Pulse wave analysis during supine rest may identify subjects with recurrent vasovagal syncope

Jan SIMEK*, Dan WICHTERLE†, Vojtech MELENOVSKY§, Jan MALIK*, Jaroslava SVOBODOVA* and Stepan SVACINA*

*Third Department of Internal Medicine, General University Hospital, Prague, Czech Republic, †Second Department of Internal Medicine, General University Hospital, Prague, Czech Republic, and §Cardiology Division, Department of Medicine, Johns Hopkins Medical Institutions, Baltimore, MD, U.S.A.

A B S T R A C T

In the present study, we studied whether analysis of the FAP (finger arterial pressure) waveform during supine rest discriminates subjects with recurrent VVS (vasovagal syncope) from healthy controls. Signal-averaged FAP waveforms (Finapres) were obtained in 32 head-up tilt-test-positive subjects with recurrent VVS (35 ± 13 years) and in 32 sex- and age-matched healthy controls. The DT (time delay) between the systolic and diastolic peaks of the FAP waveform was measured and large artery SI (stiffness index) was calculated as a ratio of body height and DT. VVS patients had significantly shorter DT compared with controls (303 ± 31 compared with 329 ± 18 ms; $P < 0.001$) and higher SI (5.79 ± 0.70 compared with 5.20 ± 0.36 m/s; $P < 0.001$). The differences were independent of heart rate and blood pressure. SI > 5.45 m/s identified subjects with syncope with a sensitivity of 72% and a specificity of 84%. Age-corrected DT (cDT = DT + age − 350) identified subjects with syncope with a sensitivity of 75% and a specificity of 84%. Combined use of cDT < 0 ms and SI > 5.45 m/s increased sensitivity and specificity to 81% and 96% respectively. The discriminative power of FAP descriptors improved further when younger subjects were excluded. In subjects aged > 30 years (median age), the combination of cDT and SI identified subjects with syncope with a sensitivity of 93% and a specificity of 100%. These results suggest that FAP descriptors during supine rest might be useful in the diagnosis of VVS in middle-aged subjects.

INTRODUCTION

VVS (vasovagal syncope) represents the most frequent form of syncope in the outpatient setting [1,2]. The diagnosis is based on clinical history and reproduction of symptoms during tilt table testing; however, a battery of expensive and time-consuming examinations is often required to exclude other possible causes that include mainly structural heart disease and neurological disorders [1,2]. These examinations are frequently conducted during hospitalization and have an enormous social and economic impact [3,4]. Routinely applied tilt table testing is time-consuming and has a high incidence of false-negative results. Therefore an investigation of new methods, which would facilitate the diagnosis of VVS, has gained increasing importance [5–7].

Recent studies have suggested that there may be a link between syncope and increased arterial wave reflection. Patients with recurrent syncope had an increased augmentation index of central arterial BP (blood pressure)

and a shorter transit time of the reflected pressure wave assessed by the use of carotid tonometry [8]. This study, however, investigated subjects with various aetiologies of syncope, including postural hypotension and cerebrovascular dysautoregulation.

It is not known whether similar findings can be observed in subjects with pure VVS and if alternative methods may be used to estimate pulse wave reflections. Indeed, the peripheral pulse wave contour provided information on both the intensity and timing of the reflected pressure waves [9–11]. Since the measurement of the continuous non-invasive FAP (finger arterial pressure) is routinely used during tilt table testing [1], our present study aimed to investigate whether analysis of the FAP waveform during supine rest discriminates between subjects with recurrent VVS and matched healthy controls.

METHODS

Patients

We studied 32 consecutive patients with recurrent VVS and inducible vasovagal response during passive tilt table testing (Westminster protocol; tilting at an angle of 60° for $\leqslant 45$ min). On the basis of the modified VASIS (Vasovagal Syncope International Study) criteria [2], positive responses to tilt testing were classified as type 1 (mixed; $n = 8$), type 2A (cardio-inhibitory; $n = 2$), type 2B (severe cardio-inhibitory; $n = 4$) and type 3 (vasodepressor; $n = 18$). None of the patients exhibited orthostatic hypotension, chronotropic incompetence or excessive rise in heart rate. Patients were non-smoking normotensives (BP < 140/90 mmHg), with no evidence of cardiovascular disease. None of them was receiving any medication with cardiovascular effects. All patients had a history of at least two syncopal spells within the last 6 months.

