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SHORT EDITORIAL

Assessment of Quality of Life after Diagnosis of Reflex Syncope: A Subjective Outcome of Great Clinical Importance with Multifactorial Cause

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Editorial referring to the article: Quality of Life After Diagnosis of Neurally Mediated Reflex Syncope by Tilt Test

Syncope, a clinical syndrome characterized by transient loss of consciousness (TLOC), is defined by specific elements, namely: sudden onset and rapid recovery, loss of postural tone, full recovery of consciousness, amnesia of the event, nonresponsiveness, and a typical event duration of up to 5 minutes (usually lasting seconds). The pathophysiology of syncope involves global cerebral hypoperfusion, primarily due to a drop in blood pressure (BP), with various factors contributing individually or in combination to syncope (Figure 1). Even brief periods of cessation of cerebral blood flow (6–8 s) or a systolic BP of 50–60 mmHg at the level of the heart (equivalent to 30–45 mmHg at the level of the brain in the upright position) can lead to TLOC. Pathophysiological mechanisms may include a decrease in peripheral vascular resistance, cardiac output, or a decrease in both. The etiology of syncope is didactically classified into three types: 1) orthostatic hypotension (OH); 2) reflex syncope (also termed vasovagal or neurally mediated syncope); and 3) cardiac syncope.[1]

Once syncope has been diagnosed, the next step is to stratify patients' risk of death for two primary purposes: 1) to identify low-risk patients in order to prevent unnecessary hospitalizations through appropriate education, and 2) to identify high-risk patients who may require urgent evaluation, sometimes requiring immediate hospitalization. High-risk patients typically present with syncope, with structural heart disease and/or primary electrical heart disease as the primary risk factors for sudden death. Conversely, low-risk patients are more likely to present with reflex syncope, which typically has an excellent prognosis.[2]

Reflex syncope is the predominant cause of syncope in all age groups. The prevalence of syncope has a bimodal distribution, with two peaks of incidence: the first occurring between the ages of 10 and 30, and the second occurring after the age of 65. While reflex syncope is a significantly more common cause of TLOC in younger individuals, older people often present with multiple underlying causes, leading to potential challenges in relying on history compared to younger populations.[3,4]

In reflex syncope, afferent pathways transmit signals from circulatory and visceral receptors to the brain. Hemodynamic instability (manifested as hypotension or tachycardia), gastrointestinal symptoms, pain, phobia, fear, and certain situations (e.g., swallowing, coughing, phlebotomy, defecation, micturition, playing brass instruments, or after exertion) are recognized triggers that activate the vagal reflex. The primary efferent responses of the vagal reflex include bradycardia or asystole, along with dilation of capacitance vessels in the splanchnic region and lower limbs, resulting in subsequent hypotension. The interaction of vasodepressor (VD) effects and bradycardia may result in VD, cardioinhibitory (CI), or mixed reflex syncope (Figure 1). In addition, higher brain functions, including emotional triggers, may facilitate or directly trigger vagal reflex activation. After the age of 40, evaluation for carotid sinus hypersensitivity (CSH) becomes critical in cases of unexplained syncope or syncope preceded by vagal autonomic prodromes, especially when venous pooling is not the primary trigger.[5]

Because of the low risk of mortality associated with reflex syncope, assessment of quality of life (QoL) is an important outcome measure for these patients. QoL

