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The utility of neural network in the diagnosis of Cheyne–Stokes respiration

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The aim of this study was to design a diagnostic model to identify patients with Cheyne–Stokes respiration (CSR-CSA) based on indices of oximetric spectral analysis. A retrospective analysis of oximetric recordings of 213 sleep studies conducted over a one-year period at a Veterans Affairs medical facility was performed. A probabilistic neural network (PNN) was developed from salient features of the oximetric spectral analysis, desaturation events and the delta index. A fivefold cross-validation was used to assess the accuracy of the neural network in identifying CSR-CSA. When compared to overnight polysomnography, the PNN achieved a sensitivity of 100% (95% confidence interval [CI] 85%–100%) and a specificity of 99% (95% 97%–100%) with a corresponding area under the curve of 99% (95% CI 99%–100%). When combined with overnight pulse oximetry, PNN offers an accurate and easily applicable tool to detect CSR-CSA.

Introduction

Sleep disordered breathing (SDB) is estimated to occur in about 60% of patients suffering from congestive heart failure (CHF) [1]. Cheyne–Stokes respiration (CSR-CSA) is by far the most common form of SDB encountered with an estimated prevalence of 40% followed by obstructive sleep apnea (OSA) with an estimated prevalence of 11% [1,2]. CSR-CSA is characterized by rhythmic rises and falls in tidal volume and breathing frequency that lead to oxygen desaturation, increased arousal, poor sleep quality and altered sleep architecture. These features result in complaints of daytime somnolence, fatigue and insomnia.

The pathophysiology of CSR-CSA is not completely understood, but it has become more evident that the effect of altered breathing patterns extends beyond the deterioration in psycho-cognitive function. The increase in urinary and plasma norepinephrine levels in patients with congestive cardiac failure (CHF) and CSR-CSA compared to those with CHF alone has been implicated in an accelerated loss of cardiac function, and an increased risk of death and cardiac transplantation [3,4]. Nasal continuous positive airway pressure (nCPAP) has been advocated as an effective non-pharmacological treatment for patients with congestive heart failure and CSR-CSA. Recent studies have shown that nCPAP can abolish CSR-CSA, improve respiratory muscle strength [5], increase left ventricular ejection fraction [3], and may increase transplant-free survival [6].

In the absence of an accurate screening test, home pulse oximetry has been proposed as an alternative tool for detection of CSR-CSA [7]. These model studies however have lumped the variation of oxygen saturation into a single measure without regard to the frequencies at which this variability occurs. In recent years, there has been a growing interest in spectral analysis as a tool for non-invasive assessment of biological function [8,9]. Although CSR-CSA has never been defined rigorously [10], its crescendo–decrescendo pattern of breathing suggests that the major variation is in the form of a regular sinusoidal wave.

Neural networks have been proposed as a powerful alternative to conventional statistical methods because of their inherent property of seeking information embedded in relations among variables believed to be independent. They have been used successfully in medical applications [11,12] and have been shown to outperform physician and to equal or exceed traditional statistical modelling in the prediction of outcomes [13]. We conducted this investigation to test the hypothesis that a trained probabilistic neural network could accurately classify Cheyne–Stokes respiration from data derived from oximetric spectral analysis.

Methods

Patients

We conducted an analysis of the oximetry recordings of 213 sleep studies, conducted at our sleep centre between February 1999 and January 2000, referred for evaluation of sleep related breathing disorder. Twenty-three patients had evidence of CSR-CSA, 132 had OSA and 58 had no evidence of sleep related breathing disorder. The study was approved by the Health Sciences Institutional Review Board of the University at Buffalo.