Healthy subjects

Thirty-two sex- and age-matched asymptomatic non-smoking controls were recruited from the Outpatient Department of Preventative Medicine at our institution. An additional 15 healthy men were selected for the reproducibility substudy.

Examination protocol

The study was approved by the Local Ethics Committee. All participants gave their written informed consent, and all procedures were carried out according to the Declaration of Helsinki.

All subjects underwent a 5 min ECG recording (Delta 1 Plus; Cardioline, Vignate, Italy) and continuous non-invasive FAP measurement (Finapres; Ohmeda, Englewood, CO, U.S.A.) from the middle finger of the right hand. Recordings were obtained in the supine position after 20 min at rest. Examination was performed
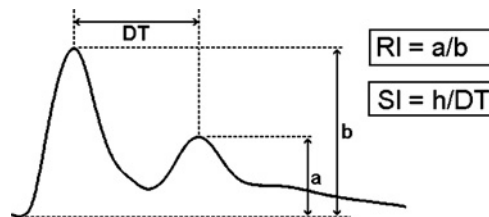

Figure 1   Representative signal-averaged FAP waveform and its descriptors

RI was calculated as a ratio of the DBP (a) and SBP (b) peak amplitudes. SI was calculated as a ratio of body height (h) and DT between the SBP and DBP peak.

between 10:00 and 12:00 hours in a quiet temperature-controlled laboratory (24–25 °C) with dimmed lighting.

SBP (systolic BP) and DBP (diastolic BP) were measured in the left arm using an automated oscillometric method (HEM-703C; Omron Healthcare, Hoofddorp, The Netherlands) at the end of the examination. MBP (mean BP) was calculated as $DBP + (SBP - DBP)/3$.

The reproducibility of FAP indices was studied in 15 healthy men aged 27.4 ± 3.7 years. Two measurements within 2 ± 4 days were performed under identical conditions.

Signal processing

ECG and FAP were sampled at 1000 Hz with 12-bit resolution and stored digitally for off-line analysis. The signal processing was performed by the custom-made software. QRS complexes were automatically detected using a combination of threshold and derivative methods. Signals were carefully inspected to confirm all detected QRS complexes, to remove all non-sinus beats and to exclude incidental noise. All non-distorted FAP waveforms were signal-averaged using R waves of QRS complexes as triggers.

Definition of FAP indices

Dicrotic BP was measured at the point of the diastolic BP peak. RI (reflection index) was determined as a ratio of amplitudes of the DBP and SBP peak [10,11] (Figure 1). A descriptor of the pulse wave reflection timing [SI (stiffness index)], which was recently defined and validated on a finger photoplethysmogram waveform [10,11], was calculated as a ratio of body height and the DT (time delay) between the SBP and DBP peak of the FAP waveform (Figure 1).

Statistical analysis

Patients and sex- and age-matched healthy controls were compared by unpaired two-tailed Student's t test. To test whether differences in FAP indices between studied groups are independent of simple clinical variables, ANCOVA (analysis of covariance) was performed. All clinical variables, which were found to be significantly different between both groups, were entered as covariates.

Table 1   Clinical characteristics of controls and VVS patients

Values are means $\pm$ S.D. *P* value was determined by an unpaired Student's *t* test.

	Controls	Patients	*P* value
Sex (male/female)	9/23	9/23	1.0
Age (years)	35.4 $\pm$ 13.1	35.4 $\pm$ 13.1	1.0
Body height (cm)	170.6 $\pm$ 8.7	172.2 $\pm$ 7.7	0.45
BMI (kg/m^2)	22.9 $\pm$ 3.2	22.5 $\pm$ 3.7	0.68
SBP (mmHg)	107.4 $\pm$ 10.0	113.3 $\pm$ 11.7	0.03
DBP (mmHg)	63.4 $\pm$ 9.1	70.5 $\pm$ 9.5	0.003
MBP (mmHg)	78.1 $\pm$ 8.8	84.8 $\pm$ 9.3	0.004
Heart period (ms)	975 $\pm$ 127	896 $\pm$ 191	0.056

Discrimination power of the FAP indices was described by sensitivity, specificity and PPV and NPV (positive and negative predictive value respectively). Optimum cut-off points for individual indices were determined using ROC (receiver-operating-characteristic) curves as the values that maximized sensitivity and specificity, i.e. minimized the expression of $([1 - \mathrm{sensitivity}]^2 + [1 - \mathrm{specificity}]^2)^{1/2}$. Dichotomized indices were studied individually and in mutual combinations.

