Europace (2004) **6**, 48–54

ELSEVIER

EUROPEAN SOCIETY OF CARDIOLOGY

Transient modification of baroreceptor response during tilt-induced vasovagal syncope

Nemer Samniah, Scott Sakaguchi, Cengiz Ermis, Keith G. Lurie, David G. Benditt*

Cardiac Arrhythmia Center, Cardiovascular Division, Department of Medicine, University of Minnesota, 420 Delaware Street SE, MMC 508, Minneapolis, MN 55455, USA

Submitted 25 February 2003, and accepted after revision 13 September 2003

KEYWORDS
vasovagal syncope;
head-up tilt table testing;
baroreceptor sensitivity

Abstract **Aims** Normally, arterial baroreceptors attempt to minimize systemic hypotension by initiating reflex vasoconstriction and tachycardia. However, in the setting of vasovagal syncope (VVS), these usual compensatory mechanisms either fail to be triggered or the response is inadequate. We hypothesized that in VVS prone individuals, arterial baroreceptor response (BRR) is normal under most conditions, but that a transient functional BRR disturbance occurs during an evolving vasovagal faint and may in part account for failure of the usual compensatory response.
Methods and results This study assessed BRR in the baseline state and again in association with either VVS induced head-up tilt (HUT) or after a prolonged period of upright posture without VVS. To minimize impact on HUT outcome, BRR was estimated non-pharmacologically by measuring blood pressure and heart rate changes, induced when subjects were returned to the supine position after undergoing diagnostic 70° HUT evaluation. Beat to beat heart rate and arterial blood pressure changes were recorded in 13 patients with syncope and another 16 individuals with negative HUT (control group). Baseline BRR was initially evaluated at the end of a 3 min symptom free HUT (HUT#1), and the measurement was repeated after a 45 min duration HUT in the control group or in conjunction with syncope in VVS prone individuals (HUT#2). Baseline BRR did not differ significantly in controls and VVS prone individuals (controls: 3.37 ± 1.56, VVS prone: 6.0 ± 2.02 ms/mmHg, $p = 0.27$). Further, at the end of 45 min HUT#2, BRR was unaltered from baseline in control subjects (4.92 ± 1.36 ms/mmHg, $p = 0.48$), but was markedly reduced from baseline value in individuals who experienced a faint, -3.30 ± 0.81 ms/mmHg ($p < 0.0003$ vs baseline).
Conclusion Compared with individuals who do not manifest VVS during HUT, VVS prone individuals appear to demonstrate functional diminution of baroreceptor responsiveness. This altered response may undermine the normal expected

* Corresponding author. Tel.: +1-612-625-4401; fax: +1-612-624-4937.
E-mail address: bendi001@tc.umn.edu (D.G. Benditt).

1099-5129/$30 © 2003 The European Society of Cardiology. Published by Elsevier Ltd. All rights reserved.
doi:10.1016/j.eupc.2003.09.004

Downloaded from https://academic.oup.com/europace/article/6/1/48/471842 by Akdeniz Universitesi user on 20 September 2021

compensatory response to evolving systemic hypotension. The basis for this transient disturbance in baroreceptor responsiveness is currently unknown.
© 2003 The European Society of Cardiology. Published by Elsevier Ltd. All rights reserved.

Introduction

Vasovagal syncope occurs as a consequence of the triggering of a neural reflex resulting in a self-limited but inappropriate period of both peripheral vasodilation (vasodepressor response) and marked or relative bradycardia (cardioinhibitory response). The result is a transient period of systemic hypotension leading to cerebral hypoperfusion with loss of consciousness and postural tone [1,2].

The pathophysiology of the vasovagal reflex is only incompletely understood. Nevertheless, the reflex appears to be composed of an afferent limb originating from any of a number of possible central nervous system or peripheral 'trigger' sites [3—5], an efferent limb with both parasympathetic and sympathetic neural components [6,7], and a baroreceptor 'feedback' limb. The last one is the focus of interest in this study.