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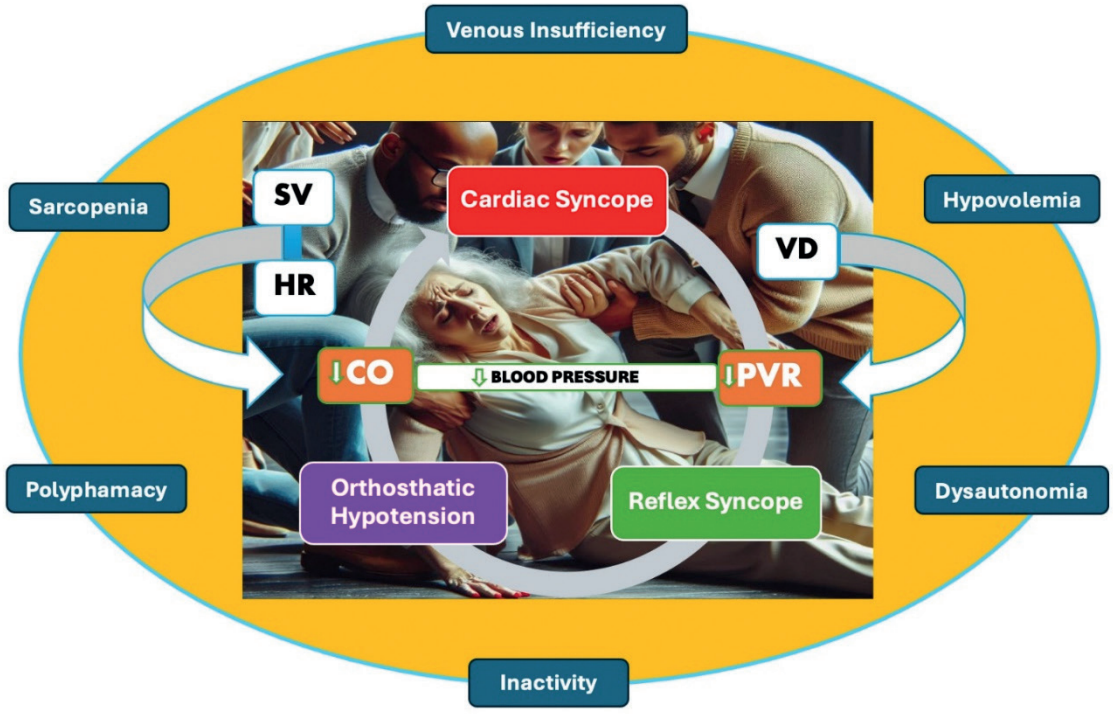

Figure 1 – Multifactorial Etiology of Syncope. Syncope arises from a decrease in blood pressure resulting from diminished cardiac output (stroke volume x heart rate) and/or decreased peripheral vascular resistance. It is classified into three primary causes: reflex syncope, cardiac syncope, and orthostatic hypotension. Various factors contribute to the occurrence of syncope, including sarcopenia, dysautonomia, polypharmacy, inactivity, hypovolemia, and venous insufficiency.
CO: cardiac output; PVR: peripheral heart vascular resistance; SV: systolic volume; HR: heart rate; VD: Vasodilation. Created by: Microsoft Copilot

appears to be correlated with recurrence rates, physical trauma from falls, and lack of symptom improvement following medical education and implementation of nonpharmacologic interventions for initial treatment. Even pharmacological treatment may have an impact on worsening QoL, considering that reflex syncope predominantly affects young patients. In addition, there is a direct relationship between the presence of depression and anxiety and poor QoL in patients with reflex syncope.[6] The recurrence rate of reflex syncope is usually 25–30% in 1 year. The number of episodes is the most important predictor of recurrence, directly related to worsening QoL.[7] Hence, reflex syncope has an important impact on QoL, especially in refractory cases.

Based on these concepts, Miranda et al.[8] conducted an important prospective and longitudinal study of 82 patients with a history of reflex syncope and a positive head-up tilt test (HUTT) to analyze the influence of the type of response in the HUTT (CI or VD) on QoL and event recurrence after the test. The study protocol consisted of administering the SF-36 and Impact of Syncope on Quality of Life (ISQL) questionnaires for 12 months after the HUTT. Syncope recurrence was analyzed using a Kaplan–Meier curve. Exclusion criteria were the presence of cardiac implantable electrical devices and chronic comorbidities. The patients were between the ages of 22.9 and 64.5 years with recurrent reflex syncope (at least more than one event prior to HUTT) and a preselection Calgary score compatible with a high likelihood of reflex syncope. They were followed for a mean of 8.4 months. Most of the population was female, 12 patients (14.7%) had syncope without prodrome, and 40.2% had trauma because of syncope. The most used HUTT protocol was the modified Italian (nitrate-sensitized test) one.

The authors found a non-significant more frequent CI response (n = 46) versus VD response (n = 36) in the population studied (72 HUTTs showed CI or VD response). There was a significantly more frequent recurrence of CI response after HUTT (56.5% in CI versus 27.7% in VD). CI response was significantly more frequent in younger patients (mean 30 years in CI versus 61.2 years in VD) and presented with significantly shorter time to event

in HUTT (mean 20.5 minutes in CI versus 24.3 minutes in VD). During follow-up, 36 patients (43.9%) had recurrences with a mean age of 35.7 years. The higher recurrence rate occurred until the fourth month, with stabilization from the eighth month. The recurrences were much more frequent in the CI response group than in the VD one, from the second month, with equal stabilization from the eighth month in both. This occurred despite the medical education and nonpharmacological treatment initiated in most patients (85.4%).

