UNIVERSITE DE GENEVE

FACULTE DE MEDECINE
Section de médecine clinique
Département de Médecine Interne
Unité de médecine interne d'accueil et d'urgences

Thèse préparée sous la direction du Docteur François Sarasin C.C.

L'IMPORTANCE DU BILAN INITIAL DANS LA PRISE EN CHARGE DES SYNCOPES

Thèse
présentée à la Faculté de Médecine
de l'Université de Genève
pour obtenir le grade de Docteur en médecine

par

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Thèse n° 10465

GENEVE
2006

Remerciements

En premier lieu, j'aimerais remercier chaleureusement le Dr Sarasin pour la confiance qu'il m'a accordée dans la réalisation de ce projet et en particulier pour l'autonomie qu'il m'a donnée dans l'organisation de la période de recherche initiale. Son soutien et son apport critique au quotidien m'ont permis d'avancer sereinement.

Je voudrais également exprimer mes remerciements à la Dresse Louise Simonet pour son encouragement et ses commentaires réguliers durant la phase de recrutement des patients et au Dr Jacques Metzger, pour les nombreuses heures passées à la supervision de la lecture des examens cardiologiques et pour le soutien sans faille qu'il m'a accordé, ainsi que pour sa contribution au bon déroulement de l'étude.

Je tiens tout particulièrement à remercier le Prof Alain Junod pour la confiance dont il a témoigné à mon égard durant cette période ainsi que durant les années qui ont suivi au sein de sa clinique.

Finalement je souhaite exprimer ma gratitude à mes frères et à mes parents qui m'ont constamment motivé et encouragé durant la rédaction de cette thèse.

A ma femme et à ma fille.

L'importance du bilan initial dans la prise en charge des syncopes

La syncope est un symptôme fréquent, défini comme une perte de connaissance subite et transitoire associée à un affaiblissement du tonus postural suivi d'une récupération spontanée avec un retour rapide à un état de conscience normal. Elle peut être causée par une multitude de conditions et présente donc un très large diagnostic différentiel étiologique. Il est important de reconnaître la syncope comme un symptôme de ces causes et non comme un diagnostic étiologique en elle-même.

La syncope est un phénomène qui a été rapporté à travers l'histoire écrite, et dont le mécanisme a pendant longtemps été moins bien compris. Hippocrate semble avoir été le premier à fournir une description d'un patient présentant un épisode syncopal. Dérivée du grec *synkoptein* signifiant "coupé court", elle a continué à être mentionnée depuis. Les avancées les plus remarquables dans la compréhension de la syncope ont dû attendre les 19eme et 20eme siècles avec les travaux de John Newport Langley sur le système nerveux autonome, d'Albert von Bezold sur l'arc reflex afférent du cœur et de Sir Thomas Lewis ayant démontré des épisodes de syncope liés à des hypotensions artérielles sans bradycardie.

La syncope a par ailleurs été reconnue comme souvent liée à des pathologies pouvant menacer la vie et présageant d'une mort subite. C'est parce qu'elle peut être prédictive d'un mauvais pronostic vital qu'il est crucial que la syncope soit reconnue et distinguée d'autres phénomènes qui peuvent parfois se présenter d'une manière en partie similaire mais dont le pronostic est autre. De plus, il est impératif de distinguer les causes cardiaques des causes non cardiaques, car les premières on été associées à une mortalité plus élevée.

Au cours des dernières années, l'intérêt qu'a engendré la syncope n'a cessé de croître, probablement en partie dû à sa fréquence relativement élevée et également au taux d'hospitalisation qui lui est lié, pouvant représenter jusqu'à 3% des motifs de consultations dans un centre d'urgence et de 2 à 6% des causes d'hospitalisation toutes confondues. La syncope survient dans toutes les classes d'âge, avec cependant une nette augmentation de prévalence avec l'âge croissant et associée à une morbidité traumatique importante. Le taux de récurrence est également élevé, lié aux causes vasovagales et cardiaques.

On retrouve dans la littérature jusqu'au début des années 80 des revues de la pathophysiologie ainsi que des descriptions d'entités étiologiques, puis la littérature des années 80 à commencé à s'intéresser à l'importance pronostique de l'identification des causes sous-jacentes; l'utilité de certains examens diagnostics a également fait l'objet d'évaluations. Cependant, depuis ces études, la démographie de la population, l'augmentation des maladies cardiovasculaires ainsi que l'émergence de la revascularisation percutanée associée à la prévention cardiovasculaire secondaire ont sans nul doute modifié la valeur de certains de ces résultats et l'épidémiologie de la syncope elle-même a sans nul doute évolué.

Les causes sont multiples, mais l'épisode syncopal est ultimement le résultat soit d'une diminution de la quantité, soit de la qualité de la perfusion sanguine cérébrale. Le métabolisme cérébral est intimement lié à cette perfusion et une interruption transitoire d'approximativement 8-10 secondes est suffisante pour induire une perte de connaissance. Le simple changement de la position en décubitus dorsal à la position debout peut induire un déplacement de 500 à 800 ml de sang vers l'abdomen et les membres inférieurs, suffisant pour diminuer le retour veineux, diminuer en conséquence la pré charge et donc le débit cardiaque. L'hyper contractilité du cœur sur des cavités cardiaques moins remplies forme la base du phénomène de Bezold Jarish, phénomène qui se produit à travers un arc reflex partant de récepteurs cardiaques via des centres nerveux du tronc cérébral, conduisant ultimement à un effet paradoxal associant une bradycardie et une hypotension artérielle. Une partie de cet arc reflex est également la base des syncopes vasovagales.

L'évaluation des patients est souvent contraignante, comprenant une vaste panoplie d'examens cardiovasculaires effectués de manière indiscriminée, menant rarement à une amélioration de rendement diagnostique mais dont le coût devient de plus en plus élevé. L'évaluation du coût de la prise en charge des syncopes au Etats Unis en 2005 s'élève à $2.4 milliards avec $5,400 par hospitalisation. Au vu de ces coûts exorbitants, ce défi diagnostique appelle donc à une approche de la prise en charge diagnostique basée sur des preuves, qui pourrait ainsi améliorer le rapport coût-efficacité de la prise en charge. Selon les études effectuées durant les années 80 et au début des années 90, la proportion des patients avec diagnostic de syncope d'origine inexpliqué pouvait varier de 5 à 47%. Cette variabilité de résultats est due à l'hétérogénéité des populations étudiées, du tout venant dans un centre d'urgence aux patients des soins intensifs, de centres de santé primaires aux centres tertiaires. Par ailleurs l'utilité diagnostique de l'anamnèse et de l'évaluation initiale a été peu étudiée.

C'est dans ce contexte d'augmentation des techniques d'investigations à disposition, d'une augmentation de l'incidence des syncopes probablement due en partie au changement démographique ainsi que de la nécessité de développer des approches diagnostique avec un meilleur rapport coût-efficacité que cette étude a été menée afin d'évaluer le rendement diagnostique d'une approche systématisée et standardisée dans une population non sélectionnée se présentant aux urgences dans un centre de santé de premier recours. L'étude a également permis d'évaluer le spectre étiologique de la syncope dans cette population.

Les patients de 18 ans révolus se présentant à l'Hôpital Cantonal de Genève avec comme plainte principale une syncope ont été inclus dans l'étude après avoir obtenu leur consentement écrit. Ils ont subi une évaluation standardisée effectuée aux urgences, comprenant une anamnèse détaillée, un examen physique, un électrocardiogramme, la recherche systématique d'hypotension orthostatique artérielle par un test de Schellong ainsi qu'une recherche d'hypersensibilité des sinus carotidiens. Les données ont été répertoriées dans un protocole servant également de rappel aux médecins en charge des patients des critères diagnostiques des diverses causes.

L'évaluation initiale a permis de classifier les patients en trois groupes: (a) les patients chez qui un diagnostic était fortement suspecté; (b) les patients chez qui une cause était suspectée sur la base des symptômes et signes mais qui nécessitait une confirmation par un examen diagnostique dirigé; et (c) les patients chez qui l'origine de la syncope est restée indéterminée après le bilan initial.

Ce dernier groupe a par la suite subi une évaluation cardiovasculaire plus étendue avec un monitoring électrocardiographique prolongé à l'aide d'un enregistrement Holter et un enregistrement électrocardiographique sur une semaine à l'aide d'un "dispositif d'enregistrement en boucle", une échocardiographie transthoracique, l'analyse des potentiels tardifs ainsi qu'une épreuve d'orthostatisme prolongé ("Tilt test"). Une étude électrophysiologique a été pratiquée chez les patients présentant une atteinte cardiaque structurelle, des anomalies électrocardiographiques détectées durant le monitoring prolongé ou des potentiels tardifs et ceci selon les recommandations actuellement retenues.

Les diagnostics ont été établis selon les définitions reconnues dans la littérature médicale, chaque cas ayant été discuté et confirmé selon les critères explicites et reproductibles. Le suivi des patients a été assuré chaque 6 mois pendant les 18 mois suivant la date d'inclusion. Durant la période d'inclusion, 788 patients ont été admis aux urgences pour syncope, dont 650 ont pu être inclus.

Les résultats ont démontré qu'il est possible d'assigner une cause chez presque 70% des patients se présentant aux urgences avec une syncope sans l'utilisation étendue d'examens complémentaires. En particulier, l'anamnèse et l'examen clinique, associés à la recherche systématique d'hypotension artérielle orthostatique ont prouvé avoir le meilleur rendement, permettant de poser un diagnostic et évitant une prise en charge inappropriée. Le suivi médical a de plus confirmé une mortalité presque doublée chez les patients présentant une syncope d'origine cardiaque par rapport à une cause non cardiaque ou inexpliquée. En outre, le rendement diagnostique des examens complémentaires cardiovasculaires été plus élevé dans le sous-groupe de patients chez qui une "anomalie" anamnestique, clinique ou electrocardiographique avait été décelée durant le bilan initial.

Cette étude indique l'importance d'une évaluation initiale bien conduite et montre que l'efficacité de celle ci est améliorée par l'utilisation d'un protocole d'évaluation standardisé, rappelant les critères diagnostics, ainsi qu'une application rigoureuse de ces critères, semble donc être cruciale pour une approche diagnostique offrant un avantage en terme de rapport coût efficacité, diminuant l'utilisation d'examens complémentaires qui s'avèrent peu rentables s'ils ne sont pas dirigés. Par ailleurs cette évaluation permet également de diminuer le nombre de patients dont l'origine de la syncope reste indéterminée.

THE VALUE OF THE INITIAL ASSESSMENT OF PATIENTS WITH SYNCOPE

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THE VALUE OF THE INITIAL ASSESSMENT OF PATIENTS WITH SYNCOPE

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1.0 Summary

1.1 Abstract

Syncope is a common symptom, defined as a sudden loss of consciousness and postural tone with spontaneous recovery. It is caused by a wide spectrum of etiological entities, all resulting in a decrease in the quantity or quality of cerebral perfusion. Syncope has been reported throughout recorded history, for a long time less well understood, but having been recognized as often heralding sudden death. Because it can be predictive of life-threatening conditions, it is important that syncope be distinguished from other entities that may have be similar in presentation but which nevertheless present a benign prognosis. Furthermore it is imperative to distinguish between cardiac and non cardiac causes as the former have been shown to be associated with the highest mortality. Interest in syncope has grown significantly in recent years, probably because of its relatively frequent occurrence and the fact that the incidence of patients hospitalised as a result of it is high, representing up to 3% of emergency room visits and from 2-6 % of all hospital admissions. Although syncope occurs in all age groups, its incidence increases with age. Furthermore the evaluation of such patients is often fastidious with broad ranging cardiovascular testing often been practiced indiscriminately in all patients, rarely leading to a significant increase in diagnostic yield, but resulting in an ever increasing cost. The problem therefore calls for evidence-based approaches to its diagnosis and management. Initially reviewing the pathophysiology and descriptions of individual etiological entities, the literature in the 1980's began reviewing the prognostic importance of identifying the underlying cause and the relative usefulness of certain diagnostic tests. Since then however, the general demography of patients, the increase in cardiovascular disease but also the emergence of frequent coronary revascularisation and cardiovascular secondary prevention has almost certainly changed the overall epidemiology of syncope. In this context, this study aimed to evaluate in a primary care centre the etiological spectrum of syncope in a non selected population and to further evaluate the diagnostic yield of a systematic and standardized initial workup protocol. The study demonstrated that up to 70% of patients presenting to an emergency room with syncope could have a likely cause of syncope ascribed without the use of extensive complementary exams. The initial history and physical examination appeared to be of most important value offering the highest diagnostic yield. Systematic search for orthostatic hypotension showed the second highest yield. Using a standardized protocol focusing on these aspects as well as acting as a reminder of specific disease diagnostic criteria and a rigorous application of these criteria appears key to a cost-effective workup of syncope and decreases the number of patients with syncope of undetermined origin.

