The role of auto-adjustable Continuous Positive Airway Pressure

in Obstructive Sleep Apnoea Syndrome

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List of abbreviations

AHI: apnoea- hypopnoea index

APAP: automatic/auto-adjustable CPAP

$APAP_{fl}$: APAP guided by detection of flow limitation

$APAP_{fot:}$ APAP guided by forced oscillation technique

BiPAP: bilevel positive airway pressure

BMI: body mass index

CPAP: continuous positive airway pressure

EDS: excessive daytime sleepiness

ESS: Epworth Sleepiness Scale

FPAP: fixed CPAP pressure

MAD: mandibular advancement device

OSA: obstructive sleep apnoea

OSAS: obstructive sleep apnoea syndrome

P_{max}: maximum positive airway pressure

P_{mean}: mean positive airway pressure

P_{median} or $P_{50:}$ median positive airway pressure

P_{pred}: predicted CPAP pressure

P_{95}: 95th percentile, pressure which is not exceeded during 95% of the time

PSG: polysomnography

RCT: randomized cross-over trial

RERA: respiratory event related arousal

UARS: upper airway resistance syndrome

I. Introduction

I.1. Obstructive Sleep Apnoea Syndrome

I.1.1. Prevalence

Obstructive Sleep Apnoea Syndrome (OSAS) is a highly prevalent disease affecting millions of people worldwide. Even though it is the most common organic sleep disorder causing excessive daytime sleepiness, it is still widely unrecognised an undiagnosed. Prevalence data vary remarkably depending on the population under study. The prevalence of OSAS is 1-4% according to various cross-sectional studies in the general population, but may be more than 4 to 8% between the age of 40 to 59 years (1-6). The different prevalence data in these studies can in part be explained by differences in study population. Sleep disordered breathing is related to age, gender and body mass index (BMI), and these parameters vary among different study populations. Moreover, statistical outcomes are also influenced by the way respiratory events are defined.

I.1.2. Definition

In the early days, the definition of OSAS seemed to be quite simple. An obstructive apnoea was defined as a complete upper airway collapse, detected by thermistors. A cessation of airflow during at least 10 s, followed by an arousal of at least 3 s, qualified as an apnoea. The OSA syndrome was defined as > 5 respiratory events per hour sleep and the presence of excessive daytime sleepiness (EDS) (7).

Over the years, with the development of more sensitive detection methods, e.g. oesophageal manometry and nasal pressure cannulae, milder degrees of disturbed breathing were detected. Hypopnoea was defined, although rather arbitrarily, as a reduction in airflow of at least 50% or a clear reduction less than 50% with an oxygen desaturation of 2-4% and/or an arousal. (7-9).

Moreover, it was recognized that discrete increases in upper airway resistance could also result in sleep fragmentation with concomitant clinical symptoms. This led to the description of events like flow limitation followed by 'respiratory event related arousals' (RERA's), which are implicated in the pathogenesis of the Upper Airway Resistance Syndrome (UARS).

Many attempts have been made to quantify sleep-disordered breathing, hoping this would improve the ability to predict and correlate with daytime symptoms. One study by Hosselet et al. found that the number of apnoeas, hypopnoeas and flow limitation events best predicted sleepiness, but only with a sensitivity of 71% and a specificity of 60% (10). Currently, the gold standard to quantify OSAS has remained the apnoea-hypopnoea index (AHI), calculated as the sum of apnoeas and hypopnoeas divided by total sleep time (hours).

I.1.3. Clinical presentation and physiological consequences

Many symptoms of OSAS are non-specific and therefore poor predictors for clinically significant disease. Generally, symptoms develop over years and progress with weight gain, aging, transition to menopause, alcohol or sedatives use. Frequently, patients are unaware of having a medical problem and are referred by their bed partner who complains of snoring or is worried about witnessed apnoeas. Snoring is the most frequent symptom of OSAS, occurring in 70-95% of patients (11); but is also very prevalent in the general population; 35-45% of men and 15-28% of women report habitual snoring (12). Patients themselves complain most often about excessive daytime sleepiness, insomnia or unrefreshing sleep. EDS is a consequence of the sleep disruption and changes in oxygenation caused by disordered breathing. A standard method to quantify subjective sleepiness is the Epworth Sleepiness Scale (ESS), a questionnaire asking for the probability of falling asleep in eight well-defined circumstances. Neurocognitive dysfunction can show as impaired work performance,

concentration or memory deficits or increased rate of traffic accidents (13;14). Personality changes such as irritability, anxiety, depression or aggressiveness may be observed. Some patients report matinal headaches, dry mouth, nocturia, oesophageal reflux, a sensation of choking or dyspnoea (15).

In general, important differences between subjects may exist in susceptibility of the central nervous system to biological effects of sleep-disordered breathing on one hand, and perception of symptoms on the other hand. This may explain the imprecise correlation between the severity of symptoms and the AHI (16).

In recent years, it has been proven that OSAS is a risk factor for cardio- and cerebrovascular diseases, independent from the association with obesity (17). An increased incidence of day- and nighttime hypertension has been reported. Arterial hypertension is probably caused by sympathetic overactivity triggered by intermittent hypoxemia, large negative fluctuations in intrathoracic pressure and arousal from sleep (18). OSAS has also been implicated in the pathogenesis of pulmonary hypertension, nocturnal arrhythmias and atherosclerosis (19-22), and has been proven to be an independent risk factor for stroke, myocardial infarction, heart failure and metabolic syndrome (23).

I.1.4. Diagnosis

Although the immense economic burden and the relative simple cure, this disease is still widely underdiagnosed. One of the reasons is a general lack of awareness in patients and doctors with inappropriate referral, due to lack of training in sleep medicine; another reason are the long waiting lists in the diagnostic and therapeutic pathway.

First of all, the likelihood of OSAS has to be determined by obtaining the history, by identifying risk factors and comorbidity and by performing a thorough physical examination.

Through the history taking one should also be able to assess the disease severity with the impact on quality of life, social and occupational function.

Nevertheless, clinical assessment alone is not sufficient for the diagnosis of OSAS, since none of the current symptoms is specific enough (24). Clinical prediction models have been developed to calculate the probability of a patient having OSAS, using symptoms combined with anthropometric and demographic data. These prediction models seemed to have a high sensitivity (76-96%) but a low specificity (13-54%), and they were not validated in populations other than those seen in sleep clinics (15;25;26).

