

# Early hemodynamic response to the tilt test in patients with syncope

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## Abstract

**Introduction:** Our aim was to evaluate the differences in the early hemodynamic response to the tilt test (HUTT) in patients with and without syncope using impedance cardiography (ICG).

**Material and methods:** One hundred twenty-six patients (72 female/48 male;  $37 \pm 17$  years) were divided into a group with syncope (HUTT+),  $n = 45$  patients) and a group without syncope (HUTT-),  $n = 81$  patients). ECG and ICG signals were continuously recorded during the whole examination, allowing the calculation of heart rate (HR), stroke volume (SV), and cardiac output (CO) for every beat. The hemodynamic parameters (averaged over 1 min) were analyzed at the following points of the HUTT: the last minute of resting, the period immediately after the tilt (0 min), 1 min and 5 min after the maneuver. The absolute changes of HR, SV and CO were calculated for 0, 1, and 5 min after the maneuver in relation to the values at rest ( $\Delta HR$ ,  $\Delta SV$ ,  $\Delta CO$ ). Also, the percentage changes were calculated (HRI, SVi, COi).

**Results:** There were no differences between the groups in absolute and percentage changes of hemodynamic parameters immediately after and 1 min after tilting. Significant differences between the HUTT(+) and HUTT(-) groups were observed in the 5<sup>th</sup> min of tilting: for  $\Delta SV$  ( $-27.2 \pm 21.2$  ml vs.  $-9.7 \pm 27.2$  ml;  $p = 0.03$ ),  $\Delta CO$  ( $-1.78 \pm 1.62$  l/min vs.  $-0.34 \pm 2.48$  l/min;  $p = 0.032$ ), COi ( $-30 \pm 28\%$  vs.  $-0.2 \pm 58\%$ ;  $p = 0.034$ ).

**Conclusions:** In the 5<sup>th</sup> min the decrease of hemodynamic parameters ( $\Delta SV$ ,  $\Delta CO$ , COi) was significantly more pronounced in HUTT(+) patients in comparison to the HUTT(-) group.

**Key words:** vasovagal syncope, head-up tilt test, hemodynamic parameters, impedance cardiography.

## Introduction

The head-up tilt test (HUTT) is an integral part of diagnosis of unexplained syncope of suspected vasovagal origin [1, 2]. Despite the numerous investigations, the pathomechanism of vasovagal syncope has not been established yet [1]. Usually, the hemodynamic parameters are limited to ECG and arterial blood pressure (BP) [3], due to the technical difficulties and ethical reservations. Application of other hemodynamic parameters, describing ventricular function, could help in interpretation of the HUTT outcome. There have been a few attempts to correlate these parameters measured at rest and during early minutes of the response to HUTT with the late outcome of this time-consuming test [4–9].

We are aware of a few attempts to perform a similar study using impedance cardiography (ICG). This technique seems well suited to monitoring relatively easily and continuously the changes of stroke volume (SV) and some other cardiac hemodynamic parameters during the potentially long lasting HUTT procedure [4, 8, 10–15]. Moreover, the change in body position will not compromise the value of ICG measurement [16].

Echographic studies suggested a higher rate of stroke volume (SV) decrease in patients with a positive outcome of HUTT in comparison to those with no syncope [5–7]. In contrast to echocardiographic studies, Novak *et al.* [4], using ICG, found a similar decrease of SV in two groups of patients (with and without a positive HUTT outcome). Bellard *et al.*, [8] using this technique, compared such groups and found a significant difference in a timing parameter describing the late part of the ventricular ejection, only. This interval was shorter at rest in fainters and increased significantly after the tilt only in this group, whereas it remained almost unchanged between the 5<sup>th</sup> and 10<sup>th</sup> min in non-fainters. This study demonstrated that ICG could predict the outcome of HUTT.

