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Greater Early Epinephrine Rise with Head-up Posture: A Marker of Increased Syncope Susceptibility in Vasovagal Fainters

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Abstract

BACKGROUND: Head-up tilt (HUT) is widely used for diagnostic evaluation of patients with suspected vasovagal syncope (VVS), but also offers an opportunity to study VVS pathophysiology. In this regard, it is known that plasma epinephrine (Epi) levels and Epi / norepinephrine (NE) ratio (Epi/NE) are markedly increased from baseline at the time of HUT-induced VVS. However, whether these changes contribute to VVS susceptibility remains uncertain.

OBJECTIVE—We hypothesized that if catecholamines contributed to VVS directly, then a greater increase of plasma Epi and Epi/NE ratio early during HUT would be associated with shorter time to syncope.

METHODS: The patient population comprised 33 individuals (14 men, 43±2 years) with suspected VVS in whom 70° HUT reproduced symptoms. Arterial Epi and NE concentrations were collected at baseline (supine) and 2 minutes (min) of HUT. Linear, exponential, and multiple regression were used to assess the association between changing catecholamine levels and time to syncope.

RESULTS: Mean (±SD) time to positive HUT was 11(7.6) min. Higher plasma Epi levels (pg/ml) both at baseline and at 2 min upright correlated with shorter time to syncope (baseline, $R=-0.35$, $P=0.048$; and 2 min, $R=-0.58$, $P=0.001$). Similarly, a greater Epi/NE ratio at 2 min head-up correlated with earlier time to syncope ($R=-0.49$, $P=0.007$). These relationships remained significant after adjusting for age and sex ($P=0.006$ and $P=0.02$ respectively).

CONCLUSION: Greater Epi levels and Epi/NE ratio early during HUT were associated with shorter time to VVS, suggesting a possible contribution to VVS susceptibility.

Keywords

syncope; vasovagal syncope; catecholamines; head-up tilt test; epinephrine

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Introduction:

Head-up tilt table testing (HUT) is widely used for evaluating patients with suspected reflex vasovagal syncope (VVS) in whom the medical history alone is non-diagnostic (1,2). However, HUT is also a useful tool for improving understanding of VVS pathophysiology (1,2).

In regard to pathophysiology, HUT-induced VVS episodes are associated with marked alterations of neuroendocrine activity (3–8). Prominent among the neuro-humoral changes has been that at the time of HUT-induced VVS, circulating plasma epinephrine (Epi) and, to a lesser extent, circulating norepinephrine (NE) levels are substantially higher than baseline values (5–9). However, whether these increases in Epi and NE levels participate directly in triggering VVS, or are simply secondary to the evolving hemodynamic stress, is as yet unknown. To address this issue, we hypothesized that if Epi and NE changes contribute directly to VVS, then a greater increase of catecholamine levels triggered by head-up posture would be associated with a shorter time to syncope among tilt-test ‘positive’ patients.

The objective of this study was to determine whether there is a measurable impact of Epi and/or NE changes early during HUT on subsequent VVS occurrence using a shorter ‘time to syncope’ as a marker of increased VVS susceptibility. Clinically, if catecholamine changes seem to enhance VVS onset, then further assessment of beta-blockade for VVS prevention may be warranted.

Methods:

Patient Population

Data used in this study were obtained prospectively during assessment of circulating catecholamine changes during evolving VVS episodes in patients suspected of having recurrent VVS and in whom HUT was deemed appropriate as part of their overall evaluation. In each case, patients presented with a history of recurrent apparent syncope (>2 in past 6 months) and pre-syncope symptoms suspected to be of vasovagal origin during initial clinical evaluation, but in whom the cause remained uncertain after a detailed medical history and physical examination, 12-lead electrocardiogram, and echocardiogram,

