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EDITORIAL

What is the best method to diagnose a vasovagal syncope?

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Vasovagal reflex syncope (VVS) is the most common cause of transient loss of consciousness (TLOC) in any setting and at any age. Although the vasovagal reflex is benign and typically occurs in otherwise healthy persons, the morbidity and injuries resulting from VVS can be significant. It is therefore key to efficiently diagnose VVS [4, 13]. The intermittent nature of VVS, with a normal cardiovascular function outside the episodes, prompted the use of the tilt-table test in the clinical setting to reproduce an episode, thus confirming the diagnosis, and its use has become widespread [14]. While the use of the tilt-table test has contributed to the understanding of its pathophysiology [10], many ask whether the test is necessary for the diagnosis of VVS compared to a clinical diagnosis based on anamnesis and physical examination [11]. Compelling data are now available to provide a convincing and clear answer to this question. No, a tilt-table test is not necessary to diagnose VVS. There are, however, some indications for its use in particular cases of suspected VVS.

There are two different approaches to diagnose a VVS. One is to support the diagnosis on a tilt-table test, the other is to support it on the medical history. Methodologically, these are obviously quite different. The probability of VVS as the cause of a patient's TLOC when the patient has a VVS while on a tilt-table test refers to a *single* test result, based on the frequency in *groups* of patients with suspected VVS. A statistical Bayesian approach is applied. Subjects who never suffered a VVSs may experience one during a tilt-table test, and in many with a history of VVS in the past, a tilt-table test may not trigger one. The clinical history refers to the summing up of *all* historical data of the *individual* patient by a clinician and leads to a subjective, epistemic probability of VVS [9].

In the context of diagnostic certainty, verbal expressions can be translated into numerical probabilities [9, 16]. Verbal expressions like *possible, atypical,* or *nonclassical* often used in syncope studies are very problematic because the range of numerical probabilities attached to these terms by clinicians is wide. To solve this, the *Fainting Assessment Study* (FAST), by van Dijk and colleagues, introduced a classification of diagnostic probabilities of TLOC/syncope as *certain* (100% probability) or *highly likely* (80–99% probability) [18]. In this study, 60–70% of patients received a *certain* or *highly likely* diagnosis during the initial evaluation by attending physicians. With additional evaluation by an experienced syncope physician, the yield increased to ~ 85% [15]. This classification of diagnostic probabilities was later adopted by the *European Society of Cardiology* (ESC) 2018 diagnostic recommendations for syncope [4].

Using the ESC 2018 guidelines for the diagnosis of syncope, a recent prospective study by de Jong and colleagues validated the diagnostic yield, accuracy, and safety of history taking in patients with suspected TLOC/syncope in a tertiary referral syncope unit [7]. The study classified causes as *certain* (100% probability), *highly likely* (80–100% probability), and *possible* (60–80% probability) -we would prefer the term *likely* instead of *possible*- and considered cardiogenic syncope/epileptic seizure unlikely if the probability was < 5%. It should be noted that even with a possible (likely) diagnosis (i.e., 60–80% probability) of VVS, a clinician can still explain the presumptive cause, treat the patient, and avoid unnecessary diagnostic tests. The overall diagnostic yield after history taking by an experienced syncope physician in the study by de Jong et al. [7] was very high at 94.7%. Autonomic function testing increased the physician's certainty only marginally (2.3%) and never

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changed the patient's diagnosis based on the medical history. The overall diagnostic accuracy was also high (90.6%) with the lowest diagnostic accuracy of patients with a possible diagnosis (67.5%). Diagnoses were inaccurate in 9.4% of the patients, but no serious conditions like cardiac syncope or epileptic seizure were missed. In contrast, the overall positive rate of a tilt-table test in patients in whom VVS is highly likely based on the medical history is only about 60% [17]. In both the FAST study and in the study by de Jong and colleagues, long-term (> 1 year) follow-up, including ancillary testing and additional information obtained during follow-up by a multidisciplinary expert review committee, was used as a test of reliability. A dedicated follow-up is accepted as a reference/gold standard in the literature of diagnostic testing [1].