The gold standard for diagnosis remains in-laboratory polysomnography (PSG) attended by a sleep technologist (7;27-29). However, this technique is expensive, labour-intensive, and the use of different equipment and diagnostic criteria makes it difficult to compare PSG data between different labs. The main index obtained from PSG regarding OSAS is the AHI, which is however poorly correlated with clinical outcomes such as EDS (16). While most research on treatment outcomes was performed in OSAS patients with a moderate (AHI > 15/h) to severe (AHI > 30/h) degree, the actual definition also includes mild cases (AHI > 5/h) and the presence of excessive daytime somnolence (7). In Belgium, criteria for reimbursement of CPAP treatment are an AHI > 20/h and an arousal index > 30/h.

I.1.5. Treatment

The mainstay for treatment of OSAS is administration of nasal Continuous Positive Airway Pressure (CPAP) during sleep, which reverses airway collapse by increasing intraluminal pressure, thus providing a mechanical splint that stabilizes the upper airway (30). A lot of work has been done to determine which patients would benefit from therapy with CPAP. OSAS therapy was primarily aimed at improving quality of life by controlling excessive daytime sleepiness. This approach was based on several studies showing that OSAS

patients with EDS benefit the most from CPAP therapy with a significant reduction in sleepiness assessed with subjective and objective measures. Even in mild OSAS and/or when using subtherapeutic levels of CPAP this effect could be demonstrated (31-34). Studies performed in asymptomatic patients with severe OSAS could not prove significant clinical improvement with CPAP therapy (35). Moreover, CPAP has been shown to have a favourable impact on neurocognitive functions, including task performance such as driving simulations, memory function or current daily tasks. Even 3-4 hours of CPAP use per night improved cognition and daytime vigilance (13;14;36).

Considering this evidence, the question remained whether asymptomatic patients would need treatment. Several studies found that CPAP treatment reduced diurnal and nocturnal blood pressure in hypertensive OSAS patients (37-40). Furthermore, favourable effects were seen in patients with congestive heart failure. Appropriate treatment resulted in a substantial reduction in cardiovascular risk, thus influencing patient mortality (40-44).

When initiating CPAP, current guidelines advise to perform a full, attended PSG during which positive pressure is adjusted in order to determine the optimal pressure needed for maintaining airway patency in all sleep stages and body positions (45).

Alternative modes of pressure therapy are seldom indicated. Sometimes bilevel positive airway pressure (BiPAP) is needed, mostly in patients with reduced chest wall compliance or in obesity hypoventilation where high pressures are required in order to maintain normal ventilation (45). This technology allows the deliverance of higher pressures during inspiration, while expiration is facilitated by lowering the pressure.

Similarly, there is no convincing evidence that automatic positive airway pressure (APAP) is superior for long-term treatment in CPAP-intolerant patients (46-48). In the next chapter this item will be further addressed.

For those patients who are intolerant to CPAP, mandibular advancement devices (MAD) can be considered, especially when apnoeas are caused by pharyngeal narrowing at the tongue base. MAD's can be considered as an alternative treatment only in mild OSAS. Therapeutic response is not always predictable and should therefore be confirmed by PSG (49;50).

Over the years, several surgical procedures have been proposed, but there is ongoing debate about effectiveness and indications, which seem to be limited to habitual snoring or mild OSAS (28;29;51).

Last but not least, the importance of weight loss should be emphasized in every obese patient, either by adjusting lifestyle and diet or by bariatric surgery. In a study performed in mildly overweight individuals (BMI < 30), it was stated that a 1% weight change resulted in an approximately 3% change in AHI, although the most favourable results were reported in morbid obesity (52-54).

I.2. The role of APAP in the treatment of OSAS

I.2.1. The gold standard: manual titration

Ever since Sullivan described CPAP (30), this therapy is still considered the gold standard treatment for patients with moderate to severe OSAS. It is widely accepted that adequate CPAP pressure has to prevent any degree of upper airway obstruction in all sleep stages and body positions, in order to restore normal sleep (55). In general, higher pressures are required during REM sleep and in the supine sleep position (56;57). However, the method to determine the optimal CPAP pressure is an unsettled subject for debate. For years, the standard operating procedure was to perform a full PSG in the sleep lab attended by a sleep technician. This allows the technician to manually adjust the pressure as needed and to intervene for problems such as mask fitting or leaks. Subsequently, the optimal pressure for home treatment is derived from the PSG data obtained throughout the night. It is advised to set the final pressure to a level that is sufficient to control sleep-disordered breathing in all body postures and sleep stages **(55)**. Considering the higher pressure requirements in REM or supine periods, the eventual fixed pressure could be considerably higher than necessary for the rest of the night. This higher pressure could increase mask and mouth leaks, pressure intolerance and possibly reduce CPAP compliance. An undeniable drawback of this gold standard procedure is the lack of an unequivocal and standardized algorithm, resulting in considerable intra-technician variability. The procedure is expensive and labour-intensive, while most sleep labs have to deal with long waiting lists for diagnostic and therapeutic PSG.

I.2.2. Alternative titration methods

Because of the mentioned problems accompanying conventional titration, alternative CPAP initiation methods were investigated. In order to meet economic considerations, some

groups started to perform split-night PSG combining diagnostic and titration PSG in one night (58;59), others suggested the use of daytime titration procedures (60).

Another approach was already suggested in the early nineties of last century by the group of Hoffstein. They stated that the optimal CPAP level could be predicted reliably by an equation based on three simple and easily available parameters: body mass index (BMI), neck circumference, and apnoea/hypopnoea index (AHI) (61). Prospective studies validated this equation and found that the predicted pressure (P_{pred}) ranged within ± 2 cm H_2O from conventionally determined CPAP. It was suggested that P_{pred} was a good starting pressure for CPAP titration, in order to optimize or shorten manual titration PSG, not to replace it (62-64). Hukins found that an "arbitrary pressure" based on BMI alone resulted in similar clinical outcomes as manual titration. This was a good starting point for CPAP initiation, allowing to select only the compliant patients for a conventional titration PSG (65). Another randomized crossover trial compared conventionally determined pressure to P_{pred}, which the patient could adjust at home when needed, and found similar results in efficacy, clinical improvement and treatment adherence. They concluded that home self-titration was as efficient as in-laboratory manual titration (66). The group of Stradling also promoted an outpatient-based approach to initiate CPAP therapy using an algorithm based on neck circumference and OSAS severity (number of oxygen desaturation dips > 4 %/h) (67;68). In the end, none of these methods were able to undermine the manual titration as the gold standard.

