NIGHT TIME MANAGEMENT OF CCHS PATIENTS

Karin Ljubič*, Iztok Fister Jr**, Iztok Fister**

*University of Maribor, Faculty of Medicine, Taborska 8, 2000 Maribor, Slovenia
**University of Maribor, Faculty of Electrical Engineering and Computer Science, Smetanova 17, 2000 Maribor, Slovenia

Abstract: In this article we discuss possible technological solutions for CCHS patient management. CCHS is a chronic condition needing chronic ventilatory support. The most optimal solutions are diaphragmatic pacing and positive pressure ventilatory support, the first one during the day and the second one at night. A new device for nighttime management of these patients has been presented in 2013. It is simply designed, user-friendly. It dynamically monitors the SpO_2 (blood saturation with oxygen) values in blood and progressively and gently wakes up the caregiver when needed. We proposed an upgrade for this device based on currently commercially available Android applications for sleep cycle analyzing.

1. INTRODUCTION: WHAT IS CCHS?

Congenital central hypoventilation syndrome (CCHS) is a rare genetic disorder which is predisposed by a mutation in PHOX2B (paired home-box 2B) gene. Different laboratories from all over the world have now collectively diagnosed nearly 1000 cases by PHOX2B mutation-confirmed CCHS [1]. However, it is estimated that the actual prevalence is much higher due to the extreme clinical variability. This mutation causes autonomic nervous system dysregulation [2]. The most prevalent symptom is a failure to automatically control breathing, and is present from birth. Patients have absent or sluggish ventilatory sensitivities to high CO_2 or low O_2 in the circulating blood when asleep or/and awake. Deep sleep stages are the most critical, while patients usually demonstrate adequate ventilation during wake. During sleep, children with CCHS experience progressive rising in circulating CO2 and lowering O2 and lack the arousal responses and sensations of dyspnoea (a subjective feeling of difficulty breathing) which would wake them up from sleep. Therefore, mechanical ventilators are connected to them during sleep, trying to provide sufficient oxygen exchange in the lungs. Childreen with CCHS also have other disturbances of autonomic functions with both sympathetic and parasympathetic components. They have clinically apparent abnormalities in the autonomic regulation of blood pressure, cardiac rhythm, pain and anxiety perception, papillary reactivity, temperature regulation, gut motility, urinary retention and more [3].

CCHS was first described in 1970 by Mellins and colleagues, and since then its relation to PHOX2B mutation has been confirmed [4]. The literary misnomer “Ondine´s curse” has been used in prior literature to refer those with CCHS. The misnomer is based on a mythical story where a mortal knight Hans betrays Ondine the mermaid. Poseidon, God of the Sea and father of Ondine, cursed Hans in such a way that his bodily functions would fail unless he was conscious of them. As a consequence Hans died of forgetting to breathe. The misnomer “Ondine´s curse” today should not be used to refer to those with CCHS.

In the first part of the article we present modalities of ventilatory management of these patients. In the special section we emphasize the importance of sleep and distinct physiological features of sleep cycle in childhood. It is important to understand the physiology of REM and NREM sleep. We present the current night time management of these patients and propose a theoretical upgrade based on sleep tracking applications.

2. VENTILATORY MANAGEMENT

Patients with CCHS need ventilatory support. In order to provide an optimal ventilatory outcome, invasive ventilation must be provided until 6-8 years of age at the earliest [5]. As mentioned, the need for ventilatory support is the highest in the nighttime when patients are asleep and highly prone to undergo hypoventilation periods. There are four main ways of providing chronic ventilatory support: positive pressure ventilators via tracheostomy, diaphragmatic pacing, bi-level positive airway pressure and negative pressure ventilators. For the purpose of this article we will focus on the first two options, as they are the most frequent and important for further topic of this article.