Inclusion criteria included; 1) a positive drug-free HUT in which syncope was deemed to have reproduced spontaneous symptoms, 2) absence of excessive obesity (Body Mass Index <30), hematologic or biochemical abnormalities, or use of drugs known to predispose to orthostatic hypotension, 3) absence of left ventricular systolic dysfunction (estimated ejection fraction >50% by echocardiogram or radionuclide evaluation), 4) withdrawal of all cardio-active medications for at least 5 half lives prior to HUT. Exclusion criteria comprised patients not meeting the above criteria, as well as those with a history of paroxysmal tachycardia or autonomic dysfunction associated with neurologic disorders including Parkinsonism, autonomic failure, peripheral neuropathy or postural tachycardia syndrome (POTs).

The study was undertaken with Institutional Committee approval and written informed consent was obtained from all individuals prior to study using an approved consent form.

Upright Tilt-Table Testing Protocol

The clinical laboratory methods used in this study have been described previously (7). At the time these data were collected, arterial pressure was recorded using a 5-French femoral artery catheter with side-arm (placed approximately 60 minutes prior to initiating the tilt-test procedure) and a fluid-filled system calibrated to right atrial level. Prior to study approximately 500cc of normal saline was administered at 120cc/hour to account for the estimated 4 hour fast requested of each patient before initiating the procedure. The infusion was started shortly after the patient arrived in the hospital.

The patient was gently secured (using Velcro straps) to the tilt-table, assuring appropriate positioning to permit use of a foot-board for weight bearing. Beat-to beat blood pressure and heart rate were recorded throughout using CardioLab® (GE Healthcare).

A minimum 10-minute equilibration time, with the patients resting in the supine position in a darkened quiet procedure, was allowed prior to commencement of baseline recordings for the tilt-table testing procedure. During the equilibration period each individual received approximately 500 ml of normal saline (approximately 100 ml for each 'fasting hour' prior to the study in order to approximate a euvoletic state), and was maintained with a normal saline intravenous infusion of 50 ml/hour.

The protocol comprised a 70° head-up tilt for up to approximately 25 minutes duration in the absence of provocative drugs. Upright posture was maintained until either development of syncope or intolerable near-syncope symptoms, or completion of maximum tilt duration. If syncope occurred the table was promptly returned to the supine position. Only patients who developed frank syncope or intolerable near-syncope that were deemed to have reproduced their spontaneous symptoms were included in this study.

Catecholamine Sampling and Measurements

Blood samples were obtained from the side port of the arterial catheter with the patient resting in the supine position (baseline), and at approximately 2 minutes of upright tilt. No patient developed symptoms prior to the 2-minute blood draw. Measurement of epinephrine (Epi) and norepinephrine (NE) plasma concentrations was undertaken by High Pressure Liquid Chromatography (HPLC) technique. Since blood sampling required slow withdrawal and fluid reinfusion to minimize hemodynamic impact, the timing of samples is approximate (i.e., within 30 sec of stated time). In all cases, care was taken to re-infuse excess blood and to replace fluid by equivalent volume of normal saline.

Statistical Analysis

In each individual, heart rate and mean arterial blood pressure were recorded continuously throughout the study. Those values (average of 3 consecutive cycles) most closely corresponding to the relevant catecholamine measurements were used in this report. Unless otherwise indicated, all data are expressed as mean $\pm$ standard deviation (SD) and Inter-

quartile range (Q1, Q3). Patient's data were compared by paired T-test and Mann-Whitney U test. In addition, we used both linear and exponential regression models to evaluate the relationship between time to syncope and the change in Epi and NE during the first 2 minutes of HUT in all patients, as well as in males and females separately. Multiple regression models adjusted for age and gender alone, and age, gender and baseline values were also assessed. A p value of <0.05 was considered statistically significant.