1.2 Résumé

La syncope est un symptôme fréquent, défini comme une perte de connaissance subite et transitoire associée à un affaiblissement du tonus postural suivi d'une récupération spontanée avec un retour rapide à un état de conscience normal. Les causes sont multiples, toutes menant ultimement à une diminution, soit de la quantité, soit de la qualité de la perfusion sanguine cérébrale. La syncope est un phénomène qui a été rapporté à travers l'histoire écrite, et dont le mécanisme a pendant longtemps été mal compris, mais qui à été reconnue comme souvent présageant d'une mort subite. C'est parce qu'elle peut être prédictive d'un mauvais pronostic vital, qu'il est important que la syncope soit reconnue et distingué d'autres phénomènes qui peuvent parfois se présenter d'une manière en partie similaire mais dont le pronostic est autre. De plus, il est impératif de distinguer les causes cardiaques des causes non cardiaques, car les premières on été associées à une mortalité plus élevée. Au cours des dernières années, l'intérêt qu'a engendré la syncope n'a cessé de croître, probablement en partie dû à sa fréquence relativement élevée et également au taux d'hospitalisation qui lui est lié, pouvant représenter jusqu'à 3% des motifs de consultations dans un centre d'urgence et de 2 à 6% des causes d'hospitalisation toutes confondues. La syncope survient dans toutes les classes d'âge, avec cependant une nette augmentation de prévalence avec l'âge. De plus, l'évaluation de ces patients est souvent contraignante, comprenant une vaste panoplie d'examens cardiovasculaires effectués de manière indiscriminée, menant rarement à une amélioration de rendement diagnostique mais dont le coût devient de plus en plus élevé. Ceci appelle donc à une approche de la prise en charge diagostique basée sur des preuves. Après avoir revu la pathophysiologie et présenté des descriptions d'entités étiologiques, la littérature des années 80 a commencé à s'intéresser à l'importance pronostique de l'identification des causes sous-jacentes à la syncope et de l'utilité de certains examens diagnostiques. Cependant, depuis ces études, la démographie de la population, l'augmentation des maladies cardiovasculaires ainsi que l'émergence de la revascularisation percutanée associée à la prévention cardiovasculaire secondaire ont sans nul doute modifié l'épidémiologie de la syncope. C'est dans ce contexte que cette étude a été menée afin d'évaluer le spectre étiologique de la syncope dans une population non sélectionnée se présentant dans un centre de santé de premier recours. L'étude a également évalué le rendement diagnostique d'une approche systématisée et standardisée. Elle a démontré qu'il était possible d'assigner une cause chez presque 70% des patients se présentant aux urgences avec une syncope comme motif de consultation sans l'utilisation large d'examens complémentaires. L'anamnèse et l'examen clinique, associés à la recherche systématique d'hypotension artérielle orthostatique ont prouvé avoir le meilleur rendement. L'utilisation d'un protocole d'évaluation standardisé, prêtant attention à ces aspects et rappelant les critères diagnostiques, ainsi qu'une application rigoureuse de ces critères, semble être cruciale pour une approche diagnostique offrant un avantage en terme de rapport coût efficacité. Par ailleurs elle permet également de diminuer le nombre de patients dont l'origine de la syncope reste indéterminée.

2.0 Introduction

2.1 Background

Syncope is defined as a sudden loss of consciousness and postural tone with spontaneous recovery. It can be caused by a multitude of underlying conditions and thus has a large differential diagnosis. It is crucial to understand syncope as a symptom of these conditions and not as a diagnosis in itself. In syncopal episodes, loss of consciousness is ultimately the result of a transitory decrease in the quantity or quality of cerebral perfusion. Because it can be predictive of life-threatening conditions, it is important that syncope be distinguished from other entities that may have a similar presentation but which are nevertheless not indicative of life-threatening problems. In particular those which are not strictly characterized by a loss of consciousness, such as vertigo, dizziness and light-headedness, those without spontaneous recovery, such as prolonged hypoglycaemia, and from entities such as generalized tonic clonic seizures.

Furthermore, the literature shows that establishing the cause of syncope is essential for several reasons. The first is the fact that mortality and morbidity is increased in patients with an underlying cardiac cause as compared to patients with a non-cardiac or unknown cause. Syncope can thus be disabling and a forewarning of sudden death. The second is that although a number of complementary exams are available in the workup of syncope, the literature up until the 1990's was replete with controversy about the diagnostic usefulness of specific diagnostic tests and identifying high risk patients remains difficult.

Interest in syncope has grown significantly in recent years. There are probably a number of reasons for this. The first is its relatively frequent occurrence and the fact that the incidence of patients hospitalised as a result of it is high. Syncope represents up to 3% of emergency room visits and from 2-6 % of all hospital admissions [1]. Although syncope occurs in all age groups, its incidence increases with age and in industrialised and post industrialised countries where the denominator of people

potentially at risk of syncope has grown dramatically, the problem calls for evidence-based approaches to its diagnosis and management [2].

It is in this context that we conducted a study aimed at evaluating the diagnostic yield of a systematic and standardized initial workup protocol in a primary care centre in a non selected population which is the focus of this thesis. The study was also designed to further evaluate the etiological spectrum as well as determine the usefulness of further cardiovascular testing the results of which have been published [3-6].

2.2 Historical interest in syncope

Syncope has long presented a diagnostic interest and challenge to medicine. It appears that Hippocrates was the first to provide a description of a patient a syncopal episode [7, 8]. Deriving from the Greek *synkoptein* meaning "to cut short", it has continued to be mentioned and researched since then. Evidence of continuing interest in syncope in the Middle Ages comes from descriptions of Tanswuth (dancing mania) "in which music caused victims to dance until they fainted.." and "…stimulating music and fits of wild dancing, leaping, hopping and clapping that ended in syncope" [9, 10]. Physicians at that time described and documented a variety of classic symptoms such as hyperventilation, tachycardia, palpitations, histories of recent food deprivation and lack of sleep. They characterised syncope at the time as predominantly affecting young unmarried women.

The role played by emotions in syncope has also been an area of interest, and references to emotional faints and spells have been found in ancient Egyptian paperii. In the 18th century Robert Whytt argued that "nervous connections mediated all sensations, motions, and other functions", enabling "strong passion to cause a fit" with a vision of "the unity of the body and the mind as mediated by the nervous system", thus permitting the role of emotions in syncope to be seen for the first time in a physiological manner [11].

Caleb Hillier Parry's 1799 work on *syncope anginosa*, however, placed the cause of syncope within the cardiovascular system and "thus took syncope out of the head and into the body", changing the belief that the circulatory changes during syncope were the effect of an ill-defined disturbance of the cerebral hemispheres. He proposed that the origin of syncope was in the arterial system and that the "…brain is affected only secondarily, in consequence of the want of blood determined to it by the heart. It is true indeed, that certain sensations and passions, as we have before observed, produce Syncope; and as these are affections of the mind, it is obvious that the original operation of the causes producing them is on the brain, But I contend that they would not occasion Syncope, without an intermediate and corresponding diminution of the action of the heart and the arteries, operating in a manner which I have already explained. In other words, the brain is in these cases nothing more than the medium of sensation to the arterial system, which is then effected with that inaction which constitutes Syncope".

With the discovery by Le Gallois and Bichat that the rhythmicity of the heart was modulated by nervous influence and that there was both sensory and sympathetic myocardial innervations, a neurogenic theory of heart function emerged. This was supported by experiments in the 18th centrury by the Weber brothers that showed the slowing of the heart by galvanomagnetic stimulation of the vagus nerve. A reflex arc theory was developed that explained the cardioinhibitory effects of a series of stimuli (see pathophysiology) and after these initial experiments demonstrating a neural control of the heart, interest in the site of afferent signals and receptors in the heart, great vessels and lungs [11] grew rapidly.

During the so-called golden age of Irish medicine in the 19th century, two physicians, Robert Adams and William Stokes, characterised what later would be referred to as Stokes-Adams attacks, that involved unpredicted collapses associated with a loss of consciousness lasting a few seconds [12]. They described patients as being initially pale but then becoming flushed on recovery. In "Observations of some cases of permanently slow pulse" [13], Stokes cited one of Adams' 1827 descriptions of a case of syncope (published in 1846) which was associated with bradycardia. Typically associated with complete heart block, Stokes-Adams attacks have also been referred to as the tachy-brady syndrome [14].

Around the same period the novelist, Sir Arthur Conan Doyle made numerous mentions of conditions involving seizures, stroke and syncope, ascribing a particular power of observation an deductive reasoning to his most famous detective, Sherlock Holmes [15].

While working as a house officer at Guy's Hospital London in 1873, Alfred Lewis Galabin went on to document atrioventricular block and using an apexcardiogram was able to demonstrate atrioventricular block graphically. He presented his findings in a case report [16] of a 34 year old patient who he described as having had a number of attacks of "faintness" or near syncope.[17] Early clinical observations of the practice of blood letting also provided additional insights into the mechanisms of syncopal loss of consciousness and more specifically the combined effect of both decreased heart rate and blood pressure [11]. Research in this area went on to permit a better understanding of the neuroanatomic connections between the brain and the heart, and more specifically the glossopharyngeal (IX) the vagus (X), and the accessory (XI) cranial nerves as well as the sympathetic chain), which under some form or other had been described since the time of Galen of Pergamon (AD 129-199).

Meanwhile a series of parallel discoveries by John Newport Langley in 1898 led him to introduce the term "autonomic nervous system" [18]. Nahm's article on syncope and the history of nervous influences on the heart [11], states that "…the first experimental studies regarding syncope were primarily structural and largely based on neuro-anatomic connections between the heart and the brain…". It was not until the 19th century, when electrophysiological methods allowed a more functional study of the nervous influences on the heart and their effect on syncopal events, that a more comprehensive view emerged than had been possible using observations of bloodletting.

Studies conducted as early as 1866 had described a depressor nerve that was thought to originate in the heart and to have negative effects on both heart rate and blood pressure when stimulated at its central end. Albert von Bezold and a colleague showed that "injections of veratrine into the ventricles of experimental animals produced a powerful depressor effect" [11] and a century later, in 1949, studies by Jarish and colleagues [19], showed that "the depressor reflex was conducted via

afferent fibres that originated in the ventricles". They described thin, unmyelinated C fibres, and postulated that these fibres were part of a nociceptive reflex mediating the decrease in blood pressure due to the veratrine injections of von Bezold. The decrease in blood pressure resulting from the stimulation of ventricular depressor afferents is today referred to as the Bezold-Jarisch effect. Later experiments went on to suggest that large pressure gradients generated when the ventricular muscle contracts on an empty chamber stimulated these fibres.

Eventually it was suggested that syncopal episodes could result from both a vagally mediated reflex bradycardia and a mixed vasodepressor and bradycardic response due to afferent signals often originating from the left ventricle as well as from non cardiac sites, such as the carotid artery and aorta. The latter was demonstrated through research with heart transplant patients, where there was no re-innervation. This notion that as well as being an effector, the heart is equally an afferent source of stimuli in syncopal episodes forms the basis for the use of ß-blockers in the treatment of certain patients.

In the late 19th century, Sir William R Gower described patients' "pallor and coldness" associated with "symptoms, such as epigastric, respiratory, and cardiac discomfort" leading to vasomotor spasms [20] and then the " return of strength to the pulse and of colour to the face". His understanding of the pathophysiology of syncope and in particular neurocardiogenic syncope was nevertheless wrong, even though his term "vasovagal" remains in use today [21]. Vasovagal syncope is now recognized as the entity redefined and characterized by Sir Thomas Lewis, founder of the journal Heart in 1909, in his 1918 article on fainting attacks [22, 23]. His studies of young soldiers suffering from "irritable heart" condition demonstrated that hypotension could not systematically be attributed to bradycardia, and after studying the clinical significance of syncopal episodes without associated bradycardia he reported what he described was a pathophysiological mechanism and in so doing generated new interest into the neural control of blood pressure.

Despite the progress made in understanding syncope, it is noteworthy that an overall view of the pathophysiology of neurally mediated syncope was not put forward until the mid 20th century. Brown-Séquard and others in the mid 19th century had

postulated that blood pressure was not merely a result of decreased cardiac output resulting from bradycardia, but was also independently controlled by a distinct system of sympathetic vasomotor nerves. They had suggested that a "depressor reflex" had two distinct pathways, one stimulating the vagus nerve leading to bradycardia, the other leading to the inhibition of vasomotor centres in the medulla, thus leading to vasodepression. It was not until much later that advances in medicine and investigative procedures went on to shed light on the range of cardiovascular causes of syncope.

