Early Prediction of Tilt Test Outcome, with Support Vector Machine Non Linear Classifier, Using ECG, Pressure and Impedance Signals

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Abstract

The tilt test is a valuable clinical tool for the diagnosis of Vasovagal Syncope. No practical system has been implemented to predict the tilt test outcome at the beginning in the procedure. Our objective was to evaluate and benchmark, over a sufficient database, the predictive performance of the proposed parameters in the literature. We analyzed a database of 727 consecutive cases of tilt test. Previously proposed features were measured from heart rate and systolic/diastolic pressure, in several representative signal segments. A support vector machine (SVM) was used to predict the test outcome with the available features. Also the inclusion of additional physiological signals (impedance) was intended to improve the performance. The predictive performance of the nonlinearly combined previously proposed features was limited ($p<0.03$ and area under ROC curve 0.57 ± 0.12), especially in the beginning of the test, which is the most clinically relevant period. The improvement with additional available physiological information and SVM was limited (area under ROC curve 0.59 ± 0.22). We conclude that the existing methods for tilt test outcome prediction knowledge should be considered with caution.

1. Introduction

Vasovagal Syncope (VVS) is a frequent symptom, corresponding to 3-5% of all hospital emergencies, and counting for almost 1-3% of admissions. Approximately 20% of adult population has suffered at least one syncopal or pre-syncopal event [1]. Tilt Table Test (TTT) is today the most widely used tool to diagnose patients with unknown origin syncope, becoming the standard for this disorder. In summary, TTT induces orthostatic stress that reflects the patient's susceptibility to syncope [2], and to investigate the potential mechanism of this loss of consciousness.

The long duration (up to one hour) required by TTT, in addition to patient discomfort for being exposed to a syncopal (or pre-syncopal) event, together with the high economical cost (mostly due to the test duration), have motivated the search for methods allowing the early prediction of the test [3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20]. The aim of these methods has often been to give a measurement, taken from an easily available cardiac signal such as heart rate (HR) or blood pressure (BP), which predicts the result of the test. Despite all efforts, no practical system has been implemented to date for early prediction of tilt test outcome. Even more, some recent studies have questioned the actual predictive value of some of the formerly proposed parameters [21].

The main objective of this study is to benchmark the predictive value of literature proposed parameters over a wide database, and to evaluate the potential incremental prediction of machine learning techniques.

2. Methods

We analyzed 14 methods reported in literature [3, 4, 5, 6, 7, 8, 9, 10, 11, 13, 15, 17, 18, 20]. Out of these 14 articles, only 9 containing VVS prediction were eligible for implementation and comparison [3, 4, 6, 10, 11, 13, 15, 18, 20].

2.1. Database and TTT protocol

A structured database was built from a representative and extensive TTT records catalogue. These records included the physiological signals registered during indicated tests performed for clinical reasons from 1998 to 2007. The database comprised 727 cases from Universitary Hospital Virgen de la Arrixaca of Murcia (Spain). The database incorporated all clinical information and signals recorded using the Task Force Monitor©. All signals were imported, structured, and pre-processed, using add-hoc developed software using MatLab© platform. The code included a user friendly interface for researchers (MDs and engineers) to interact with the system using a visual front-end. The computational process generated, starting from the imported raw data, the signals representation, and R-R sampled data records of the following signals: HR, Systolic Blood Pressure (SBP), Diastolic BP (DBP), RR interval (RRI), CEV (Cardiac Stroke Volume), Stroke Volume Index, Cardiac Output, and Cardiac Index, among others.

The Italian protocol was applied to all patients. TTT was performed in a comfortable, temperature controlled and quiet room. Patients were asked not to eat two hours before the test. After 10 minutes of supine rest, subject was tilted head-up to 60º without drug administration. In the case of no symptoms after 20 minutes, nitro-glycerine sublingual spray was administered (400 µg) as an inductor-drug. Fifteen minutes after drug administration or earlier if the syncope was reproduced, the TT was considered ended. Carotid sinus massage was applied one minute before tilt and just after tilt.

2.2. Processing

Prior to any processing of recorded signals, preprocessing for noise reduction was applied. The database was subject to direct visual inspection analysis from a trained researcher. All signals not containing valid information were eliminated. The researchers proceeded to manually and semi-automatically remove ectopic beats and their effects on recorded signals. Finally all signals were properly segmented for further processing. Ad-hoc code for signal processing was developed to follow as tightly as possible the methodology described by authors. Sensitivity (SEN), Specificity (SPE), Positive Predictive Value (PPV), and Negative Predictive Value (NPV), were evaluated for each analysis.