Results:

Study Population, Heart Rate, and Catecholamine Levels

The study population comprised 33 syncope patients (mean age 43 ± 20.8 years, 14 men) as described above. For the population as a whole, HUT for mean 11 ± 7.6 [Q1, Q3: 5, 16] minutes resulted in syncope or intolerable near-syncope symptoms in all patients. Men tended to develop syncope earlier during HUT than did women ($P=0.04$) (Table 1). Women had shorter baseline cardiac cycle lengths (i.e., higher heart rates) ($p=0.04$, Table 1)

Changes in cardiac cycle length from baseline to 2 min of HUT were evaluated to determine if heart rate change was associated with greater VVS susceptibility as assessed by earlier time to syncope (Table 2). The latter did not prove to be the case. Neither men nor women exhibited any apparent relationship between cardiac cycle length shortening during early upright posture (i.e., increased heart rate [HR]), and time to VVS onset.

Plasma Epi levels (pg/ml) increased significantly from baseline to 2 minutes of head up posture (baseline: 74 ± 49.1 [Q1, Q3: 40.5, 105.5] and 2 minutes: 259 ± 278.5 [Q1, Q3: 74, 406.5], ($P=0.0005$). Similarly, plasma NE levels increased significantly (baseline: 254 ± 126.3 [Q1, Q3: 165.5, 307] to 2 minutes: 375 ± 117.4 [Q1, Q3: 283, 444.5], $P<0.0001$). However, Epi increases were proportionately greater than NE changes in the first 2 minutes of HUT as evidenced by the finding that Epi/NE ratio increased significantly with HUT (baseline: 0.32 ± 0.21 to 2 minutes: 0.73 ± 0.90 at 2 minutes) ($P=0.0151$). There were no apparent gender based differences of neuro-humoral changes.

Catecholamine Changes and Time to HUT-induced Syncope

In the population as a whole, linear regression revealed a significant correlation between higher baseline and 2-minute plasma Epi level and shorter time to syncope (baseline: R-Squared=0.12, $P=0.048$, and 2 minutes: R-Squared=0.33, $P=0.001$) (Table 2, Figure 1). Similarly, there was a significant correlation between greater Epi/NE ratio at 2 minutes and shorter time to syncope ($R=-0.49$, $P=0.007$) (Figure 2). Finally, a greater increase of Epi levels and Epi/NE ratio from baseline to 2 minutes of HUT (i.e., difference 2 min Epi minus baseline Epi) was associated with a shorter time to syncope (Figure 3, Table 2). On the other hand, with respect to NE alone, apart from a solitary baseline observation in men, neither 2-minute HUT levels nor change from baseline values correlated with time to syncope in HUT in either men or women (Table 2).

Inspection of the early HUT Epi changes data summarized in Figure 3 reveals considerable scatter especially at low values of plasma Epi. Given that observation, we evaluated whether

an exponential model would provide a better data fit. The latter seemed to be the case with logarithmic regression resulting in an $R = -0.61$ and $p = 0.0006$ (Figure 4).

Effect of Sex and Age

Heart rates (HR) at baseline and 2 minutes of head up posture were higher in women than men (Table 1). However, neither plasma Epi nor NE at baseline and 2 min respectively differed significantly by sex (Table 1).

In females, greater plasma Epi levels and Epi/NE ratios at 2 min strongly correlated with shorter time to syncope (Epi: $R = -0.65$, $P = 0.005$ and Epi/NE ratio: $R = -0.60$, $P = 0.011$). Epi change showed a similar trend in males, albeit not statistically significant (Epi: $R = -0.55$, $P = 0.064$).

Multiple regression models examined catecholamine changes in relation to time to syncope controlling for gender and age (Model 1), and both gender and age but also correcting for baseline values (Model 2). In both models, a greater increase at 2 minutes of HUT from baseline for both plasma Epi (Model 1: $P = 0.006$ and Model 2: $P = 0.02$) and Epi/NE ratio (Model 1: $P = 0.02$ and Model 2: $P = 0.03$) were associated with a shorter time to syncope (Table 3).