Of all cardiac causes, heart block is now felt to account for only a small minority of syncope events, while arrhythmias and obstructive causes are recognized as responsible for most. Notably, the diagnostic classification of the aetiology of syncope has meant that previously described incidents such as Stokes-Adams attacks now have specific causes ascribed to them. Of interest, however, slow heart rates are now associated with decreased arterial blood flow, reduced myocardial contractility and subsequent reduced tissue perfusion that contributes to symptoms of both cerebral and myocardial ischemia (sometime leading to death), corresponding to the classical Stokes-Adams attack [24, 25]. Today, both cardiac as well as central nervous afferent signals are known to lead to syncope by affecting parallel efferent pathways leading to "differential degrees of reflex bradycardia and hypotension" [11], and it is this consideration that is at the centre of the classification of various neurocardiogenic responses to tilt-table testing.

2.3 Definition of syncope and distinguishing it from seizures

Recognizing syncope is primordial in clinical settings. Efficient diagnosis can guide both the initial evaluation and further workup [26]. In a two step process, syncope as defined by a transient loss of consciousness, has to be identified and an underlying cause established as quickly as possible.

Differentiating syncope from epileptic seizures is a common problem in emergency room and clinical practice settings in general. Convulsions are an integral aspect of

the brain's response to hypoxia and the latter has potent epileptogenic effects. Reported frequencies vary, but most reports obtained from prospective studies with recorded syncopal events suggest that between 70%-90% of syncopal episodes [27, 28] are associated with convulsions. The fact that they are less frequently documented by eyewitnesses probably reflects the fact that they tend to be brief and of variable intensity. In contrast to epileptic related muscle activity, syncopal myoclonic movements are not rhythmic and are rarely sustained for more than 30 seconds. The tonic muscle activity is usually mild and does not resemble the forced extensor posturing of a generalized tonic clonic seizure. Very little evidence exists to suggest that syncopal convulsions reflect epileptic activity [29]. Muscle activation during syncope appears to be subcortical and probably originates from abnormal discharges in the reticular formations in the lower brain stem [30].

Clinically, eyes remain open during syncope, as in epileptic seizures but not in psychogenic fits. However, complex movement automatisms are less frequent in syncope, but when they are present they tend to be brief and less repetitive. Postictal confusion is discriminatory for epileptic seizures with postictal disorientation lasting more than 30 seconds suggesting the latter. Tongue bites can be present in both, but predominate in epilepsy. Urinary incontinence and head injury appears equally in both groups. Furthermore there is often a precipitating event in syncopal events; this occurs rarely in generalized tonic clonic seizures. A study of 671 patients using a "Syncope Symptom Study" questionnaire, established a simple point score based on elements of the history and has been suggested as capable of distinguishing syncope form seizures [31], but this has yet to be prospectively validated. A previous prospective study of 94 consecutive patients was nevertheless able to identify features of the history such as post-event disorientation in favour of seizure, and preceding nausea or sweating in favour of syncope [32].

Although some features of syncope may appear "epileptic" but are non-epileptic pathophysiologically, in rare cases, predominantly in children, syncopal and epileptic mechanisms have been reported to interact and thus be active concomitantly. In situations such as these the underlying cause leading to syncope may secondarily lead to an epileptic seizure.

Further elements of interest are the common accompanying cardiac arrhythmias in temporal lobe epilepsy; these are, however, rarely sufficiently severe to lead to syncope. It has been suggested that certain seizure foci (particularly in the temporal lobe) can result in clinical scenarios similar to syncope, especially mimicking vasovagal syncope. Confirming these diagnoses is difficult and may indeed be impossible [33].

2.4 Epidemiologic considerations

Data from industrialised countries where reporting is thorough suggest that syncope is a widespread clinical problem. In these countries it accounts for approximately 3% of all hospital emergency visits, and 1-6 % of a general hospital's medical admissions [34-38]. Although there has been little research on any geographical variations in its incidence and prevalence, syncope appears to be a common occurrence in most ethnic groups, although syncope in different ethnic subgroups may have different etiological spectrum.

According to some sources, up to 30% of adults are thought likely to present an episode of syncope to at some point in their lives. Age variations are nevertheless evident and two incidence peaks are discernable, one in the 15-19 year old age group and one in the 60-70 year old group. The most common age at which patients first present with syncope of vasovagal origin tends to be around 13 years [39], but syncope increases with age [40, 41] and is generally associated with morbidity secondary to accidental falls [42]. Gender differences have also been reported; some studies suggest that women may be more at risk, while other studies such as the Framingham one, suggested a more balanced gender incidence [41].

Syncope is more common among elderly people and in elderly patients is more likely to be associated with more serious co-morbidity than in younger people. One study of 711 patients with an average age of 87 found an incidence of 6% per year and a prevalence of 23% over 10 years, with a recurrence rate of up to 13 % and relatively

high mortality. However, because elderly people are more likely to present with several chronic illnesses as well as being on several medication regimens, including drugs for hypotension, it is often difficult to attribute a single cause to syncopal episodes [43]. An age-specific evaluation of syncope in a group of 210 elderly patients with a mean age of 71 years, and 190 younger patients, found that overall mortality and incidence of sudden death was similar in both groups. However in elderly people with a diagnosis of non-cardiovascular and unknown cause, mortality and incidence of sudden death was higher[44].

An evaluation of the incidence and prognosis of syncope due to specific causes among participants in the Framingham Heart Study (1971 to 1998) [41, 45, 46] also revealed that for people with a mean age of 51 years, the overall incidence of first reported syncope was 6.2 per 1000 person-years. This increased with age, producing a sharp spike around 70 years. The age-adjusted incidence rate of syncope among people with cardiovascular disease was nearly twice that among participants free of cardiovascular disease. The overall incidence of syncope in men and women was similar. Overall mortality was 30% higher among participants with syncope that those without. Cardiac-related syncope doubled the risk of death from any cause, and was also associated with an increased risk of fatal and nonfatal cardiovascular events. Identifying prognostic factors is therefore of primordial importance.

2.5 Economic aspects of syncope

A number of factors have contributed to the growth of costs associated with syncope. Health care costs in general have increased significantly in all industrialised and post-industrialised countries and costs associated with the diagnosis and treatment of patients presenting with syncope is no exception to this. In the USA, the cost in 1982 was estimated to be in the order of $800 million per year, and in 1993 the average annual cost incurred for people admitted with syncope but then discharged with another diagnosis was $4,942[47]. The average annual cost of managing patients with recurrent syncope considered to be of unknown origin was $5,165 in the 1980's.

Since then cost have grown considerably. The direct medical costs of syncope-related hospitalizations in the United States was re-evaluated in 2005 [48], with a staggering figure of $ 2.4 billion being suggested, and a mean cost on $ 5,400 per hospitalisation. In Europe the cost of diagnosis and treatment of patients presenting with syncope and then admitted to cardiology units has been estimated at 11,158 € Euros; the highest costs are associated with cases secondary to ventricular arrhythmias [49].

The cost of care is largely associated with the work-up which is typically extensive, fastidious and often fails to improve the diagnostic yield or reduce the rate of recurrence of syncope. A review in 1982 [50] carried out at a tertiary care centre, estimated that up to $16,000 of unnecessary diagnostic testing may be being performed on patients who ultimately receive a diagnosis of vasovagal syncope, further reinforcing the fact that establishing a diagnosis is difficult in many cases. A more recent study [51] of the cost implications of two testing strategies in patients with unexplained syncope compared a conventional workup with a prolonged monitoring one, using an implantable loop recorder. The results show that a conventional strategy has a lower diagnostic yield at a greater cost per patient and a greater cost per diagnosis than a primary monitoring strategy ($ 7,891 as compared to $ 5,875).

About 10% of falls in the elderly are due to syncope, and serious injury is more frequent when syncope precedes the fall. The cost of treating falls in the elderly exceeds $7 billion annually in the United States [43] and is likely to grow in all countries.

Establishing a cost effective and clinically rational evaluation protocol as well as safely limiting certain syncope-related admissions may ultimately allow substantial health care cost savings.

3.0 Causes and prognosis of syncope

3.1 Etiological spectrum of syncope

In addition to the historical descriptions of syncope and the research done on its pathophysiology prior to the 1980's there has been a significant and steady growth of interest in the natural history of the phenomenon [1, 35, 38], which is often related to its aetiology. Conceptually, causes of syncope can be distinguished between those that produce a quantitative and those that produce a qualitative decrease in cerebral perfusion.

The epidemiology and pathophysiology of syncope point to a category of conditions where decreased cardiac output and/or a systemic hypotension can produce cerebral hypoperfusion and eventual loss of consciousness. This category of causes result in a quantitative decrease in cerebral perfusion and includes conditions that decrease cardiac output, such as certain cardiomyopathies, pulmonary embolus as well as conditions resulting in hypotension as in the case of neurally mediated syncope or drug induced hypotension. It also includes conditions that lead to an impossibility of increased cardiac output, such as structural heart diseases (for example aortic stenosis and obstructive cardiomyopathies) and conditions that lead to the loss of peripheral vascular tone and anomalous central nervous vasculature or increased resistance.

The causes resulting in a qualitative decrease of cerebral perfusion include metabolic conditions such as hypoglycaemia, hypocapnia (which can contribute to induced cerebral vasculature vasoconstriction) and hypoxic conditions such as intra or extra-cardiac shunts (although rarely leading to complete loss of consciousness).

The overall classification of syncope is typically based on such etiological subgroups that encompass, *inter alia,* vascular, cardiac, non cardiac, neurological, metabolic and psychiatric substrates.

The literature suggests (see table 1) that the most common causes to be listed to date are vasovagal syncope (1% to 30%), situational syncope (1% to 8%), orthostatic

hypotension (4% to 12%) and drug-induced syncope (2% to 9%). Structural heart disease accounts for 3% to 11% and arrhythmias from 5% to 30% of causes. The range of percentages and subsequent uncertainty of these figures are based on the fact that previous studies have been conducted in heterogeneous settings, from primary care centres to tertiary care referral centres, often not distinguishing younger form elderly populations.

Table 1 Clinical spectrum and major causes of syncope

		Relative frequency Range (%)
Reflex mediated	Neurocardiogenic: - Neurally mediated syncope - Situational - Carotid sinus hypersensitivity	8-56
Vascular	Orthostatic: - Hypovolemia - Drug induced - Autonomic insufficiency Subclavian steal	2-24
Organic heart disease	Obstructive: - Aortic stenosis - Hypertrophic cardiomyopathy - Mitral stenosis - Atrial myxoma - Pulmonary embolus - Pulmonary hypertension	1-8
Arrhythmic hearts disease	Arrhythmias: - Bradyarrhythmias/AV block/SND - Supra and ventricular tachyarrhytmias	4-38
Miscellaneous	Neurologic (Seizures/TIA) Metabolic (Hypoxemia/hypoglycaemia) Psychogenic	3-32
Syncope of unknown origin		13-41

Adapted from [43, 52, 53].
AV block: refers to high degree atrioventricular conduction block, TIA: refers to transient ischemic attacks, SND: refers to sinus node dysfunction

3.2 Pathophysiology

3.2.1 Mechanisms of syncope

Although the etiological spectrum of syncope is wide, the fundamental cause of syncope is a decrease in quantitative or qualitative cerebral perfusion, with in the former situation, loss of consciousness resulting from a reduction of blood flow to the reticular activating system located in the brain stem. The metabolism of the brain is particularly dependent on perfusion and a transient interruption of cerebral blood flow of approximately 8-10 seconds is sufficient to induces loss of consciousness [35, 54]. A non reversed decrease of the systolic blood pressure under 60-70 mmHg, or of the mean pressure under 30-40 mmHg can provoke a decrease in cerebral perfusion followed by syncope [35].

Conditions leading to hypotension, and in particular hypovolemia, shifts in blood beds such as occurs in post-prandial conditions with visceral blood pooling (accentuated by decreased muscle tone, such as in upright tilt testing) and hypotensive drugs, increase the probabibilty of decreased brain perfusion and thus syncope. The simple changing of position from the decubitus position to the upright standing one results in a shift of 500 to 800 ml of blood to the abdomen and lower extremities resulting in an important reduction in venous return to the heart, and a decrease in the pre-charge and cardiac output. The resulting reflex arc leading from baroreceptors to an increased sympathetic outflow is designed to increase heart rate, cardiac contractility and vascular resistance [54]. Any defect in this blood pressure control system or any factor altering its integrity increases the probability of a decrease in blood pressure sufficient to cause a loss of consciousness. The cardiac causes of syncope, both arrhythmic as well as obstructive lesions, all tend to decrease cardiac output. Some of them do so sufficiently that even alone they produce a decrease in cerebral blood flow; others do so through a combination of decreased blood pressure and the reflex arc described above.

Age-related physiological changes also predispose to syncope by leading to the sudden reduction in the supply of oxygen delivered to the brain. These include lack of auto-regulation of cerebral blood flow, abnormal vascular reactivity, endothelial dysfunction and changes in the sympathetic nervous system (increased plasma levels of norepinephrine due to greater spillover from sympathetic nerve terminals and a reduced clearance rate, diminished B-adrenergic mediated cardioacceletory response). Cerebral blood flow, which decreases with age, renders elderly patients particularly susceptible to syncope [43, 55, 56].

