Syncope and Signal Processing

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1. INTRODUCTION

Syncope is a sudden loss of consciousness due to transient cerebral hypoperfusion. Although the understanding of this problem has evolved appreciably over a century of study coupled with improvements in technology, controversy still abounds over the suggested etiologies and diagnostic evaluations. A physician attempting to prescribe effective treatment first has to decide whether the syncopal patient suffers from neutrally mediated syncope (including vasovagal syncope), orthostatic hypotension, structural cardiac or cardiopulmonary disease, cardiac arrhythmia, or a vascular steal syndrome.

Much of the recent research on syncope involves sophisticated instrumentation and signal processing. In fact, while many physicians continue to use conventional techniques, advanced tools which address, for example, heart or blood pressure variability, electroencephalographic activity, or cerebral blood flow, have the potential to supersede them one day. In the meantime, these new technologies may help to elucidate progressively more of the mystery surrounding syncope. This report outlines some of the more popular research thrusts; naturally, owing to the breadth of the field, not all perspectives can be included.

2. HISTORICAL BACKGROUND OF SIGNAL GATHERING AND PROCESSING

The following timeline aims to outline the history of technological contributions used in syncope research, many of which are applicable to other fields as well. The division into two chronologically overlapping phases is the author's interpretation of events and is not corroborated.

FIRST PHASE: *Development of basic instruments*

1816 - René Théophile Hyacinthe Laënnec invents the stethoscope.

1881 - Samuel Siegfried von Basch invents the sphygmomanometer, allowing the first non-invasive measurement of blood pressure. (Earlier devices were somewhat bloody.)

1905 - Nikolai Korotkoff fully describes auscultatory sounds, using the two previous inventions and setting the standard for today's most common method of blood pressure measurement.

1929 - Hans Berger introduces the EEG. For several decades the technique remains fairly primitive.

1936 - Karl Matthes invents a basic oxygen saturation meter for the ear using two wavelengths of light. Soon, hypoxia during World War II aviation prompts Glen Millikan to lighten the device.

SECOND PHASE: *Development of complex instrumentation and signal processing techniques*

1901 - Karl Pearson invents Principal Components Analysis, an image transformation technique closely

related to Factor Analysis.

1943 - As a simple precursor to neural networks, Warren McCulloch and Walter Pitts produce the first artificial neuron. Computer simulations will not follow until the next decade.

1950s - Positron emission tomography (PET) is conceived.

1957 - Henri Gastaut describes how to use the electroencephalogram (EEG) to differentiate syncope from epilepsy, disproving the prevailing belief that "it is in the [cerebral] hemispheres that syncope and epilepsy have common ground" [M28].

1958 - The International 10-20 system for EEG lead placement is introduced, standardizing brain wave measurement [M40].

1965 - Interest in heart rate variability (HRV) is stirred when E.H. Hon and S.T. Lee discover that foetal distress and its resultant heart rate change are preceded by alterations in interbeat heart intervals.

1965 - James Cooley and John Tukey invent the modern version of the Fast Fourier Transform (FFT). (Earlier attempts to speed up Fourier transforms in fact date as far back as Gauss.)

1972 - Godfrey Hounsfield and Allan Cormack independently invent computerized tomography (CT), one of the most significant milestones in biomedical signal processing.

1972 - Takuo Aoyagi invents the modern version of the pulse oximeter.

1973 - Paul Lauterbur publishes what will become the foundations of MRI.

1975 - The first PET scanner becomes available.

1977 - Jobsis van der Vliet outlines the use of near-infrared spectroscopy (NIRS) as a tool to monitor oxygenation. Decent systems are later developed in the 1980s and it is used to monitor cerebral blood flow.

1977 - Arthur Dempster *et al* develop the Expectation Maximization algorithm. (The importance for this report stems from the algorithm's ability to estimate the model parameters of a learning Kalman filter.)

Late 1970s - Reasonable *in vivo* MRI images begin to be taken. By the mid-1980s, MRI is acknowledged as a useful medical tool.

Late 1970s and early 1980s - Progress in neural networks enhances interest in the field, which was previously suffering from the shortcomings of single-layer methods.

1980 - Nellcor produces the first reliable commercial pulse oximeter.

1989 - Masimo Corporation (worthy competitor to Nellcor) is founded.

Late 1980s - HRV's possible role in risk stratification makes a step forward. It is thought to be a predictor of mortality after an acute myocardial infarction. (Later this is shown to be activity dependent.)

1992 - Heart rate and blood pressure are chosen as the two key parameters in a classification scheme aimed at subdividing vasovagal syncope [M7A].

1996 - A Task Force of the European Society of Cardiology standardizes the common HRV techniques.

3. PARAMETERS FOR SIGNAL PROCESSING

A popular classification paradigm for vasovagal syncope [M7A] relies on just two parameters: systemic blood pressure, and heart rate. Indeed these are the two most common signals involved in syncope diagnosis, although minimal signal processing is required. Beat-to-beat assessments of these figures are useful to keep abreast of transients circa the time of syncope; hence devices such as Ohmeda's Portapres or Finapres are useful. Arthritic fingers in the elderly can hinder the Finapres' digital pressure readings. One study experienced difficulties in 45% of patients because of this problem [M2], but at the Radcliffe Infirmary it does not appear to be such a problem.

