Increased Arterial Wave Reflection May Predispose Syncopal Attacks

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Summary

Background: The incidence of syncope increases with age, while aging is also associated with increased arterial wave reflection.

Hypothesis: The study was undertaken to determine whether increased arterial wave reflection is a predisposing factor of syncope.

Methods: We recruited 38 patients (28 men and 10 women, mean age 57.2 ± 20.3 years, range 17–87 years) with a history of syncope within 6 months of entry. The etiology of syncope was documented for each patient by a complete assessment of vasomotor function and cerebral flow. All patients received a comprehensive echocardiographic evaluation of cardiac structure and function. Carotid augmentation index (AI) was estimated noninvasively with the tonometry technique. The results were compared with those from 54 age- and gender-matched controls.

Results: The most frequent diagnoses of syncope were postural hypotension (13 patients) and cerebrovascular dysautoregulation (10 patients), and the cause could not be determined in 9 patients. Compared with the control group, the syncope group had a greater AI (20 ± 21 vs. $10 \pm 15\%$, $p = 0.013$). Subgroup analysis of 20 patients aged > 50 years and with the aforementioned diagnoses showed even more striking results: AI, 29 ± 10 vs. $11 \pm 15\%$, $p < 0.001$. The enhanced augmentation in the patients remained when age, systolic blood pressure, height, and heart rate were accounted for. Analysis of the carotid pulse wave suggested that both the

timing and intensity of wave reflection were enhanced in patients with a history of syncope compared with controls.

Conclusions: Our results support the hypothesis that enhanced arterial wave reflection is associated with the occurrence of syncope, especially in the elderly.

Key words: syncope, aging, arterial stiffness

Introduction

Syncope is a sudden and temporary loss of consciousness and postural tone due to a diminished blood flow to the brain. It is synonymous with a faint or fainting. Syncope is a very common medical phenomenon. Notably, the incidence of syncope increases dramatically with age.^{1–5} In the population of patients older than 65 years, the annual incidence is 6%, and the lifetime prevalence in adults may reach 30 to 100%.⁴ It remains to be determined why the elderly subjects are prone to syncopal attacks.⁵

Arterial properties change with age, as does the level of arterial pressure.⁶ With aging, the aortic systolic and pulse pressures increase markedly due to increased wave reflection.^{7–10} Peak central aortic systolic pressure depends on the timing and intensity of wave reflection, which is a function of the state of the peripheral microvasculature and the elastic properties of the large conduit arteries.⁶ Aging affects both the terminal and central vasculature and heightens the augmentation of the central aortic systolic pressure by enhanced wave reflection. More than 20% of central aortic systolic blood pressure appears to be caused by the reflection wave in older subjects.^{11, 12} The elevated central aortic systolic blood pressure is a major determinant of left ventricular (LV) afterload in the elderly^{13, 14} and may also contribute to the reduction of the baroreflex sensitivity that predisposes them to syncope.^{15–17}

Thus, the purpose of the present study was to examine whether the increase of arterial wave reflection is a predisposing factor of syncope.

Methods

Study Population

Patients with at least two episodes of syncopal attacks within the recent 6 months were referred from our Neurology

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Department. Every patient had undergone extensive cerebral blood flow and vasomotor function evaluation at the Neurology Department to investigate the etiology of syncope. A written consent form was obtained from every patient. Our diagnostic criteria for the various etiologies of syncope included (1) postural hypotension: a blood pressure fall of at least 20/10 mmHg (systolic/diastolic) within 3 min upon orthostasis (standing up or head-up tilt of 70°) for at least two measurements taken at least 4 h apart, after exclusion of the presence of congestive heart failure, severe anemia, or hypovolemia;¹⁸ (2) cerebrovascular dysautoregulation: an excessive mean middle cerebral artery flow velocity (MCAFV) drop upon orthostasis (change of MCAFV of >20% without concomitant blood pressure drop and not caused by hyperventilation, postural hypotension, hypovolemia, severe anemia, or cardiac disorders;^{19,20} (3) vasovagal syncope (neurocardiogenic syncope): a characteristic syncopal or presyncopal attack during tilt table study; it is accompanied by a sudden severe blood pressure drop and/or severe bradycardia, is completely reversible upon resuming supine position, and is not caused by cardiac disorders such as sick sinus syndrome or other arrhythmias;²¹ (4) micturition syncope: syncope occurring at the beginning, during, or immediately at the termination of urination, with no other cause for the episode.

