

Summary of the thesis

„Research on the role of hypocapnia in producing Cheyne Stokes respiration and new modalities to optimize its therapy“

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Respiratory diseases are amongst the most complex pathophysiological entities in medicine. There is no such thing as a one-item disease in our field, which brings the appeal of respiratory diseases for basic and clinical scientists. The most prevalent respiratory diseases are chronic, exhibiting multiple mechanistic pathways that can vary during the course of the disease.

Cheyne-Stokes breathing is a special form of sleep-disordered breathing with a specific pattern of characterized by progressively deeper and sometimes faster breathing, followed by a gradual decrease that results in central apnoea and hypopnoea. Since its first description, almost 200 years ago, in a patient who suffered from cardiac failure with atrial fibrillation and sustained a stroke (1), Cheyne-Stokes breathing has been regarded as an ominous sign of the gravity of the underlying disease and as a forecast of looming death. Therefore, this pattern of hyperpnoea periods alternating with central apnoea/hypopnea has been used to describe Cheyne Stokes breathing, but not to denote any specific underlying aetiology.

The current thesis is a singular study, which focuses on Cheyne-Stokes breathing caused not only by heart failure, as this pathology concerns the majority of existing studies. Medical conditions like kidney failure and stroke also predispose to a higher prevalence of periodic breathing. Our data proves that this pattern of waxing and waning ventilation with prolonged cycles of hyperpnoea and apnoea/hypopnea phases of over 40 seconds (2) is present even in Cheyne-Stokes respiration caused by other conditions than cardiac failure. We propose that although, through different routes (as there are multiple underlying conditions), the key mechanism of producing Cheyne-Stokes breathing lays in the variations of partial pressure of carbon dioxide in the arterial blood (PaCO_2).

Further investigations with larger interventional studies were necessary to clarify the natural history, clinical consequences, pathomechanism and therapeutic outcomes of this disorder. We analysed and compared the dynamics of respiratory events and blood gases parameters in patients with and without: heart failure, renal failure, atrial fibrillation, obesity and associated obstructive events, in search of a difference that could elucidate the main pathomechanism and predict which type of therapy would be the most appropriate. This may have important clinical implications, as this special sort of central sleep apnoea has been associated with adverse clinical sequelae, including increased risk for heart disease and cardiovascular mortality (3;4). Presently, scientific evidence has accumulated that proves that Cheyne-Stokes respiration harms the failing heart (5). Quality of life and sleep, as well as ventricular function suffer from frequent periodic breathing; therefore, Cheyne-Stokes breathing has been identified to shorten the life of heart failure patients (6). Pharmacological (7) and nonpharmacological therapies (8-11) are able to suppress or counteract this type of central events, and specific types of treatments have been shown to improve ventricular function as well as quality of life (11-20).

In the third study, we also analysed the efficiency of current modern treatments in Cheyne-Stokes breathing in 142 patients, and specifically dependent on its aetiology. Until now, there is no standard procedure in the treatment of Cheyne-Stokes breathing; we propose an original treatment algorithm, which encompasses all types of Cheyne-Stokes respiration. In addition, we performed an analysis of differences in age, gender, anthropometric measures, lung functions, daytime sleepiness, blood gases analysis and associated medical conditions, which could

explain why some patients cease their periodic breathing under oxygen (O₂) therapy and other under PAP ventilation.

We believe that present thesis brings novel and crucial information about Cheyne-Stokes breathing furthering the current state of knowledge about the consequences, pathomechanism and especially about the effectiveness of all available specific therapies. We found that the level of the PaCO₂ is of crucial importance in the pathophysiology of Cheyne-Stokes breathing irrespective of the underlying diseases. Therefore, the elevation of the actual PaCO₂ could break through the periodicity of hyperventilation and restore the normal breathing pattern. This increase in PaCO₂ was achieved in all effective O₂ therapies with an apnoea-hypopnoea index $\leq 5/h$. There were no statistically significant differences in the effectiveness of the applied specific therapies: 67% for O₂ therapy, 63% under continuous positive airway pressure (CPAP) and 62,7% for bilevel positive airway pressure spontaneous-timed (BiPAP ST) mode ventilations, respectively. Adaptive servo-ventilation (ASV) proved itself effective in all cases with therapy failure under the above mentioned treatments, nevertheless the raised cost of this therapy grant its reimbursement only when the ineffectivity of the other therapies was proofed.

