Similar Orthostatic Defense in Active, Healthy Young Adult and Late Middle-Aged Men

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Orthostatic defense is commonly validated with a 60° to 80° head-up tilt test, addressing the step response rather than the response to permanent orthostasis. During the initial phase of tilt, neural factors predominate, while later, the slower humoral factors fade in. It has been demonstrated that, during adaptation of the circulatory system to the standing conditions, overshoot and undershoot occur. These oscillations hamper straightforward interpretation of a tilt test, and may contribute to the inconclusiveness of current studies regarding the aging of orthostatic defense. Gradual, progressive, orthostatic load testing seems a valuable alternative. We used a novel, incremental, head-up tilt protocol (0° to 80°, 13 increments) to impose graded orthostatic stress on 46 healthy young adult men (mean age ± SD 25 ± 3 years), and on 16 healthy late middle-aged men (60 ± 4 years), while recording the electrocardiogram and the blood pressure. A first-order estimate of the heart rate range associated with the sympathovagal transition was made by combined analysis of heart rate and heart rate variability trends. We observed similar responses in heart rate, heart rate variability, and blood pressure. Supine heart rate (61 ± 8 vs 61 ± 7 beats/min), heart rate at the maximal tilt angle (86 ± 13 vs 84 ± 12 beats/min), sympathovagal transition (112 ± 82 vs 111 ± 76 beats/min), percent increase of the rate-pressure product (49 ± 23% vs 43 ± 20%), and the slope of the linear regression of the mean blood pressure on the sine of the tilt angle (8.7 ± 8.3 vs 9.2 ± 7.1 mm Hg) did not differ significantly. We conclude that aging, per se, does not impair orthostatic defense under gradually increasing orthostatic stress.

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Commonly, orthostatic defense is validated with head-up tilt testing. Such testing addresses the ability of the circulation to deal with a sudden change in posture, rather than the ability to cope with permanent orthostatic load. Following a step in orthostatic loading, neural factors predominate initially, while in the long term, the slower humoral factors fade in. Oscillations during adaptation (e.g., under- and overshoot of systolic blood pressure and heart rate [HR])[1,2] may hamper straightforward interpretation of the test, and might even cause vasovagal symptoms (the initial existence of which is often the reason for such testing). As an alternative, the interplay of neural and humoral factors in orthostasis can be studied under slow, gradually increasing loading conditions. This allows the humoral factors to keep pace with the neural ones, thus preventing over- and undershoot phenomena. We developed a novel head-up tilt protocol involving 13 angles between 0° and 80°, each angle being maintained during 6 minutes.[3] With this novel protocol, we revisited the question of whether aging, per se, affects orthostatic defense.

METHODS

Subjects: For the study, we approached healthy men, aged 20 to 35 years (young adult group) or 50 to 66 years (late middle-aged group). After giving their informed consent, 46 young adult men (mean age ± SD 25 ± 3 years; range 21 to 35 years) and 16 late middle-aged men (age 60 ± 4 years; range 52 to 66 years) participated. Prior to inclusion, the subjects had a physical examination, a diagnostic 12-lead electrocardiogram, and a medical history taken. None of the subjects used any medication. The subjects in the young adult group were all nonsmokers; of the late middle-aged group, 3 subjects smoked. All subjects were physically active in daily life as well as in leisure sports.

Measurement session: The measurement sessions were held between 0900 and 1200 A.M. in a quiet, comfortable room (temperature 22°C). Consumption of caffeine- or alcohol-containing beverages and smoking were not allowed in the 12 hours before the study. The subjects were placed on a tilt table, secured by a waist belt, and supported by a footrest. Respiration was free, and speaking was not allowed.

During the sessions, a 2-lead electrocardiogram and a single-lead respiration signal (thoracic impedance) were recorded on a Marquette Holter recorder (Marquette Electronics Inc., Milwaukee, Wisconsin). Arterial blood pressure was measured at the right upper arm with an automatic oscillometric blood pressure monitor (Accutorr 3, Datascope Corp., Montvale, New Jersey).

Progressive orthostatic stress was induced by incremental tilting, without supine restabilization. The protocol involved tilt angles of 0°, –5°, –10°, –15°, –10°, –5°, 0°, 10°, 20°, 30°, 40°, 45°, 50°, 55°, 60°, 65°, 70°, 75°, and 80°. The sweep with the negative angles allowed hemodynamic and autonomic stabilization of the subject. Also, when returning from the negative angles, the subjects became familiarized with the progressive tilt angle increments that characterized the remaining part of the tilt protocol. The same measurements were done at the subsequent series of ≥0°.