Control subjects were selected from a large database of a community study that employed the same technique for echocardiographic and tonometric studies.²² All had no previous history of syncope or presyncope. The controls were selected based on the closeness of age, gender, weight, height, and blood pressure levels. No matching controls could be found for two patients aged >80 years, while there were two controls for most of the patients. None of the patients or control subjects was taking any vasodilators or antihypertensive agents during the day of cardiovascular study. None of the patients or controls had a clinical diagnosis of diabetes mellitus.

Head-Up Tilt and Transcranial Doppler Monitoring

A detailed description of the methodology for the head-up tilt and transcranial Doppler monitoring has been published.²⁰ In brief, each patient stayed in supine position on a motorized tilt table with foot board support. Instantaneous arterial blood pressure was recorded noninvasively by servo-controlled infrared finger plethysmography (Finapres, Model 2300, Ohmeda Monitoring Systems, Englewood, Conn., USA) fixed to the index finger of the right hand. Heart rate and rhythm were continuously evaluated using a standard electrocardiographic (ECG) monitor. Bilateral MCAFV was recorded by a bilateral transcranial Doppler sonography monitor (Multi-Dop-X/TCD7, DWL, Sipplingen, Germany). Each participant stayed supine in horizontal position for 5 min before the table was tilted head-up to 70° for 20 min. Finally, the table was tilted back to horizontal position for additional 5 min to complete the investigation. The difference of mean MCAFV between supine rest and head-up tilt was expressed as percentage of the supine mean MCAFV to represent the extent of orthostatic MCAFV change.

Echocardiography

Echocardiographic examination was performed simultaneously with a Hewlett Packard Echo system (Model 2500, Agilent Technologies, Newberg, Oregon, USA) incorporated with a 2.0–2.5 MHz phase-array transducer. Measurements of LV end-systolic and end-diastolic dimensions from two-dimensionally (2-D) guided M-mode echocardiography were performed on-line according to the American Society of Echocardiography recommendations.²³ Standard measurements including aortic diameter, left atrial (LA) dimension, LV internal dimensions in systole (LVIDS) and diastole (LVIDD), and thickness of interventricular septum (IVS) and posterior wall (PWT) were recorded. Left ventricular mass (LVM) was calculated from the 2-D guided M-mode echocardiogram²⁴ and was indexed (LVMI) by body surface area (BSA). Left ventricular ejection fraction (EF) and cardiac output (CO) were calculated from M-mode-derived LV volumes. Mitral inflow Doppler parameters including peak E wave, peak A wave, and E/A ratio were measured to index LV diastolic function.

Brachial systolic (SBP) and diastolic (DBP) blood pressures were recorded during the echocardiographic examination with an automated noninvasive blood pressure monitor employing the oscillometric technique. Pulse pressure (PP) and mean blood pressure (MBP) were calculated from SBP and DBP. Total peripheral resistance (TPR) was calculated as $80 \times \text{MBP}/\text{CO}$.