Discussion:

Main Findings

This study provides three main observations with regard to associations between changes in circulating Epi and NE soon after movement to upright posture and the subsequent development of HUT-induced reflex vasovagal syncope (VVS) in susceptible individuals. First, the greater the increase of Epi and Epi/NE ratio induced by head-up posture early during HUT (i.e., 2 minutes), the shorter the time to tilt-induced VVS. Further, the relation between catecholamine change from baseline to 2 min of HUT and time to syncope fit well with an exponential regression model. Second, multiple regression analysis correcting for sex, age and baseline values provided further support for the finding that greater early HUT-induced Epi and Epi/NE ratio changes were associated with shorter time to syncope in both men and women. Finally, data scatter illustrated in the graphs suggests that apart from catecholamine changes, other factors (some possibly neuro-humoral in nature) likely contribute to VVS susceptibility. Alternatively, the prominent data scatter at low Epi levels may suggest that there is an Epi concentration threshold that must be achieved prior to an effect on VVS susceptibility becoming evident. In any case, taken together, these findings may be interpreted to suggest that greater early Epi increments triggered by movement to an upright posture contribute to earlier onset of HUT-triggered VVS, a measure that we employ as a surrogate marker of increased VVS susceptibility.

Catecholamine Levels and Heart Rate Changes during HUT

HUT is useful to enhance understanding of VVS pathophysiology. In this regard, previous reports have documented markedly higher Epi levels and lesser increase of NE levels at the time of syncope in tilt-table test positive patients compared to control subjects (3,5–7).

Additionally, several studies indicate that Epi levels begin to rise before measurable blood pressure changes are detected (3,7–11). However, whether alterations of circulating catecholamines play a direct role in triggering VVS or altering VVS susceptibility, or on the other hand are primarily responsive to the evolving hemodynamic stress remains uncertain.

In a seminal report examining the pathophysiology of VVS using HUT methodology, Jardine et al. (3) assessed hemodynamic and neuro-humoral changes during 60° HUT in patients who developed VVS and in non-fainting controls. In particular, they noted that within the initial 5 minutes of upright posture, while patients remained hemodynamically stable without blood pressure change (i.e., phase-1 [8], approximately 16 minutes before mean time to syncope), arterial epinephrine (Epi) and norepinephrine (NE) levels tended to be higher in fainters than in control subjects. More recently, Nilsson et al (12) reported Epi measurements at 3 minutes of head-up posture in patients with VVS induced by HUT alone or by the combination of HUT and nitroglycerin. They observed that those patients in whom HUT alone was sufficient to trigger VVS, the 3-minute epinephrine levels were higher than in those cases in whom nitroglycerin was needed. These observations by Nilsson et al (12) are consistent with our view that a greater rise of epinephrine with head-up posture may be a marker of greater VVS susceptibility.

With respect to HUT-induced HR observations, it has been suggested that higher HRs with upright posture may be a marker of greater VVS susceptibility. In this regard, Sra et al (5) noted that HR increment early in HUT tended to be higher in fainters compared to controls. However, the HR differences were modest. Similarly, Jardine et al (3) reported that HR increased to a greater extent in patients who went on to faint than in controls. On the other hand, Chaddha et al (13) found that HRs were lower during HUT in patients who went on to have a positive test than in tilt-negative subjects. In any case, while the HR differences in the above reports remain to be resolved, the studies did not attempt to ascertain whether ‘within group’ HR differences resulted in demonstrable differences in VVS susceptibility. In our study, HR increment was not related to the time to syncope, and consequently did not offer a predictor of increased susceptibility to HUT induced VVS (Table 3). Since HR changes reflect not only sympathetic neuro-endocrine changes but also parasympathetic influences, HR change alone may not be expected to be a robust marker of VVS susceptibility.