Furthermore, we examined a subgroup of patients, in whom because of hypoxic respiratory failure a daytime O₂ therapy followed for duration of 4 hours. Based on the lack of significant variation in PaCO₂ value, obtained before and after the administration of O₂ for 4 hours and 8 hours, respectively, we developed a prediction model of efficient O₂ treatment. Currently, non-invasive ventilation, including positive airway pressure support in the form of CPAP or BiPAP, appears to be most powerfully counteracting Cheyne-Stokes respiration, but the jury is still out on whether non-invasive ventilation may also prolong the lives of cardiac insufficient patients. In the present thesis, we perform a review of the current literature on prevalence, risk factors, consequences and therapies of Cheyne-Stokes breathing and compare it to our data. The available data suggests that PAP ventilation (especially CPAP) may improve survival if titrated to achieve a therapeutic reduction of AHI. Conversely, positive pressure ventilation has no effect on survival if not adequately titrated (21). Nevertheless, a key limitation observed in many of the studies was that CPAP or BiPAP therapy was not titrated; therefore, its effectiveness was unclear. As a consequence all our therapies were titrated in order to achieve therapeutic efficacy and patients' compliance.

The effects of Cheyne-Stokes breathing on sleep-related symptoms and quality of life are not very well established. Excessive daytime sleepiness has been observed previously in its clinical presentation as these patients experience nocturnal hypoxemia and sleep disruption that may be as severe as that associated with significant obstructive sleep apnoea. We assessed if there was a correlation between Cheyne-Stokes breathing and excessive daytime sleepiness, sleep architecture, obesity and ventilation dysfunctions, respectively.

A further contribution and novelty brought by the current thesis is the relationship between Cheyne-Stokes breathing and the presence of associated obstructive respiratory events. It appears that even minor association of obstructive events play a major role in its pathomechanism (especially elevating PaCO₂) and its correction under the different types of therapy. Therefore, this combination of sleep apnoeas is the principal determinant in the type of effective therapy, as stated further on in the dedicated chapter about originality of the thesis.

Cheyne-Stokes breathing impairs the quality of life and increases cardiac mortality in patients, thus its diagnosis should be actively pursued, not only in patients with severe heart failure, but also caused by with underlying diseases. When Cheyne-Stokes breathing persists despite optimal therapy of heart kidney failure and/or neurological condition, we propose an original treatment algorithm in order to optimally and efficiently handle this disorder.

We believe that our studies contribute with more information to this field of respiratory medicine, provided by larger patients' number, inclusion also of patients with neurological conditions and/or kidney failure, non-

selected, focusing on a comparison of all available therapies while striving for therapy efficiency. In addition, based on our research on the basics of Cheyne-Stokes breathing's physiopathology, we conclude that other criteria should be taken into consideration when therapeutic interventions in Cheyne-Stokes respiration are recommended.