Ordinarily, standard statistical analysis systems - including multivariate analysis for the more complex cases - are used to arrive at results concerning heart rate and blood pressure changes. The student's t test, analysis of variance (ANOVA), chi-squared test, etc. are all popular in syncope research. These tools have allowed a consensus to form on several fronts. With few exceptions [L9], most studies find that upon tilt, systolic blood pressure drops, yet within one or two minutes begins to recover some of its loss, heading for a new equilibrium lower than supine blood pressure [L1, L12, L13, M3]. Diastolic blood pressure can increase or decrease [M3, L9, L10, L13, J15-J18] after tilt. A clear consensus exists that heart rate increases in both normal and symptomatic patients upon tilt [L1, L5, L6, L8-13, L16, L19].

The remainder of this section will outline the more sophisticated signal processing techniques, including cardiac (e.g. heart rate variability), cerebral (e.g. cerebral blood flow and related entities, electroencephalography), and other analyses (e.g. positron emission tomography, magnetic resonance imaging).

3.1 Heart Rate Variability

3.1.1 INTRODUCTION TO HEART RATE VARIABILITY

Heart rate variability (HRV) is a measure of the beat-to-beat fluctuations in heart rate. A normal resting heart undergoes periodic variations in its R-R interval, and the frequency spectrum of a tachogram (i.e., a plot of R-R interval *versus* time) usually reveals two or three peaks, at known frequencies:

0.15-0.4 Hz (often peaking near 0.25 Hz):
This variation in R-R interval occurs in phase with respiration, and hence is known as respiratory sinus arrhythmia (RSA). RSA reflects a cardio-deceleration during expiration (due to vagal efferent traffic to the sinus node), and a cardio-acceleration during inspiration (due to the sudden absence or attenuation of such parasympathetic activity).

0.04-0.15 Hz (often peaking near 0.1 Hz):
Although a peak in this range is very common, the cause of these "Mayer waves" (including the "ten-second rhythm") is less clear. They may be due to a delay in baroreflex feedback mechanisms [J4], but other possibilities exist, most notably an oscillator in the brainstem mandated to modulate peripheral resistance.

Less than 0.04 Hz:
Besides the two common peaks, there often exists a strong spectral component below 0.04 Hz as well. The physiological origin is uncertain; for example, one possibility is the influence of circadian rhythms. Understandably, some HRV measurement techniques ignore this spectral contribution altogether.

In addition, spectral density at different frequencies may be regulated not only by central and peripheral neural input, but also by complicating factors such as the beta-adrenergic/muscarinic receptor density ratio in the heart [M61-M63].

There are various quantifications of heart rate variability, using the time domain, frequency domain, or both [O2]. Moreover, in 1996 the Task Force of the European Society of Cardiology aimed to standardize HRV measurement [M8], and its compilation of existing techniques is often referenced in later literature. Popular examples include:

- SDANN, the standard deviation of the averages of NN intervals (i.e. "normal-to-normal" intervals, which are the RR intervals resulting from sinus node depolarization) in all 5-minutes segments of a recording
- pNN50, the number of pairs of adjacent NN intervals differing by more than 50 ms in the recording, divided by the total number of all NN intervals
- RMSSD, the square root of the mean of the sum of the squares of differences between adjacent NN intervals
- Autoregression analysis
- LF/HF ratio, the ratio of the power in the low frequency range (0.04-0.15 Hz) divided by that in the high frequency range (0.15-0.4 Hz); typically within a five-minute segment

3.1.2 HEART RATE VARIABILITY AND TILT TESTING

A number of papers have examined HRV behaviour during head-up tilt table testing (HUT). It has been shown that under these circumstances, an autoregressive method can be as effective as an FFT method [L7]. Some problems may exist with the reproducibility of time domain HRV metrics in syncopal patients [M52], but the HRV Task Force recommended that both time and frequency domain methods be used regardless of the problem being studied [M8].

One of the limitations which many common HRV measurements suffer from is the requirement of stationarity; often a window of several minutes is examined. Jasson *et al* [L5] applied instead the SPWVT (smoothed pseudo-Wigner-Ville transform) to assess instantaneous HRV, and found it to be a suitable substitute within the context of head-up tilt testing. SPWVT differs from typical HRV measurement techniques by calculating the beat-by-beat instant centre frequency (ICF) of the tachogram. A later study showed that the smoothed pseudo-Wigner-Ville distribution is as effective as autoregression [M53].

3.1.3 HEART RATE VARIABILITY AND SYNCOPE

Many studies have investigated the putative link between HRV and the sympathovagal balance. HRV is probably a less straightforward measure of autonomic system activity than plasma catecholamine concentration, baroreflex sensitivity, or sympathetic activity as measured by microneurography. However, there exists a consensus that, in healthy individuals, HRV increases upon orthostatic stress (e.g. head-up tilt testing), whereas autonomic neuropathy (for example from aging or diabetes) curbs this HRV increase and in fact can lead to a decrease in HRV during HUT [L1, L9, L16].

