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On the feasibility of tilt test outcome early prediction using ECG and pressure parameters

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Abstract

The tilt test is a valuable clinical tool for vasovagal syncope (VVS) diagnostic, and its early prediction from simple ECG and blood pressure-based parameters has widely been studied in the literature. However, no practical system is currently used in the clinical setting for the early prediction of the tilt test outcome. The objectives of this study were (1) to benchmark the early prediction performance of all the previously proposed parameters, when nonlinearly combined; (2) to try to improve this performance with the inclusion of additional information and processing techniques. We analyzed a database of 727 consecutive cases of tilt test. Previously proposed features were measured from heart rate and systolic/diastolic pressure tachograms, in several representative signal segments. We aimed to improve the prediction performance: first, using new nonlinear features (detrended fluctuation analysis and sample entropy); second, using a multivariable nonlinear classifier (support vector machine); and finally, including additional physiological signals (stroke volume). The predictive performance of the nonlinearly combined previously proposed features was limited [area under receiver operating characteristic curve (ROC) 0.57 ± 0.12], especially at the beginning of the test, which is the most clinically relevant period. The improvement with additional available physiological information was limited too. We conclude that the use of a system for tilt test outcome prediction with current knowledge and processing should be considered with caution, and that further effort has to be devoted to understand the mechanisms of VVS.

Keywords: tilt test, sympathovagal syncope, support vector machine, heart rate, systolic pressure, prediction

1. Introduction

Syncope is a temporary loss of consciousness and posture, described as fainting, usually related to temporary insufficient blood flow to the brain, which has high medical, social, and economic relevance. Only in the United States, around one million patients are annually evaluated for this disorder, accounting for 3-5% emergency department visits and 1-6% of hospital admissions. Up to 20% of adults have suffered a sudden fall at least once in their life. Vasovagal syncope (VVS) accounts for about 40% of syncope episodes, and it represents the most usual cause of consciousness loss [1]. VVS is a neurally mediated reflex syncope, consisting of a sudden drop in blood pressure with an associated fall of heart rate (HR); as a result of a peripheral vasodilatation and increase of vagal modulation, all these phenomena being regulated by the autonomous nervous system [2].

VVS management may be complicated because it is based on the exclusion of other causes, often leading to significant unnecessary diagnostic testing [1]. The tilt table test (TTT) has become a standard for the induction of syncope under controlled conditions in patients with suspected VVS. The long duration of the TTT, up to 1 h in some protocols, has a high economic impact. In addition, the patient may feel very uncomfortable when the presyncopal or syncopal symptoms are reproduced. These problems have motivated the search for methods allowing the early prediction of the TTT [3-16]. The aim of these methods has often been to obtain a simple measurement, taken from an easily available cardiac signal (such as HR or pressure tachogram) at the beginning of the test, which would be used as a predictive criterion for the final result. Despite all this literature, no system has been implemented to date allowing the early prediction of the TTT outcome in the

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clinical setting. Moreover, some recent studies have even questioned the actual predictive value of some of the formerly proposed parameters [17].

Therefore, the aim of this study was twofold. First, we evaluated the predictive performance of the proposed parameters in the literature when jointly and nonlinearly combined. For this purpose, a nonlinear support vector machine (SVM) classifier was employed in a database consisting of 727 consecutive TTT. Second, we explored how to improve the performance of the (possibly nonlinear) combination of features with the inclusion of additional information, namely: (a) by analyzing several relevant time periods of the test; (b) by introducing new nonlinear indexes [detrended fluctuation analysis (DFA) and sample entropy (*SampEn*)], which had been previously shown to be valuable in other ECG analysis problems; (c) by introducing new monitored signals currently available in some TTT equipments, specifically, the impedance signal (stroke volume–SV) tachogram.

The scheme of this article is as follows. In Section 2, we present the basic background on VVS mechanisms, the most relevant TTT protocols, and the methods in the literature for early prediction. In Section 3, we introduce the different aspects to be considered for improving the predictive performance. Section 4 contains the description of our database and the results of the experiments. Section 5 has the discussion and the conclusions on the limitations of the TTT early prediction of outcome from the parameters in the literature.

