



Original Article

Variability of Pulse Signal Frequency Obtained Using Nocturnal Pulse Oximetry in Patients with Sleep Apnoea/Hypoapnoea Syndrome

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ABSTRACT

Introduction: The measurement of central tendency (MCT) is a non-linear analysis technique which applied to second order differences diagrams enables the degree of variability to be quantified in a data series. In the present study an attempt is made to quantify and characterise the changes in heart rate obtained by pulse oximetry in patients with a clinical suspicion of sleep apnoea/hypoapnoea syndrome (SAHS) using the MCT and to evaluate its diagnostic use.

Patients and Methods: A total of 187 patients were included in the study, on whom a nocturnal polysomnographic and pulse oximetry study was performed. To evaluate the variability of the heart rate the MCT applied to graphs of second order differences obtained from the heart rate record.

Result: Patients with SAHS had a higher heart rate variability than patients without SAHS (0.449 vs 0.666, $P < .001$). In the multivariate analysis, the heart rate, the minimum saturation and the desaturation index of 4% were independently associated with the heart rate variability. As a diagnostic method, the MCT of the heart rate gives a sensitivity of 69.3%, a specificity of 77.6% and a diagnostic precision of 72.7%.

Conclusions: Patients with SAHS have a greater variability in heart rate during the night, evaluated by applying the MCT of the heart rate to diagrams of second order differences. As a screening method, the MCT applied to the heart rate has a moderate sensitivity and specificity.

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Variabilidad de la señal de frecuencia de pulso obtenida mediante pulsioximetría nocturna en pacientes con síndrome de apnea hipopnea del sueño

RESUMEN

Palabras clave:

Síndrome de apnea del sueño

Medida de tendencia central

Frecuencia cardíaca

Diagnóstico

Introducción: La medida de tendencia central (MTC) es una técnica de análisis no lineal que aplicada a diagramas de diferencias de segundo orden permite cuantificar el grado de variabilidad de una serie de datos. En el presente estudio, se pretende cuantificar y caracterizar las modificaciones de la frecuencia cardíaca obtenidas por pulsioximetría en pacientes con sospecha clínica de síndrome de apnea hipopnea del sueño (SAHS) mediante la utilización de la MTC y valorar su utilidad diagnóstica.

Pacientes y métodos: Se incluyen en el estudio 187 pacientes, realizándose un estudio polisomnográfico y pulsioximétrico nocturno. Para la valoración de la variabilidad de la frecuencia cardíaca, se utilizó la MTC aplicada a gráficos de diferencias de segundo orden obtenidos del registro de la frecuencia cardíaca.

Resultados: Los pacientes con SAHS presentaron una mayor variabilidad de la frecuencia cardíaca que los pacientes sin SAHS (0,449 vs. 0,666, $p < 0,001$). En el análisis multivariante, la frecuencia cardíaca, la saturación mínima y el índice de desaturación del 4% presentaron una relación independiente con la variabilidad de la frecuencia cardíaca. Como método diagnóstico, la MTC de la frecuencia cardíaca proporcionó una sensibilidad de 69,3%, una especificidad de 77,6% y una precisión diagnóstica de 72,7%.

Conclusiones: Los pacientes con SAHS presentan durante la noche una mayor variabilidad de la frecuencia cardíaca, valorada mediante la aplicación de la medida de tendencia central a diagramas de diferencias de segundo orden de la frecuencia cardíaca. Como método de despistaje, la MTC aplicada a la frecuencia cardíaca presenta una sensibilidad y especificidad moderada.

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Introduction

Sleep apnoea/hypopnoea syndrome (SAHS) is a common condition characterised by recurrent upper airway collapsibility during sleep. These episodes of reduction or absence of air flow lead to characteristic modifications in both oxygen saturation and heart rate (HR).

Heart rate is a reflection of a subject's cardiovascular state and increased HR has been associated with the presence of cardiovascular alterations and higher morbidity and mortality.¹⁻³ In healthy subjects, heart rate shows complex fluctuations, tending to drop during sleep, especially the non-REM phase. Although the heart rate's response to obstructive apnoeas can vary, patients with SAHS are normally considered to have a characteristic pattern of bradycardia during sleep.⁴⁻⁶ These variations in heart rate seem to depend on alterations in the autonomic nervous system and the air flow. In this respect, modifications in heart rate have been considered to be a marker of autonomic arousals in patients with SAHS.