It was the development of auto-adjustable CPAP devices (APAP), however, that brought on a revolution in thought. These "intelligent" devices monitor a combination of apnoeas, hypopnoeas, flow limitation or snoring and try to find the ideal pressure by adapting the pressure level.

I.2.3. APAP technology

Currently, a wide variety of APAP devices has been commercialised. They use different methods to detect upper airway obstruction and different algorithms to adapt the pressure accordingly. In general, the devices monitor airway vibration (snoring), airflow reduction (apnoea or hypopnoea), flow vs. time profile (flow limitation) or impedance with the forced oscillation technique. Most devices start at a low baseline pressure (4 cm H_2O) and gradually increase or decrease the pressure in the presence or absence of respiratory events. As a consequence, during wakefulness the pressure can be minimal, while during sleep it will slowly adapt according to the degree of upper airway obstruction in all sleep stages and body positions. This should allow APAP to constantly deliver the minimum effective pressure, not only during one night, but also from night to night.

APAP devices are used mainly to titrate the fixed CPAP level or to treat the patient at home, more seldom they are used as a screening device for identification of OSAS. A titration procedure with APAP can occur in attended conditions, allowing the technologist to intervene when needed and to titrate several patients at the same time. Performing unattended APAP titration at home, however, could reduce waiting lists in the sleep lab and realize cost savings, provided that APAP devices are reliable in determining the pressure in unattended conditions in a majority of CPAP patients. When using APAP for chronic treatment at home, it is suggested that the lower pressure levels could improve patient comfort and eventually adherence and compliance (69;70).

I.2.4. APAP performance in research

At first, studies using APAP in a **titration** setting compared APAP to conventional titration as a method to determine the fixed pressure level for home treatment. They concluded that APAP titration was as effective as manual titration since it was equally

efficient in lowering the AHI to acceptable levels (AHI <10/hr) in most of the patients studied (71-79). Unsuccessful titration was reported in a few patients, mostly due to artefacts such as severe mask or mouth leak. In these patients the pressure increased to inappropriately high levels due to inappropriate event detection (79).

After APAP titration, a fixed pressure can be derived for **home treatment** or APAP can be used as a substitute for CPAP in home treatment. Several cross-over trials confirmed that both treatment modalities were comparable to conventionally determined fixed pressure (FPAP) in terms of respiratory control (as defined above) and impact on sleep quality (reduction in arousal index <20/hr and increased slow wave and REM sleep). The same results were reported for clinical outcomes showing reduced subjective and objective measures of sleepiness (80-96).

As hypothesized, several studies confirmed that there was a tendency to lower mean or median **pressure levels** with APAP than with conventionally determined FPAP (71;73;75-78;80-82;92;97). FPAP was mostly 1-2 cm H_2O higher but could exceed the mean APAP by as much as 6 cm H_2O.

The **acceptance** of CPAP therapy by patients was similar or even slightly better after APAP titration leading to a lower drop out rate in one study (98) and a subjective preference for APAP in others (77;81). It was also stated that APAP improved patient adherence and compliance since lower pressure profiles offered more patient comfort. Compliance data derived from APAP time-loggers over variable periods (2 weeks to 6 months) confirmed a tendency to higher APAP usage (77;82;85;87;88;94). Although a larger benefit in compliance was expected, previous research had already shown that pressure (in)tolerance was less important in this matter. Patient preference and compliance are influenced mostly by education and motivation by health care professionals and by treating side effects, more than by the characteristics of the machine itself (99-102).

Most investigators admitted having difficulties to identify (a subgroup of) OSAS patients who would benefit more from APAP than from CPAP. Some found good results in those patients with highly variable pressure needs, for example patients with sleep stage and body position dependent OSAS (103) or in patients needing high pressure levels (> 10 cm H_2O) (87).

As a conclusion to all these optimistic results, several studies stated that APAP was safe and efficient as a titration tool and as home treatment, even in unattended conditions (81;82;88;94;95;104;105). It was suggested that APAP technology could alleviate the need for a titration PSG (106).

Optimism seemed to be less appropriate when several devices were compared to each other in clinical trials. Devices reacted differently or even inadequately to respiratory events and a considerable lack of agreement in pressure levels was found (89;107-110). Also, data on compliance, patient adherence and preference, were contradictory in several trials and predicting factors for better tolerance with APAP remained unclear (86).

Considering the often contradictory and confusing results obtained by clinical studies, another approach to test the performance of APAP devices was mandatory. **Bench models** were developed capable of reproducing realistic and well-defined sleep-disturbed breathing patterns. The advantage of bench testing over clinical studies is that inter- and intra-patient variability is eliminated. It allows determining whether an APAP device performs adequately in detecting respiratory events and in adapting the pressure according to its specific algorithm. Bench testing, however, only confirmed the considerable differences in pressure profiles, as seen in clinical trials (111-114).

Recent studies compared the main CPAP initiation methods. Patients were randomized to manual titration, unattended APAP titration at home or P_{pred} with domiciliary adjustment when needed (residual snoring or apnoeas) (115). After CPAP treatment for three months, the

PSG variables and Epworth Sleepiness Scale showed statistically significant improvement in the three groups. The residual AHI under treatment with P_{pred} was slightly higher, but this was not translated to differences in clinical outcomes. Although the APAP group reported more side effects, compliance data and dropout rates were similar (115). West et al. compared clinical outcomes after home treatment for six months in three groups: 1) APAP, 2) FPAP determined after one week of APAP (P_{95}), 3) FPAP determined by a prediction formula. Pressure levels were significantly different in the three groups; in particular the P_{95} group received remarkably higher pressures than the two other groups. Nevertheless, subjective and objective measures of sleepiness, quality of life scores, but also 24 hour blood pressure were similar in all three groups. They concluded that the method of determining CPAP pressure makes no significant difference to clinical outcome measures and that the use of APAP has no advantage over simpler methods of pressure determination (116).

I.2.5. Limitations of APAP (research)

A major problem of APAP technology is that manufacturers commercialize devices without standardized clinical testing. The designers implement their own proprietary algorithms, the detail of which is usually kept undisclosed for commercial reasons. Accordingly, the available APAP devices appear as "black boxes" able to modify pressure according to rules which are not revealed to the sleep specialist (117).