In contrary to echocardiographic studies, Shen *et al.* [12], using ICG, found a small decrease in SV, and increased heart rate (HR) and cardiac output (CO), in patients with an inducible vasovagal response to tilt. They observed a significantly greater decline in SV and CO, and a smaller, non-significant increase in HR, in non-responders and in patients with a negative HUTT outcome but a pos-

itive isoproterenol tilt test. Bellard *et al.* [8] did not find any significant differences in other ICG signal derived parameters related to SV, during early minutes after the maneuver. Considering the inconsistency of SV results obtained using ICG and echocardiography, we decided to compare changes in SV and CO occurring during the first minutes after tilting between patients with positive and negative outcomes of the HUTT.

## Material and methods

### Groups of patients

One hundred twenty-six patients (78 female and 48 male, age 36 ±16 years) referred to our clinic for tilt table testing because of unexplained syncope were included. The study was approved by the local ethical committee and subjects gave informed consent to participate in it. Patients underwent the test HUTT according to the ESC standards [1]. On the basis of the HUTT results patients were subdivided into 2 groups. The group with a positive result of the test (HUTT(+)) consisted of 45 patients (18 female, 27 male, age 35 ±20) and the control group (HUTT(-)) consisted of 81 patients (60 female, 21 male, age 36 ±14) with no syncope during the tilt test. The detailed characteristics of the patients are presented in Table I. Among positive responders there were significantly more males, and fewer patients had a test with nitroglycerine (27% vs. 41%).

### Methodology of the tilt test

According to ESC standards [1] all tilt tests were performed before noon, in the fasting state, in a quiet, warm, properly ventilated and lightened room. An intravenous cannula was inserted into patients' peripheral veins. Patients were supine positioned on the tilt table for at least 30 min. After this time the patients were tilted at 60° for 45 min [1]. In case of a positive reaction during this time, the patient was returned to the supine position. In case of a negative outcome, if the systolic blood pressure exceeded 100 mm Hg and there were no other contraindications, we administered 0.25 mg of nitroglycerine sublingually and continued the test for the next 20 min. In case of contraindication for nitroglycerine, we continued the test without any drugs up to 60 min [16].

**Table I.** Clinical characteristics of patients with and without syncope during the tilt test

Parameter	Age	F/M	% F	Passive/NTG	% of passive
HUTT(-)	36 ±14	60/21	74	48/33	59
HUTT(+)	35 ±20	18/27	40	33/12	73
Value of <i>p</i>	NS	< 0.05		< 0.05	

*F* – female, *M* – male, *NTG* – nitroglycerine, *HUTT(+)* – positive tilt test, *HUTT(-)* – control group without syncope during the tilt test.

## Measurements

During the whole study an electrocardiogram was monitored continuously. The arterial blood pressure was measured manually using the Korotkoff method (every minute, in the case of symptoms every 15–20 s). The SV and CO were continuously monitored using the ambulatory ICG monitoring system ReoMonitor [17–19]. This system enables beat-to-beat noninvasive monitoring of SV and CO. The methodology of the central hemodynamic measurements by ReoMonitor and the characteristics of the device were precisely described in previous studies [17–19].

## Impedance cardiography technique

The ambulatory ICG recorder (ReoMonitor) is a wearable device constructed for noninvasive acquisition of central hemodynamic data during the patient's everyday activity. It is 200 × 111 × 50 mm in size and weighs 810 g (including batteries). The analog part comprises a one-channel ECG and the miniaturized impedance cardiograph. The system is controlled by a digital part based on the 80C552 family micro-controller, with 8 bit A/D converters working at 200 Hz sampling frequency.

The ambulatory ICG device was used during each examination for continuous collection of hemodynamic data (SV, CO), which were analyzed in both groups after the test. Changes in the thoracic impedance, reflecting the SV, were measured using the tetrapolar method. The alternating current of 100 kHz (and stable amplitude < 5 mA) oscillated between application electrodes and the voltage (reflecting the impedance) was measured on the receiving electrodes. Stroke volume was evaluated using the Kubicek formula [20]. The validation and reliability of ICG have been reviewed many times [21–24]. Ambulatory monitoring by means of SV was verified using echocardiographic technique in both supine and tilted position [17].

