ORIGINAL RESEARCH

Arterial baroreflex function in older adults with neurocardiogenic syncope

Kenneth M. Madden MSc, MD, FRCP
Chris Lockhart BSc

VITALITY (Vancouver Initiative to Add Life To Years) Group, Department of Medicine, University of British Columbia, Vancouver, British Columbia, Canada

Manuscript submitted 14th January, 2009
Manuscript accepted 25th March, 2009

Clin Invest Med 2009; 32 (3): E191-E198.

Abstract

Purpose: Neurocardiogenic syncope (formerly vasovagal) accounts for large numbers of falls in older adults and the mechanisms are poorly understood. This study examined the differences in baseline arterial baroreflex function in older adults with and without a neurocardiovascular response to orthostatic stress.

Methods: Subjects were divided into two groups based on the presence (TT+ group) or absence (TT- group) of a neurocardiovascular response to upright tilting (70 degree head-up tilt for 10 minutes after 400 micrograms of sublingual nitroglycerin). A neurocardiovascular response was defined as presyncopal symptoms (lightheadedness) in association with at least a 30 mm Hg decrease in blood pressure. Before being divided into groups, baroreflex function was assessed using the spontaneous baroreflex method (baroreflex sensitivity, BRS). This method involves the analysis of “spontaneous” swings in blood pressure and heart rate that are mediated by the arterial baroreflexes.

Results: 42 older adults (mean age 70.3 ± 0.7 yr) were recruited, of which 18 were in the TT+ and 24 were in the TT- group. At baseline, the TT+ group demonstrated increased arterial baroreflex sensitivity in response to negative blood pressure sequences only (BRS_{down} , 11.2 ± 1.9 vs. 7.3 ± 1.0 ms/mm Hg, $P=0.011$). During tilt, the TT+ group demonstrated a much larger decrease in overall arterial baroreflex sensitivity than the TT- group (-6.8 ± 1.2 vs. -3.2 ± 0.9 ms/mm Hg, $P=0.012$). There was a negative correlation

between BRS_{down} and length of tilt table test ($r=-0.329$, $P=0.041$) in the TT+ subjects.

Conclusion: Older adults with neurocardiogenic syncope have exaggerated arterial baroreflex sensitivity at baseline.

Neurocardiogenic syncope (NCS), formerly known as vasovagal syncope, was first defined as a constellation of “vagal” symptoms that includes a fall in blood pressure and a slowing of the ventricular rate.¹ Although initially felt to be primarily a diagnosis in younger patients², the use of tilt-table testing has uncovered a more bimodal distribution for this condition.³ In fact, NCS has been found to account for 30 to 50 percent of syncopal spells in outpatient populations of older adults.^{3,4}

The mechanisms behind neurocardiogenic syncope remain poorly understood, and consequently there are few effective pharmacological treatments for this condition.⁵ Classical explanations invoking cardiac ventricular receptor stimulation due to venous blood pooling (the Bezold-Jarisch reflex) have been disproved in animal studies.⁶ An appropriate baroreflex response is vital to maintaining blood pressure in older subjects in the face of an orthostatic stressor.⁷

Enhanced baroreflex sensitivity (BRS) has been shown to be a characteristic of young subjects with tilt-induced neurocardiogenic syncope.^{8, 9} Neurocardiogenic syncope remains common³ in older adults despite the fact that normal aging is associated with a reduction in BRS.¹⁰ This suggests that neurocardiogenic syncope in older adults might have a different mechanism; one in which altered arterial baroreflex function may or may not be playing a part. In the current study, we measured arterial baroreflex function both at baseline and during upright tilt in older adults with and without neurocardiogenic syncope. We hypothesized that exaggerated BRS would not be a predictor of vasovagal response to upright tilt, contrary to the results seen in younger adults.