Sleep studies

The sleep studies were conducted at the Veterans Affairs Medical Center of Western New York. Continuous electroencephalogram, electrooculogram, electrocardiogram, submental and anterior tibial electromyogram were recorded on a 16-channel poly-

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graph using standard technique, and digitized on a computerized system (Acquitron®; Mallinckrodt, St Louis, MO, and Alice 3®; Respironics, Pittsburgh, PA). Airflow was measured qualitatively by an oral–nasal thermistor (EPM Systems, Midlothian, VA). Measurement of arterial oxygen saturation was performed with a pulse oximeter, Nonin 8500M™ (Nonin Medical Inc. Plymouth, Minnesota), with the probe placed on the patient's finger. Thoracoabdominal movements were recorded using piezoelectric belts.

Sleep stages were scored in 30 s epochs using the Rechtschaffen and Kales sleep scoring criteria [14]. Each epoch was analysed for the number of apneas, hypopneas, arousals, oxygen desaturation and disturbances in cardiac rate and rhythm. Apnea was defined as the absence of airflow for more than 10 s. An obstructive apnea was defined as the absence of airflow in the presence of rib cage or abdominal excursions. Central apneas were defined by the cessation of airflow for 10 s accompanied by an absence of chest wall movement. Hypopnea was defined as a visible reduction in the airflow lasting more than 10 s associated with either a 3% decrease in arterial oxygen saturation or an electroencephalographic arousal, or both. Hypopnea was labelled obstructive if paradoxical thoracoabdominal excursions, if the airflow decreased out of proportion to the reduction in the thoracoabdominal excursions, or snoring occurred. The apnea–hypopnea index (AHI) was defined as the number of apneas and hypopneas per hour of sleep. The presence of CSR-CSA was defined as a central apnea–hypopnea index of $\geq 10\,h^{-1}$ of sleep in which greater than 85% of events are central, in combination with the characteristic pattern of crescendo–decrescendo pattern of hyperpnea alternating with central apnea. Alternatively, obstructive sleep apnea was defined as all others with $AHI > 5\,h^{-1}$ including those with mixed apneas. Arousals were defined according to the ASDA position paper [15]. All sleep studies were reported by one of two board certified sleep physicians. Both sleep physicians who were blinded from each other's opinion reviewed the sleep studies of all patients with CHF to determine the level of agreement in identifying patients with CSR-CSA by polysomnography. Interobserver agreement was assessed by the kappa value. The few discrepancies were resolved by consensus.

Frequency domain analysis

We used the lowest value of the oxygen saturation by pulse oximetry over 4 s intervals for spectral analysis. The sampling rate of the pulse oximetry was 70 Hz with a moving average of 3 s. The data were stored as the average over a 1 s interval. After the data was decimated into 4 s intervals, it was processed to remove any artefacts by eliminating all changes of oxygen saturation between consecutive sampling intervals of greater than 4% per second, and any oxygen saturation less than 20%. The data was then divided into segments of 20.84 min long without discontinuities due to artefacts. The length of the segment was selected so that it would contain 10 cycles of the slowest frequency at which CSR-CSA has been recorded (i.e. 0.008 Hz or cycles of 125 s). Each segment was detrended to reduce the effects of nonlinearities.

A power spectral density, which represents the distribution of power as a function of frequency, was calculated by the maximum entropy method on each segment [16]. The Bayesian information criterion was chosen to select the model order [17].

The power spectrum was calculated at 100 equidistant frequencies on a logarithmic scale ranging from 0.0008 to 0.04 Hz. At each frequency, the mean power was calculated from the average of the power of all segments at that particular frequency. The salient features of the CSR-CSA power spectrum that were selected for further analysis were the frequency and the magnitude of the power attained at the highest local maximum (f_1, m_1), and the frequency and the magnitude of the power attained at the next highest local maximum (f_2, m_2). The randomness of the variability in oxygen saturation was estimated from the entropy, which was quantified using equation (1):

$$\text{Entropy} = -\sum[m(f) * \log_e\{m(f)\}] \,. \qquad (1)$$

$\sum$ denotes the summation of the magnitudes of the spectrum and $m(f)$ represents the magnitude at a particular frequency, f, expressed as a fraction of the total magnitudes.