As a group, the catecholamine and HR observations summarized above suggest that the triggering of sympathetic neuro-humoral activation and/or parasympathetic withdrawal during HUT in VVS susceptible patients occurs in the initial hemodynamically stable period (phase-1 [8]) of the evolving VVS event. This stable period occurs well before measurable hemodynamic changes would be expected to trigger arterial baroreceptor activity. Consequently, it is possible that low pressure atrial mechanoreceptors, triggered by gravitationally initiated volume displacement and diminished right atrial (RA) filling early during head-up posture may be contributing, but such a role is unproven. In fact, Jardine et al (3) argued against such a mechanism by pointing out that left atrial dimensions were comparably diminished by upright posture in both fainters and controls. However, with acute postural change the impact on RA volume would be more critical than those affecting the left atrium; unfortunately, RA volumes are difficult to assess by conventional techniques (14).

Effect of Gender

The relationships among gender, posture-induced neuroendocrine changes, heart rate response to orthostatic stress and development of HUT-induced VVS has been the subject of several studies (15–17). However, the relationship of these features to ‘time to syncope’ (a presumed surrogate of VVS susceptibility) has not previously been assessed. Thus, in the report by Pietrucha et al (15) there was no evident relationship between gender and positive HUT. Specifically, in a review of findings in 537 patients referred for HUT, women predominated (women: 313 vs men: 224) but the proportion of positive studies was comparable in both women and men (women 77.3 vs men 70.5).

As summarized by Convertino (16), there is substantial evidence that healthy women exhibit lower tolerance to orthostatic stress than do men, although the differences may not be solely associated with catecholamine differences. Other factors, such as lesser muscle mass, may contribute by diminishing muscle pump effectiveness. On the other hand, lesser muscle mass may reduce postural caudal blood volume displacement. In any case, with respect to catecholamine effects, neuroendocrine findings in men and women during HUT have been examined (17). In brief, baseline circulating Epi and NE values, as well as measures during HUT for as long as 10 min were not significantly different between men (age 23–50 years) and women of a similar age group. Nevertheless, Convertino (16) and others (18) reported that healthy women were less tolerant of Lower Body Negative Pressure (LNBP) stress than were healthy men. Additionally, while women developed pre-syncope at an earlier stage of LNBP stress with lower cardiac outputs and stroke volumes than observed in men, HRs were similar in both groups (16). Consequently, it has been hypothesized that healthy women exhibit a lesser baroreceptor response to hypotension, although as calculated by Convertino (16) the baroreflex difference between genders was small. In any case, while gender-based HR differences did not predict earlier VVS in our study, our findings tend to suggest that there are observable, albeit small, gender-related sympathetic neuroendocrine differences in VVS susceptible patients subjected to HUT. Specifically, both genders trended in the same direction with regard to Epi increase and shorter time to syncope. However, it appeared that a greater change in Epi levels from supine to 2 minutes upright was more closely associated with shorter time to syncope in women ($P=0.006$) than in men ($P=0.059$). The same was true of Epi/NE ratio findings (Table 2). Further, when adjusted for age, gender and baseline values, both Epi and Epi/NE ratio were strongly correlated with shorter time to syncope suggesting that these neuro-humoral changes may in fact contribute directly to greater VVS susceptibility (Table 3).

Clinical Implications

In terms of treatment to prevent future episodes, the vast majority of patients who seek medical attention after experiencing VVS need only with reassurance, and education regarding typical warning symptoms. Frequent recurrences requiring more aggressive treatment interventions are a problem in only a small subset of the patient population. On the other hand, for those latter cases in whom pharmacologic intervention is warranted for prevention of VVS recurrences, clinicians have long been interested in the possibility that beta-adrenergic blockers might be useful (1,2,19). The latter possibility is supported by several clinical observations including: 1) the concept that the VVS reflex might be triggered