Notwithstanding this, autonomic neuropathy is merely one of the many possible causes of syncope [M13A], and this multifactorial nature may be responsible for some of the controversy amongst HRV analysis findings. Upon tilting syncopal patients, HRV tends to rise in the young and yet drop in the elderly [M64-M67]; hence HRV changes cannot be correlated with syncope test positivity, despite studies which argue the opposite [L9]. However, consideration of the patient's age may assist prognosis: Lipsitz *et al* [M65] found that amongst young people, HUT-positive patients experience a greater increase in HRV than HUT-negative patients; further, Ruiz *et al* [L4] found that age is the major determinant of autonomic behaviour during head-up tilting. In summary there is a need for interpreting HRV data in the context of

the patient's age and medical history, which together will narrow down the suspected causes of syncope. Guzman *et al* [L15] looked only at one type of syncope (vasovagal) for their study. Within that cohort, it was shown that those with cardioinhibitory and "mixed"[1] syncope experience a rise in HRV during HUT, whereas vasodepressive patients experience a drop. This HRV comparison may be used to support the suspicion that cardioinhibitory syncope is due to the Bezold-Jarisch reflex (involving hypersensitive cardiac mechanoreceptors) whereas a peripheral component is suspected in vasodepressive syncope.

3.2 Other ECG Techniques

Information from a simple electrocardiogram provides helpful information in 5 to 10% of patients. For example, the presence of a bundle branch block in a syncope patient indicates the presence of His-Purkinje disease [O10]. As demonstrated in the previous section, examining ECGs for HRV can prove fruitful. Other methods include:

Holter monitoring
This is the most common method of ECG monitoring for patients with syncope [M7A]. An external cassette tape-recorder is connected to ECG patches on the patient for twenty-four hours. A Holter analysis system, such as that made by Phillips, Mortara, or Spacelabs, can then perform signal processing, which may include:

- Heart rate variability (time or frequency domain; see Section 3.1)
- ST segment analysis and QT interval analysis
- Event sampling
- Trending
- Detailed reporting

Implantable Loop Recorders
Continuous-loop recorders are used for long-term monitoring lasting many months (often more than a year). Arrhythmias are detected during syncope in 8 to 20 percent of patients [M11B].

This report will not investigate the details of particular pacemaker algorithms, such as rate drop response.

3.3 Electroencephalography

3.3.1 INTRODUCTION TO ELECTROENCEPHALOGRAPHY

Electroencephalography provides information about cerebral function by monitoring the brain's electrical activity. Plots of electrical field potentials *versus* time reflect cortical oscillations resulting ultimately from chemical events occurring beneath electrodes placed on the scalp. The positions of these electrodes are standardized according to the International 10-20 system, yet little standardization exists between laboratories regarding the number of electrodes.

Frequency range	***Name of rhythm***	***Typical amplitude***
1-4 Hz	Delta	20-30 mV
4-7.5 Hz	Theta	low to moderate
8-13 Hz	Alpha	rarely >100 mV
13+ Hz (up to 100 Hz)	Beta	rarely >30 mV

Table 1. *The four EEG frequency bands.*

1 "Cardioinhibitory" and "mixed" are terms used in [M7A]'s classification scheme. The third type of syncope is "vasodepressor".

Frequency-domain analysis of the resulting electroencephalogram (EEG) is usually followed by division into several bandwidths. Table 1 lists the common four divisions, and Table 2 describes an alternative system. The quantification of each band's spectral contribution is known as quantitative EEG, or QEEG. Typical epoch length is 1 to 30 seconds, balancing the need for lower frequency analysis with the proliferation of artefacts in longer epochs. Typical data collection rates are 100 to 500 Hz, to meet the Nyquist criterion [J11].

When the FFT (Fast Fourier Transform) is applied to the EEG, interelectrode comparisons not possible using conventional EEG methods become possible. Two common examples are phase (related to the arrival time of various frequency components for a tracing at two separate electrodes) and coherence (the synchronicity of short distance and long distance cortical fibres at different leads) [J11].

Frequency range	***Name of rhythm***
0-4 Hz	Delta
4-8 Hz	Theta
8-10 Hz	Alpha 1
10 - 12 Hz	Alpha 2
12-16 Hz	Beta 1
16-20 Hz	Beta 2
20-30 Hz	Beta 3

Table 2. *An alternative classification scheme for EEG frequency bands.*

3.3.2 ELECTROENCEPHALOGRAPHY AND SYNCOPE

For more than 45 years [M28], EEG has been applied to syncope patients, primarily to rule out epilepsy. However, although electroencephalography was commonplace in the syncope work up twenty years ago, today it is not as popular. This may be perhaps in part due to the misbelief that "there are no specific EEG findings for any loss of consciousness other than epilepsy" [M13A]. In fact, it recently became known that regardless of the cause of syncope, certain interesting characteristic EEG changes are observed, such as background rhythm slowing, delta rhythm appearance, and EEG flattening [J8].

