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Head-up Tilt Testing with Continuous EEG Monitoring for the Anticipated Detection of Vasovagal Syncope

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Abstract

Syncope is often referred as the sudden loss of consciousness, associated with inability to maintain postural tone, with a spontaneous and rapid recovery. Even though it is not associated with an increased risk of mortality, it is potentially dangerous in those with high-risk occupations and in older patients who lack warning symptoms because the transient loss of consciousness (TLOC) may lead to falls and injury. Vasovagal syncope (VVS) is typically characterized by precipitating triggers and prodromal symptoms. Usually is performed an head-up tilt test (HUTT) to induce syncope, serving as a widely used modality for diagnosing this condition.

The HUTT usually starts with a period of supine rest, followed by a period of passive tilt (without the use of pharmacological enhancement) and then a period of active tilt (with the use of pharmacological enhancement). The test is ended when the protocol is completed in the absence of symptoms, or there is occurrence of syncope. The HUTT is positive with the induction of syncope or presyncope and is negative if the patient completes the protocol with no characteristic hemodynamic changes. It is thought that the introduction of EEG monitoring during head-up tilt testing could significantly improve the understanding of the cerebral events occurring during tilt-induced vasovagal syncope since the EEG provides an objective marker of brain dysfunction during the cerebral hypoperfusion that accompanies syncope. During a syncopal episode, the EEG generally is said to show a diffusely slowed background initially and then high-voltage delta activity. This way, the objective of this dissertation is to implement an algorithm that detects the sequence of changes in the EEG signal, when patients are in imminent syncope, or show symptoms of it.

The data was measured by me with a wearable EEG band that has BITalino as its functional core while patients performed the test. Data were taken from 36 patients, 20 of whom had a positive test and 16 had a negative test, being that among the negative, 8 had symptoms during the test and 8 did not. Due to the similarity in the signal characteristics between the positive cases and the negative cases of patients who had symptoms during the test, a division was made between these 28 cases and the 8 cases of patients who did not experience any symptoms. The data was processed, filtered and segmented in intervals of interest, these being, 1 minute during the supine rest phase, the first minute of the active phase and 1 minute, 30 seconds and 10 seconds respectively before syncope, or the end of active phase in the case of a negative test. Data were analyzed in terms of amplitude, where a large increase in signal amplitude was observed during syncope, which was not observed in negative cases without symptoms. In frequency, the power spectrum of the signal in each interval was made, and this was then divided according to the frequency spectrum intervals known in the literature. A large increase in the power of delta waves from the supine rest interval to the intervals before syncope was noted, which did not occur in the negative cases without symptoms or in with the other frequency spectra.

It was concluded that what would be more reliable and more adjusted to the intended objective, would be to develop the prediction classifier based on symptoms and not on syncope. It was verified an increase in values of both amplitude and frequency in symptomatic patients from the supine rest interval to the first minute of the active phase, and a further increase to the intervals before the end of the active phase. The characteristics in the EEG signal during a syncopal episode studied by other investigations were verified in the results obtained, where these variations were used to develop a classifier model to categorize the results in symptomatic patients and non-symptomatic patients. The classification was done through a train support vector machine (SVM) classifier for the variation in amplitude and

frequency values between the supine rest and the 1-minute interval and the 30-seconds interval before syncope.

It is inferred that the model has some reliability, having managed to correctly categorize all observations. For the model with the results of variations between the supine rest interval and 1 minute before the end of the active phase, its accuracy had a mean value of 100% and for the 30-second interval had a test accuracy with a mean of 93.8%. It is thought that with a larger number of samples, it can be implemented in a practical context. Thus, it is concluded that the study carried out has very promising and innovative results in terms of the pattern found, as well as in its classification.

Key-words: Vasovagal syncope (VVS), Head-up tilt test (HUTT), Wearable EEG band, Power spectrum, Train support vector (SVM) classifier.

Resumo

A síncope é frequentemente referida como a perda súbita de consciência, associada à incapacidade de manter o tónus postural, com uma recuperação rápida e espontânea. Mesmo que não haja risco de mortalidade, é potencialmente perigoso em pessoas com profissões de alto risco e em pacientes mais velhos que não apresentam sintomas de alerta porque a perda transitória de consciência pode levar a quedas e lesões. O processamento avançado de sinais em combinação com a integração de sistemas inovadores construídos com sensores *wearable* abriram caminho para o desenvolvimento de novas abordagens para a detecção precoce de síncope iminente. O desenvolvimento destes sensores e a análise de dados de pré-síncope podem permitir o estabelecimento de um sistema preditivo capaz de alertar o paciente antes do desmaio, prevenindo muitos riscos e fazendo com que a sua qualidade de vida aumente substancialmente. A síncope vasovagal é tipicamente caracterizada por desencadeadores precipitantes e sintomas prodrómicos devido à ativação do sistema autónomo. Normalmente é realizado um teste de inclinação para induzir a síncope, sendo que este serve como um método amplamente utilizado para avaliar a suscetibilidade do indivíduo à síncope neuromediada. Este teste também pode ser um método valioso para educar os indivíduos suscetíveis sobre o diagnóstico de uma condição sem risco de vida e também pode ajudar esses pacientes a identificar sintomas de alerta.

O teste geralmente começa com um período de repouso em posição supina, seguido por um período de inclinação passiva (sem o uso de reforços farmacológicos) e depois um período de inclinação ativa (com o uso de reforços farmacológicos). As respostas ao teste podem ser classificadas em três tipos: tipo 1 ou misto; tipo 2A ou cardioinibitório sem assistolia; tipo 2B ou cardioinibitório com assistolia; e tipo 3 ou vasodepressor. O teste é terminado quando o protocolo é concluído na ausência de sintomas ou quando ocorre síncope. Este é positivo com a indução de síncope ou pré-síncope, e negativo se o paciente completa o protocolo sem nenhumas alterações hemodinâmicas características.

Com o objetivo de se obter um diagnóstico mais preciso de pacientes com perda transitória de consciência e distinguir síncope, crises epilépticas e eventos psicogénicos, o teste de inclinação com a adição de registo de eletroencefalograma (EEG) é proposto para fornecer informações clínicas adicionais. O EEG permite a avaliação dinâmica da função neurológica e fornece um marcador objetivo da disfunção cerebral durante a hipoperfusão cerebral que acompanha a síncope. Consequentemente, a introdução da monitorização de EEG durante o teste pode melhorar significativamente a compreensão dos eventos cerebrais que ocorrem durante a síncope vasovagal induzida pela inclinação e o potencial perigo que pode ser causado ao paciente por este procedimento diagnóstico. Durante um episódio sincopal, foi observado em vários estudos que geralmente o EEG inicialmente mostra um fundo difusamente retardado e, posteriormente, atividade delta de alta voltagem, geralmente após um intervalo de cerca de 10 segundos e seguido por vezes de um silêncio eletrocerebral transitório se a hipoperfusão persistir. Desta forma, o objetivo desta dissertação é implementar um algoritmo que detete a sequência de alterações no sinal EEG, quando os pacientes estão em iminência de síncope ou apresentam sintomas.

Uma vez que a medição do electrocardiograma e da pressão arterial apenas são capazes de diagnosticar, mas não podem prever a iminência da síncope, foi proposto o uso de uma banda que mede a atividade cerebral através de encefalografia, tendo o BITalino como o seu núcleo funcional. Os dados foram recolhidos por mim com esta banda EEG móvel enquanto os pacientes realizavam o teste no Hospital de Santa Marta. Foram recolhidos dados de 36 pacientes, dos quais 20 tiveram um teste positivo e 16 um teste negativo, sendo que, entre os negativos, 8 apresentaram sintomas durante o teste e 8 não.

Devido à semelhança nas características do sinal entre os casos positivos e os casos negativos de pacientes que apresentaram sintomas durante o teste, foi feita uma divisão entre esses 28 casos e os 8 casos de pacientes que não apresentaram qualquer tipo de sintomas durante o teste.

Posteriormente, os dados foram processados, filtrados e segmentados em intervalos de interesse, sendo estes: 1 minuto durante a fase de repouso em posição supina, o primeiro minuto da fase ativa e 1 minuto, 30 segundos e 10 segundos respetivamente antes da síncope, ou do final da fase ativa no caso de um teste negativo. Os dados foram analisados em termos de amplitude e frequência. Em termos de amplitude, foram analisadas apenas as suas variações de intervalo para intervalo, com um grande aumento da amplitude do sinal observado durante a síncope, que não foi observado nos casos negativos sem sintomas. Para a frequência, foi feito o espectro de potência do sinal usando o método de Welch em cada intervalo, sendo este então dividido de acordo com os intervalos do espectro de frequência conhecidos na literatura. Notou-se um grande aumento na magnitude das ondas delta do intervalo de repouso para os intervalos anteriores à síncope, o que não ocorreu nos casos negativos sem sintomas ou nos outros intervalos de frequência.

Concluiu-se então que o que seria mais confiável e mais adequado ao objetivo pretendido, seria desenvolver o classificador de predição baseado na ocorrência de sintomas e não na síncope, uma vez que só assim o paciente pode ser avisado com antecendência e podem ser tomadas as devidas precauções. Os valores das frequências delta de certa forma refletem o que acontece com os resultados da amplitude. Foi verificado um aumento destes valores em pacientes sintomáticos do intervalo de repouso até o primeiro minuto da fase ativa, e um aumento ainda maior para os intervalos anteriores ao término da fase ativa.

As características do sinal EEG durante um episódio sincopal estudado por outras investigações foram verificadas nos resultados obtidos, onde essas variações foram utilizadas para desenvolver um modelo classificador baseado na categorização desses dados. Um método de classificação dos resultados em pacientes sintomáticos e não sintomáticos teve que ser desenvolvido para que os resultados obtidos pudessem ser colocados em prática e testados num contexto prático para confirmar a sua veracidade. Desta forma, os dados de cada paciente individual foram classificados de acordo com o seu valor, tanto na análise realizada em termos de amplitude como na de frequência. A classificação foi feita através de um classificador de vetores de suporte, dividindo os dados num conjunto de treino e num conjunto de teste. Esta metodologia foi aplicada na variação dos valores de amplitude e frequência entre o intervalo de repouso e o intervalo de 1 minuto antes do fim da fase ativa, bem como entre o intervalo de repouso e o intervalo de 30 segundos antes do fim da fase ativa. Foi desenvolvido ainda um hiperplano para as duas variáveis em função uma da outra de modo a separar as classes e classificar o conjunto de teste.

Infere-se que o modelo possui alguma confiabilidade, tendo conseguido categorizar corretamente todas as observações. Para o modelo com os resultados das variações entre o intervalo de repouso e 1 minuto antes do término da fase ativa, a sua precisão de teste teve um valor médio de 100%, sendo que para o intervalo de 30 segundos teve uma precisão de teste com uma média de 93,8%. Pensa-se que com um número maior de amostras este modelo poderá ser implementado num contexto prático. Assim, conclui-se que o estudo realizado apresenta resultados muito promissores e inovadores tanto no que diz respeito ao padrão encontrado nos dados recolhidos, como na sua classificação, apesar de todas as limitações inerentes ao teste de inclinação e ao estudo em questão. O trabalho a ser feito no futuro passa justamente por implementar este algoritmo, num sistema móvel de EEG conectado ao telemóvel do paciente, que o avise com tempo suficiente para que a sua qualidade de vida aumente substancialmente.

Palavras-Chave: Síncope vasovagal, Teste de inclinação, Banda EEG móvel, densidade espetral, classificador de vetores de suporte.

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List of Acronyms

VVS – Vasovagal syncope

ECG – Electrocardiogram

EEG – Electroencephalogram

HR – Heart rate

TLOC – Transient loss of consciousness

HUTT – Head-up tilt test

BP – Blood pressure

ILR – Internal loop recorder

AV – Atrioventricular

OH – Orthostatic hypotension

POTS – Postural orthostatic tachycardia syndrome

bpm – Beats per minute

SVM – Support vector machine

Chapter 1. Introduction

1.1. Motivation

Syncope is often referred as the sudden loss of consciousness, associated with inability to maintain postural tone, with a spontaneous and rapid recovery [1]. This condition has a massive medical, social and economic impact on the general population, being that the underlying mechanism is transient global cerebral hypoperfusion [2]. It has been estimated that syncope assessment accounts for 3–5 % of emergency department visits and 1–6 % of hospital admissions [3]. Generally, the mortality rate is low but may be up to 33% at 1 year in patients in which the pathology has a cardiac origin [4].

Neurally mediated reflex syncope, commonly referred as vasovagal syncope (VVS), is the most common type of syncope and approximately 35% of people between 35−60 years old have had at least one VVS episode. The introduction of the term 'vasovagal' was first made by Sir William Gowers in 1907 to describe a constellation of 'vagal' symptoms related with vasomotor spasm [5]. This condition has a high lifetime prevalence of nearly 40% [6] and may be severe enough to have a significant reduction in the patient's quality of life. Even though it is not associated with an increased risk of mortality [5], it is potentially dangerous in those with high-risk occupations and in older patients who lack warning symptoms because fainting may lead to falls and injury [7].

The age distribution of syncope is bimodal, peeking in teenagers and in the elderly, being that the lifetime cumulative incidence is higher in women than in men. Yet the true incidence of syncope is tricky to establish due to the constant variation in definition, disparities in population prevalence and underreporting [8]. This incidence has an enormous impact that ranges from consequences on education in the younger populations, through impaired social life and capability to drive in adolescence, restricted career opportunities in adult life and risk of fractures and other injuries in later years [9].

Despite the elevated number of patients with this condition, only a small proportion of them make use of hospital emergency services. Nevertheless, huge quantities of money are spent on these patients to diagnose the underlying cause of these syncope. When syncope is suspected, a head-up tilt table test is commonly performed to induce the loss of consciousness and confirm the diagnosis. This test is accompanied by a series of exams (e.g. computed tomography of the heart, implantable loop recorder, 24-hour electrocardiogram (ECG), 24-hour electroencephalogram (EEG), etc.), as well as the use of other auxiliary devices.

Advanced signal processing in combination with the integration of innovative systems in wearable sensors have paved the way to develop novel approaches for early detection of impending syncope [6]. The development of wearable sensors and the analysis of pre-syncope data may allow the establishment of a predictive system capable of alerting the patient before fainting, preventing many risks and causing the quality of life of patients to increase substantially. This way, the objective of this dissertation is to implement an algorithm that detects the sequence of changes in the EEG signal, measured with a wearable band, when patients are in imminent syncope, or show symptoms of it. This detection will eventually allow sending an alert to their cell phone, so that they can know in advance that they are on the verge of lose consciousness.

1.2. Mechanisms of Vasovagal Syncope

Vasovagal syncope (VVS) is a form of reflex syncope usually induced by emotional or orthostatic stress, normally preceded by prodromes of autonomic activation (such as sweating, pallor and nausea) [10]. In reflex syncope, cardiovascular reflexes that regulate the circulation become intermittently dysfunctional resulting in hypotension and/or bradycardia. Syncope is typically classified based on the efferent pathway most involved, i.e. sympathetic (hypotension or "vasodepressor") or parasympathetic (bradycardia or "cardioinhibitory") [8]. Classification of syncope based on the underlying pathophysiological process is described in **Figure 1.1**.

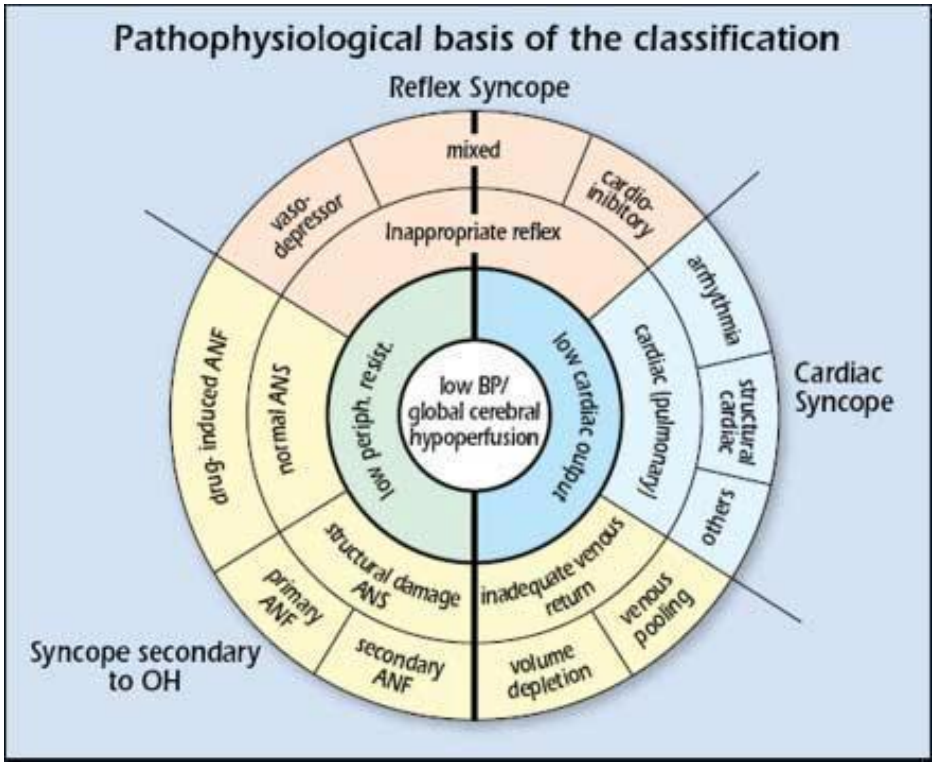

Figure 1.1 *- Pathophysiological basis of Classification of Reflex Syncope. ANF = autonomic nervous function; ANS = autonomic nervous system; BP = blood pressure; OH = orthostatic hypotension; low periph. resist. = low peripheral resistance* [8].

1.2.1. Pathophysiology

An upright position leads to pooling of between 500-1000 ml of blood in the lower limbs and splanchnic area. This leads to a decline in venous return, ventricular preload and cardiac output [8]. The increased venous pressure in the lower limbs leads to a rise in trans-capillary hydrostatic forces with plasma leaking out into the interstitium further reducing the total plasma volume by 10% at 5 minutes and 15-20% after 10 minutes. The reduction in venous return to the right atrium causes the right atrial pressure to fall from 5-6 mmHg to almost 0 mmHg, leading to decreased right ventricular filling during diastole and a reduced stroke volume and cardiac output [2].

Consequent reduction in distension of the baroreceptors in the aortic arch and carotid sinuses, and mechanoreceptors in the heart results in attenuated baroreflex afferent signals to the cardiovascular center in the brain stem. This triggers parasympathetic inhibition and sympathetic activation with sympathetic vasoconstriction, leading to an increase in heart rate (HR) (to maintain the mean arterial pressure) and total peripheral resistance, to maintain the mean arterial pressure. However, in patients with VVS, these adaptation mechanisms are insufficient to maintain adequate blood perfusion pressure, with consequent vasodepression and/or bradycardia. Most therapies are focused on maneuvers which attenuate peripheral pooling and increase intravascular volume, modification of medications which contribute to hypotension or bradycardia and raising awareness of prodromal symptoms [2,8].

1.2.2. Clinical Presentation

Vasovagal syncope (VVS) is typically characterized by 1) precipitating triggers such as emotional distress or orthostatic stress (prolonged standing) and 2) prodromal symptoms due to activation of the autonomic system, such as awareness of fast heart rate, nausea, vomiting, abdominal discomfort, sweating and pallor. In addition to autonomic symptoms, prodromes due to cerebral and retinal hypoperfusion, such as dizziness, light-headedness, blurred vision, and heightened awareness of senses, particularly auditory, are commonly reported. The duration is short, with prompt recovery on assuming the supine position [8,11]. If the role of a trigger (emotional or orthostatic) remains uncertain, tilt testing may be indicated, and the diagnosis of VVS can be made if this test is positive in the absence of any competing diagnosis [11].

Characteristic episodes occur when on the upright position, during prolonged standing or after exercise [8], and are mostly observed in young subjects, more infrequently in the elderly [11]. Episodes are triggered by fasting, dehydration, alcohol, hot weather, hot showers/baths, crowded places, and menstruation. Symptoms may arise for the first time after stressful life experiences or periods of emotional strain, being the patient's clinical history also very important to the diagnosis.

Despite the above-mentioned typical presentation, a significant percentage of patients do not present the typical prodromal symptoms, translating a gradual autonomic activation but rather a more sudden, almost prodromal-free form of VVS. For these patients, the typical therapeutic maneuvers, are useless, as they depend on the detection of prodromes. This form of atypical VVS is classified as "severe" if persistent or if associated with injury or the need for hospital admissions. As it is triggered by orthostatic stress, this type of syncope can be classified as vasovagal, even if not spontaneous (tilt testing), being that numerous attributable causes might be present, increasing with age. Atypical VVS is often detected in older patients, who regularly experience shorter prodromes, if any. Before the introduction of the head-up tilt test (HUTT) into clinical practice, a diagnosis was very challenging to perform in these subjects [8,11].

1.2.3. Diagnosis

Preliminary investigations comprise comprehensive anamnesis and physical examination, ECG and orthostatic blood pressure (BP) measurements [8]. A detailed clinical history of the patient is essential for the diagnosis in most cases. Further investigations, such as HUTT, may be helpful based on medical

history and initial investigations. Diagnostic scores have been established to help diagnose, however, they have a low specificity, potentially misdiagnosing cardiac syncope such as VVS.

1.2.3.1. Head-up Tilt Table Testing

Tilt tables (**Figure 1.2**) have long been used by physiologists to study the changes occurring during movement from the supine to the head upright position. Later, these same techniques were utilized to study the changes that might occur during the stresses of aerospace travel [12]. It was observed through those studies that hypotension and bradycardia would cause a sudden TLOC on a few subjects. However, in mid 1980s, Kenny et al. [13] used HUTT to induce neurocardiogenic (vasovagal) syncope by providing a passive continuous orthostatic stress, resulting in decreased venous return and increased catecholamine levels. Since then, HUTT serves as a widely used modality for assessing the individual's susceptibility to neurally mediated vasodepressor syncope.

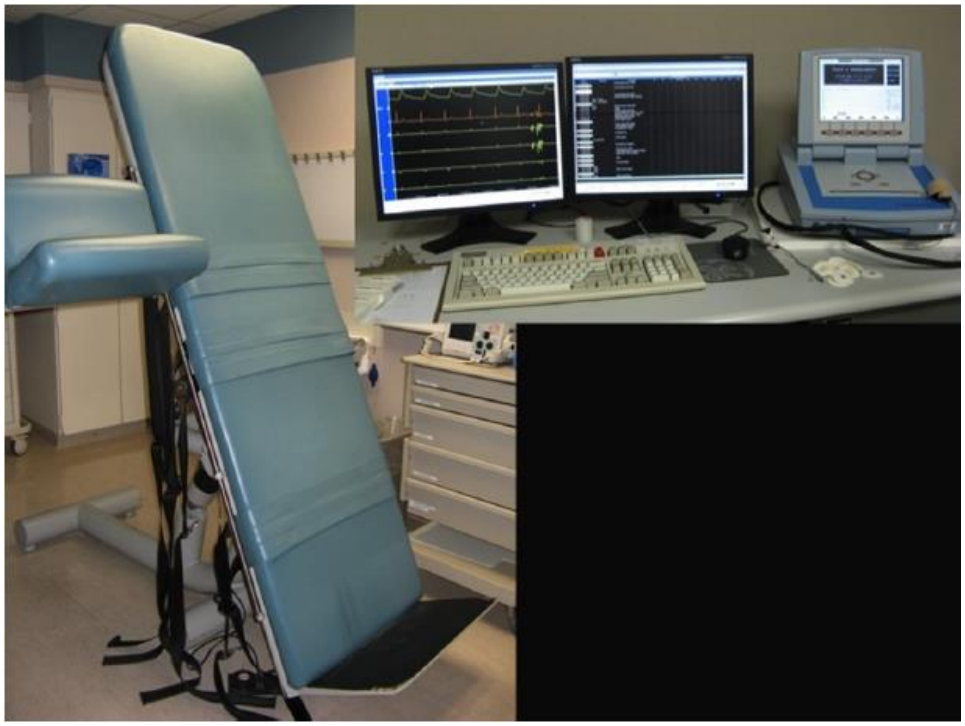

Figure 1.2 *- Table tilted at an angle of 70 degrees, with footrest and rest for the upper limb. The Velcro straps allow securing the patient in case of loss of postural tone. The necessary equipment is (from the right to the left): device for noninvasive monitoring of blood pressure, beat to beat, and blood pressure curve and ECG monitoring devices* [14].

A HUTT is normally not required in individuals with a single, isolated episode of VVS since the diagnosis is made based on the patient's anamnesis and typical physical examination in conjunction with a normal surface 12-lead ECG. The duration of loss of consciousness is usually brief and is followed by a rapid and complete recovery, although a short period of disorientation and fatigue may be reported. A HUTT should, however, be considered in individuals with an atypical history or in whom an accurate description cannot be obtained. Patients may report atypical convulsive movements on the upper and lower limbs associated with TLOC, leading to the suspicion of epilepsy.

This test can also be a valuable method to educate the susceptible individuals of the diagnosis of a non-life-threatening disorder. HUTT can also help these patients to identify warning symptoms not previously recognized as well as for the training of counterpressure maneuvers to prevent the development of syncope. A diagnosis of VVS may also be useful and required for people with high-risk professions, for simple activities like driving, or to differentiate epilepsy from convulsive syncope.

1.2.3.2. External Monitoring

Tilt table testing is the most often used diagnostic approach in patients with recurrent syncope of unknown origin and no structural heart disease, to verify a vasovagal etiology of their syncopal attacks [15]. However, in patients with a negative HUTT and prevalence of symptoms, syncope continues to be a diagnostic challenge. This being said, the next diagnostic method in these patients focuses on the detection or ruling out of paroxysmal arrhythmias.

Cardiac monitoring may identify bradycardia/asystole however, if patients have syncopal episodes with no sign of bradycardia/asystole, a diagnosis of vasodepressor subtype can be made by exclusion. Rebound sinus tachycardia may be evident during heart rate recording in these patients [8]. Due to a lack of reliable long term monitoring technologies for BP, the vasodepressor component of VVS is not easy to capture in real time.

24-hour holter monitoring is unlikely to be of benefit because of the short duration of monitoring. Most authors recommend continuous rhythm monitoring with an external loop recorder, which may be more useful as they allow for activation during symptoms and longer duration of monitoring. However, patients are unlikely to comply for more than a few weeks. VVS events tend to cluster, and this is unlikely to be picked up on short duration monitoring. More prolonged monitoring is often required, like an internal loop recorder (IRL) [8,15].

1.2.3.3. Internal Loop Recorders

An ILR is a subcutaneous implantable system that continuously monitors the HR and is preprogrammed to signalize abnormal rates and rhythms. ILRs enable prolonged cardiac monitoring, improving the likelihood of achieving symptom-rhythm correlation in patients with TLOC [8]. ILRs are implanted in patients with recurrent unexplained syncope or in high-risk patients in which an underlying cause has not been identified in a thorough evaluation. The International Study on Syncope of Uncertain Etiology (ISSUE) trials have revealed a role for early ILR implantation with a permanent pacemaker therapy, permitting a safe, effective and specific therapy in patients with unexplained syncope [16]. Recently, in The recent Falls and Unexplained Syncope in the Emergency Department (FUSE) study in which patients over 50 with unexplained TLOC, recurrent falls and normal initial cardiac evaluation had an ILR implanted, demonstrated 20% of patients had underlying cardiac arrhythmias which was attributable as the cause of their fall [17].

A subtype of reflex syncope documented during cardiac monitoring, is vagally arbitrated by atrioventricular (AV) block. This is well-defined as a paroxysmal first-, second- or third-degree AV block. The latter is distinguished from intrinsic AV block by a simultaneous sinus slowing. Syncope due to vagally mediated AV block should be managed as reflex syncope. [8]

1.3. EEG Recordings

Electroencephalography is defined as a noninvasive medical technique for the measurement of the brain's activity through its electric fields. It is measured from the surface of the scalp in several regions as an electrical activity with the assistance of metal electrodes and a conducting medium. These electrodes record voltage potentials resulting from current flow in and around neurons [18,19], and are coated with a conductive gel. Usually, they are applied to the scalp and kept in place by adhesives, suction, or pressure from caps or headbands [20]. The international 10-20 system is typically the basis of the positioning of these recording electrodes, in which the placement of electrodes is determined on the measurements of four standard positions on the head: the nasion, inion, and right and left preauricular points (**Figure 1.3**).

Due to local currents produced when neurons in the brain are activated during synaptic excitations of the dendrites, the recordable electrical activity is generated on the head surface and is measured as EEG. Differences of electrical potentials are caused by summed postsynaptic graded potentials from pyramidal cells that produce electrical dipoles between soma (body of neuron) and apical dendrites (neural branches) [18]. However, it is important to emphasize that EEG can detect only a portion of all the forms of electrical activity going on in the brain [19].