2. Background

Intrinsic autonomous reflexes mediate the response of the cardiovascular system to stress and yield internal compensatory reactions to guarantee the blood supply to the vital organs. The mechanism of VVS has not fully been elucidated. External stimuli, such as strong emotions, hot places, or sustained standing, induce blood redistribution and a decreased cardiac output. As a consequence, a sympathetic surge occurs, leading to the activation of afferent vagal mechanoreceptors in the left ventricle, and to a paradoxic vagal reflex that promotes inappropriate vasodilatation and bradycardia ending in a syncopal event [18-20]. Although other additional or alternative mechanisms have been proposed [21,22], this ventricular theory is the most widely accepted.

The TTT is used to reproduce the clinical event in patients with suspected VVS. The patient is initially lying on a table in supine position that is tilted to a 60° angle after 5-10 min. Several ECG leads and a noninvasive BP signal, usually from finger plethysmography, are recorded throughout the test. In patients prone to VVS, the initial response consisting of vasoconstriction and reflex tachycardia elicits the vasovagal response and reproduces the clinical syncope after a variable lapse of time. If no changes are observed after 20-25 min, a stressor drug, usually nitroglycerine or isoproterenol, is administered and the orthostatic challenge is maintained for 15-20 additional minutes. The test finishes whenever the monitoring period is over and no symptoms have been observed (negative response), or when a syncopal (or pre-syncopal) event takes place with decreased arterial pressure (AP), HR, or both (positive response). Changes in HR or in AP with no symptoms are not valid positive responses. The spontaneous syncope and the TTT-induced syncope are considered as equivalent, as they usually have the same previous symptoms and a similar hemodinamic pattern [23,24].

A number of methods have been proposed, which mostly analyze the HR and the AP signals, for early prediction of TTT outcome. In general, the increase of HR during the first minutes of the test has been suggested as a predictive parameter for positive TTT result [6]. Also, AP in patients with positive TTT has shown a trend toward significantly lower values at systolic phases, and larger systolic-diastolic differences [11]; and brain blood supply did not fluctuate during the TTT in patients with VS in some studies, though more recent ones showed changes when measured by Transcranial Doppler Ultrasounds. Some other potential risk factors for syncopal recurrence are the number and frequency of preceding syncope episodes, as well as nausea, dizziness, and diaphoresis (profusely sweating), as they were pointed out as predictive on the positive result of the TTT [25]. Finally, age, sex, bradychardia, and hypotension during the test were not found to influence the outcome prediction.

Many studies have proposed specific TTT outcome prediction procedures. In [3], a set of time and frequency parameters from the ECG was presented using 24 Holter recordings and compared to the TTT result. The study included 50 consecutive patients with positive TTT and 23 control cases. The pNN50 (percentage in number of the differences in beat periods larger than 50 ms) was first identified as the best decision statistic (82.6% specificity, 51.8% sensitivity), and then spectral analysis parameters were shown to have low predictive power. Subsequently, in [4], the response of HR during TTT was analyzed under the hypothesis that the underlying mechanism to the vaso-depressor response is because of an increment in the sympathetic tone as a response to the orthostatic stress. The study included 28 patients (11 negative; 17 positive, from them 10 with isoproterenol). Database was previously filtered of patients with given conditions. Classical statistic analysis on HR and AP parameters yielded 100% specificity and 41% sensitivity. During the rest period, no significant differences were found, whereas during the tilt period,

cardiac variability decreased significantly in those patients with negative test patients, and the average RR intervals decreased in both groups compared to rest.

The analysis in [6] focused on the early prediction of the negative TTT, searching for the reduction of the test duration, and analyzing the increment in HR before and after the orthostatic stress. This possible mechanism was explained therein according to an excessive sympathetic reaction, causing an opposite reaction to the initiated by an abnormal activation of mechanoreceptors activation, and also causing the activation of the afferent vagal fibers. On 110 patients (no drugs, substudy 1) and 109 patients different from the previous ones (isoproterenol, substudy 2), the results of HR yielded 100% specificity and 88.8% sensitivity in patients in substudy 1 with HR increased under 18 bpm during the first 6 min. After these results, another research group [10] proposed the same methodology for a new protocol using a 80° table slope during 30 min and without inducing drug (in 115 patients; 29 positive test result, from them 16 had syncope during the first 15 min). In this database, the HR yielded 76% sensitivity and 62% specificity. Later [12], a retrospective analysis showed that an increment equal or lower than 18 bpm sustained during 20 s during the first 6 min of the TTT predicts a negative result (110 patients, after excluding syncopes during the first 10 min and low quality in HR signal). Results reached 65% specificity and 75% sensitivity.