Under most conditions, a normally functioning baroreceptor system would be expected to compensate for decreasing systemic pressure by increasing the heart rate and initiating increased vasoconstriction. In vasovagal syncope, however, the baroreceptor feedback mechanism either fails entirely to counteract evolving hypotension, or is only partially effective, resulting in blood pressure and heart rate oscillations [6,8,9].

The objective of this study was to acquire further understanding of the role played by baroreceptor feedback in vasovagal fainters. To this end, we attempted to quantify changes in baroreceptor responsiveness associated with head-up tilt table induced vasovagal syncope (VVS).

Methods

Baroreceptor function was evaluated by measuring global baroreceptor responsiveness (BRR) using a non-invasive method analogous to that described by Takahashi et al. [10]. By using rapid return to supine posture as a means of assessing BRR, we were able to quantify BRR status as it was 'set' at the moment just before the postural change, and presumably before it had an opportunity to adjust to the subject's new position. This method was chosen in order to permit baroreceptor assessment without using drug interventions (especially phenylephrine) that would be expected to alter head-up tilt test outcome. Specifically, BRR was calculated from linear regression analysis relating changes in beat to beat systolic blood pressure (SBP) values with changes in cardiac cycle length (RR intervals) recorded immediately after return to supine position from 70° head-up tilt.

In normal volunteers who were tilted for 20 min, Takahashi et al. [10] found a linear correlation between the slope of the regression line and the baroreceptor sensitivity (BRS) estimate obtained by a traditional phenylephrine testing method. The principal difference between the baroreceptor response (BRR) measurement technique used in this study and that reported by Takahashi et al. [10] was the duration of the exposure to upright posture prior to returning the table to horizontal position. The duration of 20-min tilt study employed by Takahashi et al. would have subjected a significant number of our vasovagal syncope susceptible patients to syncope or near syncope. In that circumstance, it would not have been possible to obtain a 'baseline value' for BRR in many of our subjects. Consequently, we chose to use a shorter head-up tilt (3 min) for estimating baseline BRR (see later). These methodological differences may account for differences in baseline BRR values in this study compared with those reported by Takahashi et al. [10].

Patients included in the study reported here comprised consecutive individuals with clinically suspected vasovagal syncope having a positive head-up tilt table test, and patients with symptoms of dizziness, lightheadedness or symptoms of chronic fatigue but who had no history of syncope and had a negative head-up tilt study. None of the subjects included in this study had any evidence of structural heart or cardiovascular disease by medical history, physical examination, 12-lead ECG, or echocardiographic assessment when deemed necessary. Similarly, none of these subjects was diabetic, or exhibited signs of a primary dysautonomia. The subject subgroup with a negative tilt study is designated as 'tilt-negative subjects'. Conversely, individuals with a positive HUT were designated as 'tilt-positive'. Among the latter patients, patient selection was not affected by the type of HUT response (i.e., cardioinhibitory, vasodepressor, or mixed), but individuals with positive HUT at <3 min were of necessity excluded as it

Downloaded from https://academic.oup.com/europace/article/6/1/48/471842 by Akdeniz Universitesi user on 20 September 2021

was not possible to determine a baseline BRR value in such cases (see later).

In the present study, BRR was evaluated in each individual both after 3 min duration head-up tilt (baseline value, HUT#1), and full duration tilt (i.e., either 45 min or until syncope occurred, HUT#2). The 3 min duration in HUT#1 was chosen in order to obtain an orthostatic challenge comparable to that induced during conventional longer duration diagnostic head-up tilting, but without induction of syncope. Among tilt-positive subjects, none exhibited prolonged atrial asystole, but several exhibited sinus pauses of >5 s which reversed upon return to head-down posture. Thus, the tilt-positive population incorporated individuals with substantial cardioinhibition.

All studies were conducted with subjects in the fasting non-sedated state. Written informed consent was obtained. On the study day, all patients were either in a drug free state or had stopped all drugs for a period of at least five drug half-lives. Approximately 30 min prior to the first head-up tilt test, the right femoral artery was cannulated using a 4 French side arm sheath for continuous blood pressure monitoring. Heart rate was continuously recorded by a computer-based electrophysiology laboratory system. All data were recorded and stored on optical disks.