Positive pressure ventilator via tracheostomy is the most common method of providing home mechanical ventilation in CCHS [6]. They are commercially available, relatively portable and have battery capability. A tracheostomy is required for positive pressure ventilator to access the airway. The tracheostomy means a hole in the trachea (windpipe) made by an incision in this area. A circuit is required to deliver air from a positive pressure ventilator to the patient through a heated humidification system (essential for infants and children; the desired temperature range is 26°C to 29°C) connected to the tracheostomy with a swivel adapter. Two to three circuits are generally provided for home care, and they are changed every day. The circuits should be appropriate for the weight of the child. The important part of the device is also a pulse-oksimeter. Pulse-oximeter is a device for monitoring a patient´s O_2 saturation in the blood. It is a non-invasive method wit a sensor placed on a thin part of the patient´s body like fingertip or an earlobe. In the case of an infant it can also be placed across a foot. The saturation level above 95% (SpO_2> 95%) is considered as safety level. Nowadays the only alarm systems available for the CCHS patients are the ones integrated in ventilator and pulse-oksimeter. If the ventilator fails or if the saturation level falls below safety level the alarm is initiated. The pros and cons of this will be presented later on.

Diaphragmatic pacing generates breathing using the child´s own diaphragm (the main respiratory muscle) as the main breathing pump [7]. The system consists of the battery-operated external transmitter which generates pulses. The pulses are transmitted via an external antenna which creates a radio frequency signal. The signal is communicated to the subcutaneously implanted receivers bilaterally. The subcutaneously implanted receivers convert the radio frequency into an electrical current. The electrical current is transmitted via stainless steel wires to the monopolar platinum phrenic nerve electrodes. The electrical stimulation of the phrenic nerve causes diaphragmatic contraction, which generates the breath. At night positive pressure ventilation via tracheostomy is still recommended because diaphragmatic pacing without tracheostomy can result in upper airway occlusion. Furthermore the system does not have any associated alarms and if the components fail then the results for the patient can be devastating.

3. THE IMPORTANCE OF SLEEP

The importance of this physiological process-sleep-could not be overemphasized. It is important to provide an optimal technological solution for nighttime monitoring of infants and children with CCHS as well as their caregivers. For infants sleep is important because of brain maturation and a lack of sleep in children can cause deficits in physical and cognitive development. Sufficient sleep is one of the basic needs of each human being. However, sleeping is not a uniform process because it shares various phases. There are two main phases of sleeping called NREM (non rapid eye movement) and REM (rapid eye movement) sleep. NREM sleeping is sleeping in a classic sense. It is characterized by a gradual slowing of brain activity. At this stage of sleep a child sleeps motionless although with preserved muscle tone. The body is relaxed, fingers half-bent and the face is without expression with closed eyes. This sleep alternates with REM sleep in which the basic brain activity is similar to that of wakefulness. It is characterized by rapid eye movements with closed eyes and muscular atony. Activity of the whole body is very intense with frequent stereotyped movements of the limbs and trunk. We can see various facial grimaces at this stage of sleep in neonates. Breathing and heart rate are irregular and accelerated. In this stage of sleep we have dreams. Each REM phase followed by a NREM phase is called a cycle. Figure 1 shows a characteristic layout of cycles throughout the night in children and adults. We can see that children undergo many more cycles than an adult person. Moreover the total amount of deep, motionless NREM sleep is higher than in adults. They often wake up in between cycles, usually up to eight times. This fact should be kept in mind for further understanding.

Newborn after birth sleeps around two-thirds of the day. In the coming months, the need for sleep decreases to 14-15 hours a day and especially during the day the child is becoming more awake. This amount of sleep does not change a lot until the age of four. At the age of 10 the chills still needs about 10 hours of sleep per day. In the teenage period this amount is gradually reduced to 8 hours per day.