## Data presentation

We calculated the average values (over 1 min) of HR, SV, and CO for the following periods: the last minute before tilting, time immediately after the tilt, 1 min (Tables II and III) after and 5 min (Table IV) af-

ter the tilt. The change ( $\Delta$ ) and percent change ( $\Delta\%$ ) of these parameters immediately after, 1 min after, and 5 min after tilt were calculated with respect to values at the end of rest in a supine position.

## Statistical analysis

Data are expressed as mean  $\pm$  SD. The Student *t*-test for independent samples was used to compare the groups of patients with and without a positive tilt test response assuming the level of  $p < 0.05$  as significant. For nonlinear parameters the  $\chi^2$  test was used.

## Results

Absolute values of HR, SV and CO at the last minute of resting did not reveal any differences between groups (Table I).

Immediately after tilting and 1 min after, there were still no significant differences in absolute values of HR, SV, and CO (Tables II and III). However in the HUTT(–) group there was a non-significant increase in SV and CO just after tilting, followed by a decrease of those parameters below resting values 1 min after tilting. In the 5<sup>th</sup> min the values of SV and CO were similar to those at 1 min after tilt (Table IV). However, in HUTT(+) the time course of SV and CO showed a tendency to decline during this period. Thus, the greatest differences between HUTT(–) and HUTT(+) were achieved in the 5<sup>th</sup> min after tilting in both SV and CO. Changes in CO were caused mainly due to changes in SV, because the HR response was similar in both groups. However, the differences between groups in SV and CO values attained in the 5<sup>th</sup> min were not significant. When absolute and percent changes were considered, the decline of SV and CO in HUTT(+) was significantly more pronounced than in the HUTT(–) group ( $\Delta$ SV: 27.2  $\pm$  21.2 ml vs. 9.7  $\pm$  27.2 ml,  $p = 0.03$ ;  $\Delta$ CO: 1.78  $\pm$  1.62 l/min vs. 0.34  $\pm$  2.48 l/min;  $p = 0.032$ ;  $\Delta\%$ SV: 9  $\pm$  51 vs. 34  $\pm$  32;  $p = 0.064$  (NS),  $\Delta\%$ CO: 30  $\pm$  28 vs. 0.2  $\pm$  58;  $p = 0.034$ ) during the 5<sup>th</sup> min after tilting (Table IV).

## Discussion

We found that there were no differences between the HUTT(+) and HUTT(–) groups in HR, SV,

**Table II.** Absolute values of hemodynamic parameters before, just after and 1 min after tilting

Parameter	Rest		Just after tilting		1 min after tilting	
	SV [ml]	CO [l/min]	SV [ml]	CO [l/min]	SV [ml]	CO [l/min]
HUTT(–)	63 $\pm$ 21	4.94 $\pm$ 2.08	69 $\pm$ 39	5.49 $\pm$ 4.01	52 $\pm$ 33	4.35 $\pm$ 2.73
HUTT(+)	69 $\pm$ 25	5.14 $\pm$ 2.19	62 $\pm$ 22	4.71 $\pm$ 1.98	49 $\pm$ 22	3.86 $\pm$ 1.74
Value of <i>p</i>	0.5	0.78	0.5	0.41	0.7	0.5

SV – stroke volume, CO – cardiac output, HUTT(+) – positive tilt test, HUTT(–) – control group without syncope during the tilt test.