In recent years, the analysis of heart rate variability has aroused much interest, taking as a reference the electrocardiogram RR interval⁷⁻⁹ as a measure of autonomic control. However, few studies have tried to characterize heart rate behaviour in patients with SAHS¹⁰⁻¹² using pulse oximetry and describe its diagnostic use in patients with a suspicion of SAHS. Most of these studies use linear processing techniques. Like other physiological signals, heart rate behaves in a complex, irregular way, even in healthy subjects, so non-linear techniques are probably more suitable for analysing it. Among this kind of procedures is the measure of central tendency (MCT) applied to diagrams of second order differences.¹³ Diagrams of second order differences are a very useful graphic method as they provide a rapid, visual analysis of the behaviour of a series of data. The graphs are centred on the origin, enabling the degree of chaos in a dataset to be evaluated. Thus, a diagram showing points clustered around the centre is associated with less variability of the series of data. MCT can be used to assess the second order diagrams objectively, enabling variability to be quantified. A low MCT value would imply greater variability of the signal analysed.

This prospective study aims to quantify and characterize the variability of pulse signal frequency obtained using pulse oximetry in patients with breathing disturbances during sleep, using measure of central tendency applied to diagrams of second order differences; we also aim to evaluate its diagnostic use with patients with a clinical suspicion of SAHS.

Patients and Methods

One hundred and eighty-seven subjects (147 men and 40 women) referred consecutively to the pneumology department at the *Hospital Clinico Universitario* in Santiago de Compostela with a clinical suspicion of SAHS were included in the study. All the subjects simultaneously underwent nocturnal polysomnography (Ultrasom Network, Nicolet, Madison, WI, USA) and recording of heart rate and oxyhaemoglobin with a pulse oximeter (Criticare 504 oximeter, CSI, Wankeska, WI, USA), using a finger probe with a sampling frequency of 0.2Hz. The nocturnal polysomnography included the monitoring of electroencephalogram, electro-oculogram, oronasal flow by thermistor, thoracoabdominal movement, electrocardiogram, snoring and body position. Sleep was analysed following standard criteria.¹⁴ Apnoea was defined as

the absence of air flow for over 10 s and hypopnoea as a noticeable reduction in air flow or chest wall movement, accompanied by a desaturation of over 3% or the presence of arousal. The apnoea/hypopnoea index (AHI) was calculated by dividing the number of apnoeas and hypopnoeas by the number of hours of sleep. Patients were considered to have SAHS with an AHI over 10. All the patients were clinically stable while both studies were performed. SAHS was considered mild to moderate if the AHI was under 30, and severe when over 30. The polysomnography and pulse oximetry data were analysed independently.

Patients previously diagnosed with autonomic neuropathy or autonomic dysfunction were excluded from the study, as were those with heart rate disorders. Seventeen point one percent had a history of cardiovascular disease. None of the patients included took anti-arrhythmic drugs. All the patients were stable while the polysomnography study was being performed. The study was approved by the ethics committee of the hospital.

Measure of Central Tendency

To quantify the variability of the pulse signal frequency obtained using nocturnal pulse oximetry, we used the measure of central tendency applied to diagrams of second order differences. Diagrams of second order differences are dispersion graphs centred on the coordinate origin. This kind of graph of the data obtained from a recording provides information quickly and visually about the dispersion (variability) of a series of analysed data. Thus, it is a very useful graphical tool for the analysis of biomedical data recordings. In this type of graph, the difference between two shifted versions of the signal under study is represented on each coordinate axis, which is why they are called second order differences. The MCT is used to numerically and objectively quantify the degree of dispersion of the data, which can also be visualised in the diagrams of second order differences. Both tools (graphical and numerical) are combined to characterize all the biological recordings, which in this case is heart rate (n). To do this, it is necessary to choose a circle with a fixed radius (r) around the origin, count the number of points inside the circle and normalize with regard to the total number of points. If the dispersion of the data in the diagram of second order differences is very high, that is, the points are scattered over the whole diagram, then a high percentage of them will fall outside the circle. This will give rise to a low MCT value, towards 0 (high variability). If, on the other hand, the dispersion of the data in the diagram is small and, therefore, the values tend to be concentrated around the coordinate origin, most of the data will be inside the circle. This will give rise to a high MCT value, towards 1 (low variability).