by mechanoreceptors subjected to the vigorous contraction of an ‘empty’ ventricle, 2) studies, some of which were alluded to earlier, showing increased circulating epinephrine during the evolution of VVS episodes (3,5,7–12), and 3) the triggering of VVS events by the beta-adrenergic agonist isoproterenol. The finding in this study that circulating epinephrine levels may contribute directly to greater VVS susceptibility further suggests that beta-adrenergic blockade should be a useful element in the overall treatment strategy. To date, however, the value of adrenergic blockade for VVS prevention has not been impressive. The POST (Prevention of Syncope Trial) study offers the most important insights in this regard (19). In POST, metoprolol was evaluated for VVS prevention, but in the population as a whole it did not demonstrate a statistically significant benefit. However, there did appear to be a potential benefit of metoprolol in the ‘older’ portion of the study population (i.e., >42 years of age), although the study was not adequately powered to make a definitive statement in this regard. Nonetheless, the possibility that beta-adrenergic blockade may be more useful in older fainters is consistent with previous observations indicating that circulating epinephrine levels tend to be greater in younger than older VVS sufferers (20). Potentially, due to lower circulating levels during an evolving VVS event, it may be easier to block epinephrine in older patients, whereas beta-adrenergic blockade dosing may need to be much greater to achieve benefit in younger patients than was tested in POST. The currently ongoing POST5 study is re-examining the utility of beta-adrenergic blockade in older individuals and should help clinicians better understand whether beta-blockade can offer a useful treatment adjunct to VVS prevention in certain patient populations (21). For the present, however, we cannot exclude the possibility that catecholamine changes during VVS may be epiphenomena. In such a circumstance, beta-adrenergic blockade would not be expected to provide an effective prevention strategy. On the other hand, it would be difficult to explain the observations in this report that greater Epi increase early during upright posture was accompanied by a shorter time to syncope.

Limitations:

Several important limitations impact the interpretation of the observations in this study. First, the number of patients included in this study was small, and inter-patient variability undermines definitive interpretation of the physiological significance of observed changes. Second, it is recognized that the catecholamine levels relied on in this study are predominantly derived from adrenal and/or synaptic ‘overflow’. Unfortunately, direct measures of adrenal medullary and/or sympathetic neural output are not readily applicable to studies such as are reported here. Even micro-neurographic techniques are limited to single nerves. Third, we utilized ‘time to syncope’ during HUT as a surrogate measure of VVS susceptibility. However, there is as yet no firm evidence that this is a reasonable association. Fourth, we did not utilize data from non-fainting controls. Measurements in control subjects have been provided in previous reports (3,5–7,19), and the primary goal of this report was to isolate a potentially useful measure of VVS susceptibility (i.e., time to HUT-induced syncope). Fifth, blood sample withdrawal may impact neuroendocrine status in patients. To minimize this potential confounder, we took blood samples from an arterial line outside of the patient’s view. Also, care was taken to re-infuse comparable amounts of fluid in an

attempt to minimize any hemodynamic affects. Finally, data scatter suggests that other factors, not assessed in our report, likely also contribute to VVS susceptibility.

Conclusion:

Our findings suggest that a greater increase of Epi and Epi/NE ratio at an early time during an evolving HUT-induced VVS is accompanied by a shorter time to syncope. The latter association is suggestive that these neurohumoral changes triggered by upright posture, contribute to VVS susceptibility.

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Abbreviations

Epi	epinephrine
HUT	head-up tilt
NE	norepinephrine
VVS	vasovagal syncope

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Figure 1 -

Linear correlation model of relation between plasma epinephrine level at 2 minutes HUT (abscissa) and time to syncope (ordinate). Dashed lines indicate 95% confidence limits. y ; regression line, R ; correlation coefficient, R -squared; decision coefficient, P ; P value.

Figure 2 -

Exponential correlation model of relation between epinephrine at 2 minutes of HUT (abscissa) and time to syncope (ordinate). R-squared; decision coefficient, P; P value.

Figure 3 -

Exponential correlation model examining the relation between the change of plasma epinephrine level from Baseline to 2 minutes HUT (abscissa) and time to syncope (ordinate). Data in men are shown in blue and women in orange. Logarithmic regression of this relation is provided in Figure 4.

