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Sleep Disordered Breathing and Respiratory Failure in Pompe Disease

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*(cf. scientific publication in NEUROLOGY - for abstract please click **here**)*

Twenty-seven Pompe patients were studied at Ruhrlandklink-Essen, Essen, Germany. The aim of the study was to characterize respiratory problems in patients with Pompe disease through pulmonary function, respiratory muscle force, sleep, and sleep breathing measurements. Given the rare incidence of Pompe disease, the number of study participants is remarkably large and indeed unprecedented in the Pompe literature. The study has provided important insights into the progression of Pompe disease and the interaction between breathing and home mechanical ventilation (HMV). Also, the study has achieved a major breakthrough in that it provides health professionals and patients and their families with an "early warning system." In fact, it is now possible to evaluate residual respiratory function, identify incipient respiratory muscle weakness, and predict the likely course of the disease before daytime respiratory failure occurs. Moreover, there are now objective criteria on which to decide when mechanical ventilation is best started. This event is unpopular because it marks a major change in a Pompe patient's life but it may also significantly improve their quality of life, thus perhaps making it a bit easier to opt for HMV.

Using language that can be understood by the medically interested general reader and avoiding medical jargon as far as possible, this report summarizes the key results and teaching points of the study as they affect patients' and their families' lives. I wish to thank Dr. Mellies for his kind help and support. A scientific publication of the results of this study was published by Dr. Mellies and colleagues in the medical journal *Neurology*.

This report was kept as short and simple as possible for easy reading and for the benefit of the skimming reader. Click on highlighted terms to bring up definitions or additional information in the right frame.

Thomas Schaller

Intro: Pompe Disease and Breathing

Pompe disease is characterized by involvement of cardiac, skeletal, and respiratory muscles. Respiratory muscle failure is a frequent cause of death in both the juvenile and adult forms of the disease. As Pompe disease is a rare disease (showing a **prevalence** of 1 in 40,000 to 1 in 100,000), little is known about the progression of respiratory muscle weakness, the role of that particular **weakness of the diaphragm**, and sleep disordered breathing (**SDB**). All accounts in the literature on the clinical course of the juvenile and adult forms are case reports mentioning paralysis of the diaphragm, sudden respiratory failure, and/or severe SDB. SDB occurs in 40-70% of patients with neuromuscular diseases. A clear correlation between SDB and daytime respiratory failure has not been established for other muscle diseases either, and it has been impossible to predict either SDB or the time of daytime respiratory failure. As noninvasive mechanical ventilation (**NIV**) is now available for HMV, it is particularly important to identify nocturnal hypoventilation. A timely start of NIV may significantly improve symptoms, quality of life, and life expectancy.

Study Objectives

Respiratory drive and respiratory muscle force are reduced during sleep also in health. Normal breathing can therefore not be maintained in neuromuscular disorders with respiratory muscle involvement (such as in Pompe disease). Sleep disordered breathing precedes daytime respiratory failure and is a sign of incipient respiratory muscle involvement. Little is known about the cause and time-course, and there are no data on SDB in Pompe disease.

Study objectives:

1. To characterize the progression of Pompe disease in the format of a cross-sectional study;

2. To identify and describe the relationship between breathing while awake and breathing while asleep;

3. To explore the progression of respiratory muscle weakness typical of Pompe disease; and

4. To identify SDB predictors from these data.

Study Details

Participants

Seven juvenile and 20 adult patients aged 3-27 and 23-63 years, respectively, took part in the study. Based on their ability to walk, they were categorized into five disability classes (DC):

DC-1	Can walk and can climb stairs unassisted
DC-2	Can walk but needs assistance (aid) when climbing stairs
DC-3	Can walk only with assistance (walking aid)
DC-4	Cannot walk but needs no assistance to transfer (say, from bed to wheelchair)
DC-5	Cannot walk and needs assistance to transfer

Measurement of Respiratory Capacity

Measures included:

- **Inspiratory vital capacity (IVC);**
- **Peak inspiratory pressure (PIP).**

The measurements were made on the sitting or supine patient, if possible. The supine results were used for comparison with nocturnal breathing data.

Restrictive ventilatory defect was defined as an **IVC** of less than 80% of predicted.

The degree of restrictive ventilatory defect was graded by the following IVC classes:

60-79%	Mild
40-59%	Moderate
20-39%	Severe
<20%	Very severe

Weakness of the diaphragm was defined as a greater than 20% fall in supine **IVC** versus [baseline] sitting IVC.

Respiratory muscle force was assessed by measuring **PIP** and other variables.