Selecting the right radius value (r) to calculate the MCT is very important. Generally, the radius selected depends on the type of data analysed. In our study the choice of radius for the circular area was made to look for the most significant differences between the groups of patients with and without SAHS. To do this, the MCT was calculated for each heart rate recording with different radii within a range determined by the nature of the data (from $r = 1$ to $r = 10$ in steps of 0.1). Then, the student test was applied and the radius giving the most significant differences between samples was chosen, which in our case was $r = 1.5$. Due to the length of the sleep recordings, to process the signals with the MCT, each of the recordings was divided into epochs of 200 samples, enabling several episodes of apnoea to be included in each epoch. Finally, an average was worked out, taking

into account the total number of epochs to obtain one single MCT value for each recording.

Statistical Analysis

Data are expressed as means and standard deviation. The Mann-Whitney test was used for comparison between groups. To study the correlation between variables we used the Spearman correlation test. Multivariate linear analysis techniques were used to analyze the variables, using the stepwise least squares method. To assess the diagnostic accuracy of the MCT applied to nocturnal pulse signal frequency, receiving operator characteristic (ROC) curves were used. A Matlab® programme was used to construct the curve. A one way analysis of variance was also performed using the Student test to compare the group with SAHS and the one without $P < .05$ was considered to be statistically significant. Data were analysed using the SPSS v 16.0 statistics programme.

Results

Nocturnal polysomnography made it possible to diagnose 59.3% of the subjects in the study with SAHS. The patients' clinical characteristics are shown in table 1.

At the start of polysomnography recording, the patients with SAHS had a higher heart rate than those without SAHS (74.5 vs 69.3 bpm; $p < 0.05$). Figures 1 and 2 show characteristic diagrams of second order differences for heart rate of a subject without and with SAHS, respectively. In figure 1, the diagram shows a series of data with little variability, so the points are near to the origin (no SAHS). Figure 2 corresponds to a patient with SAHS and the diagram shows greater graphic dispersion of the heart rate values. Using the MCT with the second order diagrams makes it possible to evidence that the patients with SAHS have lower MCT values than those with SAHS (0.449 ± 0.225 vs 0.666 ± 0.168 , $P < .001$) and therefore greater heart rate variability (Figure 3).

The MCT values for pulse frequency showed a negative correlation with: heart rate at the start of recording ($r = -0.30$, $P < .001$); AHI ($r = -0.425$, $P < .001$); desaturation index (DI) 4% ($r = -0.426$, $P < .001$); DI 3% ($r = -0.408$, $P < .001$); DI2% ($r = -0.379$, $P < .001$); mean saturation ($r = 0.361$, $P < .001$); minimum saturation ($r = 0.460$, $P < .001$); and the percentage of time at SaO_2 below 90% ($r = -0.324$, $P < .001$). These correlations remain significant when adjusted for age and BMI. We found no relationship between the MCT for heart rate and either BMI or sex, but there was a positive relationship with age ($r = 0.174$). The patients with severe SAHS had greater variability with regard to those with mild SAHS (0.514 vs 0.413 , $P < .05$).

In the multivariate analysis, the variables with the highest explanatory power of the MCT (variability) for pulse frequency were minimum saturation, the desaturation index 4%, and basal heart rate,

which would explain 26.18% of the behaviour of the MCT value for heart rate.

Figure 4 shows the ROC curve for pulse frequency variability, used as a method to help diagnose SAHS. The best results are obtained with a cut-off point of 0.576, reaching a sensitivity of 69.3%, a specificity of 77.6%, a diagnostic accuracy of 72.7%, and with an area under the curve of 0.778 (CI 95% 0.712-0.836). The true positive rate was 3.10 (2-4.79) and the true negative rate was 0.39 (0.29-0.53) (Table 2).

In patients without SAHS, we found no differences between the false positives (CTM < 0.576 and AHI < 10) and the true negatives with regard to age (59.4 vs 51.6), BMI (27.7 vs 30) and AHI (2.03 vs 2.01), but we did find differences with respect to minimum saturation (87.4 vs 79.9) and desaturation index (0.87 vs 2.9) ($P < .05$). In patients with SAHS, those whose oximetry test gave false negative results showed significant differences with regard to the severity of AHI (31.5 vs 44), age (62.9 vs 56), minimum saturation (73.4 vs 68.1), and a lower desaturation index (11.3 vs 25.05).