Most APAP devices feature an electronic memory that stores pressure data from previous use. This information is available to the sleep specialist, who may extrapolate these pressure profiles to derive an 'optimal' pressure level for subsequent FPAP use. Some clinicians select FPAP after visualization of the raw data and eliminate periods of significant air leaks (98), others use the P_{95}, being the pressure that is not exceeded during 95% of the time. It was shown that the P_{95} correlated well to a manually determined pressure and was

therefore suitable as a fixed pressure for home treatment (74;79;108;118). One of these studies, however, demonstrated that the P_{95} could differ considerably between APAP devices (108). In this study there was a bias of 3 cm H_2O and a complete lack of agreement between the two devices tested (limits of agreement – 3.2 to 9.3 cm H_2O), leading to the conclusion that unattended automated titration is not reliable enough to replace manual titration.

The limited information this "black box" provides does not allow checking if false events or artefacts are properly identified. Examples of artefacts are coughing, mouth or mask leaks, speaking, sighing, swallowing or movements during arousals. These artefacts may confuse the operational algorithm and cause inappropriate pressure increases (119). Little research was done on safety and side effects of APAP, especially in patients with central apnoea or cardiopulmonary disease, since these patients were excluded systematically in most trials. Two publications mentioned the occurrence of central apnoeas under APAP, increasing when high pressures were applied (120;121). It was reported that the occurrence of central apnoeas could activate APAP to perform a pressure increase without resolving the events, but, on the contrary, eventually causing more central apnoeas (122). Another fact is that patients with lung disease or obesity hypoventilation in association with OSAS may have residual oxygen desaturation that could be missed during unattended APAP titration or therapy. Thus, the need for treatment with higher pressures, supplemental oxygen or switch to BiPAP may be overlooked.

Most clinical trials used a reduction in AHI < 10/h as a criterion for acceptable treatment, although reduction to < 5/h and elimination of airflow limitation could be necessary to reverse symptoms like sleepiness in individual patients (123;124). Not all APAP devices, however, are able to detect flow limitation.

Based on these controversial data, a review paper by the American Academy of Sleep Medicine recommended the use of APAP titration only in attended conditions since it was

found not reliable enough to be used as a substitute for attended CPAP titration. They stated that the evidence for and against the premise that APAP treatment would increase acceptance and adherence was conflicting (27;47).

I.3. Aim of the research

When we started to perform clinical trials with APAP, there were no published data comparing the effectiveness of different APAP technologies. Whilst most APAP technologies seemed to be efficient with respect to lowering the AHI, pressure outcomes differed significantly. Moreover, this different performance was not translated into an important difference in clinical outcomes. The aim of the present research was to carry out a face-to-face comparison of different APAP devices in a CPAP titration setting, the hypothesis being that different pressure adjustment algorithms can result in different outcomes regarding sleep and respiratory variables.

Our first two randomized cross-over trials (RCTs) compared two APAP devices from different manufacturers using different detection methods and algorithms. In the third RCT APAP devices were compared operating by the same detection method, but responding with a different algorithm. Finally, in order to put on trial the superiority of APAP titration, we compared this method to P_{pred} based on the Hoffstein prediction formula.

I.4. Materials and methods

I.4.1. Subjects

The target population were patients diagnosed with OSAS according to Belgian criteria for reimbursement of nasal CPAP (i.e. AHI > 20/h and arousal-index > 30/h). After the diagnosis of OSA was established, patients were habituated on CPAP treatment at home on a pressure level derived from a prediction formula based on BMI, neck circumference (NC) and AHI [(0.13*BMI)+(0.16*NC)+(0.04*AHI)-5.12] (61). During follow-up consultation after one month it was evaluated whether adjustment was needed based on residual symptoms of sleepiness or snoring. After the habituation period a standard overnight polysomnography was carried out in the laboratory. The exclusion criteria and reasons for drop out are described in the research articles. Patients were asked to participate in the trials as they were readmitted to hospital for their titration PSG.

I.4.2. Study design

In a double blind randomized order, two titration methods were used for each patient during the same night using a split-night protocol. Both methods were compared regarding their effect on relevant sleep and respiratory variables, and pressure levels were collected from the PSG data. The morning after the titration study a subjective evaluation of sleep quality was carried out, using a questionnaire and visual analogue scales. In addition, the patients were asked to indicate their preference for one of the devices as if they would have to choose between them for continued use at home. This subjective preference was compared with objective preference, which was defined in terms of better AHI control.

I.4.3. Sleep studies

Polysomnography was carried out using a 19-channel digital polygraph (Morpheus™, Medatec, Brussels, Belgium). To record airflow, thermocouples plus nasal pressure cannulae were used during baseline studies (125). In order to correct for the nonlinearity of the pressure signal derived from nasal prongs, the square root was performed on this signal (126). During the A-CPAP trial, airflow was evaluated by measuring the respiratory pressure fluctuations in the nasal mask, which was connected via 4 mm diameter flexible tubing to the built-in manometer (Honeywell 164PC01D37, Freeport, Illinois, USA). This recording closely resembles the signal derived from nasal cannulae, and allows reliable detection of apneas, hypopnoeas and flow-limitation(127). Respiratory movements were recorded using thoracic and abdominal piezo-sensors (Sleepmate™, Midlothian, VA, USA). Respiratory events were manually scored according to contemporary guidelines (128). An apnea was defined as a total cessation of airflow during at least 10 seconds. For a hypopnoea a decrease of airflow of at least 50% was needed, or a clear decrease less than 50% with an oxygen desaturation > 3% and/or an arousal. The AHI was calculated as the sum of apneas and hypopnoeas divided by total sleep time (hours). Inspiratory snores were manually counted. The snoring-index was computed as the sum of inspiratory snores divided by total sleep time (hours). Sleep stages were identified according to standard criteria (129). The scoring of arousals was based on published guidelines (130). The arousal-index was the sum of arousals divided by total sleep time (hours). Sleep stages, respiratory and snoring events, arousals and CPAP levels were assessed in epochs of 30 sec. CPAP was determined as the average pressure level over the 30 sec epoch.

I.4.4. Functional algorithms and characteristics of the APAP devices

All APAP's used in our trials are pro-active devices responding to early indications of airway obstruction in an attempt to avoid the occurrence of frank apnoeas or hypopnoeas.

