Evaluation of the Behaviour of the Time Interval from the Onset of the QRS Complex to the Onset of Radial and Carotid Pulse Waves with the Result of the Titl Test

ALEJANDRO M. VILLAMIL[†, 1], CARLOS PERONA[1], GABRIELA S. CARNERO[1], YENIFERS TORRES[1], JAVIER A. MARIANI[2], CARLOS D. TAJER[MTSAC, 2], JUAN MARTÍN FIAMENGO[1], NOEMÍ PRIETO[MTSAC1]

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Address for reprints:
Dr. Alejandro Villamil
Hospital F. Santojanni
Servicio de Electrofisiología
Pilar 950 - Ciudad Autónoma de Buenos Aires, Argentina
Phone number: 011 4746-9294
e-mail: amvillamil@intramed.net

SUMMARY

Evaluation of the Behavior of the Time Interval from the Onset of the QRS Complex to the Onset of Radial and Carotid Pulse Waves with the Result of the Tilt Test

Background
The tilt test (TT) is a diagnostic tool used to evaluate autonomic function in patients with syncope. However, as TT has a high rate of false positive results and the duration of the test is long, new strategies are emerging. A device developed in Argentina allowed establishing a non-invasive, reproducible and reliable method to measure pulse wave velocity in the carotid and radial arteries during a conventional TT and to determine its likelihood to predict the result of the test.

Objective
To assess the usefulness of time delay of the pulse waveform from the onset of the QRS complex in order to predict the result of the tilt test.

Material and Methods
We conducted an observational study on consecutive patients with syncope referred to the tilt test laboratory. During the test blood pressure, heart rate and carotid and radial pulse waves were recorded simultaneously with a specially designed polygraph. Univariate and multivariate analyses were performed to assess the ability of time delay of the pulse waveform from the onset of the QRS complex to predict the result of the TT. This ability was evaluated with the analysis of ROC curves.

Results
A total of 43 patients were included; 24 (55.8%) were women. The TT was positive in 18 patients (11 women). Univariate analysis determined that changes in systolic blood pressure ($p=0.02$) and diastolic blood pressure ($p<0.01$) measured at 10 minutes, the use of ACEI/ARB ($p=0.01$) and time delay of the carotid pulse wave ($p<0.01$) were related to the result of the TT. At multivariate analysis, only time delay of the carotid pulse wave was a significant predictor of the result ($p=0.036$). The C statistic of the time delay of the carotid pulse wave was 0.88 (95% CI 0.76 to 0.99).

Conclusions
Measurement of the time delay or the carotid pulse wave at 5 minutes is an independent predictor of the result of the TT, allowing a correct classification in 88% of patients before the development of symptoms.

Key words > Syncope - Diagnosis- Tilt Table Test

Abbreviations >

ARB	Angiotensin II receptor blocker	**SBP**	Systolic blood pressure
ACEI	Angiotensin-converting enzyme inhibitor	**TT**	Tilt table testing
IQR	Interquartile range		

[MTSAC] Full Member of the Argentine Society of Cardiology
[†] To apply as full member of the Argentine Society of Cardiology
[1] Hospital Donación Francisco Santojanni, Department of Cardiology, Electrophysiology Section, Autonomous City of Buenos Aires. Buenos Aires, Argentina
[2] GEDIC. Grupo de Estudio y Docencia de la Investigación Clínica. Buenos Aires, Argentina

BACKGROUND

Syncope is a frequent manifestation in the general population affecting 3% of people over 30 years of age. (1) In patients with syncope, one third of medical consultations at the outpatient clinics are due to vasovagal syndrome (2), which is the most frequent cause of syncope in young people with no evidence of underlying structural disease. (3) The diagnosis is based on the medical record and on the reproducibility of symptoms during the head-up tilt table testing (TT). Tilt table testing is a diagnostic tool routinely used to evaluate autonomic function in patients with syncope. By means of a controlled orthostatic stress the test reveals the predisposition to present neurally mediated orthostatic hypotension and bradycardia. The most widely used protocol includes a tilt table that permits calibrated upright tilt angles ranging from 60° to 80° for 45 minutes or until syncope or presyncope occur. (4, 5)

Among the disadvantages of the test one should mention the high number of false negative results, the duration of the procedure which takes approximately 1 hour, the fact that the patient may feel uncomfortable and the its high cost. (6, 7) Thus, the development of new methods that may facilitate the diagnosis of vasovagal syncope has gained increasing importance. Novel techniques have been published, as the analysis of pulse wave morphology or variations in impedance due to postural changes. (8-10)

In 2003, the Section of Hypertension of the *Hospital Santojanni* conducted studies on arterial distensibility, which were published in 2004, using the Sphygmocor system (11). These studies stimulated us to explore whether measuring pulse wave velocity might be useful to evaluate the physiopathology of patients with vasovagal syncope. A year later, and after making some technical modifications and overcoming testing stages, a device developed in Argentina allowed to establish a non-invasive, reproducible and reliable method to measure pulse wave velocity in the carotid and radial arteries during a conventional head-up TT.