The gold standard is lacking in the guidelines issued by the ESC and other societies of tilt-table testing as a diagnostic test as a Class 2A recommendation (i.e., weight of evidence/opinion is in favor of its usefulness) [4, 13]. These recommendations are based on studies that did not apply a reference/gold standard for the diagnosis of VVS, a key issue in studies of diagnostic accuracy. Without a reference/gold standard sensitivity and specificity of a test cannot be properly assessed [2]. Moreover, it is important to note that the Class 2A classification for diagnostic tilt testing applies to evidence from clinical trials rather than real world diagnostic studies [2].

In this issue of *Clinical Autonomic Research*, experts from the European Federation of Autonomic Societies (EFAS) recommend considering the temporal relation between the onset of asystole and loss of consciousness as helpful to guide pacemaker implant decisions for patients with tilt-induced asystolic VVS (defined as a 3-s sinus pause) [17]. This recommendation is based on a landmark study by Saal and colleagues that included video monitoring and electroencephalography recordings during tilt testing. In about 30% of their patients, the time between asystole and loss of consciousness was too short to have been the cause of TLOC, making a pacemaker likely ineffective [12]. In the remaining 66% of their patients, asystole occurred "in a sufficiently long time to allow asystole to play a role in triggering unconsciousness." Whether asystole was the primary mechanism in these patients, however, remains questionable because mean blood pressure (BP) had already fallen to very low levels (a median value of 45 mmHg) before the onset of asystole. Therefore, even in these patients, asystole was unlikely to be the principal mechanism of the VVS [8].

The Vasovagal Syncope International Study (VASIS) classification of tilt-table test results based on the changes in BP and heart rate (HR) during the procedure was an attempt to improve the identification of the patients who would better benefit from a pacemaker [3, 6]. Patients with a VASIS type 2B response (i.e., asystole > 3 s, with the fall in HR *coinciding with or preceding the* BP fall) are considered ideal candidates for a pacemaker [17]. Recent clinical trials (SPAIN, SUP2, and BIOSync) "reinterpreted" the type 2B VASIS response as asystole of > 3 s *regardless of the timing of the asystole* and used this as the main inclusion criterion for implantation of a pacemaker. This "reinterpretation" is relevant because, as a result, patients with asystole during tilt-table testing occurring too late and, therefore, unlikely to be the primary cause of their loss of consciousness- received pacemakers [8]. Consequently, the positive results of the recently published cardiac pacing BIOSync trial using closed-loop stimulation (CLS) on top of dual-chamber pacing remain unexplained [5]. An explanation is that patients and clinicians were unblinded, although a physiological effect of CLS pacing cannot be excluded. The supposed principle by which the CLS device works is high-rate early pacing, but the detection of an increase in contractility by the CLS device as an early marker of impending VVS is still a hypothesis. Evidence that this new pacing algorithm is physiologically sound with additional safety and efficacy data are warranted.

An intriguing, but perhaps revealing observation in an ISSUE-3 sub-study is that the benefit of pacemaker in patients with presumed VVS was greater when the pre-implant tilt-table test was unrevealing. This suggests that patients with no syncope in the tilt-table test who had asystole registered by implantable loop recorders and an excellent response to pacing actually had no VVS in the first place [8].

The EFAS recommendations that a tilt test can be useful to explain to patients the cause of their problem and to teach awareness of premonitory symptoms to implementing physical countermaneuvers that can prevent and abort fainting is well taken [17]. That the physician has witnessed and monitored the patients' blood pressure and heart rate during their TLOC and has therefore confirmed the diagnosis can be reassuring to some patients. This aspect of tilt testing is straightforward, but a problem in clinical practice is that the positive rate of a tilt-table test in highly likely cases (80–100% probability) is only about 60%. In this case, a tilt-table test may contribute to -rather than reduce- the patients' (and physician's) anxiety. A tilt-table test performed by a *syncope physician* as "part of the physical examination" while evaluating a patient with complex unexplained syncope can be valuable because the patient often reports important but previously concealed diagnostic clues [15].

In conclusion, a structured history taking is the best method to diagnose a VVS. We fully agree with the EFAS recommendations that a tilt-table test and other cardiovascular autonomic tests in conditions that may cause TLOC should be based on a medical history. With a precise, structured medical history, the role of the tilt-table test for diagnosing VVS is minor, and its role as a guide for pacemaker

recommendations is questionable. But tilt-table testing does can serve other purposes: it can assess the susceptibility to VVS in patients with unexplained syncope after structured history taking, and it can be helpful when confirmation of the diagnosis is necessary to reassure and educate patients (and parents), or when required for medicolegal reasons [17].

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Declarations

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