3.2.2 Neurally mediated syncope

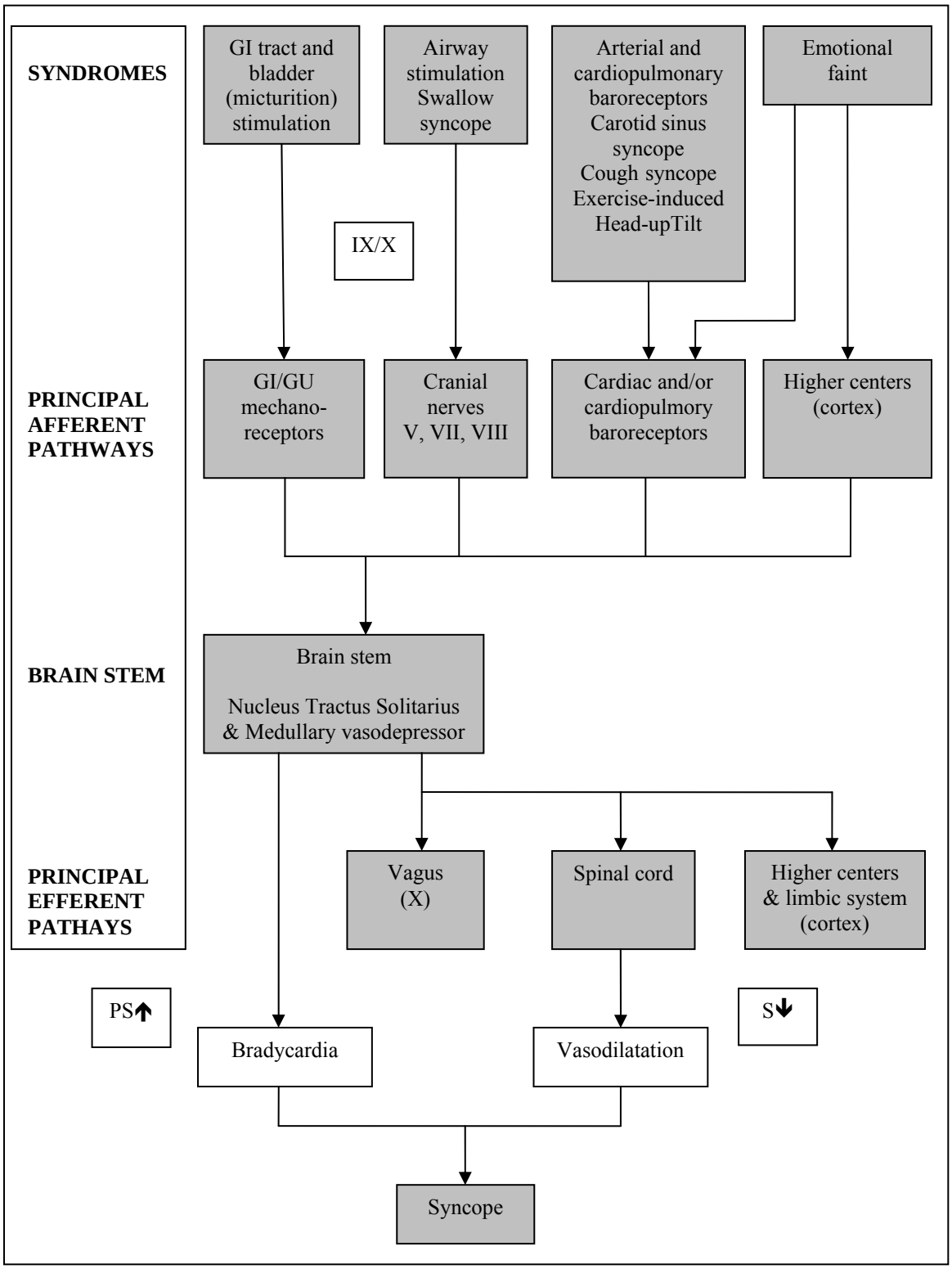
Vasovagal syncope (also known as neurally mediated, neuro-cardiogenic or vasodepressor syncope) represents the most frequent cause of syncope in patients with or without structural heart disease. A review of its specific pathophysiology is therefore important. As indicated above in the historical perspective, the reflex-mediated syncopes are based on a reflex arc with an afferent limb and an efferent response limb. The response component is common to all of this group of entities with a resulting increase in vagal tone and a decrease in the peripheral sympathetic tone leading to bradycardia, vasodilation, hypotension and ultimately to loss of consciousness. The classification of the neurally mediated syncopal entities is based on the different afferent limbs and their mechanisms of activation of mecano, baro or other neural receptors all of which are able to trigger the reflex arc [57-59].

Different situational syncopal entities are defined by the location of the trigger such as in the bladder in micturition syncope, gut wall in defecation syncope, upper gastrointestinal tract in deglutition syncope and in the carotid sinus in carotid sinus hypersensitivity. They all lead to hypotension with or without bradycardia. Emotional impulses (involving higher neural centres) resulting from acute stress situations and impulses from pain, prolonged standing, extreme fatigue or warm environments can lead to a decrease in ventricular filling through venous pooling and /or an increase in catecholamine secretion [54]. A paradoxical reflex is initiated by a left ventricle contracting vigorously on a reduced blood volume leading to the

stimulation of non-myelinated C-fibres from the heart and pulmonary outflow tract, leading to the dorsal vagal nucleus of the medulla and a paradoxical reduction of peripheral sympathetic tone and an increase in vagal tone leading to vasodilatation and bradycardia (the classical Bezold-Jarisch phenomenon) (see figure 1)

The reflex arc is thus triggered by excessive afferent discharge from the receptors resulting in a rise in parasympathetic efferent activity causing bradycardia and parallel inhibition of the sympathetic system leading to concomitant arterial vasodilation and hypotension. It has been postulated that central nervous system modulators such as serotonin, adenosine, opioids, endorphins and others may be active in vasovagal syncope. Nitric oxide has also been implicated in the vasodilatory response associated with vasovagal syncope [57].

Figure 1 Pathophysiologic basis for neurocardiogenic syncope



Mechanisms for various reflex-mediated vasomotor syndromes, showing similarities and differences in the mechanisms of the entities. IX and X refer to the ninth and tenth cranial nerves; PS and S to the parasympathetic and sympathetic nervous systems respectively. **Adapted from [60-62]**

3.3 Prognosis and risk stratification of syncope

Kapoor [63] showed that patients with syncope can be subdivided into diagnostic categories that have a prognostic importance. Notably, patients with a cardiovascular cause have a higher incidence of sudden death than patients with a noncardiovascular or unknown cause.

In itself, syncope is not a risk factor for increased overall and cardiac mortality or cardiovascular events [64]. It is typically the presence of underlying comorbid heart diseases that present risk factors for mortality regardless of whether the patient has syncope or not. The major focus of the evaluation of patients with syncope should therefore be to identify and treat underlying heart disease, since it is this that determines prognosis. Patients with cardiac causes are reported to have a one-year mortality of 18%-33%, as compared to 6%-12% in patients with syncope of non-cardiac or unknown origin [36, 63, 65-68]. In some studies arrhythmic syncope accounted for up to 70% of all cardiac causes, with an incidence of sudden death at 30% over 5 years in the cardiac groups of patients. Decreased left ventricular function, coronary artery disease and outflow obstruction has been correlated to this increased risk of mortality. The absence of heart disease therefore appears to be a marker of better prognosis. Ventricular arrhythmias and in particular inducible monomorphic ventricular tachycardia during electrophysiological studies appearing on a substrate of previous myocardial ischemia [69-71] have been suspected to be associated with a poor prognosis. Ventricular tachycardia, which is classically feared in arrhythmogenic syncope, is however much less frequent than presumed. One study reported the incidence of acute cardiac ischemia among patients with syncope at around 7% [72].

Sudden cardiac death is an important reported cause of mortality in adults in industrialized countries [73] and some studies suggest that syncope can be a predictor of sudden death. Certain specific cardiac causes of recurrent syncope do indeed

sometimes initially present through episodes of syncope but in the literature they constitute a small fraction of all causes [74]. The incidence of sudden death is reported to be ~24% in patients with a cardiovascular cause as compared to ~4% in patients with a non- cardiovascular cause and 3% of in syncope of unknown cause. It is interesting to note that Hippocrates, more than 2,400 years ago (approximately 400 BC), described situations in which "those who are subject to frequent and severe fainting attacks without obvious cause die suddenly".

Arrhythmic syncope can often lead through a common pathway to an arrhythmic death. These include conditions such as congenital long QT syndrome, Wolff-Parkinson-White syndrome, Brugada syndrome, hypertrophic cardiomyopathy, congenital artery syndromes, arrhythmogenic right ventricular dysplasia, idiopathic restrictive and dilated cardiomyopathy, and Stokes-Adams attacks with atrioventricular block and/or transient asystole [14] can all cause syncope and predispose to sudden death through arrhythmias, often ventricular fibrillation [75].

Symptoms, although essential in the diagnostic workup and in assigning non-cardiac causes as an aetiology, do not appear to help in risk-stratifying patients whose cause of syncope remains of unknown origin after an initial history and physical exam. A prospective study of 497 patients evaluating this precise question [76] concluded that triage decisions and management plans should be based on pre-existing cardiac disease or electrocardiographic abnormalities

A retrospective study [77] of 210 patients presenting to a British accident and emergency department with syncope proposed that stratification of patients according to prognostic indicators using American College of Physicians guidelines as opposed to stratification according to diagnosis, allowed a more efficient and apparently safer workup, including helping physicians to decide whether or not to hospitalize patients, the aim being to identify high risk individuals (those with underlying heat disease). The article concludes that management decisions are more important than diagnoses, and that physicians should assign a prognosis rather than a diagnosis and make decisions accordingly

Age has an important impact on prognosis, especially where elderly patients have a poorer prognosis independent of the diagnostic category, as opposed to younger patients in whom prognosis is intimately dependant on the underlying cause, in particular with an increase in sudden death where cardiovascular causes are present [44].

The usefulness of specific diagnostic tests in identifying clinical entities causing syncope was increasingly reported during the 1980's. Studies evaluating prolonged electrocardiographic monitoring (Holter) showed for example, that it is rarely helpful in assigning causation of syncope. However non-diagnostic abnormalities emerged and these increased the likelihood of patients going through further electrophysiologic testing [78-80]. Studies of electrophysiological testing have raised a number of limitations linked to the lack of sensitivity and specificity for diagnosing bradyaryhthmias and polymorphic ventricular tachycardia. Certain facts emerged nonetheless, showing that these tests were rarely abnormal in patients with normal heart and electrocardiogram, whereas a left ventricular ejection fraction < 40%, left bundle branch block and a history of coronary artery disease were predictors of positive electrophysiologic studies [81-89].

The use of basic laboratory tests, computed tomography scans, non invasive carotid studies and electroencephalography and stress tests rarely established a diagnosis [1, 35, 38], and were only recommended after careful history-taking and physical examination when clinical presentation was highly suggestive of the entities being considered.

Tilt table testing has been widely used in the evaluation of neurally-mediated syncope in patients with unexplained syncope after extensive and negative workup [90]; a diagnosis specificity of more than 90% was established in one study of 505 patients.

A risk classification system for patients presenting to emergency departments with syncope was evaluated in two prospective studies [91]. A cohort of 252 patients was followed in one group to develop the classification; a second group of 374 patients was used to validate the system. The key determinants for the stratification of patients' risk of arrhythmias and mortality within one year of presenting to the emergency department were history and electrocardiographic findings at the time of presentation.

However, despite extensive investigations, the recurrence rate of syncope appears high, in particular in cases of cardiac and vasovagal syncope. Furthermore, syncope of certain specific cardiac origins is genuinely a predictor of sudden death and overall mortality, and these causes must therefore be searched for in specific groups of patients.

4.0 Investigation

4.1 Introduction

Numerous reviews have summarized syncope-related work-up strategies [35, 43, 53, 92-96]. Studies done at the beginning of the 1980's [63, 65, 97] found that anywhere between 5-47% of syncope cases were classified with an "unknown origin" despite extensive work-ups. Notably a prospective evaluation in 1983 [63] of 204 patients assigned a cause in only approximately 50% of cases (107 patients; 53 cardiovascular, 54 noncardiovascular) leaving 97 patients with syncope of unknown origin. Overall mortality was ~14%, with mortality however, significantly higher in the patients with a cardiovascular cause at ~30% as compared to ~12% in the noncardiovascular group and ~6% in the group with syncope of unknown origin.

Several studies have reviewed the value of clinical histories, physical examination, selected diagnostic tests and their capacity in identifying high-risk subgroups of patients with poor prognosis. These studies remain inconclusive, however, in part because the sample populations have often been biased, and for example have at times involved patients who had been referred to specialized clinics. Furthermore, the yield of different tests has been relatively disparate. For example the range for the yield of history-taking and physical examination in identifying the cause of syncope is 32%-75% [36, 65-67]. The reason for this variability is in part, the fact that the populations being studied were highly heterogeneous, varying from emergency room to intensive care unit patients and from primary care centre to referral tertiary care hospitals.