The current penetrates between electrode and neuronal layers, through skin, skull, and numerous other layers. Since the signals detected through recording electrodes are weak, they are amplified, digitized, and stored to computer memory [18]. This amplification operates by connecting electrodes to amplifiers in predetermined patterns, or montages, to enable the electrical activity of various areas to be recorded in sequence. The recording arrangements can be altered, or the EEG can be reconstructed after digital recording, with the purpose of the measurement of the potential difference either between pairs of scalp electrodes (bipolar derivation) or between individual electrodes and a common reference point [19].

EEG has the capacity to record both normal and abnormal electrical activity of the brain, making it a useful medical tool. The highest influence on EEG arises from electrical activity of the cerebral cortex, due to its surface position [18]. It also has the ability of providing a noninvasive means of localizing structural abnormalities, such as brain tumors. Nevertheless, the EEG is a complement, rather than an inconsequential alternative, to newer procedures like computed tomography (CT) scanning and magnetic resonance imaging (MRI), because it reflects the function of the brain. A further use of electroencephalography is in the investigation of patients with specific neurologic, metabolic or sleep disorders that produce characteristic EEG abnormalities which, although nonspecific, help to suggest, establish, or support the diagnosis. Finally, electroencephalography is most useful in the investigation and management of patients with epilepsy [20].

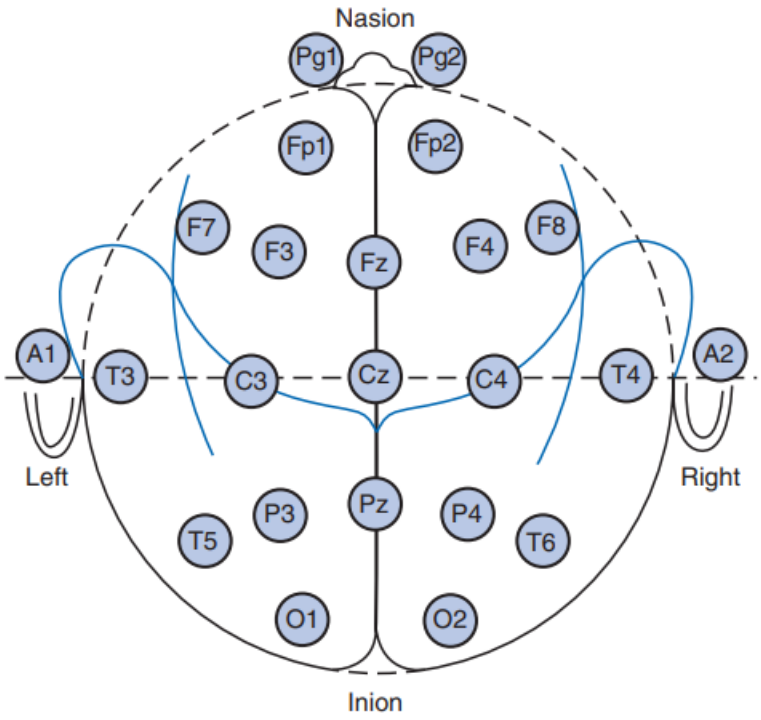

Figure 1.3 *– The international 10-20 system of electrode placement. A = earlobe; C = central; F = frontal; Fp = frontal polar; P =, parietal; Pg = nasopharyngeal; T = temporal; O = occipital. Right-sided placements are indicated by even numbers, leftside placements by odd numbers, and midline placements by z* [20].

1.3.1. Brain Waves

The oscillating electrical voltages in the brain are designated as brain waves, measuring only a few millionths of a volt [18]. Although the mechanisms accountable for the presence of widespread rhythmic activity in the brain are not known, some means of generating rhythmic activity must be implicated. Some method of synchronizing the activity of different cerebral regions must be involved as well. Experiments on animals have created substantial evidence to suggest that the rhythmic activity naturally recorded from the scalp has a cortical origin, being derived from the graded postsynaptic potentials of cortical neurons [20]. The cortical activity has a regular rhythmicity that appears to depend on the functional integrity of subcortical mechanisms. It has been acknowledged generally that the thalamus operates as the pacemaker of certain of the cortical rhythms that are recorded during EEG, but intracortical circuitries may also be involved significantly.

There are five commonly recognized brain waves, and the main frequencies of these EEG waves, as well as their characteristics. Different regions of the brain do not emit the same brain wave frequency simultaneously. An EEG signal between electrodes located on the scalp consists of several waves with different characteristics. The large amount of data obtained from even one single EEG recording makes interpretation difficult. The brain wave patterns are unique for every individual [18]. Most forms of EEG analysis require some filtering of the data. Filtering generally refers to selectively attenuating some frequencies for the purposes of enhancing others [21].

1.3.1.1. Frequency Patterns Recorded

Evaluation of the EEG for clinical purposes requires definition of the frequency, amplitude, and distribution of the electrical activity that is present, and of its response to external stimulation such as eye-opening. For descriptive purposes, EEG activity is frequently characterized on the basis of frequency [20]. Generally, the amplitude of the EEG pattern increases as the frequency decreases, being that the amplitude in an EEG is the strength of the pattern. The higher the amplitude, the stronger the signal, indicating more synchronized brain activity from multiple neurons. The higher the frequency the signal has, the more work the brain is doing, and the greater the intensity of the brain activity [22].

It is possible to decompose the EEG through fast Fourier transforms into a series of patterns manifested in sine waves to create a frequency spectrum of the data. These waves can be characterized at each point in time by their amplitude, power in the case of a rectified signal, and phase, which is where the sine wave is positioned in a cycle. The frequency bands are normally a priori delimited, with the brain wave samples for different waveforms shown in **Figure 1.4**. For example, many studies divide the EEG regarding the frequency spectra into delta (δ: ~0.5–4 Hz), theta (θ: ~4–8 Hz), alpha (α: ~8–12 Hz), beta (β: ~12–30 Hz), gamma (γ: ~30–90 Hz) and (very) high frequencies (>90 Hz). These subdivisions have subsequently been shown to have empirical bases [19]. Insights into a variety of mental states can be provided by the understanding of these frequencies of brain activity, in conjunction with the locations in the brain where neurons are activated. It is also valuable for understanding some mental disorders, such as epilepsy, since distinct patterns in brain activity can indicate the onset of a seizure [22].

Delta activity is the designation for patterns that are slower than 4 Hz. These are usually high amplitude, as much of the brain is focused on the same activity [22]. Activity of this kind is the predominant one in infants and is usually found during the deep stages of sleep in older subjects. Nevertheless, when delta activity is present in the EEG of awake adults is an abnormal finding. The spontaneous occurrence, interictally of posterior, of rhythmic slow waves is well illustrated in patients with absence seizures. The slow activity has a frequency of about 3 Hz, is identifies during wakefulness, is responsive to eye-opening, and may be heightened by hyperventilation. [20].

Activity with a frequency between 4 and 8 Hz is referred to as theta activity [20]. These brain-waves are identified during sleep, and may be induced by deep-state meditation or when carrying out a ‘mindless’ repetitive task [22]. Theta and slower activity are normally very conspicuous in children but becomes less prominent as they mature. Some theta activity is frequently noticed in young adults, particularly over the temporal regions and during hyperventilation. However, in older subjects, theta activity with amplitude greater than about 30 mV is found less commonly, except during drowsiness. Focal or lateralized theta activity may be indicative of localized cerebral pathology. More diffusely distributed theta activity is a common finding in patients with a variety of neurologic disorders, but it also may be caused by nothing more than a change in the patient’s state of arousal.

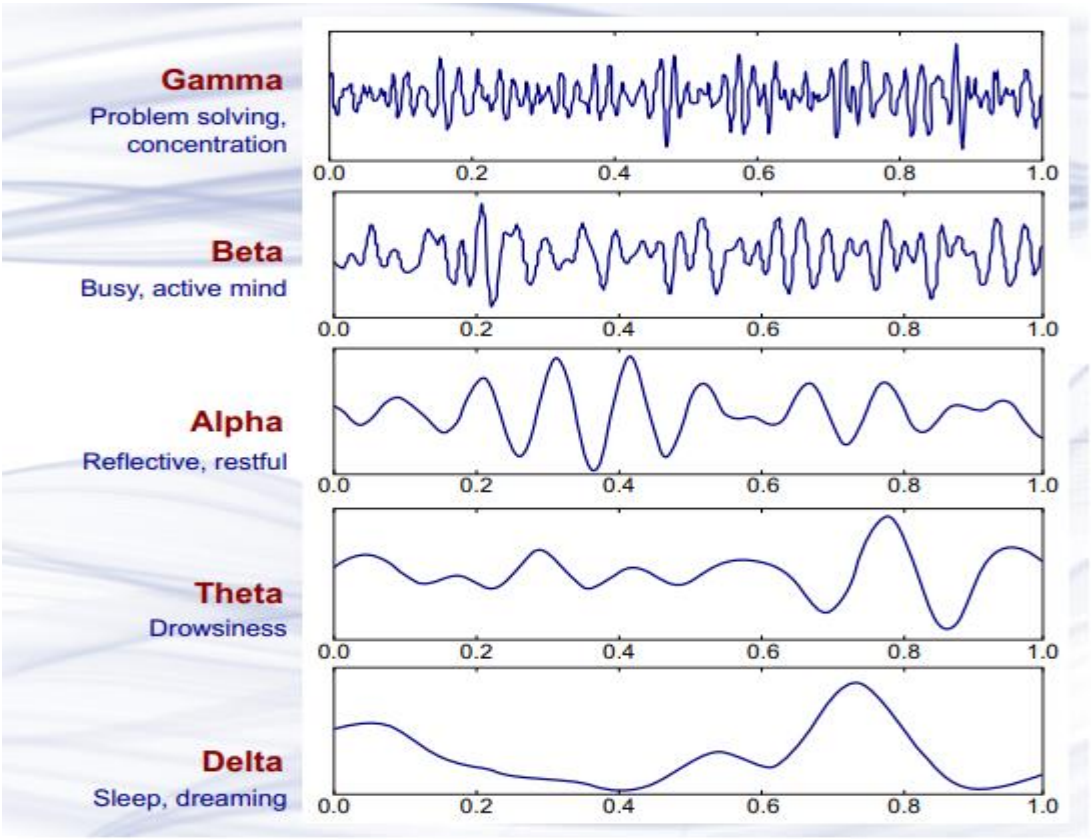

Figure 1.4 *- Brain wave samples with their patterns and chatracteristics reflected on the patient's state of mind for beta, alpha, theta, and delta bands and gamma waves* [18].

Alpha rhythm is found most naturally over the posterior portions of the head during wakefulness, but it may also be present in the central or temporal regions. This rhythm is seen best when the patient is resting with the eyes closed and is attenuated or abolished by visual attention, is affected transiently by other sensory stimuli, by other mental alerting activities (e.g., mental arithmetic) or by anxiety [20]. This is the 'idle' frequency, occurring when the patient is awake but not really doing anything beyond day-dreaming or practicing meditation [22]. Between the two hemispheres is frequently found a minor asymmetry regarding the amplitude of the alpha pattern as well as the extent to which it reaches anteriorly. In particular, alpha rhythm may typically be up to 50% greater in amplitude over the right hemisphere, possibly due to the fact that this is the nondominant hemisphere or due to the variation in skull thickness. Some normal adults have an alpha rhythm that is more conspicuous centrally or temporally than posteriorly or has a widespread distribution.

A rhythmic activity with a frequency greater than 13 Hz is indicated as beta activity. Activity of this kind is found anteriorly in the EEG of normal adults. This wave pattern occurs when the patient is concentrated on something, focusing on a problem or making decisions. These are 'fast' brain-waves and have been associated to depression and anxiety. Beta waves are usually representative of a period of time when the brain is working on various things at once, meaning that lots of neurons are in action, but their activity is not necessarily strongly connected/synchronous, so their high frequency comes with a low amplitude. Beta activity, responsive to eye-opening, is sometimes found over the posterior portions of the hemispheres and is then best regarded as a fast variant of the alpha rhythm. Beta activity that fails to react to eye-opening is a frequent finding and normally has a generalized distribution, however, in some instances it is located centrally and is attenuated by tactile stimulation or contralateral movements [20]. It typically has an amplitude of less than about 30 mV. The amount of such activity

fluctuates considerably among normal subjects. Activity with a frequency between 18 and 25 Hz is generally more conspicuous during drowsiness, light sleep, and rapid eye movement (REM) sleep than during wakefulness. It might also be augmented by cognitive tasks.

The activity with the higher frequencies is designated gamma activity and includes all frequencies greater than 30 Hz. These higher frequencies of brain-waves generally are the result of processing information in various parts of the brain at the same time [22]. Gamma activity is correlated with learning, and the working memory. An irregular pattern of brain activity for this frequency has been associated with Alzheimer's and Parkinson's disease, and schizophrenia and epilepsy as well.

1.3.1.2. Artifacts

Because EEG electrodes are placed on the skull rather than directly onto the brain, the electrical signals recorded by the electrodes are not solely due to electrical fields generated in the brain [21]. A variety of artifacts may arise from the electrodes, recording equipment, and recording environment, as is seen in **Figure 1.5**. The artifacts in the recorded EEG may be either patient-related or technical. Patient-related artifacts, or bioelectric artifacts, are unwanted physiological signals that may significantly disturb the EEG. Bioelectric artifacts are noncerebral potentials that arise from the patient and include ocular, cardiac, swallowing, glossokinetic, muscle, and movement artifacts [20]. Technical artifacts, such as alternate current power line noise, can be reduced by decreasing electrode impedance and using shorter electrode wires [18].

Eye-movement artifacts are created by the corneoretinal potential, which is in the order of 100 mV [20]. The EEG signals that are related to this movement cause a slow signal (<4 Hz) corresponding to mechanical movement, since the eyes make a dipole, which moves closer to or away from some electrodes and creates the signal [18]. Eye movement leads to a positive potential recorded by the electrode closest to the cornea. The signals occur mainly in the frontal and temporal areas and are propagated more often than blinks. This signal is not symmetrical between the two hemispheres [20].

Cardiac artifacts are associated with the ECG or the ballistocardiogram and are particularly conspicuous when examining for electrocerebral inactivity in brain-death suspects or in referential recordings concerning the ears. Pulse artifact may appear at any site but usually is localized to a single electrode and appears as a recurrent slow wave that occasionally has a saw-toothed appearance and is time-locked to the ECG. It happens when an electrode is placed over or close to an artery, being that the dislocation of the electrode in question will eliminate it. Pacemaker artifacts consist of spike discharges that precede the ECG.

Muscle artifacts are comprised of brief-duration spike discharges that are too instant to be cerebral in origin [20]. EEG signals corresponding to muscular activity generate high frequency signals (>13 Hz) and can be much larger in amplitude than electrical activity generated by the brain [20,21]. Some neuronal activity of interest such as gamma oscillations, for instance, does occur above 30 Hz, so this way of removing muscle artifact will also remove the signal of interest [21]. The main head muscle is the jaw, which can create an important signal in the temporal area (0-5 sec). Frontal muscles can appear as well since they are located just under the electrodes [18]. Any movements may produce artifacts as well, and these will vary in appearance depending on the nature and site of the movement, as one can see from the variation in the signal demonstrated in **Figure 1.5**.

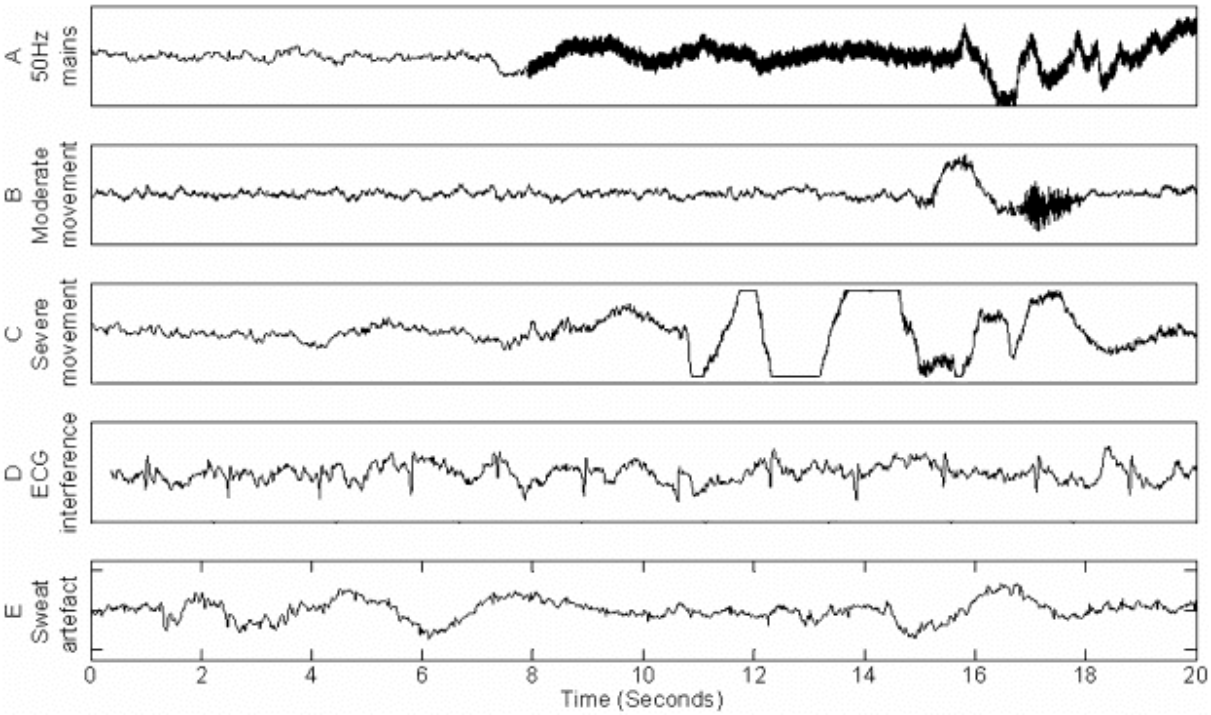

Figure 1.5 *- Common EEG artefacts. (A) 50 Hz mains interference appears as a thickened signal caused by superposition of 50 Hz mains waves on the EEGs. (B) Movement causes a sudden and significant deviation from the background EEG and (C) severe movement can clip the EEG. (D) ECG interference appears as a pulsed EEG, it occurs when the pulses on the ECG are superimposed on the EEG. (E) Sweat artefact is a slow drift of the baseline EEG.* [23].

EEG signals associated to wire or electrode movements create a low-frequency artifact (<2 Hz) on one electrode, that usually has high amplitude [18]. Sometimes it is identified background 60-Hz noise in a restricted number of channels, and it is frequently connected to mismatched electrical impedance of electrode pairs or to the inadequate application of electrodes, meaning that the slight movement modifies transiently the impedance of an individual electrode [20]. It is also feasible that a mechanical artifact appears following a head movement, and in this case a signal emerges on several electrodes.

1.3.2. EEG Systems

With the advent of digital technology, EEG systems are being developed in various directions. Digital systems have advantages which make them capable of special applications. Signal storage, retrieval, numeric processing, and novel display are among the capabilities of digital systems. Post-acquisition tools such as spectral arrays are available and the development of digital EEG for routine recording has produced a relatively cheap and robust replacement for EEGs that used paper technology. Recordings are carried out on digital machines and can be viewed with different montages, filter settings, and display speeds; additional procedures such as voltage mapping or frequency analysis can also be carried out.

Brain activity may be recorded by means of wired or wireless EEG systems. With wired EEG systems the subject must remain constrained in one location, so recently developers have optimized wireless EEG systems that simplify mobile recordings of the brain activity. These offer an advantage in

comparison to wired systems because the subject is less restricted in movement range and types. The electronics are much smaller as well comparing to conventional devices, and do not require a cable to transmit the data from the EEG cap to the computer.

Wired EEG systems take advantage of years of expertise in amplifier design and manufacturing. Easily identifiable electrode input using the international 10-20 placement layout is helpful in placing the electrodes on the scalp. The user interface with liquid crystal display allows information such as electrode impedance checking, amplifier calibration, photic stimulator control, and connection status to be observed. In addition, more than 72h of EEG data can be acquired, which can be useful for studying seizures. However, they are time-consuming since setting up an EEG can take 25-45 min. Their loose, spread-out wires result in an antenna effect and can cause electrical artifacts and spurious results, as well as restricting the mobility of the subject [18].

Wireless EEG systems on the other hand eliminate the wire connection with the use of a wireless transmission unit such as Bluetooth and Zigbee modules, making the system portable. These units are easy to wear, wireless, small, light, intuitive and are present only on the head, compared to previous ambulatory units which commonly required an instrumentation box to be worn on a belt near the waist with long wires to connect to the electrodes. Wearing during acquisition is easy, so the postures and movements of users are comfortable, taking the technique beyond laboratory experiments and into everyday-life applications. Recently, with growing interest, wireless BCI systems have been applied in entertainment. For example, the Emotiv and Neurosky companies, that will be talked on later, have released wireless BCI headsets for entertainment uses such as brain gaming and mind monitoring. However, the demerits include limited features with less accuracy as it can interpret only simple messages from user intentions, as well as cognitive states and event-related potentials, to be easily affected by external noises [18].

Chapter 2. State of the Art

2.1. Practical Considerations for Tilt Table Testing

HUTT allows reproduction of neurally mediated symptoms in the presence of healthcare professionals, thus patients can be reassured with objective measures of hemodynamics and given biofeedback, training of physical counter maneuvers and other methods to prevent events. Therefore, this test has been the commonest provocative method used in diagnosing VVS. HUTT stresses the arterial baroreceptor reflex, increasing parasympathetic activity and reducing sympathetic activity, leading to reflex bradycardia, vasodilation, and hypotension. A positive test demonstrates a hypotensive susceptibility, which plays a role in causing syncope irrespective of its etiology.

Despite some limitations, including lack of reproducibility and numerous changes in protocols, HUTT remains a central part of the work up for VVS. It is particularly useful for diagnosing atypical VVS, psychogenic pseudosyncope, distinguishing syncope from seizures, diagnosing orthostatic hypotension (OH) and Postural Orthostatic Tachycardia Syndrome (POTS).

2.1.1. Recommended Methodology

The HUTT requires a tilt table that quickly moves the patient from a supine to an upright position, while the subject is secured to it with restraints and a footboard. ECG and BP are continuously monitored (mostly by noninvasive methods). The HUTT is relatively simple; however, several protocols have been published with the differences mainly in the angle of the tilt (60 to 90 degrees), its duration and use of pharmacological enhancement. The procedure usually starts with a period of supine rest, followed by a period of passive tilt and then a period of active tilt. **Figure 2.1** shows an example of the procedure conducted during the test.

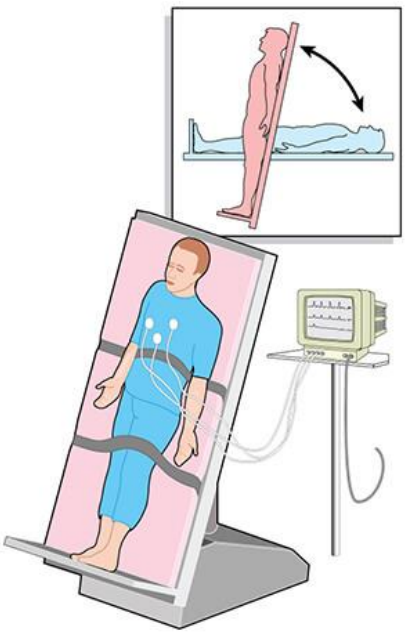

***Figure 2.1** - Methodology of the test performed. The patient lies on a table that moves from a flat position parallel to the floor to an upright position nearly perpendicular to the floor, while ECG, BP and HR are monitored [73].*

The test must be conducted in a quiet environment, with dimmed lighting and pleasant temperature. The monitoring is carried out by doctors and nursing technicians, trained for the test. The patient should be comfortably dressed, and not consume caffeinated drinks or heavy meals prior to testing. All usual medications should have been taken, particularly if they were considered potential culprit medications. Intravascular instrumentation should be avoided whenever possible, as it may reduce test specificity. The specificity of tilt table testing is defined by the portion of the subjects who have never fainted and have had a negative test result, while the sensitivity is defined by the portion of patients who have had positive results.

2.1.1.1. Passive Tilt

Passive tilt consists of a period of time in which the patient is elevated to the tilting angles between 60° to 90° for up to 45 minutes and does not use any provocative agents to induce the syncope. Regardless of the utilization or not of the agents, it has been well-recognized that the "sensitivity" of HUTT for the diagnosis of VVS is frequently not correctly determined, since the clinical diagnosis is usually presumptive and the origin of syncope in patients undergoing tilt table testing is usually unknown.

Depending on the selected patient population and tilt table protocol, it has been estimated that during passive tilt table testing, a vasovagal response develops in 25% to 75% of patients with unexplained syncope. A research by Fitzpatrick et al. [24] reported that the mean time to syncope was 24 ± 10 minutes when the tilt was at a 60° angle. From this study, it was proposed that the minimum duration of a HUTT should be 45 minutes (mean time to syncope). Most passive tilt studies have been conducted at a 60° angle, and specificity has ranged from 90% to 100%. Natale et al. [25] investigated the influence of various tilt angles and reported decreased specificity during tilt table testing at 80° compared with that at 60° and 70° angles.

2.1.1.2. Active Tilt

After a negative passive phase, the administration of various sensitizing drugs was tested in an attempt to increase the diagnostic accuracy of HUTT. Currently, isoproterenol and nitrate are the drugs most commonly used for this purpose. In the numerous studies conducted, the sensitivity of the test with nitrate showed variations between 57.5% and 87%, and the specificity between 70% and 100%, while the test with isoproterenol ranged between 42% and 69% and between 70 and 90%, respectively [26,27]. Isoproterenol is being abandoned due to the lower sensitivity, inconvenience of intravenous access and side effects, especially in patients with ischemic heart disease [14].

Initially, nitrate was administered in the beginning of the active phase in the form of intravenous nitroglycerin, with sensitivity of 53% and specificity of 92% [28]. After these results, researchers evaluated the effect of sublingual nitroglycerin in a subsequent study [29]. The protocol consisted of 45 minutes of passive tilt with an angle of 60° which resulted in low sensitivity (25%) and high specificity (100%). After administration of 300 µg of sublingual nitroglycerin, a positive response was observed in more than 26% of the patients, resulting in a specificity of 94%. The European guidelines on syncope, published in 2004 [30], reported an analysis of investigations that consisted of 20 to 45 minutes of passive tilt followed by an active phase with nitrate. The conclusion attained was that the sensitivity of tests of shorter or longer duration is similar (69% versus 62%), without any decrease in specificity (94%). Since these findings, it is recommended that the test should consist of 20 minutes of passive phase followed by 20 minutes of active phase, with nitroglycerin or isoproterenol. Thus, the classical protocol (without the use of sensitizing drugs) has been replaced by the protocol that combines the passive phase followed by the sensitized phase [14].

The HUTT with an isoproterenol infusion was first described by Almquist et al. [31], who reported that combined tilt testing and isoproterenol infusion reproduced the symptoms in 9 of 11 syncopal patients (82%) with negative electrophysiological studies and negative passive HUTTs. They reported an acceptable false positive rate of 13%, compared to a sensitivity of 27% and false positive rate of 11%

with passive tilt testing. Isoproterenol is contraindicated in uncontrolled hypertension, coronary artery disease and left ventricular outflow tract obstruction. It is poorly tolerated in the elderly, who are more likely to develop dysrhythmias or angina. Side-effects such as warmth, tremulousness, palpitations, headache, nausea, and diaphoresis are also frequently reported. Due to its poor tolerability, it is only recommended the use of the isoproterenol HUTT as a third-line investigation in individuals with no contraindications and in whom a diagnostic test is required [2]. The shortened isoproterenol test as described by Shen et al. [32] is considered the more convenient protocol, which consists of 10 minutes of supine rest, while isoproterenol is infused at a rate of 0.05 µg/kg/min (not exceeding the maximal dose of 5 µg/min) for 5 minutes, followed by a tilt of 70º for a further 10 minutes whilst continuing the infusion.

Edrophonium, clomipramine and adenosine have also been studied as potential provocation agents, however, still need further evidence supporting their use is available. The use of adenosine or its precursor, adenosine triphosphate (ATP) as a provocative agent for HUT is controversial [33]. Individuals with positive ATP-HUTT are older, with fewer syncopal episodes, and are less likely to report typical precipitating factors and prodromal symptoms [2]. Therefore, it remains unclear whether a positive adenosine test indicates unmasking of VVS with cardio-inhibition, sinus node disease or a high-degree AV block.

Lower body negative pressure is the only non-pharmacological provocation available for the HUTT [34]. This protocol requires a vacuum chamber sealed to the tilt-table and subject at the level of the iliac crest. After 20 minutes of passive tilt, lower body suction is applied at -20mmHg for 10 minutes, and -40mmHg for a further 10 minutes. In this study, syncope occurred in 85% of patients developing symptoms and signs of presyncope, suggesting that lower body negative pressure is a powerful model of orthostasis. It is required careful patient selection for this method, is considered a third-line investigation, and is reserved for situations where reproduction of syncope is vital [2].

2.1.2. Types of Tilt Table Test Protocols

In the descriptions of previous protocols studied, the terms “sensitivity” and “positivity” get mixed up as a result of the absence of a gold standard test for diagnosing VVS [14]. The term "HUTT sensitivity" has been employed since the clinical diagnosis is known to be the gold standard, and the subject was selected according to the clinical background. The term “positivity” is usually applied when the examination is performed in patients with unexplained syncope.

