Reproducibility of asystole during head-up tilt testing in patients with neurally mediated syncope

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Tilt induced prolonged asystole has been considered to identify a distinct subgroup of patients with neurally mediated syncope and management including permanent pacemaker implantation has been suggested. To evaluate the reproducibility of asystolic response during head-up tilt testing (HUT), 33 patients with neurally mediated syncope and asystolic response (≥3 seconds) during HUT prospectively underwent two consecutive tests 13 ± 15 days apart. On repeat tilt testing asystole was reproduced in 12 patients (36%), while 8 patients still had a positive HUT, but without asystole. Remarkably, 13 patients (40%) had a negative repeat HUT. Among 12 patients with asystole on both HUTs there was no significant difference in duration of asystole (14 371 ± 11 430 ms vs 13 707 ± 10 470 ms, P=ns) and time to syncope (36 ± 20 min vs 37 ± 20 min, P=ns) during initial and repeat HUTs. In conclusion, asystole during tilt testing does not seem to be a reproducible response.

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Key Words: Head-up tilt test, asystole, reproducibility.

Introduction

Head-up tilt testing (HUT) is a very useful tool for the diagnosis of neurocardiogenic syncope in patients with recurrent unexplained syncope. Positive test results are usually classified as vasodepressor, cardioinhibitory or mixed, depending on the relative degree of hypotension and bradycardia[1]. Tilt induced prolonged asystole has been advocated to identify a distinct subgroup among patients with neurally mediated syncope; for such patients management including permanent pacemaker implantation has been suggested[2–4]. Recently it was proposed that cardioinhibition during HUT identifies patients who may benefit from pacemaker implantation[5]. Very little data are available about reproducibility of asystolic response during tilt testing[6,7]. The purpose of this prospective study was to evaluate the reproducibility of asystolic response during tilt testing, by means of 2 consecutive tests performed on different days.

Methods

Study population

The study population consisted of 33 patients (11 men, mean age 34 ± 19 years, median 30, range 11–78) with recurrent syncope of unknown origin and a positive HUT with asystolic response. Patients were diagnosed as having unexplained syncope if no cause was found after a standard diagnostic evaluation[8]. No patient had structural heart disease.

Head-up tilt table testing

After giving informed consent, all the patients underwent head-up tilt testing with sublingual nitroglycerin stimulation, as previously described[8]. Patients underwent HUT in the morning, after at least 4 h fasting, in a quiet room. No patient was taking cardioactive and vasoactive drugs. After an initial stabilization phase of 10 min in the supine position, patients were tilted at 60° for up to 45 min. If syncope did not occur, 400 μg sublingual spray nitroglycerin was administered with the patient remaining in the same tilted position for a further 20 min. During the test heart rate and blood pressure were continuously monitored and recorded every 1 to 5 min or continuously at the onset of
was defined as the development of ventricular asystole of

All data were reported as mean value

Mean duration of asystole was 14,054 ms (median 13,707 ms). Eight patients (24%) had asystolic syncope during drug-free phase, 25 patients (76%) had a positive asystolic test after nitroglycerin administration. The mean time to onset of syncope during initial HUT was 41 ± 17 min (median 49). On repeat HUT 12 patients (36%) had asystolic syncope, 8 patients (24%) still had a positive test, but without asystole (3 patients had a cardioinhibitory VASIS type 2A response, 5 patients had a mixed response), while 13 patients (40%) had a negative test. Reproducibility of asystole during drug-free phase was 50% (4 of 8 patients), while after nitroglycerin administration it was 32% (8 of 25 patients). The overall reproducibility of an asystolic response was 36%. The reproducibility of the asystolic pattern was not influenced by gender, age, number of syncopal episodes in the patients' clinical history, duration of symptoms, time between last spontaneous syncope and initial HUT and time between initial and repeat HUT. Among patients with both asystolic positive tests there was no significant difference in duration of asystole (14,371 ± 11,430 ms vs 13,707 ± 10,470 ms, P = ns) and time to syncope (36 ± 20 min vs 37 ± 20 min, P = ns) during initial and repeat HUT.

**Definitions**

Syncope was defined as sudden transient loss of consciousness with inability to maintain postural tone and with spontaneous recovery. A positive response to head-up tilt test was defined as reproduction of the spontaneous syncope in association with hypotension, bradycardia, or both. The positive responses of HUT were classified according to the VASIS classification in mixed (type 1), cardioinhibitory (type 2A and 2B) and vasodepressor response (type 3)\(^1\). An asystolic response was defined as the development of ventricular asystole of ≥ 3 s duration\(^1\).