With the objective of finding the optimal threshold for prediction, the better relationship between SEN and SPE was used, following the optimal definition (OPT) described by [12]. Additionally a new optimization parameter *(OPT')* was developed including PPV and NPV. Both OPT and OPT' parameters are formulated according to the following equation:

$$OPT = \sqrt{(1 - SEN)^2 + (1 - SPE)^2}$$

$$OPT' = \sqrt{\ldots + (1 - PPV)^2 + (1 - NPV)^2}$$

2.3. Benchmarking method

The area under Receiver Operating Characteristic curve (ROC) was used as the merit figure for benchmarking (the higher value, the better method performance). ROC curve represents the resulting pairs, sensibility / specificity (SEN/SPE) [22, 23], corresponding to the progressive decision threshold evolution of all possible values.

2.4. Machine learning technique

The learning procedure using SVM was proposed by Vapnik [24] as a method for building separating hyperplanes with maximum margin in possibly nonlinearly separable data, by using Mercer's kernels. This technique has its theoretical foundations on the information transformation into a new space, called Reproducing Kernel Hilbert Space (RKHS), where the samples of two different classes can be linearly classified. The problem consists therein in a minimization of classification and margin loss, combined with margin maximization. These pattern recognition techniques have shown excellent performance in a number of practical applications, especially in terms of generalization capabilities, such as handwritten character recognition, 3-dimensional object recognition, or remote sensing [25, 26].

In our study, soft-outputs computed for every method were used as input for the statistical learning machines (SVM) in order to enhance the classification capability to validate the models proposed by authors.

2.5. Optimal signals segments

In addition to the segments defined by the authors of the considered studies (*BaseLine* and *Test*), we defined and analyzed pre and post tilt *Guard Bands*. Area under ROC curve was evaluated for all different possible *Guard Bands*, *BaseLines,* and *Test* segments. A suitable segment selection was observed to significantly enhance prediction outcome (see example in Figure 1 and Table 1). The observed behavior was the following:

(a) *Pre-tilt Guard Band.* In the only allowance of a 1% downfall from the maximum of area under ROC curve, a 52 to 59 seconds pre-tilt guard band length should be included. This finding was coherent with prior medical hypothesis from the fact that carotid sinus massage, when applied one minute prior to tilt, had a maximum of 60 seconds physiological effects on hemodynamic signals and variables. Attending to this finding, a sixty seconds prior to tilt signal segment was always excluded from the analyzed segments.

(b) *Post-tilt Guard Band.* For post tilt guard band, a 90% downfall was needed to find a common scope for all the analyzed methods. The obtained guard band ranged from 58 to 62 seconds. The same rationale applied for pre-tilt carotid sinus massage was issued according to immediately post tilt carotid sinus massage, and the first tilting minute was excluded for any analysis.

(c) *Baseline.* In the allowance of 5% downfall, the optimal length was found within a 180 seconds segment.

(d) *Test segment length*. In the allowance of a maximum 10% downfall from the maximum of the merit figure, the optimal length was found within the 180 seconds segment.

Table 1. Segment preset analysis for 1% downfall allowance. All values in seconds.

	Pre-Tilt Guard Band		Post-Tilt Guard Band		Base-Line Length		Test Length	
	Min	Max	Min	Max	Min	Max	Min	Max
Lippman	52	59	37	49	101	124	126	179
Mallat	0	100	38	53	10	310	52	86
Sumiyoshi	3	9	58	60	10	25	182	184
Movahed	2	100	23	79	115	310	99	310
Bellard	56	100	70	77	75	310	12	17
Pitzalis	76	86	34	41	65	153	116	133

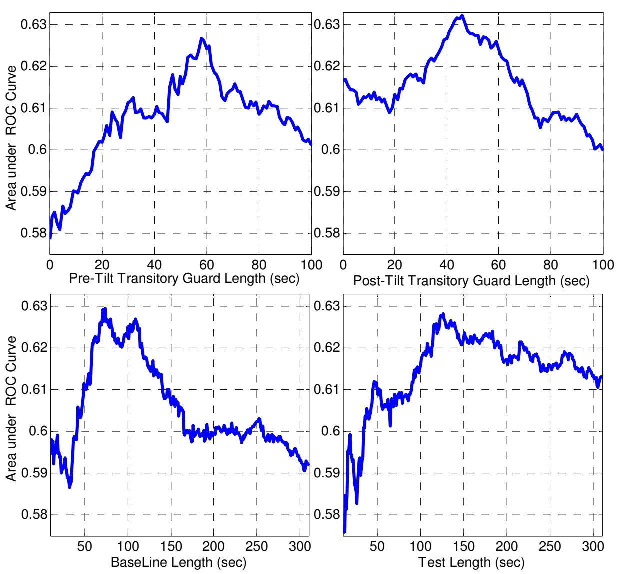

Figure 1. Segments analysis for prediction method in [5].

