ERS Long-Term Research Fellowship: Applicant´s Personal Statement

The home mechanical ventilation (HMV) program in Chile is young, thus few pneumologists have experience in long-term non-invasive ventilation (NIV) therapy. During 2014-2016, thanks to a scholarship from my University, I made a training fellowship in HMV with Prof.Dr. Wolfram Windisch at Cologne Lung Center. After an initial period where I optimized my hands-on skills with the ventilators, I was trusted to conduct my first designed interventional study *Obesity hypoventilation syndrome, can we switch to CPAP?* recently presented at the ERS congress 2017.

I am now focused in learning a complementary field of research that gives me a broader understanding of the complexities of long-term mechanical ventilation, namely Sleep Medicine. Few researchers, have expertise in both areas, thus several scientific questions are still unresolved. In this sense, my project proposal integrates these fields aiming to resolve a current debate: are sleep studies (polysomnography and transcutaneous CO_2 monitoring) needed to optimize the ventilator's settings of patients under HMV? To date no study has systematically evaluated the role of sleep studies in these complex patients. The results could provide information that lead to a more standardized protocol of follow-up checks of patients on HMV in a cost-effective manner.

I am honored that Prof. Dr. Winfried Randerath at Bethanien hospital in Solingen, Germany has accepted to be the supervisor of my LTRF application. He is a highly acknowledged active researcher with multiple contributions to the field of Sleep Medicine. The Bethanien hospital disposes of a large Sleep Unit and an extended program of HMV.

Upon my return home, my chances to obtain a research grant from Chile's funds (grants FONDECYT) will be significantly strengthen. These annual grants support with 400.000 U$/year for up to 4 years innovative research projects with international collaboration. My workplace Pontificia Universidad Católica de Chile University is very keen in supporting faculty´s research in order to maintain its first place at the QS top Latin-American Universities ranking. Therefore, once back home, I will continue my duties in clinics and teaching, but 50% of my worktime will be dedicated to clinical research.

Since in Chile there is no formal training program in either HMV nor sleep medicine for pneumologists, these areas are leaded by neurologists only. Therefore, my home unit is very enthusiastic to add the vision of a pneumologist in the Sleep Unit (8 beds) research/clinical group. Also importantly, I directly work with pneumology fellows, and will engage to contribute to their training in the mentioned fields.

If honored as an ERS Fellow, I would be pleased to serve at ERS activities where I am considered as a contributor.
Sincerely yours, Maria Paola Arellano-Maric

Project: The Debated Role of Sleep Studies in Patients under Established Home Mechanical Ventilation

INTRODUCTION

Worldwide, programs of home mechanical ventilation (HMV) through non-invasive ventilation (NIV) are expanding. Related to this expansion is its positive impact on mortality and health-related quality of life in patients with chronic hypercapnic respiratory failure.[1-5] The type of diseases supported by HMV varies from country to country, being the most relevant: chronic obstructive pulmonary disease, obesity hypoventilation syndrome (OHS), neuromuscular diseases and restrictive lung diseases.[6-9]

Since HMV is a comparatively young therapy, it is understandable that there are still controversies and heterogeneous practices across different centers and countries.[10] One of these open questions relates to which is the best way to perform check-ups on patients on long-term NIV therapy.[11]

The current inconsistency of follow-up protocols for these patients has many possible explanations: variability in resource availability, clinician's preference and lack of scientific evidence. [10] Follow-up controls might be ambulatory, hospitalized or home-based. Another significant difference relates to which studies are performed at every check-up visit. Lung function tests and blood gas analysis seem to be incorporated in almost every check-up protocol. Nevertheless, the biggest discussion is about the need to perform more sophisticated measurements such as polysomnography (PSG) or polygraphy and transcutaneous carbon dioxide monitoring ($PtcCO_2$). While some advocate that these sleep studies are pivotal to provide an optimal NIV therapy,[12] they are expensive, time-consuming and not widely available.

It is important to bear in mind that patients suffering chronic hypoventilation are complex; and NIV parameters' should be set-up according to the underlying pathophysiological mechanisms.[13] Now, given that NIV titration is mostly performed while the patient is awake, problems arising while sleeping on NIV therapy would remain undetected. Furthermore, minute ventilation decreases significantly and variably during the different sleep stages,[13] introducing an additional potential source of error on ventilator's set-up.

Importantly, patients requiring HMV tend to suffer a diminished quality of life.[4] Clearly, the use of a ventilator can imply a new burden in their lives, especially when considering that it should be used on a daily basis for a period of hours and preferably while sleeping. Hereby, the ventilator´s settings should be able to overcome hypercapnia and maintain a permeable upper airway. A further important challenge is to provide a gentle ventilation that does not impair sleep quality, and does not compromise cardiac output.[14]

Consequently, sleep studies could be a useful tool to fine-tune ventilator's settings. [12] Then, they could foster NIV effectivity and patient satisfaction, thus therapy's compliance. To our knowledge, no study has systematically evaluated the role of sleep studies as a NIV optimization tool in patients on established HMV.