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TABLE I Response (mean ± SD) to Orthostatic Stress Measured in the Supine State and at Maximal Head-Up Tilt Angle in Healthy Men

Variable	Young Adult Group Aged 21 to 35 Years (n = 46)	Late Middle-Aged Group Aged 52 to 66 Years (n = 16)
Supine Values		
HR (beats/min)	61 ± 8	61 ± 7
%LF (%)	58 ± 16	57 ± 19
CV (%)	8* ± 3*	5* ± 1*
SBP (mm Hg)	117 ± 8	122 ± 12
DBP (mm Hg)	65* ± 7*	73* ± 10*
MBP (mm Hg)	86 ± 6*	91 ± 13*
RPP (beats/min•mm Hg)	7,184 ± 1,246	7,515 ± 1,428
Values at Maximal Tilt Angle (50° to 80°, by patient comfort)		
HR (beats/min)	86 ± 13	84 ± 12
%LF (%)	87* ± 6*	79* ± 15*
CV (%)	8* ± 3*	4* ± 1*
SBP (mm Hg)	123 ± 13	126 ± 14
DBP (mm Hg)	72* ± 10	84* ± 11
MBP (mm Hg)	92* ± 12	101* ± 11
RPP (beats/min•mm Hg)	10,644 ± 2,060	10,625 ± 1,923
Percentage Increase from Supine to Maximal Tilt Angle		
ΔHR	41 ± 17	37 ± 19
Δ%LF	68 ± 74	56 ± 68
ΔCV	3.7 ± 98*	–7 ± 42*
ΔSBP	5.7 ± 11	4 ± 9
ΔDBP	12 ± 17*	15 ± 10*
ΔMBP	6.4 ± 12	12 ± 9
ΔRPP	49 ± 23	43 ± 20

*Significantly different between groups (*t* test, $p < 0.05$).

CV = coefficient of variation; DBP = diastolic blood pressure; HR = heart rate; %LF = percent low-frequency heart-rate variability; MBP = mean blood pressure; RPP = rate-pressure product; SBP = systolic blood pressure; Δ = change.

Each tilt angle was maintained for 6 minutes. During minute 1, hemodynamic and autonomic adaptation to the new tilt angle[4] occurred. Minutes 2 to 5 were used for measurement of HR and the percent low-frequency HR variability (%LF, details below). During minute 6, blood pressure was measured twice. The measurements were terminated after the 80° tilt episode, or at any sign of discomfort or presyncope. To prevent mental stress or falling asleep during the long session (maximally 114 minutes), the subjects were entertained with a videotape.

Data analysis: The electrocardiograms were analyzed with a Marquette Series 8000 Holter Analyzer. Accurate determination of the onsets of the QRS complexes was accomplished by an extensive review and edit procedure, also using the CCTOC program of the Marquette 8000 Holter research modules. The resulting interbeat interval series was further analyzed on a personal computer.[5] A full disclosure printout of the respiration signal was used to verify a steady respiration at a rate >0.20 Hz.

HR and HR variability were computed at each tilt angle from the interbeat intervals within minutes 2 to 5 (4 minutes of data) as follows. First, the coefficient of variation (CV) was computed according to its definition[6] (interbeat interval SD divided by mean interbeat interval). Then, episode stationarity was verified by applying reverse arrangement tests at the 10% level to the interval means and variances in 12 subsegments of 20 seconds.[7] Subsequently, %LF was computed over the complete 4-minute episode, using an algorithm that has been described elsewhere.[3] Briefly, the intervals were normalized to the mean interval. Then, linear trend removal and 10% left and right zero tapering were done. After padding the data series with zeros to the nearest power of 2, the power-density spectrum was computed by means of a fast-Fourier algorithm. Following this, the spectral powers in the 0.05 to 0.15 Hz band (LF) and the 0.15 to 0.40 Hz band (HF) were computed by integration. Finally, %LF was computed as $\%LF = 100 (LF/[LF + HF])$. Note here that we choose to use LF and HF for absolute power values, and %LF for relative values. Hence, an increasing value of %LF implies, by definition, an increase of LF with respect to HF, or a decrease of HF with respect to LF.