Methods

Subjects (Table 1)

Fifty older adults (30 male and 20 female, mean age 70.1 ± 0.7 yr) were recruited ranging in age from 65 to 83 yr. All subjects had to be > 65 yr and were excluded if they had a history of angina, myocardial infarction, stroke, chronic pulmonary disease, or smoking in the last 5 yr. Since orthostatic hypotension is a separate condition from neurocardiogenic syncope, subjects with this condition were excluded during the initial screening visit by a series of five orthostatic maneuvers. Each orthostatic maneuver consisted of changing position from lying to standing for 3 min, and was followed by a 5-min rest period. Orthostatic hypotension was defined as a drop in systolic blood pressure > 20 mmHg during one of these maneuvers.¹¹ Subjects were also excluded if they took beta-blockers, calcium channel blockers, or any other agent with the potential to influence autonomic function. Entry requirements also included a normal physical examination, normal resting electrocardiogram, normal hematocrit, fasting blood glucose, and creatinine. On this basis we excluded 8 subjects ($n=42$; 26 male and 16 female).

This study was approved by the Human Subjects Committee of the University of British Columbia, and all subjects gave written informed consent.

Study Design

Each subject participated in two separate data collection sessions. The first (Session #1) allowed us to measure baseline arterial baroreflex function. The second (Session #2) allowed us to divide the subjects into two groups based on the presence (TT+ group) or absence (TT- group) of a neurocardiovascular response to upright tilting. Since baseline arterial baroreflex function (Session #1) was determined before Session #2 (tilt-table session), both the subject and the technician responsible for measuring arterial baroreflex measures were blinded as to subject group. Since baseline arterial baroreflex function data was analyzed after both sessions were complete, both the subject and technician were blinded as to each subject's arterial baroreflex function during Session #2.

During both sessions, the study room was temperature-controlled ($25 \pm 1^\circ\text{C}$). All study sessions were performed between 9 AM and noon for all subjects to avoid bias due to circadian rhythms. Each subject was supine for 45 min prior to the start of data collection in order to reach steady state. Subjects were fasting, had refrained from the consumption of alcohol or caffeine, and had not exercised for the 24 hours prior to each session.

Session #1—Baseline Arterial Baroreflex Function

Session #1 was performed with the subject supine. Twenty minutes of resting heart rate and blood pressure data was collected after a 45-min resting period prior to data collection in order to reach a steady state. Heart rate was monitored continuously using a 3 lead-electrocardiogram. Blood pressure was monitored using a Finometer (Finapres Medical Systems, The Netherlands). The Finometer measures beat-to-beat blood pressure noninvasively using infrared plethysmography through a finger-cuff. Use of the Finometer

and infrared plethysmography for monitoring blood pressure changes has been well established as a non-invasive measure of beat-to-beat blood pressure¹², has been extensively validated against intra-arterial blood pressure monitoring in older adults¹³, and is validated for the assessment of arterial baroreflex function.¹⁴ The Finometer uses waveform filtering, level correction and an additional return-to-flow calibration to reconstruct brachial artery pressures.¹⁵

Session #2—Tilt Table Testing

After receiving 400 µg nitroglycerin (GTN) *sl*, each subject was placed in a 70° head-up tilt for 10 min. Since there is no recognized gold standard for tilt table testing¹⁶, this protocol was chosen because, unlike other drug provocation agents, GTN produces a positivity rate in older adults similar to younger age groups.¹⁷ A 10 min tilt time was selected because this duration has higher specificity for neurocardiogenic syncope than tilt-table tests of longer duration.¹⁶ The tilt table test was considered positive if the subject demonstrated presyncopal symptoms (lightheadedness or ‘dizziness’) in association with ≥ 30 mm Hg drop in blood pressure compared with baseline, or developed outright syncope. Heart rate and blood pressure were monitored continuously as described above in Session #1.