The use of AP for TTT outcome prediction was introduced in [11], combined with HR. In 178 patients, changes were more significant during the first 5 min in HR, systolic AP (SAP), and differential AP for patients with positive test outcome (diastolic AP–DAP–did not change significantly), providing a set of results ranges for different analysis: 68-55% specificity, and 53-72% sensitivity. For a prediction of a positive TTT outcome, a database of 318 patients with unexplained syncope was studied in [13], by measuring AP before and after tilt. A reduction of AP during the initial 15 min after tilt was observed for positive cases (58% sensitivity, 93% specificity). One of the most exhaustive studies in the literature in terms of number of patients [15] used a database of 1,155 (759 positive, 396 negative). HR and AP were continuously monitored during TTT, as well as during the preceding 180 s before tilt. Signals were processed and combined developing an incremental risk model. The weights assigned for the different signals were more relevant for the AP contribution compared to the HR in terms of syncope prediction, yielding 95% sensitivity and 93% specificity. However, 51% of predictions took place during the last minute before syncope; this being a strong limitation for early prediction purposes. The use of transthoracic impedance (TI) was introduced in [16], comparing a set of parameters during rest by using a SVM nonlinear classifier (128 patients, 65 with positive), which yielded 94% sensitivity and 79% specificity. As other studies, this one did not consider TTT with drug intervention.

Other studies have analyzed the VVS in terms of the previously mentioned signals [5,7-9,14], but did not focus on early prediction. Nevertheless, some recent studies have pointed out the difficulties that are found when the early prediction results are to be replicated in different patient databases. In [17], authors conclude that the early increase in HR during the first 10 min of the TTT has limited prediction power.

3. Methods and proposed improvements

To study the nonlinear combination of the parameters in the literature, we propose to use the SVM classifier. The learning procedure using SVM was proposed by Vapnik [26], as a method for building separating hyperplanes with maximum margin in possibly nonlinearly separable data, by using Mercer's kernels. These pattern recognition techniques have shown excellent performance in numerous practical applications, especially in terms of generalization capabilities, such as handwritten character recognition, three-dimensional object recognition, or remote sensing [27]. We used the standard ν-SVM classifier, with a Gaussian Mercer kernel, for classification purposes. In this formulation, the free parameters $\nu \in (0,1)$ (parameter controlling the number of support vectors), and σ (kernel width) have to be fixed by some additional criterion, such as cross validation. A detailed presentation of these techniques can be found in [28].

As previously detailed, most of the preceding study in the literature on TTT outcome prediction used straightforward time- and frequency-domain features of HR and AP. Alternative features can be given by nonlinear indices, which have widely been used in cardiac signals (such as HR) [29,30]. According to the time scales of the signals in the TTT, we propose here to use the low-scale index α_1 in DFA and the *SampEn* for further characterizing the available signals during TTT monitoring.

The DFA method has been used for giving a quantification of fractal correlation in physiological time series with nonstationary properties [31]. This index gives a statistically quantification of the affinity of a signal with respect to itself, and the mathematical presentation of the method is detailed elsewhere [32,33]. Due to the time-window used for defining the tachogram segments to be analyzed during TTT, only the short-term index α_1 makes sense to be used in our case. On the other hand, indexes for calculating the entropy in time signals have widely been used in many fields of medicine, such as in HR for cardiac-risk stratification, in the estimation of electroencephalographic organization, and in the

evaluation of changes in the cardiac rhythm, among others [30,34]. *SampEn* index (denoted in our study by *s*) is a statistical index that quantifies nonlinear regularity, and allows us to establish a criterion for order and complexity quantification in a signal. The mathematical formulation can be found in [31,35], as well as the method and criteria followed in this study described in [30], for setting *m* (the dimension of the phase space) and *r* (the scaling or normalization parameter).