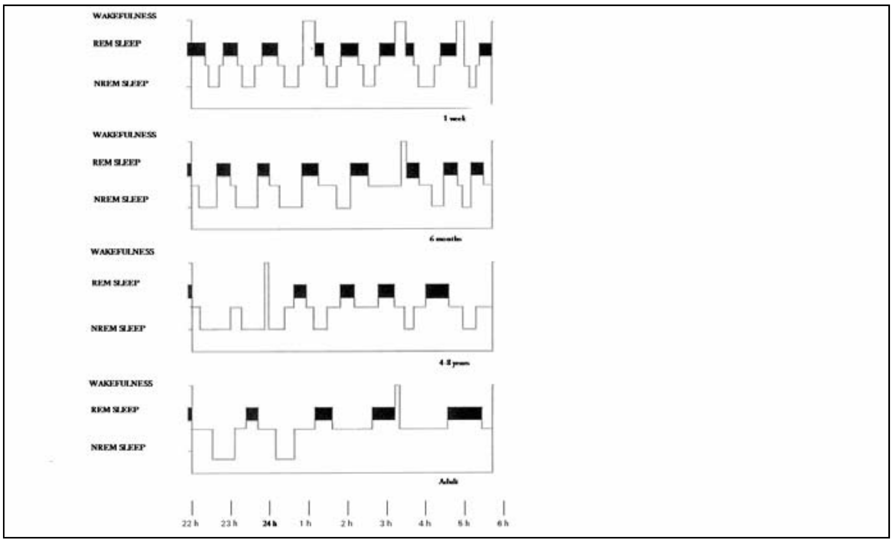

Figure 1: Comparison of sleep cycles in children and adults.

4. A THEORETICAL UPGRADE OF A NEW DEVICE FOR THE CARE OF CCHS PATIENTS DURING SLEEP

As already mentioned, positive pressure ventilatory support via tracheostomy is the most frequent form of chronic ventilatory support for children with CCHS. Again, this system has two integrated alarms, one integrated in ventilator and one in pulse-oksimeter. If the ventilator fails or if the saturation level falls below safety level the alarm is initiated. A caregiver or a parent is needed all night long to serve as a supervisor and to take proper action if the situation worsens. During one night, ventilator or pulse-oximeter alarms may activate several times for different causes. For example if the patients moves, this causes a single artefact on SpO_2 measures and this is enough to produce an alarm which fractions sleep for supervisors and patients. Since CCHS is a chronic disease this may predispose to a chronic state of strees and anxiety. Furthermore, parents and supervisors can become less responsive to frequent and repeated stimuli, so called habituation. This might lead to disregarding alarms.

Recently a novel device has been introduced that can acquire real-time data from a pulse oximeter and display it on an android tablet [8]. The components of this device are shown in Figure 2.

This device collects data from a pulse-oximeter and monitors blood oxygenation throughout the night. It dynamically monitors SpO_2 levels in blood. This device might replace the alarms in ventilator and pulse-oksimeter. The core of the device is an Android tablet. The tablet acquires SpO_2 from a commercial pulse-oximeter. A tablet pc CEM2918S1 with Android 2.3.1 (API Level 9), 1.2 GHz, single core processor, 512 MB RAM and 7 inches touch screen has been chosen. It is easy to use for everybody. A specific application running on the Android decodes the SpO_2 data and implements the stimulation strategies if required. The IOIO module is an electronic board for communication with an Android device through a standard USB port and it represents the interface between the Android tablet and the external modules. Many easy-to-use libraries for IOIO management are available, such as the IOIOBT v1.5 and other. A pulse-oximeter is connected to the IOIO board via the pulse-oximeter interface. Pulse-oximeters can have a digital output or an analog output. The digital output carries the SpO_2 data in a codified form, it is not affected by ambient noise and is more reliable. But on other hand it requires the development of customized decoding algorithms for each oximeter. Till now, there are two protocols developed for the acquisition of digital data from two commercially available pulse-oximeters: Nonin Avant 9600 and Nonin Avant 4000. The IOIO output activates the actuators if required. Three different actuators are currently used: a piezoelectric buzzer (CET12A 3.5) with resonance frequency of 2048Hz, a small air fan (operated at 12V) that sends an air flow to the subject´s face and a commercially available vibrating massage pillow. How does the stimulation strategy work? As mentioned before, till today there were only intrinsic alarms in the ventilator and pulse-oximeter. These alarms initiate every time the SpO_2 level falls below 95%, no matter the time lasting. Moreover, many times it is a false alarm, because of SpO_2 artifacts made by child¨s movement in the bed during sleep. This new proposed device dynamically monitors SpO_2 level in the blood and turns on the actuators when the period of time of lower SpO_2 goes beyond safety levels. So, the stimulation strategy gives importance to the length of time when the SpO_2 is below the normal threshold and the SpO_2 level itself, since even a mild hypoxia represents a danger for a patient if it goes on for a long time. Four different severity levels (SL) have been selected. Each SL is defined by two parameters respectively: the minimum level of SpO_2 and the maximum time allowed for this value to remain between the minimum and the normal SpO_2 value. SL0 (normal state) is defined only by one parameter: SpO_2 normal level 95% or more. SL1 (95% > SpO2 ≥ 90%, maximum allowed time is 1,5 minute) is defined as mild hypoxia. SL2 (90% > SpO2 ≥ 85%, maximum allowed time is 1 minute) is defined as moderate hypoxia. SL3 (85% >, 0 minutes allowed) is defined as severe hypoxia. In this state the patient must be urgently woken up to establish the conscious control of their own breathing that saves their lives. Each SL state has a set of stimulation parameters that defines which actuators to use and also the intensity and frequency of stimulus. These settings can be defined individually. For example, in SL1 state you can choose to use the vibrating pillow only and in SL2 you can increase the pillow stimulation frequency and add another actuator, such as air fan.