The diagnostic usefulness of clinical histories in identifying causes of syncope has also been poorly reviewed, and because the cost of evaluations is increasing dramatically, it is generally accepted that risk-stratifying strategies must be developed so that patients can be identified quickly in terms of those who are likely to benefit from workups and those who are less likely to. This lack of a rational and cost-effective diagnostic approach to evaluating patients presenting in primary care centres

with syncope can mean that a large proportion of these patients continue to undergo excessive diagnostic testing whose proven clinical benefits.

The recommended assessment of patients presenting with syncope includes taking an initial history and physical examination, a 12 lead ECG, search for orthostatic hypotension and testing for carotid hypersensitivity, where the findings should guide further non-invasive or invasive testing. In patients with syncope of undetermined origin, those with established structural heart disease should be tested for arrhythmias, but with an unknown sequence of exams; those with negative findings might require tilt testing. In patients without clinical evidence of structural heart disease, the likelihood of arrhythmias is very low [35, 65] and therefore the need for prolonged electrocardiography monitoring is questionable. In patients without clinically evident heart disease, but "possible" underlying heart condition, the role of cardiac evaluation such as echocardiography is unknown. In all age groups, vasovagal and psychiatric disorders should be considered, but whether upright testing and psychiatric assessment should be systematically performed is also unknown.

4.2 Aim of the investigation

It is in this context that this study was conceptualised and conducted. The study was a prospective evaluation of patients with syncope, and was designed to determine the diagnostic yield of a standardized sequential evaluation of patients with syncope in a primary care teaching hospital, representing a community-based sample of patients.

A secondary aim of the research was to describe the spectrum of clinical entities causing syncope in an unselected population of patients presenting to the emergency department of a primary care centre. Most clinical studies describing the underlying causes of syncope were performed prior to 1980 or in the 1980's, well before the era of coronary artery reperfusion procedures and systematic secondary prevention after myocardial infarction (for example antithrombotic and beta-blocker therapy). This

means that the current etiological spectrum may be different, and that the prevalence of arrhythmias is possibly lower than suggested by earlier studies.

Another aim of the study was to assess the diagnostic yield of the history, clinical examination and specific diagnostic examinations (baseline ECG, 24-hour Holter monitoring, signal-averaged electrocardiography loop recorder, echocardiography and upright tilt testing) using established diagnostic criteria (see annexe) as a measure of their performance.

This workup represented the initial recommended assessment. The study also set out to assess rates of recurrence of syncope, cardiovascular events and mortality. The specific yield of the clinical history and physical examination in assessing the risk of syncope of cardiac origin together with the predictive values of complementary diagnostic tests was also tentatively assessed.

It was understood that when investigating a "symptom" such as syncope, surrogate endpoints needed to be used to accommodate the lack of a diagnostic "gold standard". No specific diagnostic test can be considered to either objectively confirm the "syncopal" event or establish its cause. Because of this lack of a gold standard, sensitivity and specificity for specific evaluation components and tests cannot be determined, and therefore the notion of a *diagnostic yield* was evaluated. The diagnostic yield represented the number of patients with a positive diagnostic test result divided by the number of tested patients. The use of a two-year observational follow up of patients with a final established diagnosis based on strict criteria also served as a substitute for such a gold standard in assigning a diagnosis.

4.3 Methods

4.3.1 Study setting and design

Patients aged 18 years or older, presenting to the emergency department and the inpatient services of the Hôpital Cantonal of the University of Geneva, with a chief complaint of syncope in the study period between July 1, 1997, and March 31, 1999, were prospectively enrolled, after obtaining their informed written consent. The patients were identified on a daily basis through the admissions records file and through regular visits to emergency and internal medicine interns. Syncope was distinguished from other entities, in particular those not characterized by a loss of consciousness, those without spontaneous recovery and from generalized tonic clonic seizures, which all enter another differential diagnosis and necessitate specific workups.

A standardized evaluation (see table 2) was performed in the emergency department on all patients. This included a complete history (age, gender, number of previous episode of syncope, presence or absence of premonitory signs or symptoms), physical and neurological examination, a laboratory workup (hematocrit, serum levels for creatinine kinase and glucose), a 12-lead electrocardiogram, testing for orthostatic hypotension and bilateral carotid massage in patients without contraindications. Baseline data from the clinical history, physical examination, current medications, cardiovascular risk factors, the Charlson Co-morbidity Index score [98] conditions and results of all tests were collected daily using a standardized evaluation and follow up form (see appendix 7.4). The protocol also provided specific diagnostic criteria for the disease categories, collecting information on seizures, stroke or transient ischemic attacks, aortic stenosis and pulmonary embolism as well as serving as a reminder of these criteria; questioning of witnesses was done whenever possible.

This initial and preliminary evaluation enabled patients to be classified into three groups: (a) patients in whom the aetiology of the syncopal episode was strongly suspected; (b) those in which an aetiology was suspected based on suggestive

symptoms or signs, requiring confirmation by selected diagnostic exams; and (c) those in whom the cause of syncope remained undetermined (see figure 2).

The latter category of patients underwent further and more extensive cardiovascular testing including prolonged electrocardiographic monitoring using 24–hour Holter and continuous-loop event recorders, transthoracic echocardiography, signal average electrocardiography and upright passive tilt table testing.

Electrophysiological testing was carried out selectively in patients with structural heart disease and electrocardiographic abnormalities detected during prolonged monitoring or with late potentials in the signal average electrocardiogram, as recommended in the literature guidelines. Initial diagnoses were based on disease specific diagnostic literature based definitions and criteria (see appendix 7.1 and 7.2) and confirmation of diagnosis was based on the prospective and observational study follow up as well as strict adherence to these diagnostic criteria.

Figure 2 **Flow diagram of the study design**
After an initial evaluation patients were categorized into three groups, conditioning further examinations

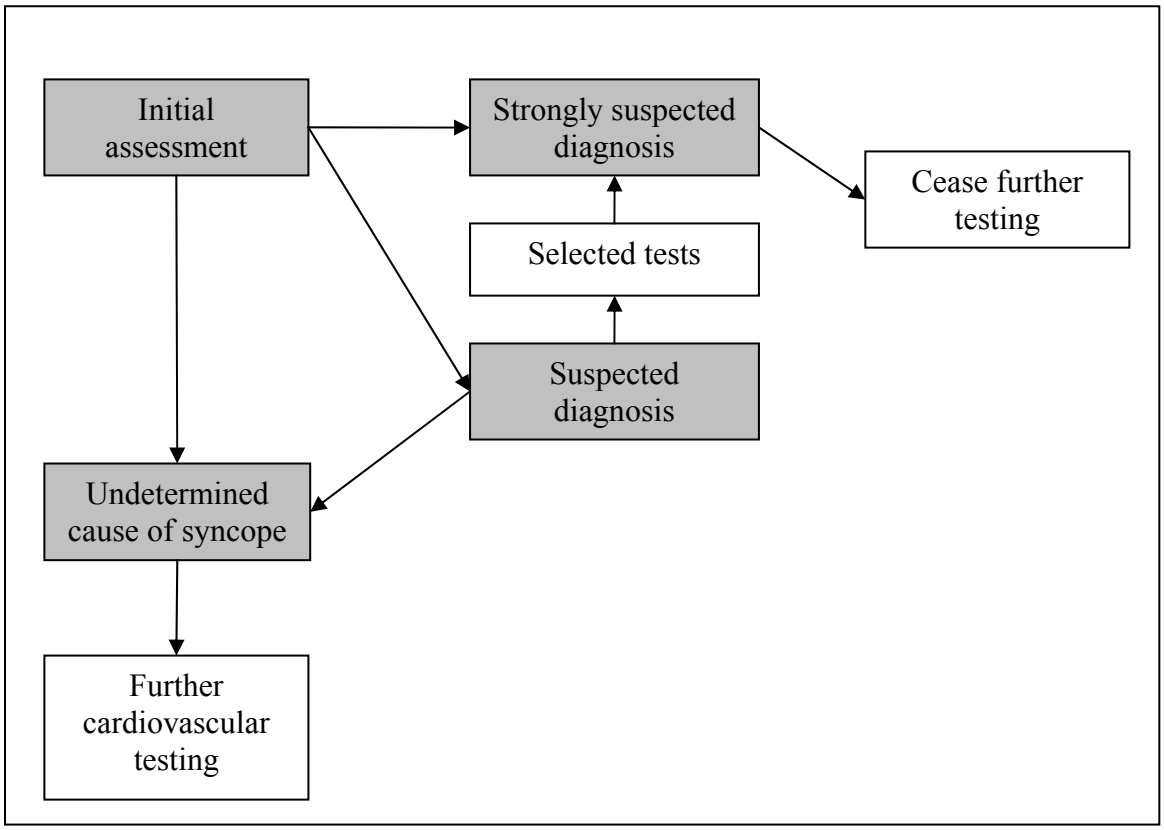


Table 2 **Initial evaluation and complementary exams**

The initial workup comprised:	- a complete history - a physical and neurological examination - a succinct laboratory workup (hematocrit, creatinine kinase and glucose) - a 12-lead electrocardiogram - testing for orthostatic hypotension - bilateral carotid massage (in patients without contraindications)

Complementary exams included:	- prolonged electrocardiographic monitoring:
	  - 24 –hour Holter
	  - continuous-loop event recorders
	- transthoracic echocardiography
	- signal average electrocardiography
	- upright passive tilt table testing
	- electrophysiological testing in selected patients

4.3.2 Diagnostic criteria

Each patient case of syncope was discussed by a committee of two internists (Dr Francois Sarasin and Dr Martine Louis-Simonet, Internal Medicine department, HUG) and a cardiologist (Dr Jacques Metzger, Cardiology department, HUG), in order attribute a final diagnosis. This was done using explicit and reproducible criteria that are summarized in the annex. In certain specific cases when the relationship between the syncopal episode and clinical findings was indispensable to assigning a diagnosis, as with certain cases of orthostatic hypotension or neurally mediated syncope during tilt testing, reproduction of syncopal or presyncopal symptoms was required to formally attribute a diagnosis.

4.3.3 Follow up

The prospective evaluation was an observational study, with an 18 months inclusion period, followed by an 18 months follow-up period after enrolment, during which syncope recurrence and mortality data was obtained from primary care physicians and through telephonic contact with the patients or their relatives at 6 months intervals.

5.0 Results

During the enrolment period, 788 (1.1%) of the 67,837 patients admitted to the emergency department presented with a chief complaint of syncope. Of these, 650 patients (82%) were included in the study; 115 did not complete the initial standardized evaluation and 23 patients refused to participate (see table 3).

The evaluation protocol, the classification of patients in three presumed diagnostic groups and the complementary exams determined an overall etiological spectrum, 89 % (581 patients) of overall cases being attributed to non cardiac and 11% (69) to cardiac causes (see tables 4, 8 and 9) [3].

The initial testing strategy allowed an etiology to be *strongly suspected* and therefore assigned in 446 patients (69%) and *suspected* in a further 67 patients (10%), requiring further targeted diagnostic testing, being confirmed in 49 (73%) of them (see figure 3). The detailed history and clinical examination led to a diagnosis in 245 patients (38%), with neurocardiogenic causes, including vasovagal (212 patients) and situational disorders (22 patients), representing the largest diagnostic subgroup with 53 % of cases (234 patients) (see table 5). The characteristics of this latter group, diagnosed in the emergency room, show a generally younger group of individuals, with fewer comorbid cardiovascular diseases. Systematic and standardized measurements of orthostatic hypotension was performed in 611 (94%) of patients, and allowed an orthostatic causes to be attributed in 156 (24%) patients [4], with a further subdivision related to concomitant details; 59 (38%) of these presented with drug-related hypotension (80% with angiotensin-converting enzyme (ACE) inhibitors), 34 (22%) were diagnosed with hypovolemia, 19 (12%) had postprandial hypotension and 44 (28%) had idiopathic hypotension.

The 12-lead electrocardiogram was able to strongly suggest a cause in 33 (5%) of the patients; 24 of them had documented arrhythmias and 9 presented with acute coronary syndromes. The overall proportion of patients with arrhythmias was nevertheless relatively low.