In addition to the HR and the arterial pressure, we proposed the use of the variable SV tachogram, defined as the amount of blood (ml), driven by the left ventricle within a beat into aorta. Hence, this new variable is added to the hemodynamical characterization given by indirect measurements, and complements the electrical information in HR and AP tachogram signals. Although the SV itself had never been used in this context, a related one (TI) was used in [16]. The analysis developed in this study includes the complete TTT, a larger sample base, and the use of the tachogram, instead of the continuous signal.

4. Experiments

Our database included 727 consecutive TTT, during the period from 1998 to 2007 in Hospital Universitario Virgen de la Arrixaca de Murcia (Spain), with their clinical information. Signals registered using the Task Force Monitor©, then imported and structured, and later on processed, using an *ad hoc* developed software (*Synkopa*, see Figure 1) on MatLab©. This code converts raw data from the Task Force Monitor into an structured database, and represents various signals, such as HR, SAP, DAP, and SV.

Before any signal processing or model application, signals were pre-processed.

First, signals with invalid information were removed; second, unwanted elements (such as noise and ectopic beats) were also removed, by trained researchers using semisupervised tools. Invalid signal information was considered when (i) significant part of the signal was missing in the segments of interest; (ii) signals had high level of noise; (iii) patients had implanted pacemaker; (iv) patients suffered from cardiac conditions affecting normal physiological response in signals of interests (i.e., arrhythmia or tachycardia). Resulting HR signals at this point were considered as gold standard, and they were subsequently extended to the rest of the components SAP, DAP, and SV. Second, signals were segmented attending to prior knowledge regarding the expected response of TTT, as shown in Figure 1.

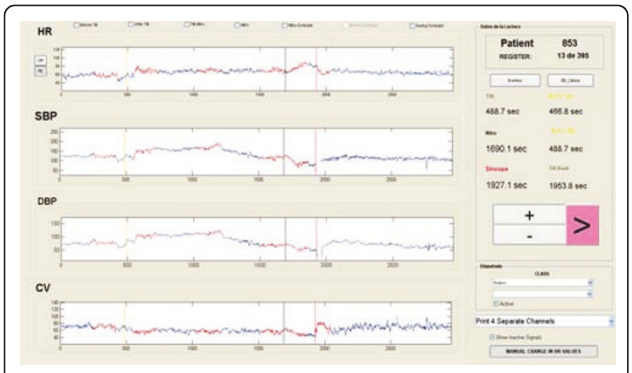

Figure 1 Tool developed for visual and mathematical analyses.

4.1. Time domain methods

Lippman [4] and Madrid [3] proposed prediction methods using statistical analysis of cardiac signals, where the protocols analyzed did [4] and did not [3] envisage the creation of a reference variable (baseline). Both authors studied RR interval and HR fluctuations, and both based their methods on the differences or variability between successive NN [36] as (a) *rMSSD* being the square root of mean square of successive NN (in ms); (b) *pNN50* being the percentage of total pairs of adjacent NN differing more than 50 ms. Other authors [6,10-13] focused on simple measurements of HR and AP (SAP, DAP, and differential AP), such as average, maximum, or minimum for a certain segments definition.

We implemented all these proposed indices (see Table 1), and we extended them to a wider statistical description of the preceding parameters, given by (a) *mean*, being the average HR of a given signal segment; (b) *std*, being the standard deviation of the HR segment; (c) MRR, the mean NN intervals (ms); (d) STRR, the standard deviation of NN intervals (ms); (e) SDRR, the mean of standard deviation of NN intervals (ms); (f) NN50, number of NN pairs that differ by more than 50 ms; (g) NN10, number of NN pairs that differ by more than 10 ms; (h) pNN10, percentage of total pairs of adjacent NN that differ more than 10 ms; (i) NN*xx*, number of NN pairs that differ by more than *xx* ms, were *xx* was between 1 and 100 ms; (j) pNN*xx*, percentage of total pairs of adjacent NN that differ more than *xx* ms.

4.2. Frequency domain methods

Studies in literature based on spectral analysis did not improved early prediction of TTT outcome [7,8], although these studies provided significant contributions in terms of knowledge of the systems and mechanisms involved in syncope [15]. Power spectrum has been evaluated with parametric (auto-regressive [8,5]) and non-parametric methods (Fast Fourier Transform [7] and Wavelet [14]), yielding equivalent results. Hence, spectral indices were not included in the set of analyzed indices.