3. Results

3.1. Segments preset results

The evaluation of optimal segments showed that a three minutes baseline and test segment duration, together with 1 minute before and after tilt guard band, conferred the best performance simultaneously, in terms of area under ROC curve, for all the considered methods. Guard band were consistent with medical hypothesis of physiological effects of Carotid Sinus Hyper-sensibility simultaneously during TTT in the considered medical protocol.

3.2. Predictive capability

The predictive capability of considered methods did not compare positively with the *Complete TTT* (including inductor administration). Those cases in which inductor drug was not given were removed from the analyzed data, given that they corresponded to a minority of patients with positive *Passive TTT,* thus having an accused propensity to VVS. In this subgroup, we obtained very similar results to studies based on test without inductor administration. The results for *Complete TTT* outcome early prediction did not provide areas under the ROC curve above 0.64 (see Table 2). The use of machinery learning tools (SVM in our study) improved the predictive capacity in all cases. Age and/or sex as an additional variable for SVM input space did not improve results.

4. Conclusions

In this work we can conclude that a suitable segment selection is needed in order to improve the prediction accuracy. The three minutes segments (baseline and test) provided improved results in our data base.

The predictive capacity of the reproduced methods compared positively in the Passive TTT (without inductor agent), with the only exception of the method proposed in [Pitzalis]. However, this was not the case for the complete TTT, and results obtained for early prediction of complete TTT did not provide, in any of the cases, values of area under the ROC curve above 0.64.

In addition to the information given by previously published methods, the incorporation of SVM classifiers in the early prediction of complete TTT for individual methods increased the predictive capacity in the validation set. However, for those methods providing the highest values in validation phase, a significant reduction in the areas under the ROC curve was obtained when the model was applied to test sample set.

Table 2. ROC area for Published Method, Optimal Segment, and SVM multiple training and validation resampling analysis.

	Author (Pasive TTT)	Author (Complete TTT)	Optimal Segment	SVM for Multiple Trainings
Madrid	n.a.	0.51	0.58	0.60±0.08
Lippman	n.a.	0.48	0.64	0.58±0.10
Mallat	n.a.	0.64	0.62	0.60±0.13
Sumiyoshi	0.66	0.57	0.62	0.58±0.12
Movahed	0.73	0.59	0.64	0.59±0.11
Bellard	0.70	0.63	0.62	0.57±0.13
Pitzalis	0.57	0.49	0.57	0.59±0.11
Virag	n.a.	0.51/0.59	0.59	n.a.

The values obtained in this study in terms of area under the ROC, during both the learning and the test stages, showed a limited generalization ability of currently proposed methods for early prediction of the TTT outcome, therefore, new indices should be investigated in this setting, with emphasis on their physiological meaning and understanding.

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References

[1] Gimeno Blanes JR, Valdés Mas M, Lacunza Ruiz J, García Alberola A, Valdés Chávarri M. Síncope. Medicine 2005;9:2447.

[2] Fenton AM, Hammill SC, Rea RF, Low PA, Shen WK. Vasovagal Syncope. Annals of Internal Medicine 2000;133:714–725.

[3] Madrid AH, Moro C, Marin Huerta E, Novo L, Mestre JL, Lage J, Ricoy E. Usefulness of the RR variability in the diagnosis of neurogenic Syncope. Rev Esp Cardiol 1994;47:536–43.

[4] Lippman N, Stein K, Lerman B. Failure to decrease parasympathetic tone during upright tilt predicts a positive tilt-table test. Am J Cardiol 1995;75:591–5.

[5] Stewart JM, Eer M, Sorbera C. Heart Rate Variability and the Outcome of Head-Up Tilt in Syncopal Children. Pediatric Research 1996;40:702.

[6] Mallat Z, Vicaut E, Sangare A, Verschueren J, Fontaine G, Frank R. Prediction of Head-Up Tilt Test Result by Analysis of Early Heart Rate Variations. Circulation 1997;96:581–584.