Time domain analysis

Oxygen desaturation events for 2%, 3% and 4% were calculated from overnight oximetry. The definition of a desaturation event was based on the work of Taha *et al.* [18]. Every data point was examined sequentially to determine if criteria were met to define an event. The criteria for an event were a decrease of at least the set amount (2%, 3% or 4%) in oxygen saturation from the initial data value for at least 10 s, and at a rate that is greater than $0.1\%\,s^{-1}$. In addition, the oxygen saturation must return within 60 s to within 1% of the initial value, or increase from its nadir by 1.5 times or more of the set amount of the dip. Once the criteria were met, a new search for an event was initiated at the next data point after the event.

Artificial neural network

Artificial neural networks (ANN) are computation systems that mimic the analytic approach of biological systems by using a large number of interconnected artificial neurons [19]. Just as humans apply knowledge gained from past experience to new problems or situations, a neural network takes previously solved examples to build a system of 'neurons' that makes new decisions, classifications and forecasts. Neural networks look for patterns in training sets of data, learn these patterns, and develop the ability to correctly classify new patterns or to make forecasts and predictions. Neural networks excel at problem diagnosis, decision-making, prediction and other classifying problems where *pattern recognition is important and precise computational answers are not required.*

For the purpose of this study, we have used a probabilistic neural network (PNN). These networks are a type of supervised network known for their ability to train quickly on sparse datasets and separate data into a specified number of output categories. The PNN is a three-layer network: an input layer, a hidden layer and an output layer. The input layer included the salient features of the spectral analysis. These features comprised of the frequency and the magnitude attained at the highest local maximum; the frequency and the magnitude of the power attained at the next highest local maximum; and the randomness of the variability in oxygen saturation. Other input variables included the desaturation events for 2%, 3% and 4% and the delta index [20].

The number of hidden units was derived from the total number of patterns minus the evaluation set. The output layer provided a classification of the input patterns into three groups: CSR-CSA, OSA, or no sleep related breathing disorder.

Because of the preponderance of patients with obstructive sleep apnea, patients with CSR-CSA were weighted by a factor of 5. A fivefold cross-validation was used for evaluation [21]. The data were divided randomly into five mutually exclusive subsets. Four of the subsets were pooled and used for training; the remaining subset was used as an evaluation set during training. The entire process was repeated four additional times by rotating the subset that was used as the evaluation set during training. For each model a kappa value was obtained to assess reproducibility. The neural network closest to the median was selected for further analysis.

Statistical analysis

A receiver operator characteristic (ROC) curve was generated to assess the accuracy of the neural network. The c-index, which is equivalent to the area under the ROC curve, was used to estimate the diagnostic accuracy of the model. The c-index and its standard error were calculated by the bootstrap method [22]. Kappa statistics were calculated from software available in the public domain [23].

Results

Patient characteristics

A review of medical records revealed that all 23 cases with CSR-CSA had evidence of systolic dysfunction with a mean left ventricular ejection fraction of 25.0 ± 8.4, and were considered for heart transplantation. All were receiving optimal oral therapy and were clinically stable at the time of the sleep study.

Of the 132 patients with polysomnographic evidence of OSA, 39 (30%) had severe OSA with *AHI* $> 30\,h^{-1}$, 35 (27%) had moderate OSA with AHI ranging between 15 and $30\,h^{-1}$, and 58 (43%) had mild OSA with AHI between >5 and $<15\,h^{-1}$. There was excellent agreement between the two physicians in interpreting the overnight polysomnography with a kappa of 0.84 ± 0.14SE. There were only four discrepancies all of which were resolved by consensus meetings.