In a previous study with incremental head-up tilt in healthy young adult men,[3] we found that %LF increased linearly with HR within subjects. The extrapolated virtual extreme values of %LF = 0 and %LF = 100 can be associated with HRs at which the vagal or sympathetic branches of the autonomic nervous system, respectively, predominate. Within this concept, the slope (a) of the linear relation $\%LF = (a)HR + b$ is a first-order estimate of the width of the sympathovagal transition: the range of HRs associated with combined sympathetic and vagal control.[8] To detect possible changes in sympathovagal transition with age, we computed individual linear regressions of %LF on HR in all subjects of the young adult and late middle-aged groups. The sympathovagal transition was then computed for each subject as 100/(a).

Statistics: The 2 blood pressure measurements that were done at each tilt angle were averaged. Then, individual regressions were made of the systolic, diastolic, and mean blood pressure values on the sine of the tilt angle. The slope of a regression line was considered to differ significantly from zero for a p value <0.05 (*t* test).

To characterize the responses of the young adult and the late middle-aged group to tilt, analysis of variance was done on the HR, %LF, CV, and blood pressure values at all tilt angles; p values <0.05 were considered to be significant. Statistical comparisons between the 2 groups were made by *t* tests (for the means) and by F tests (for the SDs); p values <0.05 were considered to be significant.

RESULTS

Twenty of the 46 subjects (43%) in the young adult group could be measured up to and including the 80° tilt angle. In the remaining 26 subjects, the measurements were terminated earlier because of discomfort or presyncope: in 1 subject at 50°; in 3 at 55°; in 1 at 60°; in 8 at 65°; in 3 at 70°; in 7 at 75°; and in 3 at 80° tilt.