Table 3 Inclusion rate

Data	Number (%)
Syncope as a chief complaint	788/67,837 (1.1%)
Enrolment	650/788 (82%)

Table 4 Epidemiological characteristics of the 650 included patients with syncope

Characteristics	Number (%)
Age (years)	60 ± 32
Age range (years)	18-93
Number ≤ 65 years old	341 (52)
Male sex	310 (48)
Previous syncopal episode	
None	362 (56)
One	143 (22)
Two or more	145 (22)
Last episode in preceding year	130 (20)
Comorbid conditions	
Coronary artery disease	104 (16)
Previous myocardial infarction	57 (9)
Heart failure	61 (9)
Hypertension	229 (3)
Diabetes Mellitus	54 (8)
Peripheral vascular disease	57 (9)
Chronic obstructive pulmonary disease	26 (4)
Charlson Comorbidity Index score	
O	417 (64)
1 or 2	184 (28)
3 or 4	36 (6)
5 or more	13 (2)

Figure 3 Diagnostic yields after initial evaluation phase of the 650 patients

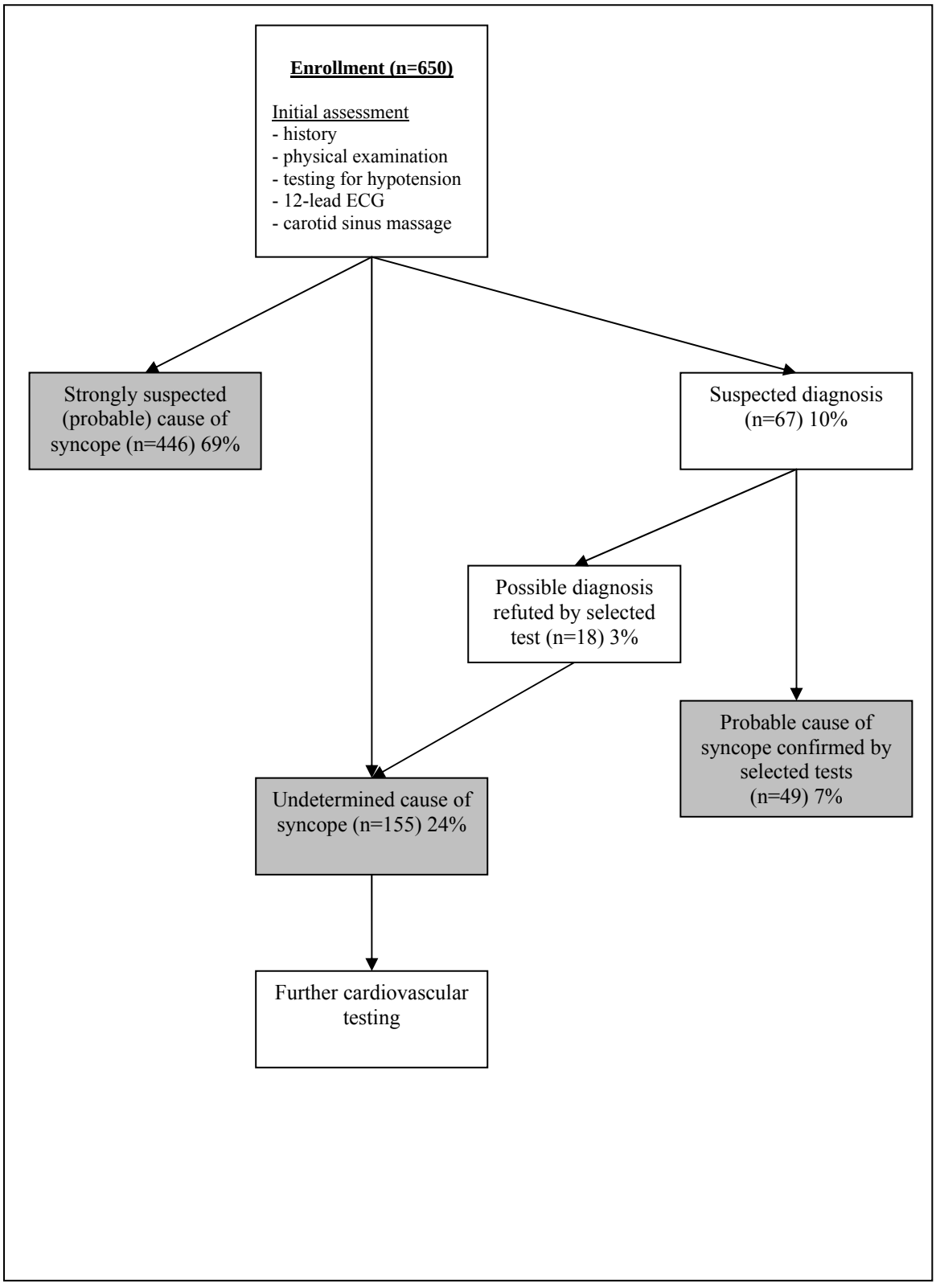


Table 5 **Etiological spectrum of syncope after the initial non invasive evaluation in 446 patients in whom a diagnosis was assigned**

Etiology of syncope	Number of patients (%)
Noncardiac causes	
vasovagal	212 (48)
situational	22 (5)
hypotension	156 (35)
idiopathic	44 (10)
drug related	59 (13)
hypovolemia-related	34 (8)
post-prandial	19 (4)
carotid sinus hypersensitivity	4 (1)
Cardiac causes	
Arrythmia	24 (5)
atrioventricular block	8
sinus bradycardia or pause	8
supraventricular tachycardia	4
ventricular tachycardia	3
pacemaker malfunction	1
Acute coronary syndrome	9 (2)
Psychiatric	11 (2)
Others	8 (2)
hypoglycemia	3
gastrointestinal hemorrhage	2
sub-archnoid hemorrhage	1
subdural hematoma	1
intracranial hemorrage	1

.Carotid sinus massage was performed in 432 (67%) patients. It was abnormal in 16 patients, but considered diagnostic in only 4 (0.5%) of them. Laboratory exams identified anemia with subsequent gastrointestinal hemorrhage being confirmed in 2 patients and hypoglycemia in 3 patients.

A specific cause of syncope was thus able to be attributed to 446 patients (see tables 5 and 6) after the initial evaluation, and a further 49 after selected testing (see table 7), leaving 155 (24%) with an undetermined cause. Extensive cardiovascular testing in a further 122 of these patients enabled a diagnosis to be assigned found in another 30 (25%) of these. Although beyond the scope of this thesis, the specific diagnostic yield of Holter monitoring, ambulatory loop recorder, echocardiographic examination, upright tilt testing, late potentials on signal averaged electrocardiogram and electrophysiological studies (in selected patients) were also independently evaluated [5, 6]. Results showed that the yield of these examinations was proportional to the pretest probability and the presence or not of a positive history and abnormal baseline 12-lead electrocardiogram. In particular, the echocardiographic examination, performed in 122 patients, did not reveal any unexpected cardiac abnormalities. Furthermore, the yield of prolonged electrocardiographic monitoring was only 10% amongst non selected patients, but increased to 19% when applied to patients with an abnormal baseline electrocardiogram.

Cardiac causes and orthostatic hypotension were more prevalent in the elderly population. The mean age of patients with a cardiac cause was 74 years, with 61% of all cardiac causes being determined in patients over the age of 75 years; the mean age of patients with orthostatic hypotension was 63 years

Follow-up data was collected in 611 (94%) patients at 18-months, with a 9% (55 patients) mortality rate, 8 of which were attributed to sudden death (see table 8). The data also showed that 15% (95) of patients presented at least one episode of recurrence of syncope, and 8% (37 patients) two or more. Of note, 60% (57) of them recurred within one year. The recurrence rates for patients with vasovagal syncope was 17% (41 of 242), 15 % (24 of 158) for patients with hypotension, 15 % (14 of 92) with unexplained syncope and 9% (6 of 69) of patients with a cardiac cause to their syncope.

Table 6 Diagnostic yield of initial evaluation 446 patients

Examination	Yield Number of patients (%)
History & physical examination	245 (38)
Testing for hypotension	156 (24)
12-lead electrocardiogram	33 (5)
Carotid sinus massage	4 (0.5)

Table 7 Etiological spectrum of syncope after the initial non invasive evaluation in 67 patients in whom a diagnosis was suspected

Suspected cause	Number (%)	Confirmed (%)
Seizures	31	22 (71)
Stroke/ transient ischemic attack	11	8 (73)
Pulmonary embolism	11	8 (73)
Aortic stenosis	10	8 (80)
Others	4	3 (75)
arrhythmia	2	2
mastocytosis	1	1
subdural hematoma	1	0

Table 8 **Overall etiological spectrum and mortality of syncope in the 650 patients**

Etiology of syncope	Number (%)	18-month Mortality Number (% of category)	Sudden death Number (% of category)
Cardiac	69 (11)	18 (26)	5 (7)
Arrythmias	44 (7)		
- Sinus bradycardia or pause	15		
- Atrioventricular block	15		
- Ventricular tachycardia	9		
- Supraventricular tachycardia	4		
-Pacemaker malfunction	1		
Acute coronary syndromes	9		
Aortic stenosis	8		
Pulmonary embolism	8		
Noncardiac causes	456 (70)	28 (6)	3 (0.7)
Vasodepressor syncope	242 (37)		
Orthostatic hypotension	158 (24)		
Carotid sinus hypersensitivity	6 (1)		
Neurologic	30 (5)		
Psychiatric	11 (1.7)		
Other	9 (1.4)		
Unknown	92 (14)	6 (7)	0
Incomplete evaluation	33 (5)		0

Other includes: Hypoglycemia (n=3), gastrointestinal hemorrhage (n=2), subarachnoid hemorrhage (n=1), subdural hematoma (n=1), intracranial hemorrhage (n=1) and systemica mastocytosis (n=1)

Table 9 **Cardiac versus noncardiac causes of syncope**

Cardiac Number (%)	Non cardiac or unknown Number (%)
69 (11)	581 (89)

6.0 Discussion

Interest in syncope continues to grow. The need for efficiency in its timely diagnosis is predicated on a number of conditions. The first and most important is the need to provide the type of assessments that permit patients to be treated in ways that are most appropriate to their condition and the risk(s) they may be exposed to as a result of that condition. The second is the growing reality that as the technology of diagnosis becomes more sophisticated so do the economic and psychosocial costs associated with workups and hospitalization. Improving our understanding of syncope and translating that knowledge into operational guidelines and methods can begin to satisfy both those pressing requirements.

This prospective observational study demonstrated that up to 70% of patients presenting to a primary care emergency room with syncope could have a likely cause of syncope ascribed without the use of extensive complementary exams. That is to say that additional examination and assessment might only be necessary for 30% of patients presenting with the condition, a vast saving in time, economic costs to the system and psychological and social costs to the patient and his/her family.

The study demonstrated that the value of the initial history and physical examination are the most important actions and that they provide the highest yield. Systematic searches for orthostatic hypotension showed the second highest yield. Using a standardized protocol focusing on these aspects as well as acting as a reminder of specific disease diagnostic criteria and a rigorous application of these criteria appears key to a cost-effective workup of syncope and decreases the number of patients with syncope of undetermined origin. Secondly, targeted testing was also shown to be an effective way of assigning an etiology in up to 7% more patients, thus avoiding costly and probably unnecessary further cardiovascular testing.

The value of further cardiovascular testing in patients whose cause of syncope remained undetermined after the initial workup greatly depended on the history and

baseline 12-lead electrocardiogram. Overall mortality and in particular sudden death was highest amongst patients to whom a cardiac cause attributes, confirming previous data available. The recurrence rate at 15% also coincides with statistics previously published.

As was postulated, the established etiological spectrum differed from other population-based studies, with a higher proportion of neurocardiogenic causes, be it vasovagal or situational. This is possibly due to the fact that the standardized protocol searched for specific symptom elements and precipitating factors in the history and conveyed the criteria on which the diagnosis could be established, avoiding areas of possible doubt or subjective interpretation. Considering the fact that during the 18-month follow-up period, the incidence of sudden death was extremely low in this group of patients, it seems unlikely that syncope of cardiac origin was mistakenly considered as a neurocardiogenic disorder.

The high occurrence of orthostatic hypotension can possible attributed to the increased use of anti-hypertensive drugs in this era of ever more rigorous guidelines on the treatment of hypertension and the concomitant higher use of these drugs in post myocardial secondary prevention. Of particular note is the increased use of angiotensin converting enzyme inhibitors. Also, the high prevalence of post prandial hypotension in the elderly population accounts for a significant number of cases.

Finally, the study was conducted in an era of regular revascularization in patients with coronary artery disease and presenting with acute coronary syndromes. This, associated with secondary cardiovascular prevention, might explain the lower the previously published proportion of patients with cardiac arrhythmias as an established cause of syncope.

Although beyond the scope of this thesis, it is relevant to underline that baseline history and 12-lead electrocardiographic abnormalities, significantly determined the relative diagnostic yield of further cardiovascular testing, emphasizing the importance of such stratification. Be it prolonged electrocardiographic monitoring, echocardiography or passive tilt table testing, the yield was overall low in the category of patients with unexplained syncope. Specifically, baseline

electrocardiographic abnormalities, irrespective of underlying heart disease appeared as a primary determinant of the yield.

A left ventricular ejection fraction of less than 40% was systematically correlated with a history of heart disease and an abnormal electrocardiogram. The determination of the ejection fraction emerged however, both in this study and others, as fairly important to in estimating the prognosis of more than in establishing the etiology of syncopal episode.