[7] Kochiadakis GE, Orfanakis A, Chrissostomakis SI, Manios EG, Kounali DK, Vardas PE. Autonomic Nervous System Activity During Tilt Testing in Syncopal Patients, Estimated by Power Spectral Analysis of Heart Rate Variability. Pacing and Clinical Electrophysiology 1997;20:1332–1341.

[8] Furlan R, Piazza S, Dell'Orto S, Barbic F, Bianchi A, Mainardi L, Cerutti S, Pagani M, Malliani A. Cardiac Autonomic Patterns Preceding Occasional Vasovagal Reactions in Healthy Humans, 1998.

[9] Liu JE, Hahn RT, Stein KM, Markowitz SM, Okin PM, Devereux RB, Lerman BB. Left Ventricular Geometry and Function. Proceeding Neural Mediated Syncope, 2000.

[10] Sumiyoshi M, Nakata YYM, Tokano T, Yasyda M, Nakazato Y, Yanagysgi H. Does an Early Increase in Heart Rate During Tilting Predict the Results of Passive Tilt Testing? Pacing and Clinical Electrophysiology 2000;23:2046–2051.

[11] Bellard E, Fortrat JO, Vielle B, Dupuis JM, Victor J, Leftherioitis G. Early predictive indexes of head-up tilt table testing outcomes utilizing heart rate and arterial pressure changes. The American journal of cardiology 2001;88:903–906.

[12] Bellard E, Fortrat JO, Schang D, Dupuis JM, Victor J, Leftheriotis G. Changes in the transthoracic impedance signal predict the outcome of a 70º head-up tilt test. Clinical Science 2003;104:119–126.

[13] Movahed MR, Hassapoyannes CA. Prediction of non-occurrence of syncope during a tilt-table test by early heart rate variations. J S C Med Assoc 2001;0pt97(5):207–10.

[14] Movahed MR. Predictor of a Negative Tilt-Table Test Result Based on Early Heart Rate Variation in Patients With a History of Syncope. American Heart Hospital Journal 2007;5:247–249.

[15] Pitzalis M, Massari F, Guida P, Iacoviello M, Mastropasqua F, Rizzon B, Forleo C, Rizzon P. Shortened Head-Up Tilting Test Guided by Systolic Pressure Reductions in Neurocardiogenic Syncope, 2002.

[16] Pitzalis M, Parati G, Massari F, Guida P, Di Rienzo M, Rizzon B, Castiglioni P, Iacoviello M, Mastropasqua F, Rizzon P. Enhanced reflex response to baroreceptor deactivation in subjects with tilt-Induced syncope. Journal of the American College of Cardiology 2003;41:1167–1173.

[17] Suzuki M, Hori S, Nakamura I, Nagata S, Tomita Y, Aikawa N. Role of Vagal Control in Vasovagal Syncope. Pacing and Clinical Electrophysiology 2003;26:571–578.

[18] Virag N, Sutton R, Vetter R, Markowitz T, Erickson M. Prediction of Vasovagal syncope from heart rate and blood pressure trend and variability: Experience in 1,155 patients. Heart Rhythm 2007;4:1375–1382.

[19] Schang D, Bellard E, Plantier G, Dupuis JM, Victor J, Leftheriotis G. Comparison of computational algorithms applied on transthoracic impedance waveforms to predict head-up tilt table testing outcome. Computers in Biology and Medicine 2006;36:225–240.

[20] Schang D, Feuilloy M, Plantier G, Fortrat J, Nicolas P. Early prediction of unexplained syncope by support vector machines. Physiological Measurement 2007;28:185.

[21] Turk U, Alioglu E, Kirilmaz B, Duygu H, Tuzun N, Tengiz I, Zoghi M, Ercan E. Prediction of Head-Up Tilt Test Result: Is it Possible? Pacing and Clinical Electrophysiology 2010;33:153–158.

[22] Zweig MH, Campbell G. Receiver-operating characteristic (ROC) plots: a fundamental evaluation tool in clinical medicine. Clin Chem 1993;39:561–77.

[23] Robertson EA, Zweig MH. Use of receiver operating characteristic curves to evaluate the clinical performance of analytical systems. Clinical Chemistry 1981;27:1569–1574.

[24] Vapnik V, Chervonenkis A. Theory of pattern recognition, 1974.

[25] Schölkopf B, Simard P, Smola AJ, Vapnik V. Prior knowledge in support vector kernels. Advances in neural information processing systems 1998;640–646.

[26] Cristianini N, Shawe-Taylor J. An introduction to support Vector Machines: and other kernel-based learning methods 2000.

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