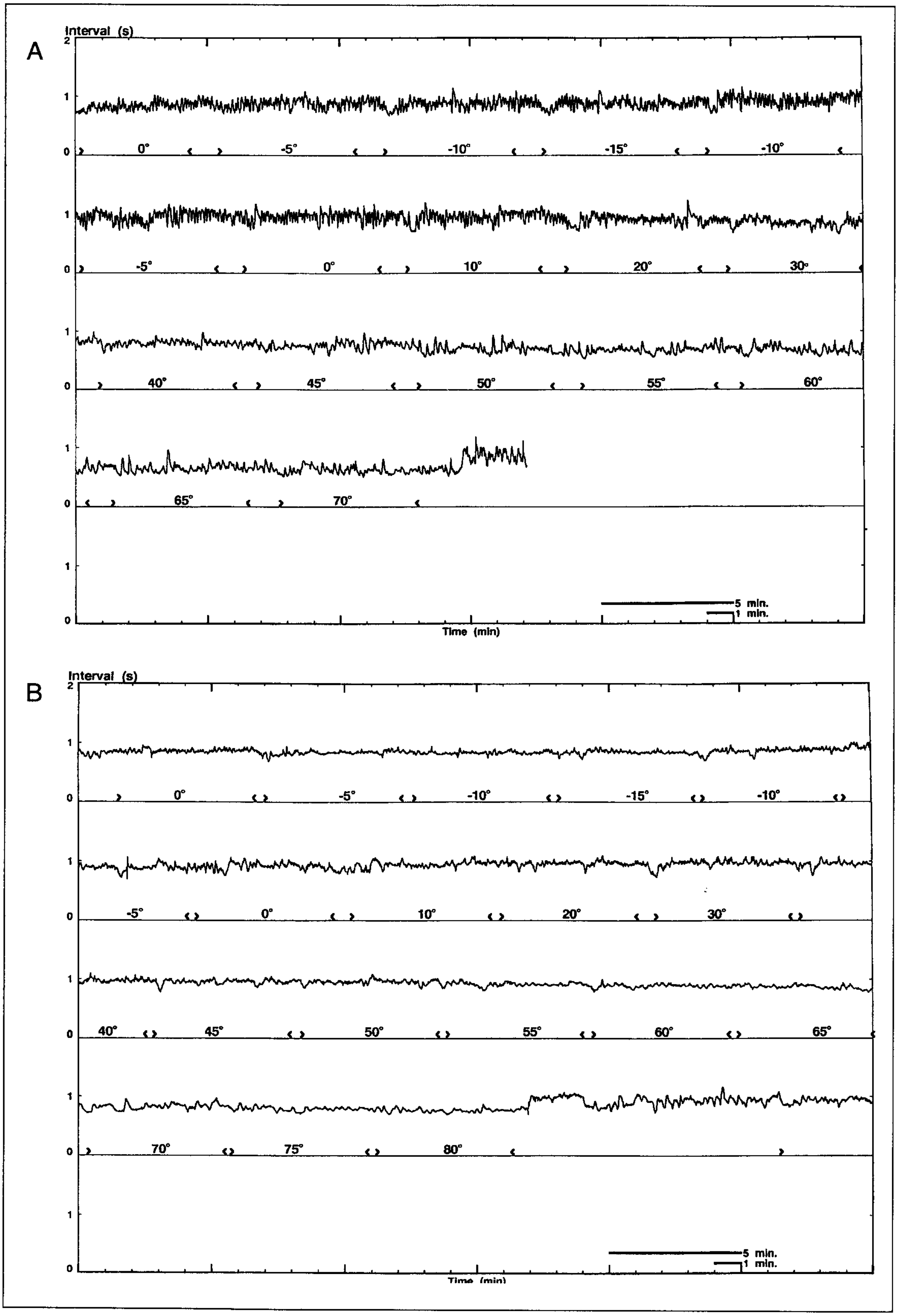

FIGURE 1. Interval tachograms (5 consecutive 30-minute tracings) recorded during the head-up tilt session of a healthy subject from the young adult group *(A)*, and from the late middle-aged group *(B)*. *Right arrowheads* mark the beginning of the next tilt angle, and *left arrowheads* mark the beginning of the blood pressure measurement at the current tilt angle. The subject in the young adult group reached a maximal tilt angle of 70°, and the middle-aged subject completed the protocol with a maximal tilt angle of 80°. The difference in the amplitude of the heart rate variability between subjects is striking, and representative for what we measured in both groups.