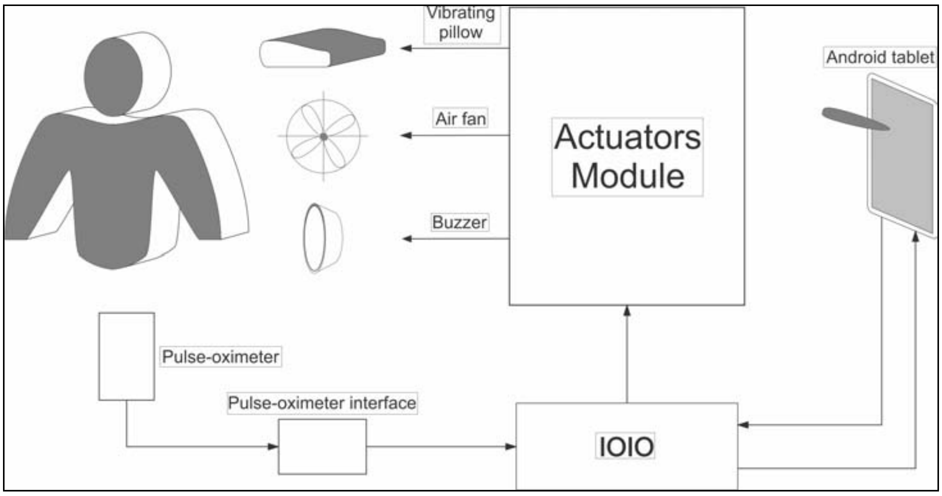

Figure 2: The device for nocturnal controlling of CCHS patients.

The main components are: pulse-oximeter, IOIO board, actuators, Android tablet. The actuators wake up the patient and the caregiver when required.

So far, the device is now being tested by volunteering families of patients with CCHS. They have already reported a better quality of sleep, false alarms have been reduced and progressive awakening in the case of false alarms. They report of reduction of stress and anxiety.

This new device offers a lot of upgrading possibilities. We would like to present some important theoretical ideas in order to provide the maximum sleep comfort and quality of life of CHS patients. Currently there are many free available Android applications for sleep cycle control. They can be used on smart phones which have an incorporated motion sensor fitted as standard. This easy-to-use Android application with a motion sensor placed on a patient´s bed could monitor the cycles of patient´s sleep. One important fact that should be emphasized is the following: recent studies demonstrated an improvement in breathing of CCHS patients when doing passive motion or active exercise during sleep [9]. As mentioned in the chapter about the physiology of sleep, the children sleep more than adults and overall they tend to have longer period of deep NREM sleep. As mentioned, the body is usually motionless in this phase of sleeping. We propose the following solution to avoid hypoxic periods by gently stimulating the patient once during the NREM phase. We propose the following application called SleepBoot. The application serves as a sleep tracker. It simply distinquishes between REM and NREM sleep based on information from motion tracker placed on patient´s bed. When there is no motion, this is the NREM sleep. Of course there are many free and commercially available sleep tracking applications. We chose SleepBoot randomly.

When the application would detect a non-movement phase of sleep, a 15 minute (or less, depending on the setting) countdown would start. After this time, one of the actuators could be activated for a period of 30 seconds (again, depending on the settings), preferably a vibrating pillow at low frequency, that would gently force a patient to change his sleeping position and move without waking the patient up. That way we could preventively avoid long lasting periods of being motionless and more prone to hypoxic state. Of course, there are few drawbacks. The appropriate amount of stimulation time should be tested, because we do not want to wake up a patient, only force him gently to move the position of sleeping without waking up.