The goal of the present study was to evaluate if the outcome of the head-up TT may be predicted by the information obtained through a non-invasive measurement of the time delay from the onset of the QRS complex to the onset of radial and carotid artery pulse waves at rest compared with a similar measurement obtained with the patient tilted at an angle of 70°.

MATERIAL AND METHODS

We conducted a prospective cohort study including patients consecutively referred to the Electrophysiology Laboratory of the *Hospital Santojanni*, between April 2007 and July 2008 with an indication of tilt table testing as part of the evaluation of probable neurocardiogenic syncope or presyncope. Patients were excluded when it was not possible to obtain an adequate record of the radial and carotid artery wave pulses due to issues related to measuring instruments (signal) or patients (anatomical defects) and in presence of arrhythmias that affected the interval between the QRS complex and the onset of the pulse wave.

We gave the patients verbal information about their inclusion in the study, but they were not asked to sign an informed consent form for many reasons. Firstly, this was an observational study. Secondly, the onset of carotid artery and radial artery pulse waves was measured in a non-invasive fashion. Thirdly, the TT protocol usually used in our institution was not modified. Finally, we did not perform patient follow-up.

Protocol for Tilt Table Testing

Patients were instructed to fast for 3 hours before the test which was performed on a tilt table with an initial phase with the patient in the supine position during 15 minutes. Heart rate was determined, and blood pressure was measured using conventional sphygmomanometry, and the non-invasive measurements of the QRS-radial artery wave (QR) and QRS-carotid artery wave (QC) intervals using calipers with a precision of ± 2 ms were recorded simultaneously on a polygraph at 100 mm/s (Figure 1) The measurements were recorded at baseline, immediately on assuming the upright posture, and every 5 minutes during a 70° upright tilt lasting 45 minutes or until syncope or presyncope developed. The parameters were recorded continuously on a multichannel polygraph (EXXER, software VX.X) at a high paper speed (100 mm/s) with simultaneous recordings of electrocardiographic signals, radial artery and carotid artery pulse waves (with a custom-built pressure transducer).

The TT response was considered positive when syncope, presyncope, or symptoms associated with hypotension (SBP < 80) and/or bradycardia developed.

Statistical Analysis

The sample size was not formally calculated as this was a hypothesis-generating and feasibility study. In consequence, and given the exploratory nature of this analysis, our results should be interpreted with caution.

Categorical data are expressed as numbers and percentages and continuous variables as medians and interquartile range (IQR).

Patients were divided into two groups according to the result of the head-up TT (positive and negative), and the

Fig. 1. Example of radial artery and carotid artery pulse waves record.

delay in the pulse wave was evaluated. The chi square test or Fisher's exact test were used to compare baseline categorical variables, and the Mann-Whitney U test was used for continuous variables.

We evaluated the association between the delay from the onset of the QRS complex to the onset of the radial and carotid arteries pulse waves at 5 and 10 minutes and the result of the TT and between the difference of the initial delay and the delay at 5 and 10 minutes or Δ (calculated as the delay from the onset of the QRS to the pulse wave at 5 and 10 minutes - delay from the onset of the QRS to the baseline pulse wave) and the result of the TT. The same procedure was used to study the relation between blood pressure and heart rate with the result of the TT.

Univariate models were created to evaluate predictors of the result of the TT. These models included baseline characteristics and information regarding the pulse wave delay (evaluated as absolute time -in milliseconds-and difference of time –Δ– between the onset and at 5 and 10 minutes) measured in the radial and carotid arteries. Those variables with a p value < 0.05 were included in a step forward multivariate model.

Our predictive model prioritized the difference between blood pressure baseline and final values with pulse wave delay (Δ) above the values at different moments of the TT, as the relation between the formers with the results of the TT was greater and might result more useful in the clinical practice.

After having identified the independent association between Δ pulse wave delay and the result of the TT, ROC curves were constructed to evaluate the discrimination capability of the parameter and to detect the threshold that had the best sensitivity and specificity to predict the result of the TT. The discrimination capability between the positive and the negative test results was evaluated by the C statistic with its corresponding 95% confidence interval. The C statistic should be interpreted as the likelihood that a randomly chosen patient will have a positive TT. A value of 0.5 indicates that the predictor is not better than chance, while a value of 1.0 indicates a perfect discrimination capability. Values > 0.8 suggest a good discrimination.

