Characterization of Different Responses to Tilting Table Test in Children and Teenagers with Neurocardiogenic Syncope

Thesis

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Introduction

The loss of consciousness has been a subject of wonder and uncertainty in humans, and for this reason it has been the object of medical investigation since the beginning of time. Even actually, it is certainly an unresolved clinical problem. Many centuries ago, complicated exorcisms and remedies were used on these unfortunate patients, who upon regaining consciousness would find themselves soaked in miraculous liquids, ingesting curative potions, and often on the way to be burned accused of being possessed ***(Gonzalo et al., 2003).***

In the seventeen century, physicians began to relate loss of consciousness and hemodynamic changes. William Harvey was perhaps the first to describe a circulatory response (vasovagal reaction) during a phlebotomy in the year 1628: "...Yet it fear or any other cause, or something do intervene through passion of the mind, so that the heart do beat more faintly, the blood will be no means pass through but drop after drop…" ***(Gonzalo et al., 2003).***

During the nineteenth century, loss of consciousness was the object of studies and research, and the vagally mediated cardioinhibition, as a primary cause, was noted by Foster who proposed that profound bradycardia diminished cerebral perfusion to a level inadequate to maintain consciousness ***(Gonzalo et al., 2003).***

At this time, it was reported the first use of the tilt-table test ***(Gonzalo et al., 2003).*** Commonly referred to as fainting or loss of consciousness, from last century the preferred medical

term is syncope, which itself is derived from the Greek term "syncoptein" meaning "to cut short". Syncope is defined as the sudden loss of consciousness and postural tone with spontaneous recovery. In 1907, Gowers was the first person to use the term vasovagal syncope ***(Gonzalo et al., 2003).***

In 1918 was published the work in which Cotton and Lewis described for the first time the clinical characteristics that are still used today to recognize the syncopal reaction ***(Gonzalo et al., 2003).*** However, it was not till 1932 when Lewis described this reaction as being characterized by a combination of bradycardia, hypotension, and syncope, and he coined the term vasovagal syncope for the first time ***(Gonzalo et al., 2003).***

It is estimated that up to 15% of children will experience a syncopal episode before the end of adolescence ***(Benditt et al. 1996).***

Syncope is a relatively frequent symptom in children and its evaluation is an important aspect in pediatric medical practice ***(Kilic et al., 2002).*** Although the incidence of pediatric syncope is difficult to assess, it appears to peak around the age of 15 years, with 20% to 50% of females reporting to have experienced at least one syncopal episode by the age of 20 years ***(Ganzeboom et al., 2003).***

Aim of the Work

The aim of the work is to demonstrate different responses to tilting table test among children and teenagers with suspected neurocardiogenic syncope.

Syncope

Definitions:

Is syncope a symptom?

The word "symptom" is generally accepted to mean "a sensation or change in health function experienced by a patient." This definition certainly applies to "syncope," but this, of course, is insufficient to fully characterize the term "syncope" ***(Benditt et al., 2007).***

- **Syncope** is a symptom defined as a transient spontaneous loss of consciousness with a rapid onset, and self-limited, complete, and usually prompt recovery the underlying mechanism of which is a transient global cerebral hypoperfusion ***(Benditt et al., 2007).*** The most common type is neurocardiogenic syncope (NCS) which accounts for 10-40% of episodes ***(Grubb et al., 2005).***

- **Presyncope** is a state of light headedness usually associated with decrease of vision or sensation of hearing voices distally or slow response to verbal stimuli or nausea or vomiting ***(Zeng et al., 1998).***

Syncope is a symptom, but is it the same as transient loss of consciousness (TLOC)?