Derived Measurements

All post-collection analysis of the data was done in a blinded fashion. Before all derived measurements, each segment of raw blood pressure and electrocardiogram signal was manually examined in order to exclude artifacts. Two measures of arterial baroreflex function were determined using a custom-written software program (Matlab Release 13, 2002). Arterial baroreflex function was measured by the sequence method, which provides baroreflex sensitivity (BRS, in ms/mm Hg) and baroreflex effectiveness index (BEI, percent). Both the BRS¹⁸ and BEI¹⁹ have been used previously to examine baroreflex function in

older adult subjects and are well validated against traditional measures such as the Oxford method.²⁰

The Sequence Method of Assessing Arterial Baroreflex Function

This involves the analysis of “spontaneous” swings in blood pressure and heart rate that are mediated by the arterial baroreflexes. Data is examined for progressive increases in both systolic blood pressure (SBP) and RR-interval (RRI) or progressive decreases in SBP and RRI. BRS is defined as the mean slope of the regression lines for all these baroreflex-mediated sequences (+RRI/+SBP or -RRI/-SBP) and is measured in ms/mm Hg.²⁰ This method of baroreflex assessment has the advantage that it can be performed noninvasively and can provide multiple sequential observations (as opposed to methods that involve the direct intravenous injection of vasoactive medications).²¹ Parameters used for our spontaneous baroreflex analysis were the inclusion of all baroreflex-mediated sequences of 3 or more beats that had a correlation coefficient > 0.80 , a threshold of blood pressure change of 1 mm of Hg, and a threshold for change in RR-interval of 4 msec. For the purpose of our analysis there is a +1 shift between the SBP data and the RRI data (the SBP pulse is plotted against the following RRI for the purpose of regression analysis). This set of conditions for spontaneous baroreflex is standard for the literature²⁰, has been shown to maximally correlate with the bolus intravenous phenylephrine method²² and has high intrasubject reproducibility.¹⁸ Spontaneous baroreflex measures allows for a separate examination of arterial baroreflex sensitivity for sequences characterized by a decrease (BRS_{down}) or increase (BRS_{up}) in blood pressure. As used previously²³ this method allows the comparison of BRS regardless of the length of the data segment.²⁴ This method allows us to compare BRS at baseline (20 min data collection) with the last 2 min of tilt²⁵.

The sequence technique also allows the calculation of the BEI, an alternative noninvasive measure of

the arterial baroreflex. The BEI quantifies the number of times the arterial baroreflex is activated in response to non-baroreflex influences that create swings in blood pressure. This is assessed by the ratio of the number of baroreflex-mediated sequences (+RRI/+SBP or -RRI/-SBP) to the total number of all significant swings in blood pressure (+SBP or -SBP). The BEI has been shown to be specific for detection of arterial baroreflex dysfunction and is thought to be complementary to the calculation of BRS²⁶, examining the interaction between the arterial baroreflex and other nonbaroreflex mechanisms controlling the sinus node.²⁶

Statistical Analysis

Data analysis was done in a blinded fashion. Results are expressed as the mean $\pm$ standard error. Given that we had four primary outcomes measures (BRS, BRS_{down}, BRS_{up} and BEI), a value of $P < 0.013$ was considered significant after Bonferroni correction for multiple comparisons.²⁷ Mean values for each variable were determined for each minute of upright tilt. A one-way Analysis of Variance (ANOVA) was used to compare our primary outcomes at baseline between the TT+ and TT- groups.²⁷ Two-way ANOVA with repeated measures was used to compare alterations in

BRS with upright tilting seen in the TT+ group with the TT- group. The Pearson correlation coefficient was used to evaluate the relationship between BRS_{down} and tilt table test duration.

Results

Subject Characteristics

The subjects had an overall average age of 70.3 ± 0.7 yr. Overall mean weight (82.9 ± 2.3 kg) and mean height (166.7 ± 1.9 cm) resulted in a subject population that was mildly overweight but not obese²⁸ with a mean body mass index of 29.5 ± 0.7 kg/m². Of the 42 subjects studied, 18 had a positive tilt-table test (TT + group) and 24 had a negative tilt-table test (TT- group). The TT+ group had an average tilt-table tolerance of 5.14 ± 0.36 min, ranging from 2.52 to 8.39 min. Baseline characteristics for both the TT+ and TT- groups showed no difference with the exception of BMI which tended to be higher in the TT- group (see Table 1).