I.4.4.a. Forced oscillation technique (FOT): Weinmann SOMNOsmart[TM]

The "forced oscillation technique" is a noninvasive method to measure the upper airway impedance in order to quantify and assess the degree of airway obstruction. It consists of superimposing a small pressure oscillation on spontaneous breathing through a nasal mask. Airflow is measured using a pneumotachograph; resistance is calculated as the $\Delta P/V$ ratio. Respiratory impedance is derived from pressure and flow signals recorded at the nasal mask, and is the resistance to oscillatory flow. During obstructive hypopnoeas the inspiratory impedance is intermittently increased, whereas during obstructive apnoeas a permanent elevation of the impedance is present. In central apnoeas the impedance is either low (open airway) or high (closed airway).

In the SOMNOsmart[TM] pressure oscillation is applied with a frequency of 20 Hz and a pulse wave of 200μbar. The impedance is calibrated between 0% (nasal mask open to the air) and 100% (nasal mask manually occluded). When obstructive apnoeas occur the impedance rises to 100%, whereas in central apnoeas the impedance remains at a low level.

First a five minutes adaptation period is carried out, during which the patient breathes quietly through the nasal mask. The device calculates the average impedance, which is characteristic to the individual patient. If snoring is detected, the pressure will rise with 0.5 mbar each 20 seconds, starting after one minute. After this initialization phase slow changes in baseline impedance (e.g. nasal congestion) are detected and the individual impedance value is continuously adjusted.

I.4.3.b. Flow limitation

The respiratory flow-contour is rounded (sinusoidal) in normal unobstructed breathing. Upper airway obstruction is heralded by a flattening of the flow-contour in the mid-inspiratory portion. The arch of the flow-contour may be quantified by the curvature index (c.i.), which is the mid- inspiratory flow calculated as a fraction of the mean inspiratory flow. A low curvature-index indicates a high degree of flattening.

The **RESMED AutoSet^{TM}** responds differently to various degrees of flattening. Severe flattening (c.i. 0.05) will induce pressure increases of 0.2 mbar/tidal volume ($\pm$ 2 mbar/min), whereas the pressure will remain unchanged with mild flattening (c.i. 0.15). Unobstructed breathing is characterized by absence of flattening (c.i. 0.25), resulting in an exponential decline in CPAP using a time constant of 20 minutes. Since snoring is associated with a more severe degree of upper airway obstruction, the pressure will be raised with a rate of 1 mbar/tidal volume. The mask pressure and the bias flow of the device are also monitored by an electronic circuit. When the patient takes of the nasal mask, the flow is automatically stopped. Air leak, due to loosening of the mask or opening of the mouth, is represented as average flow measured with a low-pass filter ($t_{1/2}$ 20 sec). Autotitration is reliable up to a leak of 0.4L/sec.

The **REMstar Auto^{TM}** algorithm actively tests for flow limitation instead of waiting for it to occur. Two types of tests are performed in order to determine the critical (P_{crit} test) and optimal (P_{opt} test) pressures. The P_{crit} test involves reducing the pressure and examining the flow signal for flattening. Pressure is ramped down towards the minimum pressure until an increase in flow limitation is detected and the pressure subsequently begins to increase. It may ramp down through several pressures to find the critical pressure. The P_{opt} test increases the pressure at a rate of 1 cm H_2O every two minutes while the flow signal is examined for a reduction in flow limitation. In the absence of improvement the pressure

returns to the previous value, in the presence of improvement pressure increases will continue. These two tests allow the pressure to be maintained at a level where obstruction is not likely to occur, without raising it to unnecessarily high levels.

During operation the system may be in a testing or non-testing mode. In the testing mode, P_{crit} and P_{opt} tests will be performed to determine the proper therapeutic pressure. In either mode, the system monitors breathing and looks for snoring, apnoeas and hypopnoeas. The system will stay in the testing mode for five minutes, or longer if variable breathing is detected.

The **ResMed Spirit**^{TM} also calculates and delivers the optimal treatment pressure by analyzing respiratory airflow data. The pressure is automatically and continuously adjusted to the optimal level sufficient to prevent airway obstruction. The system does not differentiate between open and closed apnoeas. Response to apnoeas is limited to an increase of the pressure to a maximum of 10 cm H_2O. However, the device will continue to raise the pressure in response to flow limitation and snoring,

II. Research

II.1. Efficacy of flow- versus impedance guided auto-adjustable CPAP: a randomized cross-over trial

Pevernagie D, Proot P, <u>Hertegonne K</u>, Neyens M, Hoornaert K, Pauwels R.

This paper compared the titration capacity of two APAP devices whose operation is based on different modes of sensing incipient upper airway obstruction. Thirty patients were included in a double-blind randomized cross-over trial. Using a split-night protocol every patient could use both devices during the same night in a randomized order. The AutoSet^{TM} uses a pneumotachograph to detect flow limitation of inspired air (APAP$_{fl}$); whereas the SOMNOsmart^{TM} uses the forced oscillation technique (APAP) to measure changes in impedance, aiming to keep the resistance below a given percentage of wakefulness values. On both APAP devices favourable outcomes had already been reported when studied in an attended titration setting and for unattended home treatment. Since it has been shown that devices can respond differently to changing pressure demands, we hypothesized that this would occur in these two devices running on different detection methods and algorithms. This study was designed to compare the titration efficacy of these two APAP technologies in terms of effects on sleep quality, respiratory disturbance and snoring indexes. It was also evaluated whether the pressure output was appropriate in terms of magnitude and variability.

APAP$_{fl}$ provided a significantly better control of snoring than APAP$_{fot}$, and resulted in a lower AHI (although not significant). The pressure levels rose significantly with the transition from wakefulness to sleep for APAP$_{fl}$, but fell paradoxically for APAP$_{fot}$. In addition, APAP$_{fot}$ was subject to significantly higher pressure variability.

II.2. Comfort and pressure profiles of two auto-adjustable positive airway pressure devices: a technical report

Hertegonne KB, Proot PM, Pauwels RA, Pevernagie DA

In this trial the AutoSet[TM] and the SOMNOsmart[TM] were also compared to each other, but in terms of subjective tolerance and pressure parameters. For all 50 patients included, the overall comfort of both devices was satisfactory. Subjective preference for one of both devices was equally divided. The pressure profiles, however, were remarkably different. The SOMNOsmart[TM] produced significantly lower values for P_{50} and $P_{95,\ whereas}$ P_{max} values were not significantly different. Interestingly, the AutoSet[TM] pressure profiles correlated significantly better with P_{pred} than those of the SOMNOsmart[TM].