Determining whether TLOC actually occurred in a given clinical situation may not be easy; it can only be derived from careful evaluation of the history taken from the patient or from eye witnesses. In the absence of TLOC the diagnosis of syncope should be excluded. However, the concept of TLOC is much broader than just "syncope." TLOC incorporates many other conditions that cause self-limited loss of consciousness but are not due to cerebral hypoperfusion (e.g., epilepsy, concussion, and intoxication) ***(Benditt et al., 2007).***

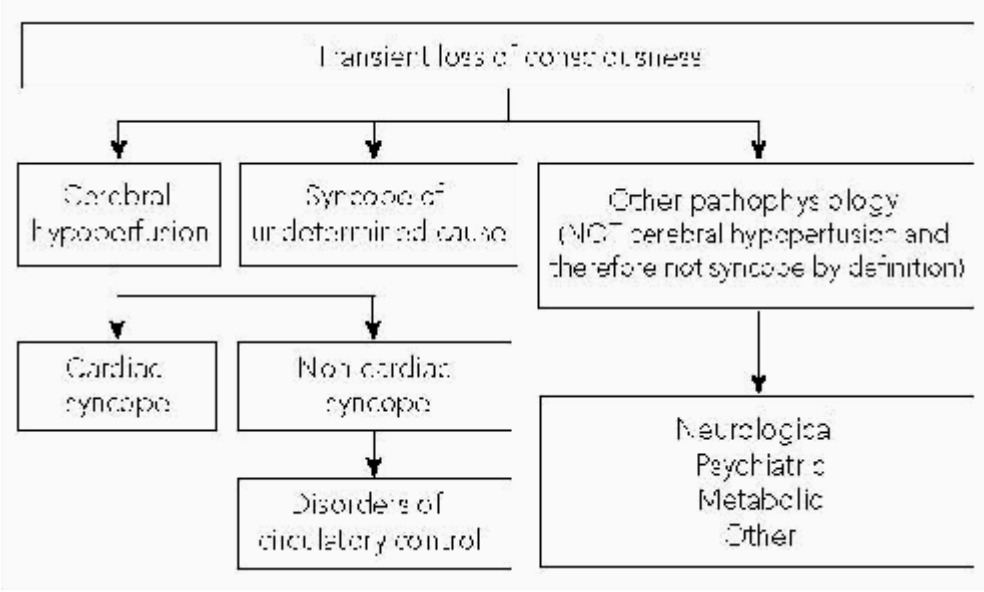

Figure (1): Physiological classification of transient loss of consciousness ***(Vaddadi et al., 2007).***