Polysomnography

Overnight polysomnography (PSG) involved the recording of the following measures during nocturnal sleep:

- **Sleep stages;**
- **EEG**
  (electroencephalogram, i.e., a recording of the electrical activity of the brain);
- **EOG**
  (electro-oculogram, i.e., a tracing of the movements of the eyeball);
- **EMG**, submental
  (electromyogram, i.e., a tracing of the indirect measurement of muscle tone);
- **ECG**, unipolar
  (electrocardiogram, i.e., a recording of the electrical activity of the heart);
- **Oronasal airflow**
  (i.e., the flow of air through the mouth and nose);
- **Breathing movements** of the rib cage and diaphragm;
- **Oxygen saturation;**
- **Transcutaneous partial pressure carbon dioxide.**

No oxygen therapy was administered.

Based on generally accepted criteria, the recorded data were used to identify apneas (brief cessations of airflow), hypopneas (brief reductions in airflow or respiratory effort), and hypoventilation (sustained reduction in the amount of air entering the tiny airsacs that make up the lungs).

Significant SDB was defined as at least 10 apneas and/or hypopneas per hour of sleep associated with oxygen desaturation of 4% or more and/or EEG evidence of arousal.

Hypoventilation was defined as a continuous increase of carbon dioxide pressure to over 50 mmHg either only during REM sleep or during more than 50% of total sleep time.

Mechanical Ventilation

Noninvasive mechanical ventilation (NIV) was used in patients with daytime respiratory failure and/or advanced SDB if patients had symptoms that could be abolished by NIV. The ventilator was set individually for best gas exchange and maximum respiratory muscle assistance.

Statistical Analysis

Statistical correlation and regression analyses were performed to identify and confirm correlations between respiratory capacity, respiratory muscle function, PSG variables, and gas exchange.

Results

Patient Characteristics

All patients showed various degrees of weakness of the hip girdle and leg muscles typical of Pompe disease. Distribution by disability classes was as follows:

11	DC-1
7	DC-2
8	DC-3
1	DC-4

The degree of limb muscle weakness showed a statistically highly significant correlation with respiratory insufficiency. In other words, the greater the muscle weakness and the shorter the walking distance, the smaller the respiratory muscle power, the smaller the IVC, and the more pronounced SDB.

Statistical Data on Disease Progression:

	Juvenile form	Adult form
Age at which first symptoms of muscle weakness occurred	5.1 ± 6.0 years	36,3 ± 9,5 years
Time from first symptoms to diagnosis	0,2 ± 4,0 years	5,1 ± 5,2 years
Time from first symptoms to dyspnea on exertion	14,0 ± 1,7 years	9,3 ± 6,1 years
Time from dyspnea on exertion to start of mechanical ventilation	1 year	2,0 ± 0,5 years

Only three patients with the adult type of Pompe disease showed faster progression, the time from first symptoms to dyspnea on exertion being 2, 3, and 4 years, respectively. Fourteen patients had no symptoms suggestive of sleep disordered breathing, and no shortness of breath.

Pulmonary Function and Respiratory Muscle Function

IVC showed significant correlations with **PIP** and daytime **gas exchange** (oxygen and carbon dioxide pressures in the blood). IVC was slightly lower in patients with the juvenile form (53.2% ± 31.2%) than in those with the adult form (68.9% ± 25.7%).

Weakness of the Diaphragm

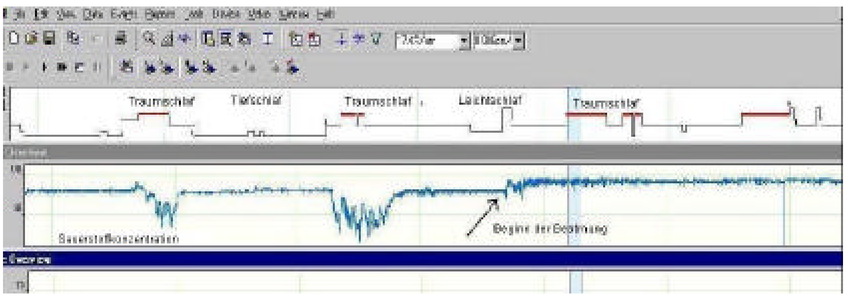
Diaphragm weakness was present in 13 patients, especially in those with longstanding disease (14.1 ± 6.8 years versus 9.4 ± 3.8 years in patients without weakness of the diaphragm). Patients with weakness of the diaphragm had a lower **PIP** and a lower **IVC**.