**Table III.** Changes of hemodynamic parameters just after and 1 min after tilting compared to the values before tilting

Parameter	Just after tilting				1 min after tilting			
	$\Delta$ SV [ml]	$\Delta$ CO [l/min]	$\Delta$ %SV [%]	%CO [%]	$\Delta$ SV [ml]	$\Delta$ CO [l/min]	$\Delta$ %SV [%]	%CO [%]
HUTT(-)	-3.0 $\pm$ 38.9	-0.35 $\pm$ 4.2	-8.3 $\pm$ 58.1	-0.11 $\pm$ 0.69	12.7 $\pm$ 33.7	0.75 $\pm$ 3.29	0.14 $\pm$ 0.53	0.06 $\pm$ 0.59
HUTT(+)	7.3 $\pm$ 10.9	0.44 $\pm$ 1.4	9.5 $\pm$ 14.5	6.6 $\pm$ 24.6	20.2 $\pm$ 15.8	1.28 $\pm$ 1.45	27.1 $\pm$ 24.1	21.2 $\pm$ 28.9
Value of <i>p</i>	0.208	0.389	0.142	0.232	0.34	0.483	0.302	0.265

$\Delta$ SV – decrease of stroke volume,  $\Delta$ CO – decrease of cardiac output, SVi – relative stroke volume decrease in percentage (see text), COi – relative cardiac output decrease in percentage (see text), HUTT(+) – positive tilt test, HUTT(-) – control group without syncope during the tilt test.

**Table IV.** Changes of heart rate and hemodynamic parameters 5 min after tilting in comparison to values before tilting

Parameter	SV [ml]	CO [l/min]	$\Delta$ HR [1/min]	$\Delta$ SV [ml]	$\Delta$ CO [l/min]	$\Delta$ %HR [%]	$\Delta$ %SV [%]	$\Delta$ %CO [%]
HUTT(-)	53.6 $\pm$ 29.9	4.6 $\pm$ 2.82	6.4 $\pm$ 14.3	9.7 $\pm$ 27.2	0.34 $\pm$ 2.48	10 $\pm$ 17	9 $\pm$ 51	0.2 $\pm$ 58
HUTT(+)	41.8 $\pm$ 18.6	3.36 $\pm$ 1.44	7.7 $\pm$ 13.4	27.2 $\pm$ 21.2	1.78 $\pm$ 1.62	12 $\pm$ 21	34 $\pm$ 32	30 $\pm$ 28
Value of <i>p</i>	0.13	0.07	NS	0.03	0.032	NS	0.064	0.034

$\Delta$ HR – increase of heart rate 5 min after tilting,  $\Delta$ SV – decrease of stroke volume,  $\Delta$ CO – decrease of cardiac output, HRI – relative heart rate increase (see text), SVi – relative stroke volume decrease (see text), COi – relative cardiac output decrease (see text), HUTT(+) – positive tilt test, HUTT(-) – control group without syncope during the tilt test.

and CO at rest. Tilting provoked a different pattern of early hemodynamic response in these groups. In the HUTT(-) group there was a non-significant increase in SV and CO immediately after tilting, followed by a constant decrease of those parameters. In HUTT(+) these parameters showed a tendency to decline in the whole early period of the response (5 min).

Bellard *et al.* [8] used transthoracic impedance technique but did not calculate SV and CO. Instead, they used timing parameters (describing two phases of the ejection period), the contractility index and an SV-related parameter (the maximum amplitude of the first derivative of the impedance signal). There were two differences between “fainters” and “non-fainters”: in supine rest (for the slow phase of ejection) and just before the syncope (or at the end of the test in non-fainters) for the amplitude parameter. They did not observe any significant differences in the early phase of the HUTT between two groups. They also observed a tendency, similar in both groups, of a decrease in the amplitude parameter (SV related) in the 5<sup>th</sup>–10<sup>th</sup> min of the test. In our study, SV in the same time also declined in both groups, but the rate of this change was more pronounced in HUTT(+). Some authors did not find significant differences between HUTT(+) and HUTT(-) groups. The variance of hemodynamic parameters within the group is very high. However, the application of changes instead of absolute values enhanced the contrast between the groups. From our earlier experience in SV monitoring during postural stress [11, 17] we would expect that ICG should also reveal the differences in hemodynamic

responses to tilt, between the positive and negative HUTT patients, similar to those demonstrated in studies using echocardiography [5–7].

