellows instead of a piston. The substantial advantages were their low weight – only 12 kg – and the facility to compensate for leakages, with up to 3000 ml additive tidal volume. One particular feature of the new technology was the introduction of a new pre-set facility, namely pressure. With improved leakage compensation we had at our disposal, for the first time, a means to deliver safe, non-invasive ventilation to babies and infants. We were now able to ventilate SMA I patients from the 7th month of life onward.

Another step forward was the great improvement in patients' mobility, achieved by the introduction of turbine-driven respirators. The weight of the devices dropped from 12 to 1.5-3 kg. It thus became much easier to attach them to an electric wheelchair (Fig. 4).

Pre-set inspiratory pressure, however, is a disadvantage when the patient has an infection, which results in increased resistance owing to retention of secretions: the pre-set respiratory pressure cannot be increased to an adequate level. For that reason the inspiratory pressure has to be elevated with every infection of the airway in order to guarantee a sufficient tidal volume. With volume pre-set, the tidal volume is always achieved, even in the event of increased peak inspiratory pressure (24, 25).

Proliferation and acceptance of home ventilation in Germany

Home ventilation was already widespread in France (26), Great Britain (27), Italy (28), the Netherlands (29), Belgium (30), Denmark (31), and the USA (32) when it finally also triumphed in Germany. It was first used in hospitals that had patients with par-

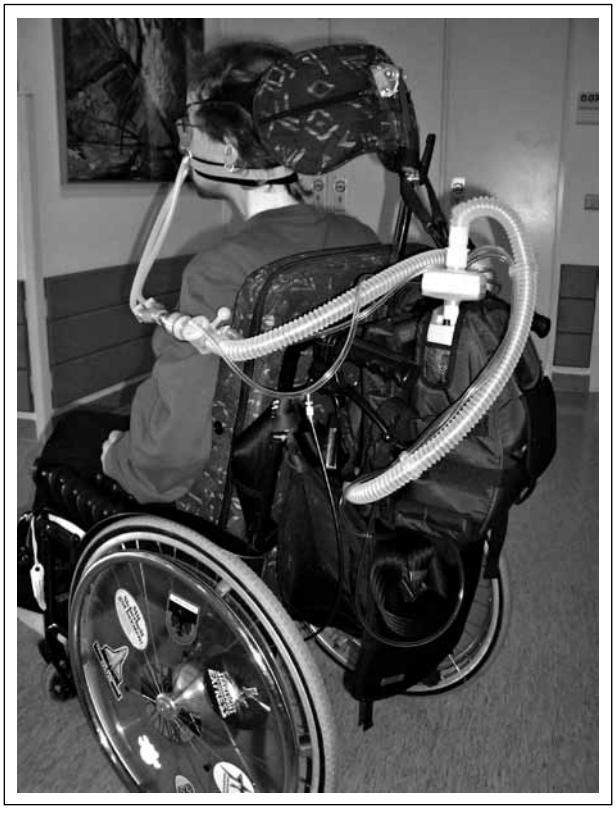

Figure 4. Duchenne boy on 24-hrs non-invasive ventilation using a mobile Legendair® ventilator with internal and external energy supply.

ticular conditions, such as tetraplegics or patients with acute lung disease who needed long-term ventilation. These were big hospitals for lung diseases specialising in internal medicine. After the foundation of a network of muscle centres – stipulated by the advocacy group of the Deutsche Gesellschaft für Muskelkranke (DGM) following the British example of the muscle centre in Newcastle upon Tyne (33) – Duchenne patients now receive adequate interdisciplinary care all over Germany.

Home ventilation was only fully accepted when the patients themselves declared their satisfaction. At the beginning of the 1990s, masks were, at best, received reluctantly; the majority of doctors and parents declined them categorically. Since then, the sense and the practicability of mask ventilation have been fully embraced. The introduction of DRGs (Diagnosis-Related Groups) and the continued endeavours to shorten the duration of hospital stays has furthered the use of respirators outside the clinics.

During the early days of development, benefactors were also rather hesitant to approve funding. Now, however, they all support this well established option for treatment. In 1994, for the first time, physicians, professional care providers, benefactors, the health insurance medical services (MDK) and patients, all met to assess the situation of those patients who had to receive ventilatory support outside the hospital setting. Improvement in patient-centred team care was also on the agenda. Meanwhile, from this very small group of interested individuals, an independent association has grown: the DIGAB (Deutsche interdisziplinäre Gesellschaft für ausserklinische Beatmung – German Interdisciplinary Association for Extra-Clinical Ventilation) which holds annual meetings. This association has overseen the establishment of guidelines for respiratory care outside the clinical setting (34, 35).

The current situation for patient-centred care at home

The majority of our patients live with their parents and are cared for by them, and – where applicable – by their brothers and sisters (36). All children and adolescents receive education. During and after schooling they are often in special facilities for handicapped persons for the whole day, or sometimes round the clock. During school time there is, as a rule, a carer present. Only occasionally are professional caring services involved in the care of Duchenne patients at home (37).