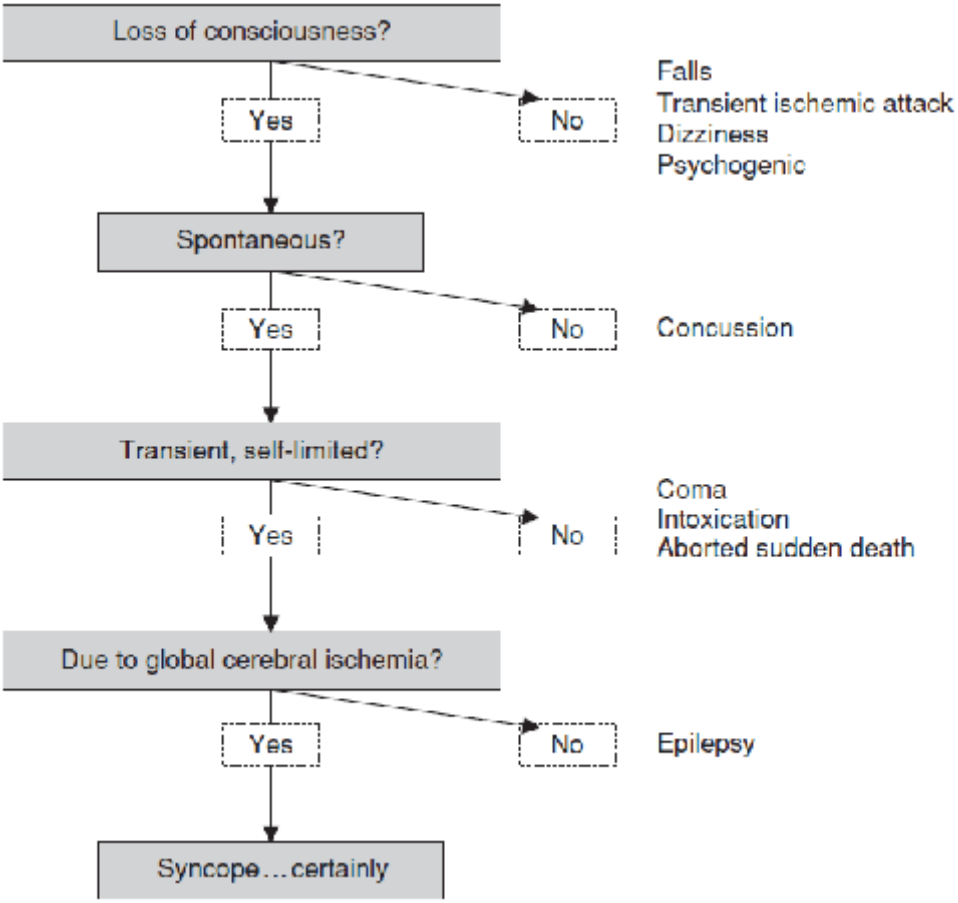

Figure (2): Flowchart summarizing the diagnosis strategy from TLOC to syncope ***(Benditt et al., 2007).***

Epidemiology:

Syncope results in 3% of emergency room visits, 1%–6% of hospital admissions and costs $750 million per year to

diagnose and treat ***(Maisel et al., 2002).*** Although sometimes associated with sudden death, the causes of syncope can be difficult to diagnose ***(Kapoor, 2000).***

The overall incidence rate, a ratio of number of patients with syncope to number of person-years, of a first report of syncope is 6.2 per 1000 person years ***(Soteriades et al., 2002).*** It is 2.6%–5.7% in the 20–69 years age group, increasing to 11.1% after 70 years. In octogenarians, it is 16.9% in men and 19.5% in women ***(Soteriades et al., 2002).***

Morbidity, even from "benign" causes of syncope, is profound: 70% of people experiencing recurrent syncope suffer impairment to activities of daily living, 6% suffer fractures, 64% restrict their driving and 39% change employment ***(van Dijk et al., 2006).***

When does syncope start?

The age of a "first faint" in a population of children and adolescents less than 22 years was highest between ages 15 and 19 years ***(Driscoll et al., 1997).*** Vasovagal syncope appears to be quite uncommon before age 8 years, and the incidence of first faint accelerates rapidly through adolescence ***(Serletis et al., 2006).*** The modal age at first faint—the age at which the largest proportion of people have their first faint—is about 14 years, and the median age of first faint is about 18 years. Males and females begin to faint at the same age. Very few people, about 6%, have a first faint after age 40. Indeed, an early age of

onset of syncope is almost pathognomonic of vasovagal syncope ***(Serletis et al., 2006).***

Fainting and the female gender

Societal myths abound that fainting is a female problem; the simple swoon of Victorian romances ***(Benditt et al., 2007).*** *Is there truth in this? By age 60, 31% of males and 42% of females had fainted* ***(Serletis et al., 2006).*** Even more strikingly, although both males and females begin fainting at the same age, the proportion of females who faint reaches an asymptote by about age 30, while the proportion of males who faint reaches its asymptote by about age 50. Therefore, not only are females more likely to faint than males, but young females are particularly more likely to faint than young males ***(Benditt et al., 2007).***

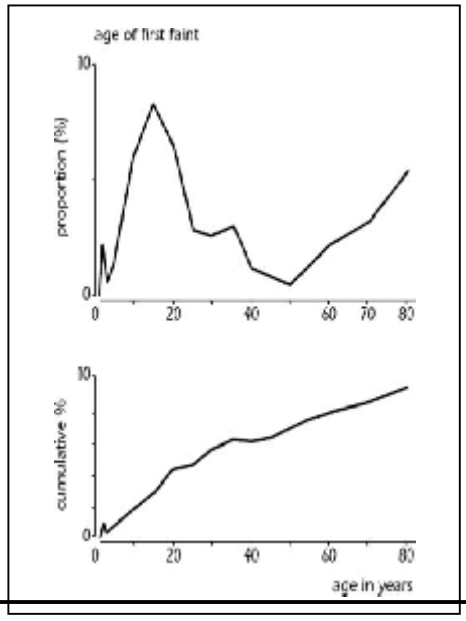

Figure (3): Schematic presentation of the distribution of age and cumulative incidence of first episode of syncope in the general population from subjects up to 80 years is shown ***(ESC Guidelines., 2009).***