Zaidi *et al.* [25], using noninvasive ICG in 20 patients, compared stroke volume and cardiac output at the 2<sup>nd</sup> and 5<sup>th</sup> min of a HUTT using different angles of tilting. They observed a significant decrease of these parameters. Because of short (5 min) tilts they were not able to differentiate the groups.

Shen *et al.* [12] found that the baseline hemodynamic variables would not help in pre-selection of patients with vasovagal syncope. However, before the symptom was developed during a tilt test, a significant decrease of total peripheral resistance (TPR) in patients was observed whereas BP remained relatively stable. They suggested that distinct hemodynamic profiles in response to various provocative maneuvers potentially can be defined by non-invasive, continuous monitoring. Novak *et al.* [4] found a small negative trend in blood pressure and total peripheral resistance for at least 250 s before the onset of syncope. However, stroke volume remained stable during this presyncopal period and increased at syncope. The profile of stroke volume changes using ICG mirrored those obtained using Doppler. Also, the echocardiographic measurements of cardiac chamber size were obtained in five subjects and did not change during tilt, presyncope or syncope. Their data show that there is no significant decrease in cardiac volume before syncope that could serve as a trigger of syncope

Liu *et al.* [5] analyzed different echocardiographic data during a 60-degree, 30-minute head-

up tilt test. Measurements were performed at the 3<sup>rd</sup> and 5<sup>th</sup> min. The patients with a positive response had a higher mean heart rate baseline and during the initial period of tilting. At 5 min after tilting, the HUTT(+) group had significantly lower left ventricular end-diastolic volume index, stroke volume and stress-corrected fractional shortening. There were no differences in fractional shortening, midwall shortening or ejection fraction. However, patients with syncope had a significantly greater fall in meridional and circumferential end-systolic stress and stress-corrected midwall shortening (myocardial contractility) and a greater reduction in end-diastolic volume index and cardiac index. During the initial upright tilt the percentage of thickening of the inferior wall (area of greatest density of C-fibers) was less in positive responders. However, procedural difficulties are the reason to search for easier methods of hemodynamic measurement during a tilt test. The same suggestion was made by Kozłowski *et al.* [26], who using echocardiography observed a reduction of both end-diastolic and end-systolic diameter, with no change of ejection fraction before syncope. They also observed greater left ventricular posterior wall slope values before and during tilting in patients with syncope. They emphasized that the use of echocardiography reduced sensitivity of the tilt test. In their study, syncope was induced in 7 of 39 patients (18%).

Yamanouchi *et al.* [6] tested the hypothesis that patients who have vasovagal syncope during head-up tilt have a greater decrease in their left ventricular volume in response to tilt than do normal subjects. They found that the rate of reduction of the end-diastolic volume index during tilt was faster in the vasovagal group than in normal subjects. A more significant reduction of stroke index and ejection fraction during tilt was found in the vasovagal group than in normal subjects, possibly because of more peripheral translocation of blood volume in the venous system during tilt and an early vagal effect on ventricular contraction.

Leonelli *et al.* [7] analyzed the differences in mechanisms of head-up tilt-induced syncope between normal controls and patients with neurocardiogenic syncope. They continuously monitored heart rate and blood pressure. Also, epinephrine and norepinephrine plasma levels, left ventricular dimensions and contractility determined by echocardiography were measured at baseline and at regular intervals during the test. They reported that mechanisms of syncope during HUTT appeared to be different in normal volunteers and patients with neurocardiogenic syncope. In the latter, there was evidence of an impaired vascular resistance response from the beginning of the orthostatic challenge. Furthermore, in the patients

there was more rapid peripheral blood pooling, as indicated by the echocardiographic measurements of left ventricular end-diastolic changes, leading to more precocious symptoms. They suggested that in syncopal patients, the higher level of plasma epinephrine probably mediated the increased cardiac contractility and possibly contributed to the impaired vasoconstrictive response.