After obtaining arterial access, a 30—40 min equilibration period was allowed during which intravenous normal saline was infused at 75 ml for each fasting hour. Thereafter, subjects underwent head-up tilt at 70° for 3 min. The table was then returned to the horizontal position. Only one patient developed symptoms during this phase of the study and data from this patient were excluded from analysis. Following completion of the 3-min tilt, a second equilibration period of 40 min was initiated. Subjects then underwent a second 70° head-up tilt for a total duration of 45 min or until syncope occurred.

Data collection and processing

Haemodynamic parameters were recorded by reviewing data stored on optical disks. On a beat-by-beat basis, systolic blood pressure (SBP) and the subsequent RR interval were measured encompassing a time window beginning immediately upon the subject having been returned to the horizontal position ('down tilt') and ending when the blood pressure achieved a steady state (Fig. 1). In each case, these same measurements were obtained for both HUT#1 and HUT#2.

BRR was measured by calculating the slope of the linear regression line between change in

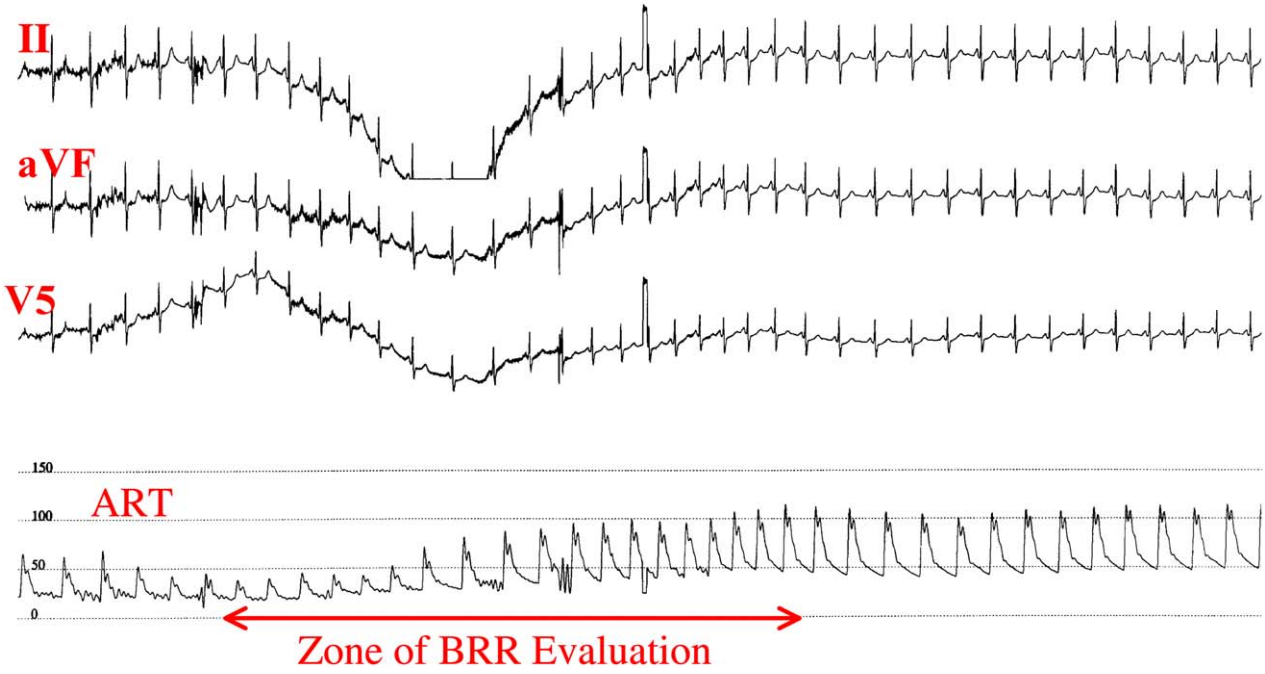


Figure 1 Simultaneous electrocardiographic and blood pressure recordings obtained from a HUT positive patient during induced VVS. Three surface ECG leads are shown (lead II, lead aVF, and lead V_5), and a femoral artery blood pressure tracing (ART) is provided. Note: the time window during which baroreceptor sensitivity (BRS) values were obtained is labelled as ''zone of BRR evaluation''. This time window occurs immediately following the return of the table to supine position.