However, in order to simplify the definition of the HUTTs, the term "sensitivity" was standardized for both circumstances, although it is commonly understood that, in many cases, the term reflects only the positivity of the test. The application of clinical diagnosis as the gold standard has been criticized due to the subjectivity inherent in medical judgment. Nevertheless, to date, no other method has proved to be more accurate.

Within the methods already developed, three protocols stand out as the most used:

- Basal or Westminster protocol - In 1991, a group at the Westminster Hospital of London published their methodology showing the greater specificity of the test performed on a table with footboard support at an angle of 60° for 45 minutes without intravenous cannulation or

infusion of vasoactive substances. They described a sensitivity of 75% and a specificity of 93% [24].

- Italian protocol - Head-up tilt testing potentiated by sublingual nitroglycerin, advocated by an Italian group, is a simple and safe but still not a standardized, diagnostic tool for the investigation of syncope [35]. In fact, owing to its quick spread, the original protocol received, often arbitrarily, many subsequent modifications. The best methodology of the test is defined on strictly evidence-based criteria as: rest phase of 5 minutes in the supine position; passive phase of 20 minutes at a tilt angle of 60 degrees; provocation phase of further 15 minutes after 400 µg of nitroglycerin sublingual spray. Test interruption is made when the protocol is completed in the absence of symptoms, or there is occurrence of syncope, or occurrence of progressive orthostatic hypotension.

- Front-loaded protocol – With this method subjects rested supine for 10 minutes after which 800 µg of sublingual nitroglycerin was administered in the spray form. They were then tilted to the 70° position for 20 minutes, or again until positivity criteria were reached [36]. This protocol provided a higher diagnostic rate than passive tilt testing, and a rapid alternative to conventional methods though false positivity rates are higher.

2.1.3. Types of Response to Tilt Table Testing

Some authors consider the HUTT positivity criterion when there is reproduction of the spontaneous symptoms associated with the hemodynamic collapse [14]. There is plenty of controversy surrounding the interruption of the test prior to the occurrence of syncope, as many researchers consider that it is proper to stop the HUTT when the doctor assumes that the loss of consciousness is imminent – a process called a presyncope – and there is no necessity to subject the patient under massive discomfort due to hypotension or bradycardia [30,37]. The positivity criterion is considered in more recent studies as the induction of syncope or presyncope, when combined with bradycardia or hypotension, which will allow defining the vasovagal response [26,27]. Hemodynamic changes occurring in the absence of symptoms or syncope render the test falsely positive. The test is negative if the patient completes 40 minutes of tilt with no characteristic hemodynamic changes [2].

The most accepted classification to define the types of response of the HUTT is a modified one of VASIS (Vasovagal Syncope International Study): type 1 or mixed; type 2A or cardioinhibitory without asystole; type 2B or cardioinhibitory with asystole; and type 3 or vasodepressor [30]. Usually, these types of response are defined by a set of characteristics in the signal, as it is seen in **Figure 2.2**:

1. Vasodepressor syncope - when HR increases initially but decreased afterward to less than 10% of the maximum peak with hypotension during syncope [38].

2. Cardioinhibitory syncope - when the HR decreased to <40 beats per minute (bpm) during syncope for more than 10 seconds, or when asystole was observed for more than 3 seconds, occurring concomitantly with hypotension [38].

3. Mixed syncope—when hypotension occurred prior to or concomitantly with bradycardia, and (a) HR increased before symptoms occurred, and decreased afterward,

although it remained higher than 40 bpm; (b) heart rate was lower than 40 bpm for <10 seconds; or (c) asystole occurred for <3 seconds [38].

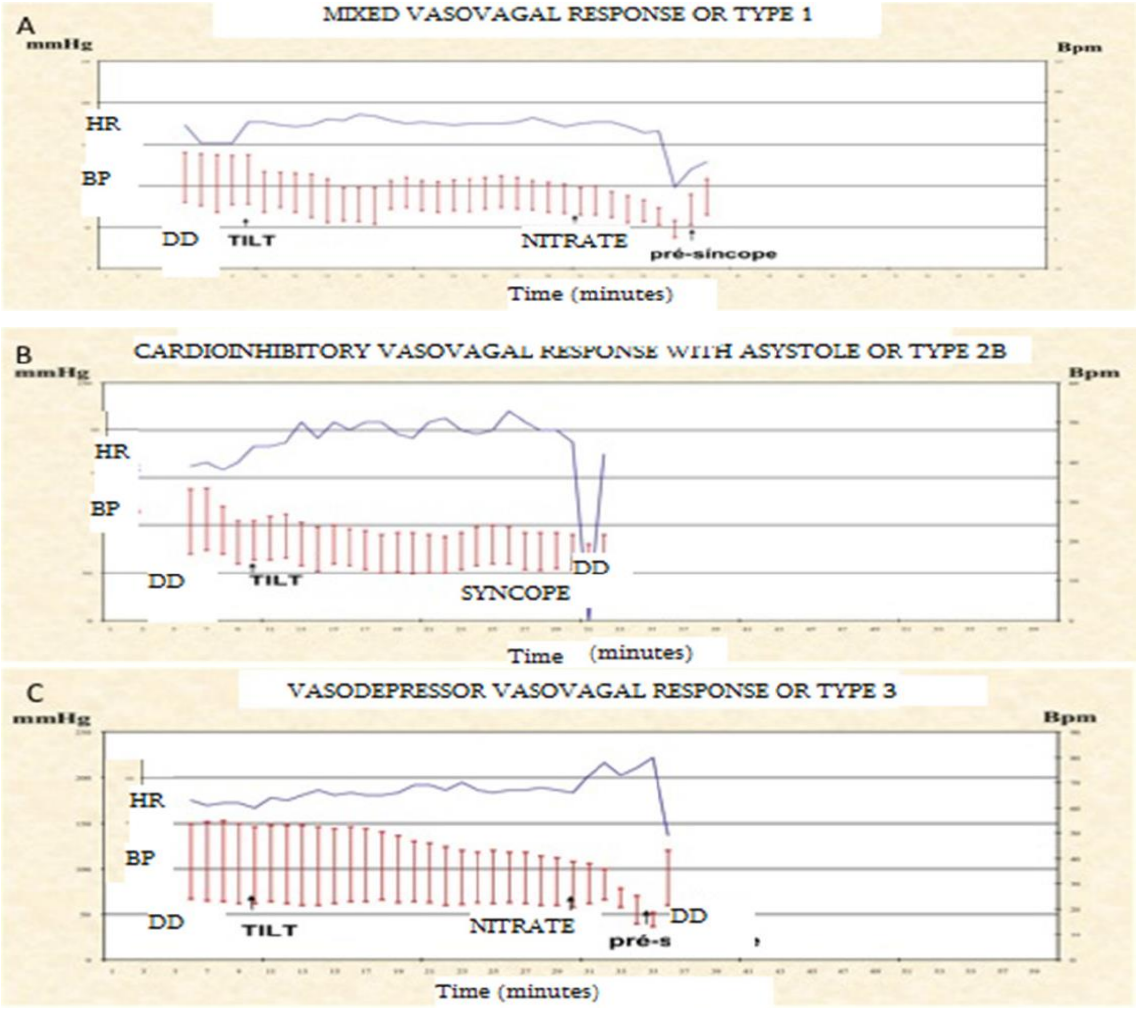

Figure 2.2 *- Charts showing the behavior of BP and HR during different vasovagal responses. A - mixed vasovagal response or type 1; B – cardioinhibitory vasovagal response with asystole or type 2B; C - vasodepressor vasovagal response or type 3* [14].

The vasovagal reaction typically last about 3 minutes before a loss of consciousness occurs, with syncope occurring approximately a minute after the onset of the prodrome. A fall in BP to below 90 mmHg is associated with impending syncope and to below 60 mmHg with syncope [2].

However, the type of response to HUTT does not essentially define the hemodynamic pattern of the patient's clinical syncope [14]. Brignole et al. [39] shown that 36% of patients with mixed or vasodepressor response to HUTT had asystole during a spontaneous episode documented by the loop recorder. Therefore it has been considered in more recent studies that the most important aspect of the response to tilt testing is the differentiation between reflex syncope and other forms of orthostatic intolerance [10].

2.1.4. Clinical Use and Limitations of Tilt Table Testing

Due to its capacity to reproduce the patient's symptoms in the presence of healthcare professionals, as well as the corroboration of hemodynamic changes, the HUTT has been used to confirm the diagnosis of VVS for 30 years. Specific guidelines recommend the use for diagnosis of syncope of unexplained origin, presyncope, dizziness, falls and seizures [14].

In 2006, the American Heart Association Scientific Statement proposed that the HUTT slightly contributed to the diagnostic investigation [40], and raised significant questions about the sensitivity, specificity, diagnostic yield and reproducibility. Only four references were provided to justify the disqualification of the test. As a response, the Ad Hoc Syncope Consortium claimed that such document did not sufficiently address a number of long-standing clinical misconceptions regarding the evaluation of individuals with TLOC, showed only a partial view of the disease context and failed to mention current and important evidence, such as the European Guidelines on syncope [41].

Other authors have also doubted the validity of HUTT [10] since the lack of protocol standardization for HUTT has made comparison between research reports problematic [2]. Published studies have fluctuated in their selection of patients, tilt angle, duration of the passive and active phase and the use or non-use of provocation agents, affecting the results depending on the method and the determination of the sensitivity and specificity. The variation in results is justified exactly by the assessment of studies that use very distinct methodologies, which is one of the reasons that led to the standardization of the test in the European Guidelines [14]. Petkar et al. [42] criticized the low sensitivity of the test for the weak reproduction of spontaneous features and the decline in specificity when sensitizing drugs were used, by citing a study that found 55% false positives in a HUTT with the use of isoproterenol as a provocative agent. However, in this study, the test was performed with a tilt angle of 80°, which is known to reduce the specificity and it is not recommended.

Likewise, when more recent studies are analyzed, it is possible to note a significant decrease in specificity when, in sensitized protocols, the duration of the passive phase is equal to or more than 30 minutes. Therefore, limiting the total duration of the examination seems to guarantee good specificity. Also, the sensitivity of the passive phase alone is highly variable, but most studies have found low rates of positivity. Considering that the combination with drugs significantly increases the sensitivity of HUTT and that the decrease in specificity may be acceptable, the combined protocol is most suitable for clinical use in the diagnostic investigation of syncope [14].

A positive response to HUTT is also not reproducible with repeated testing, therefore, HUTT is not an accurate measure of treatment response, despite the common usage of tilt-positivity or time to syncope as a surrogate endpoint in intervention studies for VVS [2].

2.2. EEG Solutions and Applications

Amongst non-invasive daily life brain activity monitoring modalities, EEG is the only that uses sensors and fitting capabilities such that it can be worn in the course of free locomotion [43]. The key benefits of encephalography compared to certain brain imaging techniques are that it has an incredibly high time resolution—able to track events within the brain with millisecond accuracy—and that it can be portable allowing real-world neuroimaging to be performed outside of clinical and lab environments

[44]. Despite the many applications of EEG in the clinical domain, it is rarely utilized in daily life applications, because the added freedom for the patient can come at a cost to the acquisition of clean useful data, as the in-home environment is poorly controlled for extraneous sources of measurement noise [45]. Even though current research attempts on understanding the brain mainly focusing on invasive EEG recordings, mainly in animals and occasionally in humans, there is still a lot to be studied about non-invasive EEG monitoring.

2.2.1. Clinical Utility of Qualitative and Quantitative EEG during Tilt Table Testing

It is well established that convulsive movements often accompany syncopal events, yet many patients with these clinical features are misdiagnosed with seizures [46,47] and often referred to epilepsy centers because they are refractory to treatment with anticonvulsant medications [48]. HUTT is the gold standard for diagnosing vasodepressor syncope, however this test alone does not provide details about clinical movements that may accompany a positive study, failing to provide clinical details that help distinguish convulsive physiologic syncope from epileptic seizures and psychogenic events [49].

In addition, patients may experience transient symptoms during tilt table testing (with or without a change in BP) that are not a reproduction of their habitual event, which can lead to a false positive test [48]. This way, to have a more precise diagnostic of patients with TLOC and distinguish syncope, epileptic seizures and psychogenic events, HUTT with the addition of video EEG recording is proposed to provide additional clinical information. Such a diagnostic method has a relevant potential for the dynamic assessment of cerebral electrophysiological modifications in different clinical settings. The benefits of HUTT in clinical practice have been well documented [50], however the additional value of continuous video EEG monitoring during HUTT has not been consistently demonstrated [51]. Prior studies have reported multiple patterns of EEG changes with presyncope and syncope [48,52], however these findings have not been replicated and their clinical implications remain uncertain.

Electroencephalography allows dynamic assessment of neurological function and provides an objective marker of brain dysfunction during the cerebral hypoperfusion that accompanies syncope, while head-up tilt testing is currently used to induce a vasovagal syncope in susceptible individuals. Accordingly, the introduction of EEG monitoring during head-up tilt testing could significantly improve the understanding of the cerebral events occurring during tilt-induced vasovagal syncope and the potential danger that could be caused to the patient by this diagnostic procedure [53,54].

To correlate encephalography and VVS induced by head-up tilt testing, a study was performed by Ammirati et al.[53] in 63 patients with a normal baseline EEG. Patients with a negative response to the head-up tilt, as well as all control subjects, demonstrated no significant EEG abnormalities or modifications during the HUTT. Of the 36 patients, 16 had a positive vasodepressor response to the HUTT and showed homogeneous behavior throughout EEG monitoring. TLOC was preceded by prodromal symptoms in these patients, being that these symptoms were not associated with any significant EEG modification. Successively, the initially normal EEG pattern was followed by a diffuse generalized high-amplitude, 4 to 5 Hz (theta range) slowing of brain activity starting at syncope incidence. Such variations were subsequently followed by an additional increase of brain wave amplitude and slowing at 1.5 to 3 Hz (delta range), seen in **Figure 2.3**.

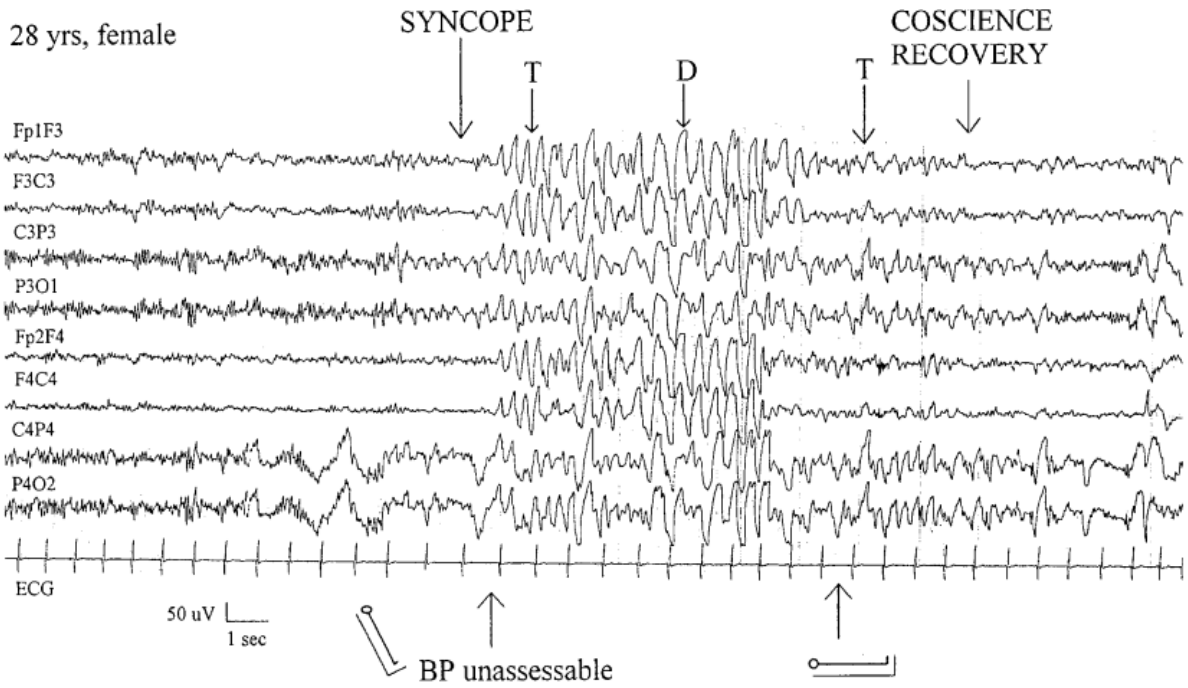

Figure 2.3 *- EEG modifications in a patient with vasodepressor vasovagal syncope during HUTT. T = theta waves; D = delta waves; BP = blood pressure* [53].

Of the 11 patients with a positive cardioinhibitory reaction to the HUTT, was noted a distinct but again homogeneous pattern of modifications in the EEG signal. The prodromal symptoms preceding syncope had a significantly shorter duration in patients with response of type 2, in comparison with those experienced by the patients with a vasodepressor response and were not correlated with any EEG modification. The EEG pattern that was initially normal, transformed abruptly at the onset of syncope in a generalized, diffuse, high-amplitude, 4 to 5 Hz (theta range) brain-wave slowing, rapidly followed by an additional brain-wave amplitude increase and slowing at 1.5 to 3 Hz (delta range). Was then noticed a sudden reduction in both amplitude and frequency of brain waves, leading to the disappearance of electrocerebral activity.

With the aim of characterizing the prevalence and characteristics of apparent neurologic events occurring during neurocardiogenic syncope, a study was performed by Rassman et al.[55] in 694 patients for the evaluation of syncope using the HUTT. In this study, selected neurologic evaluation, including encephalography, computed tomography, and magnetic resonance imaging, of the patients with either tonic-clonic seizure–like activity or non–tonic-clonic neurologic events failed to reveal a specific neurologic finding in any patient. The hemodynamic changes present in neurocardiogenic syncope are less evident than when the event is associated with tonic-clonic seizure–like activity and non–tonic-clonic neurologic events. While the tonic-clonic seizure–like activity that might occur during neurocardiogenic syncope, and may seem similar to epileptic seizures, the underlying mechanism is distinct. Simultaneous measure of EEG and performance of HUTT shows non-epileptiform theta and delta wave slowing during syncope [56]. The auxiliary use of encephalography with tilt table testing has been employed to differentiate epileptic seizure and tonic-clonic activity during vasodepressor syncope from seizures of psychogenic origin that lack significant hemodynamic or EEG changes.

Additionally, a study performed by LaRoche et al. [48] showed a retrospective analysis performed on 40 consecutive patients who underwent tilt table testing with concomitant video-EEG monitoring. 17 patients were initially diagnosed with suspected epilepsy and were on antiepileptic drugs. Continuous ECG monitoring, BP, and HR were recorded throughout the study, along with a 16-channel video EEG, which was also recorded simultaneously. Documentation of EEG findings included baseline background activity, and the presence of EEG changes during patient events including background slowing, EEG suppression and epileptiform activity. Documentation of video findings included level of consciousness, atonia, and tonic, clonic or myoclonic movements [48].

17 of the 40 patients were diagnosed with vasodepressor syncope with TLOC accompanied by hypotension and/or bradycardia. Involuntary abnormal movements were observed in 9 of these 17 patients including tonic posturing, multifocal myoclonic jerks, and head version. EEG changes were seen in all patients, which is seen in **Figure 2.4**, consisting of diffuse high amplitude delta slowing that progressed from theta to delta frequencies, EEG suppression and a period of asystole on ECG.

In these patients, the addition of video was critical in documenting the presence of involuntary movements that were previously thought to represent epileptic seizures [48]. EEG is the only approach that can confirm that an apparent loss of consciousness is actually physiological and secondary to a decrease in cerebral perfusion [49,57]. However, while EEG alone can discern physiological from non-epileptic cases, the specifics of the related clinical movements are not given. This documentation of associated clinical accompaniment is necessary for confirmation that a typical syncopal event was captured.

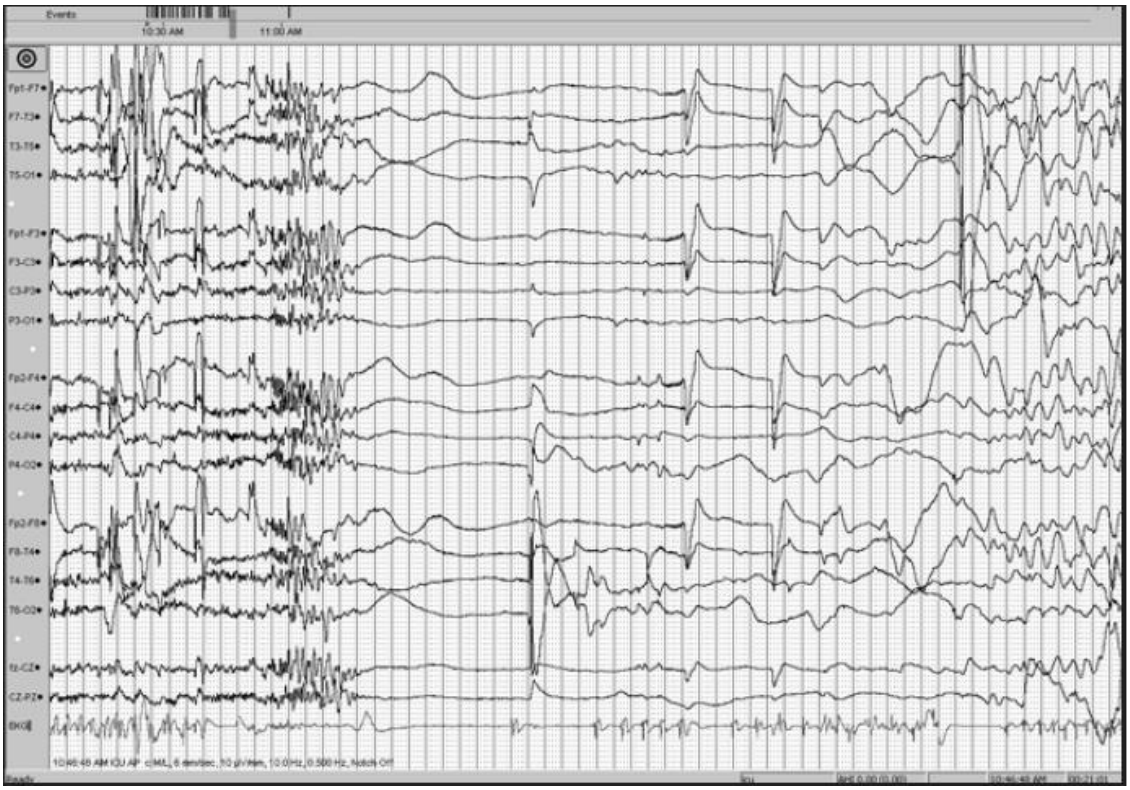

***Figure 2.4** - EEG findings of diffuse delta slowing transitioning to complete EEG suppression accompanying a typical event of vasodepressor syncope with asystole [48].*

These EEG alterations characterize the expression of cerebral function impairment due to the critical decrease of cerebral blood flow caused by the vasovagal hypotension and bradycardia. In these presented studies two patterns in the EEG have been described which correspond and are directly associated to the two main hemodynamic patterns that distinguish tilt-induced vasovagal syncope [53]. A diffuse, generalized brain-wave slowing was found in patients who developed hypotension alone (vasodepressor syncope), whereas periods of electrocerebral silence (flat EEG) were always recorded in subjects with hypotension and bradycardia (cardioinhibitory syncope). A 'slow-flat-slow' pattern is characterized by an initial slow phase in which delta waves are identified and wave amplitude increases, followed by a sudden flattening of the EEG, and a return to normal brain activity through a slow phase [54]. A 'slow' pattern comprises only an increasing and decreasing slowing. The slow-flat-slow pattern was considered to be a sign of more severe cerebral hypoperfusion and has been detected more frequently in cardio-inhibitory syncope compared with the other subtypes. It is associated with the presence of convulsive movements during syncope.

Despite these findings, except for small studies and the specific evaluation of convulsive-like movements during syncope, few studies have investigated both EEG patterns and signs and symptoms during syncope. Thus, although syncope is mostly diagnosed with ECG, and EEG is used only to distinguish between syncope with seizures and epilepsy, it is possible to observe changes in EEG signal when syncope is imminent. Consequently, it is thought that if brain activity is also measured during the tilt test, this information can be very useful for predicting syncope, especially in patients who do not have symptoms.

2.2.2. EEG Wearable Solutions

Nearly a decade ago investigators introduced the concept of wearable EEG as "the evolution of ambulatory EEG units from the bulky, limited lifetime devices available today to small devices present only on the head that can record EEG for days, weeks, or months at a time" [44]. With this concept EEG investigations would have a wider range out of the laboratory in motion rich environments for both clinical and non-clinical applications that have never been viable before, because it would eliminate the wires, make units much more portable and long lasting.

A range of wearable EEG units are available from different manufacturers, at the cost of relatively limited battery lives [44]. Some academic investigations studied the use of EEG during walking on a treadmill [58,59], demonstrating substantial potential for use in therapeutical applications but less representative of real-world motion, since the walking speeds used in these works are slower than real-world walking. EEG recording has recently been demonstrated during full running and jumping over obstacles on a treadmill [60], as well as during cycling [61,62], and, more recently, during a full free movement task where the subject could move around (in this case a simulated shop environment) with no constraints placed on their movements [63].

Substantial modifications were required to the EEG hardware/experiment process to perform these investigations, in order to generate EEG sufficiently free from motion artefacts. As an example, in the study with the subjects running and jumping over obstacles on a treadmill [60] a novel electrode in conjunction to the EEG signal components, was employed to record the motion noise, enabling this noise to be extracted by software filtering. In the case of the simulated shop environment [63], a simultaneous wearable eye tracker was used to collect and analyze EEG data during only the short

periods in which the participant was motion-free and looked at an area of interest in the experimental environment. It will possibly take some time for both approaches to become completely developed and commonly used, but both are very promising and contribute to the evolution of wearable EEG. The EEG systems that are commercially available include Neurosky's MindWave and MindSet, Emotiv Epoc headset, or InteraXon Muse [43], which are shown in **Figure 2.5**.

Although some adjustments and improvements still need to be made, wearable EEG systems are increasingly being introduced by the application of modern wearable EEG hardware. These adjustments include battery life and robustness, however, there are two major barriers that need to be overcome. Firstly, in the EEG electrodes which remain difficult to put on and keep in place on the head, especially when applied by non-specialist users. Secondly, in the EEG hardware and making this lower power, more robust to artefacts, and even more miniaturized to be socially discrete [44]. With these bottlenecks overcome, it is easier to convince both clinicians and patients that the benefits of wearing an EEG wearable unit outweigh the effort required in terms of set up time and social stigma.

***Figure 2.5** - (from left to right) Neurosky's MindWave and MindSet on the top; Emotiv Epoc headset and InteraXon Muse on the bottom [64–66].*

Chapter 3. Materials and Methods

In order to fulfill the project objective and prevent syncope, the aim is to find an algorithm that detects the sequence of changes in the EEG signal when patients are in imminent syncope or show symptoms of it. Thus, it was proposed to measure brain activity through a wearable band while several patients performed HUTT at Hospital de Santa Marta.

The work done so far at Hospital de Santa Marta is being able to diagnose the patients, but only ECG, HR and BP are being measured. Since the measurement of these variables is not able to predict loss of consciousness, it was proposed to monitor brain activity during the test. This way, a BITalino based headband developed at IBEB (Instituto de Biofísica e Engenharia Biomédica) was used to register the EEG data while the patient is taking the test at Hospital de Santa Marta. The test follows the front-loaded protocol with the administration of 375 µg sublingual nitrates and is terminated either by a positive response or 20 minutes after nitrate administration. All tests were performed under ethical committee approval, and with signed consent

3.1. Population in Study

The study group consisted of 36 patients with complaints of dizziness or TLOC of unknown origin after extensive clinical and instrumental evaluation. In general, patients had already undergone several tests to rule out other diagnoses and identify vasovagal syncope, with the tilt test being a last resort in this diagnosis. Among the exams were ECG, exercise stress test, echocardiogram or 24-hour holter monitoring. No test was purposely performed for this study, but in the context of the syncope appointment, being the HUTTs prescribed with justification only based on the normal clinical follow-up of the patients.

Regarding the test result, 20 were positive and 16 were negative, being that among the negative, 8 patients had symptoms during the test and 8 did not. Of the positive results, 14 are female and 6 are male, corroborating what was already been mentioned that women are more prone to drops in BP and loss of consciousness. The negative results show a more uniform gender balance with 9 females and 7 males.

3.1.1. Positive Test Results

Fourteen of the 20 patients were women and 6 were men, with a mean age of 52 years (range 18 to 83 years). The age of patients is one of the most important variables when it comes to assessing the incidence of TLOC. As previously stated, vasovagal syncope is more common in young and older people, and data from the study population substantiate this. Dividing into age groups, of the 20 patients with positive tests for VVS, 1 is less than 20 years old, 4 are between 20 and 30 years old, 2 belong to the 30 – 40 age group, 4 belong to the 50 – 60 group, 6 to 60-70 and 3 are over 70 years old.