Hosaka *et al.* [27] using radionuclide monitoring compared hemodynamic parameters between the 2<sup>nd</sup> min of tilt with the last minute before syncope. They observed that during the tilt there was no change in left ventricular diastolic volume in contrast to increasing progressively ejection fraction along with the decrease in left ventricular end-systolic volume. They observed different reactions between cardiodepressive patients, vasodepressive patients and non-responders. The decrease of end-diastolic volume was significantly greater in vasodepressive patients compared to the others. The difference between ejection fraction at the end of the procedure and the 2<sup>nd</sup> min after tilting was significantly higher in the cardiodepressive group. There were two important limitations of the proposed method: application of expensive, sophisticated equipment and a lack of possibility to compare parameters before and after tilting because of movement of the detector during a change of position.

Wang *et al.* [28], using the thermodilution method in 32 patients (12 with no syncope, 12 with cardioinhibitory vasovagal reaction, 8 with vasodepressive vasovagal reaction), observed during vasovagal reaction a significant decrease of the cardiac index and vascular resistance (sympathetic vasoconstriction tone). However, this method seems not to be clinically useful because it is invasive.

There have been some studies in which ICG and other noninvasive methods were used to measure the hemodynamic parameters immediately after and 5 min after tilting [5, 29], more rarely also 10 min after tilting [8] or at the moment of syncope [5, 26, 27] or immediately after [28]. In our study we measured these parameters in the last minute of resting, immediately after, 1 min after and 5 min after tilting, with the aim of enabling early differentiation between the two groups, i.e. with a positive and a negative result of the head-up tilt test.

Comparison of results is difficult also because different protocols of tilt tests (all accepted by ESC standards). The type of drug used for provocation has a great influence on the results [1, 30]. Bellard *et al.* [8] used the passive Westminster protocol, some authors used accessory provocation with isoproterenol [5, 27], while others used different protocols. In our study we used the most popular provocation with nitroglycerine, or, if contraindi-

cated, a prolonged passive test. However, sensitivity and specificity of this test depend on duration of the passive phase before nitroglycerine [10], so we used the most sensitive protocol with a 45-minute passive phase.

There are diverse opinions on the possibilities of HUTT outcome prediction. A group of skeptics support the opinion that it is a difficult or even impossible task. For example, Krahn *et al.* [31] studied this possibility in patients with unexplained syncope undergoing prolonged monitoring. They concluded that the etiology of recurrent syncope is diverse and cannot be predicted by baseline clinical variables. Also, Turk *et al.* [32] suggested that the early increase in HR during the first 10 min of the HUTT may not be a useful parameter for predicting the test result. They pointed out that many factors (e.g. late exaggeration in sympathetic activity during HUTT and age-dependent reduction in baroreflex sensitivity) may attenuate the predictive value of early HR increase. Schroeder *et al.* [33] tested the hypothesis that detailed anthropometric and hemodynamic measurements predict orthostatic tolerance in neurally mediated syncope patients. They concluded that in those patients in the clinical laboratory, having a wide range of anthropometric and cardiovascular measurements, it is difficult to predict the orthostatic tolerance. Moreover, they also found that orthostatic tolerance correlates poorly with syncope occurrence in real life.

On the other hand, the results of some studies show that it is possible to predict the outcome of HUTT with varying anticipation time. A very interesting study was performed by Schang *et al.* [34], who introduced several indices allowing for prediction using only the supine position recordings. The methods were evaluated retrospectively in a group of 70 patients and prospectively in a group of 59 patients. They concluded that among classical threshold algorithms, principal component analysis and neural networks, the latter gave the best results. Thus during supine rest, age, sex, and proposed indices, extracted from the impedance waveform and the first derivative of the impedance waveform, introduced in a neural network, could reliably predict a positive outcome to a 70-degree HUTT with 88% sensitivity and 64% specificity in a prospective group of 59 patients. These results contribute to a new approach in the early detection of a positive outcome and thus could help to reduce the duration of a 70° HUTT. They also suggest that despite significantly better sensitivity and specificity than the literature, those values could certainly be improved by contribution of additional variables (arterial blood pressure, etc.). Also Mereu *et al.* [35] found that using the derivative of the ratio between RR in-