**Second tilt-table test**

Patients underwent a second HUT after a mean period of 13 ± 15 days (median 7). All patients gave informed consent before repeat HUT.

**Statistical analysis**

Comparisons were made with the Fisher’s exact test for frequency data, with a t-test for paired parametric data, and the Wilcoxon signed-rank test for paired nonparametric data. A P value <0.05 was considered significant. All data were reported as mean value ± SD.

**Results**

The baseline clinical characteristics of the 33 patients at enrolment are shown in Table 1. On initial HUT the mean duration of asystole was 14,054 ± 12,262 ms (median 9,640, range 3,380 to 58,000 ms). Eight patients (24%) had asystolic syncope during drug-free phase, 25 patients (76%) had a positive asystolic test after nitroglycerin administration. The mean time to onset of syncope during initial HUT was 41 ± 17 min (median 49). On repeat HUT 12 patients (36%) had asystolic syncope, 8 patients (24%) still had a positive test, but without asystole (3 patients had a cardioinhibitory VASIS type 2A response, 5 patients had a mixed response), while 13 patients (40%) had a negative test. Reproducibility of asystole during drug-free phase was 50% (4 of 8 patients), while after nitroglycerin administration it was 32% (8 of 25 patients). The overall reproducibility of an asystolic response was 36%. The reproducibility of the asystolic pattern was not influenced by gender, age, number of syncopal episodes in the patients’ clinical history, duration of symptoms, time between last spontaneous syncope and initial HUT and time between initial and repeat HUT. Among patients with both asystolic positive tests there was no significant difference in duration of asystole (14,371 ± 11,430 ms vs 13,707 ± 10,470 ms, P = ns) and time to syncope (36 ± 20 min vs 37 ± 20 min, P = ns) during initial and repeat HUT.

**Discussion**

The most important finding of this prospective study is the poor reproducibility of an asystolic response during head-up tilt testing in patients with neurocardiogenic syncope. In our study only 36% of patients with an initial asystolic HUT had an asystolic response on repeat HUT. Of the other patients, 24% still had a positive response, but without asystole, while 40% of patients had a negative repeat HUT.

Brignole et al.\(^7\) reported a reproducibility of asystolic response of 54%, but in that study patients with positive carotid sinus massage were also included, and the HUT protocol was different (passive tilt testing at 60° for 60 min, without a pharmacological challenge). In the VASIS study\(^6\), in the no-pacemaker arm the reproducibility of asystolic pattern on repeat HUT was of 41%: this result is similar to ours.

A low reproducibility was also reported, when tilt induced cardioinhibitory syncope was evaluated according to VASIS classification (type 2): Del Rosso et al.\(^9\) found a reproducibility of 56%, while Sutton et al.\(^6\) reported a reproducibility of 50%. The reproducibility of an asystolic pattern during HUT appears to be lower than the reproducibility of the outcome of the test itself. In fact the reproducibility of drug-free, isoproterenol and nitroglycerin HUT are reported to be between 60 and 77%, 57 and 92%, 67 and 79% respectively\(^9\).

Another remarkable result of our study was the high rate of negative repeat HUT after a first asystolic positive HUT: in fact 40% of our patients had a negative second HUT. Reibrouck et al.\(^10\), in their study on tilt training, reported even a higher rate of negative repeat HUT.
HUT: in that study 8 of 14 patients (57%) with pro-
longed asystole during first HUT had a negative second
HUT.

The reasons for low reproducibility of asystolic
response during HUT are still unknown. One possible
cause is the selection of patients: differences in baseline
clinical characteristics may affect reproducibility rate of
asystolic HUT. The pattern of response and its repro-
ducibility may also be influenced by the HUT protocol
and the type of pharmacological challenge. Recently, a
case of asystolic neurocardiogenic syncope associated
with chronic exaggerated vagal tone was described[11]. A
day-to-day variation in basal vagal tone could be
implied in poor reproducibility of asystolic response
during HUT[12]. Dhala et al.[13] reported a tilt induced
asystolic syncope in asymptomatic ‘normal’ patients and
concluded that asystolic response during tilt testing does
not enhance the specificity of the test. Recently the
ISSUE trial demonstrated that spontaneous syncope
seems to be much more frequently asystolic than
expected according to tilt testing response, which conse-
quently does not appear to be predictive of the type of
response of the spontaneous attack[14].

The poor reproducibility of tilt-induced asystole raises
important issues about its clinical relevance. Any
therapeutic decision exclusively based on the occurrence
of asystole during tilt testing seems to be un-justified.
Similarly, repeat tilt testing appears not to be useful in
planning treatment strategies.

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