Loss of consciousness was recurrent (two or more episodes) in most patients with a positive test (13 cases - 65%) and was accompanied by physical injury in 5 (25%) cases.
Among the triggers that lead to light-headedness, discomfort or even syncope, 2 (10%) patients indicate cough with syncope precipitator, 5 (25%) indicate anxiety or moments of more stress, and 9 (45%) indicate changes of position. Regarding their medical history, 2 (10%) have epilepsy or signs of it, 3 (15%) have an implanted pacemaker, and 1 (5%) has Hodgkin's disease.

Regarding the type of test response, 9 patients had a type 1 response (mixed - 45%), 5 had a type 2 response (cardioinhibitory - 25%), 2 of these had a 2a response and 3 patients had 2b, and 6 had a type 3 response (vasodepressor - 30%). 2 (10%) patients did not have any type of symptoms at the time of syncope. Those who did, had a lack of strength in the lower limbs, dizziness, sweating, nausea, discomfort, among others. Additionally, 3 (15%) patients performed myoclonic movements when they lost consciousness, these having a type 2 response.

3.1.2. Negative Test Results

Nine of the 16 patients were women and 7 were men, with a mean age of 57 years (range 23 to 78 years). Dividing into age groups, of the 16 patients with negative tests for vasovagal syncope, 2 are between 20 and 30 years old, 1 belongs to the 40 – 50 age group, 6 belong to the 50 – 60 group, 4 to 60-70 and 3 are over 70 years old.

Among the triggers that lead to light-headedness or discomfort, 2 (12.5%) patients indicate cough with syncope precipitator, 2 (12.5%) indicate anxiety or moments of more stress, and 4 (25%) indicate changes of position. Regarding medical history, 3 (18.75%) have epilepsy or signs of it, and 1 (6.25%) has asthmatic bronchitis. As it was previously stated, 8 (50%) patients did not have any type of symptoms during the test, and 8 did (50%)**,** being these dizziness, nausea or discomfort. 3 (18.75%) patients vomited during the test, and 4 (25%) performed counter-pressure manoeuvres. In these patients, TLOC was recurrent (two or more episodes) in 7 (43.75%) of them, being these more common in the patients who had symptoms during the test and was accompanied by physical injury in 3 (18.75%) cases.

3.2. Wearable EEG Band

Since ECG and blood pressure measurements are only able to diagnose but cannot predict the imminence of syncope, it has been proposed to use a band built at IBEB that measures brain activity through encephalography and has BITalino as its functional core. The idea in this project would be to use the band to measure brain activity throughout the test and, depending on the results, assess which would be the most suitable analysis and whether it would be possible to draw any conclusions that could lead to use these results to predict syncope with enough time for the subject to take precautions.

3.2.1. Wearable EEG Band Operation and Constitution

Biosignals contain information that is useful can be utilized to understand the underlying physiological mechanisms of a specific biological event. For this reason, the monitoring of these signals is critical for medical diagnosis and treatment. Biosignals can be acquired by numerous devices, specifically electronic devices, equipped with the implementation of electronic circuits ranging from simple to advanced, depending on the application. They comprise important data that must be properly analyzed to extract valuable information [67]. For this purpose, BITalino is one of the options currently available on the market with greater reliability and better results. It is a low cost, modular biosignal sensor kit that makes it quicker and easier to build medical devices and health tracker apps.

In order to be able to collect the data during the test using BITalino, it was inserted inside an elastic band with velcro closure, as it is seen in **Figure 3.1**. The band contains two pairs of electrodes on the inside, which are positioned in the central part of the patient's forehead, making the EEG measurement, as well as a light sensor to track blood volume pulse data, that is positioned in the ear by means of a clip.

Figure 3.1 *- Wearable EEG band used to collect the data with the two pairs of electrodes on the inside to positionate in the forehead of the patient, as well as the light sensor to track blood volume data in the form of a clip.*

The signature BITalino (r)evolution Board kits have an all-in-one hardware design (**Figure 3.2**), with all the blocks pre-connected and ready-to-use, making it one of the best options for biosignal exploration. The kit contains all the basic accessories needed to get started, specifically the hardware modules, battery, cables and electrodes. Along with the cross-platform OpenSignals software, it enables instant biosignal data visualization and recording. The sensors found in the kit can interface with computing platforms such as Arduino (and derivatives) and Raspberry Pi, containing also Bluetooth connectivity to be used in desktop and mobile environments. This kit is the outcome of a collaboration between portuguese bio-sensor maker, PLUX – Wireless Biosignals, and a not-for-profit research centre in Portugal, called Instituto de Telecomunicações. BITalino (r)evolution, the biosignal acquisition platform, is shipped as an all-in-one board. All the sensors (ECG, EEG, electromyography, electrodermal activity, accelerometer), actuators, and other electronic blocks are already connected to each other and ready to use out-of-the-box [68].

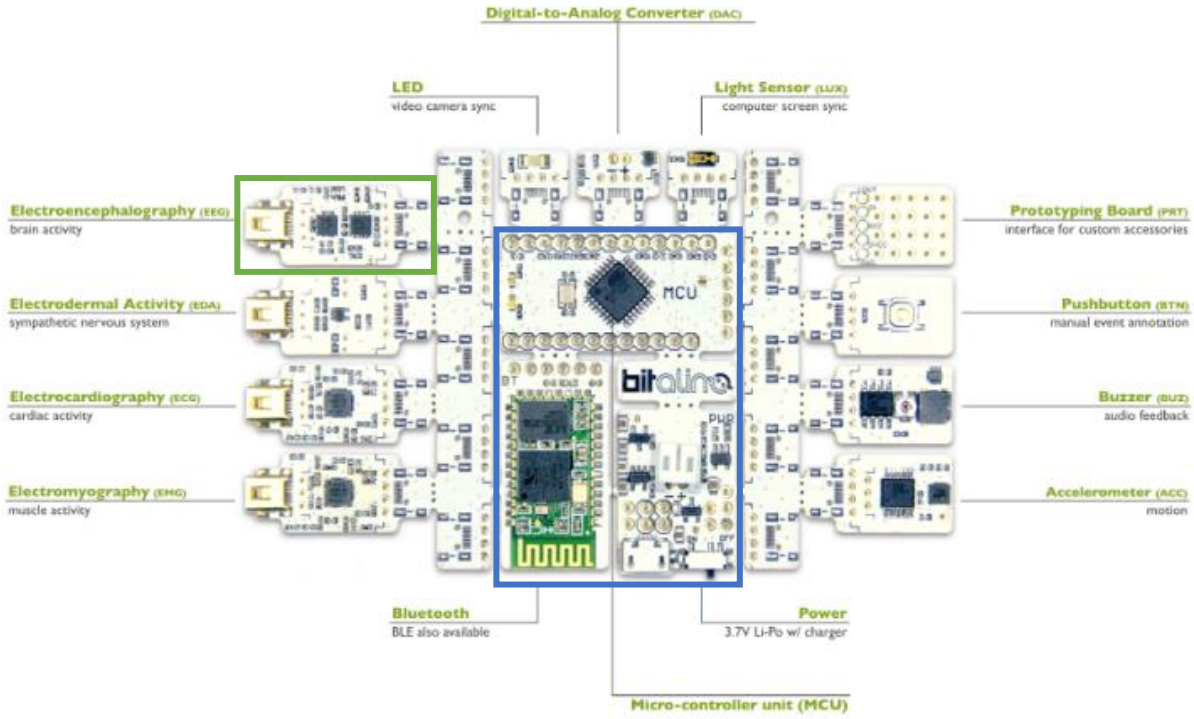

Figure 3.2 *- BITalino (r)evolution Board with Bluetooth connectivity.*

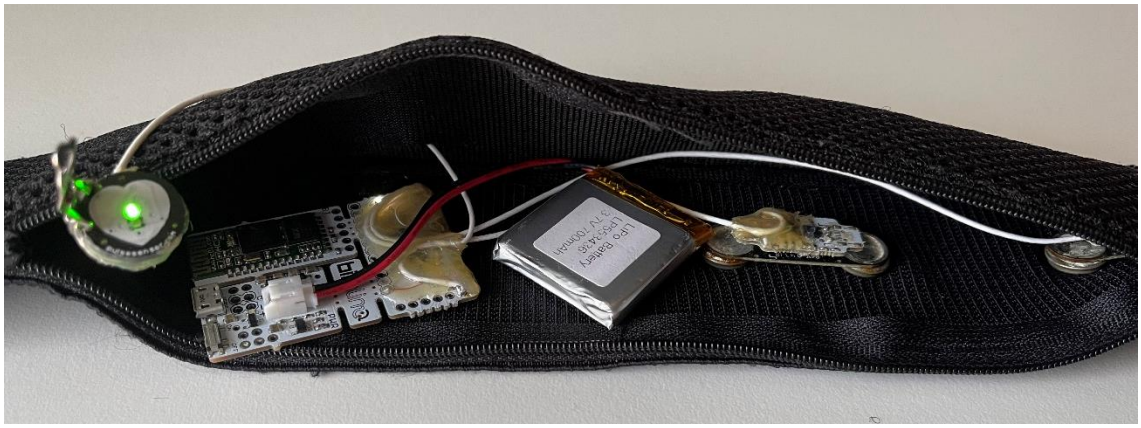

Figure 3.3 *- Inside of the EEG wearable band with all the elements and the connections, these being micro-controller unit with the Bluetooth connector, as well as the two EEG units.*

The board that was placed within the band as its functional core and which allows the acquisition of EEG data, only includes the parts necessary for the proposed objective, these being the micro-controller unit with the Bluetooth connector, the on and off switch, and the charging port via a mini-USB cable (squared in blue in **Figure 3.2**). This part of the board, made up of these units, is connected to a battery and to the part that contains the EEG sensors (squared in green in **Figure 3.2**). The latter are in duplicate, one to be connected to each pair of electrodes. The inside of the band used for data collection, with all the components that make it work and the way they are connected, can be seen in **Figure 3.3**.

3.2.2. Software Settings and Functions

OpenSignals (r)evolution was the software used to collect the data, which is capable of real-time biosignals visualization and compatible with all PLUX devices. Core functionality comprises the sensor data acquisition from multiple channels and devices, data visualization and recording, as well as loading of pre-recorded signals. It has an open and collaborative architecture, with a free software base, ready to use upon installation (no license keys needed) [69]. The installation was done on a portable computer since the installation on the mobile phone did not allow the acquisition of the desired results due to several errors. These included the constant disconnection between the wearable EEG band and the program, leading to the interruption of data collection, as well as the frequent shutdown of the program. It was then concluded that the results on the computer were easier to acquire and would give less origin to errors in data acquisition, as the program on the mobile phone was constantly disconnecting from the band.

OpenSignals (r)evolution can establish a Bluetooth connection to any PLUX device in the OpenSignals (r)evolution device manager. However, it can also be done manually, adding its MAC-address, found on the backside of the device, if this connection is not automatically made and the signal acquisition device is not listed as an available device. The OpenSignals (r)evolution device manager lists and manages all known and available OpenSignals compatible PLUX devices and their acquisition configurations, as well as select device(s), channels, channel labels, trigger, sample rate and resolution.

Several PLUX devices can be displayed in the device manager without having any effect or being used in acquisitions. This happens when devices are turned on and available, but not activated nor configured for signal acquisitions. For each device it is still possible to modify some important aspects such as sampling resolution, sampling rate and channel configuration. In this case only one device was added, with a 16-bit sampling resolution, and a sampling rate of 1000 Hz.

The channel configuration allows to activate and deactivate channels for the signal acquisition session and to configure which sensors are connected to the single channels of the device. The action of choosing a sensor specific channel type ensures that the signal will be displayed in its physical units in the real-time acquisition mode and in the visualization mode. However, the files storing the acquisition signals will only store the digital values (raw data). All the available channel types for BITalino (r)evolution are listed in **Figure 3.4**, and the type of channel used was raw.

TYPE	SENSOR
RAW	Compatible with every sensor
ACC	Accelerometer
ECG	Electrocardiography
EDA	Electrodermal Activity
EEG	Electroencephalography
EMG	Electromyography
LUX	Light
TEMP	Temperature
CUSTOM	Customizable channel configuration

Figure 3.4 *- BITalino channel types available for the collection of data.*

The acquired signals are visualized in the signal acquisition window (**Figure 3.5**), which contains the signals of all acquiring channels, along with channel unit, channel information and visual setup. The software also has a functionality to register events and put markers along the signal. Once all the desired signal has been acquired, OpenSignals (r)evolution allows to save the acquired sensor data into TXT, H5 or EDF files, and the program automatically saves all files in the folder where all program information is contained. In this case, the files were manually saved in TXT format to be later exported to a third party software for the signal to be analysed.

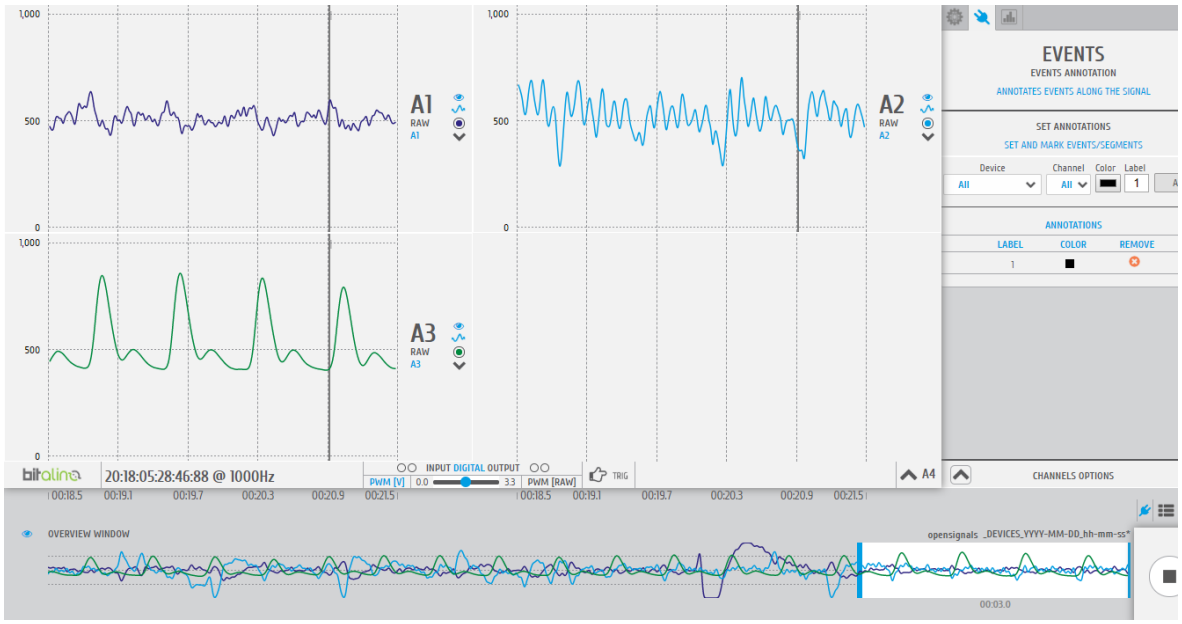

Figure 3.5 *– Signal acquisition window separated in three windows (A1, A2 and A3), being that A1 enables the visualization on EEG channel 1, A2 the EEG channel 2 and A3 the BP. During the acquisition the events annotation function is being used, marked with a vertical black line in every window..*

3.3. Data Collecting

Since the early detection of syncope had never been done using EEG data collected while the patient was performing HUTT, the collection was done by myself with the band mentioned above. The collection process began with an interview carried out by the technicians who performed the test, where they gathered information about the patient's medical history, the symptoms that brought them there and other issues, such as if they smoke or if they have a family member who has died of sudden death. The patients then proceeded to fill out a questionnaire whose objective was to understand and register the impact that light-headedness and TLOC had on their lives, thus being able to calculate the quality-of-life index. During the entire process, I took note of all the relevant information to analyse each patient separately and know what impact their comorbidities would have on the results obtained.

Once all the information about the patient had been collected, preparation for the exam began, placing all the necessary electrodes and equipment in the right places. Lastly, I carefully placed the band on the patient's forehead, with each pair of electrodes centered with each eyebrow, as well as the light sensor to measure BP in the patient's ear. It was quite important that the band was relatively tight and

not placed too high above the eyebrows. These precautions were necessary so that the band would not move, since patients often had myoclonic movements during syncope, thus being more favourable to dislocate the band. In addition, with the right position and the right amount of tightness, the signal had as little noise as possible, and a reliable signal was available. Since the channel 1 of the EEG presented several periodic variations of high amplitude in the signal, it was verified during the entire test if there was any stimulus or any wire that was in contact with other equipment causing interference, however no reasons were found for such stimuli during any of the tests.

With the patient already lying on the table and all measurements already calibrated and ready to be collected, the lights were turned off and the test began. During the 10 minutes in the supine position, a quiet environment was maintained for the patients to rest and be in their most relaxed state, some of them even falling asleep. After this period, a 375 µg sublingual nitrates were administered and the table was raised to 70º. With the change to the active phase, the OpenSignals events annotation function was used to mark in the signal the beginning of the table's ascent. During the active phase patients were instructed to always say what they were feeling, these moments being also marked, if any, along the signal.

In case the test was positive, the active phase took between 3 to 6 minutes, and when the patient lost consciousness, the table was immediately lowered to a slightly negative inclination, for the patient to recover quickly. The lights were turned on, and the beginning of the table's descent was also marked in the program. In most cases, the patient woke up shortly after lowering the table, the only exception being the patients with test result type 2, and who had some type of asystole. After regaining consciousness, the patient would return to the initial position and would recover a bit more until he felt able to stand up and leave the hospital. HUTT leaves patients weak and prostrate, hence the need to go with a companion.

In case the test was negative the procedure was simpler. During the 20 minutes of the active phase, the moments where the patient felt any of the identified prodromes, if any, were also marked. At the end of the 20 minutes, the table was lowered, the lights were turned on, being the beginning of the table's descent also marked. In these cases, the recovery was much faster.

After regaining strength, before leaving, all patients were instructed with some measures to improve their condition and quality of life. These include drinking more water, wearing compression stockings, and performing counter-pressure manoeuvres. Within the data studied, there are some negative test results that are quite similar to the results obtained in the positive tests. This is due to the fact that these patients presented characteristic symptoms of VVS but did not lose consciousness, precisely due to the performance of the counter-pressure manoeuvres or a very exacerbated sympathetic nervous system.

3.4. Data Analysis

The EEG and BP data, along with the clinical information of each patient were organized in folders and numbered to keep the data confidential, making it easier to be identified and referred to. Although the band has a blood pressure measurement feature, these values were treated and used only to improve the visualization of the drop in BP during syncope. This occurs because BP values are not the objective of the study, with some patients (3 of the 20 patients with positive tests) not even having

a drop in blood pressure prior to loss of consciousness. In addition, the measurement of blood pressure is a well-known variable used in several studies, as well as in the day-to-day life of patients. Thus, with the aim of putting together an innovative study, only the EEG data were treated, segmented and analyzed, both in frequency and in amplitude.

3.4.1. Data Processing

Since the EEG signals are very irregular due to the large amount of existing noise, especially the channel 1 of the EEG as was already mentioned, data had to be filtered to enable its analysis. Thus, the choice of filter used, and its cutoff frequencies was a very important variable, enabling the results to be well analyzed. A high-pass filter and a band-pass filter with similar cutoff frequencies were evaluated and the results of the two were compared. It was then concluded that the bandpass filter minimized the artifacts created by the band and presented much cleaner results.

Hence, a bandpass filter was applied using the *bandpass* function in the MATLAB® R2021 program, and several cutoff frequencies were tested in order to understand which ones removed the greatest amount of noise and artifacts caused by eye blinks, head movements or by the system possible. This would have to be done in order to remove these constituents, while keeping the relevant features of the signal. Great care had to be taken not to erase the delta and theta waves, which, based on the study of other researches, were the ones where there were more changes in the EEG during a syncopal episode. In particular, attention had to be paid to the artefacts made by the system, due to their low frequency, similar to delta waves. The chosen frequencies were 0.5 and 40 Hz for the first cut-off frequency and the second, respectively, with the aforementioned sampling frequency of 1000 samples per second.

3.4.2. Data Segmentation in Intervals of Interest

After having the data processed, it is now possible to carry out the analysis, which was done through MATLAB® R2021. However, it made no sense to analyze the signal in its entirety, since the parts of greatest interest are in the active phase and its comparison with the values in supine rest.

As for these, it was not adequate to analyze the 10 minutes in the supine position, but only a segment of an interval large enough to be able to draw reliable conclusions. Therefore, the 1-minute interval was chosen, and was measured after the signal stabilized in each case. This is essentially because the patient at the beginning of the test still had many interactions going on around him, causing the sympathetic system to be very exacerbated, still taking 1 or 2 minutes to fully relax.

It is important to discuss how long in advance it is possible to predict syncope and whether this time is enough to warn the subject Accordingly, the initial plan was to predict syncope 10 seconds in advance. However, it was concluded that this time interval was not large enough, not only to perform a reliable analysis, but also for the subject to be able to perform some activities, such as driving any type of vehicle or just cooking. This idea is supported by the data analysis, which will be explained later, where it is possible to see that the patient 10 seconds before syncope is already in a limbo between awareness and syncope, not being conscious enough to make any kind of decision or do something.

Since the above-mentioned range was unreliable, it was concluded that it would take more than one time interval with different durations for them to be compared and consequently choose the best one. Thus, two intervals were chosen, these being 30 seconds and 1 minute before syncope, both ending at syncope and differing only in duration. It was discussed whether 30 seconds earlier would be enough to efficiently warn someone with enough time to be secure. Therefore, it is thought that this will already be an interval with a much greater room for maneuver, making it possible to do plenty more activities in a safer way. Ideally the 1-minute interval would be employed, since the data considered, and the duration are longer.

Additionally, the interval of the first minute in the active phase was considered only to compare both the supine rest and the intervals before syncope, due to the same reasons that caused the signal to be instable in the first 10 minutes of the test. Since it is a time of interaction with the patient, with the administration of sublingual nitrates and the lifting of the table, one would expect an area where the signal had an alteration translated into a greater amplitude as well as a greater frequency. Consequently, the signal in this interval was also studied in order to assess how the subject is alert during the examination and the exacerbation of the sympathetic nervous system.

In the case of negative tests, where there is no syncope, the time intervals considered are the same already mentioned, with the only difference being that instead of 1 minute, 30 seconds and 10 seconds before syncope, it is before the table is lowered, that is, before the end of the active phase. This way, the results are as homogenized as possible, since it is only by understanding how the sample works as a whole that it is possible to find a reliable pattern.

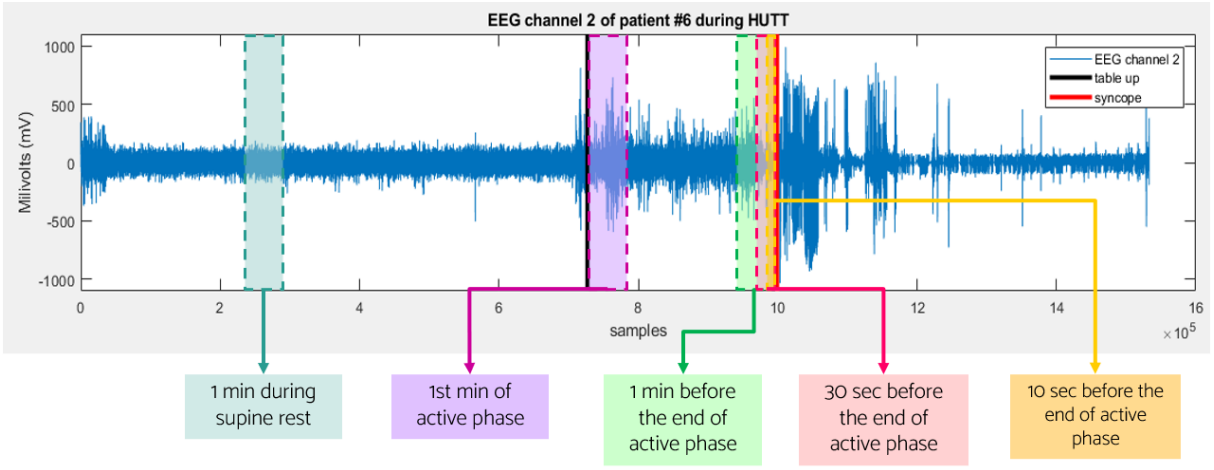

***Figure 3.6** - EEG channel 2 signal of patient #6 positive with the illustration of every interval of interest considered.*

With the signal already segmented, the next step is to analyze the data, in the interval of 1 minute in supine rest, first minute in the upright position, and 1 minute, 30 seconds and 10 seconds before syncope, as it is illustrated in **Figure 3.6**. By observing the signal and how it progressed throughout the exam, as it is seen in on the data of one of the patients in **Figure 3.7**, it was concluded that would make sense to perform an analysis in amplitude and in frequency. This stems from the fact that the difference in amplitude is notorious and the frequency of the signal is something that generally reflects well the differences when there is some cause that could alter the signal.

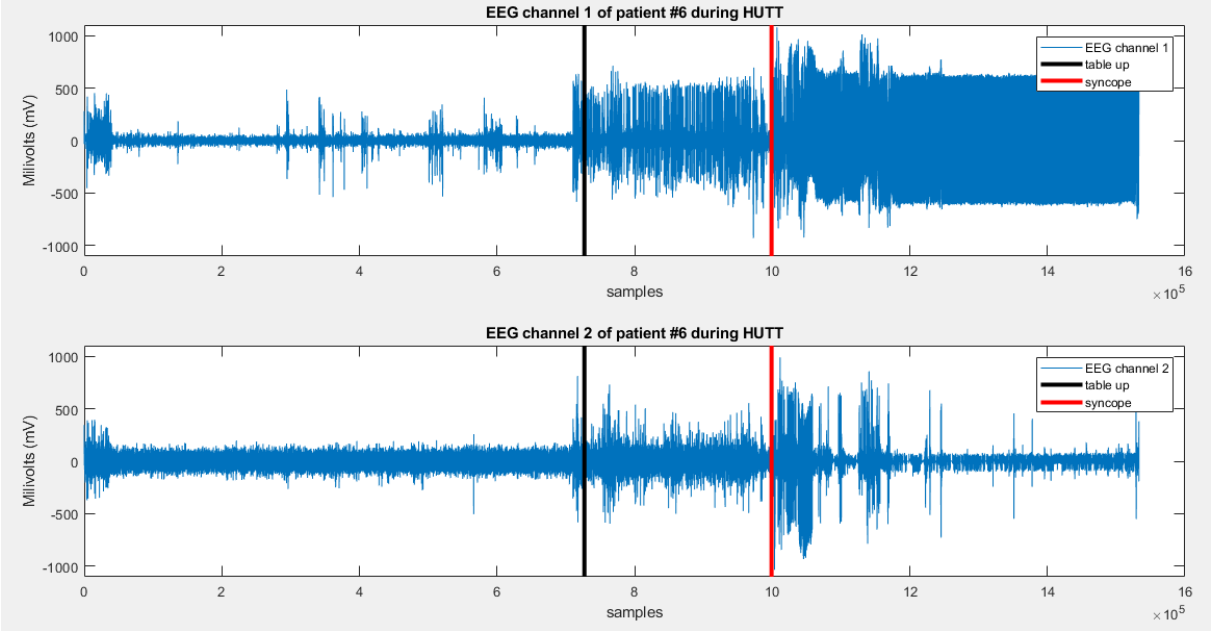

Figure 3.7 *- EEG channel 1 and 2 of patient #6 during the HUTT, with the beginning and the end of the active phase marked with a vertical black and red line, respectively.*

3.4.3. Amplitude Analysis

Initially, the amplitude analysis was performed, before the frequency analysis, as this was something that could be seen with the naked eye. This analysis only needed to be quantified in order to draw more credible conclusions and be able to associate it to the frequency analysis and use the values to create the algorithm.

Thus, the procedure went through finding the signal peaks on the y-axis, using the *findpeaks* function in the MATLAB® R2021 program, and making an average of these values, using the *mean* function of the same program in each considered interval. A minimum distance was defined in the function of 6 values between each peak, preventing the peaks to be considered erroneously. Since the signal is somewhat symmetrical in relation to the x axis with center at 0, the result of the average obtained would be a value close to 0, which would not allow drawing any kind of conclusions. For this reason, a minimum height of 0 was defined for the peaks in the function, only to consider the positive peaks.

The results of the mean positive peak values in each interval for each patient were then copied to a table to be analyzed, comparing both positive and negative results, as well as patients with a negative test who had symptoms and those with no symptoms. In **Figure 3.8** it can be seen the result of the function used to find the peaks, circled in red along the signal. In the figure the whole signal was considered instead of the chosen windows just for the purpose of being easier to exemplify. These values were considered for both channels, however, as channel 1 was always more unstable and was more inconsistent with small activities performed by the patient, such as talking or making small movements, channel 2 was always given more priority. Additionally, the mean amplitude results were plotted for the supine rest intervals, 1 minute and 30 seconds before syncope or, in the case of negative tests, before lowering the table.