terval and systolic blood pressure (dRR/SBP) they were able to predict syncope  $44.1 \pm 6.6$  s in advance with a sensitivity of 86.2% and a specificity of 89.1% when the area under the ROC curve was 0.877 ( $p < 0.001$ ). Thanks to this method the authors were able to predict syncope in all three forms of neuromediated syncope: cardioinhibitory, mixed and vasodepressor. Similar results were found using the derivative of the ratio between RR and pulse pressure (dRR/PP). Meyer *et al.* [36] used analysis of simultaneously recorded heart rate (HR) and pulse wave during 70° head-up tilt table testing to develop a syncope warning system. Syncope prediction was improved by combining detecting the slope of HR changes with monitoring pulse arrival time. The prediction alarm occurred  $99 \pm 108$  s before syncope.

### Implications and limitations of the study

The importance of extended monitoring by ICG during the tilt test was pointed out by Nowak *et al.* [15]. They suggested that the analysis of hemodynamic parameters may “help to develop individualized therapeutic concepts”.

Anticipation of negative result of the tilt test at the 5<sup>th</sup> min may reduce time-consuming examination in patients without a vasovagal reaction. Before clinical application of these results we have to check them in a progressive study. We also should check when during a tilt test the first significant change in hemodynamic parameters occurs.

Impedance cardiography is a safe, simple and inexpensive method for measurement of hemodynamic parameters during the head-up tilt test [8, 17]. However, the precision and accuracy of this method are still discussed. Some authors have accepted ICG as a reliable method for determining both the absolute values of these parameters and their changes [21, 22, 37]. However, some other authors [23, 32] reserved this method to measure only the changes in SV and CO. In our study the changes in hemodynamic parameters better differentiated both groups than absolute values. Therefore, this finding allows one to avoid the use of controversial absolute values of ICG, questioned by several investigators [23, 38].

Based on the recent literature, reviewed in a previous paper [39], it seems to us that the ICG method is entering clinical fields in which it was previously absent [40, 41], including Holter-type applications [42]. It is also increasing its role in orthostatic syncope diagnosis and may be useful for explanation of the orthostatic syncope mechanism. Tahvanainen *et al.* [43], thanks to the application of ICG, observed a major decrease in systemic vascular resistance in subjects with presyncope during a 0.25 mg nitroglycerin-stimulated tilt table test, in the absence of changes in cardiac

output. These findings showed that even a small dose of nitroglycerin significantly decreased arterial resistance and cardiac afterload.

Also, DeMarzo noted that hypertensive patients have diverse cardiovascular abnormalities that can be quantified by ICG [44]. He tried to show how ICG waveform analysis with postural change can be used to detect subclinical cardiovascular disease in patients with high blood pressure. He suggested that by stratifying patients with ventricular, vascular, and hemodynamic abnormalities, treatment could be customized based on the abnormal underlying mechanisms with the potential to rapidly control blood pressure, prevent progression of cardiovascular disease, and possibly reverse remodeling.

In another paper, DeMarzo also noted that the ICG test could be used as part of a prevention program for early detection of cardiovascular disease [45]. He suggested that “an abnormal ICG test could expedite the initiation of customized treatment that targets the subclinical cardiovascular disease”.

The papers of Shen *et al.* [12], Bellard *et al.* [8] and our study show that ICG may be useful in revealing the differences between the HUTT(+) and HUTT(-) groups of patients, in early stages of the tilt test. However, the results are not consistent, and application of the ICG method requires further investigations.

In conclusion, in the 5<sup>th</sup> min of the tilt test we observed a significant decrease of hemodynamic parameters in those patients who developed vasovagal syncope later during the test.

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