Carotid Tonometry

Carotid tonometry was performed with a pencil-type tonometer incorporating a high-fidelity strain-gauge transducer in a 7 mm-diameter flat tip (model SPC-350, Millar Instruments, Inc., Houston, Tex., USA).^{25, 26} Tonometric carotid pressure signals were digitized instantly at a rate of 200 Hz for off-line analysis. For each subject studied, 10–15 consecutively recorded pulses were averaged, their alignment being triggered at the occurrence of the peak of the ECG R wave. The averaged pulse was then calibrated by matching the brachial MBP and DBP. Augmentation index (AI), defined as the ratio of amplitude of the pressure wave above its systolic shoulder (Δp) to the total carotid PP (Fig. 1, upper portion),^{25, 27} was calculated by a custom-designed software²⁸ that locates the inflection point of the wave reflection on the upstroke or downstroke of the pressure wave according to the zero-crossing timings of the fourth derivative of the pressure (Fig. 1, lower portion).²⁹ When the inflection point falls on the downstroke of the pressure wave, Δp and AI become negative. The absolute augmented pressure equals Δp when Δp is positive and is defined as zero when Δp is negative. The time from the foot of the pressure wave to that of the inflection point (Δt) represents the travel time of the pulse wave to peripheral reflecting sites and its return (Fig. 1).³⁰ Left ventricular ejection time (LVET) was measured from the foot of the pressure wave to the diastolic incisura (Fig. 1).³⁰ The pressure waveform registration was obtained from one experienced operator and the pressure

FIG. 1 Carotid pulse analysis. A calibrated averaged pulse wave is shown in the upper portion and its fourth derivative wave is shown in the lower portion of the figure. The dotted lines indicate the timings of the foot, inflection point, peak pressure (PP), and incisura of the pulse wave, respectively, from left to right. The timing of the inflection point is determined from the zero crossing from above to below of the fourth derivative wave. LVET = left ventricular ejection time.

waveform analysis was performed by another blinded observer. The interobserver variability of the carotid AI in this laboratory has been determined from another 62 patients with an intraclass correlation coefficient of 0.95 and a 95% confidence interval of 0.88 to 0.98 between two independent observers.³¹

Statistical Analysis

Data were presented as mean $\pm$ standard deviation. Between-group comparisons were performed with the unpaired Student's *t*-test or a chi-square test. Pearson's product-moment correlation coefficients among variables were calculated. Analysis of variance (ANOVA) was used to account for the confounding effects from age, systolic blood pressure, heart rate, and height. For further examination of the relationship between arterial wave reflection and syncope in the elderly, a subgroup analysis for those subjects aged > 50 years and with postural hypotension, cerebrovascular dysautoregulation, or undetermined etiology was performed. The two octogenarians were not included because of a lack of matching controls. Patients with vasovagal syncope were not included in the subgroup analysis because elderly subjects are somewhat protected from the occurrence of vasovagal syncope^{2, 32–35} and the pathophysiology of vasovagal syncope probably does not involve the arterial stiffening.³⁶

Results

The clinical characteristics of the subjects with a history of syncope and the controls are shown in Table I. A cause of syncope was assigned in 76.3% (29/38) of the patients. The diagnoses included 13 postural hypotension, 10 cerebrovascular dysautoregulation, 5 vasovagal syncope, 1 micturition syn-

cope, and 9 undetermined etiology. Both syncope and control groups were comparable in age, gender, weight, body mass index (BMI), BSA, and blood pressure variables. Patients with a history of syncope were significantly taller and had a slower heart rate (HR) than the control group.

The correlations of age, height, weight, SBP, and AI with other variables are shown in Table II. Most cardiovascular variables were dependent upon age, height, weight, and SBP. Specifically, AI was positively related to age, SBP, mitral inflow peak A velocity, and negatively related to height, weight, HR, and mitral inflow E/A ratio.