Table 1 Parameters proposed by authors applied on developed data base

	Rest			Tilt test		
	Positive response	Negative response	*P*-value	Positive response	Negative response	*P*-value
Madrid	0.011 ± 0.03	0.005 ± 0.02	0.022	0.002 ± 0.006	0.0014 ± 0.0037	0.16
Lippman	29.3 ± 19.3	24.8 ± 14.0	0.027	19.6 ± 10.9	19.4 ± 9.7	0.84
Mallat	67.4 ± 11.3	48.3 ± 10.7	0.43	82.0 ± 13.3	79.8 ± 14.6	0.14
Sumiyoshi	67.3 ± 11.3	68.3 ± 10.7	0.43	86.8 ± 13	83 ± 14	0.047
Movahed	67.4 ± 11.3	68.3 ± 10.7	0.43	85.8 ± 15.2	84.0 ± 17.0	0.33
Bellard	67.4 ± 11.3	68.3 ± 10.7	0.43	75.8 ± 13.4	74.4 ± 14.3	0.38
Pitzalis	106.4 ± 17.6	109.2 ± 16.7	0.15	3.6 ± 5.6	3.7 ± 5.9	0.85
Virag	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.

4.3. Receiver operating characteristics

The area under ROC is used as the benchmarking parameter, indicating the higher ratio, the better method performance. ROC curve represents the resulting sensitivity/specificity (SEN/SPE) pairs, corresponding to the progressive decision threshold evolution of for all the possible values [37,38].

Attending to complete TTT (including the stressor agent), and the area under ROC curve, no major finding was obtained either using the methods presented in the literature or with the new ones proposed in this study, when considered in isolation, as shown in Table 1.

4.4. Results on nonlinear SVM

Classical classification methods require the establishment of a set of training and validation samples. After a thorough analysis of possible training and validation sets, we decided to use 40% of the samples for training, 40% for validation, and 20% for test. To ensure the statistical independence of data and made several iterations, random order selection of the samples was incorporated before separation in training, validation, and test. To facilitate the learning process, balancing algorithms were implemented. The balancing strategy discarded the excess samples of any of the qualifying groups before submitting the sample number to the training process. The absence of this balance had resulted in a technical malfunction of the SVM, causing depletion of the support vectors of any of these classes. Validation and test did not incorporate the process of balancing classes.

All the tests were made by setting the range of the SVM free parameters, as shown in Figure 2, and maximizing the area under the ROC curve. The resolution of these search ranges has been adjusted to the needs on a case-by-case basis, printing in a higher-resolution the analysis with significant results once further details were required. Results were also plotted and inspected visually, one-by-one (see example in Figure 2), to detect the optimal regions and to set free parameters ranges. In all the cases, when a potential high-performance region was found, it was rechecked with higher resolutions to evaluate if the finding could respond to occasional actual circumstances (local minima).

After the individual models in the previous literature were analyzed, all the authors' variables and indexes were also analyzed. In this case, prior to SVM analysis, highly correlated variables were removed.

As a result, as shown in Table 2, incorporation of SVM classifiers in the early prediction of complete TTT for individual methods increased the predictive capacity in the validation sample set. Moreover, after the methods provided the highest values in validation, they showed significant reductions in the areas under the ROC curve when applied to test sample set.

In addition, the combined TTT outcome prediction capability of the methods in the literature, including or not including age and sex, with or without pre-selection of noncorrelated components, using SVM classifier, was not able to improve the individual methods (results not shown).

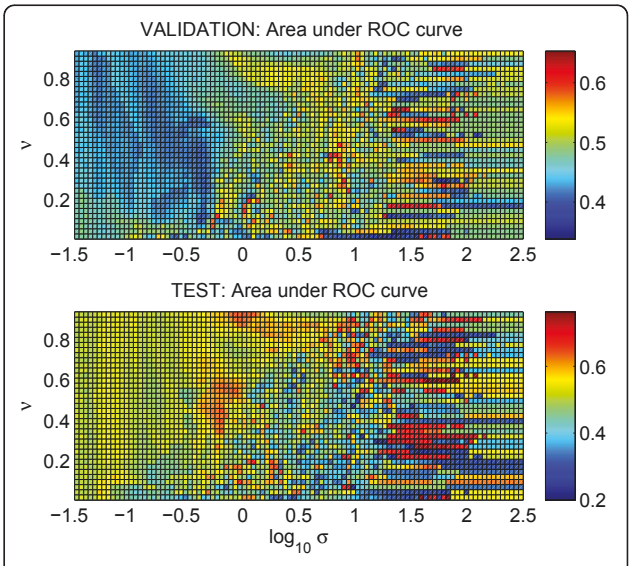

Figure 2 Surface detailed visual analysis of under ROC curve area with validation and test sample set, for SVM analysis for all preceding models after high correlation variables removal.

