

## Predicting Therapy Duration and Recurrence in Patients with Vasovagal Syncope: Is There Light at the End of the Tunnel?

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Vasovagal syncope (VVS) is the most common cause of recurrent syncope and affects a large population of usually younger and overall healthy individuals. Nonetheless, 20% - 30% of patients are highly symptomatic and VVS can severely impair their quality of life<sup>1</sup>. Despite a significant effort in clinical research the sad reality is that we are still looking for appropriate therapeutic measures. By in large most patients are reassured by the result of tilt table testing clearly reproducing the symptoms that have been frequently neglected or misinterpreted by one or usually more physicians. These patients do fairly well by simply increasing water and sodium ingestion as well as being trained to identify prodromal symptoms early and intervening with physiologic maneuvers that are easy to implement. However, those of us that care for these patients are well aware of the significant proportion of patients that require one or a combination of pharmacological therapies. Given the fact that most of these patients are young and highly functional several questions are usually raised by these patients; how long should I take these medications, will I have this happen again, is this "disease" life-threatening?

Clinical research has provided some of these answers however the jury is still deliberating particularly regarding the issue of therapy discontinuation. In order to define how to appropriately manage these patients a number of issues need to be considered. First; how symptomatic was the patient prior to initiating pharmacological therapy?

Second; can we predict the recurrence rate in patients with VVS?

Third; is tilt table testing useful in identifying chronic recurrent VVS?

The answer to these questions is indeed clinically relevant and of prime importance for the patient. There is little doubt that VVS markedly disrupts patient's lives and undermine quality of life. However, how frequent it is really a problem is an issue that remains to be addressed. It is reasonable to assume that patients with at least 3

yearly episodes are highly symptomatic and merit therapy. This is of course a highly subjective matter and little evidence is available to support this practice. At any rate some clinical decisions need to be taken simply based on experience and not necessarily guided by evidence particularly when there is no evidence available.

Can we predict the recurrence rate of patients with VVS? Sheldon et al have elegantly identified that patients with more than 6 lifetime syncopal episodes have a strikingly high recurrence rate of 72% and 60% at 1 and 2 years respectively<sup>2</sup>. So it is generally accepted that patients with a high frequency of VVS episodes are at higher recurrence rates and this population should be targeted for therapy. Similarly patients with a recurrence within a year of having been tilted have a similar risk as above. This information clearly indicates that we can predict with a certain degree of accuracy which patients with VVS will have recurrences and potentially target this population for therapy.

Finally, whether tilt table testing is useful to identify recurrence of VVS is a matter that is certainly controversial. Suffice to say that most "tiltologists" agree that tilt table testing is not useful for selection of therapy or to determine treatment efficacy<sup>3,4</sup>. The reasons being primarily the poor reproducibility of tilt testing in the long-term and the marked placebo or therapeutic effect that tilt table test has by its own. Hachul et al have previously reported a lower recurrence of syncope in treated patients with a follow-up negative tilt test compared to those that remain with inducible VVS during tilt<sup>5</sup>. These observations are provocative but are limited by the fact that this data was not derived from a randomized study. Where do we stand today when our VVS patients ask us "Dr., How long should I take these medications?"

In this issue of the journal Bastos et al provide some insight into this issue<sup>6</sup>. These investigators assessed 37 highly symptomatic patients with a median of 3 syncopal episodes per year that received in a non-randomized

fashion pharmacological therapy primarily with beta-blockers and fludrocortisone. All patients had a clear history of recurrent VVS with at least 2 syncopal episodes in the previous year as well as a positive tilt test. Only patients that had a negative tilt test during the course of treatment and that remained asymptomatic after therapy were included. Patients were instructed to discontinue pharmacological therapy and subjected to a tilt test 30 days after discontinuing medication. No treatment was prescribed regardless of the result of the tilt test. The main observations of this study were a recurrence rate of 23% and 36% after 6 and 12 months of follow-up respectively. Of note 76% of patients recurred at the end of follow-up approximately 4 years. Interestingly 35% of patients had a positive tilt test after discontinuation of medication and the remaining 65% had a negative tilt test. Furthermore 84% of patients with a positive tilt test had recurrence of VVS within 12 months. Similarly the average time to the first recurrence was significantly different between positive and negative responders to tilt with an average time to recurrence less than 8 months for the positive tilts compared to 24 months to the negative tilt subjects. This study also confirmed previous clinical observations such as the fact that patients with a higher burden of syncope indeed have higher recurrence rates. Of interest women appear to be more susceptible to recurrence than men at least in the age group reported. These investigators should be commended for improving our understanding on several aspects of the management of patients with VVS. Where do we go from here and what is the clinical impact of this study?

Firstly there are some methodological issues that need to be acknowledged before implementing the strategy of using tilt table testing results to determine the potential

for recurrence of VVS after therapy for at least 2 years. This was a highly selected sample of patients that had to be asymptomatic on therapy and underwent a tilt table test after a period of time on pharmacological therapy. Similarly the use of tilt testing was not randomized potentially introducing some bias. Interestingly patients with a positive tilt table test had earlier and higher recurrence rates. Is this truly related to the response to tilt testing? This is difficult to support based on the fact that we know that patients with VVS have very characteristic personalities and it is possible that those with a positive tilt test simply identifies patients in which certain triggers may induce VVS. These patients may simply acknowledge that they are still susceptible and may fear recurrences because are without medication and this lead to earlier and higher recurrence rates. The alternative explanation can be that indeed the positive tilt test after therapy withdrawal identifies patients at a higher risk of recurrence. The reason for this finding remains to be determined. At any rate regardless of the tilt table results clinical observations such as frequent episodes and possibly gender may be simple markers to determine whether a patient should continue therapy indefinitely. The question of how long should therapy be given remains part of the riddle to be solved. Recently we have reported that the median age of presentation of VVS is 13 years indicating that these patients have a life lasting risk of having recurrences<sup>7</sup>. In the end VVS is a reflex that will appear if the necessary trigger is present. The study by Bastos et al, is a step forward in our understanding of this complex clinical situation and provides some light at the end of the tunnel. The lingering challenge is to be able to put this information into clinical perspective in an attempt to improve our patient's quality of life.

## REFERENCES

1. Soteriades ES, Evans JC, Larson MG et al. Incidence and prognosis of syncope. *N Engl J Med* 2002;12:878-85.
2. Sheldon R, Rose S, Flanagan P. Risk factors for syncope recurrence after a positive tilt-table testing in patients with syncope. *Circulation* 1993;93:973-81.
3. Morillo CA, Klein GJ, Gersh BJ. Can serial tilt testing be used to evaluate therapy in neurally mediated syncope? *Am J Cardiol* 1996;77(7):521-3.
4. Moya A, Permanyer-Miralda G, Sagrista-Sauleda J et al. Limitations of head-up tilt test for evaluating the efficacy of therapeutic interventions in patients with vasovagal syncope: results of a controlled study of etilefrine versus placebo. *J Am Coll Cardiol* 1995;25(1):65-9.
5. Hachul D, Scanavacca M, Sosa E. Does a role exist for tilting-guided therapy in the management of neurocardiogenic syncope? *Arq Bras Cardiol* 2002;78(2):167-71.
6. Bastos S, Scanavacca M, Darriex F et al. Clinical outcome of patients with neurocardiogenic syncope after therapy interruption. *Arq Bras Cardiol* 2006; 86:256-60.
7. Sheldon RS, Sheldon AG, Connolly SJ et al. Age of first faint in patients with vasovagal syncope. *J Cardiovasc Electrophysiol* 2006;17:49-54.