Sleep Disordered Breathing

SDB manifesting as brief desaturations mainly during REM sleep or as **hypoventilation** occurred in 13 patients. Eleven patients had weakness of the diaphragm. From a wealth of data, (supine) **IVC** and **diaphragm weakness** could be identified as significant indicators of SDB. Weakness of the diaphragm was associated with an 80% likelihood of SDB. An IVC of less than 40% of predicted was also associated with an 80% probability of nocturnal hypoventilation.

Mechanical Ventilation

Two patients with juvenile Pompe disease and five with the adult form received noninvasive mechanical ventilation (**NIV**). Two mechanically ventilated patients received NIV for nocturnal hypoventilation and five for daytime respiratory failure. NIV normalized breathing while asleep and daytime **blood gases**.



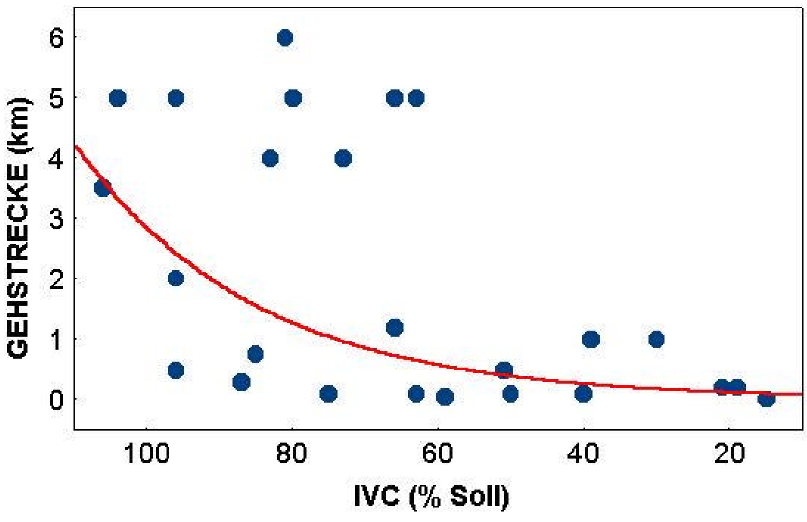
Example of PSG with and without mechanical ventilation
(Click on the picture for an enlarged view)

Patient with an IVC of 26% of predicted and weakness of the diaphragm. In the first half of the night without mechanical ventilation, the patient experienced hypoventilation with an oxygen saturation (blue) of about 90% and, during REM sleep, diaphragm weakness-related deep desaturations to as little as 70%. After starting mechanical ventilation, gas exchange returned to normal even during REM sleep.

Conclusions

Relationship Between General Muscle Weakness and Respiratory Muscle Weakness

Although there was a narrow statistical correlation between **IVC** and walking distance or disability class, these were not capable of predicting breathing problems. This is so because respiratory muscle weakness does not necessarily occur in synchronicity with trunk, limb girdle, and leg muscle weakness. Some patients in the study were able to walk only with a walking aid but still had near-normal pulmonary function, whereas one young man required emergency mechanical ventilation for acute respiratory failure although he had ridden his bike shortly before the event.



Relationship between inspiratory vital capacity and walking distance
(Click on the picture for an enlarged view)

*Statistically significant correlation between inspiratory vital capacity (**IVC**, in % of predicted value for age [= "Soll"]) and walking distance [= "Gehstrecke"] covered without a walking aid (self-assessment): While walking distance decreases with decreasing IVC, some patients with normal pulmonary function (>80% of predicted) or minor respiratory insufficiency (60-80% of predicted) can walk not at all or only a couple of yards, whereas others easily manage several miles. These data are based on 25 patients.*

In this regard, Pompe disease differs clearly from other, more common muscle disorders. In Duchenne muscular dystrophy, for instance, breathing problems never occur while the patient can still walk. The same is true for other neuromuscular diseases. This is why many physicians tend to think that respiratory problems occur only in wheelchair-bound patients, frequently resulting in delayed diagnosis of respiratory insufficiency in Pompe patients.

Relationship Between Respiratory Muscles and Pulmonary Function

In Pompe disease, there is a close correlation between residual **respiratory muscle power**, **IVC**, and **gas exchange** both while awake and while asleep. This logical relationship has failed to be so clearly established for other neuromuscular disorders.

Diaphragm involvement has a major impact on outcome in Pompe disease. In both the juvenile and adult forms of the disease, the time from first symptoms of muscle weakness to breathlessness as evidence of **weakness of the diaphragm** was 12 years on average.