Regarding the QoL questionnaires, for question 2 of the SF-36 questionnaire used to compare general health over the previous year, 47.6% of the total population responded that they were the same as before. Looking at the groups, similarly, most of the CI response group (43.5%) and VD response group (52.8%) also answered that they were the same as before. The authors have already shown that the best scores, both on the ISQL and the SF-36 and their domains for pain and social aspects, occurred in patients without trauma in previous syncope, despite the weak correlation between the QoL questionnaires and the variable of trauma. Worse QoL occurred in nonyoung patients (patients with VD reaction) and was not influenced by syncope recurrence before and after diagnostic evaluation. Patients with recurrence had a lower mean age, which reflected the CI response group.

Several considerations may be made on the basis of the results of this study. First, the originality and clinical importance of comparing different response groups (CI and VD) in terms of QoL are remarkable. However, it may be difficult because the vagal response in HUTT does not always faithfully reproduce spontaneous syncope. Furthermore, the significant age difference between these groups must be stressed, with the VD group being twice as old as the CI group. This age discrepancy could introduce bias into the interpretation, as older patients, who are predominantly represented in the VD response sample, often have classic or late (neurogenic) OH as a common cause of syncope. In addition, the most appropriate HUTT protocol to evaluate syncope in older individuals would be the Westminster protocol (without nitrate sensitization), as nitrate-induced venous pooling in older individuals may exacerbate OH unrelated to vagal reflex triggering during orthostasis. Since most studies used a sensitized protocol, this could also contribute to interpretation bias. Based on this conceptual premise, it is extremely important to pay close attention to the behavior of the heart rate (HR) during the onset of BP fall in HUTT. If HR increases or does not change, it is likely to be due to OH (and sometimes the consequence of nitrate action), rather than to the vagal reflex, since HR is supposed to decrease to some extent in the true vagal response. Therefore, publishing data on the dynamics of HUTTs would be extremely important to rule out potential biases.

The age difference between the CI and VD groups may introduce another confounding factor, as older individuals typically experience poorer QoL compared to younger individuals due to a variety of factors unrelated to the simplistic assessment of syncope as a determinant of poorer QoL in this age group.

The present study also introduces the notion that the recurrence rate, which was higher in the CI response group, does not seem to correlate with worsening of QoL as expected. This poses a challenge in providing a plausible explanation, as previous literature has linked recurrent episodes and effective management of CI syncope with interventions such as pacemaker (PM) implantation or cardioneuroablation (CNA), leading to an improvement in QoL.[9–13] However, based on the SF-36 questionnaire, there was an overall unchanged perception of general health-related QoL throughout the follow-up period in the entire study population, which was also documented in the CI response subgroup. The persistent perception of stable general health observed in the CI group may be due to the higher recurrence rate, although this remains unproven. In the CI response group (n = 46), the vast majority (n = 42) presented a type IIB response according to the modified VASIS classification,[14] in which there is asystole lasting more than 3 seconds and a pressure drop that either precedes or occurs simultaneously with the HR drop. It is recognized that such a CI vagal response in individuals over 40 years of age typically reproduces spontaneous events with good accuracy. They may then benefit from PM implantation, preferably using Closed Loop Stimulation (CLS) algorithms, given the increased recurrence rate and associated trauma due to the absence of prodromes. The medical literature shows a significant and clinically relevant improvement in QoL in this age group following PM implantation.[13] In this study, only four patients in the CI response group underwent PM implantation. Although this is a younger age group (mean age of 30 years and maximum age of 42.9 years), there is uncertainty as to whether all patients older than 40 years received PM implantation. If not, this may have contributed to the higher recurrence rate in the CI group, which seems inconsistent with the best QoL found in this group.

For young patients with recurrent and refractory CI (type IIA and 2B) and even mixed (type I) reflex syncope, CNA has emerged as a therapeutic alternative and may soon be an attractive choice for PM implantation. This consists of an endocardial ablation technique of vagal ganglion plexuses in the right and left atrium with initially satisfactory preliminary results. The scientific evidence in favor of CNA is still limited to observational studies and one randomized trial, but all of them reported a significant reduction in events, including studies that led to extraction of the previously implanted PM for this purpose. To date, it must be a shared decision between patients and physicians that can have an impact on CI reflex syncope recurrences and QoL.[9,10,15]

Finally, it is prudent to point out that the HUTT is a test designed to reproduce symptoms (which may include syncope or presyncope) exactly as they occur during spontaneous events. Therefore, if the patient experiences syncope before the test, any complaint other than syncope may be misinterpreted as a positive result when it should not be. For example, during HUTT, if the VD response begins with a symptom other than syncope and the study is interrupted before syncope occurs, this may introduce a bias in the interpretation of the true response that leads to syncope during spontaneous events. Thus, it is not clear from the description of this study whether all of the tests effectively reproduced the spontaneous symptoms that prompted the HUTT. In addition, CSH, a common cause of reflex syncope in older people, does not appear to have been included in the HUTT protocol of this study. All of this could potentially introduce bias in the assessment of QoL between the groups studied.