Baseline Arterial Baroreflex Function (Figure 1)

Subjects with positive tilt table tests (TT+ group) demonstrated increased arterial baroreflex sensitivity

TABLE 1. Subject Characteristics

	TT + Group n=18	TT - Group n = 24	All Subjects n = 42	P
Age (years)	70.1 $\pm$ 1.1	70.4 $\pm$ 1.1	70.3 $\pm$ 0.7	0.451
Weight (kg)	80.0 $\pm$ 2.4	86.5 $\pm$ 4.2	82.8 $\pm$ 2.3	0.165
Height (cm)	168.7 $\pm$ 2.0	166.7 $\pm$ 1.9	166.7 $\pm$ 1.9	0.224
Body Mass Index (kg/m ²)	28.3 $\pm$ 0.6	31.2 $\pm$ 1.2	29.5 $\pm$ 0.7	0.029*
Systolic Blood Pressure (mm Hg)	142 $\pm$ 5	149 $\pm$ 4	145 $\pm$ 3	0.292
Diastolic Blood Pressure (mm Hg)	86 $\pm$ 3	86 $\pm$ 2	86 $\pm$ 2	0.784
Mean Blood Pressure (mm Hg)	104 $\pm$ 3	107 $\pm$ 3	106 $\pm$ 2	0.480
Heart Rate (beats per minute)	68 $\pm$ 3	63 $\pm$ 2	66 $\pm$ 3	0.162
Glycosylated Hemoglobin (Percent)	6.9 $\pm$ 0.2	6.6 $\pm$ 0.1	6.7 $\pm$ 0.2	0.320
Total Cholesterol (mmol/L)	5.2 $\pm$ 0.3	4.6 $\pm$ 0.3	5.0 $\pm$ 0.2	0.176
Total Cholesterol/High Density Cholesterol	3.4 $\pm$ 0.2	3.4 $\pm$ 0.2	3.4 $\pm$ 0.2	0.827

Demographic data for subjects with a positive tilt table (TT+ group), subjects with a negative tilt table (TT- group) and all subjects is shown as mean $\pm$ standard error. P values are shown for differences between the two groups (independent t-test). $P < 0.05$ is indicated by *.

FIGURE 1. Measures of baseline arterial reflex function * Sig diff between the TT+ and TT- group ($P<0.013$). TT+, Tilt-table positive group; TT-, Tilt-table negative group; Baroreflex sensitivity, BRS; Baroreflex sensitivity for upward blood pressure sequences, BRS_{up}; Baroreflex sensitivity for downward blood pressure sequences, BRS_{down}.

in response to negative blood pressure sequences (BRS_{down}, $P=0.011$). The TT+ group demonstrated a nonsignificant trend towards overall higher baroreflex sensitivity ($P=0.037$) but no difference in BRS_{up}. There was no difference in baroreflex effectiveness between the TT+ and TT- groups (0.384 vs. 0.386). During baseline rest, there was no difference in the number of detectable blood pressure swings between the TT+ and TT- groups (387 ± 21 vs. 400 ± 41). There was also a weak but significant negative correlation between BRS_{down} and tilt table test duration ($r=-0.329$, $P=0.041$) in the TT+ subjects.

Changes in Arterial Baroreflex Function During Upright Tilting

Upright tilting resulted in an overall decrease in arterial baroreflex sensitivity when all subjects were exam-

ined together. As shown in Figure 2, BRS ($P<0.001$), BRS_{up} ($P<0.001$) and BRS_{down} ($P<0.001$) all demonstrated an overall decrease in sensitivity. BEI did not show any change with upright tilting ($P=0.603$). The TT+ group demonstrated a much larger decrease in overall arterial baroreflex sensitivity ($P=0.012$) mainly due to a much larger decrease in BRS_{down} ($P=0.005$). The response of BRS_{up} to upright tilting was no different between the TT+ and TT- groups.

Discussion

Older adults with a neurocardiovascular response to upright tilt have exaggerated arterial baroreflex sensitivity in response to downward blood pressure sequences (BRS_{down}) at baseline. Upright tilting itself also results in a decrease in BRS, which was exaggerated in the TT+ group due to a larger magnitude decrease in BRS_{down}.