In terms of cardiac structure, subjects with syncope had similar chamber size (LA, 3.4 ± 0.5 vs. 3.4 ± 0.5 cm; LVIDD, 4.8 ± 0.6 vs. 5.0 ± 0.5 cm), wall thickness (IVS, 1.0 ± 0.2 vs. 1.0 ± 0.2 cm; PWT, 0.9 ± 0.2 vs. 1.0 ± 0.2 cm), and LVM (173 ± 59 vs. 173 ± 54 g; LVMI, 100 ± 30 vs. 103 ± 28 g/m²) compared with controls. The syncope group had slightly smaller LV dimension in systole than the control group (LVIDS, 2.7 ± 0.4 vs. 2.9 ± 0.5 cm, $p = 0.04$). In terms of LV systolic function, the syncope group had similar EF (76 ± 6 vs. $73 \pm 9\%$) but lower CO (5.4 ± 1.5 vs. 6.3 ± 1.8 l/min, $p = 0.007$) due to slower HR. The diastolic function indices in both groups were similar (peak E, 71 ± 17 vs. 64 ± 16 cm/s; peak A, 70 ± 20 vs. 69 ± 16 cm/s; E/A ratio, 1.2 ± 0.6 vs. 1.0 ± 0.4). The aortic diameter was similar between the groups (3.1 ± 0.5 vs. 3.2 ± 0.4). The syncope group had greater TPR than controls (1436 ± 371 vs. 1271 ± 341 dyne·s cm⁻⁵, $p = 0.033$).

Carotid waveform analysis revealed that patients with a history of syncope had significantly greater AI than controls ($20 \pm 21\%$ vs. $10 \pm 15\%$, $p = 0.013$). The AI normalized with height was also greater in these patients (0.12 ± 0.12 vs. 0.06 ± 0.09 %/cm, $p = 0.016$) (Table III). The AI remained significantly greater in the syncope group when age, SBP, height, and HR were accounted for ($p < 0.001$). The absolute augmented pressure was significantly greater in the syncope group than in the controls (9.0 ± 6.7 vs. 5.2 ± 7.3 mm Hg, $p =$

TABLE I Clinical characteristics

	Syncope (n = 38)	Control (n = 54)	p Value
Age (years)	57.2 $\pm$ 20.3	60.5 $\pm$ 15.1	NS
Sex (male:female)	28:10	39:15	NS
Hypertension history	8 (21%)	15 (27%)	NS
Weight (kg)	64.1 $\pm$ 13.3	63.1 $\pm$ 10.3	NS
Height (cm)	167 $\pm$ 7	161 $\pm$ 6	<0.001
BMI (kg/m ²)	22.9 $\pm$ 3.8	24.2 $\pm$ 3.6	NS
BSA (m ²)	1.7 $\pm$ 0.2	1.7 $\pm$ 0.1	NS
SBP (mmHg)	123 $\pm$ 19	125 $\pm$ 18	NS
DBP (mmHg)	75 $\pm$ 10	78 $\pm$ 10	NS
PP (mmHg)	48 $\pm$ 14	47 $\pm$ 15	NS
HR (beats/min)	66 $\pm$ 12	72 $\pm$ 10	0.01

Abbreviations: BMI = body mass index, BSA = body surface area, SBP = systolic blood pressure, DBP = diastolic blood pressure, PP = pulse pressure, HR = heart rate, NS = not significant.

TABLE II Correlation matrix of the variables

	Age	Height	Weight	SBP	AI
Age (years)					0.35 ^c
Height (cm)	0.05				-0.23 ^a
Weight (kg)	-0.03	0.51			-0.22 ^a
SBP (mmHg)	0.33 ^b	<0.01	0.22 ^a		0.24 ^a
DBP (mmHg)	-0.04	0.08	0.35 ^b	0.61 ^c	0.04
HR (beats/min)	-0.10	-0.07	-0.06	0.21 ^a	-0.34 ^c
LA (cm)	0.32 ^b	0.09	0.49 ^c	0.43 ^c	0.16
IVS (cm)	0.36 ^c	0.20	0.44 ^c	0.41 ^c	0.13
PWT (cm)	0.47 ^c	0.26 ^a	0.45 ^c	0.39	0.07
LVIDD (cm)	0.29 ^b	0.20	0.36 ^c	0.23 ^a	0.05
LVIDS (cm)	0.06	0.13	0.17	0.07	-0.02
LVM (g)	0.42 ^c	0.29 ^b	0.52 ^c	0.40 ^c	0.10
LVMi (g/m ²)	0.49 ^c	0.08	0.28 ^b	0.41 ^c	0.20
EF (%)	0.14	-0.01	0.04	0.09	0.06
CO (l/min)	0.25 ^a	0.12	0.29 ^b	0.34 ^c	-0.14
Peak E (cm/s)	-0.60 ^c	-0.09	0.02	-0.22 ^a	-0.07
Peak A (cm/s)	0.58 ^c	-0.09	0.27 ^a	0.49 ^c	0.33 ^b
E/A ratio	-0.77 ^c	0.04	-0.15	-0.39 ^c	-0.29 ^b
Aortic diameter (cm)	0.62 ^c	0.36 ^c	0.33 ^c	0.28 ^b	0.01