Among others, the following findings could be recognized under sleep studies, revealing inappropriate ventilator's settings: Treatment-emergent central sleep apnea, [15] undetected/residual OSA [16], dyssomnias, patient-ventilator-asynchrony, [12] arousals related to NIV therapy, leakage and hypoventilation on supine body position. [17]

The aim of this study is to learn the findings of sleep studies when they are performed on stable HMV patients due to chronic hypoventilation syndrome as part of their routine check-ups. In this context, it will be assessed whether the sleep studies' findings lead to a change (adjustment) of the NIV therapy. Moreover, we plan to investigate whether the absence of sleep studies would result in missing important events that require an adjustment of therapy.
The results of this study could provide information that lead to a more standardized protocol of follow-up checks of patients on HMV in a cost-effective manner.

METHODS

Subjects

Patients on the HMV program of Bethanien hospital for more than 6 months will be eligible. These patients will be asked to attend to an ambulatory consult. If they are willing to participate a signed informed consent will be obtained. The ethic commission approval is expected in March 2018. In order to participate in the study, patients must meet the following *inclusion criteria:* Chronic hypercapnic respiratory failure secondary to one or more identified condition(s) (COPD, OHS, neuromuscular diseases, restrictive lung diseases) on HMV for at least 6 months, age ≥18 years. The e*xclusion criteria* are previous NIV therapy adjustment under sleep studies ≤6 months, any medical or psychological condition impairing the patient's ability to provide informed consent, missing informed consent.

Design

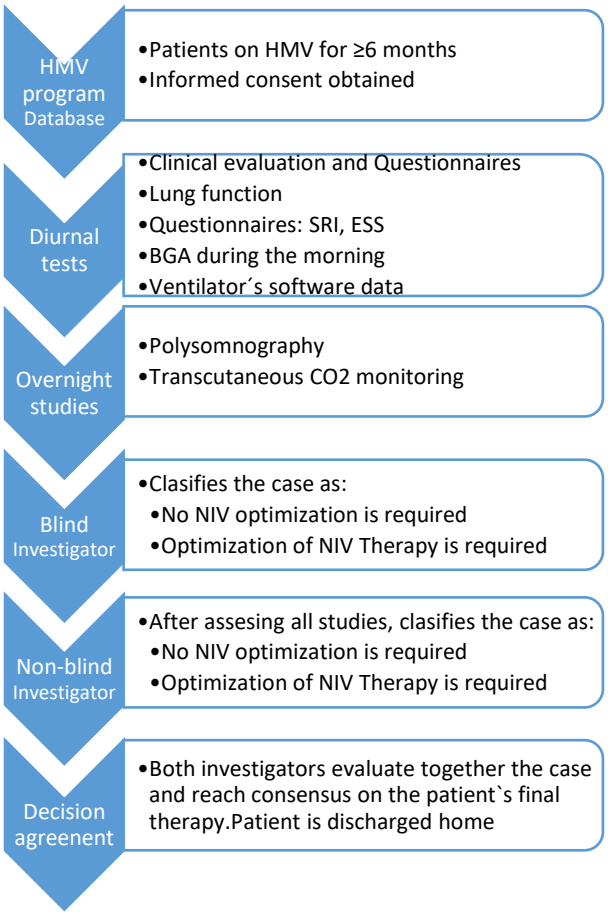
This is a prospective monocentric simple-blind study performed at the Sleep Unit of Bethanien Hospital/University of Cologne. Routinely, HMV patients spend 1-2 days hospitalized to complete their yearly therapy evaluation. During this stay, sleep studies will be added to their standard evaluation.

In a previous trial sleep studies were performed in 42 NIV-experienced OHS patients; 16% of them needed a therapy adjustment that was detected under PSG and/or $PtcCO_2$. [18] It is assumed that in a heterogeneous cohort of patients on HMV, around 20% of them will need a NIV adjustment. Therefore, 97 patients would be needed to show that 20% of patients require a NIV adjustment (primary endpoint) after analyzing their sleep studies with a precision of 8% (12-28%

confidence interval). Eligible patients will be consecutively enrolled until 97 datasets with evaluable PSG and $PtcCO_2$ are available.

Figure 1 shows the study's protocol and timeline. After obtaining the informed consent, the following data will be obtained: clinical evaluation, arterial blood gas analysis in the morning (after ventilator removal), lung function tests (Spirometry and 6-minute walk test), analysis of ventilator's downloaded data; questionnaires, sleepiness (Epworth Sleepiness Scale) and health related quality of life (Severe Respiratory Insufficiency questionnaire). During the night the sleep studies (PSG and $PtcCO_2$) under their usual NIV therapy will be performed.

a)



b)

Study Phase	Milestone
Study Start-up	Ethic committee Approval (expected in March-April 2018) Registry in clinicaltrials.gov
Study Conduct	"Ready to recruit" 1.08.2018 • 01.08.18 - 30.10.18: 33 patients recruited • 01.11.18 - 30.01.19: +33 patients (66) • 01.02.19 - 30.04.19: +33 patients (99) • 01.05.19 - 30.06.19: +22 patients (121) ❖ If at 5th month < 48 patients are recruited, the study will be converted to multicentric (Augustinerinnen hospital)
Study Close-up	01.07-01.08.19 Database analysis Manuscript preparation