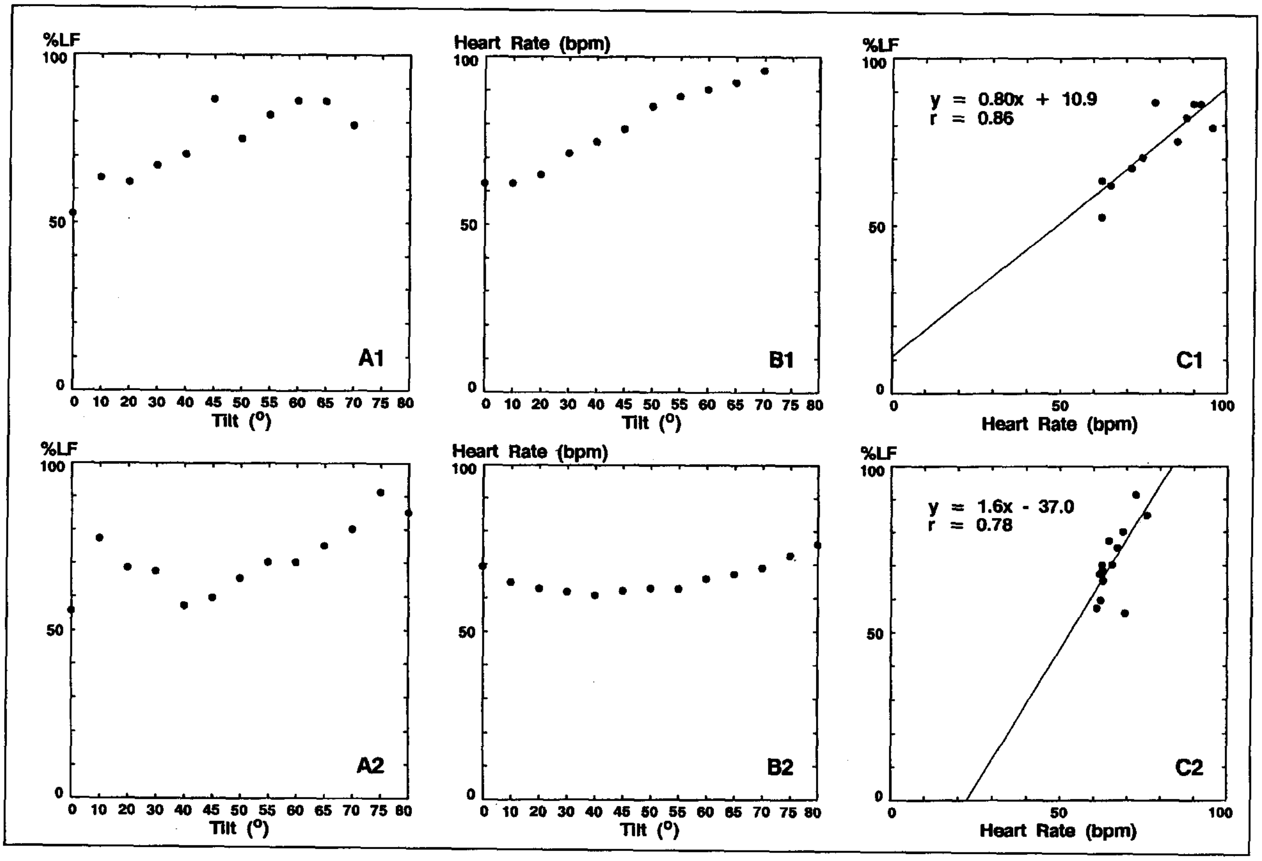

FIGURE 2. Values of %LF *(A)* and heart rate *(B)* as measured at each tilt angle, and the regression of %LF on heart rate *(C)*; same subjects as in Figure 1. *Top panels* (A1, B1, and C1) regard the subject from the young adult group whereas *bottom panels* (A2, B2, and C2) regard the subject from the late middle-aged group. %LF = percent low-frequency heart-rate variability.

Nine of the 16 subjects (56%) in the late middle-aged group could be measured up to and including the 80° tilt angle. In the remaining 7 subjects, the measurements were terminated earlier because of discomfort or presyncope: in 1 subject at 65°; in 3 at 70°; and in 3 at 80° tilt. In both groups, the reported feelings of discomfort were dizziness, nausea, restlessness, and mild pain in the legs. All measurement episodes from 0° up to and including the maximally reached tilt angle satisfied the conditions for a stationary cardiac rhythm and for a steady respiration at a rate >0.20 Hz, and could hence be used for further analysis.

The incremental-tilt protocol induced gradual increases in HR, %LF, and systolic, diastolic, and mean blood pressure in both groups; representative examples of the responses in HR and HR variability are given in Figures 1 and 2. The tachogram (Figure 1) comprises the conditioning phase (negative angles) as well as the measurement phase (angles ≥0° tilt). The figures show that the tilt protocol evokes gradual changes in HR and HR variability. During the decremental head-down tilt to −15°, and the subsequent incremental head-up tilt back to 0°, the mean beat-to-beat interval barely changes, and rapid fluctuations predominate the tachograms. In the course of further incremental head-up tilt, the tachograms change gradually: the mean interval decreases and the rapid, high-frequency fluctuations vanish while slow, low-frequency fluctuations fade-in. Analysis of variance of the data for ≤45° tilt in the young adult group revealed that HR, %LF, and the systolic, diastolic, and mean blood pressure increased significantly in all 46 subjects; the same was true for ≤80° tilt for the 20 subjects who fully completed the protocol. In the late middle-aged group, HR, %LF, and the diastolic and mean blood pressure, but not the systolic blood pressure, increased significantly in the complete group for ≤65° tilt, and for ≤80° tilt in the 9 subjects that fully completed the protocol. CV did not change significantly in either group.

Table I gives group values (mean ± SD) of (1) the supine values of HR, %LF, CV, the systolic, diastolic, and mean blood pressure, and the rate-pressure product; (2) the values of the same measures at the maximally reached tilt angle; and (3) the percent increase of the same measures from the supine state to the maximally reached tilt angle. Of the supine measures, reflecting the subject's initial state, the CV and the diastolic blood pressure mean and SD values differed significantly between the young adult and the late middle-aged groups. Of the values at the maximally reached tilt angle, the means of %LF, CV, diastolic, and mean blood pressure differed significantly between the young adult and the late middle-aged groups. Of the %LF and CV values, the SDs also differed significantly. When comparing the percent increase from the supine state to the maximally reached tilt angle, only the SDs of the CV and the diastolic blood pressure differed significantly between the 2 groups.