The relationship between FAP descriptors and age was quantified in the pooled population of healthy controls and patients ($n = 64$) by the correlation coefficient (r) of univariate regression analysis. FAP descriptors, which were highly correlated with age, were age-adjusted using the appropriate regression equation.

Reproducibility was quantified by the coefficient of variation. A paired two-tailed Student's *t* test was performed to establish whether differences between two repeated measurements were significant.

Statistical analysis was performed using Statistica 5.1 for Windows (StatSoft, Tulsa, OK, U.S.A.). A value of $P < 0.05$ was considered statistically significant. Results are presented as means $\pm$ S.D.

RESULTS

Clinical characteristics of healthy subjects and patients are shown in Table 1. The majority of subjects were women; however, the distribution of age between genders was similar. Both groups were comparable in body height and BMI (body mass index). There was a trend towards higher heart rate in patients with VVS. Brachial artery SBP, DBP and MBP were significantly higher in subjects with recurrent VVS.

Differences in FAP descriptors between both groups are shown in Table 2. Subjects with VVS had a shorter DT interval and higher SI compared with healthy controls. These differences remained significant after controlling for MBP and heart period (ANCOVA). Both groups did not differ in dicrotic BP and RI. There were no significant differences in FAP descriptors between subgroups of

Table 2   Differences in FAP indices between VVS patients and matched healthy controls

Values are means $\pm$ S.D. *Adjusted for MBP and heart period.

| | | | *P* value | |
| | | | Unpaired Student's | |
	Controls	Patients	*t* test	ANCOVA*
DT (ms)	329 $\pm$ 18	301 $\pm$ 31	0.00005	0.006
SI (m/s)	5.20 $\pm$ 0.36	5.79 $\pm$ 0.70	0.00008	0.005
Dicrotic BP (mmHg)	97.8 $\pm$ 14.7	100.2 $\pm$ 11.3	0.46	0.29
RI (%)	42.3 $\pm$ 7.4	41.1 $\pm$ 9.4	0.59	0.40
cDT (ms)	14.2 $\pm$ 18.5	$-$ 13.9 $\pm$ 24.5	0.000003	0.0002

Table 3   Discrimination characteristics of FAP indices

	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
All ages				
SI > 5.45 m/s	72	84	82	75
cDT < 0 ms	75	84	83	77
SI > 5.45 m/s and cDT < 0 ms	81	96	95	82
Age > 30 years				
SI > 5.45 m/s	94	75	79	92
cDT < 0 ms	81	100	100	84
SI > 5.45 m/s and cDT < 0 ms	93	100	100	92

patients with mixed, cardio-inhibitory and vasodepressor response to tilt testing (results not shown).

Optimum cut-off values of SI and DT for the discrimination of patients with VVS from controls were > 5.45 m/s and < 315 ms respectively. DT was significantly correlated with age ($r = -0.46$; $P < 0.001$; DT $= -1.005 \times$ age $+ 350$). Therefore age-corrected DT (cDT $=$ DT $+$ age $- 350$) was used for further analysis. After this correction, discrimination characteristics of SI > 5.45 m/s and cDT < 0 ms (optimum cut off-value) were comparable (Table 3) with areas under the ROC curves of 0.75 and 0.82 respectively (Figure 2). The discrimination power of cDT and SI improved markedly when used in combination and/or when younger (age < 30 years) subjects were excluded (Table 3 and Figure 3). In this combined approach, a total of 14 subjects (22 %) and six subjects aged > 30 years (9 %) had indeterminate FAP waveforms, i.e. SI was normal and cDT was abnormal or vice versa.