Frequency analysis

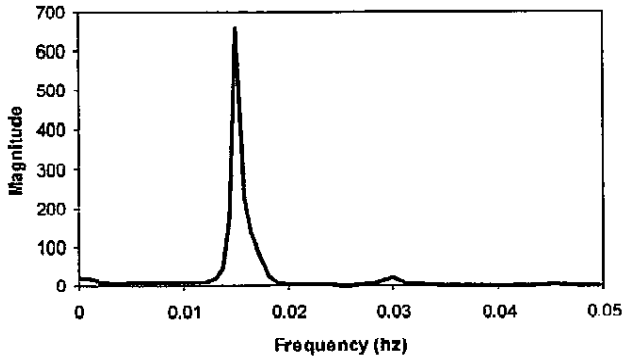
The power spectrum for CSR-CSA patients is characterized by a sharp spectral peak with a large primary local maximum displayed at low frequency (<0.02 Hz) (figure 1). In contrast, the power spectrum in OSA consists of multiple, broadband spectral peaks that are lower in magnitude, with the highest local maximum located at a frequency ≥0.02 Hz. In normal subjects, no apparent peak was detected (figure 2).

PNN performance

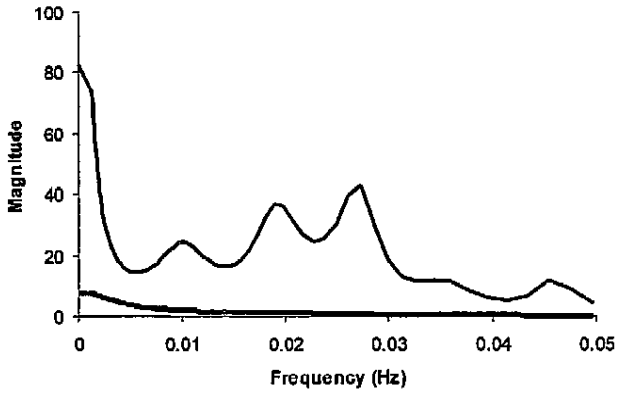
The predictive accuracy of the PNN in detecting CSR-CSA achieved a sensitivity of 100% (95% CI: 85% to 100%) and a specificity of 99% (95% CI: 97% to 100%) (figure 3). The neural network was able to identify accurately all cases who had CSR-CSA. In total, there were three misclassifications (table 1). One patient with OSA was predicted to have CSR-CSA, and two with OSA were mislabelled as having no sleep related disordered breathing. The patient with OSA misclassified to have CSR-CSA had an AHI of 38 while the two patients reported as having no sleep related disordered breathing had an AHI of 6 and 9, respectively.

Discussion

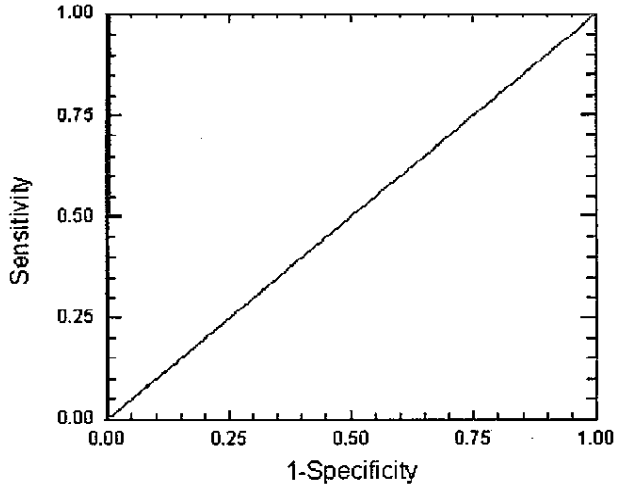
The present study has shown the utility of an artificial neural network as a screening tool for detecting CSR-CSA. The overall accuracy of the neural network in classifying sleep disordered breathing stemmed from delineating the various relationships among the multitude of input parameters selected. In this case, the spectral indices of patients with CSR-CSA displayed features with distinctive discriminative attributes compared to other sleep disordered breathing. While the power spectra of normal subjects was shown to have no apparent peak, and of OSA patients to have broad-band peaks, the patients with congestive heart failure often had a unique distribution of spectral peaks conforming to a long-period oscillation in oxygen saturation. The



1. Power spectrum of pulse oximetry in a patient with Cheyne–Stokes respiration.



2. Power spectra of pulse oximetry of a normal patient (lower line), and of a patient with obstructive sleep apnea (upper line).