A few studies [J6, J9A/B] have further shown that electroencephalography can differentiate between specific types of vasovagal syncope - namely, vasodepressive *versus* cardioinhibitory. These studies found that the prodrome for vasodepressive syncope involves no EEG change, and syncope is followed by the appearance of theta waves which are then temporarily replaced by delta waves. Soon after the reappearance of the theta waves, the EEG returns to normal and the patient regains consciousness. Cardioinhibitory patients experience a similar sequence but with a few exceptions: first, the prodrome is shorter and may be associated with a slower, weaker EEG; second, there is a greater chance that the EEG will flatten and hence the patient may experience tonic-clonic jerks; finally, there is usually a longer duration before consciousness returns. It has been suggested [J6] that cardioinhibition increases the degree of cerebral hypoperfusion and hence the severity of EEG changes.

There may exist EEG differences between syncope and "pre-syncope", the latter referring to a common condition in which the patient feels as though syncope is imminent. Theta and delta waves are perhaps more likely to occur prior to syncope rather than prior to pre-syncope, although background suppression (EEG amplitude consistently less than 10 $mV)^2$ is observed in both cases [J7] (Figure 1). This difference in EEG behaviour may or may not point to two separate etiologies for syncope and presyncope.

2 Background suppression is not to be confused with electrocerebral inactivity (ECI), related to brain death. ECI occurs when the EEG amplitude is limited to less than 2 mV.

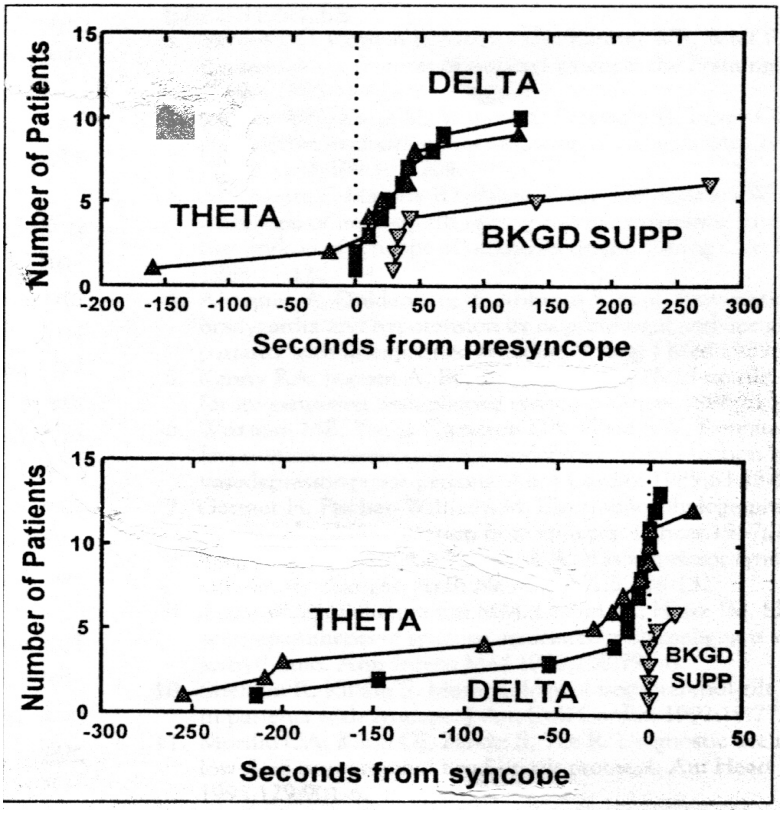

Figure 1. *Development of electroencephalographic (EEG) changes in patients with presyncope (top) and syncope (bottom). Although EEG abnormalities are frequent during presyncope, a profound change in the EEG pattern often occurs at the time of transition from presyncope to syncope. Bkgd supp = background suppression. [J7]*

3.4 Cerebral Blood Flow and Related Parameters

Most syncope diagnostic procedures focus on heart rate and blood pressure, and hence fail to assess local cerebrovascular and metabolic autoregulation capacities. However, by definition syncope is intimately related to cerebral hypoperfusion. To maintain consciousness, the brain requires roughly 11-19 mL/min/100 g of blood flow [J7]. Average flow is approximately 55 mL/min/100 g, with much of that servicing gray matter [O11]. This so-called CBF (cerebral blood flow) can be measured in several ways [O11]:

- Transcranial dopplerimetry
- Xenon-133 uptake
- Single-photon computed tomography (SPECT)
- Carotid angiography
- Near-infrared spectroscopy (NIRS)

The last method is most relevant to the author's research. To use near-infrared spectroscopy, a sensor unit is placed over an eyebrow. Changes in tissue haemoglobin can be calculated on the basis of light diffusion theory.