Reproducibility of measurements

There were no significant differences between the first and the second measurement of the FAP indices. The coefficients of variation for DT, SI, dicrotic BP and RI were 2.42 %, 2.42 %, 5.27 % and 5.32 % respectively.
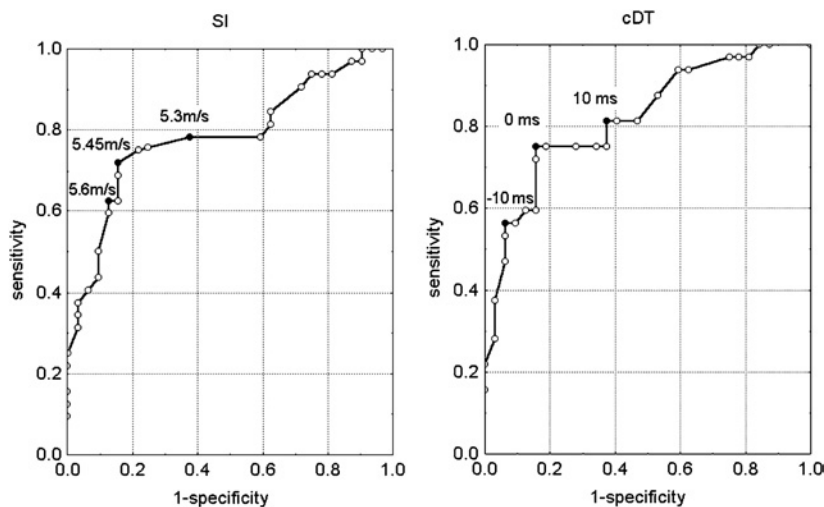
Figure 2   ROC curves for SI (left-hand panel) and cDT (right-hand panel) for the total population of subjects studied

Note that optimum cut-off values were 5.45 m/s and 0 ms for SI and cDT respectively.
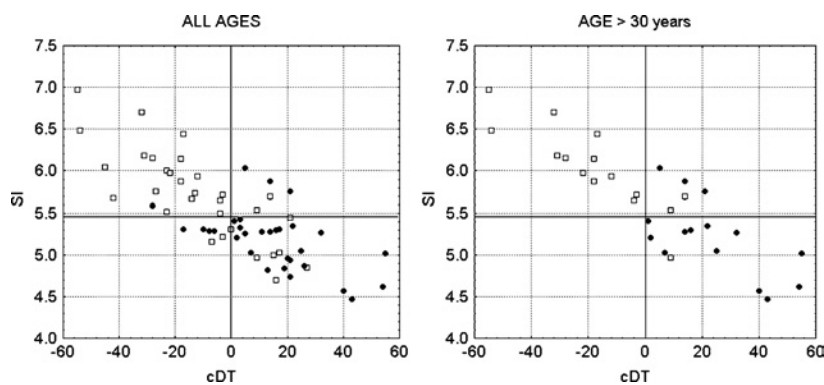

Figure 3   Scatter diagrams of SI and cDT categorized according to study groups for all subjects (left-hand panel) and subjects aged > 30 years (right-hand panel)

Combination of SI > 5.45 m/s and cDT < 0 ms discriminated best the subjects with VVS. VVS subjects (□) in the upper-left and lower-right quadrants represent truly positive and false-negative cases respectively. Controls (●) in the lower-right and upper-left quadrants are truly negative and false-positive cases. Subjects in the lower-left and upper-right quadrants represent those with inconclusive FAP indices.

DISCUSSION

The major finding of the present study was that the SI and cDT descriptors of the FAP waveform during supine rest are potent discriminators of patients with recurrent VVS from healthy controls.

The DT interval is related to the transit time of the pressure waves from the aortic valve to the sites of reflection, localized mainly in the lower body, and back to the aortic arch. As the pressure wave propagation distance is proportional to body height, SI is related to PWV (pulse wave velocity) in large arteries and closely correlates with carotid-to-femoral PWV [10,11]. Because PWV is inversely related to arterial distensibility by the Bramwell–Hill equation, higher SI and/or decreased DT in patients with VVS, which were observed in the

present study, might reflect decreased elasticity of large arteries. On the contrary, disorders leading to large artery stiffening, such as atherosclerosis and hypertension, are not associated with higher prevalence of VVS. Therefore increased arterial stiffness itself is unlikely to play a major role in the pathophysiology of VVS. Shorter DT interval could also result from an increased intensity of pulse wave reflection and altered structure of the arterial tree with the distribution of reflection sites closer to the heart.