Several other interventions have been proposed to reduce recurrence and improve QoL in patients with reflex syncope (Figure 2). Silva et al.[7] demonstrated that weekly psychotherapy sessions reduced recurrence and improved QoL based on the SF-36 questionnaire in patients with refractory reflex syncope. The authors' logical explanation is based on the existence of reciprocal connections between the autonomic nervous system and the insular cortex as well as the limbic and cardiovascular systems. In addition, the emotional status of affected patients is often compromised. Similarly, the practice of yoga as an adjunct therapy has been shown to be superior to standard therapy

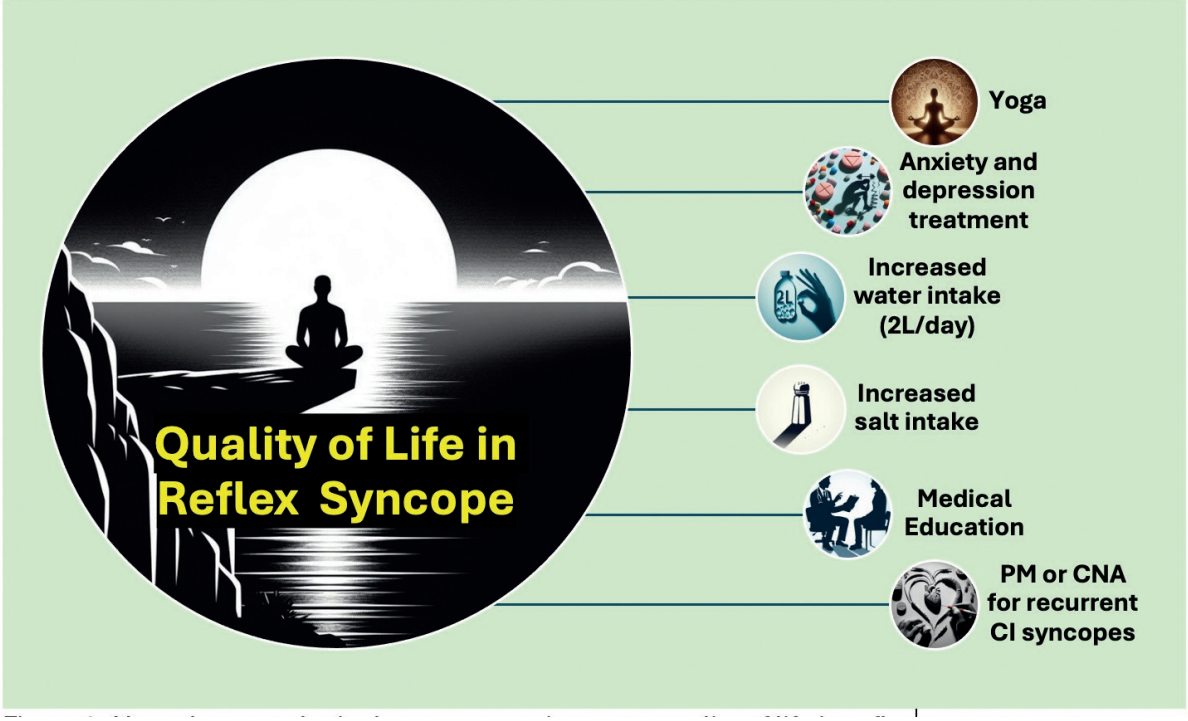

Figure 2 – Non-pharmacological measures to increase quality of life in reflex syncope.
PM: pacemaker; CAN: cardioneuroablation. Created by: Microsoft Copilot

alone in reducing symptom burden and improving QoL in patients with recurrent reflex syncope, as postulated by Sharma et al.[16] The beneficial effects of yoga may be related to the multidimensional effect of this intervention, which acts through both central and peripheral mechanisms, including physical, psychological, and autonomic pathways. All these additional therapies may affect the recurrence of syncope episodes. Therefore, the study methods must specify whether these therapies were recommended and implemented equally in both study groups.

In conclusion, the HUTT is an invaluable tool in the diagnosis of reflex syncope, provided that it accurately reproduces the symptoms and prodrome duration experienced during spontaneous events. To do so, careful observation and accurate interpretation are essential, as QoL depends on the implementation of specific treatments tailored to specific findings.

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