Downloaded from https://academic.oup.com/europace/article/6/1/48/471842 by Akdeniz Universitesi user on 20 September 2021

systolic blood pressure values and change in the subsequent RR intervals following 'down tilt'. Slopes with correlation coefficient greater than 0.8 were included in the analysis [11,12]. BRR values (obtained for both HUT#1 and HUT#2) were compared within individuals for both tilt-negative subjects (HUT negative) and patients who had syncope during head-up tilt table testing (HUT positive).

Data are presented as mean ± standard error (SEM). Variables were compared using the Student's *t*-test for paired data and ANOVA. A *p* value of <0.05 was considered statistically significant.

Results

Patient population

The study included 29 individuals in whom head-up tilt testing was undertaken as part of the evaluation for recurrent syncope or presyncopal spells, dizziness, lightheadedness or fatigue. One patient was excluded from the study due to development of syncope during HUT#1 (the 3-min tilt test). Among the remaining 28 patients, 12 had positive head-up tilt results (HUT positive group, VVS prone individuals), while the other 16 subjects had negative results (HUT negative group). In the HUT positive group there were six males and six females. The HUT negative group was composed of 10 males and six females. Demographic data of the study population are presented in Table 1.

Head-up tilt study results

All individuals in the HUT negative group underwent head-up tilt for 45 min without major haemodynamic changes or symptoms during the test. In this group, mean BRR values after HUT#1 and HUT#2 were comparable (3.37 ± 1.56 and 4.92 ± 1.36 ms/mmHg, respectively, $p = 0.48$) (Table 2 and Fig. 2).

In the HUT positive group (VVS prone individuals), tilt test results reproduced clinical symptoms. All HUT positive patients demonstrated a mixed type response (i.e., both vasodepressor and cardioinhibitory features) during tilt-induced syncope. After HUT#1, mean baseline BRR in this group was 6.0 ± 2.02 ms/mmHg. This value did not differ statistically from that observed in the HUT negative group ($p = 0.27$). On the other hand, during

Table 1 Study population: demographic data

	Study group	
	HUT (−)	HUT (+)
Number of patients	16	12
Mean age (years ± SEM)	55 ± 3.85	47 ± 4.37
Gender (male/female)	10/6	6/6

Table 2 Individual BRR values (ms/mm Hg) in HUT negative and HUT positive subjects

HUT (−) subjects ($N = 16$)		HUT (+) patients ($N = 12$)	
BRR at 3 min	BRR at 45 min	BRR at 3 min	BRR at syncope
14.1	6.25	20.12	−5.86
8.21	8.13	3.53	−1.29
0.77	0.33	5.43	−3.11
−9.0	6.21	2.08	−1.39
10.9	5.5	14.9	−1.6
5.7	6.9	4.1	−5.8
5.4	10.48	−2.6	−8.25
3.9	13.52	2.15	−1.6
−0.8	0.96	2.68	−1.0
2.1	−5.0	15.7	−3.8
0.11	2.98	−0.1	−0.85
0.5	−2.8	4.06	−6.8
−1.08	15.37		
14.5	7.11		
−2.31	−2.85		
0.85	1.09		