Syncope Burden:

"The only difference between syncope and sudden death is that in one you wake up" ***(Engel, 1978).***

Table (1): Syncope Burden ***(Sealey et al., 2004)***

Syncope Burden	
United States syncope patients	Over 1 million; increases by 500,000 new cases/yr
Hospital admission cost	$1,006/day
Emergency room cost	$320 to $700/visit
Incidence in general population	3% in men; 3.5% in women. Framingham Study: 3.3% in 30 to 62 yrs of age; increases with age
Emergency room visits	5%
Urgent hospital admissions	6%
Medicare hospital DRG charges	ranks 37th
Diagnostic testing; only 50% of all patients receive a conclusive diagnosis	>$16,000
Inpatient diagnostic yield	47% to 53% over age 65 (Medicare)
Highest morbidity and mortality	Elderly
Lifetime cost for syncope falls over age 65	$12.6 billion
Anxiety and depression	76%
Negative impact	activities and daily living, 71%; driving, 64%; physical activities, 56%; employment, 39%; sexual function, 30%; decreased relationships, 26%
Annual mortality in noncardiac syncope	5-10%
Annual mortality in cardiac syncope	20-30%

Mechanism and Pathophysiology of syncope in children & adolescents:

A sudden cessation of cerebral blood flow for only about 10 s has been shown to be sufficient to cause complete loss of consciousness. Furthermore, it has been estimated that a drop of as little as 20% in cerebral oxygen delivery is sufficient to cause unconsciousness ***(Benditt, 2006).***

In healthy young persons, cerebral blood flow lies in the range of 50–60 mL per 100 g of brain tissue per min, representing about 12–15% of resting cardiac output. A flow of this magnitude easily meets the minimum oxygen (O2) requirement to sustain consciousness (approximately 3.0–3.5 mL O2/100 g tissue/min). However, the safety factor for O2 delivery may be markedly impaired in older individuals or in those with diseases like diabetes mellitus or hypertension ***(Benditt, 2006).***

The integrity of a number of control mechanisms is crucial for maintaining adequate cerebral O_2 delivery:

- ***Arterial baroreceptor-induced adjustments*** of systemic vascular resistance, cardiac contractility, and heart rate all act to modify systemic circulatory dynamics in order to protect cerebral blood flow.
- ***Intravascular volume regulation,*** incorporating renal and hormonal influences, helps to maintain central blood volume ***(Benditt, 2006).***

- ***Cerebrovascular autoregulation*** permits cerebral blood flow to be maintained over a relatively wide range of perfusion pressures ***(Benditt, 2006).***

Transient failure of protective mechanisms or the additional effects of other factors such as vasodilator drugs, diuretics, dehydration, or haemorrhage, any of which reduce systemic blood pressure below the autoregulatory range, may induce a syncope episode. Risk of failure of normal protective compensatory mechanisms is greatest in older patients or those who are ill ***(Benditt, 2006).***