^a $p < 0.05$, ^b $p < 0.01$, ^c $p < 0.001$.

Abbreviations: AI = augmentation index, LA = left atrial, IVS = interventricular system, PWT = posterior wall thickness, LVIDD = left ventricular internal dimension in diastole, LVIDS = left ventricular internal dimension in systole, LVM = left ventricular mass, LVMi = left ventricular mass index, EF = ejection fraction, CO = cardiac output. Other abbreviations as in Table I.

0.011). The Δt was shorter in the syncope group (106 ± 45 vs. 131 ± 46 ms, $p = 0.011$), with a decreased Δt /LVET ratio ($31 \pm 15\%$ vs. $38 \pm 13\%$, $p = 0.042$).

The results in the 20 elderly patients with postural hypotension, cerebrovascular dysautoregulation, or undetermined etiology were compared with 20 age- and gender-matched controls and the comparison generally simulated that of the whole study population. The syncope group had similar cardiac structure and function compared with controls, except that the syncope group had slightly thickened IVS (1.11 ± 0.16 vs. 0.97 ± 0.23 cm, $p = 0.029$). Total peripheral resistance was

similar in both groups (1362 ± 317 vs. 1322 ± 402 dyne·s·cm⁻⁵). The results of the carotid pulse wave analysis for the subgroup are shown in Table IV. The differences between the two groups were even more substantial, and the AI also remained significantly greater in the syncope group when age, SBP, height, and HR were accounted for ($p < 0.001$).

Discussion

The role of arterial wave reflection in the augmentation of central pulse and systolic blood pressure in elderly subjects and uremic and hypertensive patients, and its detrimental effects

TABLE III Carotid pulse wave analysis

	Syncope n = 38	Controls n = 54	p Value
PP (mmHg)	37.0 ± 12.7	39.3 ± 15.0	NS
Augmented pressure (mmHg)	9.0 ± 6.7	5.2 ± 7.3	0.011
AI (%)	20 ± 21	10 ± 15	0.013
AI/height (%/cm)	0.12 ± 0.12	0.06 ± 0.09	0.016
Δt (ms)	106 ± 45	131 ± 46	0.011
LVET (ms)	344 ± 36	354 ± 66	NS
Δt /LVET (%)	31 ± 15%	38 ± 13	0.042

Abbreviations: PP = pulse pressure, AI = augmentation index, LVET = left ventricular ejection time, Δt = duration between the foot and the inflection point, NS = not significant.

TABLE IV Carotid pulse wave analysis in the age- and gender-matched subgroup

Variables	Syncope n = 20	Controls n = 20	p Value
Augmented pressure (mmHg)	12.3 ± 6.5	6.1 ± 8.9	0.017
AI (%)	29 ± 10	11 ± 15	<0.001
AI/height (%/cm)	0.175 ± 0.061	0.069 ± 0.097	<0.001
Δt (ms)	89 ± 17	134 ± 51	0.001
LVET (ms)	353 ± 32	371 ± 98	NS
Δt /LVET (%)	25 ± 4	36 ± 11	<0.001

Abbreviations as in Table III.

on cardiac function has been well documented.^{11, 14, 30, 37–43} To our knowledge, the potential role of increased arterial wave reflection in the facilitation of syncope has never been implicated. The major finding of the study is that patients with history of syncopal attacks of various etiologies had increased arterial wave reflection compared with controls. The difference of AI between the syncope and control groups was more remarkable in the subgroup of older subjects. These results support the hypothesis that increased arterial wave reflection is a predisposing factor of syncope, especially in the elderly.