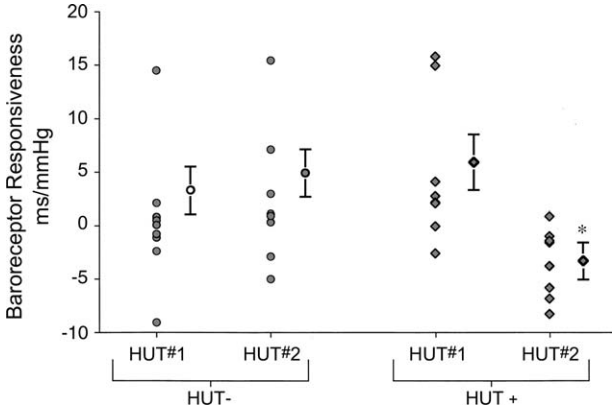


Figure 2 Values of baroreceptor responsiveness (BRR) obtained from tilt-negative individuals (HUT negative), and from HUT positive VVS prone patients (HUT positive) following 3-min tilt (HUT#1), and full duration tilt study or following syncope (HUT#2) are depicted. Mean ± standard error values are indicated. Note that mean BRR for both groups are comparable after 3-min tilt. After 45 min duration tilt table study, mean BRR values of the HUT negative group were similar to those following HUT#1, however, mean BRR values of the HUT positive VVS prone group were significantly different (*) after the induced syncopal episode.

Downloaded from https://academic.oup.com/europace/article/6/1/48/471842 by Akdeniz Universitesi user on 20 September 2021

Table 3 Mean BRR values (ms/mm Hg)

Patient group	Mean BRR at 3 min	Mean BRR at syncope or at 45 min	*p* value
HUT (−)	3.37 ± 1.56	4.92 ± 1.36	0.48
HUT (+)	6.0 ± 2.02	−3.30 ± 0.81	<0.0003
p value	0.27	<0.0003	

recovery from syncope induced during HUT#2, mean BRR was -3.3 ± 0.81 ms/mmHg in HUT positive patients. This latter BRR value differed significantly from mean BRR for both groups after HUT#1 ($p < 0.0003$) and from mean BRR for the HUT negative patients' group after HUT#2 ($p < 0.0003$) (Table 3 and Fig. 2).

Discussion

The principal finding in this study was the apparent diminution of global baroreceptor responsiveness accompanying an evolving vasovagal syncope. Further, it appeared that in the absence of VVS, both tilt-negative subjects and VVS prone individuals exhibited BRR values that did not differ significantly. Thus, VVS is associated with a transient functional change in BRR, and this change may in part account for failure of the baroreceptor system to initiate an adequate compensatory response in the setting of an evolving haemodynamic 'crisis'.

Given the apparently comparable baseline BRR values of tilt-negative subjects and VVS prone individuals, it is reasonable to surmise that the BRR change associated with syncope is a transient phenomenon occurring during specific haemodynamic circumstances, a conclusion similar to that reached by Freitas et al. [13]. Thus, when hypotension occurs as a result of a vasovagal reflex, and perhaps in other forms of neurally mediated syncope as well, there appears to be a functional disturbance of the baroreceptor feedback system. The factors responsible for this observation are currently unknown.

Normal baroreceptor function

In general terms, venous and arterial baroreceptors are the haemodynamic sensor portion of the autonomic nervous system. Their function is to monitor and initiate adjustment of heart rate, vascular tone, and neuro-endocrine status in order to maintain adequate organ blood flow during various physiological and pathological conditions. Thus, during orthostatic hypotensive stress in normal individuals, the autonomic nervous system responds by initiating parasympathetic 'withdrawal' and sympathetic activation. The result is increased heart rate, enhanced vasoconstriction, and increased renal salt and water retention [9,14]. On the other hand, volume loading of the central circulation (such as with returning an upright individual to the supine posture) table down is expected to lead not only to inhibition of sympathetic activity, but to parasympathetic activation also. The net expected outcome is slowing of heart rate and diminished vasoconstriction. In rare cases, movement from upright to supine has been reported to trigger marked neural reflex induced bradycardia, hypotension, and syncope [15]. However, following induced syncope in our VVS prone patients, the baroreceptor feedback system appeared to react in a manner distinctly different from that observed in either the tilt-negative subjects or the same individual subjected to short duration hypovolaemic stress unaccompanied by a faint (i.e., the 3 min head-up tilt). Specifically, we observed acceleration of the heart rate in conjunction with gradual increase of blood pressure during that phase of study. In essence, in temporal association with a vasovagal spell, the baroreceptor response setting appeared to be inappropriate. Instead of the heart rate slowing with 're-loading' of the central circulation and increase in systemic pressure (as the patient moved to the supine posture), the heart rate accelerated.