Figure 1. a) Study protocol, b) Timeline and Milestones
HMV, home mechanical ventilation; BGA, blood gas analysis; NIV, non-invasive ventilation

Each case will be evaluated separately by 2 investigators. One of them will be provided with the diurnal evaluations only (as routinely); the second investigator will additionally have access to the sleep studies. Each investigator will classify the case as one of the following labels (primary outcome):

1. No NIV optimization is required (all ventilator's parameters should stay *unchanged*)

2. Optimization of NIV Therapy is required (one or more of the ventilator's parameters should be re-set, irrespective of the magnitude)

The unblinded investigator will also fulfill a detailed form describing the findings during the sleep studies. Finally, both investigators will reach consensus about each patient´s final NIV settings based on known recommendations.[19] Patients will be discharged home and continue their routinely medical controls.

The sleep studies results will be evaluated first as a whole, then as if only every single test were available (PSG, $PtcCO_2$). At the end of the study, it could be concluded which is the relevance of performing the more sophisticated sleep studies versus having part of them versus not performing them at all.

REFERENCES

1. Köhnlein T, Windisch W, Köhler D et al. Non-invasive positive pressure ventilation for the treatment of severe stable chronic obstructive pulmonary disease. **Lancet Respir Med**. 2014 Sep;2(9):698-705.
2. Murphy PB, Rehal S, Arbane G et al. Effect of Home Noninvasive Ventilation With Oxygen Therapy vs Oxygen Therapy Alone on Hospital Readmission or Death After an Acute COPD Exacerbation. **JAMA** 2017; 317(21):2177-2186.
3. Masa JF, Corral J, Alonso ML et al. Efficacy of Different Treatment Alternatives for Obesity Hypoventilation Syndrome. Pickwick Study. **Am J Respir Crit Care Med**. 2015 Jul 1;192(1):86-95.
4. Windisch W, Quality of life in HMV study group. **Eur Respir J**. 2008 Nov;32(5):1328-36.
5. Annane D, Orlikowski S, Chevret J et al. Nocturnal mechanical ventilation for chronic hypoventilation in patients with neuromuscular and chest wall disorders **The Cochrane Library** 2009;3: 1–36
6. Lloyd-Owen SJ, Donaldson GC, Ambrosino N et al. Patterns of home mechanical ventilation use in Europe: results from the Eurovent survey. **Eur Respir J** 2005;25(6):1025–1031
7. Garner DJ, Berlowitz DJ, Douglas J et al. Home mechanical ventilation in Australia and New Zealand. **Eur Respir J** 2013;41(1):39-45
8. Nasiłowski J, Wachulski M, Trznadel W et al. The evolution of home mechanical ventilation in poland between 2000 and 2010. **Respir Care**. 2015;60(4):577-85.
9. Arellano-Maric MP, Roldán Toledo R, Huttmann SE et al. Intermittent noninvasive ventilation at San José Hospital in Chile: report of a German donation. **Pneumologie**. 2015 Mar;69(3):144-6.
10. MacIntyre EJ, Asadi L, Mckim DA et al. Clinical Outcomes Associated with Home Mechanical Ventilation: A Systematic Review. **Canadian Respiratory Journal** 2016;ID 6547180,10 pages, doi:10.1155/2016/6547180
11. Rose L, McKim DA, Katz SL et al. Home mechanical ventilation in Canada: a national survey. **Respiratory Care** 2015; 60(5): 695–704
12. Gonzalez-Bermejo J, Perrin C, Janssens JP et al. Proposal for a systematic analysis of polygraphy/ polysomnography for identifying and scoring abnormal events occurring during non-invasive ventilation. **Thorax** 2012;67:546-552
13. Böing S, Randerath WJ. Chronic hypoventilation syndromes and sleep-related hypoventilation. **J Thorac Dis** 2015;7(8):1273-85
14. Duiverman ML, Arellano-Maric MP, Windisch W. Long-term noninvasive ventilation in patients with chronic hypercapnic respiratory failure: assisting the diaphragm, but threatening the heart? **Curr Opin Pulm Med** 2016;22(2):130-7
15. Randerath W, Verbraecken J, Andreas S et al. Definition, discrimination, diagnosis and treatment of central breathing disturbances during sleep. **Eur Respir J** 2017;18;49(1)
16. Randerath W. Time for screening? **Sleep Medicine** 2014;15:1285–1286
17. Arellano-Maric MP, Gregoretti C, Duiverman M, Windisch W. Long-term volume-targeted pressure-controlled ventilation: sense or nonsense? **Eur Respir J**. 2017 ;22;49(6)
18. Arellano-Maric MP, Hamm C, Schwarz S et al.Obesity hypoventilation syndrome treated with non-invasive ventilation: can we switch to CPAP? Abstract **ERS Congress** 2017, Number 4427
19. Berry RB, Chediak A, Brown LK et al. Best Clinical Practices for the Sleep Center Adjustment of Noninvasive Positive Pressure Ventilation (NPPV) in Stable Chronic Alveolar Hypoventilation Syndromes. **J Clin Sleep Med** 2010;6(5):491-50