Finally, positive and negative predictive values were calculated from the results of sensitivity and specificity.

There was no need to impute or replace missing data as all the necessary information for the analysis was complete.

All tests were two-tailed and the significance level was set at $p < 0.05$.

Statistical analysis was performed using SPSS 11.0 statistical package for Windows (Chicago, Illinois).

RESULTS

A total of 46 head-up TTs were performed at the Electrophysiology Laboratory of the *Hospital Santojanni* during the study period; 43 were eligible to be included in the study and constitute the basis of this report (Figure 2).

Table 1 shows the general characteristics of the population according to the result of the TT. Most patients were women (55.8%, 24 patients); median age was 63.5 years (IQR 41.0 to 74.0). The percentage of hypertensive patients was 37.2% and the most frequently antihypertensive drugs used were ACEIs/ARBs (25.6%).

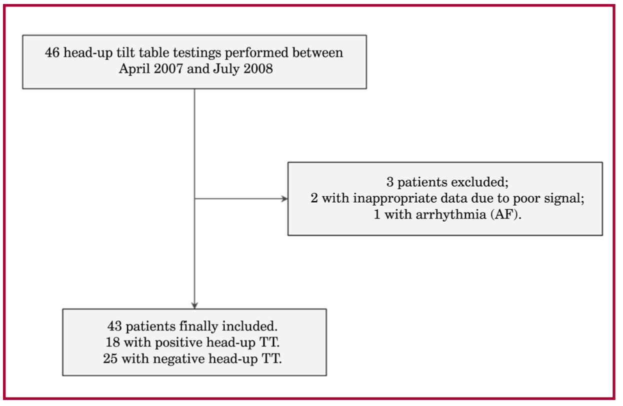

Fig. 2. Study design and patient flow chart.

Table 1. Patients' baseline characteristics

Variable	All patients	Positive head-up TT	Negative head-up TT	p
N	43	18	25	
Female gender, n (%)	24 (55.8)	11 (61.1)	13 (52)	0.55
Age, median (IQR)	63.5 (41.0 a 74.0)	67.5 (55.3 a 74)	58.5 (31.3 a 77.3)	0.44
Hypertension, %	37.2	60	35	0.14
Dyslipemia, %	14	26.7	10	0.37*
Diabetes, %	4.7	13.3	0	0.18*
Current smoking, (%)	4.7	25	5	0.15*
Prior medication, n (%)				
Beta blockers	7 (16.3)	4 (28.6)	3 (15.0)	0.41*
ACEI/ARB	11 (25.6)	9 (64.3)	4 (20.0)	0.01*
Calcium channel blockers	2 (4.7)	0 (0.0)	2 (10.0)	0.50*
Statins	3 (7)	2 (14.3)	1 (5.0)	0.56*

* Fisher's exact test
N: Number of patients ACEI/ARB: Angiotensin-converting enzyme inhibitors/Angiotensin II receptor blockers.

Patients with a positive head-up TT were treated more frequently with ACEIs/ARBs compared to patients with a negative result. We did not detect any other significant differences between both groups.

Table 2 shows the baseline physiological data and those at 5 and 10 minutes after the initiation of the head-up TT. There were no significant differences in any of the parameters evaluated between patients with a positive head-up TT and those with negative results.

The time delay from the onset of the carotid artery pulse wave was significantly greater at 5 minutes in patients with a positive test (142 ms versus 132 ms; p = 0.02). At 10 minutes, the time delay from the onset of the carotid artery pulse wave (149.5 ms versus 132 ms; p = 0.04) and diastolic blood pressure (62.5 mm Hg versus 80 mm Hg; p = 0.02) were significantly different in patients with a positive head-up TT compared to those with a negative result, respectively.

Analysis of the predictors of head-up tilt table testing outcomes

Univariate analysis showed that the Δbetween systolic blood pressure measured before the study and at 10 minutes (p = 0.02), the Δ blood pressure at 10 minutes (p < 0.01), prior ACEI/ARB (p = 0.01) and the Δ time delay of the carotid pulse wave (p < o.o1) were associated with the result of the head-up TT (Table 4). At multivariate analysis, only Δ time delay of the carotid pulse wave remained as an independent predictor of the outcome of the head-up TT (p = 0.02) (see Table 4).

Evaluation of the predictive capability and cut-off point for the time delay in the carotid artery pulse wave.