II.3. Titration efficacy of two auto-CPAP devices using different flow limitation based algorithms

<u>Hertegonne KB</u>, Rombaut B, Houtmeyers Ph, Van Maele G, Pevernagie DA

In our previous studies two APAP devices generated similar clinical results but remarkably different pressure outcomes and variability, which could be explained by the difference in operational characteristics. To substantiate this hypothesis, we compared two APAP devices that use a similar detection method, in particular the detection of inspiratory flow limitation which proved to perform better in our research. The REMstar Auto[TM] and the ResMed Spirit[TM] were used in a face-to-face comparison; both operate on flow limitation detection, but adapt the pressure according to a characteristic algorithm. This trial was also designed as a split-night protocol, in order to allow all 50 patients to use both devices in the same night, in a double-blind randomized order.

Sufficient respiratory control was obtained with both devices, but the AHI was significantly lower for the REMstar Auto[TM]. Remarkably, this result was achieved with lower pressure levels. This study also confirms that different APAP performance was not translated to differences in subjective evaluation or preference by the patient.

II.4. Titration procedures for nasal CPAP: Automatic CPAP or prediction formula?

Hertegonne KB, Volna J, Portier S, De Pauw R, Van Maele G, Pevernagie DA

In this trial, two identical REMstar Auto™ devices were used in 45 patients during the same night, one operating in the automatic titration mode and one in the fixed mode on predicted pressure. The goal of this study was to evaluate whether APAP is superior to a prediction formula in assessing the optimal FPAP for home treatment. The primary outcome was the AHI; secondary outcomes were pressure profiles and subjective evaluation of sleep quality.

The residual AHI was not significantly different in both treatment conditions, only the central apnoea index was higher in APAP than in FPAP mode. The predicted pressure was lower than APAP pressure levels and, in terms of bias, corresponded best with P_{mean} and P_{50} of APAP, not with P_{95}. However, there was a lack of precision in all APAP pressure categories or a poor agreement between individual pressure levels. There was no difference in subjective appreciation and no correspondence between subjective and objective ratings.

III. Discussion

DISCUSSION

The aim of this research was to carry out a face-to-face comparison of different APAP devices in a CPAP titration setting, the hypothesis being that different pressure adjustment algorithms could result in different outcomes regarding sleep and respiratory variables.

In our *first two trials*, we compared two APAP devices operating on different detection methods. We found that the $APAP_{fl}$ (AutoSet^{TM}) achieved lower AHI and snoring indices than the $APAP_{fot}$ (SOMNOsmart^{TM}), but only reaching statistical significance for the snoring indices. This last device generated a lower average pressure and showed marked pressure variability. Both devices differ in algorithm, which determines the speed and amount of pressure adjustment. The SOMNOsmart^{TM} shows a steeper slope of adaptation for both lowering and increasing the pressure in response to respiratory events, which can explain the higher pressure variability. Unfortunately, these fast pressure adjustments are also seen as a response to unphysiological signals, e.g. awakenings, leading to high pressure levels at inappropriate times. This could explain the inappropriate pressure increase on transition from sleep to wakefulness when using the SOMNOsmart^{TM}. The AutoSet^{TM} algorithm, on the other hand, allows slower pressure adaptation and is able to compensate for pressure drops due to excessive air leakage.

In order to substantiate our hypothesis that operational characteristics can account for different APAP performance, in our *third trial* we compared two devices that detect flow limitation, but are driven by different operational algorithms. The residual AHI was significantly lower at lower pressure levels with the use of the REMstar Auto^{TM} compared to the ResMed Spirit^{TM}. Again this paradox could be explained by algorithms. The ResMed Spirit^{TM} has a steeper slope for increasing than for decreasing the pressure. A delayed pressure decrease could lead to overprescription when the pressure is inadequately increased

as a response to artefacts. Moreover, pressure-resistance hysteresis may enable faster downward than upward titration, and a slow time constant will delay appropriate pressure decreases. The algorithm of the REMstar Auto^{TM}, on the other hand, constantly performs tests to assess the 'optimal' and 'critical' pressure, resulting in faster but smaller adjustments. When pressure increases are not followed by elimination of the detected events, the device will lower the pressure again to its previous level. Eventually, this could result in lower effective CPAP levels as found in this trial.

In our own clinical setting, we initiate OSAS patients on CPAP therapy on a pressure determined by the prediction formula of Miljeteig et al. Using this method we obtained a favourable clinical response in the vast majority of our patients. Occasionally, the pressure set to this predicted level requires slight adaptation on follow-up visits. In ***the fourth trial***, the APAP device that performed better in our previous trials, a device detecting flow limitation was compared to the fixed, predicted pressure for that patient. Again both methods succeeded in obtaining adequate respiratory control, but the APAP pressure levels were significantly higher than P_{pred}. In terms of bias, the P_{pred} corresponded best with P_{mean} and P_{50} of APAP, suggesting that the use of P_{95} as the fixed pressure for chronic treatment could result in overprescription. Our findings are in contrast to the APAP literature, in which $P_{95\ was}$ generally considered suitable as a fixed pressure for home treatment, since it correlated well to a manually determined pressure. The observed imprecision of the P_{95} in our trial could reflect random variation in CPAP requirements on one hand, but also intrinsic variability of the APAP technology on the other hand. This confirms the need to clarify the validity of P_{95} assessment for subsequent FPAP treatment.

Another finding in this study was that although P_{mean} and P_{50} strongly corresponded with P_{pred} (low bias), the correspondence between the individual values was not precise (large variance). Considering this poor agreement, Pmean or P_{50} values cannot be recommended for

determining the fixed pressure level for home treatment. The same applies to the P_{90}, P_{95} and P_{max} values which, in addition to poor agreement, have a considerable bias to the P_{pred}.

In previous research it was stated repeatedly that differences in delivered pressures were not paralleled by differences in correcting patients' sleep-disordered breathing. Moreover, proof was never offered that these differences were relevant in terms of (long-term) clinical outcomes. Our research consistently found a paradox between different APAP performance and indifferent subjective evaluation and preference. As stated above, this apparent paradox may in part be explained by methodological and design issues. Moreover, we hypothesize that there is a margin of pressure tolerance around an optimal CPAP level in a given patient at a given time. On one hand, when the pressure is reduced below the critical closing pressure of the upper airway, obstructive events will reappear. On the other hand, when the pressure is raised above an upper threshold, air leakage or even central events could be induced. This conceptual margin of pressure tolerance may amount to several centimetres of water. As long as APAP devices, regardless of pressure adjusting methods, operate in the presumed zone of pressure tolerance, a substantial control of sleep-disordered breathing will be obtained. Especially when the lower threshold (i.e. the critical closing pressure of the upper airway) is small, all devices will be efficient. This may explain why only small differences between APAP devices can be demonstrated in clinical studies.