Because major sites of the pressure wave reflection are situated in muscular arteries of lower extremities, the DT interval should be influenced by the distensibility and vasoconstriction of these arteries. In healthy subjects, DT seemed to be only marginally dependent on the vasomotor tone of small muscular arteries, as the vaso-dilation effect of nitroglycerine resulted only in modest

prolongation of the DT [10,11]. Patients with VVS, however, exhibited greater nitroglycerine-induced vasodilation [12] and an increased peripheral sympathetic nerve activity at rest compared with age-matched controls [13]. Therefore we cannot exclude the possibility that shorter DT in subjects with VVS in our present study reflects increased peripheral vasoconstriction. Further studies are needed to determine individual contributions of vasomotor tone, arterial stiffness and structure of the arterial tree to DT in subjects with VVS.

Studies of the peripheral arterial pressure contour showed that, during the tilt test, subjects with VVS exhibited an early and progressive decrease in dicrotic BP [14] and dicrotic notch [15]. However, these studies, as in our present study, failed to prove any differences at pre-tilt supine rest. RI was comparable in patients and controls in our present study. In contrast, we demonstrated that subjects with VVS differ from healthy controls in the timing of the arterial wave reflection. Thus it is likely that the time-domain approach to the pulse wave analysis is superior to the amplitude approach in the identification of subjects prone to VVS.

In our present study, VVS subjects had higher values of brachial BP. Although another large study [5] did not find any BP difference, supine hypertension was repeatedly documented in older patients with orthostatic hypotension [16,17] and in subjects with autonomic dysfunction [18]. It might be argued that our present observation of higher BP in VVS subjects resulted from an overlap between typical VVS and more complex disturbances of the autonomic nervous system [1]. However, patients in our present study did not suffer from orthostatic hypotension or chronotropic incompetence that characterize autonomic failure, but exhibited a typical VVS with a sudden fall in BP and/or heart rate during tilt table testing. Higher BP in subjects with VVS compared with controls raised the question of whether it accounts for the differences in FAP descriptors. ANCOVA revealed that the differences in FAP descriptors between the groups studied cannot be fully explained by the higher BP in subjects with VVS. Hence cDT and SI have to convey some independent discriminative information.

Improved discrimination characteristics of FAP indices obtained in older subjects support the observation of other investigators that a population of subjects with VVS is heterogeneous [19,20]. Analysis of haemodynamic responses during the early period of tilt testing showed that younger subjects are more likely to have inappropriately overactive cardiac and autonomic responses characterized by an excessive rise in heart rate or severe cardio-inhibition [19]. In contrast, older patients more frequently have postural hypotension and chronotropic incompetence, which resembles findings in patients with autonomic failure. It might be speculated that FAP descriptors perform better in VVS subjects with 'hyposensitive', rather than 'hypersensitive', autonomic regu-

lation. The present study, however, can hardly support this suggestion, because we did not find any relationship between DT and the type of response to tilt testing.

Shorter DT and higher SI in patients with VVS might result from increased muscle sympathetic activity, increased arterial stiffness and altered geometry of the arterial tree. The mechanistic link between these factors and development of VVS remains speculative. First, patients with increased resting muscle sympathetic activity might be unable to foster their sympathetic nerve outflow during orthostatic stress. Secondly, arterial and ventricular stiffening lead to an increased sensitivity of SBP to changes in circulation blood volume [21], which may contribute to orthostatic hypotension and predispose to syncope. This hypothesis is in agreement with the finding that increased fluid intake improves the tolerance of orthostatic stress in both patients with autonomic dysfunction [22,23] and healthy subjects [24,25].