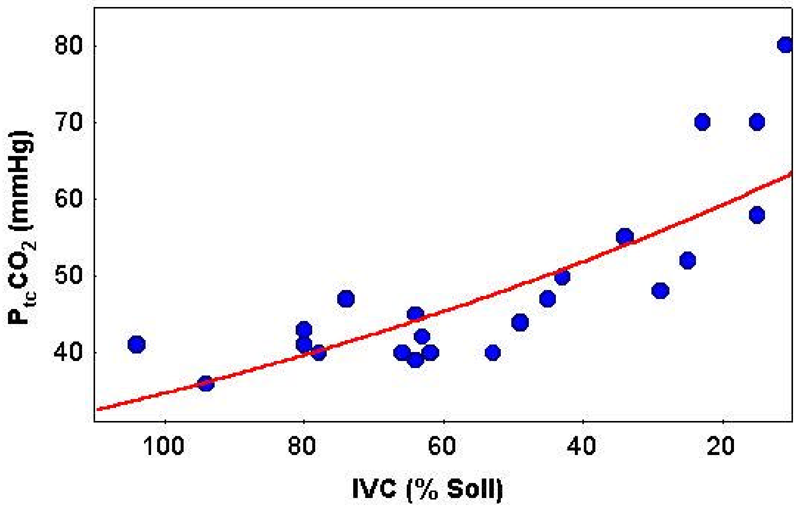
In three patients in whom general muscle weakness also showed very rapid progression, the time to diaphragm weakness was as short as 3-5 years, while the longest latency period was 20 years. Patients without weakness of the diaphragm had a significantly shorter course of the disease. As the study was a cross-sectional study, the results must not be construed as suggesting that Pompe disease will invariably involve weakness of the diaphragm. In the Pompe mouse model, however, diaphragm weakness developed invariably after a variable latency period. Moreover, two patients from the study developed weakness of the diaphragm within the past two years with a latency period of 10 and 12 years, respectively.

Patients should therefore undergo sitting and supine pulmonary function testing once or twice a year for early detection of the development of weakness of the diaphragm. Incipient weakness of the diaphragm is characterized by a decrease in supine inspiratory vital capacity by approximately 20% versus [baseline] sitting **IVC**. A few years later, when the patient has developed complete paralysis of the diaphragm, supine IVC falls by almost 50%. Detection of weakness of the diaphragm should always prompt the treating doctor to order **PSG** because diaphragm weakness is invariably accompanied by **SDB** (which may need to be treated).

Sleep Disordered Breathing

The extent of **SDB** is directly related to the residual **respiratory muscle power** and inspiratory vital capacity (**IVC**). Progression is characterized by a continuous decline in respiratory muscle power and IVC. Once IVC falls below approximately 60% of the predicted value for age, patients tend to experience brief desaturations mainly in REM sleep. While not dangerous, these desaturations may compromise sleep quality, resulting in sleepiness or tiredness during the day and/or an inability to maintain sleep at night. Mild desaturations will not produce symptoms.

Once there is diaphragm involvement, however, patients start experiencing hypoventilation, initially only during REM sleep because REM sleep is accompanied by a general loss of muscle tone (except in the diaphragm) also in health. As breathing depends crucially on the diaphragm during REM sleep, this is the time when **weakness of the diaphragm** will be unmasked. **PSG** detection of sustained oxygen desaturations during REM sleep is diagnostic of diaphragm involvement. Once **IVC** falls below approximately 40% of the predicted value for age, the **oxygen saturation** will decrease throughout sleep (see **Figure**). Typical symptoms include supine dyspnea, pronounced sleep disturbances, and morning headache (the high carbon dioxide value during sleep causes vasodilation and hence increased cerebral blood flow). Patients also tend to experience daytime dyspnea on exertion.



Relationship between inspiratory vital capacity and carbon dioxide pressure

(Click on the picture for an enlarged view)

Correlation between inspiratory vital capacity (IVC, in % of the predicted value for age [= "Soll"]) and mean carbon dioxide pressure in the blood during sleep. The CO_2 pressure is a quantitative measure of respiration and increases in hypoventilation. Note that a decrease in (daytime) IVC is accompanied by an increase in CO_2 pressure during sleep (breathing activity decreases during sleep). Data from 22 patients.