As indicated in the introduction, the lack of a gold standard against which to compare the diagnostic value of individual elements in this standardized evaluation means that the strict correlation between examination results an the assigned etiology remains somewhat uncertain, despite the use of strict diagnostic criteria in attributing the diagnosis. The follow-up period probably partially counterbalances this study limitation. Other limitations to this study include a recently established fact, which is the higher than previously thought prevalence of psychiatric conditions leading to syncope. The lack of a systematic and standardized instrument for detecting these disorders means that a certain number of such entities were potentially under diagnosed.

As medicine moves forward and attempts to address the needs of a population whose demographic and behavioral characteristics may be placing it at ever-growing risk of syncope and of cardiovascular disease, the need for evidence-based diagnostic procedures is becoming not only more evident but more fundamentally essential. Syncope is a widely occurring phenomenon affecting different age groups, but older ones more than others. For all age groups the availability of rapid diagnostic guidelines based on the type of findings this study generated could make a major difference in the way in which their health and welfare is managed in emergency room settings where most syncope patients present.

7.0 Appendix

7.1 Diagnostic criteria for non cardiac causes [63, 66, 67, 99]

Vasodepressor or vasovagal syncope (neurocardiogenic) [67, 91]
Vasodepressor syncope was diagnosed if a precipitating event such as fear, severe pain, minor injury or instrumentation was identified, in the presence of premonitory vasovagal symptoms such as nausea, diaphoresis, fatigue or dizziness.

For patients falling into the unexplained syncope category, upright tilt testing was used to attribute the diagnosis as described under the criteria for ***tilt table testing***.

Neurocardiogenic syncope was further subdived into s***ituational syncope*** with the following definitions

Cough syncope was invoked as the cause of syncope when a loss of consciousness occurred immediately following a paroxysm of sever cough with no other apparent cause for syncope.
Micturition syncope was defined as syncope occurring at the beginning, during, or immediately at the termination of urination, with no other apparent cause for the episode.
Defecation syncope was defined as syncope occurring during or immediately after defecation, with no other apparent cause for the episode

Orthostatic hypotension
Orthostatic hypotension was implicated as the cause of syncope if there was a decrease of the systolic blood pressure of more than 25 mmHg associated with dizziness or syncope on repeated orthostatic blood pressure determination over a 10 minute period following baseline values after 5 minutes in the supine position. An orthostatic systolic decrease of 10 to 25 mmHg, when associated with a systolic blood pressure decreases too less than 90 mmHg upon standing with or without symptoms, was also considered as a probable cause. Further categorisation was made based on the concomitant intake of hypotensive drugs, hypovolemia or postprandial circumstances

Seizure disorder, transient ischemic attacks (TAI) and psychiatric disorders
To implicate a seizure disorder as the cause of syncope, the patient had to either have had a witnessed episode of tonic-clonic movements of prolonged duration, unconsciousness longer than 5 minutes or a post-ictal state, with electroencephalographic findings used to confirm the presence of a seizure focus.

TIA was defined as an episode of temporary and focal cerebral dysfunction (such as symptoms of vertebrobasilar ischemia, impaired sensory or motor function or transient amaurosis)lasting up to 24 hours followed by complete recovery. Confirmation by a staff neurologist was required in order to diagnose a seizure disorder or a TIA as the cause of loss of consciousness.

Psychiatric illnesses considered as potentially diagnostic were generalized panic disorders, panic and somatization disorders, associated or not with major depression, with evaluation by a staff psychiatrist [100].

Subclavian steal syndrome
Syncope due to a subclavian steal syndrome was diagnosed when typical clinical manifestations were present and a subclavian steal was demonstrated by Doppler ultrasound or angiography

7.2 Diagnostic criteria for cardiac causes [67, 99]

(Also reviewed under diagnostic criteria for ***echocardiography***)

Aortic stenosis and hypertrophic cardiomyopathy [101]
Aortic stenosis was considered the cause of syncope clinically it was suspected with the presence of an aortic systolic murmur and syncope with exertion and when there was clear-cut findings compatible with severe outflow tract obstruction on echocardiography or if severe outflow obstruction was documented by cardiac catheterisation.

Pulmonary hypertension [102]
Pulmonary hypertension was implicated as a cause of syncope if the pulmonary artery pressure or the mean pulmonary artery pressure exceeded 30 mmHg at rest on echocardiography, and if there is no other apparent cause of syncope

Myocardial infraction
Myocardial infarction was implicated only if a patient presents with syncope and has concurrent standard criteria for the diagnosis were present such as typical evolutionary ECG changes and or compatible cardiac enzyme elevations and there was no other documented cause such as arrhythmias

Pulmonary embolism [103, 104]
Pulmonary embolism was implicated as the cause of syncope if the clinical presentation was compatible and lower limb Doppler ultrasound, lung scan or angiography confirmed the diagnosis.

Carotid sinus hypersensitivity syncope
Carotid sinus syncope was defined as a cardiac asystole of $\geq$ 3 seconds and/or a decrease in systolic blood pressure of greater than 50 mmHg when the carotid sinus was stimulated for up to 5 seconds. In addition, the syncopal episode must have been precipitated by activities which pressed on or stretched the carotid sinus

Dysrthymias
Criteria for abnormal but non diagnostic electrocardiographic findings and for diagnostic electrocardiographic findings are defined under ECG anomalies.

7.3 Diagnostic criteria for diagnostic tests [67]

Prolonged electrocardiographic monitoring was performed using 24-hour Holter and continuous-loop event recorders (R-Test Evolution, Novacor SA, France)

ECG, Holter and loop recorder

Clinical and ECG anomalies diagnostic of the origin of syncope

i. Sinus pause (asystole) ≥ 3 secondes
ii. Sinus bradycardia ≤ 35/min
iii. Second degree atrioventricular (AV) bloc, Mobitz II° type 2
iv. Complete atrioventricular (AV) bloc, Mobitz III°
v. Symptomatic or sustained ventricular tachycardia (≥ 30 seconds)
vi. Non sustained ventricular tachycardia (≤ 30 seconds) ≥ 5 seconds ≥ 100/min
vii. Supraventricular tachycardia ≥ 30 seconds at ≥ 180/min or associated with systolic hypotension (≤ 90 mmHg)
viii. Atrial fibrillation ≥ 30 seconds with a slow ventricular response or a rapid ventricular rate at ≥ 180/min.

ECG Anomalies possibly diagnostic of syncope

i. Asystole ≥ 2secondes-≤ 3 seconds with syncope or presyncope
ii. Symtomatic sinus bradycardia between 35-40/min
iii. Atrioventricular (AV) Bloc II° type 1
iv. Left or right bundle branch bloc
v. Non sustained ventricular tachycardia (≤ 30 seconds) ≥ 3 beats but ≤ 30 sec.
vii. Supraventricular tachycardia ≤ 30 seconds
viii. Atrial fibrillation ≤ 30 seconds
ix. Ventricular extrasystole ≥ 10/hour
x. ST segment elevation or decrease ≥ 1mm

Electrophysiologic studies (EPS) [105-107]

Electrophysiological studies were restricted to patients fulfilling literature based recommendations. The indications for electrophysiological testing included:

1. Patients with previous myocardial infarction associated with left ventricular fraction ≤ 40%
2. Late potentials on signal-averaged electrocardiogram associated with previous myocardial infraction or episodes of nonsustained ventricular tachycardia during Holter monitoring
3. Electrocardiographic findings suggestive of sinus node dysfunction or atrioventricular block (such as bundle branche block (with or without axis deviation) with or without 1° atrioventricular block) or permanent or intermittent AV conducting abnormalities.

Abnormal EPS with diagnostic findings

i. Prolonged corrected sinus node recovery time (CSNRT) > 550 milliseconds
ii. H-V interval > 100 milliseconds
iii. H-V with Ajmaline > 100ms or doubled or distal block (induced infra-Hisien block)
iv. Sustained ventricular tachycardia (> 30 seconds)
v. Supraventricular tachycardia or atrial fibrillation ≥ 180/min associated with hypotension (supine systolic blood pressure < 80mmHg)

Abnormal EPS with suggestive findings

i. Corrected sinus node recovery time (CSNRT) 550-600 ms
ii. Wenckebach < 120bpm (despite 1mg Atropine)
iii. H-V interval 55-100 ms
iv. H-V wuth Ajmaline 55-100 ms
v. Supraventricular tachycardia with symptoms

Signal-average ECG [108, 109]

Signal-averaged ECG is used to reduce random noise in electrocardiographic recordings and to enhance detection of low-amplitude signals in the terminal portion of the QRS complex. A HI-RES Module system (Marquette Inc., France) with bidirectional Butterworth filtering (40-250 Hz) was used in this study.

Late potentials were considered present if two out of three criteria were present, namely:
i. Total filtered QRS vector magnitude > 117 milliseconds
ii. Low amplitude signal (LAS)-40 > 38 milliseconds
iii. Root –mean-square voltage (RMS) < 20 μv

Echocardiography [110]

Diagnostic echocardiography
i. Aortic stenosis with a mean aortic gradient exceeding 50 mmHg and a valvular area ≤ 0.9 cm2
ii. Hypertrophic cardiomyopathy with or without outflow obstruction
iii. Pulmonary hypertension with mean pulmonary artery pressure exceeding 30mmHg
iv. Left atrial myxoma or thrombus with mitral protrusion and outflow obstruction

Abnormal echocardiography (structural heart disease)
i. Aortic stenosis with a gradient > 20mmHg and < 50mmHg
ii. Moderate or severe aortic insufficiency
iii. Mitral stenosis (valvular area < 2 cm2)
iv. Diffuse or localized left (right) ventricular hypokinesia
v. Left ventricular dilatation or hypertrophy (left ventricle diastolic Ø >56 mm, left ventricle systolic Ø > 400mm, left atrial Ø > 40 mm, septum Ø > 11 mm)
vi. Left ventricular ejection fraction < 55%
vii. Pulmonary hypertension with a mean pulmonary artery pressure > 20 mmHg and < 30 mmHg
viii. Interatrial septal defect, septum aneurysm, thrombus, tumor

Non significant abnormalities
i. Aortic sclerosis
ii. Aortic stenosis with a mean aortic gradient < 20 mmHg
iii. Moderate aortic, mitral or pulmonary insufficiency
iv. Moderate enlargement of left atrium

Upright tilt testing [111, 112]

Protocol During the passive upright-tilt testing protocol on a foot-plate motorized table, blood pressure was monitored using cuff blood pressure measurements at 1 minute intervals with continuous electrocardiographic tracings. After measurements of the supine baseline blood pressure and heat rate, patients were suddenly brought to an upright position, at an angle of 60 degrees for a duration of 45 minutes. The end points of a positive tilt test were the development of syncope or presyncope in association with hypotension or bradycardia (or both).

Three principal response patterns during head-upright tilt-table testing have been described, based on hemodynamic and heart rate responses:

1. Type I (mixed). Initial increase in heart rate during tilt that later decreases but remains greater than 40 bpm or is less than 40 bpm only briefly (< 10 seconds) and without asystole. Asystolic period > 3 seconds. There may be an initial increase in blood pressure, which then decreases before heart rate decreases.
2. Type IIA (cardioinhibitory). Initial increase in heart rate during tilt, which then decreases to < 40 bpm for > 10 seconds or has asystole for > 3 seconds. There may be an initial increase in blood pressure, which then decreases before the heart rate decreases.
3. Type IIB (cardioinhibitory). Initial increase in heart rate followed by a decrese tp < 40 bpm for > 10 seconds, or has asystole > 3 seconds. Hypotension occurs only at or after the time at which the heart rate decreases.
4. Type III (pure vasodepressor). Initial increases in heart rate, which decreases less than 10% from the peak value at the time of syncope. Hypotension alone accounts for syncope.

7.4 Standardized form

Bilan Initial

Rappel: syncope=perte soudaine de connaissance transitoire avec perte de contrôle postural et récupération spontanée ne nécessitant pas de cardioversion électrique ou chimique.