There are several limitations of our present study. First, we did not analyse a 'true' control group because healthy subjects did not undergo the tilt test. Since the presumed proportion of false positive results with the passive tilt table testing according to Westminster protocol is approx. 13 % [26], it might be estimated that four subjects of the total 32 healthy controls in our present study would develop a syncope during tilt table testing. It might be speculated that these subjects are more likely to have abnormal values of SI and cDT. Therefore exclusion of these subjects would increase, rather than decrease, the specificity of FAP descriptors. It should also be emphasized that the optimum control group cannot be defined. For example, subjects with recurrent syncope and a negative tilt test would certainly not represent proper controls [27]. Nevertheless, the prediction of the result of the tilt test was not the purpose of our present study. It is likely, however, that FAP descriptors would perform worse if the control group had been composed of these subjects, who might potentially have a false-negative tilt test and, at the same time, truly abnormal values of the FAP descriptors.

Secondly, our results cannot be applied to subjects with comorbidities, such as atherosclerosis and hypertension, because these disorders are associated with increased stiffness of large arteries and/or increased vasoconstriction which influence FAP descriptors.

Thirdly, the measurement of aortic PWV was not a part of our present study protocol. Since DT, cDT and SI indices cannot be considered as direct measures of large artery PWV, we were not able to differentiate which of arterial stiffness and geometry/structure of the arterial tree lies behind their discriminative power.

Fourthly, the DT interval was originally proposed and validated on a digital photoplethysmogram waveform, whereas we measured DT on a FAP waveform. It may be argued that DT and SI derived from FAP might have a different meaning. Nevertheless, FAP is related to the

digital photoplethysmogram waveform by a simple linear relationship that remains constant across a wide age range and is not influenced by the effects of hypertension or nitroglycerine administration [28]. Therefore we believe that DT and SI obtained from both FAP and digital photoplethysmogram waveforms can be interpreted in a similar way.

In conclusion, our present study has demonstrated that subjects with a history of recurrent VVS and a positive tilt table test could be effectively differentiated from healthy controls by the use of simple descriptors of the FAP waveform measured during supine rest. The best discrimination was obtained by the combined use of these descriptors in subjects aged > 30 years of age. A larger prospective study is needed to investigate whether these observations might be useful in routine clinical practice for prediction of the result of the tilt test and preferentially for the prediction of future recurrences of VVS in middle-aged subjects without associated cardiovascular diseases.

ACKNOWLEDGMENTS

REFERENCES

1   Fenton, A. M., Hammill, S. C., Rea, R. F., Low, P. A. and Shen, W. K. (2000) Vasovagal syncope. Ann. Intern. Med. **133**, 714–725

2   Brignole, M., Alboni, P., Benditt, D. et al. (2001) Guidelines on management (diagnoses and treatment) of syncope. Eur. Heart J. **22**, 1256–1306

3   Nyman, J. A., Krahn, A. D., Bland, P. C., Griffiths, S. and Manda, V. (1999) The costs of recurrent syncope of unknown origin in elderly patients. Pacing Clin. Electrophysiol. **22**, 1386–1394

4   Calkins, H., Byrne, M., el-Atassi, R., Kalbfleisch, S., Langberg, J. J. and Morady, F. (1992) The economic burden of unrecognized vasodepressor syncope. Am. J. Med. **95**, 473–479

5   Pitzalis, M., Massari, F., Guida, P. et al. (2002) Shortened head-up tilting test guided by systolic pressure reductions in neurocardiogenic syncope. Circulation **105**, 146–148

6   Gulli, G., Cooper, V. L., Claydon, V. and Hainsworth, R. (2003) Cross-spectral analysis of cardiovascular parameters whilst supine may identify subjects with poor orthostatic tolerance. Clin. Sci. **105**, 119–126

7   Bellard, E., Fortrat, J. O., Schang, D., Dupuis, J. M., Victor, J. and Leftheriotis, G. (2003) Changes in the transthoracic impedance signal predict the outcome of a 70° head-up tilt test. Clin. Sci. **104**, 119–126

8   Chen, C. H., Hu, H. H., Lin, Y. P., Chern, C. M., Hsu, T. L. and Ding, P. Y. (2000) Increased arterial wave reflection may predispose syncopal attacks. Clin. Cardiol. **23**, 825–830

9   Chowienczyk, P. J., Kelly, R. P., MacCallum, H. et al. (1999) Photoplethysmographic assessment of pulse wave reflection: Blunted response to endothelium-dependent beta2-adrenergic vasodilation in type II diabetes mellitus. J. Am. Coll. Cardiol. **34**, 2007–2014