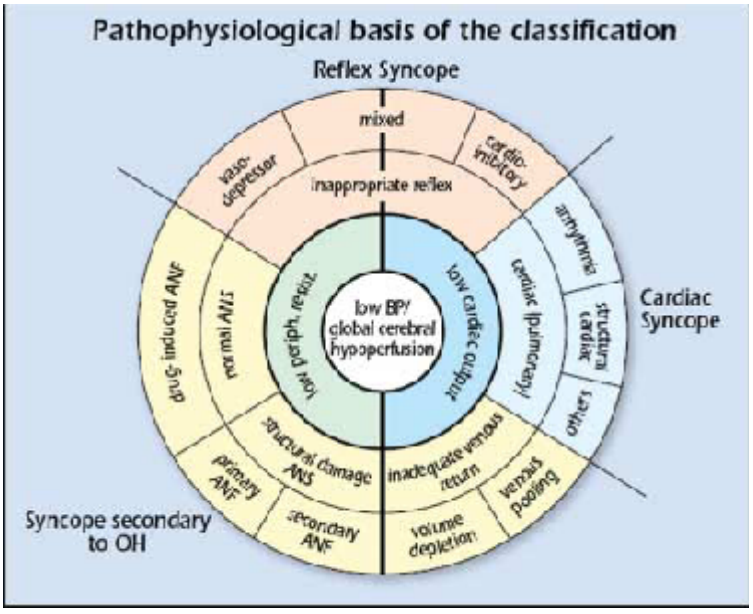

Figure (4): Pathophysiological basis of the classification. ANF= autonomic nervous failure; ANS= autonomic nervous system; BP =blood pressure; low periph. resist. =low peripheral resistance; OH ¼ orthostatic hypotension ***(ESC Guidelines, 2009).***

What is the physiology of upright posture?

When humans stand up, 500–1000 mL of blood is transferred from the chest to the distensible venous system below the diaphragm. Up to 50% of the total shift occurs within the first 10 seconds. Most of this pooled blood is contained within the large deep veins of the legs ***(Wieling and van Lieshout, 2007).*** Pooling in the splanchnic area during actual orthostasis (standing/head-up tilting) seems to be more important than that previously reported in studies using simulated orthostasis by applying lower body negative pressure ***(Taneja et al., 2007).***

Mechanical factors are important in opposing gravitational pooling of blood. Leg crossing and contraction of leg and abdominal muscles have been shown to be beneficial to prevent orthostatic and vasovagal faints ***(Krediet et al., 2005).*** Another option is to enhance the thoracoabdominal pump effect by inspiration through a narrow lumen or predetermined resistance device (impedance threshold device, ITD) that acts as a resistance ***(Thijs et al., 2007).*** In the case of the ITD, the forced increase in negative intrathoracic pressure during inspiration acts to enhance venous return to the central circulation and at the same time improve the gradient for blood flow across the cerebral circulation ***(Wieling and van Lieshout, 2007).***

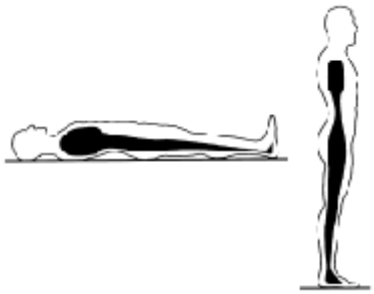

Figure (5): Schematic drawing illustrating the influence of posture on intravascular volume. Note that in the supine figure (left), central blood volume (intrathoracic) is greater than when the figure is upright (right). The shift in blood volume to the lower extremities reduces venous return and cardiac output ***(Benditt, 2006).***

The instantaneous and fast venous pooling of blood on arising results in a rapid diminution of the central blood volume. Unless compensatory adjustments are promptly instituted, arterial pressure falls and the subject faints or develops symptoms of a near faint (e.g., light-headedness and temporary diminished vision). The arterial (especially carotid) baroreceptor control of sympathetic vasomotor tone of resistance and splanchnic capacitance vessels is the most important component in the maintenance of postural normotension in humans ***(Wieling and van Lieshout, 2007).***

The adjustment to upright posture (orthostatic adjustment) may reasonably be classified into three phases: an initial response (first 30 s), an early phase of stabilization (1–2 min upright), and prolonged orthostasis (>5 min upright). This classification is both appropriate from the physiological perspective and of direct clinical relevance ***(Wieling and van Lieshout, 2007).***

- ***The first*** *(initial) phase corresponds to immediate complaints of presyncope and syncope upon arising suddenly after prolonged supine rest or after arising from the squatted position* ***(Wieling et al., 2007).***

- ***The second*** *(early) phase accounts for blood pressure measurements commonly used to assess orthostatic hypotension in the office or bedside. Depending on the clinical setting, orthostatic hypotension will be detected in 50–100% of the patients with autonomic disturbances within 3 minutes in the upright posture* ***(Gibbons and Freeman, 2006).***

- ***The third*** *phase corresponds with delayed orthostatic hypotension, such as in the postural tachycardia syndrome and susceptibility to vasovagal fainting* ***(Verheyden et al., 2007).***