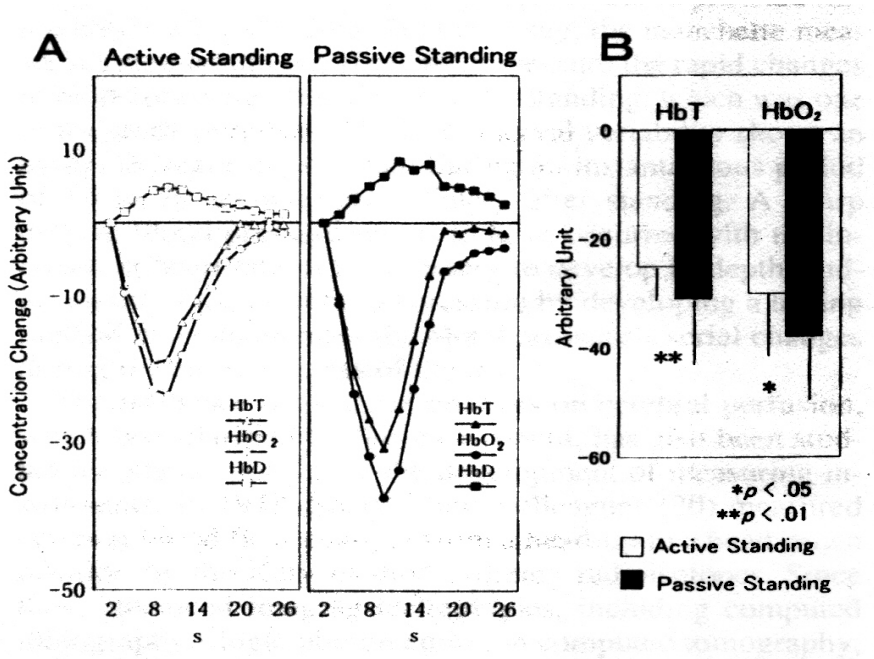

Figure 2. A*. Changes in HbT (total haemoglobin), HbO_2 (oxyhaemoglobin), and HbD (deoxyhaemoglobin) concentrations in young subjects upon standing.* ***B.*** *Comparison of the maximum variation in HbT and HbO_2 in young subjects during active and passive standing. [L1]*

Cerebral autoregulation is known to decrease as part of the aging process [L1], and hence many of the elderly Falls Clinic patients will suffer from poor cerebral blood flow. However, as mentioned previously, syncope can result from one of multiple reasons. With regards to vasovagal syncope, as opposed to orthostatic hypotension, it is not at all certain that impaired control of CBF is a cause [M38]; one reason for the ambiguity is the uncertainty that healthy patients may [M36, M37] or may not [M33] experience similar cerebrovascular changes. And another group found that cerebral vasoconstriction occurs in the prodromic phase of Type 2A syncope [J6].

Cerebral blood flow has been analysed in patients undergoing orthostatic stress. Figure 2A shows that haemoglobin deoxygenates steadily for approximately ten seconds after standing, and then returns to normal at a slightly slower rate. The degree of deoxygenation varies with the manner in which the patient assumes the upright position, as can be shown in Figure 2B. (Note that "passive standing" involves being carefully pulled upright by a nurse, minimizing patient effort.)

CBFV (cerebral blood flow velocity) can be used to calculate cerebrovascular resistance (CVR^3) in various ways. These methods include:

- **"Classic" CVR** = MCA (middle cerebral artery) mean pressure / mean CBFV
- **GPI** (Gosling's pulsatility index) [4], or **PI** = (systolic CBFV – diastolic CBFV) / mean CBFV
- **RAP** (resistance-area product): the inverse of the slope of a regression line involving CBFV and MCA BP

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3 Not to be confused with the other meaning of CVR, cerebrovasomotor response. The two represent different entities. Further, cerebrovascular resistance is different to systemic vascular resistance, which is known to decrease upon tilt [M60].

4 [M37] and several others believe this does not accurately reflect CVR.

It has been noted [M38 and references therein] that CBFV decreases before vasovagal episodes; using the classic CVR equation, this points to an increase in CVR. Given that vascular resistance decreases, rather than increases, in the splanchnic and muscular circulation during syncope, this reaction has puzzled researchers. It is most likely due to the patients' increased respiration, which lowers plasmatic CO_2 concentrations and thereby reduces CBFV [M38]. (Blood flow decreases when carbon dioxide levels drop. [O11])

It appears that respiratory rate does not change prior to syncope [M68-M70]; however, tidal depth does increase [M69, M70]. This has implications for the pathophysiology of vasovagal syncope: perhaps hypocapnia plays a crucial role. It is so far well known that increasing respiratory depth is a pressor mechanism which increases cardiac preload and constricts the veins. There exists a compromise theory that would be interesting to test: presyncope is caused by the slow fall in cerebral blood flow resulting from hypotension and/or bradycardia (contrary to the claim in [J6] that BP and HR do not cause it), while syncope is effected by the final reduction in blood flow that vasoconstriction elicits [J7].