10 Millasseau, S. C., Kelly, R. P., Ritter, J. M. and Chowienczyk, P. J. (2002) Determination of age-related increases in large artery stiffness by digital pulse contour analysis. Clin. Sci. **103**, 371–377

11 Millasseau, S. C., Kelly, R. P., Ritter, J. M. and Chowienczyk, P. J. (2003) The vascular impact of aging and vasoactive drugs: comparison of two digital volume pulse measurements. Am. J. Hypertens. **16**, 467–472

12 Takase, B., Akima, T., Uehata, A. et al. (2000) Endothelial function and peripheral vasomotion in the brachial artery in neurally mediated syncope. Clin. Cardiol. **23**, 820–824

13 Bechir, M., Binggeli, C., Corti, R. et al. (2003) Dysfunctional baroreflex regulation of sympathetic nerve activity in patients with vasovagal syncope. Circulation **107**, 1620–1625

14 Franchi, F., Lazzeri, C., Romano, S. M. et al. (2003) Baroreflex function in vasodepressive syncope: detection of early impairment, Med. Sci. Monit. **9**, 125–130

15 Moak, J. P., Bailey, J. J. and Makhlouf, F. T. (2002) Simultaneous heart rate and blood pressure variability analysis: insight into mechanisms underlying neurally mediated cardiac syncope in children. J. Am. Coll. Cardiol. **40**, 1466–1474

16 Masaki, K. H., Schatz, I. J., Burchfiel, C. M. et al. (1998) Orthostatic hypotension predicts mortality in elderly men: the Honolulu Heart program. Circulation **98**, 2290–2295

17 Tonkin, A. L. and Wing, L. M. (1994) Effects of age and isolated systolic hypertension on cardiovascular reflexes. Hypertension **12**, 1083–1088

18 Goldstein, D. S., Pechnik, S., Holmes, C., Eldadah, B. and Sharabi, Y. (2003) Association between supine hypertension and orthostatic hypotension in autonomic failure. Hypertension **42**, 136–142

19 Kurbaan, A. S., Bowker, T. J., Wijesekera, N. et al. (2003) Age and hemodynamic responses to tilt testing in those with syncope of unknown origin. J. Am. Coll. Cardiol. **41**, 1004–1007

20 Shen, W. K., Low, P. A., Rea, R. F., Lohse, C. M., Hodge, D. O. and Hammill, S. C. (2000) Distinct hemodynamic profiles in patients with vasovagal syncope: A heterogeneous population. J. Am. Coll. Cardiol. **35**, 1470–1477

21 Chen, C. H., Nakayama, M., Nevo, E., Fetics, B. J., Maughan, W. L. and Kass, D. A. (1998) Coupled systolic-ventricular and vascular stiffening with age implications for pressure regulation and cardiac reserve in the elderly. J. Am. Coll. Cardiol. **32**, 1221–1227

22 Weinberger, M. H. and Fineberg, N. S. (1991) Sodium and volume sensitivity of blood pressure. Age and pressure change over time. Hypertension **16**, 67–71

23 Shannon, J. R., Diedrich, A., Biaggioni, I. et al. (2002) Water drinking as a treatment for orthostatic syndromes. Am. J. Med. **12**, 355–360

24 Lu, C. C., Diedrich, A., Tung, C. S. et al. (2003) Water ingestion as prophylaxis against syncope. Circulation **108**, 2660–2665

25 Schroeder, C., Bush, V. E., Norcliffe, L. J. et al. (2002) Water drinking acutely improves orthostatic tolerance in healthy subjects. Circulation **106**, 2806–2811

26 Petersen, M. E., Williams, T. R., Gordon, C., Chamberlain-Webber, R. and Sutton, R. (2000) The normal response to prolonged passive head up tilt testing. Heart **84**, 509–514

27 Fortrat, J. O. and Victor, J. (2004) Limitations of studies on vasovagal syncope. Am. J. Cardiol. **94**, 149–150

28 Millasseau, S. C., Guigui, F. G., Kelly, R. P. et al. (2000) Noninvasive assessment of the digital volume pulse comparison with the peripheral pressure pulse. Hypertension **36**, 952–956