The group means ± SD of the slopes and corresponding values of the sympathovagal transition, inter-

TABLE II Response to Orthostatic Stress During Incremental Head-Up Tilt in Healthy Men

Variable	Young Adult Group Aged 21 to 35 Years (n = 46)	Late Middle-Aged Group Aged 52 to 66 Years (n = 16)
Regressions of %LF on HR		
Slope (beats/min/%)	1.28 ± 0.70	1.25 ± 0.68
Intercept (%)	−14 ± 49	−19 ± 47
Correlation coefficient (%)	82* ± 12	72* ± 14
SVT (beats/min)	112 ± 82	111 ± 76
Slopes of Regressions of BP on Sine of Tilt Angle		
SBP (mm Hg)	6.0 ± 9.2	3.0 ± 8.5
DBP (mm Hg)	10.8 ± 7.8	10.8 ± 6.2
MBP (mm Hg)	8.7 ± 8.3	9.2 ± 7.1

*Significantly different between groups (*t* test, $p < 0.05$).
BP = blood pressure; SVT = sympathovagal transition; other abbreviations as in Table I.

cepts, and correlation coefficients, regarding the individual %LF on HR regressions, and the group means ± SD of the slopes of the individual regressions of the systolic, diastolic, and mean blood pressure on the sine of the tilt angle are listed in Table II. Of the %LF on HR regressions, only the means of the correlation coefficients differed significantly. No significant differences were found in the slopes of the regressions of blood pressure on the sine of the tilt angle.

The individual linear regressions of the systolic, diastolic, and mean blood pressure values on the sine of the tilt angle characterize the individual blood pressure responses to tilt. Such a response may be called hypotensive or hypertensive if the slope differs significantly from zero. In the 46 subjects that comprised the young adult group, the response appeared to be hypertensive in 14 (30%), 26 (57%), and 26 (57%) subjects for systolic, diastolic, and mean blood pressures, respectively; a hypotensive response was measured in 2 (4%) subjects for systolic blood pressure. In the 16 subjects that comprised the late middle-aged group, the response was hypertensive in 5 (31%), 11 (69%), and 9 (56%) subjects for systolic, diastolic, and mean blood pressures, respectively; no hypotensive responses were measured. The clinical criteria[9] for hyper- or hypotension were, however, never met.

DISCUSSION

Orthostatic load, blood pressure, and reflexes: The initial and maximal angle rate-pressure products in the young adult and the late middle-aged group did not differ significantly (Table I). It is noteworthy that, although the late middle-aged group reached, on the average, higher tilt angles than the young adult group, the self-limiting design of our protocol apparently led to a similar amount of orthostatic load in both groups. Also, the slopes in the mean blood pressure were not significantly different (Table II). On extrapolation to 90° tilt, mean blood pressure rises about 9 mm Hg. This pressure rise equals about half the hydrostatic pressure difference between the aortic and carotid baroreceptors in the upright position (assuming a difference in height of about 25 cm between both baroreceptor groups). Hence, our protocol of incremental orthostatic stress induced slight aortic baroreceptor loading plus slight carotid baroreceptor unloading in both study groups. Assumably, the reflex consequences of this combined loading and unloading are small, and gradual cardiopulmonary baroreceptor unloading by a decreasing central venous pressure, rather than net arterial baroreceptor loading/unloading, will have determined the autonomic responses. As the autonomic nervous system reacts reciprocally to such types of stimulus,[10] our protocol is most likely to induce a gradually decreasing vagal tone combined with a gradually increasing sympathetic tone.

There is ample evidence that the arterial and cardiopulmonary baroreflexes—vital parts of circulatory control by their buffering action—become less effective with age.[11–13] This decrease in functionality may be understood by appraisal of various related degenerative processes that have been found in the afferent, central, and efferent structures of the arterial and cardiopulmonary baroreflexes.[14–22] Obviously, such degenerative changes did not alter baroreflex efficacy in the late middle-aged subjects in our study to such an extent that the blood pressure responses in the young adult and the late middle-aged group differed (Table II).

Heart rate, heart rate variability, and the sympathovagal transition: The average correlation coefficient of the regression of %LF on HR was significantly lower in the late middle-aged group than in the young adult group (Table II). Possibly, the smaller amount of HR variability in the late middle-aged group, as expressed by smaller values of CV (Table I), causes more noise in the HR variability spectra, and hence in %LF. This had, however, no consequences for the value of the slope of the regression line, which determines the sympathovagal transition (see Methods section). The average values of the sympathovagal transition in the young adult and late middle-aged groups were almost equal (Table II).