3.5 Other techniques

3.5.1 BRAIN IMAGING

Brain imaging techniques such as positron emission tomography (PET) and magnetic resonance imaging (MRI) are sometimes used in the workup of syncopal patients. Images of the heart may elucidate the cause of a patient's fainting (e.g. tumours, collapsed atrium, etc.), as can images of the brain (e.g. dysmyelination, atrophy, lacunae, etc.). However, so far the diagnostic yield of brain imaging is low (the average yield of computed tomography is likely less than 5%), and no studies have specifically evaluated the effectiveness of this technique for diagnosis purposes [M13A]. However, for research purposes, it is tempting to surmise that the details of cerebral flow in such images could be useful in assessing cerebral hypoperfusion during syncope.

3.5.2 QT PARAMETERS

Patients with hypertrophic cardiomyopathy can be divided into syncopal and nonsyncopal to estimate mortality rates. Some studies [M41, M43] have found that looking at QT parameters in the ECG can be helpful to discriminate between the two groups. Common QT parameters are:

- QT interval, the interval between the ECG's Q and T points
- QT dispersion, the variation in QT interval as measured by subtracting the shortest interval from the longest
- The "corrected" versions of the above two quantities, substituting "QTc" for "QT", where QTc is usually calculated using Bazett's formula: QTc = QT / sqrt(RR)

Large values of QTc may betray regional variations/disturbances in repolarization across the ventricular myocardium and hence electrical instability.

3.5.3 CHAOS

Chaos analysis is not common in syncope research but some studies [M56, M57] have tried this approach. One group [M56] aimed to develop a preventive strategy for vasovagal syncope and ventricular tachyarrhthmias but the idea has not appeared to catch on.

3.5.4 BLOOD PRESSURE VARIABILITY

Just as heart rate varies periodically with time, certain peaks can be found from the spectral analysis of blood pressure as well. However, the physiology of these oscillations is only partly related to HRV. For example, the HF component of systolic blood pressure variability (BPV) is likely not autonomically related as it rises with orthostatic stress [L12]; it is more probably related simply to respiratory mechanical effects on haemodynamics [M71]. Despite these differences, multiresolution wavelet analysis of blood pressure waves [M46, M47] may have found criteria to dissimilate vasovagal patients from non-syncopal ones.

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4. SYNCOPE PREDICTION

Many parameters, including HRV, QT dispersion, respiratory status, and systolic blood pressure, have been utilized in attempts to predict syncopal events. The benefits of a prediction system would be tremendous; while syncope is in itself non-fatal, unexpected loss of consciousness at an inappropriate time can lead to debilitation, harm to others, or death.

HRV and QT dispersion suffer from the problem of requiring several minutes of signal to make a measurement; this may hinder a system's ability to recognize rapidly evolving syncopal events [M4]. Some studies have argued that looking at the change in HRV after tilt among other phenomena may provide predictive value [L9, M45, M50, M55], but this hypothesis would benefit from further testing.

With regards to respiratory status, patients may change their respiration rate or tidal volume (more likely the latter; see Section 3.4) to stabilize haemodynamic state. As mentioned previously, respiratory variations may improve venous return and/or impact central baroreceptor activity; however this needs to be further investigated.

Finally, in one study, systolic blood pressure was used to predict a positive tilt test with 93% sensitivity [M34]. Quantifying the drop in blood pressure during the first fifteen minutes can notify the physician conducting the experiment whether it is worth continuing the test. As tests can be lengthy, this is an obvious advantage. However, one drawback is that the specificity of this test is less than 60%.

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5. SIGNAL PROCESSING IN THE SOFTWARE MONITOR

The Software Monitor uses a number of signal processing techniques [L33]. Signals are sampled at various rates, from twice per hour to 256 times per second. The feature extraction techniques employed on these signals include:

- Principal Components Analysis: e.g., to learn the morphology of normal beats, in preparation for ectopic beat rejection
- Kalman filtering: e.g., to fuse various measures of heart rate into a robust merged rate
- Independent Component Analysis: e.g., to differentiate ectopic beats from artefacts

The main data visualisation technique is an extension of Sammon's mapping known as Neuroscale. This tool can be used either to plot a temporal trajectory of patient state, or to compare one patient's state with another's. The former has enhanced patient monitoring during recovery (from a myocardial infarct, for example), while the latter has permitted the defining of "normality" within a group of patients. One future research direction involves improving the visualisation and prediction algorithms to streamline the clinical interpretation of their results.

6. CONCLUSION

Much computational effort has been brought to bear on the problem of syncope, approaching the problem from several angles: electrocardiography (for example, heart rate, heart rate variability, etc.), brain activity (electroencephalography, MRI, etc.), blood pressure analysis (absolute values and blood pressure variability), and determination of cerebral blood flow (including correlations with carbon dioxide concentrations and respiration). These techniques currently function primarily to illuminate the nature and diagnosis of syncope; no technique has risen to a level of universal acceptance by physicians, and hence more primitive methods continue to be used. The development of a system to not only contribute to the understanding of syncope, but to be used regularly by physicians, would face a few simultaneous challenges: ease of use, cost-effectiveness, and accuracy. Included in the challenge of accuracy is the need for reproducibility: any proposed new system will have little value if it classifies a given patient differently on different days. However, the gathering of multiple signals by the Software Monitor, and the capability of multiple algorithms to be applied, may prove to offer the required robustness to counteract the problem of accuracy.