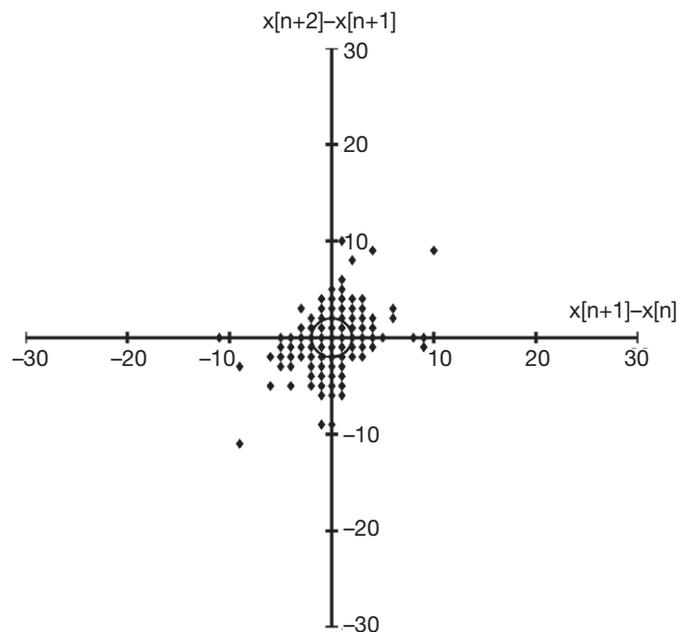


Figure 1. Diagram of second order differences showing the pulse signal frequency of a subject without SAHS. Each axis represents the difference between two shifted versions of the signal under study: $x[n]$ is the original pulse frequency recording; $x[n+1]$ is the pulse frequency recording after the time origin is shifted one sample; $x[n+2]$ is the pulse frequency recording after shifting the time origin 2 samples.

Table 1

Characteristics of the patients included in the study, grouped by those with or without sleep apnoea/hypopnoea syndrome (SAHS)

	Overall sample (n=187)	No SAHS (n=76)	SAHS (n=111)	P
Age, years	57.9 (12.8)	57.6 (12.9)	58.3 (12.9)	ns
BMI, kg/m ²	29.5 (5.5)	28.4 (6.012)	30.5 (4.9)	.03
AHI	24.6 (1.7)	2.04 (2.36)	40.1 (19.6)	.001
COPD, %	22.5%	26.3%	19.8%	ns
Males, %	78.6%	69.7%	84.7%	.02
Heart rate	72.6 (13.3)	69.3 (12.4)	74.5 (13.5)	.02

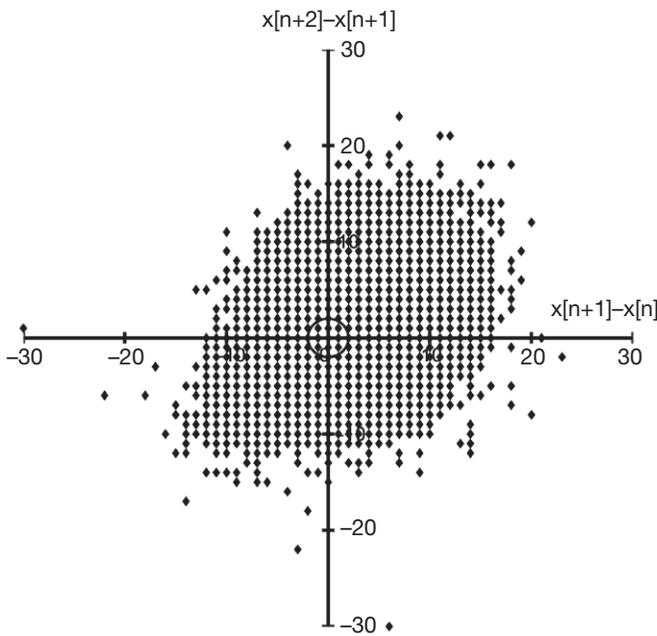


Figure 2. Diagram of second order differences showing the pulse signal frequency of a patient with SAHS. Each axis represents the difference between two shifted versions of the signal under study: $x(n)$ is the original pulse frequency recording; $x(n+1)$ is the pulse frequency recording after the time origin is shifted one sample; $x(n+2)$ is the pulse frequency recording after shifting the time origin 2 samples.