Finally, the results of the present work indicate that, in the majority of patients, it is safe to initiate CPAP therapy on a predicted pressure. There seems to be no additional advantage in performing an additional APAP titration procedure if patients are stable under this pressure, although this hypothesis needs further testing, especially regarding long term therapy outcomes regarding cardiovascular and overall mortality. If this could be confirmed in long term outcome trials, it could be justified to perform a titration procedure, only in a subgroup of patients with residual symptoms. This proposition could have favourable

consequences for the huge economic burden of OSAS, but would also increase the diagnostic

capacities of sleep labs, and in the end promote the quality of patient care.

IV. Summary
Samenvatting

SUMMARY

Since Continuous Positive Airway Pressure (CPAP) was first introduced in the early eighties for the treatment of Obstructive Sleep Apnoea syndrome (OSAS), controversy has never been cleared on the optimal method to initiate this therapy. A revolution in thought was brought about with the development of automatic CPAP (APAP) devices that were, however, manufactured and marketed without firm evidence of their added value. Each manufacturer designed devices differing in detection method and in pressure adjustment algorithm. The first clinical studies emphasized on the equivalent performance of APAP and CPAP in improving the apnoea- hypopnoea index (AHI) and sleep quality. It was proclaimed that the added advantage of APAP was the possibility to achieve this goal with lower pressures, which was hypothesized to promote patient acceptance and compliance.

The connecting thread in this thesis is face-to-face comparison of different APAP devices in a CPAP titration setting, the hypothesis being that different pressure adjustment algorithms should result in different outcomes regarding sleep and respiratory variables.

Our first trials compared devices differing in detection method and algorithm. Both devices achieved adequate respiratory control, with only a statistically significant difference for snoring. Pressure outcomes differed significantly, which could be explained by the operational characteristics of each device. The next step was the comparison of devices operating on a similar detection method but with different algorithms. The main outcomes were a lower AHI and lower pressure levels for one device, for which again the algorithm could account for. Finally, we compared APAP titration to a fixed pressure determined by a prediction formula (P_{pred}). Both methods were equally efficient in lowering the AHI, but the fixed pressure was lower than the APAP pressure levels. Moreover, the fixed pressure correlated better to the mean (P_{mean}) and median (P_{50}) APAP pressures (low bias) than to the

95th percentile APAP pressure (P_{95}), which had been recommended as the preferred pressure for home treatment. Another finding in this study was that the correspondence between the individual mean and median APAP values was not precise (large variance), so these values cannot be recommended for determining the fixed pressure level for home treatment. The same applies to the P_{90}, P_{95} and P_{max} values which, in addition to poor agreement, have a considerable bias to the P_{pred}. A consistent finding in all trials was the paradox between different APAP performance and similar subjective evaluation and preference.

Our research subscribes other publications that state that the titration method used is not of overriding importance in initiating CPAP therapy. The use of expensive APAP devices is not superior to the use of a simple and efficient prediction formula in terms of short term clinical outcomes. As long as the selected pressure is situated within a therapeutical margin of pressure tolerance around the critical closing pressure of the upper airway, respiratory control will be adequate in the majority of patients. From this point of view, we can conclude that CPAP therapy can be safely initiated on predicted pressure. If this could be confirmed in long term outcome trials, it could be justified to perform a titration procedure, only in a subgroup of patients with residual symptoms.

In our trials the APAP devices used were efficient in obtaining adequate respiratory control, but pressure outcomes differed considerably. These differences could be accredited to the detection method and the pressure adjustment algorithm a specific device operates on. The problem is, however, that the manufacturers do not provide detailed information on the algorithms. Our data support the theorem that APAP devices should be submitted to standardized clinical and bench testing before commercialization. Moreover, APAP devices should no longer be commercialized as 'black boxes', the clinician should be provided with detailed information on the mode of action of a specific device.

SAMENVATTING

Sinds de jaren '80 is *'continuous positive airway pressure'* (CPAP) via nasale weg de hoeksteen in de behandeling van matig tot ernstig obstructief slaapapnoe syndroom (OSAS). De optimale CPAP druk zou iedere vorm van slaapgebonden respiratoire belemmering ter hoogte van de bovenste luchtwegen moeten voorkomen, niet enkel apnoe's, hypopnoe's en snurken, doch eveneens *'flow limitation'*. Tot op heden bestaat controverse rond de manier waarop men die optimale therapeutische druk bepaalt. Internationaal geldende richtlijnen adviseren manuele titratie tijdens polysomnografie, doch een eenduidig protocol voor deze procedure werd nooit gevalideerd.

Als alternatief voor deze arbeidsintensieve titratiemethode werden automatische CPAP (APAP) toestellen voorgesteld die in staat zijn op ieder ogenblik de druk aan te passen aan de nood van de patiënt. Een breed gamma van dergelijke toestellen werd gecommercialiseerd, doch zonder stevig bewijs van hun toegevoegde waarde. Deze toestellen verschillen sterk in de manier waarop ze adembelemmering detecteren (de detectiemethode) en in de manier waarop ze hierop reageren (het operationeel algoritme). De eerste klinische studies benadrukten dat APAP even efficiënt is als CPAP in het verbeteren van de slaapkwaliteit en de respiratoire controle. Er werd bovendien gesuggereerd dat de toegevoegde waarde van APAP zou liggen in de mogelijkheid om deze objectieven te behalen met lagere drukken, wat de aanvaarding en therapietrouw door de patiënt zou bevorderen.

De rode draad in deze thesis is de rechtstreekse vergelijking van verschillende APAP toestellen in een titratieprocedure ter bepaling van de optimale CPAP druk. De hypothese is dat verschillende operationele karakteristieken voor adaptatie van de drukprofielen resulteren in manifeste verschillen in slaapparameters en respiratoire controle.