Only when the parents get older and the need for assisted ventilation increases does more patient-centred care become necessary. Non-invasive ventilation around the clock is usually more demanding than invasive ventilation, in particular when the patient has a bronchiopulmonary infection.

In the event of infection the rate of hospitalisation for Duchenne patients is quite low. However, each case of pneumonia is life-threatening. Our experience of the past 20 years shows that after the introduction of assisted ventilation, hospitalisation in the event of pneumonia is necessary only in exceptional cases (5 out of 21). By the same token no patient had to change from non-invasive back to invasive ventilation, i.e. to tracheostomy.

These data are supported by results from Bach (38) and Soudon (39), but are in conflict with Rideau's experience (40).

Weakness of inspiratory musculature

There is a vast literature on the effect of non-invasive ventilation on the recovery of weak inspiratory musculature (41). Recently Hahn et al (42) demonstrated a non-invasive procedure – the tension-time index – to identify a patient's predisposition to muscular fatigue in Duchenne muscular dystrophy.

Weakness of expiratory musculature

This symptom leads to immobilisation of the secretions in the pulmonary airways. During the first years of ventilation outside the clinic this matter was not given enough attention. Bach and co-workers were early to point out that support for coughing is very important (43). The introduction of cough devices in Germany met with much more resistance than that of assisted ventilation itself. In particular the benefactors did not want to commit themselves to funding this device. Doctors just could not prescribe it. This in turn resulted in emergency tracheostomies being performed that could have been avoided. Fortunately cough devices can now be prescribed.

In our cohort of patients additional administration of oxygen was only necessary in sporadic cases of infection.

Management of secretions

Performing a tracheostomy is in most cases not necessary where there is adequate management of secretions (44). Even in the case of a 15-yr-old boy under our care with very severe hypertrophy of the tongue, we have so far managed to avoid it. In contrast to the situation with ALS patients, we do not see a bulbar disorder. In addition to the excess pressure/under-pressure method with Cough assist® or Pegaso® (Fig. 5), other techniques to mobilise secretions are in use, such as oscillating pads attached to the thoracic wall: The Vest® (45) or vests with built-in motors.

Nutrition

Although feeding is disrupted during 24-hr ventilation through the nasal pathway, only a few of our adolescent patients opted for a PEG (percutaneous endoscopic gastrostomy). Rather, they learned to swallow during ongoing ventilation. In contrast to SMA children, who in early childhood have to learn to use a nasal probe or PEG because of massive swallowing problems and the danger of food aspiration, only a few DMD boys (3 out of 21) use PEG. Installation of PEG is just not requested, although, if it is done in time it is associated with fewer complications during perioperative anaesthesia. Operations are usually performed under sedation with propofol and small amounts of ketamine or opiates while nasal ventilation is continued. There is no need to intubate. Recently developed masks (mouth-nose with integrated opening for the gastroscope) resolve the problem of sealed ventilation during endoscopy. During non-invasive ventilation even an open gastrostomy can be performed without translaryngeal intubation (46). Nevertheless an elevated risk remains during procedural sedation or aneaesthesia that can be reduced giving attention to standard recommendations (47-49).

When the appropriate time for a PEG has come, there can be a problem – e.g. during an infection – if insufficient liquid and food is infused. The patient loses the strength to cough if the intake of calories is too low. In an emergency we advise oral administration of enteral food substances. In some cases a thin nutritional probe must be inserted through the nose. Nasal ventilation is then aggravated by additional leaks and the danger of bruises; however, if the probe is positioned in a slightly different place each day it is reasonably well tolerated. Using this regime we were able to save the lives of some DMD boys when their body weight fell below the critical threshold of 30 kg.

Another complication with the act of swallowing may arise in the event of an increasing cervical scoliosis compressing or reducing the diameter of the oesophagus. Then installation of a PEG tube is the only solution to securing the supply of liquids and food.

Cardiac capacity

Many of our Duchenne patients forget about the cardiac risk that prevails beyond the age of 18 yrs although more than 80% of them show abnormal systolic function (50). When they are supplied with permanent assisted ventilation they also experience less strain on their heart (e.g. a reduction of the heart rate). Cardiologic monitoring and regular exploration by transthoracal echo sound involves considerable expenditure. Therefore a therapy with ACE inhibitors, beta-blockers (51-53) or other medication that relieves the heart is often refused by the patients and their families, or conceded only at a late stage. Some patients had – before the times of ACE inhibitors and beta blockers – already been accustomed to traditional treatment with digitalis derivatives, which was in fact fairly effective. We also saw patients who had been given ACE inhibitors or beta-blockers in doses that would be correct in patients of the same age without muscle disorders. Those patients had their mobility so restricted owing to such an immense fall in blood pressure that the therapy had to be abandoned. Treatment using common cardiac medication was only accepted when the doses were reduced and the side effects were thus minimized.

We have tried to maintain regular cardiologic control and to only begin the treatment of symptoms when it became necessary. That is to say, we did not treat prophylactically. Absolute indications for therapy with ACE inhibitors and beta blockers were: a heart rate of > 100/min, cardiac arrhythmias, clear indications of heart insufficiency, and sonographic evidence of a decrease of the ejection fraction.