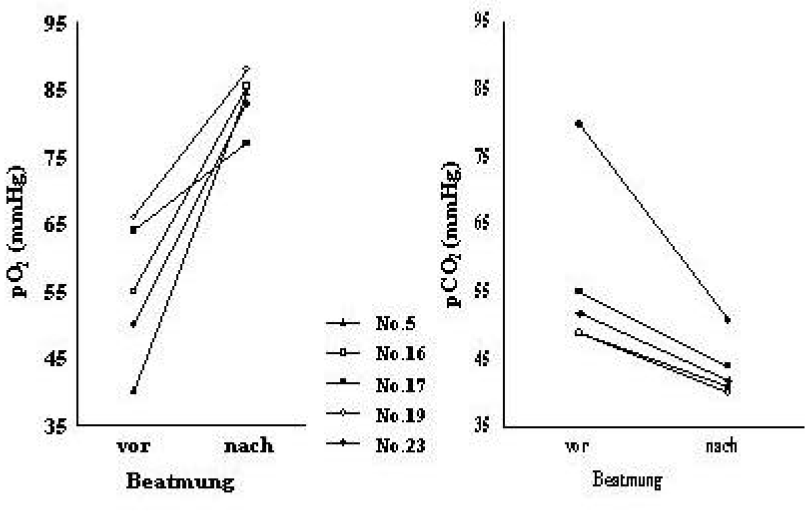
The symptoms of sleep disordered breathing are nonspecific, i.e., they tend to occur also in many other conditions (such as poor performance and daytime sleepiness from underactivity of the thyroid gland), or are misinterpreted as general or psychosomatic complaints. This may produce long delays in diagnosis. Morning tiredness, morning headache, daytime sleepiness, tendency to fall asleep during the day, loss of performance, rapid progression of muscle weakness, difficulty falling to sleep and/or maintaining sleep, frequent nightmares, dyspnea on awakening, and similar symptoms in a Pompe patient should alert the physician to the possibility of SDB. Especially when a patient's **IVC** is less than 60%, PSG should be performed in a sleep laboratory familiar with the unique aspects of muscular disorders.

Once IVC falls below approximately 20% of the predicted value for age, adequate respiration can no longer be maintained even during the day, and the patient experiences chronic respiratory failure. Without mechanical ventilation, the patient's prognosis is grim, and a respiratory infection is usually fatal.

Symptoms include increasing breathlessness even on mild exertion, such as eating or speaking, increasing weakness, and weight loss.

Mechanical Ventilation

In patients with **SDB**, nocturnal noninvasive ventilation (**NIV**) normalized breathing and gas exchange during sleep, and improved sleep quality and daytime symptoms. In patients with daytime respiratory failure, nocturnal NIV returned daytime blood gases almost to normal. Four patients who started NIV for respiratory failure have been without major respiratory complications for 4-10 years, and one patient has been using NIV also for several hours during the day. All patients on NIV have reported significant improvement in dyspnea. NIV probably also improves the prognosis of Pompe patients. These results confirm the responses to noninvasive mechanical ventilation reported for other neuromuscular diseases where NIV has achieved stabilization for years even in very advanced disease. However, NIV patients are still at greatly elevated risk especially when suffering respiratory infections and, therefore, require immediate treatment in a specialized center if this should occur.



Impact of nocturnal noninvasive ventilation (NIV) on blood gases
(Click on the picture for an enlarged view)

Nocturnal NIV has an effect on daytime blood gases. Mechanical ventilation [= "Beatmung"] was *used throughout the night. The figures show the pressures of oxygen (PO_2) and carbon dioxide (PCO_2) in the blood before and after the start of NIV. Blood gases were determined in the evening after at least 8 hours off the ventilator. Note that nocturnal NIV achieved blood gas normalization. Data from 5 patients with (variable degrees of) daytime respiratory failure.*

Summary

Relationship Between General Muscle Weakness and Respiratory Muscle Weakness:

· Unlike patients with most other neuromuscular diseases, Pompe patients who can still walk (with or without walking aids) already can have respiratory muscle involvement.

· Regular pulmonary function monitoring is therefore an essential element of the management of Pompe patients.

Relationship Between Respiratory Muscles and Pulmonary Function:

· Progressive respiratory muscle weakness - an invariable feature of Pompe disease progression - produces a concurrent decline in pulmonary function (lung volume reduction and worsening of gas exchange).

· The average time from first symptoms of general muscle weakness to weakness of the diaphragm muscle is 12 years (range, 3-20 years).

· Once there is progression from diaphragm weakness to diaphragm paralysis after a couple of years, the patient will experience daytime respiratory failure.

Incidence and Nature of Sleep Disordered Breathing:

· Sleep disordered breathing is a common finding and invariably precedes daytime respiratory failure - typically by several years.

· The extent of sleep disordered breathing depends on residual respiratory muscle force / pulmonary function.

Predictors of Sleep Disordered Breathing:

· Daytime pulmonary function test findings can predict SDB.

· Weakness of the diaphragm invariably leads to SDB.

· An inspiratory vital capacity of less than 60% of predicted is likely associated with transient or mild oxygen desaturations during sleep.

· An inspiratory vital capacity of less than 40% of predicted is likely associated with sustained or severe oxygen desaturations during sleep.