Another proposal is based on fact that even short-lasting hypoxic period with SpO_2 levels below 85% could represent a severe condition for the patient. If this state occurs, the alarm initiates immediately. This can be a very dramatic situation for the caregivers. Although they are trained to act in these situations, because of the pressure errors can occur. We have already mentioned diaphragmatic pacing in the previous chapters. In fact, diaphragmatic pacing in many CCHS patients presents the mean vetilatory support during the day [10]. So the optimal solution for chronic ventilatory support is the combination of diaphragmatic pacing in daytime and positive pressure ventilation at night. Since so far there is no automatic skip between positive pressure ventilation and diaphragmatic pacing this might be a brilliant solution for the critical situations when SpO_2 falls under 85%. A simple analog connection to battery-operated external transmitter, which generates pulses, could solve this situation.

5. CONCLUSION

CCHS is a rare and complex disorder. For many years the etiology of this disorder was misunderstood and genetic typization unknown. Today we understand the etiology of this rare disorder and therefore we can discover the relevant symptoms much earlier and faster. CCHS is a chronic condition and needs chronic ventilatory support. The most optimal solution for chronic ventilatory support is positive pressure ventilation at night and diaphragmatic pacing during the day. Each modality has its pros and cons. In this article we presented the optimal solution for night time management of CCHS patients. Proposed solutions are based on available sleep cycle tracking applications. We also propose the connection between already existing modalities of ventilatory support: the positive pressure ventilators and diaphragmatic pacing. In future, the caregivers and the patients might experience greater technological support in order to improve the quality of their lives.

REFERENCES

1. 1. Weese-Mayer Debra E, Berry-Kravis Elizabeth M, Ceccherini I, et al. An Official ATS Clinical Policy Statement: Congenital Central Hypoventilation Syndrome. Ame J of Res and Crit Care Med. 2010; 181(6): 626-644.
2. Trochet D, O´Brien LM, Gozal D, et. al. PHOX2B Genotype Alows for Prediction of Tumor Risk in Congenital Central Hypoventilation Syndrome. The American J of Hum Gen. 2005; 76(3): 421-426.
3. Arai H, Tesshu O, Sasaki A, Umetsu K, Hayasaka K. Polyalanine expansion of PHOX2B in congenital central hypoventilation syndrome: rs 17884724:

A>C is associated with 7-alanine expansion. J of Hum Genet. Nature Publishing Group. 2009; 55.
4. Mellins RB, Balfour HH, Jr, Turino GM, et al. Failure of automatic control of ventilation (Ondine´s course). Report of an infant born with this syndrome and review of the literature. Medicine (Baltimore) 1970; 49(6): 487-504.
5. Karin Ljubič, Iztok Fister Jr. and Iztok Fister. Congenital central hypovetnilation syndrome: a comprehensive review and future challenges. Journal of respiratory medicine. Hindawi. 2013. Article in press.
6. Weese-Mayer DE, Berry-Kravis EM, Ceccherini I, Keens TG, Loghmanee DA, Trang H. An Official ATS Clinical Policy Statement: Congenital central hypoventilation syndrome: genetic basis, diagnosis, and management. Am J Respir Crit Care Med. 2010;7:626–644.
7. Chen ML, Tablizo MA, Kun S, et al. Diaphragm pacers as a treatment for congenital central hypoventilation syndrome. Expert Rev Med Devices. 2005; 2: 577-585.
8. M. Cavalleri, A. Carcano, F. Morandi, C. Piazza, E. Maggioni and G. Reni. A new device for the care of Congenital Central Hypoventilation Syndrome patients during sleep.35 Annual International Conference of the IEE EMBS. Japan. 2013.
9. Shea SA, Andres LP, Shannon DC, et al. Ventilatory responses to exercise in humans lacking ventilatory chemosensitivity. J Physiol. 1993; 468:623–40.
10. Davidson Ward SL. Home mechanical ventilators and equipment. Evanston. IL: American Academy of Pediatrics; 2002.