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Head-up tilt testing for diagnosing vasovagal syncope: A meta-analysis

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ABSTRACT

Background: A systematic evaluation focused on sensitivity and specificity of head-up tilt testing (HUT) for diagnosing vasovagal syncope has not been previously performed. We conducted a meta-analysis of studies comparing HUT outcome between patients with syncope of unknown origin and control subjects without previous syncope.

Methods: We searched Pubmed and Embase databases for all English-only articles concerning case-control studies estimating the diagnostic yield of HUT, and selected 55 articles, published before March 2012, including 4361 patients and 1791 controls. The influence of age, test duration, tilt angle, and nitroglycerine or isoproterenol stimulation on tilt testing outcome was analyzed.

Results: Head-up tilt testing demonstrated to have a good overall ability to discriminate between symptomatic patients and asymptomatic controls with an area under the summary receiver-operating characteristics curve of 0.84 and an adjusted diagnostic odds ratio of 12.15 ($p<0.001$). A significant inverse relationship between sensitivity and specificity of tilt testing for each study was observed ($p<0.001$). At multivariate analysis, advancing age and a 60° tilt angle showed a significant effect in reducing sensitivity and increasing specificity of the test. Nitroglycerine significantly raised tilt testing sensitivity by maintaining a similar specificity in comparison to isoproterenol.

Conclusions: The results from this meta-analysis show the high overall performance of HUT for diagnosing vasovagal syncope. Our findings provide useful information for evaluating clinical and instrumental parameters together with pharmacological stressors influencing HUT accuracy. This could allow the drawing of tilt testing protocols tailored on the diagnostic needs of each patient with unexplained syncope.

1. Introduction

Syncope is a common clinical disorder characterized by a high prevalence at all age [1]. In the complex scenario of the different etiologies, vasovagal syncope is now accepted as the most frequent cause of fainting, especially if there is no evidence of underlying structural cardiac or cardiovascular disease [1,2]. The head-up tilt testing is at present widely recognized as a clinically useful diagnostic tool for assessing susceptibility to vasovagal faint in patients with unexplained syncope, allowing reproduction of the patient's spontaneous symptoms in a safe environment, under medical control [2].

The tilt testing is a laboratory procedure that has been used over the past 60 years by physiologists and physicians to investigate the human body's heart rate and blood pressure adaptations to changes in position [3]. Occasionally, it was noted that some individuals would develop vasovagal reactions, including syncope [3]. On the basis of these latter observations, and starting with the report by Kenny et al. in 1986 [4], a passive head-up tilt testing began to be considered as a method to induce neurally mediated hypotension and bradycardia in subjects believed to be susceptible to vasovagal syncope [3,4]. However, the low positive yield of drug-free tilt testing made pharmacological provocation necessary [2]. The absence of a gold standard clinical test for the diagnosis of vasovagal syncope has led to develop many different tilt testing protocols. In order to detect the optimal tilt test protocol for different specific populations, variations in tilt methodology were introduced in terms of different tilt angles, test duration, and pharmacological augmentation [2,3].

To the best of our knowledge, no study aimed to systematically evaluate the diagnostic performance of head-up tilt testing has been undertaken, by using advanced meta-analysis methods. Moreover, examining the set of all studies to date published, the overall influence of age, tilt angle, test duration, and different provocative agents on tilt testing outcome has not been previously estimated. To these purposes, we executed a meta-analysis of pertinent studies on tilt testing diagnostic accuracy in the evaluation of patients with unexplained syncope.

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2. Methods

2.1. Literature search

A systematic review of published evidence on the diagnostic value of head-up tilt testing in patients with unexplained syncope was performed. Two investigators (MR and FM) independently searched Pubmed and Embase sources for all articles concerning case-control studies published before March 2012 with the following strategy: "tilt AND syncope". Moreover, bibliographies of retrieved articles, review articles, and textbooks were evaluated.

2.2. Study selection

Two co-authors (MR and FM) independently reviewed each publication. According to a standardized data extraction form, they read all the abstracts to identify the potentially eligible articles, and then they managed to get the full text of these articles in order to determine whether they could be included. Discordant opinions were resolved by discussion with the participation of a third investigator (CF). The inclusion criteria were as follows: English-only articles involving symptomatic patients with history of unexplained syncope and asymptomatic control subjects without previous syncope, all of them underwent head-up tilt testing with tilt angles varying between 60° and 80°. Duplicate publications and studies enrolling less than 10 patients or controls were excluded. Furthermore, studies using a pharmacological stimulation during tilt testing different by nitroglycerine and/or isoproterenol were evaluated including only passive phase results before provocative agent administration.