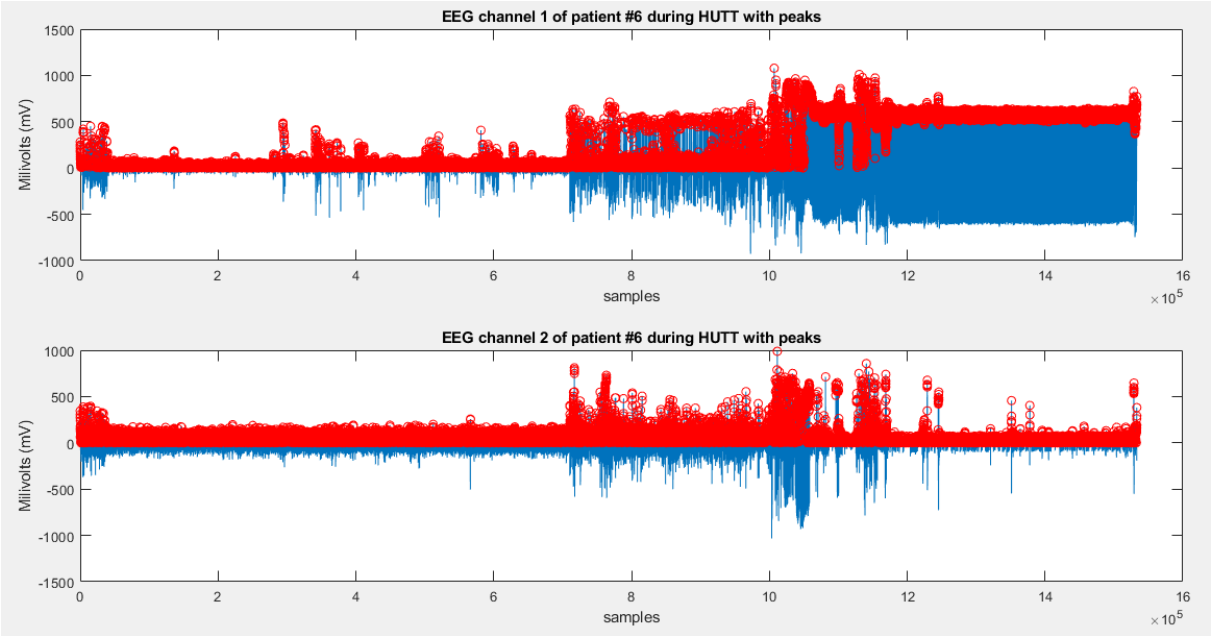

Figure 3.8 *- EEG channel 1 and 2 of patient #6 during HUTT with the signal's peaks circled in red along the signal.*

3.4.4. Frequency Analysis

With the amplitude analysis already accomplished, it was then necessary to perform the frequency analysis in order to evaluate if it would allow more reliable results. This analysis is somewhat more treacherous, as there are several methods to carry it out and in quite a few different ways. Thus, several methods were experimented to analyze the signal in frequency, in order to obtain results that would allow to find a reliable pattern to proceed with the development of the algorithm.

In a first phase, the instantaneous frequency and the mean frequency were calculated, using the *instfreq* and *meanfreq* functions, respectively, from the MATLAB® R2021 program for each interval. However, instantaneous frequency was out of the question as the results obtained after its use did not reflect reality and thus were not usable. The average frequency, on the other hand, presented more promising results, which in theory would be more reliable. However, it was not possible to find any kind of pattern in the results obtained using this method, since the values were quite dispersed. The spectrogram of the EEG data for each patient at each interval was also acquired using the *spectrogram* function. Nevertheless, the results obtained also presented very dispersed frequencies from case to case, and it was not possible to find any type of pattern that would distinguish patients with symptoms and patients without symptoms.

In a next phase, the graph of the spectral density was made using the Fourier transform and the Welch method, for each interval. Since these two methods are quite similar, the only difference being that the latter reduces signal noise in the estimated power spectrum in exchange for reducing the frequency resolution, only the Welch method was used.

The spectral density graph using the Welch method was made, using the *pwelch* function of MATLAB® R2021, plotting half of the power spectrum with 50% overlap and a Chebyshev window of

length 128. The Hanning window was also tested, however it was not possible to draw concrete conclusions from its results. The graph obtained for each of the patients in every considered interval, except first minute of the active phase, had the appearance of two lumps at the beginning (visible in the example of a patient with a positive test in **Figure 3.9**). In positive cases a difference was observed in these lumps as the interval was closer to syncope, as it can be seen, these being more accentuated, being closer or farther from each other, depending on the cases. In the graphs of negative cases that did not show symptoms during the test, no relevant change was visible with the change of interval (as it can be seen in the example of a patient with a negative test in **Figure 3.10**).

Due to this notorious difference, the signal was segmented by frequency spectra with the intervals known in the literature to make a more in-depth analysis of the spectral density graph using the Welch method, these being delta (0.5-4 Hz), theta (4-8 Hz), alpha (8-12 Hz), beta (12-30 Hz) and gamma (30-35 Hz). Afterwards, the spectral density magnitude values were averaged over each spectrum range. Although in the literature the spectrum of gamma frequencies is greater than 30 Hz, not having an upper limit, in this case one had to be defined, so that the values corresponding to this interval were included in the zone of the second lump. The value chosen for the upper limit was 35 Hz, since the graphs of all patients were analyzed in order to generalize and standardize the data as much as possible, revealing that the second lump ended at the maximum value chosen.

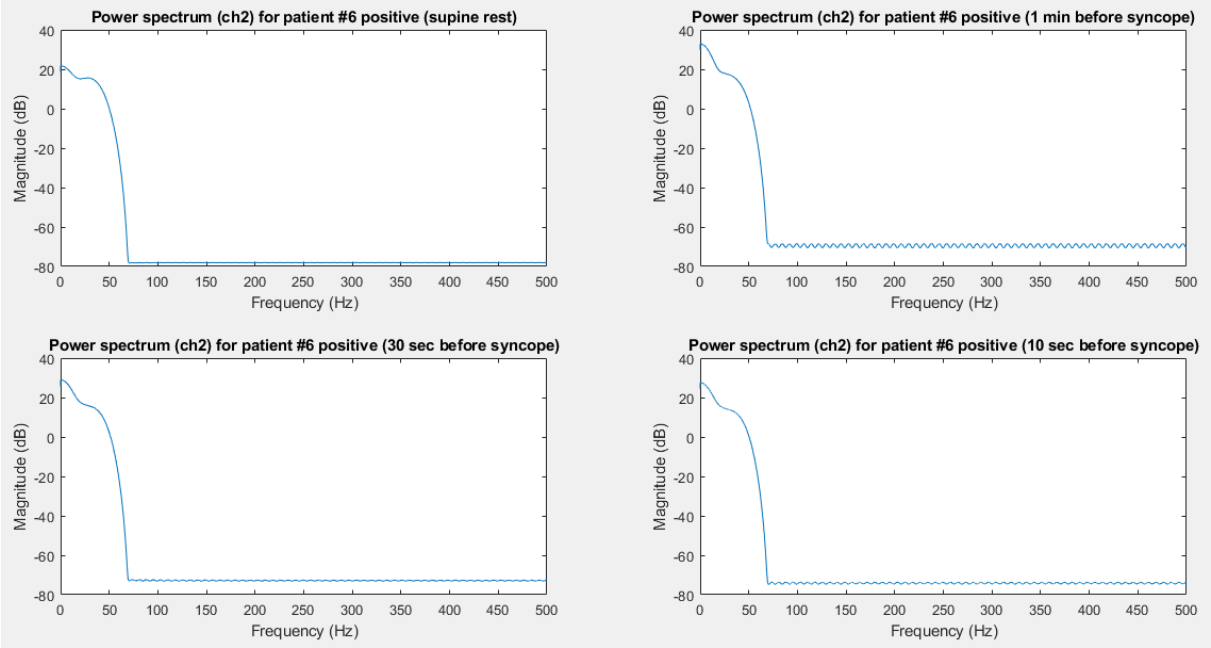

Figure 3.9 *- Power spectrum using Welch's method of channel 2 of the EEG signal for patient #6 with a positive HUTT for the intervals of supine rest, 1 minute, 30 seconds and 10 seconds before syncope.*

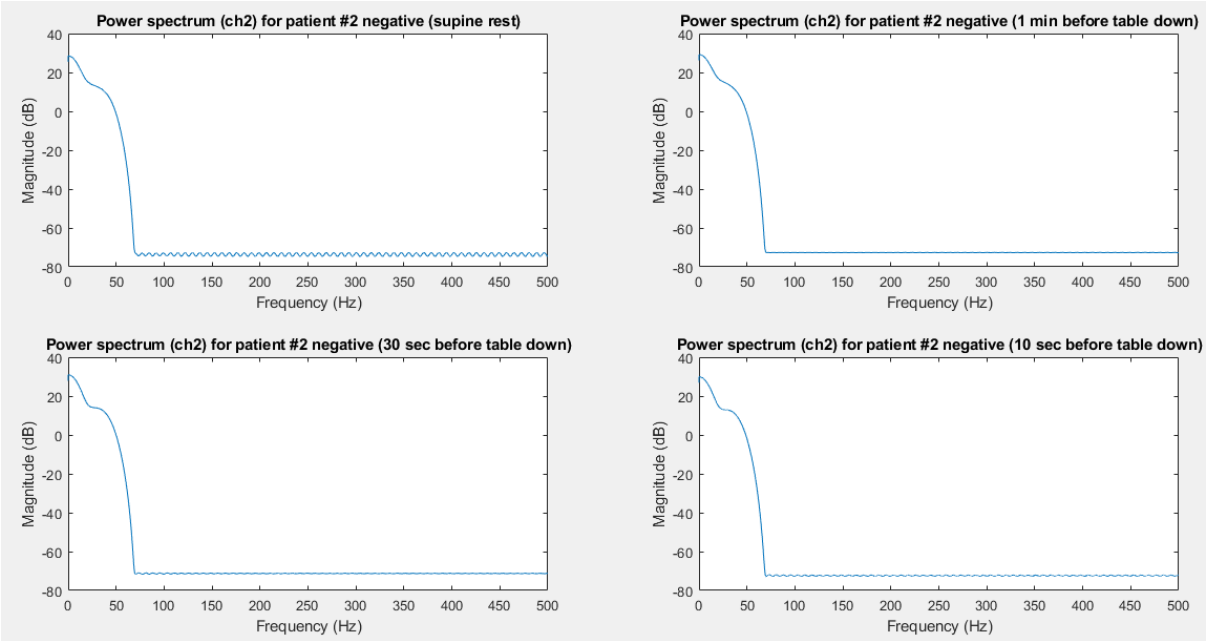

Figure 3.10 *- Power spectrum using Welch's method of channel 2 of the EEG signal for patient #2 with a negative HUTT for the intervals of supine rest, 1 minute, 30 seconds and 10 seconds before table down.*

Subsequently, the average of the spectral density values included in each frequency range for each time interval was taken, and a table was built with these values for each patient. Since the presence of the two lumps was always within two of the frequency spectrum intervals, these being delta and gamma, the delta/gamma ratio of the obtained mean values was calculated, in order to draw some conclusions about the difference between the graphs of the positive and negative cases.

Additionally, delta/gamma ratio values were plotted at supine rest, 1 minute and 30 seconds before syncope, or in the case of negative tests, before lowering the table. A graph was also made of the mean spectral density values included in the delta frequency spectrum for the same intervals as the ratio. This is due to the observation of a different behavior in these values from the rest of the frequency spectrum, with the identification of a common pattern that distinguishes the positive and negative cases with symptoms from the negative cases without symptoms. These graphs were considered only to demonstrate the evolution of values from interval to interval, making it easier to observe the sample as a whole and more easily perceive the behavior of the data of each patient, according to the divisions between patients with symptoms and patients without symptoms.

3.5. Development of the Classifier

With the amplitude and frequency analysis already done, so that these could be implemented, a method of classifying the results in symptomatic patients and non-symptomatic patients had to be developed so that the results obtained could be put into practice and tested in a practical context to confirm their veracity. The most correct way to achieve this was with the development of a classifier in machine learning with a system for organizing data into categories.

A classifier in machine learning is basically an algorithm that automatically categorizes or orders data into one or more set of "classes", incorporating the regulations used by machines to classify data. These classifiers go beyond simple data mapping, permitting users to continuously update models with new learning data and customize them to changing needs [70]. At a more detailed degree, a classifier is essentially a function that takes the values of several features (independent variables or predictors) in an example (the set of independent variable values) and predicts the class where the example fits (the dependent variable) [71].

Usually, a classifier contains a number of parameters that have to be learned from training data – a set of examples reserved for this purpose. The learned classifier is basically a model of the relationship between the features and the class label in the training set. Once trained, the classifier can be employed to determine whether the features used contain information about the class of the example. This association is tested by applying the learned classifier on a different set of examples, the test data. Naturally, the idea is that, if the classifier indeed captured the correlation between features and class, it should be able to predict the classes of examples it has not seen before. The typical assumption for classifier learning algorithms is that the training (and testing) examples are independently drawn from an 'example distribution'; when judging a classifier on a test set we are obtaining an estimate of its performance on any test set from the same distribution [71].

In this way, the data of each individual patient were classified according to their value, both in the analysis carried out in terms of amplitude and frequency. Data from 36 patients in each of the two analyses were classified into two categories, patient at risk of losing consciousness soon (i.e. symptomatic patient) and patient with normal status (i.e. non-symptomatic patient). The classification was done through a train support vector machine (SVM) classifier, using the function *fitcsvm* of the machine learning toolbox in the MATLAB® R2021 program. This model was chosen since it needs fewer samples in comparison with the function *fitcdiscr*, that returns a fitted discriminant analysis model. SVM does not require the samples to be normally distributed and is less susceptible to noise.

Taking into account the results quantitatively, the most important results for the development of the classifier is the variation in values from the supine rest interval to 1 minute and 30 seconds before the end of the active phase. It is important to emphasize that this variation was always made by subtracting the values of the supine rest interval from the values of the intervals before syncope, that is, 1 minute - rest or 30 seconds - rest.

Initially, the dataset was prepared, dividing it into a test set and a training set. Due to the similarity in sign between the positive cases and the patients with negative tests who had symptoms, and also the presentation of presyncope symptoms, these 8 cases were joined with the positive cases. As a result, the sample had 28 patients with symptoms and 8 patients without symptoms. Thus, the division between the two sets was made so that these sets contained patients of all types, both positive cases and negative cases with symptoms, as well as negative cases without symptoms. The classifier was trained in 22 patients and tested in 14, dividing the patients into two lists corresponding to each of the sets. The two lists were in the form of a matrix with 2 columns and 14 or 22 lines, depending on the type of set, with the first column containing the values of the amplitude variation and the second those of the magnitude variation of the delta frequencies. Lists were constructed for variations between the supine rest interval and the 1-minute and 30-second intervals before the end of the active phase.

Then, the validation set was prepared out of the training set, using k-fold cross-validation. This was done using the *cvpartition* function of the same program, that returns a cvpartition object that

defines a random non-stratified partition for k-fold cross-validation on the observations. The partition randomly divided the observations into 5 disjoint subsamples, or folds, each of which had approximately the same number of observations.

In a next phase, a SVM model was created using the function *fitcsvm*, and together with the train data and the train labels, the model can predict the classification of the test data. The training of this model was accomplished employing some hyperparameters and the features that are most useful for the training and the classification, these being chosen by the program in the cross-validation. After the training procedure, another SVM model was built using the same function with these hyperparameters used in the training. It was then applied the test procedure, testing this model with the test set, and allowing the categorization prediction in the data set with the best features chosen.

This procedure was performed to the variation in amplitude, and to the variation in frequency in the x-axis, with the number of patients in the y-axis (**Figure 3.11** and **Figure 3.12**). The application of the model was done separately for the two variables, as well as for the two together, in order to verify which was the most viable method that brought more accuracy to the model. In this procedure the model chose a data set as the support vectors, as it is seen in **Figure 3.11** for the difference between the supine rest and the 1-minute interval, and in **Figure 3.12** for the 30-seconds interval. The support vectors are observations that occur on or beyond their estimated class boundaries. In a final phase, a hyperplane was developed for the two variables in conjunction to separate the classes in order to classify the test set.

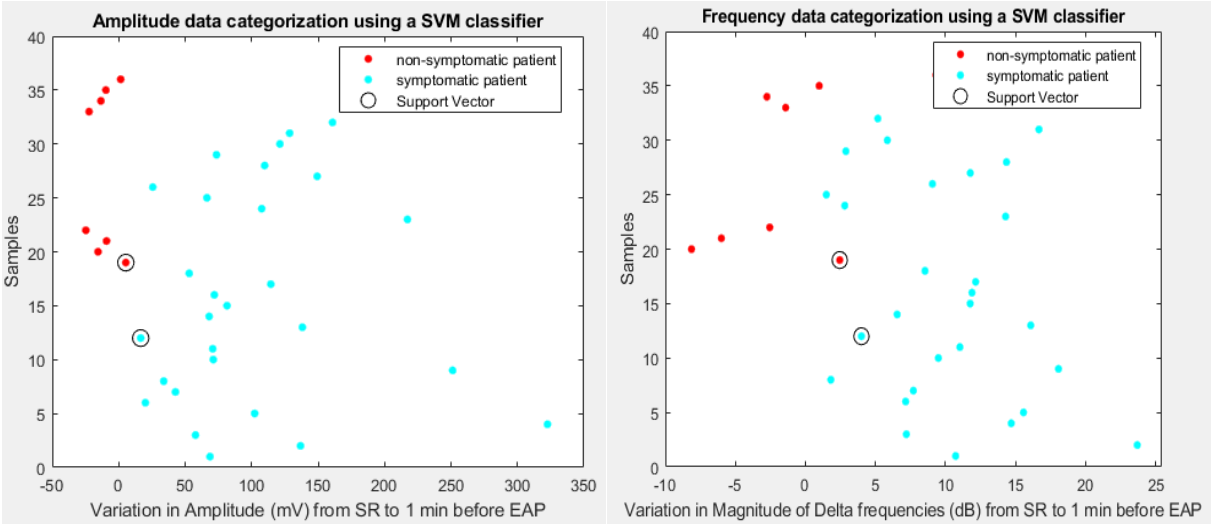

Figure 3.11 *- Amplitude and frequency data categorization using a SVM classifier for the variation in values from the supine rest interval to 1 minute before the end of active phase. EAP = end of active phase.*

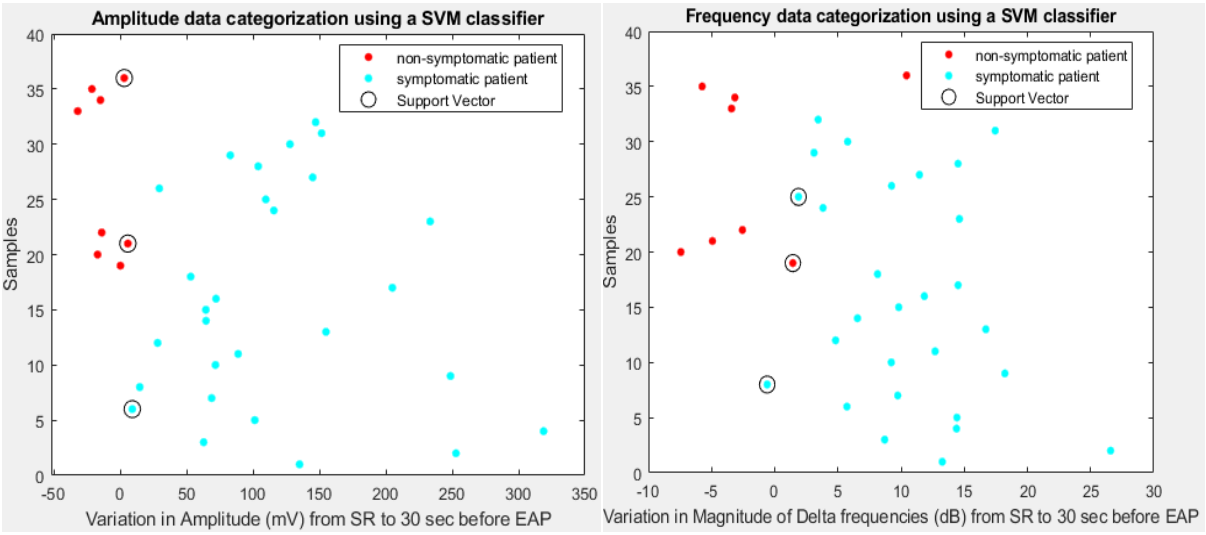

Figure 3.12 *- Amplitude and frequency data categorization using a SVM classifier for the variation in values from the supine rest interval to 30 seconds before the end of active phase. EAP = end of active phase.*

Chapter 4. Results

Of the 36 patients who underwent the test in the syncope unit, 20 had positive tests and 16 had negative tests, being that among the negative, 8 had symptoms during the test and 8 did not. Data from all patients were collected to be later analyzed, and only the results of EEG channel 2 are presented and discussed. This is due to the reasons already mentioned in section 293.3 stating that the EEG channel 1 data had much more noise and artifacts that were not possible to remove, making it impossible to analyze the data reliably. In addition, the signals collected by this channel were quite inconstant, presenting too many periodic variations where no reasons were found for such stimuli. In order not to compromise the analysis and the study carried out, it was decided not to include these data so that they would not interfere with the development of the classifier. Since both channels have electrodes in the same anatomical zone, not including channel 1 data is not so problematic. Thus, only EEG channel 2 data will be presented, according to the amplitude and frequency analysis performed.

4.1. Amplitude Variations of EEG channel 2 Signal for Positive Test Results

As a result of the amplitude analysis performed, as previously mentioned, a table was assembled (**Table 4.1**) with the mean values of the signal peaks in each considered interval, as well as a table with the variations in the values between the supine rest and the other intervals (**Table 4.2**). A graph was also constructed with these values for each patient in the intervals of most interest, these being the supine rest, 1 minute and 30 seconds before syncope. This graph (**Figure 4.1**), only assist the demonstration of the evolution of values from interval to interval. This make it simpler to observe the sample as a whole and more easily perceive the behavior of the data of each patient, facilitating the finding of the pattern that is needed to classify the data.

Regarding the results in **Table 4.1**, and considering the table as a whole, it is possible to observe that the values obtained are quite scattered from patient to patient, with a great variation of values even within the same interval. Thus, observing the results in each interval individually, in supine rest, the results are relatively uniform, with the exception of 2 patients, with most patients presenting values between 20 and 70 mV, with the mean values in this range being 63.41 mV. In the second interval, the results are considerably less uniform, ranging between 16 and 254 mV. This is due to the fact that in this interval only the reaction to external stimuli is evaluated, which can vary greatly from patient to patient, depending on the exacerbation of their sympathetic system. The remaining 3 intervals present results similar to each other, with very dispersed results, ranging between 55 and 393 mV. An increase in signal amplitude is observed in all patients with positive HUTT results, from supine rest to the intervals prior to syncope. In **Figure 4.1** is possible to observe this uniformity of the first interval, the dispersion of 1 minute and 30 seconds before syncope, as well as the clear increase in results in all patients between the first and the other two intervals.

Hence, the most effective method of analyzing these results would be to evaluate them for each patient individually, calculating the difference between the values from interval to interval. The values

of these variations are presented on **Table 4.2**. To understand better the variations in the results the difference between values will be considered in module, only assessing the variation quantitatively. Considering only the second column of **Table 4.2**, a significant increase in signal amplitude is observed between the two instants, with a mean value of 104.13 mV, as well as a minimum value of 16.56 mV and a maximum value of 322.60 mV. Regarding the third column, the results are quite similar to the previously mentioned variation, with a mean of 118.80 mV, a minimum value and a maximum value of 9.09 mV and 318.83 mV, respectively. This occurs because the results of 1 minute before and 30 seconds before syncope have very similar values, since they are very close instants, with only a small non-uniform difference in their values, with the exception of 1 case. This variation has a mean of 19.43 mV, a minimum value of 0.55 mV and a maximum value of 116.04 mV. The values of the interval 30 seconds before are mostly higher than those of 1 minute before, which is easily visible by the obtained graph (**Figure 4.1**), as well as the similarity of the values in these two intervals.

Table 4.1 *- Mean of the positive peaks per interval for each patient with a positive HUTT.*

MEAN OF POSITIVE PEAKS PER INTERVAL - POSITIVE HUTT					
	SUPINE REST	**1ST MIN OF ACTIVE PHASE**	**1 MIN BEFORE SYNCOPE**	**30 SEC BEFORE SYNCOPE**	**10 SEC BEFORE SYNCOPE**
P1	52.53	75.09	121.27	187.57	258.51
P2	21.26	16.45	158.07	274.11	351.19
P3	32.49	130.28	90.28	95.31	95.27
P4	71.29	75.93	393.90	390.13	388.02
P5	26.91	68.42	129.24	128.29	106.87
P6	51.55	102.09	71.64	60.64	60.65
P7	53.60	243.86	96.30	122.48	99.52
P8	67.85	130.25	101.75	82.58	57.47
P9	34.17	62.38	285.41	282.91	287.45
P10	28.51	84.94	99.68	100.24	149.17
P11	39.25	74.46	110.02	128.06	144.99
P12	59.47	86.41	76.03	87.68	55.09
P13	90.70	71.04	228.92	245.69	293.63
P14	60.33	254.59	277.57	293.76	273.35
P15	99.39	170.38	206.97	215.11	201.29
P16	188.78	221.74	255.19	298.39	278.15
P17	44.47	50.16	70.16	73.93	98.41
P18	58.97	127.68	208.32	203.98	183.57
P19	48.82	66.30	158.65	152.73	184.76
P20	137.80	205.32	211.41	220.67	149.76

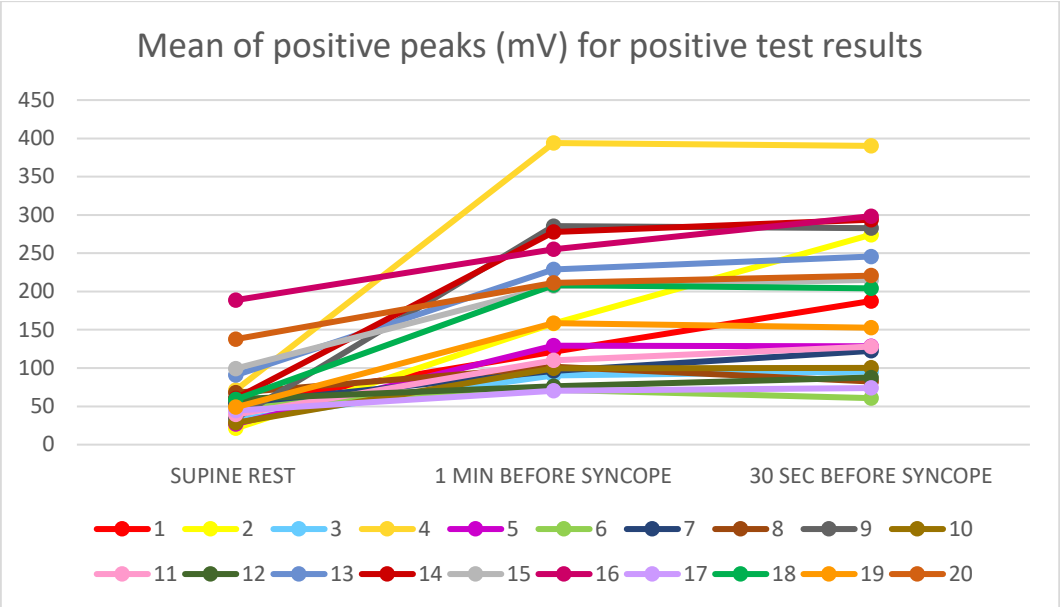

Figure 4.1 *- Mean of positive peaks (mV) for each patient with a positive test result for the intervals of supine rest, 1 minute before syncope and 30 seconds before syncope.*

Table 4.2 *- Variation in the values of the mean of positive peaks between the intervals of interest and the supine rest interval for positive test results.*

Variation in the values of the mean of positive peaks between the intervals of interest and the supine rest interval - POSITIVE HUTT				
	1ST MIN OF ACTIVE PHASE – SUPINE REST	**1 MIN BEFORE SYNCOPE – SUPINE REST**	**30 SEC BEFORE SYNCOPE – SUPINE REST**	**10 SEC BEFORE SYNCOPE – SUPINE REST**
P1	22.55	68.73	135.03	205.98
P2	-4.80	136.81	252.85	329.93
P3	97.79	57.79	62.82	62.78
P4	4.63	322.60	318.83	316.73
P5	41.51	102.32	101.38	79.96
P6	50.54	20.09	9.09	9.10
P7	190.25	42.69	68.87	45.91
P8	62.40	33.89	14.72	-10.37
P9	28.21	251.23	248.73	253.27
P10	56.42	71.17	71.73	120.65
P11	35.21	70.76	88.80	105.74
P12	26.94	16.56	28.21	-4.37
P13	-19.65	138.22	154.99	202.93
P14	194.25	217.23	233.42	213.01
P15	70.98	107.57	115.71	101.89
P16	32.96	66.41	109.61	89.37
P17	5.69	25.68	29.46	53.94
P18	68.70	149.34	145.01	124.59
P19	17.48	109.83	103.91	135.94

P20	67.51	73.61	82.87	11.95

4.2. Amplitude Variations of EEG channel 2 Signal for Negative Test Results

Analogous to the positive results, a table was also built for the negative HUTTs (**Table 4.3**), with the mean values of the signal peaks in each interval, as well as a graph with these values for the same intervals considered in the case of the positive HUTTs.