Previous investigations of young subjects have suggested that patients with NCS might have an enhanced arterial baroreflex response to changes in blood pressure, which might explain the large swings in blood pressure and heart rate observed during one of these episodes.²⁹ Congruent with our study of older adults, young adults suffering from NCS demonstrate a larger BRS_{down} when compared to normals, but no difference in baseline BRS_{up}, overall BRS or BEI.⁹ This was further supported in the present study by the fact that there was a negative correlation between BRS_{down} and tilt table test duration in TT+ subjects. With respect to the effects of upright tilting itself on arterial baroreflex function, this has also only been examined in younger populations.³⁰ As shown in Figure 2, upright tilting itself results in a decrease in BRS in older adults, and this decrease is augmented in TT+ subjects. The TT+ group decreased BRS by approximately 60 % compared with a 45 % decrease in the TT- group. Several previous investigations in young subjects with NCS demonstrated a decrease in arterial baroreflex sensitivity both during augmented (nitroglycerin)³¹ and unaugmented⁸ tilt table tests, congru-

FIGURE 2. The effect of orthostasis on arterial baroreflex function: * significant difference between the TT+ and TT- group ($P < 0.013$). BL, Baseline; TT+, Tilt-table positive group; TT-, Tilt-table negative group; Baroreflex sensitivity, BRS; Baroreflex sensitivity for upward blood pressure sequences, BRS_{up}; Baroreflex sensitivity for downward blood pressure sequences, BRS_{down}.

ent with the results of the present study. To our knowledge, we are the first to demonstrate that older subjects with NCS have exaggerated arterial baroreflex function at baseline, and that upright tilting itself results in a decrease in BRS in older adults.

Possible Mechanisms

The mechanisms underlying NCS remain poorly understood. The classical explanation for NCS suggested that orthostatic stress produces reduced cardiac filling and increased sympathetic stimulation resulting in the stimulation of ventricular mechanoreceptors.³² However, subsequent work has shown that even entirely empty dog hearts on bypass do not demonstrate a Bezold-Jarish response⁶, and NCS persists even after complete denervation of the heart.³³ Disproof of ven-

tricular mechanoreceptor stimulation as the inciting event for NCS has consequently led investigators to examine central alterations in cardiovascular control, possibly involving either opioid³⁴ or serotonin pathways.³⁵ Short-term decreases in blood pressure changes are buffered primarily by the arterial baroreflex, suggesting that NCS may be due to centrally mediated alterations in arterial baroreflex function either at baseline or during upright tilting.⁷ Our study provides support for a central as opposed to a peripheral alteration in arterial baroreflex function since we demonstrated no difference in baroreflex effectiveness (BEI) between the TT+ and TT- groups.

Clinical Implications

NCS is a common cause of fall-related morbidity and mortality in the older adult population.³⁶ Although previously felt to be rare in older adults², an examination of syncope patients presenting to the emergency room has demonstrated a second peak incidence of NCS over the age of 70 yr.³⁷ The results of our current study reinforce these findings, demonstrating that TT+ patients in the older population demonstrate similar alterations in arterial baroreflex function (both at baseline and during upright tilt) as their younger counterparts. The higher BRS_{down} seen in older TT+ adults also suggests that measures of arterial baroreflex function could be predictive of a future positive tilt table test. Although this requires much further study, perhaps this measure could eventually be used to replace tilt-table testing in frail older adults with contraindications such as severe coronary disease or cerebrovascular stenosis.³⁸

Limitations

Further research is needed to determine the clinical significance of the relationship between an exaggerated arterial baroreflex and a positive tilt-table test. It is possible that this baseline change in arterial baroreflex function is merely an epiphenomenon as opposed to a causal factor in the initiation of the NCS re-

sponse. Further study is needed to determine the exact mechanism behind the decrease in arterial baroreflex sensitivity with upright tilting and whether or not this could constitute a possible avenue of treatment for NCS.

Conclusions

Older adults with neurocardiogenic syncope demonstrate exaggerated arterial baroreflex sensitivity at baseline. Arterial baroreflex sensitivity decreases with upright tilting, and this decrease was amplified in older adults with NCS.