Regardless of whether the Software Monitor becomes a regularly used clinical tool, it has the technological potential to tackle many of the signal processing conundra - HRV predictive value, mechanisms of cerebral blood flow, etc. - in the study of syncope.

7. FUTURE WORK

The following outlines a long-term plan of work to be performed in future.

1.(a) Data analysis of heart rate and blood pressure, with the aim of differentiating between patients with various syncope etiologies. (See Figure 3.) For example, cardioinhibitory *versus* vasodepressive syncope should be an easy pair to resolve.

(b) Analysis of HRV pre- and post-tilt, comparing the five-minute windows with short-time estimation techniques. This will involve the Lomb periodogram and fast Fourier transforms (FFTs) with cubic splines.

(c) Analysis of EEG during tilt:
- (i) transition from pre-syncope to syncope (autoregressive spectral estimation)
- (ii) different types of NMS [J6]

2.Review of the literature and UCL results on changes measured with NIRS during HUT.

3.Participate in the planning of the Radcliffe Infirmary clinical trial, which will include controls.

Figure 3 (Next page). *A quantitative interpretation of the various types of syncope. Numbers in and of themselves are not sufficient for a diagnosis, and must be interpreted alongside qualitative factors, including patient history. The ideal starting point for diagnosis includes a careful history and physical examination, followed by supine and upright blood pressure measurements and a standard 12-lead ECG. Despite this, the SMP can assist with the diagnosis of three of the five types of syncope: orthostatic hypotension, neurally mediated syncope, and cardiac arrhythmias. Data presented on this page which were not credited earlier in the report are from [M13A].*

Abbreviations: ILR = Implantable Loop Recorder; CSM = Carotid Sinus Massage; CBF = Cerebral Blood Flow; SMP = Software Monitor Project; ECG = electrocardiogram.

Notes to accompany the figure:

1.While hypoperfusion is a prerequisite for syncope, a quantity has not been agreed upon. It has also been found that a CBF cessation of 6-8 seconds, a systolic blood pressure drop to below 60 mmHg, or a 20% drop in cerebral oxygen delivery (the minimum requirement usually falling between 3.0 and 3.5 mL/min/100 g) are sufficient but not necessary to cause syncope.

2.Stress testing is also used. It is positive if ECG and haemodynamic abnormalities are present and syncope is reproduced during or after exercise. Currently, the SMP cannot perform blood gas sampling.

3.For example:

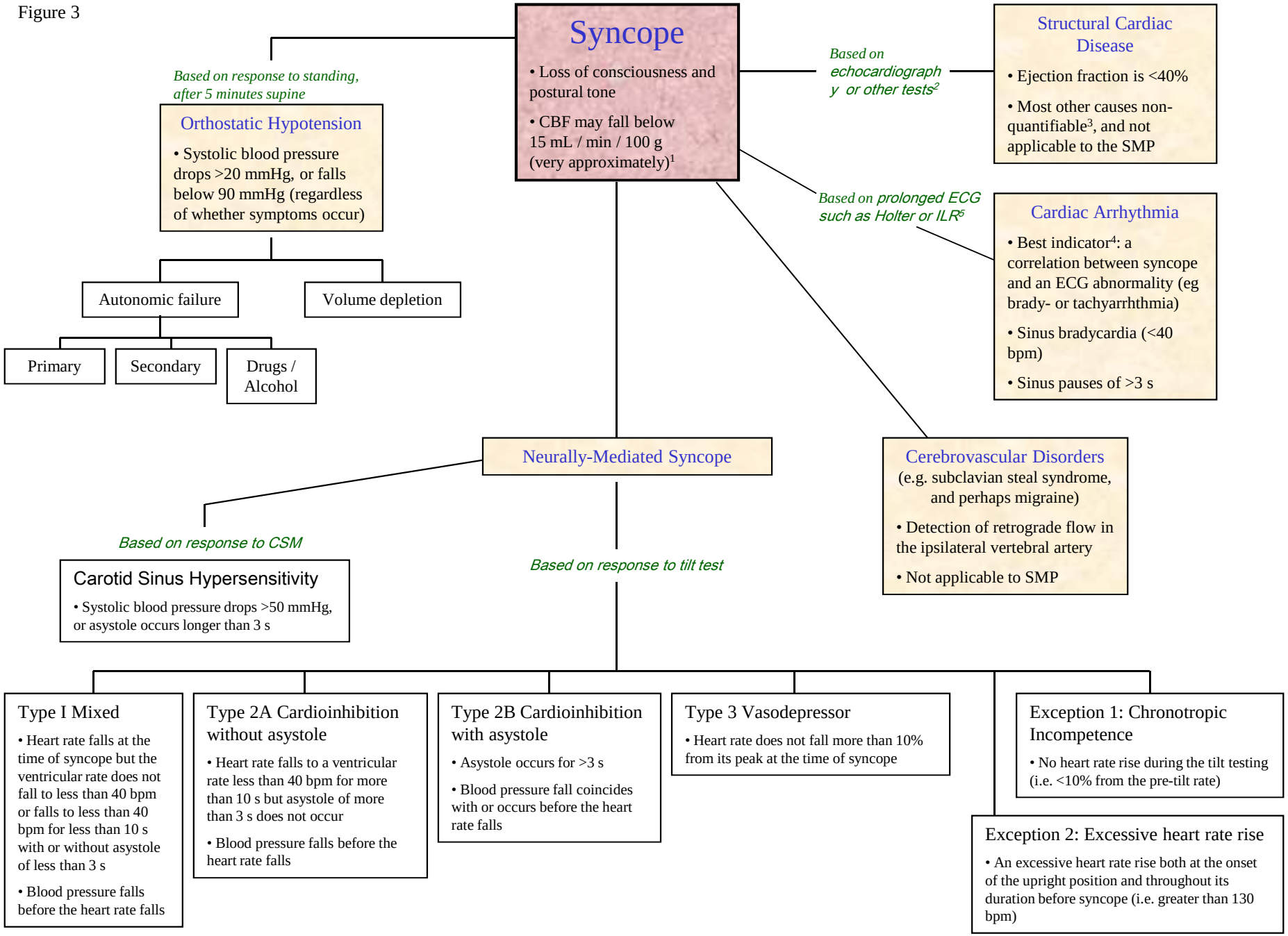
- *cardiomyopathy with episodes of overt heart failure*
- *ischaemic cardiomyopathy following an acute myo-cardial infarction*
- *right ventricular dysplasia*
- *hypertrophic cardiomyopathy*
- *congenital heart diseases*
- *cardiac tumours*
- *outflow tract obstruction*
- *pulmonary embolism*
- *aortic dissection*