Considering the table as a whole, as it was done previously, it is possible to observe again the dispersion of results from patient to patient, and from interval to interval. However, a large discrepancy was observed in the values of the subjects, being identified two different patterns in the data. In 8 of the 16 cases, there is an increase in the amplitude from the supine rest signal to the intervals before the end of active phase, similarly to what occurs with positive HUTTs. In the other patients, this increase is not verified, existing even a decrease in amplitude in some cases. Correlating these results with the notes taken during the test, it is inferred that these 8 patients with the increase in amplitude had symptoms characteristic of SVV (pre-syncope) during the active phase of HUTT, and those in which the signal maintains the amplitude did not have any symptoms. Thus, the results were divided into patients with and without symptoms, so that the analysis performed could be more precise and adjusted to each pattern.

Taking into account the variation between intervals (**Table 4.4**) and considering only the module of the difference in values, in patients who presented symptoms during the test, there is a large discrepancy between the values at supine rest and 1 minute before table down. This difference has an average of 99.98 mV, with a minimum value of 53.10 mV and a maximum value of 160.86 mV. Although the mean of these values is slightly lower than the positive results, their minimum value is much higher. Like the positive HUTTs, the values of the third column of **Table 4.4** for patients with symptoms, are quite similar to the previous difference, with an average of 110.74 mV, as well as a minimum and maximum value of 53.06 mV and 204.94 mV, respectively. In the case of these 8 patients, the results of the interval 1 minute before the end of active phase and the interval 30 seconds before table down are even closer to each other than in the positive cases. With the exception of patient 7, this difference between them has a maximum value of 23.07 mV. The values of the interval 30 seconds before are both higher and lower than those of 1 minute before, visible by the points marked on the graph (**Figure 4.2**). The latter also shows the similarity of values in these two intervals, as well as the large increase in values from the first to the second point.

In patients who did not present symptoms during the test, the module of the difference between interval values seen in the second half of **Table 4.4** is quite similar in all cases since there was no reaction by these 8 subjects at any time during the HUTT. In most cases, a slight decrease in the values from supine rest to 1 minute before table down is observed, contrary to what happens with patients with symptoms, with this difference having a mean of 12.67 mV (range 1.51 to 24.68 mV). The same occurs with the difference between the supine rest interval and the 30 seconds before the end of active phase. This equality of values is visible in the constructed graph (**Figure 4.3**), as well as the slight descent mentioned.

Table 4.3 *- Mean of the positive peaks per interval for each patient with a negative HUTT, with the division between the patients who had symptoms during the test and those who did not.*

AVERAGE OF POSITIVE PEAKS PER INTERVAL - NEGATIVE TEST RESULTS					
PATIENTS WITH SYMPTOMS - PRE-SYNCOPE					
	SUPINE REST	**1ST MIN OF ACTIVE PHASE**	**1 MIN BEFORE TABLE DOWN**	**30 SEC BEFORE TABLE DOWN**	**10 SEC BEFORE TABLE DOWN**
N12	66.24	120.28	134.32	130.88	132.74
N6	42.12	51.95	123.65	106.61	105.59
N4	40.26	75.25	112.19	112.40	105.98
N7	35.82	120.90	150.30	240.76	421.12
N10	64.18	129.27	117.28	117.24	110.51
N13	137.85	193.47	259.14	265.68	216.89
N15	99.83	129.37	228.44	251.52	285.50
N5	98.87	152.61	259.73	246.05	199.56
PATIENTS WITHOUT SYMPTOMS					
	SUPINE REST	**1ST MIN OF ACTIVE PHASE**	**1 MIN BEFORE TABLE DOWN**	**30 SEC BEFORE TABLE DOWN**	**10 SEC BEFORE TABLE DOWN**
N2	72.35	79.03	77.72	72.54	74.66
N3	64.47	41.62	48.94	47.45	41.47
N9	96.87	92.94	87.76	102.65	107.95
N11	92.83	99.22	68.15	78.88	64.26
N8	88.17	44.57	65.92	56.18	34.79
N1	64.65	87.12	51.32	49.79	55.46
N16	49.10	54.40	39.50	27.79	23.50
N14	60.68	64.23	62.19	63.71	87.50

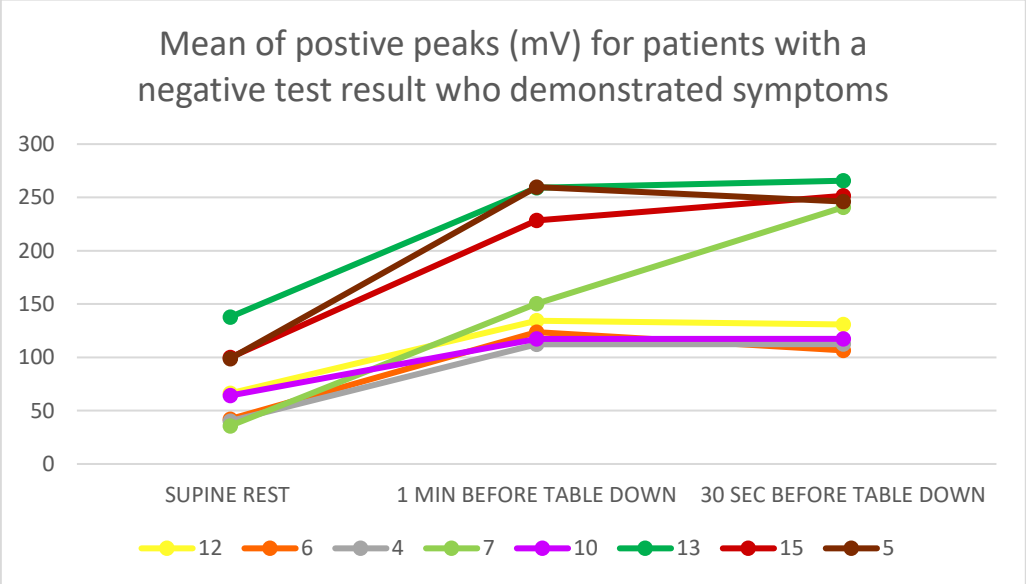

Figure 4.2 *- Mean of positive peaks (mV) for patients with a negative test result who demonstrated symptoms for the intervals of supine rest, 1 minute before table down and 30 seconds before table down.*

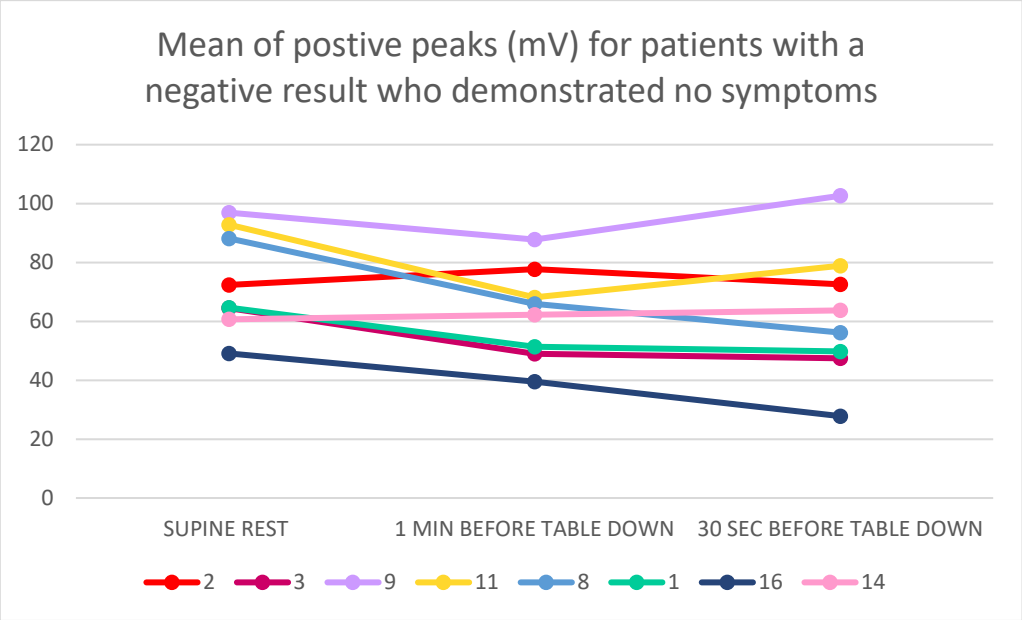

Figure 4.3 *- Mean of positive peaks (mV) for patients with a negative test result who demonstrated no symptoms for the intervals of supine rest, 1 minute before table down and 30 seconds before table down.*

Table 4.4 *- Variation in the values of the mean of positive peaks between the intervals of interest and the supine rest interval for negative test results.*

Variation in the values of the mean of positive peaks between the intervals of interest and the supine rest interval - NEGATIVE HUTT				
PATIENTS WITH SYMPTOMS - PRE-SYNCOPE				
	1ST MIN OF ACTIVE PHASE – SUPINE REST	**1 MIN BEFORE TABLE DOWN – SUPINE REST**	**30 SEC BEFORE TABLE DOWN – SUPINE REST**	**10 SEC BEFORE TABLE DOWN – SUPINE REST**
N12	54.03	68.08	64.63	66.50
N6	9.83	81.52	64.48	63.46
N4	34.98	71.93	72.14	65.72
N7	85.07	114.48	204.94	385.30
N10	65.09	53.10	53.06	46.33
N13	55.62	121.28	127.83	79.04
N15	29.53	128.61	151.68	185.66
N5	53.74	160.86	147.17	100.68
PATIENTS WITHOUT SYMPTOMS				
	1ST MIN OF ACTIVE PHASE – SUPINE REST	**1 MIN BEFORE TABLE DOWN – SUPINE REST**	**30 SEC BEFORE TABLE DOWN – SUPINE REST**	**10 SEC BEFORE TABLE DOWN – SUPINE REST**
N2	6.67	5.37	0.18	2.30
N3	-22.84	-15.52	-17.02	-22.99
N9	-3.93	-9.10	5.77	11.07
N11	6.39	-24.68	-13.94	-28.57

N8	-43.60	-22.24	-31.98	-53.37
N1	22.47	-13.33	-14.86	-9.19
N16	5.30	-9.60	-21.30	-25.59
N14	3.55	1.51	3.03	26.82

4.3. Power Spectrum Analysis of EEG channel 2 using Welch's Method for Positive Test Results

4.3.1. Magnitude of Delta Frequencies

As mentioned in the previous section, for the frequency analysis, a graph of the spectral density was performed in each interval, after which these values were averaged in each frequency spectra interval known in literature. The table built with all these values for every frequency (**Table A.1**) can be found in Appendix A, where it is possible to observe that the delta frequencies have a large increase in their value from the supine rest interval to 1 minute before syncope. Theta frequencies somewhat follow this phenomenon, being that in the other frequencies no relevant difference is observed. This way, only the values of delta frequencies are presented, since they are the ones with the most accentuated difference compared to the other frequency spectra, including theta frequencies.

Regarding the power of the delta waves in **Table 4.5**, the results are relatively uniform within each interval compared to what was noted with the signal amplitude. This uniformity is visible in the graph constructed with these points (**Figure 4.4**), where it is also observed that the interval where the results are more uniform is 1 minute before syncope, with values varying between 29 and 42 dB. In supine rest the values are more dispersed than in the other intervals, ranging from 14 to 38 dB The difference between these and the values in the first minute of the active phase is not as great as the difference for 1 minute before syncope, however, it is already a considerable difference, with an average of 7.53 dB (range 0.30 to 15.56 dB).

The variation in values (**Table 4.6**) that presents the most promising results for the development of the algorithm is the difference between the supine rest interval and 1 minute before syncope, since it presents a considerable increase in the values of the power spectrum, which does not happen for the other frequencies or for the patients who did not have symptoms during HUTT. Except for 4 cases, this increase in values varies between 7 and 23 dB, being that the module of the difference considering all cases has a mean of 10.19 dB.

Regarding the values in the 30-second interval, these are quite similar to the values 1 minute before syncope, with a maximum difference between the two intervals of 2.53 dB. This equality of values is easily visible in **Figure 4.4** constructed with the points in question, marked by the almost horizontality of the line from one interval to another. This way, the values of the third column of **Table 4.6** are also quite akin to the variation values of the second column, with a mean of 10.62 dB. Lastly, the results from the 10-second interval are unevenly distributed, with both an increase and a decrease in relation to the values of the 30-second interval. It is possible to infer that the values 30 seconds before somehow follow what happens 1 minute before syncope, however, the values 10 seconds before no longer follow the existing sequence.

Table 4.5 *- Power spectrum using Welch's method per interval for the magnitude in dB of delta frequency values for positive HUTT.*

POWER SPECTRUM USING WELCH'S METHOD PER INTERVAL FOR DELTA FREQUENCY VALUES - POSITIVE HUTT					
	SUPINE REST	**1ST MIN OF ACTIVE PHASE**	**1 MIN BEFORE SYNCOPE**	**30 SEC BEFORE SYNCOPE**	**10 SEC BEFORE SYNCOPE**
P1	24.96	31.84	35.69	38.22	40.82
P2	14.39	15.20	38.08	40.98	42.32
P3	20.55	36.07	27.76	29.25	28.57
P4	28.21	28.52	42.91	42.60	42.76
P5	16.43	31.99	32.01	30.85	27.56
P6	21.52	32.61	28.68	27.24	27.99
P7	23.86	38.99	31.56	33.59	31.92
P8	29.46	34.86	31.28	28.86	26.22
P9	21.53	30.41	39.60	39.75	39.80
P10	24.69	34.05	34.18	33.91	35.54
P11	22.11	29.97	33.13	34.80	35.44
P12	25.44	31.47	29.44	30.26	27.46
P13	22.06	28.35	38.15	38.78	40.72
P14	24.85	39.31	39.14	39.46	38.54
P15	26.19	28.67	29.01	30.01	28.53
P16	38.13	38.73	39.63	40.01	39.27
P17	21.64	25.89	30.71	30.89	31.91
P18	27.16	35.43	38.93	38.61	39.13
P19	21.05	29.59	35.40	35.56	36.52
P20	35.14	38.08	38.04	38.25	34.01

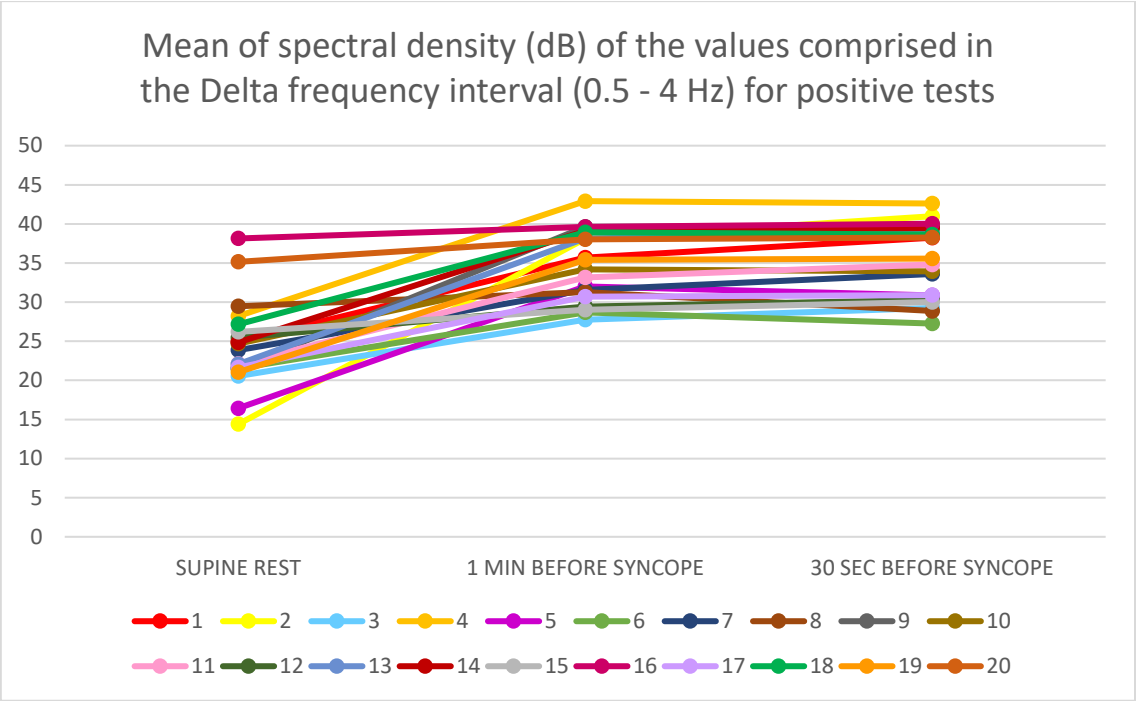

Figure 4.4 *– Mean of spectral density (dB) of the values comprised in the delta frequency interval (0.5-4 Hz) for patients with positive test results for the intervals of supine rest, 1 minute before syncope and 30 seconds before syncope.*

Table 4.6 *- Variation in the values of the power spectrum for delta frequencies between the intervals of interest and the supine rest interval for positive test results.*

Variation in the values of the power spectrum for delta frequencies between the intervals of interest and the supine rest interval - POSITIVE HUTT				
	1ST MIN OF ACTIVE PHASE – SUPINE REST	**1 MIN BEFORE SYNCOPE – SUPINE REST**	**30 SEC BEFORE SYNCOPE – SUPINE REST**	**10 SEC BEFORE SYNCOPE – SUPINE REST**
P1	6.87	10.72	13.26	15.85
P2	0.80	23.69	26.58	27.92
P3	15.52	7.20	8.70	8.02
P4	0.30	14.69	14.38	14.55
P5	15.56	15.56	14.42	11.13
P6	11.08	7.15	5.71	6.46
P7	15.12	7.70	9.73	8.06
P8	5.39	1.81	-0.59	-3.23
P9	8.88	18.07	18.21	18.27
P10	9.36	9.49	9.22	10.85
P11	7.85	11.02	12.69	13.33
P12	6.03	3.99	4.82	2.02
P13	6.28	16.09	16.71	18.66
P14	14.45	14.29	14.61	13.69
P15	2.48	2.80	3.82	2.33
P16	0.59	1.49	1.88	1.13
P17	4.25	9.06	9.25	10.27

P18	8.27	11.77	11.45	11.97
P19	8.54	14.35	14.51	15.46
P20	2.93	2.89	3.10	-1.13

4.3.2. Ratio Delta/Gamma

Due to the appearance of the spectral density graph using Welch's method, the ratio of delta/gamma frequencies was also calculated due to the presence of two lumps within the range of these two frequencies. Thus, this was calculated for all patients with positive results for VVS in all considered intervals. Due to the highly variable nature of the values and to illustrate the results more concisely, only the results of interest are presented in **Figure 4.5**, built with the values obtained for all patients in the intervals of greatest interest, these being supine rest, 1 minute and 30 seconds before syncope.

Since it depends on the values of the gamma frequencies, the results calculated for the ratio are extremely unstable, being the 30 seconds before syncope interval where the values are more uniform. The points on the graph become more and more concise from interval to interval, with supine rest being the interval that has the most dispersed results, evolving to points closer to each other in the last interval, except for 3 cases.

Regarding the difference in values between the intervals, there is a greater difference between supine rest and 1 minute before syncope, with an increase in half of the cases and a decrease in the other half. Between 1 minute and 30 seconds before syncope, the difference observed is minimal, with a maximum value in module of 0.32, existing also a relatively equal distribution among patients in terms of increase or decrease in the values.

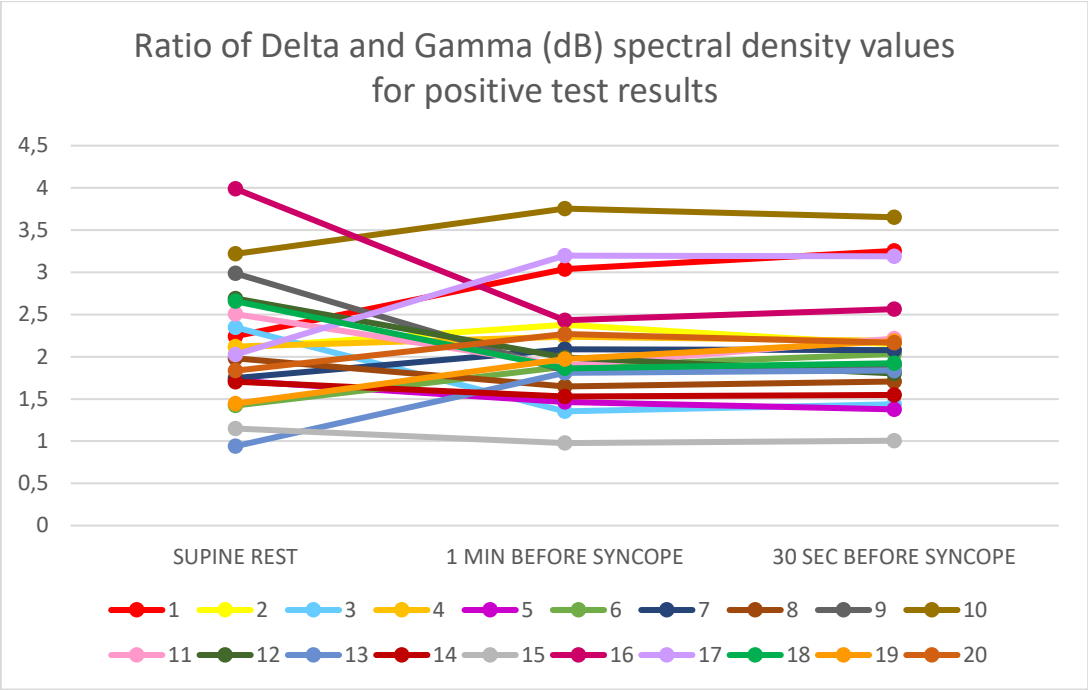

Figure 4.5 *- Ratio of delta/gamma (dB) spectral density values in each interval for positive test results for the intervals of supine rest, 1 minute before syncope and 30 seconds before syncope.*

4.4. Power Spectrum Analysis of EEG channel 2 using Welch's Method for Negative Test Results

4.4.1. Magnitude of Delta Frequencies

The same procedure that was performed for positive cases was performed for patients with negative HUTT results. The table with the spectral density values in each frequency spectrum (**Table A.2**) for these cases can be found in Appendix A. These 16 patients were further divided according to the presence of symptoms during the test in the same way as they were divided in the amplitude analysis. Once more, a difference in the values of delta frequencies was observed, so only these results will be presented (**Table 4.7**).

In patients who experienced symptoms during the test, an increase in the values from the supine rest to 1 minute before table down was observed, similarly to what happens with the positive results (visible in **Figure 4.6**). In this group of 8 patients, the results of intervals 1 minute and 30 seconds before the end of active phase have very uniform values, ranging between 31 and 39 dB. This uniformity is easily visible through the presented graph, as well as the equality of values in these two intervals. In the supine rest interval, the values are more dispersed than in the other intervals, however, are more uniform than in the positive results, ranging from 19 to 33 dB. The difference between these values and the ones in the first minute of the active phase is reiteratively not as great as the difference for 1 minute before table down, however it is already a considerable difference, with a mean of 7.06 dB (range 3.16 to 12.73 dB).

Although these results regarding the patient's state of awareness appear to be quite interesting, the values that are relevant for the development of the classifier are the ones in the supine rest interval, 1 minute and 30 seconds before table down, as well as the difference between them, presented in **Table 4.8**. In patients with presyncope symptoms, the module of the difference from the supine rest interval for 1 minute before ranges between 5.17 and 12.15 dB, with a mean of 9.82 dB. As already mentioned, the values of the interval 30 seconds before the end of the active phase are very similar to the previous interval, with a maximum value of difference between them of 2.36 dB. Therefore, the values in the third column of **Table 4.8**, which have a mean of 9.69 dB, are quite similar to the ones in the second column, with a mean of 9.82 dB. Lastly, the results of the 10 second interval before syncope have the same behavior as the results of these last intervals considered.

On the other hand, patients who did not show symptoms during HUTT have fairly distinct results from what has been observed so far in patients with positive tests and with negative tests experiencing symptoms. In this group of 8 patients, the results are quite uniform in all intervals, with no great differences in the values from interval to interval, with the exception of 1 case. This equality of values, except for patient 14, is visible in **Figure 4.7**, where the only visible differences between intervals are decreases, contrary to what happened with the rest of the cases. In the supine rest interval, the values vary between 22 and 30 dB, and the difference between these values and the ones 1 minute before table down has a maximum value of 2.45 dB, with the exception of patient 14. In **Figure 4.7** is seen the decrease mentioned in most subjects, being that in cases where there was an increase, this was minimal. By observing the graph, it is possible to infer that from 1 minute before to 30 seconds before the end of the active phase, the results obtained either are maintained or have a decrease. The results 10 seconds before syncope follow the same pattern as the previous cases, with no significant differences or pattern in any of the cases.