The Δ at 5 minutes was used to assess the capability of the time delay of the carotid artery pulse wave to predict the outcome of the head-up TT.
Figure 3 shows the results of the ROC curve constructed with the different values for the Δ time delay in the carotid artery pulse wave. The C statistic, defined as the percentage of times the parameter is capable of predicting the outcome of the head-up TT, was 0.88 (95% CI 0.76 to 0.99).

The threshold value of the Δ delay of the carotid artery pulse wave with the best sensitivity and specificity to predict the result of the TT is 17 ms.

With this cut-off point, the sensitivity, specificity, positive predictive value and negative predictive value of the Δtime delay of the carotid artery pulse wave to predict the outcome of the head-up TT were 83.3%, 84%, 79% and 88%, respectively.

DISCUSSION

The results of this pilot study suggest that the time delay from the onset of the QRS complex to the onset of the carotid artery pulse wave during the head-up TT is a simple and non-invasive measurement that has the potential to predict the outcome of the test.
The importance of this finding lies in its clinical implications. Head-up TT is frequently associated with unpleasant symptoms related to the development of syncope, and the duration of the procedure is usually

Variable, median (IQR)	Positive head-up TT (n = 18)	Negative head-up TT (n = 25)	p
Systolic BP			
baseline	140 (120 to 140)	130 (115 to 135)	0.16
5 minutes	120 (107.5 to 140)	125 (110 to 140)	0.60
10 minutes	110 (97.5 to 132.5)	120 (110 to 140)	0.11
Systolic BP			
baseline	80 (77.5 to 80)	80 (70 to 80)	0.82
5 minutes	80 (70 to 80)	80 (75 to 80)	0.40
10 minutes	62.5 (60 to 80)	80 (70 to 80)	0.02
Heart rate			
baseline	65 (58,8 to 67)	65 (60 to 70)	0.65
5 minutes	71.5 (60 to 80,5)	70 (61.5 to 76.5)	0.68
10 minutes	67.5 (60 to 77)	70 (62.5 to 79)	0.42
Carotid artery delay			
baseline	118.5 (108.8 to 126)	126 (105 to 140)	0.34
5 minutes	142 (133.5 to 153.5)	132 (110 to 146)	0.02
10 minutes	149.5 (132 to 155.8)	132 (110 to 147)	0.04
Radial artery delay			
baseline	180 (160 to 186)	180 (165.5 to 200)	0.50
5 minutes	210.5 (180 to 234.8)	190 (170 to 210)	0.13
10 minutes	213 (183 to 230)	190 (170 to 210)	0.06

IQR: Interquartile range BP: Blood pressure

Table 2. Physiological variables during head-up tilt table testing

Table 3. Modification of physiological variables from baseline values

Variable, median (IQR)	Positive head-up TT	Negative head-up TT	p
Δ Systolic BP			
5 minutes	–10 (–20 to 0)	0 (–10 to 2,5)	0.09
10 minutes	–10 (–30 to 0)	–5 (–10 to 0)	0.02
Δ Systolic BP			
5 minutes	0 (–10 to 0)	0 (0 to 0)	0.25
10 minutes	–10 (–20 to 0)	0 (0 to 0)	< 0.01
Δ Heart rate			
5 minutes	6 (0 to 16.3)	1 (0 to 10)	0.26
10 minutes	8 (-0.8 to 15.3)	7 (0 to 11.5)	0.77
Δ Carotid artery delay			
5 minutes	27 (20.3 to 33.3)	6 (0 to 10)	< 0.01
10 minutes	30 (19.8 to 38.5)	10 (6 to 15)	< 0.01
Δ Radial artery delay			
5 minutes	26.5 (18.5 to 48.3)	7 (0 to 19)	< 0.01
10 minutes	33.5 (23.5 to 42)	10 (0 to 19)	< 0.01

IQR: Interquartile range BP: Blood pressure Δ = Delta.

Table 4. Predictors of head-up tilt table testing outcomes. Univariate and multivariate analyses

Variable	Univariate		Multivariate	
	OR (95% CI)	p	OR (95% CI)	p
Reduction is systolic BP at 10’ Δ mm Hg	1.07 (1.01-1.12)	0.02	1.02 (0.94 to 1.10)	NS
Reduction is diastolic BP at 10’ Δ mm Hg	1.13 (01.03 to 1.23)	< 0.01	1.13 (01.03 to 1.23)	NS
Use of ACEI/ARB	7.2 (1.53 to 33.9)	0.01	6.88 (0.67 to 70.9)	NS
Δ Carotid artery delay at 5’ in ms	1.17 (1.07 to 1.27)	< 0.01	1.13 (1.02 to 1.25)	0.02

Δ: Delta. BP: Blood pressure ACEI/ARB: Angiotensin-converting enzyme inhibitors/Angiotensin II receptor blockers.