A. Antécédents Personnels

Cardiaque:	1- Maladie coronarienne connue:	oui ☐	non ☐
	2- Infarctus ancien:	oui ☐	non ☐
	3- Insuff. cardiaque clinique:	oui ☐	non ☐
	4- Autre cardiopathie connue:	oui ☐	non ☐
	Si oui: 5- valvulaire	oui ☐	non ☐
	6- dilatée	oui ☐	non ☐
	7- autre	oui ☐	non ☐
FRCV:	8- HTA:	oui ☐	non ☐
	9- Diabète:	oui ☐	non ☐
	10- Hyperlipémie:	oui ☐	non ☐
	11- infarctus < 50 ans c/o proche:	oui ☐	non ☐
	12- Tabagisme actif:	oui ☐	non ☐

Comorbidités connues à l'entrée (selon Charlson):

13- Maladie vasculaire périphérique	oui ☐	non ☐
14- AVC avec séquelle (hémiplégie)	oui ☐	non ☐
15- AVC sans séquelle	oui ☐	non ☐
16- Démence	oui ☐	non ☐
17- Diabète avec atteinte d'organe	oui ☐	non ☐
18- COPD	oui ☐	non ☐
19- Insuffisance hépatocellulaire	oui ☐	non ☐
20- Insuffisance rénale sévère	oui ☐	non ☐
21- Néoplasie, lymphome	oui ☐	non ☐
22- Métastases	oui ☐	non ☐
23- SIDA	oui ☐	non ☐
24- Collagénose	oui ☐	non ☐
25- Maladie ulcéreuse gastroduodénale	oui ☐	non ☐

B. Anamnèse Actuelle et Examen Physique

1) Eléments relatifs à une cardiopathie concomitante

26- Angor ? : 1.- non 2.- d'effort 3.- de repos	27- Dyspnée ? : 1.- non 2.- d'effort grade I/II 3.- d'effort grade III/IV

28- Episode de dyspnée paroxystique	oui ☐	non ☐
29- Oedèmes des MI (anamn. ou clinique)	oui ☐	non ☐
30- HTA actuelle (>160/100 mmHg)	oui ☐	non ☐
31- Présence d'un B3 (galop)	oui ☐	non ☐
32- Râles de stase	oui ☐	non ☐
33- Signes d'IC droite	oui ☐	non ☐
34- Cardiomégalie radiologique	oui ☐	non ☐ ? ☐

2) Eléments anamnestiques relatifs à l'épisode syncopal

35- Episode syncopal ? 1.- 1 er 2.- 2 ème 3.- 3 ème ou plus	36- Si pas le premier, dernier épisode < 1 an ? : oui ☐ non ☐

Signes et symptômes avant et après la syncope ?: oui ☐ non ☐

Si oui,?:

37- Durée des signes prémonitoires ?: (avant la syncope) ☐
1.- < 5 secondes
2.- > 5 secondes
3.- non précisable

	Avant	***Après***
38- nausée:	☐	☐
39- vomissements:	☐	☐
40- chaleur:	☐	☐
41- sudations abondantes:	☐	☐
42- tête vide:	☐	☐
43- palpitations:	☐	☐
44- vision trouble:	☐	☐
45- fatigue:	☐	☐
46- Autre élément anamnestique relatif à la syncope:	.....	.....

47- Facteur ayant précipité la syncope	***Oui***	***Commentaires***:
a) Blessure/injection/instrumentation:	☐	.....
b) Douleur intense:	☐	.....
c) Emotion / choc émotionnel:	☐	.....
d) Angoisse / peur:	☐	.....
e) Repas copieux:	☐	.....
f) Fatigue extrême:	☐	.....
g) Station debout prolongée:	☐	.....
h) Chaleur (bain / douche chaude, soleil, pièce bondée):	☐	.....
i) Manoeuvre de type Valsalva (eg. Soulevé poids, trompette):	☐	.....

➔ **Syncope vasovagale (si un des facteurs sous 47 = positif)**

CAVE: La seule existence de symptomes neurovégétatifs ne Pose pas le diagnostic de syncope d'origine vasovagale.

48- Syncope après toux paroxystique	oui ☐	non ☐
49- Syncope pdt ou après miction	oui ☐	non ☐
50- Syncope pdt ou après défécation/déglutition	oui ☐	non ☐

➔ **Syncope situationelle (48, 49 ou 50 = positif)**

Présence d'un signe clinique évocateur d'une crise épileptique:

51- Témoignage de mouvements tonico-cloniques	oui ☐	non ☐
52- Témoignage d'un état post-critique	oui ☐	non ☐
53- Cyanose faciale	oui ☐	non ☐
54- Morsure de langue	oui ☐	non ☐
55- Désorientation post-critique	oui ☐	non ☐
56- Perte de connaissance ≥ 5 min.	oui ☐	non ☐

➔ **Suspicion de syncope d'origine épileptique: à rechercher (consultation neurol., EEG) si 51, 52, 53, 54, 55 ou 56 =positif**

Présence d'un déficit neurologique aigu focal transitoire (<24hr) à l'anamnèse ou au status:		Aucun: ☐
Si déficit, lequel:	57- parésie	oui ☐
	58- amaurose	oui ☐
	59- troubles sensitifs	oui ☐
	60- troubles cérébelleux	oui ☐
	61- Autre:	
➔ **Suspicion de syncope secondaire à un accident vasculaire cérébral: à rechercher si présence d'un déficit neurologique aigu focal transitoire**		

62- Asymétrie de la TAH aux 2 bras ≥ 25 mmHg	oui ☐	non ☐
➔ **Suspicion de syncope secondaire à un vol sous-clavier: à rechercher si 62 = positif**		

63- Souffle systolique aortique	oui ☐	non ☐
64- Syncope à l'effort	oui ☐	non ☐
65- Syncope + douleur retrosternales	oui ☐	non ☐
66- Ralentissement montée carotidienne	oui ☐	non ☐
➔ **Supicion de syncope secondaire à une sténose aortique: à rechercher si 63,64,65 ou 66 = positif**		

67- Suspicion HTA pulmonaire (dyspnée, syncope à l'effort, B2 claqué, choc droit)	oui ☐	non ☐
➔ **Suspicion de syncope secondaire à une HTAP: à rechercher si 67 = positif**		

68- Suspicion d'embolie pulmonaire	oui ☐	non ☐
➔ **Suspicion de syncope sur EP: à rechercher (scinti, angio) si 68 = positif**		

C. Recherche d'hypotension, dysfonctions vagales, anomalies ECG ou labo

Tension artérielle (TA) *Test de Schellong*

Prise du pouls et de la tension artérielle coucher, immédiatement au lever, puis durant les minutes qui suivent	**TAH**	**Pouls**	**Observations**
Position couchée (5-10 min):			
Position debout (sans appui) ➔ temps (Min): 0			
+1			
+2			
+3			
+4			
+5			

69- Résultats: ☐

1.- Chute de la TA syst. debout ≥ 25 mmHg avec symptômes neurovégétatifs
2.- Chute de la TA syst.≥10 mmHg et ≤ 25 mmHg avec une valeur abs. de la TA syst.≤90 mmHg
3.- Pas de changements tensionnels diagnostique

➔ **Syncope orthostatique (69.1 ou 69.2 = positif)**

70- Prise concomitante de médicaments hypotenseurs: oui ☐ non ☐
Si oui, lesquels: .....
.....

71- Réaction de type anaphylactique: oui ☐ non ☐

72- Hypotension artérielle documentée: oui ☐ non ☐
(voir critères sous No.69)

➔ **Syncope médicamenteuse (si (70 ou 71) + 72 = positif)**

Hypersensibilité du sinus carotidien ou anomalies au Valsalva

73- Asystolie ≥ 3":	- au massage du sinus G:	oui □	non □
	- au massage du sinus D:	oui □	non □
	- au Valsalva:	oui □	non □
74- Chute de la TAH	- au massage du sinus G:	oui □	non □
≥ 50 mmHg:	- au massage du sinus D:	oui □	non □
	- au Valsalva:	oui □	non □
Autre anomalie ECG pendant manoeuvres:		.....	
75- Evénement compressif sur la carotide:		oui □	non □

➔ Syncope sur dysfonction du sinus ou Valsalva (73,74, ∓ 75 = positif)

***Manoeuvre de Valsalva*:**

Doit être conduit sous monitoring ECG avec tracé.

***Massage du sinus carotidien*:**

Inclure le tracé ECG (ou copie) des manoeuvres avec ce questionnaire.

N.B Si l'une (ou plus) des conditions suivantes est présente, ne pas effectuer la manoeuvre:

a) bruits carotidiens (qui évoqueraient une maladie carotidienne);
b) maladie cérébrovasculaire préexistante;
c) ischémie myocardique ou cérébral;
d) antécédents de tachyarythmies ventriculaires;
e) autre contre-indication.

Procédure: Le patient, ***connecté à un ECG continue***, est mis en position de décubitus dorsal, le cou hypertendu et la tête tournée du côté opposé à celui en train d'être testé. La bifurcation carotidienne (2 à 3 cm sous l'angle mandibulaire, derrière le chef ant. du mm SCM) est légèrement touchée avec la portion palmaire des doigts pour détecter une réponse d'hypersensibilité. Si aucun changement du rythme cardiaque n'est observé, alors on procédera a l'application d'une pression plus ferme pendant environ 5 secondes. Bien que les 2 côtés doivent être testés, on ne doit pas procéder à un massage bilatéral simultané, et on attendra en conséquence 15 sec avant de procéder à la stimulation du côté opposé.

N.B Un matériel de réanimation (eg. atropine) doit être à disposition. Les complications du massage du sinus carotidien comprennent entre autres l'asystolie prolongée et la fibrillation ventriculaire.

ECG ECG normal: oui □ non □

Si non, 76- Asystolie ≥ 3" à L'ECG oui □ non □
77- Bradycardie ≤ 35/min oui □ non □
78- Bloc A-V II° type 2 oui □ non □
79- Bloc A-V III° oui □ non □
80- Tachycardie ventriculaire soutenue (≥ 30") oui □ non □

➔ **Syncope sur arythmies: (76,77,78,79 ou 80 = positif**)

81- Ancien infarctus oui □ non □
82- Asystolie ≥ 2"-≤ 3" oui □ non □
83- Bradycardie 35-40/min oui □ non □
84- Bloc A-V II° type 1 oui □ non □
85- BB gauche ou droit oui □ non □
86- Tachy. ventriculaire non soutenue (≤ 30") oui □ non □
87- TSV > 30 sec, frequemce > 180/min oui □ non □
88- ESV multiples > 10/heure oui □ non □
89- Sus ou sous-décalage du segment ST≥1mm oui □ non □
Autre: .....

➔**Anomalies ECG non diagnostiques:**
(si 81, 82, 83, 84, 85,86,87,88, ou 89 = positif)

Si sus ou sous-décalage du segment ST ≥ 1mm ou douleur d'angine de poitrine ➔rechercher une ischémie cardiaque aigue

90- Suspicion d'ischémie cardiaque aigue oui □ non □

Labo

91- Glycémie ≤ 3 mmol/l oui □ non □
92- CPK totaux ≥ 200 U/l oui □ non □
93- Hématocrite < 30 % oui □ non □

D. Investigations en cas de diagnostic suspecté

➔ ***A remplir si ces investigations sont fait au DUMC***

Investigations en cas de suspicion de maladie neurologique (Epilepsie, AIT?)

94- EEG	oui □	non □
95- Ct Scan cérébral	oui □	non □
96- Doppler-US	oui □	non □
97- Consultation Neurologie	oui □	non □
98- Autres:		

Investigations en cas de suspicion de vol sous-clavier?

99- Bilan angiologique des MS	oui □	non □

Investigations en cas de suspicion de sténose aortique ou d'hypertension artérielle pulmonaire?

100- Echographie cardiaque	oui □	non □

Investigations en cas de diagnostic suspécté d'embolie pulmonaire?

101- Scintigraphi	oui □	non □
102- Angiographie pulmonaire	oui □	non □
103- Bilan angiologique des MI	oui □	non □
104- Dosage des D-dimères	oui □	non □

Suivi médical

Traitement de sortie: **Date:** .....

185- Pace-Maker oui ☐ non ☐
186- Défibrillateur implantable oui ☐ non ☐
187- Antiarythmique oui ☐ non ☐
188- Type d'antiarythmique: .....

Suivi à 3 mois: oui ☐ non ☐
Date: ..... Si non, raison: .....
189- Va bien oui ☐ non ☐
190- Récidive syncope oui ☐ non ☐
191- Réhospitalisation oui ☐ non ☐
Commentaires: .....
192- Décès oui ☐ non ☐
Cause du décès: 1.-Mort subite
☐ 2.-Autre: .....

Suivi à 6 mois: oui ☐ non ☐
Date: ..... Si non, raison: .....
193- Va bien oui ☐ non ☐
194- Récidive syncope oui ☐ non ☐
195- Réhospitalisation oui ☐ non ☐
Commentaires: .....
196- Décès oui ☐ non ☐
Cause du décès: 1.-Mort subite
☐ 2.-Autre: .....

Suivi à 12 mois: oui ☐ non ☐
Date: ..... Si non, raison: .....
197- Va bien oui ☐ non ☐
198- Récidive syncope oui ☐ non ☐
199- Réhospitalisation oui ☐ non ☐
Commentaires: .....
200- Décès oui ☐ non ☐
Cause du décès: 1.-Mort subite
☐ 2.-Autre: .....

Suivi à 18 mois: oui ☐ non ☐
Date: ..... Si non, raison: .....
201- Va bien oui ☐ non ☐
202- Récidive syncope oui ☐ non ☐
203- Réhospitalisation oui ☐ non ☐
Commentaires: .....
204- Décès oui ☐ non ☐
Cause du décès: 1.-Mort subite
☐ 2.-Autre: .....

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