***Table 4.7** - Power spectrum using Welch's method per interval for the magnitude in dB of delta frequency values for negative HUTT, with the division between the patients who had symptoms during the test and those who did not.*

POWER SPECTRUM USING WELCH'S METHOD PER INTERVAL FOR DELTA FREQUENCY VALUES - NEGATIVE HUTT					
PATIENTS WITH SYMPTOMS - PRE-SYNCOPE					
	SUPINE REST	**1ST MIN OF ACTIVE PHASE**	**1 MIN BEFORE TABLE DOWN**	**30 SEC BEFORE TABLE DOWN**	**10 SEC BEFORE TABLE DOWN**
N12	29.37	33.83	35.92	35.93	36.21
N6	22.17	25.45	33.94	31.99	30.81
N4	19.41	29.28	31.31	31.26	30.81
N7	21.94	34.67	34.09	36.45	38.57
N10	24.98	33.92	33.51	33.12	32.85
N13	33.49	36.65	39.34	39.26	36.95
N15	20.94	30.20	37.62	38.40	38.35
N5	31.19	35.99	36.37	34.63	37.71
PATIENTS WITHOUT SYMPTOMS					
	SUPINE REST	**1ST MIN OF ACTIVE PHASE**	**1 MIN BEFORE TABLE DOWN**	**30 SEC BEFORE TABLE DOWN**	**10 SEC BEFORE TABLE DOWN**
N2	28.22	28.97	30.67	29.66	31.73
N3	29.97	24.67	21.84	22.54	22.80

N9	30.69	29.20	24.69	25.76	25.91
N11	30.69	31.99	28.15	28.13	28.08
N8	22.69	23.51	21.28	19.27	18.79
N1	25.99	30.72	23.24	22.84	25.59
N16	29.41	31.26	30.39	23.66	19.19
N14	19.37	27.63	28.69	29.81	33.26

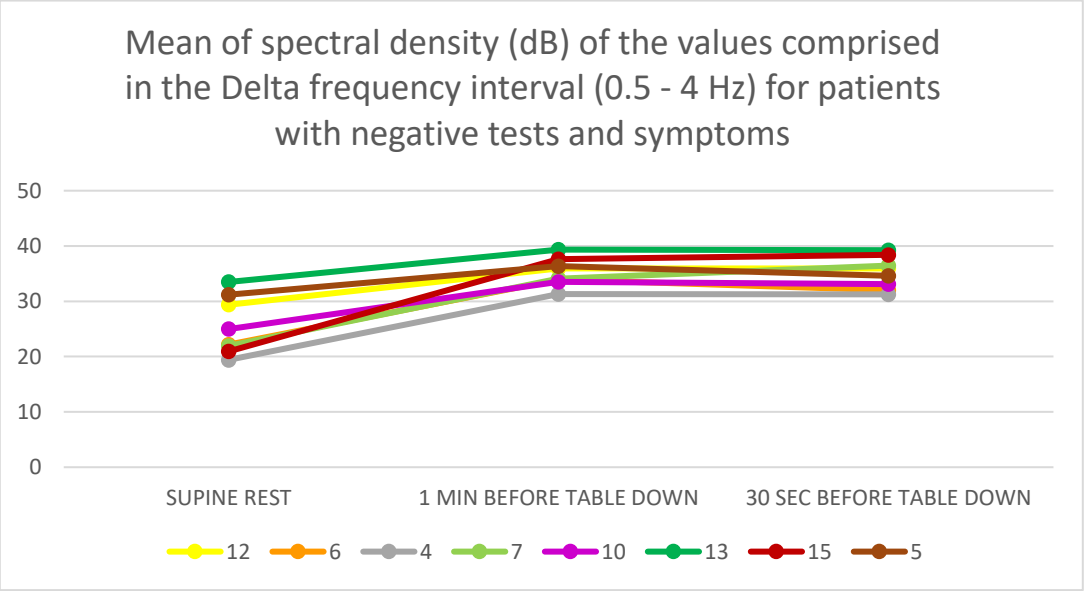

Figure 4.6 *- Mean of spectral density (dB) of the values comprised in the delta frequency interval (0.5-4 Hz) for the patients with a negative test result who demonstrated symptoms for the intervals of supine rest, 1 minute before table down and 30 seconds before table down.*

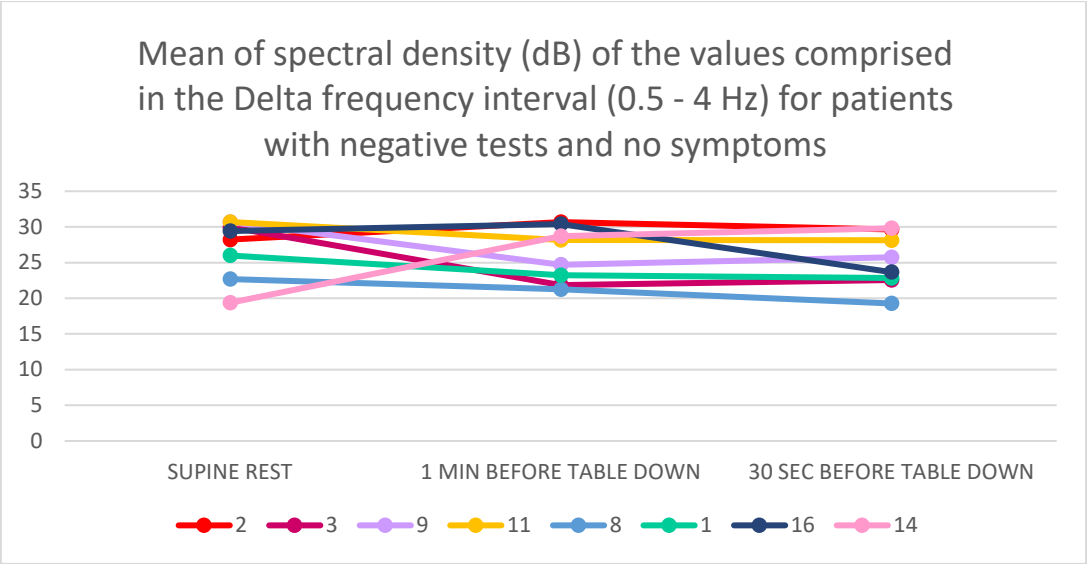

Figure 4.7 *- Mean of spectral density (dB) of the values comprised in the delta frequency interval (0.5-4 Hz) for the patients with a negative test result who did not demonstrate any symptoms for the intervals of supine rest, 1 minute before table down and 30 seconds before table down.*

Table 4.8 *- Variation in the values of the power spectrum for delta frequencies between the intervals of interest and the supine rest interval for negative test results.*

Variation in the values of the power spectrum for delta frequencies between the intervals of interest and the supine rest interval - NEGATIVE HUTT				
PATIENTS WITH SYMPTOMS - PRE-SYNCOPE				
	1ST MIN OF ACTIVE PHASE – SUPINE REST	**1 MIN BEFORE TABLE DOWN – SUPINE REST**	**30 SEC BEFORE TABLE DOWN – SUPINE REST**	**10 SEC BEFORE TABLE DOWN – SUPINE REST**
N12	4.45	6.55	6.55	6.83
N6	3.27	11.76	9.81	8.63
N4	9.86	11.89	11.84	11.39
N7	12.73	12.15	14.51	16.63
N10	8.93	8.53	8.14	7.87
N13	3.16	5.85	5.77	3.46
N15	9.25	16.67	17.45	17.40
N5	4.79	5.17	3.43	6.52
PATIENTS WITHOUT SYMPTOMS				
	1ST MIN OF ACTIVE PHASE – SUPINE REST	**1 MIN BEFORE TABLE DOWN – SUPINE REST**	**30 SEC BEFORE TABLE DOWN – SUPINE REST**	**10 SEC BEFORE TABLE DOWN – SUPINE REST**
N2	0.74	2.45	1.43	3.50
N3	-5.30	-8.13	-7.42	-7.17
N9	-1.49	-5.99	-4.92	-4.78
N11	1.29	-2.54	-2.55	-2.60
N8	0.82	-1.40	-3.41	-3.89
N1	4.72	-2.74	-3.15	-0.39

N16	1.85	0.98	-5.74	-10.21
N14	8.26	9.32	10.44	13.89

4.4.2. Ratio Delta/Gamma

For data from patients with negative tests, the same procedure of calculating the delta/gamma frequency ratio was performed, since the appearance of the power spectrum graph was similar in all cases, with the presence of the two lumps, more accentuated or not, each in the ranges of delta and gamma frequencies. The ratio values were also placed in a table with the information of all patients at all intervals, divided by the presence of symptoms during HUTT as was done in the rest of the procedures. Only the graphs (**Figure 4.8** and **Figure 4.9**) assembled with the results that are most interesting for the study in question is analyzed, which are the same as in the case of the positive tests.

Both graphs show fairly uniform results from interval to interval, with the exception of 1 or 2 cases. It is possible to see almost horizontal lines in most patients, whether they experienced symptoms or not. Regarding patients who presented symptoms, despite the distance between values being minimal, there was an increase in the values of the supine rest interval for 1 minute before the end of the active phase in most cases. Two patients had greater differences in these intervals than the other, easily visible on **Figure 4.8**, one of them being an increase and the other a decrease. Between the results from 1 minute before to 30 seconds before table down, the difference was practically null in all cases, with most patients having values in the 30-second interval lower than the values in the 1-minute interval.

Regarding patients who did not demonstrate symptoms, **Figure 4.9** also shows a small difference in results from supine rest to 1 minute before table down, which is mostly a decrease, contrary to what is verified with patients who showed symptoms during HUTT. On the other hand, the variation between the results 1 minute before and 30 seconds before, a considerable increase in values compared to the rest of the subjects is observed in patient 16, this being considered an outlier. The values of these two intervals are the ones that present greater equality of all cases from one interval to another.

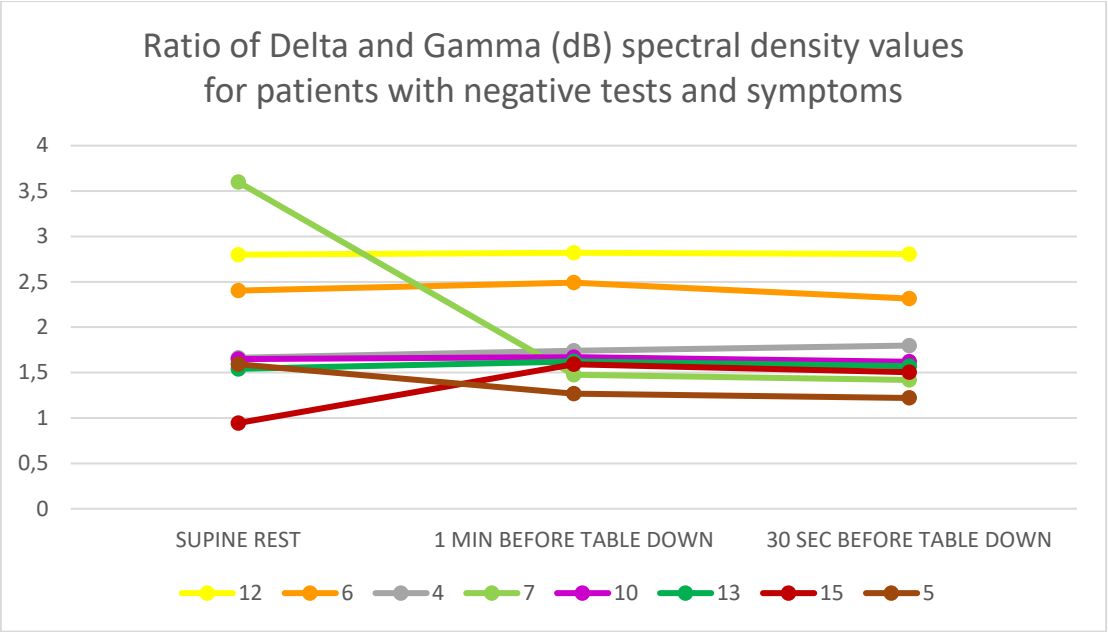

Figure 4.8 *- Ratio of delta/gamma (dB) spectral density values in each interval for patients with negative test results who demonstrated symptoms for the intervals of supine rest, 1 minute before table down and 30 seconds before table down.*

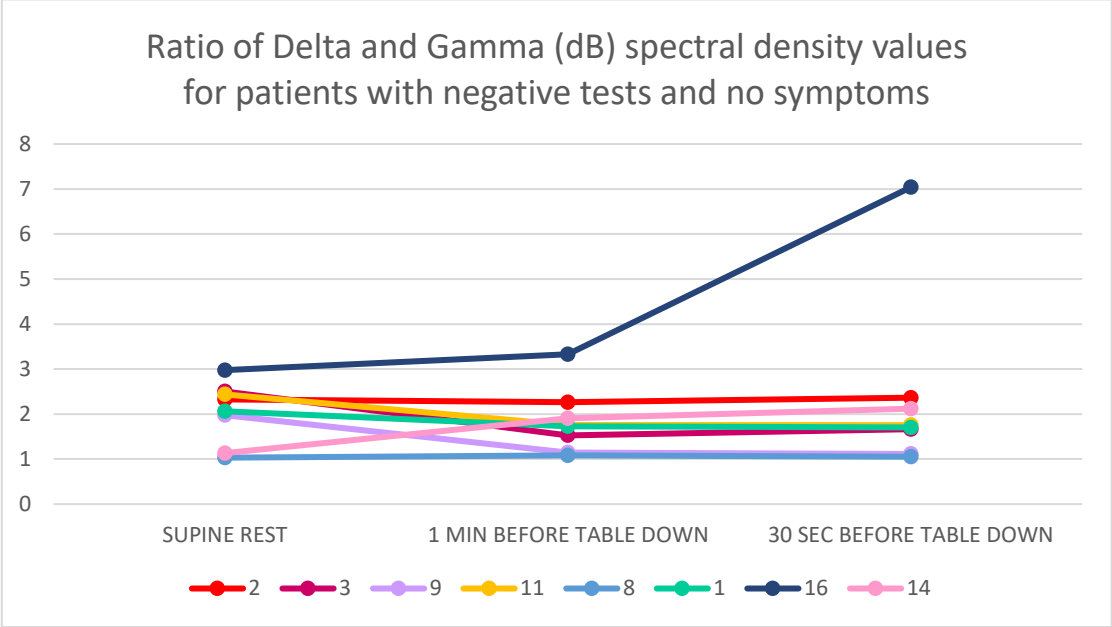

Figure 4.9 *- Ratio of delta/gamma (dB) spectral density values in each interval for patients with negative test results who did not demonstrate any symptoms for the intervals of supine rest, 1 minute before table down and 30 seconds before table down.*

4.5. Data Categorization using an Automatic Classifier

After the procedures performed with the creation and implementation of the model, as well as its training and testing, the hyperplane was created for the variation in frequency as a function of the variation in amplitude. This hyperplane was not developed for each of the variables separately, since through the graphs previously obtained with the support vectors, it was not possible to make a reliable

division in the frequency graph. Thus, and in order to make the model more reliable, the two variables were included together for the formation of the hyperplane, making the visualization of the division between the two categories became much easier. Two graphs were constructed with this division into two zones, one for the variations of the variables between the rest interval and the 1-minute interval (**Figure 4.10**), and another for the variations of the 30-second interval (**Figure 4.11**).

This way, if the results stay in the red area, the subject is categorized as a patient with a normalized situation, and as soon as the results move to the blue area, the subject would be categorized as a patient at risk of losing consciousness soon. After categorizing all the data, the next step would be to implement this classifier in a wearable EEG device that can be connected via Bluetooth to the patient's cell phone. The patient would have to use an EEG device during his/her daily life and whenever the data was marked in the category of being at risk of losing consciousness, he would be notified through a notification on his mobile phone.

In **Figure 4.10** it is possible to see the hyperplane built through the implementation of the model for the frequency and amplitude variations between the supine rest interval and 1 minute before the end of the active phase. In the figure, the crosses represent the training values, and the dots symbolize the test values. It is possible to observe that only two values were considered by the model as support vectors and that all values of each of the categories are within the zone outlined by the respective model. It is also noticed that the division between the two zones is practically vertical, depending almost only on the variation in amplitude. This observation was already possible to infer from the examination of the graphs of each variable separately (**Figure 3.11**), since in the amplitude graph it is possible to clearly separate the two categories, while in the frequency graph it is not possible, as already mentioned.

In comparison, in **Figure 4.11**, where you can see the division of categories for variations between the rest interval and 30 seconds before the active phase, these values are not divided as well as in the previous graph. In this estimate made by the model there are 6 support vectors, 4 more compared to the graph made for the 1-minute interval, meaning that there are more observations that go beyond the estimated limits of their categories. It is also possible to observe that in this case there are already 2 observations that are within the categorical zone to which they do not belong. Regarding the boundary of the division between the two zones, this one is more oblique, considering more the magnitude of the delta waves together with the amplitude, instead of what happens with the previous graph. Again, it was already possible to draw this conclusion through the graphs made individually for each variable (**Figure 3.12**), where in the frequency graph it is already possible to visualize a clearer division between the two categories. Despite a greater inclusion of the two variables for the division of the graph, this estimate presents results that are much more dispersed in relation to the 1-minute interval.

Since the test accuracy varies with each run of the program, a table is presented (**Table 4.9**) with the variability of these values for both cases through 15 runs, as well as the respective standard deviation. For the model with the results of variations between the supine rest interval and 1 minute before the end of the active phase, its accuracy had a mean value of 100% and standard deviation of 0. On the other hand, the model with the values of variations between the supine rest interval and 30 seconds before the end of the active phase had a test accuracy with a mean of 93.8%, as well as a standard deviation of 5.1.

Table 4.9 *- Variability of the test accuracy for both the 1-minute interval and the 30-seconds interval through 15 runs, as well as the respective standard deviation.*

TEST ACCURACY FOR THE 1-MIN INTERVAL		TEST ACCURACY FOR THE 30-SEC INTERVAL	
TEST ACCURACY	STANDARD DEVIATION	TEST ACCURACY	STANDARD DEVIATION
100	0	85.71	5.12
100		92.86	
100		100	
100		92.86	
100		92.86	
100		85.71	
100		100	
100		100	
100		92.86	
100		92.86	
100		100	
100		85.71	
100		92.86	
100		92.86	
100		100	

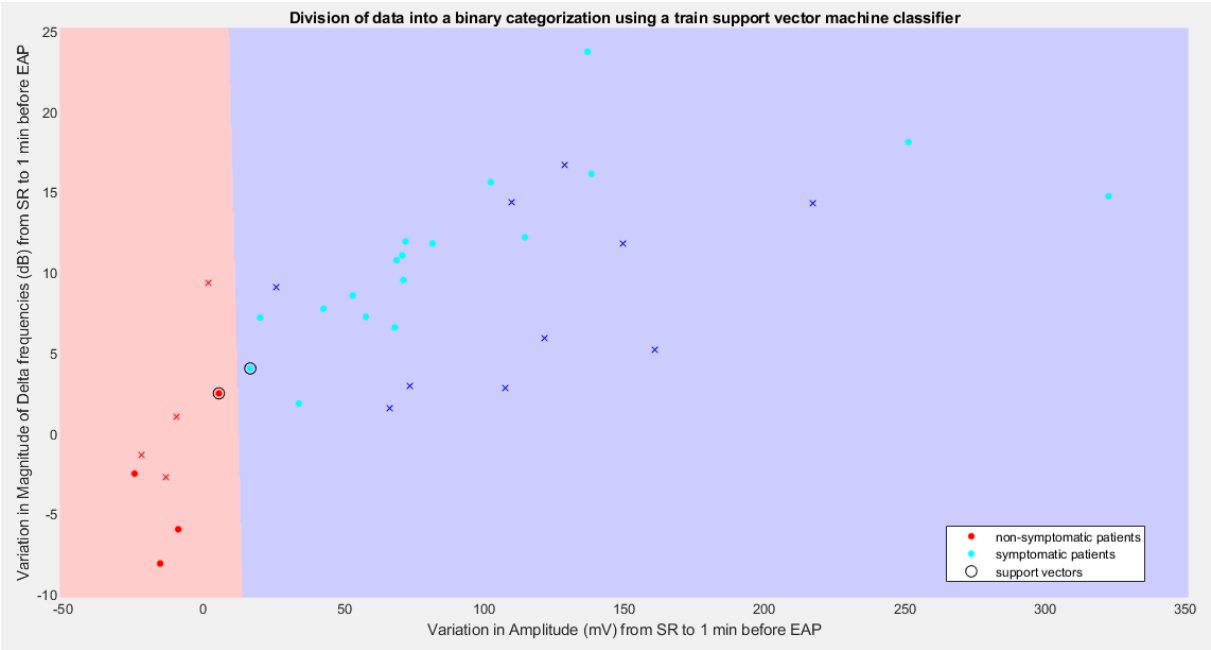

Figure 4.10 *- Division of data into a binary categorization with an hyperplane using a SVM classifier for the variation of amplitude (mV) and magnitude of delta frequencies (dB) from the supine rest interval to 1 minute before the end of active phase with the support vectors chosen by the model; EAP = end of active phase. The crosses represent the training values, and the dots symbolize the test values*

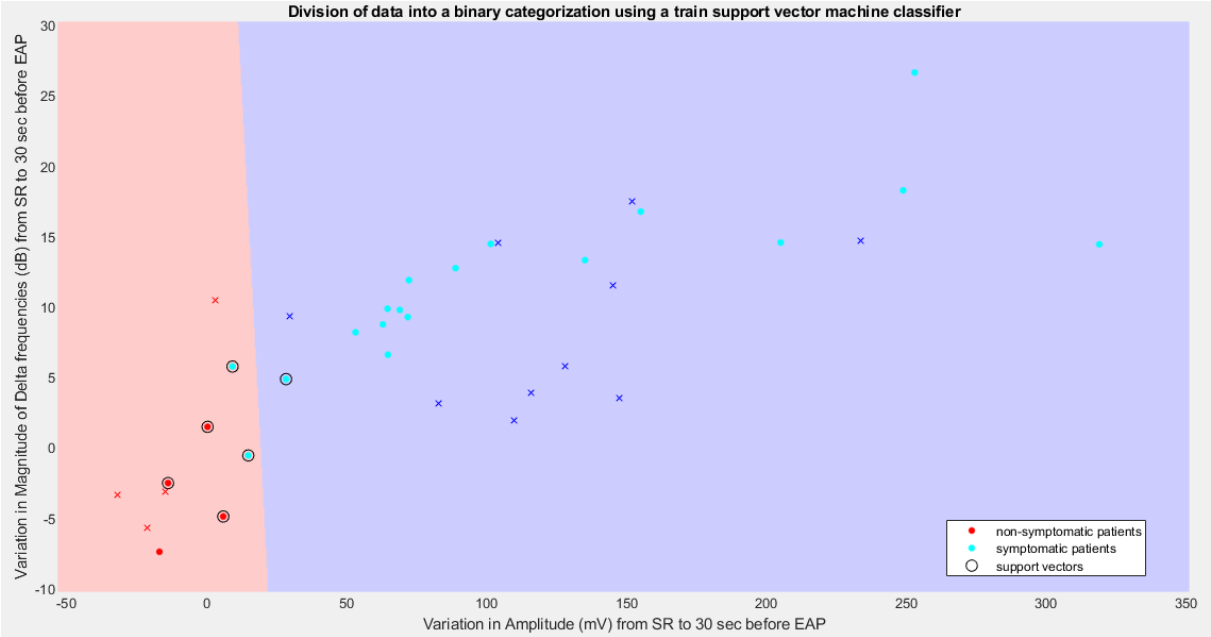

Figure 4.11 *- Division of data into a binary categorization with an hyperplane using a SVM classifier for the variation of amplitude (mV) and magnitude of delta frequencies (dB) from the supine rest interval to 30 seconds before the end of active phase with the support vectors chosen by the model; EAP = end of active phase. The crosses represent the training values, and the dots symbolize the test values*

Chapter 5. Discussion

As previously mentioned, very few studies have been carried out involving HUTT and EEG, and of those that were made, the vast majority aim to diagnose patients with suspected epilepsy or, in a smaller amount, to determine the correlation between brain waves and HUTT. Hence, no studies were found where EEG was used during the tilt test to find a pattern in the brain waves, capable of predicting the imminence of TLOC with a sufficient time gap for patients to have a safer life.

Thus, after the analysis performed to complete the proposed objective, and considering the results obtained for the analysis in amplitude and in frequency, an increase in the signal amplitude and in the spectral density corresponding to the delta waves is visible in all patients who experienced symptoms. A division was made for patients with negative tests between those who had symptoms and those who did not, since it was discussed which would be more relevant, predicting the imminence of syncope or notifying when symptoms occur. All patients who refer to the syncope unit to undergo the HUTT complain of symptoms characteristic of SVV. Despite having a negative test, it does not mean they are not affected by this condition, since the symptoms that led them there decrease their quality of life. Many of these patients who develop symptoms during the test end up not losing consciousness due in several cases to a very exacerbated sympathetic nervous system, being too aware to all stimuli, as well as, in a smaller portion of these patients, the performance of the counter-pressure maneuvers mentioned above.

Therefore, it was discussed which would be more useful and preferable in this situation, detecting symptoms or detecting syncope. Although the detection of syncope is the most obvious thing to do and the instant when the signal would probably have more variations, it was possible to observe through the results obtained both for the frequency analysis and for the amplitude analysis of the interval 10 seconds before syncope, that these do not follow the same pattern observed in the intervals 1 minute and 30 seconds before syncope. This is due to the fact that during this period of time the patient is already on the verge of losing consciousness, many of them being already in a limbo between conscious and syncope. During this interval, the results both show considerable increases in relation to the previous interval considered, as well as decreases between these intervals, and stabilization of values in some cases. This way, this interval was not used for the development of the classifier, not only due to the nature of its values, presenting evidence that the subject was no longer fully conscious, but also because the time gap is too short, it would not provide enough time to warn a patient that no longer has leeway or awareness to stop whatever he is doing.

It was then concluded that what would be more reliable and more adjusted to the intended objective, which involved giving patients a better quality of life, would be to develop the prediction classifier based on symptoms and not on syncope. With this objective in mind, the division in the negative test results section was made between patients who had symptoms and those who did not. In addition to this division, patients with negative tests who experienced signs of VVS were considered to have had a positive test, also due to the similarity of the EEG signal obtained. In the case of these 8 patients, an increase in amplitude of the filtered signal was observed in the data obtained, as well as an increase in the spectral density of the delta frequencies, similarly to the pattern found in the case of the 20 patients with positive tests.

Regarding the results obtained from the amplitude analysis, as already mentioned, an increase in the amplitude of the EEG signal was observed in the 28 patients who presented symptoms during the test. This increment is due to an increase in brain activity, due to discomfort caused by the symptoms they presented. However, an increase in brain activity encompasses all kinds of activities or interactions that the patient might do. For instance, the simple action of blinking an eye produces a signal of about 400 mV. This phenomenon can be observed by the amplitude values in the first minute of the active phase. This interval is a period in which the subject is exposed to many interactions, so one would expect a reaction on his part translated into an increase in brain activity, according to the level of exacerbation of the subject's sympathetic nervous system. Expectations are in accordance with the results obtained, since an increase in signal amplitude in this interval is verifiable in the 36 cases, regardless of the symptoms presented. This reflects the patient's state of awareness for external stimuli, no matter what the outcome of the HUTT.

In the 8 patients who did not show symptoms during the test, the increase in the amplitude from the supine rest interval to 1 minute before table down is inferior to the increase for the first minute of the active phase. However, and contrary to this fact, the variation found from supine rest to 1 minute before table down is superior in the 28 patients with symptoms to the variation for the first minute of the active phase. This feature in the data may solve one of the major limitations expected for this study. The latter is the increase in brain activity when performing small daily activities, triggering a false TLOC warning to the patient. Since there is a difference in the values of brain activity when the patient is reacting to stimuli and when he is experiencing symptoms characteristic of SVV, the developed classifier is more likely to be reliable, which can only be confirmed by its implementation in the practical context of the subjects' daily lives.

After analyzing the values of the interval of the first minute of the active phase and discarding the values of the interval of 10 seconds before syncope, it is necessary to proceed with the analysis of the amplitude values that are most essential for the study and that contribute most to the development of the classifier based on the pattern found. The values of the supine rest interval are only used as a reference to make the difference with the other intervals and to have a comparison term. The alertness of each subject varies from patient to patient, so what is most important in this case is the increment in this state, and the comparison of the EEG data of a patient in a relaxed state with a state of impending syncope. Thus, the two intervals where it is essential to analyze the results and compare them with the supine rest interval through the difference are 1 minute before and 30 seconds before.

For this analysis, it is important to consider the division of negative tests, being essential to compare the 28 cases of patients who developed symptoms during the HUTT with the 8 cases of patients who did not experience any symptoms. In literature, the higher the amplitude in an EEG signal, the stronger the signal is, indicating a more synchronized brain activity from multiple neurons. This is due to the fact that the amplitude of the EEG pattern is the strength of the pattern in terms of microvolts of electrical energy [72]. Thus, in these 28 cases where there was always an increase in the amplitude from the supine rest interval to the intervals before the end of the active phase, resulting in a stronger signal, which would be expected, since the exposure to very strong symptoms leave the patient quite prostrate, having this effect on the signal.

The variations in values in the two cases are quite similar, with only minor differences between them. Thus, and since the two intervals are relatively close and their only difference is the duration, it is important to discuss which is the most suitable and whether in each case its implementation and use by the patient would be feasible. Theoretically, the best would always be the one with the longest

antecedence, this being 1 minute before syncope, since it includes more data and allows the patient to be warned with 30 seconds of anticipation, compared to the interval 30 seconds before syncope. It is visible in **Figure 4.1** that there is a further increase in amplitude values from 1 minute before to 30 seconds before. This increase was already expected since the closer you get to syncope, the symptoms become more and more unbearable, increasing brain activity through the increase in functioning synapses. Despite this increase, there is also a decrease in some cases, more recurrent in positive cases, since this interval is more difficult to predict the behavior. This decrease may be associated with the phenomenon that happened with the data in the 10-second interval, as it is hard to know whether 30 seconds before the end of the active phase the patient would be conscious enough, considering only the positive tests, perhaps being already in the state of limbo mentioned and leading to a decrease in signal strength, translated into a decrease in amplitude.

This increase from the supine rest interval to the ones prior to the end of the active phase was not observed in the 8 patients who did not experience symptoms as there was no reaction on their part. There was no greater synchronization of brain activity because during the active phase they did not have any factors that increased the strength of the signal, this being similar to the signal at supine rest, as it is seen in **Figure 4.7**. In this figure, in some cases, there is even a decrease that is justified by the fact that the patient is even more relaxed, since in the supine rest interval the vast majority of patients are quite nervous with the test, due to the anticipation of the unknown, as most rumors circulating about it claim that it is very painful to do. Thus, at the end of the active phase, patients who have not experienced any kind of reaction to nitrates and change of position are much more relaxed knowing that the test is almost over, justifying the decrease in the amplitude.

Consequently, it is preferable to use the data 1 minute before to develop the classifier since these are more reliable. There is always an increase in the values from the supine rest interval to the latter, therefore, data are consistent and constant. The increase quantitatively will depend on the number of synapses that are made during this phase, on the state of alertness and on the magnitude of the symptoms of each patient. However, there is always a considerable variation reflecting the imminence of the end of the active phase. The most important thing to understand is whether this change in amplitude is only due to the symptoms the patient is experiencing or whether there is a change in the synapses made by the brain regardless of the symptoms. This is because if it were only coming from symptoms, the classifier would not be viable for patients who do not have symptoms prior to syncope. Since there were 2 patients in the case of positive tests, as mentioned in section 3.1.1, who did not signal the existence of any type of symptoms and who also presented an increase in amplitude, it can be inferred that this is due not only to the symptoms the patient is experiencing translated into an increase in synapses performed due to discomfort, but also just an increase in synapses performed without any kind of apparent physical trigger.

Since the EEG is an extremely variable test, with numerous variables that can easily change its amplitude, as can be seen from the results obtained, it was not possible to analyze only this variable, otherwise the classifier would not be reliable. Considering the amount of material—other brain tissue, the skull, skin and hair—between the brain and the electrodes, only signals passing through neurons within the outer cortex that can be measured by EEG. All these variables make the EEG, especially its amplitude, an exam very prone to variations. Thus, the signal frequency is the most important variable to be studied, given that its values convey a lot of information that is not so variable and is not subject to changes by the patient's alertness or state of mind. The higher the frequency of the signal, the more work the brain is doing, and the greater the intensity of the brain activity. The fact that the frequency of

the EEG signal is divided into frequency spectrum intervals known in the literature, as well as the patient's state of mind in each one of them, greatly facilitates the study of this variable.

With the spectral density using the Welch method made for the EEG signal of each patient and for each frequency range, it is possible to extract information about the magnitude of the various frequency components of a signal. By looking at the spectrum, one can find how much energy or power is contained in the frequency components of the signal. Since only one different pattern was found among the patients who had symptoms and patients without symptoms, just these data were used for the development of the classifier. Although delta waves generally only occur during deep (dreamless sleep), they are usually high amplitude, because much of the brain is focused on the same activity. As mentioned in section 1.3.1.1, delta waves are an abnormal finding in awake adults, however, have been reported to occur on individuals with absence seizures, being the mechanism of this condition very similar to syncope. These findings confirm the pattern that occurred with the results obtained, with a large increase in magnitude of delta waves in the intervals before syncope, as well as a very high amplitude in these same intervals.