Figure 4 -

Regression examining the relation between the time to syncope (ordinate) and that of the natural logarithm of the change of plasma epinephrine from baseline to 2 min of HUT. The correlation is statistically significant ($P=0.0006$). See Table 2 for the decision coefficients and P values for male and female separately. y; regression line, R; correlation coefficient, R-squared; decision coefficient, P; P value.

Table 1.

Baseline patient characteristics

Variables	All patients N=33	Male N=14	Female N=19	P value difference in sex
Age (years)	43 ± 20.8	39.3±17.9	45.5±22.8	0.41
Time to syncope (minutes)	11 ± 7.6	7.8±4.8	12.7±7.8	0.04
Mean arterial pressure (mmHg)	93.4±14.7	90.4±14.0	95.9±15.2	0.31
Measures at baseline				
Cycle Length (ms)	845.4±185.0	920.9±182.4	789.9±170.7	0.04
Plasma epinephrine level (pg/ml)	74.2±49.1	77.7±52.0	71.6±48.1	0.73
Plasma norepinephrine level (pg/ml)	254.4±126.3	274.4±140.4	239.6±116.6	0.44
The epinephrine / norepinephrine ratio	0.32±0.21	0.31±0.20	0.32±0.22	0.91

(Red indicates statistically significant differences)

Table 2.

Linear regression analysis

Explanatory variables	Objective variable	All patients		Male		Female	
		R	P value	R	P value	R	P value
Time to syncope	Measures at baseline						
	Cycle Length (ms)	−0.04	0.84	0.18	0.54	0.07	0.78
	Plasma Epi level (pg/ml)	−0.35	0.048	−0.47	0.092	−0.31	0.20
	Plasma NE level (pg/ml)	−0.25	0.16	−0.60	0.023	−0.03	0.90
	Epi/NE ratio	−0.21	0.25	0.11	0.70	−0.37	0.12
	Measures 2 minutes after baseline						
	Cycle Length (ms)	−0.31	0.098	−0.23	0.44	−0.30	0.26
	Plasma Epi level (pg/ml)	−0.58	0.001	−0.55	0.064	−0.65	0.005
	Plasma NE level (pg/ml)	−0.18	0.35	−0.42	0.15	0.06	0.82
	Epi/NE ratio	−0.49	0.007	−0.42	0.18	−0.60	0.011
	Change in measures (2 minutes ne ratio: e						
	Cycle Length (ms)	−0.30	0.11	−0.25	0.42	−0.45	0.082
	Plasma Epi level (pg/ml)	−0.57	0.001	−0.56	0.059	−0.64	0.006
	Plasma NE level (pg/ml)	0.08	0.66	0.18	0.55	0.07	0.79
	Epi/NE ratio	−0.48	0.008	−0.58	0.049	−0.57	0.017

(Red indicates statistically significant differences)

Table 3.

Multiple regression analysis

Measures (per 1 baseline SD increase)		Difference in time (minutes) to syncope	standard error	p-value
Change in measures (2 minutes - baseline)				
Cycle Length (per 185 ms higher)	Model 1	-0.71	0.57	0.22
	Model 2	-0.37	0.68	0.59
Plasma Epi level (per 49 pg/ml increase)	Model 1	-0.61	0.20	0.006
	Model 2	-0.59	0.23	0.02
Plasma NE level (per 126 pg/ml increase)	Model 1	-0.89	1.44	0.54
	Model 2	-3.54	1.56	0.03
Epi/NE ratio (per 0.2 pg/ml increase)	Model 1	-0.65	0.27	0.02
	Model 2	-0.66	0.28	0.03

(Red indicates statistically significant differences)

Model 1: Regression model adjusted for age and sex,

Model 2: Model 1 + adjustment for baseline measure.

A negative time is a faster time to syncope.