Reference List

1. Cheyne J. A case of apoplexy in which the fleshy part of the heart was converted into fat. *Dublin Hosp Rep* 1818;2:216-223.
2. Berry RB, Budhiraja R, Gottlieb DJ, et al. Rules for scoring respiratory events in sleep: update of the 2007 AASM Manual for the Scoring of Sleep and Associated Events. Deliberations of the Sleep Apnea Definitions Task Force of the American Academy of Sleep Medicine. *J Clin Sleep Med* 2012;8(5):597-619.
3. Ancoli-Israel S, Kripke DF, Klauber MR, et al. Morbidity, mortality and sleep-disordered breathing in community dwelling elderly. *Sleep* 1996;19(4):277-82.
4. Ancoli-Israel S, DuHamel ER, Stepnowsky C, Engler R, Cohen-Zion M, Marler M. The relationship between congestive heart failure, sleep apnea, and mortality in older men. *Chest* 2003;124(4):1400-5.
5. Roebuck T, Solin P, Kaye DM, Bergin P, Bailey M, Naughton MT. Increased long-term mortality in heart failure due to sleep apnoea is not yet proven. *Eur Respir J* 2004; 23(5):735-40.
6. Brack T, Thuer I, Clarenbach CF, et al. Daytime Cheyne-Stokes respiration in ambulatory patients with severe congestive heart failure is associated with increased mortality. *Chest* 2007;132(5):1463-71.
7. DeBacker WA, Verbraecken J, Willemsen M, Wittesaele W, DeCock W, Van dP. Central apnea index decreases after prolonged treatment with acetazolamide. *Am J Respir Crit Care Med* 1995 Jan;151(1):87-91.
8. Sasayama S, Izumi T, Matsuzaki M, et al. Improvement of quality of life with nocturnal oxygen therapy in heart failure patients with central sleep apnea. *Circ J* 2009;73(7):1255-62.
9. Ruttanapawan P, Logan AG, Floras JS, Bradley TD. Effect of continuous positive airway pressure on sleep structure in heart failure patients with central sleep apnea. *Sleep* 2009;32(1):91-8.
10. Sin DD, Logan AG, Fitzgerald FS, Liu PP, Bradley TD. Effects of continuous positive airway pressure on cardiovascular outcomes in heart failure patients with and without Cheyne-Stokes respiration. *Circulation* 2000 Jul 4;102(1):61-6.
11. Takasaki Y, Orr D, Popkin J, Rutherford R, Liu P, Bradley TD. Effect of nasal continuous positive airway pressure on sleep apnea in congestive heart failure. *Am Rev Respir Dis* 1989;140(6):1578-84.
12. Arzt M, Schulz M, Wensel R, et al. Nocturnal continuous positive airway pressure improves ventilatory efficiency during exercise in patients with chronic heart failure. *Chest* 2005; 127(3):794-802.
13. Arzt M, Wensel R, Montalvan S, et al. Effects of dynamic bilevel positive airway pressure support on central sleep apnea in men with heart failure. *Chest* 2008;134(1):61-6.
14. Arzt M, Schulz M, Schroll S, et al. Time course of continuous positive airway pressure effects on central sleep apnoea in patients with chronic heart failure. *J Sleep Res* 2009; 18(1):20-5.
15. Granton JT, Naughton MT, Benard DC, Liu PP, Goldstein RS, Bradley TD. CPAP improves inspiratory muscle strength in patients with heart failure and central sleep apnea. *Am J Respir Crit Care Med* 1996;153(1):277-82.
16. Krachman SL, D'Alonzo GE, Berger TJ, Eisen HJ. Comparison of oxygen therapy with nasal continuous positive airway pressure on Cheyne-Stokes respiration during sleep in congestive heart failure. *Chest* 1999;116(6):1550-7.
17. Naughton MT, Benard DC, Rutherford R, Bradley TD. Effect of continuous positive airway pressure on central sleep apnea and nocturnal PCO₂ in heart failure. *Am J Respir Crit Care Med* 1994;150:1598-604.
18. Philippe C, Stoica-Herman M, Drouot X, et al. Compliance with and effectiveness of adaptive servoventilation versus continuous positive airway pressure in the treatment of Cheyne-Stokes respiration in heart failure over a six month period. *Heart* 2006;92(3):337-42.
19. Randerath W, Bauer M, Blau A, et al. Are there alternative therapeutical options other than CPAP in the treatment of the obstructive sleep apnea syndrome. *Pneumologie* 2007;61(7):458-66.
20. Teschler H, Dohring J, Wang YM, Berthon-Jones M. Adaptive pressure support servo-ventilation: a novel treatment for Cheyne-Stokes respiration in heart failure. *Am J Respir Crit Care Med* 2001;164(4):614-9.
21. Arzt M, Floras JS, Logan AG, et al. Suppression of central sleep apnea by continuous positive airway pressure and transplant-free survival in heart failure: a post hoc analysis of the Canadian Continuous Positive Airway Pressure for Patients with Central Sleep Apnea and Heart Failure Trial (CANPAP). *Circulation* 2007;115(25):3173-80.

Keywords

Cheyne-Stokes breathing – Hypocapnia – nocturnal oxygen therapy - continuous positive airway pressure (CPAP) - bilevel positive airway pressure spontaneous-timed (BiPAP ST) - adaptive servo-ventilation (ASV)