With this information in mind, it is possible to infer that the increase in spectral density of delta frequencies is due, similarly to what happens with amplitude, not only to the strong symptoms experienced by patients, but also to changes in the intensity of brain activity per se. The values of delta frequencies somewhat mimic what happens to amplitude. There is an increase in its values in all patients from the supine rest interval to the first minute of the active phase, for the same reasons already mentioned. Similarly to amplitude, this increase is never greater, in the case of patients with symptoms, than the increase from the supine rest interval to the intervals before the end of the active phase The latter is another variable to confirm that the changes in the signal due to the alertness of the patient to all kinds of stimuli are not the same as when he is exposed to symptoms characteristic of SVV. This allows the classifier to have a higher level of confidence in the patient's everyday context.

In the intervals before the end of the active phase, it was observed the greatest discrepancy between the values of the supine rest interval for especially 1 minute before syncope. From supine rest to the interval of 30 seconds, the same thing that happened with the amplitude can be observed in the results, with the data both increasing and decreasing, for the same reason already explained. Thus, the existing increase of the supine rest interval to 1 minute before was given more priority to develop the classifier, since it is an interval with more consistent data, more striking, and with a larger time window before the subject loses consciousness. Similarly to the amplitude, in the 8 cases where the patients did not present symptoms, not only there was not an increase in the values, as was even observed a decrease in the values of delta frequencies. This is justified, as in the amplitude, by the lack of reaction on the part of the patient, causing the initial phase to be the same as the active phase, with the small difference that the patient is no longer nervous at the end of the exam, justifying the small decrease.

This variations in frequency are justified by the fact that each of the five EEG frequencies known is correlated with a different level of arousal of the cerebral cortex. Cortical arousal refers to the firing patterns of the neurons of the cerebral cortex. As the frequency of the EEG pattern decreases, the level of cortical arousal diminishes. Consequently, as the level of arousal diminishes, the EEG pattern gets higher in amplitude. Hence, in the EEG frequency and amplitude are inversely related. An EEG with a low frequency and a large amplitude usually reflects a more synchronized brain wave pattern (the groups of cells are acting in concert), whereas an EEG with a low amplitude and a high frequency generally corresponds with a desynchronized brain wave pattern (the groups of cells are involved in separate activities). This level of cortical arousal is generally correlated with various psychological and

behavioral states [72]. Taking into account the pattern found in the results obtained, it is concluded that there is an high synchronization of the brain wave pattern, due to the increase in the signal amplitude, as well as the increase in the magnitude of the delta waves.

During a syncopal episode, the EEG usually is said to demonstrate a diffusely slowed background initially followed by high-voltage delta activity, typically after an interval of about 10 seconds or so and sometimes by transient electrocerebral silence if the hypoperfusion persists. Recovery occurs in the reverse order. As already studied by other investigations, which were presented in section 2.2.1, the mechanisms of VVS translated into an EEG signal are characterized by an increase in amplitude, as well as an increase in the voltage of the delta waves prior to syncope. This fact was also verified in the results obtained, where these variations were used to develop a classifier model based on the categorization of these data. No study was found that performed this procedure for the early detection of syncope, only that analyzed and understood what kind of alterations the EEG has during VVS.

Regarding the categorization results obtained through the classifier, it can be concluded that it was successful, since in the case of the 1-minute interval the model was developed with an accuracy of 100%, and in the 30-secont interval with an accuracy with a mean of 94.15%. At first glance, and as already mentioned, the results of variations between the supine rest interval and the 1-minute interval show more promising results, since the division between the two categories is clear, with all observations within the area where they belong, existing only two support vectors. This model also had an accuracy with a mean of 100%, demonstrating concise results. However, this division is practically vertical, depending almost only on amplitude and not frequency, which is a limitation caused by a small sample of data. In the graph for the 30-second interval, this division is more oblique, but contains observations within the area where they do not belong and with more support vectors. The same limitation is seen in the two graphs—the hyperplane corresponding to patients without symptoms should have a frequency variation limit, that is, the red area should only be in the surroundings of the non-symptomatic observations. However, these limitations are the result of a small sample of data. Despite this, it is inferred that the model has some reliability, having managed to correctly categorize all observations, and it is thought that with a larger number of samples, it can be implemented in a practical context. Taking into account the benefits and implications of each of the graphs already exposed, it is concluded that the results for the 1-minute graph are more promising, both due to the better division of the data, but also due to the fact that this is a larger interval, allowing the patient a greater margin of maneuver in advance. It should also be noted that it was not possible to verify whether these variations occurred in data from patients who do not suffer from characteristic symptoms of this condition in their daily lives.

Since the values with the best results were the difference between the rest interval and 1 minute before the end of the active phase, it is important to realize whether this is an interval that would allow achieving the objective of this study in a practical context. That is, to discuss whether 1 minute before unconsciousness is sufficient for certain everyday activities and what is the maximum antecedent time limit within which the classifier can be applied. It is estimated that for activities like driving, swimming or cooking, for example, 1 minute in advance is more than enough to stop what the subject is doing and put himself in a safe position to perform the counter-pressure maneuvers instructed. This way, and theoretically, the proposed objective would be fulfilled. Once the classifier is put to the test in a practical context, these findings could be implemented. Regarding the maximum time, an interval with more antecedence was not chosen, since it would probably be more inconstant and improbable, not knowing if it was already above enough of the syncope for the EEG to have such a big change. Thus, this interval was chosen as it was not only enough before syncope to give the subject room to do various activities, but also close enough to syncope for the EEG to show considerable differences.

The results obtained from the calculation of the ratio are only to assess the patient's state of mind, not contributing to the pattern found for the development of the classifier. The calculation of the ratio between two frequency spectra has been used in several studies to assess mental stress through EEG data. It can then be concluded from the observation of the obtained graphs that it differs a lot from patient to patient in the supine rest interval, with these being more uniform in the intervals before the end of the active phase. **Figure 4.9**, which contains the data on the ratio of patients who did not experience symptoms, is where there are less changes in this value from interval to interval, thus demonstrating that the mental stress state of these patients was maintained throughout the test.

Ultimately, and taking into account the data collection methodology and the results obtained, it is possible to conclude that the setup of this experiment can be simplified, since although the band contains two pairs of electrodes and thus two channels, only the channel 2 was used for data analysis, due to the presentation of various artifacts and periodic variations of high amplitude in the signal, which, having not found justifications for such events, it is deduced that they are due to interference in the band associated with a bad construction. Since the results obtained in the analysis carried out on channel 2 of the EEG present very interesting and promising outcomes, it can be inferred that the study in question could be carried out with a setup of only one electrode, greatly simplifying the construction and idealization of a wearable device that patients could use in their daily lives without any restrictions.

5.1. Limitations of the Study

In addition to all the limitations adjacent to HUTT already mentioned in section 2.1.4, it is important to identify others that are associated with this study in particular. First, a very selected population in a highly monitored setting was analyzed in which syncope has been induced with a standardized procedure. Therefore, the same findings may not be true in either spontaneous vasovagal syncope or syncope from other causes. In particular, spontaneous syncope determines a loss of postural tone with a consequent sudden fall. Such an event allows immediate recovery of cerebral blood flow and is considered a protective mechanism. Because in the HUTT patients are secured to the tilt table, it may take a period of time to return to the supine position, which differs depending on the technical characteristics of the different laboratory tables. This time interval may contribute to the relevance of symptoms and hemodynamic and EEG modifications.

Besides the limitations of the environment from which the test was inserted, there are also limitations associated with the equipment used to collect the EEG data. It was found during data collection that the equipment had to be well positioned, tight enough and without hair or any other type of impediment in front of the electrodes. These features are very difficult to maintain throughout the test as there are many movements involved on the patient's part, whether reflexive, purposeful or associated with table movement. Additionally, to measure an EEG as accurately as possible it is necessary that the electrodes are placed on a clean surface, which in this case were the skin. During the test, many patients showed symptoms of sweating, causing the accuracy of data collection to decrease more. Moreover, it was found during data analysis that EEG channel 1 data contained too much noise and artifacts probably associated with poor band formation, which is another limitation of the study, since only one channel was analyzed.

Finally, one must consider also the limitations mentioned above, which are the sample size analyzed for the study. As was already mentioned above in the discussion about the classifier, this small sample of data caused the division made by the hyperplane to be almost vertical in the two cases, as well as a lack of upper limit in the variation of frequency. Since no tests were purposely scheduled for this investigation, there was some difficulty in obtaining data from patients with positive tests and characteristic symptoms of SVV. There is also an exacerbation of the sympathetic nervous system in each patient, which varies from subject to subject and greatly influences the EEG signal obtained, depending on this exacerbation and the interactions occurring around the subject. Finally, something that can really influence the categorization done by the classifier is the measurement of the brain waves by a wearable EEG band in a practical context. Although several studies have already studied the behavior of brain waves during a syncopal episode, and this was similar to the signal obtained, there is a possibility that the same pattern can be found during the performance of daily activities or due to other types of medical reactions, leading to categorization by the classifier and false warning to the patient. However, this limitation can only be confirmed and tested when the algorithm is implemented and put into practice.

Chapter 6. Conclusion

As was described throughout this study, VVS is a condition that affects a large proportion of the population and, although it is not mortal, on the onset of TLOC, the fall can lead to serious injuries. As already described, EEG is a tool that truly helps to understand what kind of changes are occurring in different parts of the human brain. With the constant development of devices that allow constant EEG monitoring, and with its implementation in the context of the daily lives of patients, it will be possible to predict and anticipate many conditions that would not be possible without this monitoring, since the brain is the control of the entire body, being the first place where these changes are verified. Thus, it is expected that the development of EEG wearables will be a great tool, in the anticipation of various conditions, its behavior in these situations only needs to be studied and the algorithm implemented.

With this objective in mind, in this study we managed to find a pattern in the signal of patients who had symptoms by studying the data taken by monitoring the EEG during the HUTT. Despite the small sample of patients and all the inherent limitations mentioned above, it is concluded that the variables chosen to analyze the data were correct, as well as the way in which they were analyzed. Furthermore, the pattern found in the magnitude of the delta waves, as well as in the amplitude, agrees with data already verified by other studies, reinforcing and confirming the discoveries made.

Among the advantages that this study has compared to those who had already correlated EEG signal and the HUTT, this one has the great advantage that the data was collected already with a wearable EEG device and not with the classic wired EEG system, being therefore the pattern and the algorithm found most adequate for the future work that is imposed. All studies that evaluated the relationship of the two themes, collected data with a classic 10-20 positioning EEG system, which is much more reliable since the movement made by the patient is practically nil, and therefore not adapted to the challenges posed for researches with this objective that involve implementing what was discovered in the practical context of the patient's daily life, which will only be possible if the data are collected by a wearable EEG.

Thus, it is concluded that the study carried out has very promising results in terms of the pattern found in the data collected, as well as in its classification, which is why it is a very innovative study and that with future work it could be very useful in the lives of many patients with this condition. The work to be done in the future is precisely through implementing the findings made in this research, more specifically, the idealization of a new EEG wearable with only one electrode and a more simplified system, as well as the algorithm found, on a mobile EEG wearable connected to the patient’s mobile phone, enough for the patient to be able to do all their normal life with it, and test the work done in the context of the day-to-day life of several patients, overcoming all the aforementioned limitations.

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Appendix A

Table A.1 *- Power spectrum using Welch's method per frequency spectra per interval for positive test results.*

POWER SPECTRUM USING WELCH'S METHOD PER FREQUENCY SPECTRA PER INTERVAL - POSITIVE HUTT						
		DELTA (0.5-4 Hz)	**THETA (4-8 Hz)**	**ALPHA (8-12 Hz)**	**BETA (12-30 Hz)**	**GAMMA (30-35 Hz)**
P1	**SUPINE REST**	24.97	23.85	21.56	15.11	11.13
	1ST MIN OF ACTIVE PHASE	31.85	30.34	27.05	15.53	10.40
	1 MIN BEFORE SYNCOPE	35.69	34.20	30.87	17.74	11.75
	30 SEC BEFORE SYNCOPE	38.23	36.90	33.54	19.51	11.75
	10 SEC BEFORE SYNCOPE	40.82	40.19	36.67	20.42	11.00
P2	**SUPINE REST**	14.40	13.45	11.74	8.57	6.84
	1ST MIN OF ACTIVE PHASE	15.20	14.03	11.71	5.84	2.96
	1 MIN BEFORE SYNCOPE	38.09	36.68	33.55	21.70	16.01
	30 SEC BEFORE SYNCOPE	40.98	39.77	36.64	24.96	19.09
	10 SEC BEFORE SYNCOPE	42.32	41.84	38.61	25.86	19.25
P3	**SUPINE REST**	20.55	19.20	16.49	10.93	8.75
	1ST MIN OF ACTIVE PHASE	36.08	34.60	31.33	20.01	15.43
	1 MIN BEFORE SYNCOPE	27.76	26.59	24.35	21.33	20.52
	30 SEC BEFORE SYNCOPE	29.26	28.17	25.74	21.33	20.34
	10 SEC BEFORE SYNCOPE	28.57	28.01	25.59	21.09	20.07
P4	**SUPINE REST**	28.21	26.99	24.38	16.95	13.31
	1ST MIN OF ACTIVE PHASE	28.52	27.22	24.44	17.16	14.49
	1 MIN BEFORE SYNCOPE	42.91	41.47	38.23	26.02	19.18
	30 SEC BEFORE SYNCOPE	42.60	41.35	38.12	26.04	19.46
	10 SEC BEFORE SYNCOPE	42.77	42.28	39.06	26.95	20.16
P5	**SUPINE REST**	16.44	15.51	13.77	10.90	9.58
	1ST MIN OF ACTIVE PHASE	32.00	30.59	27.51	17.05	13.19
	1 MIN BEFORE SYNCOPE	32.01	31.11	29.22	24.41	21.84
	30 SEC BEFORE SYNCOPE	30.86	30.25	28.67	24.88	22.42
	10 SEC BEFORE SYNCOPE	27.57	27.61	26.33	23.46	21.87
P6	**SUPINE REST**	21.53	20.59	18.74	15.69	15.14
	1ST MIN OF ACTIVE PHASE	32.61	31.23	28.24	19.93	16.69
	1 MIN BEFORE SYNCOPE	28.68	27.52	25.04	18.15	15.24
	30 SEC BEFORE SYNCOPE	27.24	26.16	23.59	16.38	13.40
	10 SEC BEFORE SYNCOPE	28.00	27.45	24.79	14.65	9.66
P7	**SUPINE REST**	23.86	22.79	20.66	16.19	13.66
	1ST MIN OF ACTIVE PHASE	38.99	37.65	34.70	24.04	17.11
	1 MIN BEFORE SYNCOPE	31.57	30.25	27.48	19.52	15.12
	30 SEC BEFORE SYNCOPE	33.60	32.39	29.50	20.65	16.17
	10 SEC BEFORE SYNCOPE	31.93	31.25	28.26	19.53	15.44

P8	SUPINE REST	29.47	28.09	25.15	17.74	14.87
	1ST MIN OF ACTIVE PHASE	34.86	33.57	30.73	21.73	18.01
	1 MIN BEFORE SYNCOPE	31.28	29.94	27.12	20.91	18.98
	30 SEC BEFORE SYNCOPE	28.87	27.68	24.94	18.68	16.92
	10 SEC BEFORE SYNCOPE	26.23	25.42	22.51	14.85	11.88
P9	SUPINE REST	21.54	20.42	18.12	11.04	7.21
	1ST MIN OF ACTIVE PHASE	30.42	29.10	26.20	14.47	8.54
	1 MIN BEFORE SYNCOPE	39.61	38.32	35.52	26.92	21.60
	30 SEC BEFORE SYNCOPE	39.75	38.58	35.63	26.42	20.93
	10 SEC BEFORE SYNCOPE	39.81	39.32	36.33	26.71	21.04
P10	SUPINE REST	24.69	23.21	20.08	10.85	7.67
	1ST MIN OF ACTIVE PHASE	34.06	32.56	29.23	16.09	11.31
	1 MIN BEFORE SYNCOPE	34.19	32.63	29.15	14.69	9.10
	30 SEC BEFORE SYNCOPE	33.92	32.51	29.05	14.70	9.29
	10 SEC BEFORE SYNCOPE	35.55	34.80	31.35	17.47	12.13
P11	SUPINE REST	22.11	21.03	18.80	12.46	8.83
	1ST MIN OF ACTIVE PHASE	29.97	28.63	25.82	18.84	16.00
	1 MIN BEFORE SYNCOPE	33.14	31.72	28.69	20.67	17.51
	30 SEC BEFORE SYNCOPE	34.81	33.48	30.24	20.20	15.71
	10 SEC BEFORE SYNCOPE	35.45	34.81	31.68	20.85	15.46
P12	SUPINE REST	25.45	24.45	22.34	14.91	9.46
	1ST MIN OF ACTIVE PHASE	31.48	30.12	27.17	17.04	11.64
	1 MIN BEFORE SYNCOPE	29.45	28.18	25.46	17.78	14.78
	30 SEC BEFORE SYNCOPE	30.27	29.13	26.39	19.19	16.80
	10 SEC BEFORE SYNCOPE	27.47	26.78	23.92	13.56	8.11
P13	SUPINE REST	22.07	21.34	20.13	21.01	23.46
	1ST MIN OF ACTIVE PHASE	28.35	27.05	24.34	17.74	15.53
	1 MIN BEFORE SYNCOPE	38.16	36.71	33.51	24.23	21.07
	30 SEC BEFORE SYNCOPE	38.78	37.50	34.28	24.35	21.10
	10 SEC BEFORE SYNCOPE	40.73	40.16	36.80	24.80	21.04
P14	SUPINE REST	24.85	23.78	21.62	16.84	14.58
	1ST MIN OF ACTIVE PHASE	39.31	37.89	34.69	22.96	17.84
	1 MIN BEFORE SYNCOPE	39.14	37.79	34.79	27.20	25.59
	30 SEC BEFORE SYNCOPE	39.47	38.28	35.23	27.24	25.50
	10 SEC BEFORE SYNCOPE	38.55	38.06	35.10	27.00	25.09
P15	SUPINE REST	26.20	25.27	23.64	22.90	22.77
	1ST MIN OF ACTIVE PHASE	28.68	27.83	26.45	27.06	28.03
	1 MIN BEFORE SYNCOPE	29.01	28.31	27.39	28.78	29.68
	30 SEC BEFORE SYNCOPE	30.02	29.41	28.40	29.38	29.90
	10 SEC BEFORE SYNCOPE	28.53	28.63	27.96	28.74	29.56
P16	SUPINE REST	38.14	36.92	34.09	20.13	9.56
	1ST MIN OF ACTIVE PHASE	38.74	37.59	34.91	22.44	13.99
	1 MIN BEFORE SYNCOPE	39.63	38.38	35.50	23.29	16.30
	30 SEC BEFORE SYNCOPE	40.02	38.88	35.88	23.06	15.61

	10 SEC BEFORE SYNCOPE	39.27	38.78	35.66	22.80	16.01
P17	**SUPINE REST**	21.64	20.81	19.07	13.81	10.68
	1ST MIN OF ACTIVE PHASE	25.90	24.66	22.05	14.20	10.31
	1 MIN BEFORE SYNCOPE	30.71	29.31	26.24	15.09	9.61
	30 SEC BEFORE SYNCOPE	30.90	29.65	26.63	15.35	9.69
	10 SEC BEFORE SYNCOPE	31.91	31.24	28.14	17.16	12.90
P18	**SUPINE REST**	27.16	25.89	23.23	15.23	10.22
	1ST MIN OF ACTIVE PHASE	35.43	34.06	31.09	21.59	16.92
	1 MIN BEFORE SYNCOPE	38.93	37.45	34.18	24.39	20.92
	30 SEC BEFORE SYNCOPE	38.62	37.32	34.07	23.81	20.09
	10 SEC BEFORE SYNCOPE	39.13	38.53	35.24	24.08	20.08
P19	**SUPINE REST**	21.05	20.08	18.28	15.75	14.57
	1ST MIN OF ACTIVE PHASE	29.60	28.16	25.11	17.01	13.91
	1 MIN BEFORE SYNCOPE	35.41	33.89	30.57	21.38	17.95
	30 SEC BEFORE SYNCOPE	35.56	34.18	30.79	20.59	16.28
	10 SEC BEFORE SYNCOPE	36.52	35.74	32.20	20.27	15.31
P20	**SUPINE REST**	35.15	33.73	30.61	21.75	19.15
	1ST MIN OF ACTIVE PHASE	38.09	36.71	33.64	23.20	18.95
	1 MIN BEFORE SYNCOPE	38.04	36.58	33.37	22.38	16.76
	30 SEC BEFORE SYNCOPE	38.26	36.97	33.76	22.82	17.66
	10 SEC BEFORE SYNCOPE	34.01	33.50	30.70	21.73	17.82

Table A.2 *- Power spectrum using Welch's method per frequency spectra per interval for negative test results.*

POWER SPECTRUM USING WELCH'S METHOD PER FREQUENCY SPECTRA PER INTERVAL - NEGATIVE HUTT						
PATIENTS WITH SYMPTOMS - PRE-SYNCOPE						
		DELTA (0.5-4 Hz)	**THETA (4-8 Hz)**	**ALPHA (8-12 Hz)**	**BETA (12-30 Hz)**	**GAMMA (30-35 Hz)**
N12	**SUPINE REST**	29.38	28.07	25.25	15.73	10.49
	1ST MIN OF ACTIVE PHASE	33.84	32.55	29.73	20.46	16.38
	1 MIN BEFORE TABLE DOWN	35.93	34.51	31.35	18.94	12.74
	30 SEC BEFORE TABLE DOWN	35.93	34.70	31.58	19.26	12.81
	10 SEC BEFORE TABLE DOWN	36.21	35.62	32.46	19.64	12.72
N6	**SUPINE REST**	22.18	21.10	18.95	13.14	9.23
	1ST MIN OF ACTIVE PHASE	25.45	24.23	21.73	15.33	12.07
	1 MIN BEFORE TABLE DOWN	33.94	32.54	29.51	19.36	13.63
	30 SEC BEFORE TABLE DOWN	31.99	30.77	27.83	18.57	13.82
	10 SEC BEFORE TABLE DOWN	30.82	30.13	27.18	18.97	16.00
N4	**SUPINE REST**	19.42	18.61	17.06	14.16	11.67
	1ST MIN OF ACTIVE PHASE	29.28	28.00	25.28	18.59	16.55
	1 MIN BEFORE TABLE DOWN	31.31	29.95	27.17	21.08	17.97
	30 SEC BEFORE TABLE DOWN	31.26	29.99	27.09	20.60	17.39

	10 SEC BEFORE TABLE DOWN	30.81	30.11	27.29	20.30	16.38
N7	**SUPINE REST**	21.94	20.69	18.10	10.39	6.10
	1ST MIN OF ACTIVE PHASE	34.68	33.23	30.03	19.05	14.75
	1 MIN BEFORE TABLE DOWN	34.09	34.03	33.54	29.12	23.09
	30 SEC BEFORE TABLE DOWN	36.46	36.71	36.42	32.10	25.69
	10 SEC BEFORE TABLE DOWN	38.58	40.02	40.22	35.88	29.59
N10	**SUPINE REST**	24.98	23.95	21.92	17.50	15.14
	1ST MIN OF ACTIVE PHASE	33.92	32.62	29.80	21.95	18.97
	1 MIN BEFORE TABLE DOWN	33.52	32.34	29.72	22.58	20.06
	30 SEC BEFORE TABLE DOWN	33.13	32.10	29.50	22.63	20.46
	10 SEC BEFORE TABLE DOWN	32.86	32.39	29.73	22.64	20.50
N13	**SUPINE REST**	33.49	32.14	29.28	23.02	21.73
	1ST MIN OF ACTIVE PHASE	36.66	35.27	32.25	25.48	24.36
	1 MIN BEFORE TABLE DOWN	39.34	37.90	34.72	26.71	24.25
	30 SEC BEFORE TABLE DOWN	39.27	37.96	34.73	27.12	25.01
	10 SEC BEFORE TABLE DOWN	36.96	36.39	33.43	27.58	26.11
N15	**SUPINE REST**	20.95	20.96	21.46	23.92	22.18
	1ST MIN OF ACTIVE PHASE	30.20	29.06	26.95	24.68	23.36
	1 MIN BEFORE TABLE DOWN	37.62	36.29	33.38	25.73	23.64
	30 SEC BEFORE TABLE DOWN	38.40	37.19	34.19	26.78	25.53
	10 SEC BEFORE TABLE DOWN	38.35	37.81	34.75	26.87	25.88
N5	**SUPINE REST**	31.20	29.96	27.39	21.79	19.60
	1ST MIN OF ACTIVE PHASE	36.00	34.71	31.88	23.39	20.01
	1 MIN BEFORE TABLE DOWN	36.37	35.21	32.80	29.28	28.67
	30 SEC BEFORE TABLE DOWN	34.64	33.70	31.46	28.73	28.39
	10 SEC BEFORE TABLE DOWN	37.72	37.51	35.20	29.85	28.98
PATIENTS WITHOUT SYMPTOMS						
		DELTA (0.5-4 Hz)	**THETA (4-8 Hz)**	**ALPHA (8-12 Hz)**	**BETA (12-30 Hz)**	**GAMMA (30-35 Hz)**
N2	**SUPINE REST**	28.22	26.88	24.03	15.90	12.14
	1ST MIN OF ACTIVE PHASE	28.97	27.75	25.14	17.37	13.26
	1 MIN BEFORE TABLE DOWN	30.68	29.35	26.43	16.89	13.55
	30 SEC BEFORE TABLE DOWN	29.66	28.50	25.66	16.00	12.55
	10 SEC BEFORE TABLE DOWN	31.73	31.08	28.02	16.48	11.40
N3	**SUPINE REST**	29.98	28.56	25.50	15.76	11.98
	1ST MIN OF ACTIVE PHASE	24.68	23.47	20.89	11.87	7.07
	1 MIN BEFORE TABLE DOWN	21.85	20.90	19.08	15.57	14.31
	30 SEC BEFORE TABLE DOWN	22.55	21.64	19.60	15.15	13.54
	10 SEC BEFORE TABLE DOWN	22.80	22.28	20.04	13.15	10.54
N9	**SUPINE REST**	30.69	29.51	26.94	19.29	15.54
	1ST MIN OF ACTIVE PHASE	29.20	27.98	25.54	21.47	20.39
	1 MIN BEFORE TABLE DOWN	24.70	23.72	22.04	21.67	21.57
	30 SEC BEFORE TABLE DOWN	25.77	24.81	22.96	22.76	23.12
	10 SEC BEFORE TABLE DOWN	25.91	25.30	23.18	22.98	23.70

N11	SUPINE REST	30.69	29.39	26.59	17.39	12.60
	1ST MIN OF ACTIVE PHASE	31.99	30.72	27.95	18.24	12.77
	1 MIN BEFORE TABLE DOWN	28.15	27.02	24.59	18.36	15.99
	30 SEC BEFORE TABLE DOWN	28.14	27.12	24.69	18.37	16.05
	10 SEC BEFORE TABLE DOWN	28.09	27.57	25.09	18.43	16.26
N8	SUPINE REST	22.69	22.13	21.38	22.01	21.99
	1ST MIN OF ACTIVE PHASE	23.51	22.24	19.66	13.43	10.71
	1 MIN BEFORE TABLE DOWN	21.28	20.45	19.17	19.15	19.66
	30 SEC BEFORE TABLE DOWN	19.27	18.57	17.38	17.64	18.36
	10 SEC BEFORE TABLE DOWN	18.80	18.07	15.83	11.80	10.85
N1	SUPINE REST	26.00	24.95	22.86	17.10	12.61
	1ST MIN OF ACTIVE PHASE	30.72	29.38	26.59	19.59	16.35
	1 MIN BEFORE TABLE DOWN	23.25	22.31	20.52	16.29	13.43
	30 SEC BEFORE TABLE DOWN	22.84	22.02	20.32	16.39	13.41
	10 SEC BEFORE TABLE DOWN	25.60	24.96	22.51	15.80	11.67
N16	SUPINE REST	29.41	27.99	24.86	13.31	9.88
	1ST MIN OF ACTIVE PHASE	31.26	29.81	26.68	16.23	11.99
	1 MIN BEFORE TABLE DOWN	30.40	29.02	26.03	14.08	9.13
	30 SEC BEFORE TABLE DOWN	23.67	22.44	19.58	8.81	3.36
	10 SEC BEFORE TABLE DOWN	19.19	18.18	15.12	5.50	1.09
N14	SUPINE REST	19.37	18.84	18.34	19.00	17.09
	1ST MIN OF ACTIVE PHASE	27.64	26.43	23.84	17.08	14.70
	1 MIN BEFORE TABLE DOWN	28.70	27.30	24.33	17.36	15.08
	30 SEC BEFORE TABLE DOWN	29.82	28.44	25.22	16.84	14.06
	10 SEC BEFORE TABLE DOWN	33.27	32.44	28.94	18.01	14.56