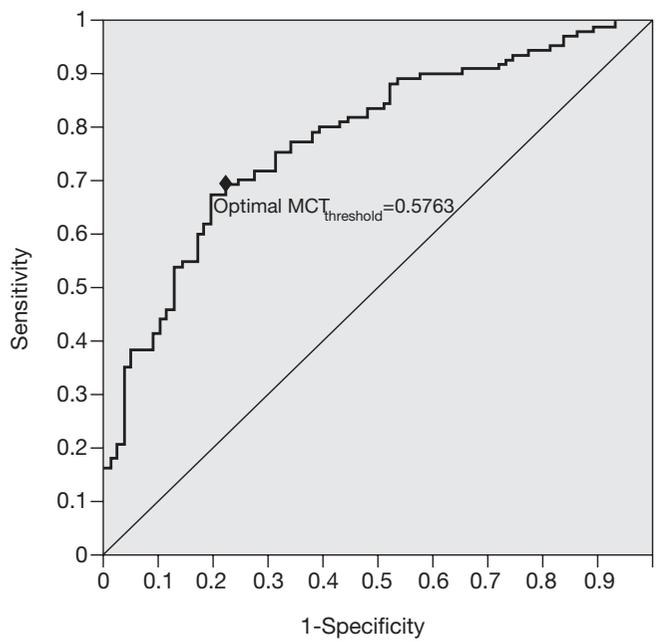


Figure 4. Diagnostic efficacy curve to evaluate the presence or absence of SAHS using the value for the measure of central tendency (MCT) of heart rate (HR) obtained using nocturnal pulse oximetry. The symbol \blacklozenge represents the optimal decision threshold.

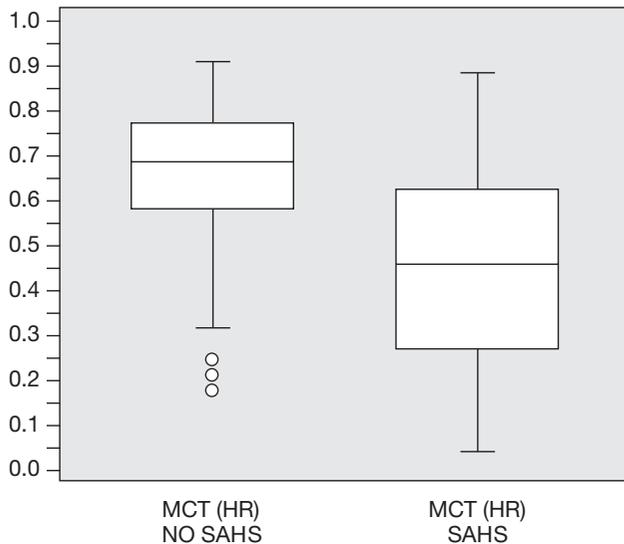


Figure 3. Box graphs showing the differences between the values of the measure of central tendency (MCT) of the heart rate (HR) in patients with or without sleep apnoea/hypopnoea syndrome (SAHS).

Discussion

The main finding of our study is that patients with SAHS have greater variability of nocturnal pulse signal frequency obtained using pulse oximetry than patients without SAHS, and therefore show greater dispersion in diagrams of second order differences.

Even at rest, healthy subjects can show variability in their heart rate, depending on different factors such as age, body position, breathing rate and vagal tone. Sleep, especially in the early stages, involves changes in heart rate activity. In patients with SAHS, the presence of apnoeas produces relative bradycardia and vasodilation,

Table 2

Diagnostic use of applying the measure of central tendency to heart rate (diagnostic threshold=0.576)

Statistics	Value	CI95%
Sensitivity	69.3	60.8-77.9
Specificity	77.6	68.3-87.0
Diagnostic accuracy	72.7	66.3-79.1
Predictive positive value	81.9	74.1-89.7
Predictive negative value	63.4	53.7-73.2
Positive likelihood ratio	3.101	2.004-4.799
Negative likelihood ratio	0.395	0.291-0.535

followed by an increase in heart rate and vasoconstriction, which could explain the greater variability in pulse frequency shown by these patients.¹⁵