In onze eerste twee studies werden twee toestellen vergeleken met een verschil zowel in detectiemethode als in algoritme. Beide methodes slaagden erin de apnoe-hypopnoe-index

(AHI) adequaat te doen dalen, doch de meting van '*flow limitation*' ($APAP_{fl}$) resulteerde in een iets betere respiratoire controle dan de impedantiemeting ($APAP_{fot}$). De verschillen in drukprofielen konden eveneens verklaard worden door de operationele karakteristieken van het respectievelijke toestel. De volgende stap was dan ook het vergelijken van twee toestellen met dezelfde detectiemethode ($APAP_{fl}$) doch met verschillende algoritmes. Het ene toestel genereerde een lagere AHI en daarenboven lagere drukken, opnieuw te verklaren door het specifieke algoritme. Tot slot vergeleken we APAP titratie met een vaste druk gebaseerd op een predictieformule (P_{pred}). Beide methodes resulteerden opnieuw in een efficiënte daling van de AHI, doch de vaste voorspelde druk was lager dan de APAP drukken. Daarenboven correleerde die vaste druk beter met de gemiddelde en mediane APAP druk (lage bias) dan met de 95ste percentiel van APAP, die nochtans in de literatuur aanbevolen werd als de optimale druk voor lange termijn behandeling. De individuele waarden van APAP en vaste druk daarentegen vertoonden een slechte overeenkomst (grote variantie), zodat de mediane of gemiddelde druk evenmin aanbevolen kunnen worden voor het instellen van de behandeling thuis. Hetzelfde werd aangetoond voor de andere APAP waarden (90ste en 95ste percentiel en maximale druk) die naast deze grote variantie nog een aanzienlijke bias vertonen tegenover de P_{pred}. Ten slotte, een consistente bevinding in al onze studies, was de paradox tussen de verschillende performantie van de APAP toestellen en de gelijkwaardige subjectieve evaluatie en voorkeur aangegeven door de patiënt.

Ons onderzoek onderschrijft andere publicaties die stellen dat bij het opstarten van een CPAP behandeling de keuze van de titratiemethode niet van doorslaggevend belang is. Met betrekking tot klinische resultaten op korte termijn is het gebruik van dure APAP toestellen niet superieur ten opzichte van het gebruik van een meer eenvoudige en eveneens efficiënte predictieformule. Een adequate respiratoire controle kan bereikt worden in een meerderheid van de patiënten op voorwaarde dat de geselecteerde druk zich bevindt binnen een

therapeutische marge van druktolerantie rond de kritische sluitingsdruk van de bovenste luchtweg. Vanuit dit standpunt kunnen we concluderen dat het veilig is om CPAP therapie te starten aan de hand van een predictieformule. Indien dit bevestigd zou worden in mortaliteitsstudies, zou men kunnen verdedigen dat enkel in een subgroep van patiënten met residuele symptomen het uitvoeren van een titratieprocedure aangewezen is. Dit voorstel zou de enorme economische last van OSAS gevoelig kunnen verminderen, maar zou ook de diagnostische capaciteit van slaapcentra kunnen verruimen, en uiteindelijk de kwaliteit van de patiëntenzorg in het algemeen bevorderen.

In onze studies toonden we aan dat alle gebruikte APAP toestellen een adequate respiratoire controle bereikten, doch met manifeste verschillen in drukprofielen. Deze konden toegeschreven worden aan de detectiemethode en de algoritmes van de specifieke toestellen. Het probleem is dat producenten van APAP toestellen om commerciële redenen geen gedetailleerde informatie verschaffen over die algoritmes. Onze data ondersteunen de stelling dat APAP toestellen dienen onderworpen te worden aan gestandaardiseerd klinisch en proefbankonderzoek alvorens wereldwijde commercialisatie. Daarenboven dient het 'zwarte doos' concept verlaten te worden, gedetailleerde informatie over het algoritme van specifieke APAP toestellen moet ter beschikking gesteld worden aan de clinicus.

V. Future perspectives

Interesting topics for future research emerge from the results of our own studies and research from other groups.

We studied several APAP devices with fundamental differences regarding detection method and operational algorithms. All proved to have a beneficial effect on sleep disordered breathing, but performed quite differently when compared to each other. As stated above, criteria need to be set for standardized clinical and bench testing to which all new APAP devices should be submitted in order to prove their efficiency before commercialization.

It would be interesting to design an APAP device that operates on a combination of different indicators for event detection, therefore combining the best of every method.

In the discussion section, the hypothesis was formulated that a safe margin of pressures tolerance exists around the critical closing pressure of the upper airway. This hypothesis could be tested by performing a titration polysomnography starting with low pressures and repeatedly increasing the pressure after a fixed time. For every pressure level the residual AHI could be calculated, as well as mask or mouth leaks and the pressure under which central apnoeas might occur. Thus a pressure-response curve could be determined analogue to pharmacodynamic studies.

Most important, I would like to emphasize that in the last decades many research has been performed on the technical performance of APAP devices, but most studies focussed on short-term outcomes. Large-scale randomised clinical trials should be performed to investigate the role of APAP titration and therapy, especially regarding long-term outcomes such as cardiovascular morbidity and mortality related to this highly prevalent disease.

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Acknowledgements

It's a long bumpy road to paradise, it seems. This and more can be said about the scientific road towards the fulfilment of a PhD thesis. Fortunately, science is an adventure in which one finds many interesting and invaluable people. The first one was the late Professor Romain Pauwels who encouraged me as well as many other young physicians to round up our education by immersing ourselves into research. It was only after my training in pulmonary medicine, however, that I was able to set my first steps into the challenging world of clinical research. It was Professor Dirk Pevernagie who introduced me into the fascinating field of sleep medicine. His never declining enthusiasm and guidance together with his innovative ideas have been a great source of inspiration during these last years. He has been not only a fine promoter and mentor for this thesis, but also offered me a valuable friendship into the bargain. For all this, I owe him a large debt of gratitude.

I would also like to thank Professor Guy Joos for welcoming me into the department as a staff member and for creating the environment in which sleep medicine can flourish in all its aspects. Of course this would not be possible without the support of the whole staff within our department and across our limited borders. Thanks to the dedication to sleep medicine of people like An Mariman, Dirk Vogelaers, Miche De Meyer, Karlien D'Hondt, Sofie Claeys and others we succeeded in organising a muldisciplinary cooperation built on solid foundations. The unremitting encouragements in troublesome times have been more than inspiring.

My humble thanks go to the fantastic team that realized the accomplishment of this journey. In particular Marleen Neyens managed to turn scientist's nebulous ideas into concrete,

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