4.Weaker possibilities, not necessarily leading to a diagnosis, include:

- *QRS duration >0·12 s (or other intraventricular conduction abnormalities)*
- *Pre-excited QRS complexes*
- *Mobitz I second degree atrioventricular block*
- *Prolonged QT interval*
- *Right bundle branch block pattern with ST-elevation in leads V1 -V3 (Brugada syndrome)*
- *Negative T waves in right precordial leads, epsilon waves and ventricular late potentials suggestive of arrhythmogenic right ventricular dysplasia*
- *Q waves suggesting myocardial infarction*
- *Bifascicular block (either left bundle branch block or right bundle branch block combined with left anterior or left posterior fascicular block)*

5.For example, electrophysiological study is also used, but is not applicable to the SMP.

Figure 3


Syncope
• Loss of consciousness and postural tone
• CBF may fall below 15 mL / min / 100 g (very approximately)[1]
Based on response to standing, after 5 minutes supine
Orthostatic Hypotension
• Systolic blood pressure drops >20 mmHg, or falls below 90 mmHg (regardless of whether symptoms occur)
Autonomic failure
Volume depletion
Primary
Secondary
Drugs / Alcohol
Based on echocardiography or other tests[2]
Structural Cardiac Disease
• Ejection fraction is <40%
• Most other causes non-quantifiable[3], and not applicable to the SMP
Based on prolonged ECG such as Holter or ILR[5]
Cardiac Arrhythmia
• Best indicator[4]: a correlation between syncope and an ECG abnormality (eg brady- or tachyarrhthmia)
• Sinus bradycardia (<40 bpm)
• Sinus pauses of >3 s
Neurally-Mediated Syncope
Cerebrovascular Disorders
(e.g. subclavian steal syndrome, and perhaps migraine)
• Detection of retrograde flow in the ipsilateral vertebral artery
• Not applicable to SMP
Based on response to CSM
Carotid Sinus Hypersensitivity
• Systolic blood pressure drops >50 mmHg, or asystole occurs longer than 3 s
Based on response to tilt test
Type I Mixed
• Heart rate falls at the time of syncope but the ventricular rate does not fall to less than 40 bpm or falls to less than 40 bpm for less than 10 s with or without asystole of less than 3 s
• Blood pressure falls before the heart rate falls
Type 2A Cardioinhibition without asystole
• Heart rate falls to a ventricular rate less than 40 bpm for more than 10 s but asystole of more than 3 s does not occur
• Blood pressure falls before the heart rate falls
Type 2B Cardioinhibition with asystole
• Asystole occurs for >3 s
• Blood pressure fall coincides with or occurs before the heart rate falls
Type 3 Vasodepressor
• Heart rate does not fall more than 10% from its peak at the time of syncope
Exception 1: Chronotropic Incompetence
• No heart rate rise during the tilt testing (i.e. <10% from the pre-tilt rate)
Exception 2: Excessive heart rate rise
• An excessive heart rate rise both at the onset of the upright position and throughout its duration before syncope (i.e. greater than 130 bpm)

REFERENCES

Key: J = James and others; L = Lionel; M = Mark; O = Other resource (i.e., not a scientific paper)

Suffix letters group related items (e.g. M11A and M11B are related)

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