Despite its importance, heart rate behaviour in patients with SAHS has not been clarified.¹⁶ In our study basal heart rate, the desaturation index (4%) and minimum saturation were found to be the main parameters independently associated with heart rate variability measured by non-linear methods, although they can only explain 26.18% of this variability. For Zwillich,¹⁷ bradycardia is a common phenomenon in apnoeas, their duration and the increase in oxyhaemoglobin desaturation being factors determining its onset. Guilleminault found that there is a close relationship between the duration of apnoeas and bradycardia phenomena.⁴ However, other authors place a great deal of importance on arousals. Haba Rubio¹⁵ found that variations in heart rate and the plethysmographic waveform of the pulse do not differ with regard to the type of apnoea, but rather with regard to the duration of the arousals associated with them. Likewise, Guilleminault describes that, in patients with upper airway resistance syndrome, apnoeas accompanied by arousals have a greater tachycardic effect, even if there is only a small reduction in blood oxygen saturation.¹⁸

As in the study by Sumi,¹⁹ we also evidenced a relationship between heart rate with the AHI and the different desaturation

indices. The MCT applied to diagrams of second order for the heart rate signal has an inverse correlation with the AHI and the classic desaturation indices. This negative correlation is due to the method itself, as greater variability is expressed by a lower MCT value. The relationship we found between the variability in heart rate and oxygen saturation in patients with SAHS is in accordance with previous studies which have evidenced a higher degree of coherence and synchrony of the fluctuation between HR and oxygen saturation in patients with SAHS, when compared with non-apnoeic patients.^{20,21}

In recent years there has been a great deal of interest in finding alternative diagnostic methods to conventional polysomnography, either related to respiratory polygraphy²² or using simplified systems based on the analysis of certain symptoms.²³ Variability in HR has been used in clinical practice, either in isolation^{7,10,12} or together with oxygen saturation,¹¹ to assess sleep fragmentation²⁴ or as a screening method for SAHS. Most of the existing studies use techniques based on spectral analysis,²⁵ however, evaluating biosignals using non-linear methods could be more suitable.^{26,27} For this, graphical techniques can be used (Poincaré maps, diagrams of second order differences), and also numerical techniques such as fractal dimension calculation, the Lyapunov equation or the measure of central tendency. In our study we have used both methods to analyse variability in heart rate in patients with SAHS, diagrams of second order differences (Figures 1 and 2) and numerical analysis using MCT. The MCT is a numerical technique derived from the chaos theory which has been introduced in recent years as a way of quantifying variability in time series data, providing precise information for what is visible in the diagrams of second order differences. The MCT has been widely used in cardiology, neurology,^{13,28-30} and more recently, it has provided good results with patients with breathing disorders during sleep.^{26,31}

Applying MCT of heart rate to diagrams of second order differences has acceptable specificity and moderate sensitivity as a diagnostic method when compared with conventional polysomnography. It shows very similar results to those obtained by analysing heart rate regularity¹² (approximate entropy) but much worse results than those provided by non-linear analysis of oxygen saturation.²⁷ In our study the patients with SAHS who showed little variability in heart rate were characterised as having less severe SAHS, less desaturation, and being older.

In our case, oximetry and heart rate recordings were performed simultaneously with polysomnography, thus avoiding night to night variability and ensuring an identical setting for the two types of recording; they were analysed independently, though. Among the study's limitations, it is worth pointing out that heart rate was measured using pulse oximetry instead of an electrocardiogram. However, recording pulse signal frequency is easier than measuring the RR interval in daily practice as the latest pulse oximeters give combined recordings of oxyhaemoglobin saturation, heart rate and the plethysmographic waveform of the pulse. On the other hand, although pulse frequency is closely correlated with heart rate,³² it does not accurately reflect heart rate variability, especially in healthy patients or those with low HR variability.³³ Another point to bear in mind is that the analysis of the behaviour of the variations in heart rate was performed on the set of recordings, without taking into consideration the different phases of sleep.

In summary, patients with SAHS have higher heart rate variability during the night, and the factors independently associated with this are basal heart rate, the desaturation index

and the minimum saturation. As a technique to help diagnose SAHS, the MCT of the heart rate gives moderate sensitivity and specificity. Using non-linear techniques like the MCT can help provide us with a better understanding of the dynamic behaviour of bio signals, beyond the limited information provided by traditional statistical methods.

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