Nitrate stimulated tilt testing: clinical considerations

Pharmacological stimulation with a nitrate during tilt testing has become a well accepted tool to elicit syncopal attacks of vasovagal origin in patients with recurring syncopal attacks [1, 3, 15]. Nitrates, well known for their ability to induce vasovagal reactions, were introduced to tilt testing in 1993 by Raviele et al. [15]. Nitrates lack the catecholaminergic effects of isoproterenol and are at least as effective as isoproterenol in a direct comparison [1, 15]. Moreover nitrates can be given orally. The precise mechanism of nitrates’ contribution to vasovagal syncope is still not clarified, but as emphasized in a recent review, a complex interaction of hemodynamic (preload and afterload) effects, neurohoromonal influences, due to alterations in baroreflex sensitivity, and even central activity of nitrate compounds appear to be involved [1].

Though the diagnostic accuracy of the test has been well established in numerous reports, the matter of test-specificity has only occasionally been addressed. Due to the absence of a gold standard, the true sensitivity and specificity of the test cannot be appropriately determined. False positive responses in normal controls have been described during passive tilting alone (especially when using steep tilt angles), with higher incidence of syncope when GTN or isoproterenol are administered intravenously [2, 11].

Reports from the 1930’s demonstrated that amyl nitrate, given to healthy controls, could induce vasovagal reactions [16]. Other factors that may influence the test result are the intravenous cannulation procedure, environmental circumstances, a steep tilt angle (80°), duration of testing and age [7, 8, 12]. Thus, one can expect that the incidence of positive responses in normal controls will vary with the circumstances of the test. The diversity of tilt-test protocols is a recognized problem, making it difficult to compare tilt studies. Also in many tilt reports, the patient selection does show considerable differences, though this seems to be a less problem (negative history) in the control groups. Obviously it is essential to screen controls for known syncope-contributing factors (like cardiovascular disease and associated medications). In this issue of the journal, Athanasos et al. used a tilt protocol potentiated by sublingual nitrate in 13 patients with unexplained syncope and 13 controls of comparable age (32 ± 9 years) and gender distribution. In the control group, 6 out of 13 (46%), had a positive response, revealing a specificity of 54%. Controls with a positive response were predominately females (5 out of 6, 83%). The authors conclude that a nitrate stimulated tilt test lacks enough in specificity to provide a true diagnosis in patients with unexplained syncope. They support their finding with references to 2 other reports with specificities of 48–63%.

These findings contrast with numerous other reports. First some methodological remarks have to be made to interpret the results of Athanasos et al. correctly. Aside from their small study size, the authors do not mention the precise details and circumstances of their protocol (was iv cannulation preceded? fasting state? nitrate dose?). Perhaps differences in these methodological details might explain why their specificity was so much lower than the 70–100% reported in previous studies [3]. Looking across other published studies, one is struck by the lack of standardized protocol and a lack of clinical characterization of the general athletic fitness, work-experience and the presence of anxiety, of both patients and control subjects. Cohen et al. reported a high anxiety level to be associated with a positive tilt test and a low level with a negative one [7]. Also on clinical grounds, one might expect that subjects who spend long periods of time on their feet versus those who lead mostly sedentary lives would have dif-
ferential sensitivity to tilting, with or without pharmacological challenge.

Secondly, in a larger report (n = 64), in older adults (> 60 yr.), by Kumar et al., a 30–40 minute passive tilt followed by 15 minutes of sublingual nitrate stimulation was used. They found a specificity of 48%. However, in this study 27% of the controls had a history of hypertension and were taking vasoactive medication at the time of the tilt test. The ability of vasoactive therapy to enhance susceptibility to vasovagal syncope was previously demonstrated by Gaggioli et al. [9]. Their finding indicates that, in controls taking vasoactive therapy, it is not appropriate to determine the diagnostic value of the tilt test. In addition Natale et al. found, in similar aged and healthy controls (n = 16), not using vasoactive medications and using a less steep tilt angle (60° vs 70°), a specificity of 88% [13].

So this report from Athanasos etal., though methodologically questionable, does remind us that neurally mediated or vasovagal syncope is not a disease related entity but the syndrome may occur in anyone. The distinguishing capacity of the tilt test is not the identification of a fixed underlying pathology but merely the demonstration of differential responsiveness to baroreceptor and other reflexes, differential susceptibility to various stressors and circumstances encountered in daily life. Most importantly, we need to recognize the importance of basic clinical factors such as the athletic conditioning of patients or controls, and the extent to which prolonged standing plays a role in their daily life. Hypothetically it might even be so that ‘false positive’ tilt responders represent those who will faint in the future [10].

It is important to note that the tilt test is not a gold standard for the diagnosis of vasovagal syncope but merely an attempt to create a standardized provocative test.

On the other hand, derived from recent tilt guided therapy studies, one should be cautious to translate a positive tilt test result into an aggressive therapeutic approach [14]. Despite the impending importance of the utilization of implantable loop recorders we still have to await new devices capable of monitoring both the hemodynamic and heart rate characteristics of spontaneous vagal episode.

The diagnosis is, in tilt positive responders, substantially subscribed by the symptom recognition and maybe also from rare cases of reproduction of hemodynamic or heart rate characteristics registered from spontaneous syncopal attacks. This method of descriptive diagnosing is similar and generally accepted in electrophysiologic studies [10]. As Benditt and Brignole remarked, when is a diagnosis a diagnosis [4]? This question is also applicable in tilt testing. The goal of the true merit of the tilt test must and will be further elaborated when we do a better job at characterizing patients in respect to their athletic status and their prior experience with long periods in the upright posture. Perhaps we may do better when results of implantable loop recording, in patients with vasovagal syncope, become available.

But until then, the tilt test remains the first choice and a cost effective investigation, and in the case of a nitrate stimulated tilt, it is a fast and accurate way of unmasking vagal origins in patients suspected by history or in those with no clue at all. This view is underscored by the implementation of the test in the guidelines of diagnosing and management of syncope in both European and North-American expert panels [5, 6].

References