2.3. Parameter examination

The number of patients and controls together with their mean age were assessed. The following parameters of tilt table testing protocols were considered: tilt angle, presence and duration of drug-free phase, presence and duration of stimulation stage, nitroglycerine and/or isoproterenol as provocative pharmacological agents. The number of positive tilt testing outcomes, as defined by each study, was analyzed for both patients and controls during either unmedicated and active phases.

2.4. Statistical analysis

Sensitivity was defined as the proportion of patients with positive response to head-up tilt testing and specificity as the proportion of control subjects with negative tilt testing result. The forest plot of sensitivity and specificity with their 95% confidence intervals (CIs) and the summary receiver-operating characteristics curves (SROC), the area under the curve, were assessed. Heterogeneity among studies was evaluated by chi-square test. Non-parametric Spearman Rank correlation coefficient was used to examine the relation between sensitivity and specificity. Mixed logistic regression models were estimated by using the exact binomial likelihood approach accounting for the within-study correlation. A first multivariate model was fitted to evaluate the variables associated with positive tilt testing outcome and the results were provided as Odds Ratios (ORs) and 95% CIs. In order to evaluate the effects of different parameters on tilt table testing sensitivity and specificity, the models were extended to explain the logit transformation of proportion of true positive and true negative responses as linear combination of study level covariates. The influence of explanatory variables on tilt testing sensitivity and specificity was given by means of regression coefficients with their standard error. Multivariate models were fitted including mean age of study population (for 10 years increase), test duration (for 10 minutes increase), tilt table angle (70° as reference category), and pharmacological provocation (nitroglycerine *vs.* isoproterenol). All statistical analyses were performed using Stata 12 (StataCorp LP, College Station, Tex, USA); p values <0.05 were considered statistically significant. The authors of this manuscript have certified that they comply with the Principles of Ethical Publishing in the International Journal of Cardiology.

3. Results

3.1. Literature search and studies' selection

The detailed procedure of study selection conducted in this meta-analysis is shown in Fig. 1. A total of 1868 and 2504 citations were retrieved from Pubmed and Embase databases, respectively. Among all these articles, 101 studies were considered for more detailed evaluation.

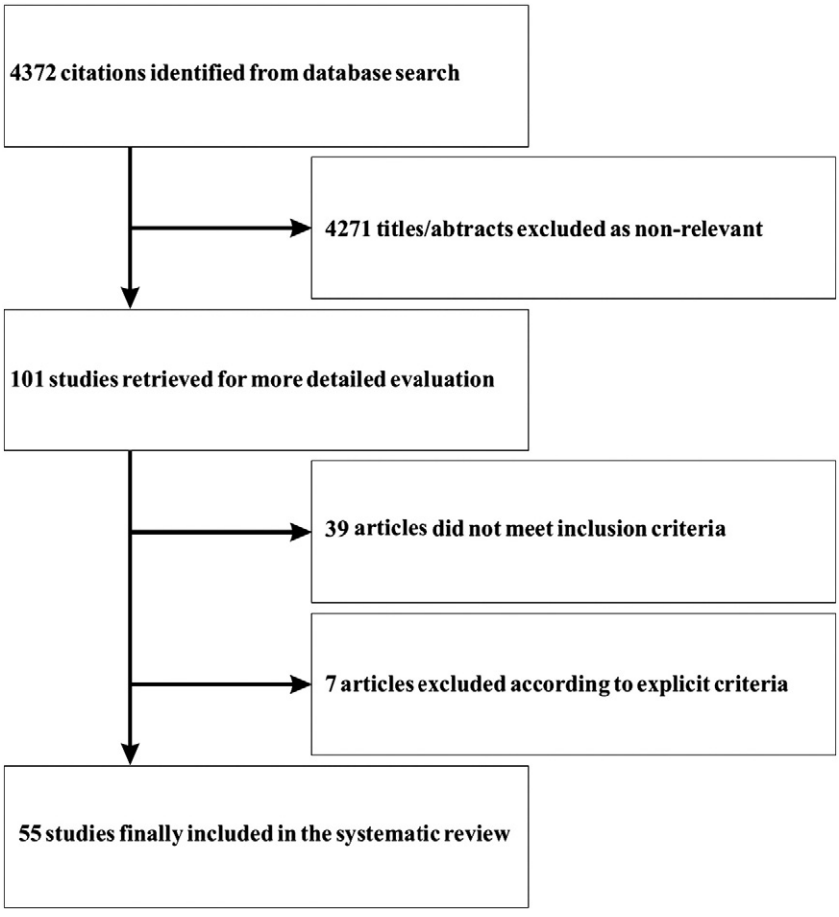

Fig. 1. Flow diagram showing the process of study selection.