Systolic arterial pressure becomes increasingly sensitive to changes in circulating blood volume and thus cardiac filling volume with normal human aging.⁴⁴ For example, systolic pressure rises with excess sodium intake, and antihypertensive efficacy of sodium restriction^{44, 45} or diuretic therapy^{46, 47} is greater in aged individuals. In the Medical Research Council trial of hypertension treatment in the elderly, systolic and diastolic pressures fell rapidly with greater immediate changes in systolic pressure in patients receiving diuretics.⁴⁸ It is conceivable that the increased dependence of systolic pressure on cardiac filling in the elderly may contribute to orthostatic and postprandial hypotension^{49–51} that may facilitate syncopal attacks.^{5, 36} We have demonstrated that aging is associated with both vascular and ventricular stiffening changes, and that each contributes independently to enhanced volume-load sensitivity of systolic arterial pressure.⁵² In the current study, we further extend that enhanced arterial wave reflection, as a component of aging-related cardiovascular stiffening, may be directly associated with syncopal attacks.

In this study, systolic function indices were not affected by age, and age was generally significantly related to LV diastolic function indices and AI. These age-related cardiovascular changes are in accord with previous reports.^{53–55} Compared with controls, older patients with nonvasovagal syncope had significantly greater AI, absolute augmented carotid pressure, and carotid pulse pressure. Why an augmented arterial wave reflection is associated with syncopal attacks remains speculative. A previous study has shown that the carotid AI was consistently lower than the aortic AI by about 50%.²⁶ Thus, although we did not measure or estimate the central aortic blood pressure directly, it can be reasonably speculated that the differences of AI and augmented pressure between the two groups at the central aorta should be even greater. The speculated greater aortic AI might indicate higher central aortic systolic pressure and greater LV afterload in the syncope group. This was partly reflected by the greater IVS in the older patients compared with controls. It has been documented that aging and high blood pressure contribute independently to the reduction of baroreceptor function.¹⁵ Since the aging-related decline of baroreceptor function of the carotid sinus is one of the major physiologic changes that predispose the elderly to syncope,⁵ we hypothesize that greater arterial wave reflection implies higher systolic and pulse pressures at carotid arteries and central aorta that may cause greater decline of baroreceptor function with aging. This may partly explain why enhanced arterial wave reflection predisposes to syncope, especially in the elderly.

The intensity of wave reflection is determined by the degree of impedance mismatch at junctions and terminations, the main contributor being the level of vasoconstriction of peripheral vascular beds together with the degree of viscous damping of the traveling wave.⁶ Propagation properties of the elastic conduit arteries determine the time of arrival through their effect on pulse wave velocity and on the degree of wave damping.⁶ The results of the carotid pulse analysis suggest that the greater AI in patients with syncope resulted from both increased intensity (suggested by increased absolute augmented pressure) and from increased propagation speed of the wave reflection (suggested by decreased $\Delta t/LVET$ ratio).^{6, 37}

An increase in height or a decrease in HR usually results in decrease of augmentation from wave reflection due to longer-lasting wave propagation.³⁰ This is also evident from the significant negative associations between AI and height or HR reported in this study (Table II). Our patients with a history of syncope were significantly taller and had slower HR than the control group. However, the patients still had significantly greater AI, even when the effects of age, SBP, height, and HR were accounted for. This may indicate that the enhanced augmentation in patients with a history of syncope resulted mainly from the changes of the property of large conduit arteries and peripheral microvasculature⁶ and not from the contribution of height and heart rate.

Conclusion

Our results demonstrated that enhanced arterial wave reflection is associated with the occurrence of syncope, especially in the older subjects. Although the mechanistic link between the wave reflection and syncope remains to be determined, our results may have important clinical relevance since the enhanced wave reflection can be modified by pharmacologic intervention.⁶

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