3. Receiver operator characteristic curve of the diagnostic accuracy of the neural network.

Table 1. Classification of neural network output.

	CSR-CSA	OSA	No sleep disorder
Actual	23	132	59
Predicted	24	129	61
True positives	23	129	59
False positives	1	0	2
True negatives	190	82	153
False negatives	0	3	0

disparity in the recordings of oximetry between CSR-CSA and OSA has its origin in the distinct pathophysiological basis of both diseases. Javaheri and others [24] have shown that those patients with congestive cardiac failure who had periodic breathing and central sleep apnea had an increased ventilatory response to carbon dioxide, and that the relation between the ventilatory response to carbon dioxide and the number of episodes of apnea is positively correlated. The increased central sensitivity to CO_2 contributes to a fall in arterial blood carbon dioxide gas tension (P_aCO_2) below the sleeping apneic threshold, resulting in a prolonged apnea. The associated hypoxemia increases the ventilatory response to hypercapnia leading to an exaggerated decrease of the P_aCO_2 below the apneic threshold, and subsequently to repeated periodic breathing. The cyclic nature of the breathing pattern translates into a unique spectral peak in the oximetry data that tends to fall between 0.01 and 0.02 Hz. In comparison, the oscillatory breathing pattern observed in OSA is rather mixed due to a combination of periodic and aperiodic patterns of pharyngeal occlusion.

This study is the first, to our knowledge, to develop a diagnostic model based on the frequency analysis of pulse oximetry to identify patients with CSR-CSA. There have been previous studies using spectral analysis of heart rate variability in sleep disordered breathing [25, 26]; none were developed for the purpose of identifying patients with CSR-CSA. A recent study of 104 subjects with CHF by Staniforth *et al.* [7] has examined the desaturation index recorded in nocturnal oximetry (number of events of oxygen desaturation $\geq$4% from baseline per hour of sleep) compared to normal controls. With a threshold of 15 dips per hour, the model yielded a specificity of 81% and a sensitivity of 87% for detecting CSR-CSA. However, the overall accuracy of the model was not provided. Those authors made no attempt to determine if pulse oximetry could be used to distinguish between CSR-CSA and OSA.

The potential application of an artificial neural network for early detection of CSR-CSA in patients with left ventricular dysfunction carries an important implication to the overall management of patients with congestive heart failure. The presence of CSR-CSA has been implicated in increased mortality up to 56% over a 3 yr period compared to 11% in those patients without CSR-CSA despite similar cardiac functional status and left ventricular function [4]. Since nasal CPAP therapy was found to have beneficial acute and chronic cardiovascular effects, early implementation might well be translated into improved cardiac function, reduced hospitalization and potentially reduced mortality, and increased transplant-free survival [6].

There are potential limitations in our study. In the absence of oesophageal pressure, the distinction between central and obstructive respiratory events has not always been possible. However, this method is not without drawbacks. It is invasive, often uncomfortable, and may not be tolerated. Furthermore, there is evidence that an oesophageal catheter may modify the pharyngeal airway dynamics [27], and impair the quality of sleep [28]. Secondly, assessment of CSR-CSA was performed only during a single night of polysomnography recording, and we did not repeat the test to establish that it persisted after the initial study. Hanly and Zuberi-Khokhar [4] has reported previously the persistence of CSR-CSA upon repeat either of polysomnography or through questionnaire obtained from bed partners of CSR-CSA patients. Thirdly, the model involves considerable mathematical analysis but with

the availability of modern software, the process is simple and can be accomplished rapidly. Understandably, the use of overnight pulse oximetry is less precise than polysomnography since it does not measure airflow or arousal, but it is simple, affordable and can be used easily in the patient's home.

In summary, the current study offers potentially an accurate and easily applicable tool to detect heart failure patients with CSR-CSA at a relatively low cost. Future studies are needed to further validate the model in the diagnosis of CSR-CSA.

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