Noteworthy results obtained at Ulm by the year of 2012

Pain management

The most important provision to avoid pain is early relief of contractures and surgical correction of the spine. Such timely intervention to avoid chronic pain should enable the patient to sit and stay free of pain. We have never seen a DMD patient admitted to hospital for skin ulcers.

If the release of contractures and, more importantly, correction of the spine is delayed to an age where surgery cannot be performed because of pulmonary or cardiac contraindications, or if the patient or his parents are indecisive or too anxious to consent to an operation, the patient will inevitably lose the option of sitting upright in a chair. This was the case with 3 of our 21 DMD patients in recent years. They could not be seated in a wheelchair, but had to lie in a reclining buggy or in a reclining wheelchair. This of course has significant implications for the patient's quality of life: daily administration of analgesics is then unavoidable.

Differences between our patient cohorts of 2002 and 2012

We have evaluated our notes obtained from ventilated DMD patients up to the year 2002 (54) and to 2012.

Assisted ventilation

In the earlier period we had two patients who died before they had decided to accept the ventilation regime which we considered necessary for their survival. In the later period the ventilation recommended was effective in all cases, and no patients rejected the treatment after its initiation.

Long-term ventilation was in all cases free of NIV failures, although one boy experienced a major obstruction to his airway caused by severe hypertrophy of the tongue. No patient with NIV had to be converted to invasive treatment as a secondary measure. Three patients were ventilated with only positive expiratory resistance because we wanted to enable them to speak without difficulty. Speaking would have been almost impossible for them with the additional leakage that would have occurred with invasive access via tracheostomy. There are indeed special tubes with perforated applications designed to enable the patient to speak, but success is by no means guaranteed in all patients.

In contrast to our practices during the 1990s, we have been using devices for supported expiration since the turn of the millennium. Whenever we now have a severe infection preventing the patient from coughing up secretions, we apply devices such as Cough assist® (Fig. 5) or Pegaso®. Eleven of the 16 ventilated patients who we care for are using one of these. Only two of these 16 patients are ventilated with pre-set volume; the rest have pre-set pressure.

For some of our patients (8 out of 21) assisted ventilation commenced, out of necessity, immediately after a severe bout of pneumonia; only in a few exceptions (4 out of 21) was it scheduled in advance. Three patients received emergency ventilation. We gradually reintroduced feeding by mouth and gave them a mask after extubation. Six DMD boys were administered only IPPB for 2 to 9 years. Four of them are still stable and do not yet need assisted ventilation.

Figure 5. The Cough Assist ® device for supported coughing.

When respiratory function is stable, life expectancy is limited partly by cardiac deficit, but more so by nutritional deficit. In cases of critical malnutrition arising from patients declining PEG tubes and enteral feeding, the calorific deficit was only compensated by oral feeding with food designed for enteral use. Education on the advantages of a PEG tube must be pushed forward, particularly in cases where severe scoliosis in the cervical region restricts the oesophagus and non-invasive ventilation is performed round the clock.

It is now realistic to expect patients with assisted ventilation to survive more than 18 yrs. The mean duration of survival for our DMD patients with assisted ventilation is 5.5 to 6 yrs. Only one of our 21 patients has died so far. He had lived for 17 years on assisted ventilation, dying at the age of 34 and with a body mass of 33 kg. He died of cardiac failure following severe pneumonia.

These data are in line with results from Bach et al. (55) who demonstrated survival prolongation of 7.4 ± 6.1 years by continuous non-invasive ventilatory support. Meinesz et al. reported a 5 year survival of 75% (56). Ishikawa et al. reported 50% survival to age 39.6 (57).

Cardiac therapy

Cardiac medication was very mixed because on-site supervision was in the hands of many different cardiologists. Currently our patients come from a radius of over 300 km encompassing several German Federal States. Of the 21 patients, 5 receive ACE inhibitors; 4 have beta-blockers; 1 receives ACE inhibitors + beta blockers; 4 receive digitalis preparations; and 2 corticosteroids. Also the point at which the drugs were administered varied greatly. In most cases they were commenced after an obvious decrease of the ejection fraction, or once the heart rate was consistently > 100/min. In no case did we find that cardiac therapy improved spontaneous breathing. That is to say, that ventilation had to be continued to relieve the heart. Cardiac medication did not reduce the amount of time each day that patients required assisted ventilation.

Medical aids and appliances in patient-centred care

The health insurance companies and other providers and benefactors initially declined to meet the costs of medical aids for 8 out of 21 patients. This comprised 2 IPPB devices, 3 respirators (as supplementary devices for the wheelchairs of patients requiring assisted ventilation round the clock), 3 cough-assist devices and 3 indi-

vidual masks). In all cases, however, payment was finally pushed through. Nevertheless, in 3 cases the help of an attorney had to be sought, and in one case the Social Court. In all cases the insurance companies or providers were ordered to pay (58). Delays brought on by bureaucracy are reported frequently in Germany.

Home care

Most of the children are, or have been, cared for by their families, primarily their parents. Although NIV respiration is usually more complex, benefactors prefer to finance cases where invasive ventilation is required. DMD patients on respiratory support enjoy a relatively high quality of life (59).

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