Factors affecting BRS during vasovagal syncope

Factors contributing to the difference between normal baroreceptor response to upright posture, and the response during tilt-induced VVS are unknown. However, the magnitude of the haemodynamic stress may play a role. In patients who are VVS prone, the extent of hypotension during induced faint is more severe than that observed in tilt-negative control subjects after 45 min of head upright tilt. The observed discrepancy in baroreceptor response between tilt-negative control subjects and VVS prone patients may reflect a response to two different haemodynamic conditions and may not necessarily imply that the response observed in vasovagal fainters is abnormal. It may well be that severe hypotension occurring during syncope dictates this type of response as an attempt to maintain reasonable perfusion. By abruptly returning the patient to the supine position, we were able to observe and quantify the status of the BRR

Downloaded from https://academic.oup.com/europace/article/6/1/48/471842 by Akdeniz Universitesi user on 20 September 2021

setting before it had an opportunity to be 're-set' back to normal.

Neurohormonal factors may play a role in determining BRR status under various haemodynamic conditions. In the setting of evolving VVS, several neurohormones including endorphins, vasopressin, renin—angiotensin, norepinephrine and epinephrine are released in large quantity. In this regard, several studies [16—18] observed a marked increase in adrenal epinephrine release during head-up tilt-induced faints in VVS prone patients, despite concomitant sympathetic neural withdrawal. Negative BRR values (i.e., heart rate acceleration despite increasing systemic arterial pressure) during tilt-down volume loading immediately post-VVS may reflect the effects of elevated serum epinephrine levels on sinus node function (i.e., a residual effect after rapid parasympathetic 'withdrawal' as the patient returns to supine state), or the result of modulation of baroreceptor response by epinephrine, or both. Alternatively, effects of endorphins or vasopressin on various components of the autonomic nervous system may affect the central nervous system response to baroreceptor afferent signals during vasovagal faint. Studies using rapid blockade of one or more of these aforementioned factors will be needed in order to elucidate this mechanism. Finally, the BRR directional response change may simply reflect the set-point at which the measurement was made (i.e., at a normal pressure in the baseline state vs a low pressure in the post-VVS state). Assessment of the latter possibility is feasible, but entails initiating a hypotensive state pharmacologically in VVS prone subjects.

Study limitations

This study evaluated BRR using a non-pharmacological method [10] in order to minimize the potential impact of drugs on HUT results. However, due to the requirement that baseline BRR be obtained without a faint, the method developed here was not identical to that proposed by Takahashi et al. [10]. This difference may account for the difference in absolute values of BRR measurements in the two reports. Furthermore, the values of baroreceptor responsiveness by the measurement method used here cannot be reasonably compared with those obtained by the more conventional pharmacological method. In choosing the 'head-down' technique, the resulting BRR estimate of necessity incorporates both venous and arterial baroreceptor responses. In this regard, the BRR values differ from conventional pharmacological measures of baroreceptor sensitivity (BRS), and thus the altered nomenclature. On the other hand, the technique is seemingly appropriate for evaluating a setting in which a spontaneous faint would be expected to initiate an abrupt postural change due to loss of postural tone. Thus, the method mimics what might be expected to occur in 'real life' as a VVS fainting patient falls to the ground. In essence, ours should be viewed as a means of assessing in a semi-quantitative fashion, transient directional change in baroreceptor responsiveness.

An additional potential limitation of the methodology used in this study is that it does not readily permit accounting for the effect of respiratory changes on baroreceptor response. We believe that this effect is small since the time window used for BRR determination was relatively short, and thereby minimized the opportunity for any effects of substantial change in respiratory depth and frequency.

Conclusion

In this study, VVS prone patients demonstrated a functional and presumably transient diminution of global baroreceptor response (BRR) in association with head-up tilt-induced syncope. Potentially, diminished BRR during evolving VVS may in part account for failure of the baroreceptor system to initiate an adequate compensatory haemodynamic response.

Acknowledgements

The authors would like to thank Wendy Markuson and Barry L.S. Detloff for their assistance with preparation of the manuscript. Dr. Samniah was supported in part by an educational grant from the Midwest Arrhythmia Research Foundation, Edina, MN.