Acknowledgements

This research was supported by the Canadian Institutes of Health Research.

References

1. Nahm F, Freeman R. Vasovagal syncope: the contributions of Sir William R. Gowers and Sir Thomas Lewis. *Arch Neurol* 2001;58:509-11.
2. Day SC, Cook EF, Funkenstein H, Goldman L. Evaluation and outcome of emergency room patients with transient loss of consciousness. *Am J Med* 1982;73:15-23.
3. Ungar A, Mussi C, Del Rosso A, et al. Diagnosis and characteristics of syncope in older patients referred to geriatric departments. *J Am Geriatr Soc* 2006;54:1531-6.
4. Colman N, Nahm K, Ganzeboom KS, et al. Epidemiology of reflex syncope. *Clin Auton Res* 2004;14 Suppl 1:9-17.
5. Tan MP, Parry SW. Vasovagal syncope in the older patient. *J Am Coll Cardiol* 2008;51:599-606.
6. Wright C, Drinkhill MJ, Hainsworth R. Reflex effects of independent stimulation of coronary and left ventricular mechanoreceptors in anaesthetised dogs. *J Physiol* 2000;528 Pt 2:349-58.
7. Lanfranchi PA, Somers VK. Arterial baroreflex function and cardiovascular variability: interactions and implications. *Am J Physiol Regul Integr Comp Physiol* 2002;283:R815-26.
8. Julu PO, Cooper VL, Hansen S, Hainsworth R. Cardiovascular regulation in the period preceding vasovagal syncope in conscious humans. *J Physiol* 2003;549(Pt 1):299-311.
9. Pitzalis M, Parati G, Massari F, et al. Enhanced reflex response to baroreceptor deactivation in subjects with tilt-induced syncope. *J Am Coll Cardiol* 2003;41:1167-73.
10. Gerritsen J, Dekker JM, TenVoorde BJ, et al. Glucose tolerance and other determinants of cardiovascular autonomic function: the Hoorn Study. *Diabetologia* 2000;43:561-70.
11. Ziegler D, Laux G, Dannehl K, et al. Assessment of cardiovascular autonomic function: age-related normal ranges and reproducibility of spectral analysis, vector analysis, and standard tests of heart rate variation and blood pressure responses. *Diabet Med* 1992;9:166-75.
12. Imholz BP, Wieling W, van Montfrans GA, Wesseling KH. Fifteen years experience with finger arterial pressure monitoring: assessment of the technology. *Cardiovasc Res* 1998;38:605-16.
13. Rongen GA, Bos WJ, Lenders JW, et al. Comparison of intrabrachial and finger blood pressure in healthy elderly volunteers. *Am J Hypertens* 1995;8:237-48.
14. Omboni S, Parati G, Frattola A, et al. Spectral and sequence analysis of finger blood pressure variability. Comparison with analysis of intra-arterial recordings. *Hypertension* 1993;22:26-33.
15. Guelen I, Westerhof BE, Van Der Sar GL, et al. Finometer, finger pressure measurements with the possibility to reconstruct brachial pressure. *Blood Press Monit* 2003;8:27-30.
16. Sheldon R, Killam S. Methodology of isoproterenol-tilt table testing in patients with syncope. *J Am Coll Cardiol* 1992;19:773-9.
17. Del Rosso A, Ungar A, Bartoli P, et al. Usefulness and safety of shortened head-up tilt testing potentiated with sublingual glyceryl trinitrate in older patients with recurrent unexplained syncope. *J Am Geriatr Soc* 2002;50:1324-8.
18. Johnson P, Shore A, Potter J, Panerai R, James M. Baroreflex sensitivity measured by spectral and sequence analysis in cerebrovascular disease: methodological considerations. *Clin Auton Res* 2006;16:270-5.
19. Johansson M, Gao SA, Friberg P, et al. Reduced baroreflex effectiveness index in hypertensive patients with chronic renal failure. *Am J Hypertens* 2005;18:995-1000; discussion 1016.
20. Bertinieri G, di Rienzo M, Cavallazzi A, et al. A new approach to analysis of the arterial baroreflex. *J Hypertens Suppl* 1985;3:S79-81.
21. Parati G, Di Rienzo M, Mancia G. How to measure baroreflex sensitivity: from the cardiovascular laboratory to daily life. *J Hypertens* 2000;18:7-19.