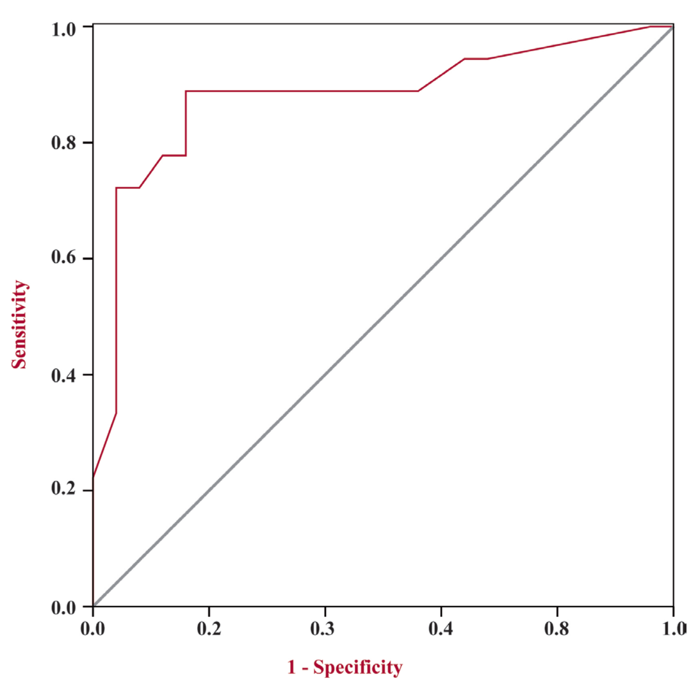

Figure 3. ROC curve of the Δ time delay of the carotid artery pulse wave and the outcome of the head-up tilt testing.

one hour. The time delay of pulse wave predicted the results of the head-up TT within five minutes after the test was initiated; the patients did not develop either disagreeable symptoms or complications associated with the method employed.

Other investigators have evaluated the association between the shape of the pulse wave recorded from several vascular beds and the recurrence of vasovagal syncope or the result of the head-up TT. (8 -10) Their results were obtained using complex tools to estimate pulse wave and arterial stiffness; in addition, the information provided by these methods was not as early as ours and thus the usefulness of these methods in clinical practice is limited. Even more, these trials did not perform a thorough evaluation of capability of these parameters to predict the outcomes of the head-up TT or symptoms recurrence. Our study could detect a measurement parameter that predicts the outcomes of the test: the analysis of the ROC curve identified a cut-off point that discriminates patients with a positive head-up TT through analysis methods recommended for the evaluation of diagnostic tests. (12)

Patients with vasovagal syncope exhibited longer time delay between the onset of the QRS complex and the carotid artery pulse wave. This might be explained by vagal modulation in the pre-ejection period or might be related to the arterial distensibility in the ejection period. In this sense, an ongoing study is investigating the ejection period at rest and at the moment of occurrence of the time delay in the carotid artery pulse wave during head-up TT using Doppler echocardiography. The results of this study might discriminate whether this phenomenon occurs mostly during the pre-ejection period or during the ejection period.

Study limitations

A few limitations should be mentioned. Firstly, as this is a pilot study, the number of patients included is small to draw any definite conclusion regarding the usefulness of the delay in the pulse wave. Secondly, the study population constitutes a highly selected group of patients with symptoms (syncope or presyncope) suggestive of vasovagal syncope referred for head-up TT. Possibly, our results might not be reproducible in a larger population of patients with less defined syncope. Thirdly, we did not include a control group of asymptomatic patients and thus we cannot explore the mechanisms responsible for these findings in patients with syncope. Fourthly, the time delay in the pulse wave is a final measurement and thus the intermediate phenomena with a mechanistic explanation are only speculative. Measurements of the conditions of arterial wall elasticity are still not available but might be useful to explain this mechanism. Finally, our findings are related to the prediction of the outcomes of the head-up TT but not with the etiology of symptoms or recurrences as we did not perform patient follow-up.

Since this pilot study ended, a larger trial is currently ongoing with the goal of confirming the findings here reported and expanding our observations to a control population constituted by asymptomatic individuals with similar characteristics.

CONCLUSIONS

Our study suggests that a simple and non-invasively measured parameter during the head-up TT has the potential to prevent the development of unpleasant symptoms and to shorten the duration of the test. Further studies including a larger population of patients with syncope, healthy controls, measurements of the conditions of arterial pulse wave transmission, and patient follow-up are needed. These studies might help us to define the real value of this finding for clinical practice and to define its physiopathological mechanisms.

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