Table 2 Area under ROC curve obtained during analysis

Classifier	Analysis performed	Maximum	Mean/SD
Linear	Individual authors methods	0.65	0.56 ± 0.06
	Individual authors methods (optimal segment preselect)	0.65	0.61 ± 0.03
SVM	Individual authors methods	0.79	0.59 ± 0.22
	Simultaneous authors methods	0.79	0.57 ± 0.1
	Simultaneous authors methods with PCA	0.76	0.58 ± 0.1
	Sample entropy	0.69	0.56 ± 0.11
	DFA	0.68	0.54 ± 0.12
	Sample entropy with PCA	0.70	0.56 ± 0.09
	DFA with PCA	0.67	0.54 ± 0.09

4.5. Nonlinear indices and additional signals

Many researchers have proposed different methods to analyze TTT signals, although up to date, all studies are based on heart rate variability (HRV) indexes developed in time and frequency domains. This study incorporated in addition to those complexity analysis using nonlinear indexes such as *DFA*, and *SampEn*. Both methods have widely been applied in HRV [29-31,34,39], but not yet in TTT signals. These two methods were applied to variables and indexes (soft-outputs) proposed by authors, as well as to optimal segments previously defined over the most frequently analyzed signals in the literature (HR, SBP, DPA). Finally, SV signal was also included as new source of physiological characterization. High-correlation variables removal, SVM machine learning algorithm, and surface area ROC analysis were also applied.

As a result (see example in Table 2), none of the newly proposed method or indicator developed using nonlinear indexes provided improvements on published methods, even when using SVM classifiers. The absence of clusters of concurrent validation areas with values over 0.6 in terms of area under ROC curve confirmed the limited generalization because of the high dependence of samples used in validation, preventing effectively the prediction of TTT outcome.

5. Discussion and conclusions

The early prediction of the result of the TTT by analyzing the HR tachogram and the SAP and DAP has widely been addressed in the literature. In this study, we aimed to reproduce and improve the performance of most of the preceding methods. The predictive capacity of the methods from the literature compared positively in the passive TTT (without inductor agent), with the only exception of the method proposed by Pitzalis. It was not the case for the complete TTT, for which early prediction did not provide in any of the cases values of area under the ROC curve above 0.64. Moreover, for those methods providing the highest values in validation, a significant reduction in the areas under the ROC curve was obtained in the test set.

The prediction methods proposed and developed in this study based on sample entropy and fractal structure over HR, SBP, DBP, and SV, individually, jointly, or by pre-selection with principal component analysis, with or without classification SVM, did not improve predictive capability compared with the application of SVM classifier on the preceding methods separately.

The moderate prediction capability of all the published methods checked over a sufficient and commune database, together with the significant but insufficient improvements, from an early outcome prediction standpoint, of the new methods proposed in this study, basically by the inclusion of SVM classifier. The SVM exhibited dependence of validation and training samples set, and it did not allow the generalization to test sample successfully. This fact might provide the coherence between the important results published by different authors in the literature, where no generalization process was performed or applied in early prediction.

Based on these results, it can be concluded that the early prediction of the TTT outcome based solely on heart signals, such as HR, BP, and SV, is not a trivial task. The use of more sophisticated signal processing parameters and techniques should be explored, and the informative capabilities of detailed physiological models, such as lumped parameter descriptions of cardiovascular system, should be explored to provide new methods for this problem.

Abbreviations

AP: arterial pressure; DFA: detrended fluctuation analysis; HR: heart rate; HRV: heart rate variability; ROC: receiver operating characteristic curve; SEN/SPE: sensitivity/specificity; SV: stroke volume; SVM: support vector machine; TI: transthoracic impedance; TTT: tilt table test; VVS: vasovagal syncope.

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Competing interests
The authors declare that they have no competing interests.

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