22. Davies LC, Francis D, Jurak P, et al. Reproducibility of methods for assessing baroreflex sensitivity in normal controls and in patients with chronic heart failure. *Clin Sci (Lond)* 1999;97:515-22.
23. Fu Q, Shook RP, Okazaki K, et al. Vasomotor sympathetic neural control is maintained during sustained upright posture in humans. *J Physiol* 2006;577(Pt 2):679-87.
24. O'Leary DD, Kimmerly DS, Cechetto AD, Shoemaker JK. Differential effect of head-up tilt on cardiovagal and sympathetic baroreflex sensitivity in humans. *Exp Physiol* 2003;88:769-74.
25. Steinback CD, O'Leary DD, Bakker J, et al. Carotid distensibility, baroreflex sensitivity, and orthostatic stress. *J Appl Physiol* 2005;99:64-70.
26. Di Rienzo M, Parati G, Castiglioni P, et al. Baroreflex effectiveness index: an additional measure of baroreflex control of heart rate in daily life. *Am J Physiol Regul Integr Comp Physiol* 2001;280:R744-51.
27. Dawson-Saunders B TR. Basic and clinical biostatistics. Toronto: Prentice Hall of Canada; 1994.
28. Lau DC, Douketis JD, Morrison KM, et al. 2006 Canadian clinical practice guidelines on the management and prevention of obesity in adults and children [summary]. *CMAJ* 2007;176:S1-13.
29. Pitzalis M, Massari F, Guida P, et al. Shortened head-up tilting test guided by systolic pressure reductions in neurocardiogenic syncope. *Circulation* 2002;105:146-8.
30. Samniah N, Sakaguchi S, Ermis C, Lurie KG, Benditt DG. Transient modification of baroreceptor response during tilt-induced vasovagal syncope. *Europace* 2004;6:48-54.
31. Verheyden B, Gisolf J, Beckers F, et al. Impact of age on the vasovagal response provoked by sublingual nitroglycerine in routine tilt testing. *Clin Sci (Lond)* 2007;113:329-37.
32. Oberg B, Thoren P. Increased activity in left ventricular receptors during hemorrhage or occlusion of caval veins in the cat. A possible cause of the vaso-vagal reaction. *Acta Physiol Scand* 1972;85:164-73.
33. Fitzpatrick AP, Banner N, Cheng A, Yacoub M, Sutton R. Vasovagal reactions may occur after orthotopic heart transplantation. *J Am Coll Cardiol* 1993;21:1132-7.
34. Evans RG, Ludbrook J, Van Leeuwen AF. Role of central opiate receptor subtypes in the circulatory responses of awake rabbits to graded caval occlusions. *J Physiol* 1989;419:15-31.
35. Grubb BP, Karas BJ. The potential role of serotonin in the pathogenesis of neurocardiogenic syncope and related autonomic disturbances. *J Interv Card Electrophysiol* 1998;2:325-32.
36. Kapoor W, Snustad D, Peterson J, et al. Syncope in the elderly. *Am J Med* 1986;80:419-28.
37. Alboni P, Brignole M, Degli Uberti EC. Is vasovagal syncope a disease? *Europace* 2007;9:83-7.
38. Kenny RA, O'Shea D, Parry SW. The Newcastle protocols for head-up tilt table testing in the diagnosis of vasovagal syncope, carotid sinus hypersensitivity, and related disorders. *Heart* 2000;83:564-9.

Correspondence to:

Kenneth M. Madden, M.D.
 Room 7185, Gordon and Leslie Diamond Health Care Centre
 2775 Laurel St.
 Vancouver, BC, Canada, V5Z 1M9
 Phone: 604-875-4931
 Fax: 604-875-5696
 Email: kmmadden@interchange.ubc.ca