References

[1] Benditt DG. Syncope. In: Evans RW, editor. Diagnostic testing in neurology. W.B. Saunders Co.; 1999. p. 391—404.
[2] Smith JJ, Ebert J. General response to orthostatic stress. In: Smith JJ, editor. Circulatory response to the upright posture. Boca Raton, FL: CRC Press; 1990. p. 1—46.
[3] Kosinski D, Grubb B, Temesy-Armos P. Pathophysiological aspects of neurocardiogenic syncope: current concepts and new perspectives. Pacing Clin Electrophysiol 1995;18: 716—24.

Downloaded from https://academic.oup.com/europace/article/6/1/48/471842 by Akdeniz Universitesi user on 20 September 2021

[4] Shepherd JT, Vanhoutte PM. The human cardiovascular system: facts and concepts. New York: Raven Press; 1979.
[5] Wallin BG. Assessment of sympathetic mechanisms from recordings of postganglionic efferent nerve traffic. In: Hainsworth R, Mark AL, editors. Cardiovascular reflex control in health and disease. London, England: W.B. Saunders; 1993. p. 65—83.
[6] Rea RF, Thames MD. Neural control mechanisms and vasovagal syncope. J Cardiovasc Electrophysiol 1993;4: 587—95.
[7] Abboud FM. Neurocardiogenic syncope [Editorial comments]. N Engl J Med 1993;382:1117—20.
[8] Lurie KG, Benditt DG. Syncope and the autonomic nervous system. J Cardiovasc Electrophysiol 1996;7:760—76.
[9] Cowley AW. Long-term control of arterial blood pressure. Physiol Rev 1992;72:231—300.
[10] Takahashi N, Nakagawa M, Saikawa T, Ooie T, Akimitsu T, Kaneda K, et al. Non invasive assessment of cardiac baroreflex; response to downward tilting and comparison with the phenylephrine method. J Am Coll Cardiol 1999;34:211—5.
[11] Smyth HS, Sleight P, Pickering GW. Reflex regulation of arterial pressure during sleep in man. Circ Res 1969;24: 109—21.
[12] Pitzalis MV, Mastropasqua F, Passantino A, Massari F, Ligurgo L, Forleo C, et al. Comparison between noninvasive indices of baroreceptor sensitivity and phenylephrine method in post-myocardial infarction patients. Circulation 1998;97:1362—7.
[13] Freitas J, Pereira S, Lago P, Costa O, Carvalho MJ, de Freitas F, et al. Impaired arterial baroreceptor sensitivity before tilt-induced syncope. Europace 1999;1:258—65.
[14] Jacob G, Ertl AC, Shannon JR, Furlan R, Robertson RM, Robertson D. Effects of standing on neurohormonal responses and plasma volume in healthy subjects. J Appl Physiol 1998;83:914—21.
[15] Iskos D, Shultz JJ, Benditt DG. Recurrent supine syncope: an unusual manifestation of the neurally mediated faint. J Cardiovasc Electrophysiol 1998;9:441—4.
[16] Klingenheben T, Kalusche D, Li Y-G, Schöpperl M, Hohnloser SH. Changes in plasma epinephrine concentration and in heart rate during head-up tilt testing in patients with neurocardiogenic syncope: correlation with successful therapy with β receptor antagonists. J Cardiovasc Electrophysiol 1996;7:802—8.
[17] Sra JS, Murthy V, Natale A, Jazayeri MR, Dhala A, Deshpande S, et al. Circulatory and catecholamine changes during head-up tilt testing in neurocardiogenic (vasovagal) syncope. Am J Cardiol 1994;73:33—7.
[18] Fitzpatrick A, Wiliams T, Ahmed R, Lightman S, Bloom SR, Sutton R. Echocardiographic and endocrine changes during vasovagal syncope induced by prolonged head-up tilt. Eur J Cardiac Pacing Electrophysiol 1992;2:121—8.

Downloaded from https://academic.oup.com/europace/article/6/1/48/471842 by Akdeniz Universitesi user on 20 September 2021