There were no significant differences in HR (supine as well as at the maximal tilt angle) between the young adult and late middle-aged groups (Table I). However, several HR variability parameters differed significantly (Table I): CV, supine as well as at maximal tilt angle, and %LF at maximal tilt angle. Until now, interpretation of HR variability measures is somewhat speculative: validation with 2-stage pharmacologic autonomic blockade, the gold standard for sympathetic and vagal tone,[23–25] is lacking. This study relies on the sympathovagal transition, which relates only to HR variability insofar that it is assumed that %LF = 0 and %LF = 100 correspond to autonomic states in which there is no sympathetic or no vagal tone, respectively. Possibly, such an assumption is relatively safe. One more reason to emphasize the importance of the sympathovagal transition in the current study is the fact that it was computed by using the measurements made at all tilt angles. This causes the sympathovagal transition to be a more robust parameter than the initial or maximal-angle HR or HR variability values.

Conclusions: We compared the responses of 46 young adult men (20 to 35 years) and 16 late middle-aged men

(50 to 66 years) to incremental head-up tilt, by measuring HR, HR variability, and blood pressure, and by estimating the associated sympathovagal transition. We attempted to rule out possible interference of disease and deconditioning with aging[26] by studying healthy and physically active subjects. Ample research by others has shown that age affects virtually every measurable factor or mechanism in neurohumoral circulatory control. This might make the organism less resistant to sudden and strong changes in stress intensity, possibly because of the occurrence of over- and undershoot in HR and blood pressure. However, the smooth application of incremental head-up tilt evoked quite similar reactions in HR and blood pressure in the young adult, and in the late middle-aged group. Moreover, the identical values of the sympathovagal transition suggest similar autonomic dynamics in both groups. In conclusion, aging, per se, does not impair orthostatic defense under gradually increasing orthostatic stress.

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1. Shannon RP, Wei JY, Rosa RM, Epstein FH, Rowe JW. The effect of age and sodium depletion on cardiovascular response to orthostasis. *Hypertension* 1986;8:438–443.

2. McIntosh SJ, Lawson J, Kenny RA. Intravenous cannulation alters the specificity of head-up tilt testing for vasovagal syncope in elderly patients. *Age Ageing* 1994;23:317–319.

3. Bootsma M, Swenne CA, van Bolhuis HH, Chang PC, Manger Cats V, Bruschke AVG. Heart rate and heart rate variability as indexes of the sympathovagal balance. *Am J Physiol*1994;266:H1565–H1571.

4. Borst C, Wieling W, van Brederode JFM, Hond A, de Rijk LG, Dunning AJ. Mechanisms of initial heart rate response to postural change. *Am J Physiol* 1982;243:H676–H681.

5. Janssen MJA, Swenne CA. Advanced arrhythmia interpretation by batch driven postprocessing of QRS annotations and ST values as obtained with a commercial Holter analyzer. In: Computers in Cardiology 1991. Los Alamitos, CA: IEEE Computer Society Press, 1992:449–452.

6. Van Hoogenhuyze D, Weinstein N, Martin GJ, Weiss JS, Schaad JW, Sahyouni XN, Fintel D, Remme WJ, Singer DH. Reproducibility and relation to mean heart rate of heart rate variability in normal subjects and in patients with congestive heart failure secondary to coronary artery disease. *Am J Cardiol* 1991;68:1668–1676.

7. Di Rienzo M, Castiglioni P, Mancia G, Parati G, Pedotti A. 24-h Sequential spectral analysis of arterial blood pressure and pulse interval in free-moving subjects. *IEEE* 1989;36:1066–1075.

8. Bootsma M, Swenne CA, Bruschke AVG. Heart rate variability during repeated incremental head-up tilt discloses time dependence of individual autonomic dynamics. *Clin Cardiol* 1995; in press.

9. Wieling W. Non-invasive continuous recording of heart rate and blood pressure in the evaluation of neurocardiovascular control. In: Bannister R, Mathias C, eds. Autonomic Failure. A Textbook of Clinical Disorders of the Autonomic Nervous System. Oxford: Oxford University Press, 1992:291–311.

10. Kollai M, Koizumi K. Reciprocal and non-reciprocal action of the vagal and sympathetic nerves innervating the heart. *J Auton Nerv Syst* 1979;1:33–52.

11. Hajduczok G, Chapleau MW, Johnson SL, Abboud FM. Increase in sympathetic activity with age. I. Role of impairment of arterial baroreflexes. *Am J Physiol* 1991;260:H1113–H1120.

12. Hajduczok G, Chapleau MW, Abboud FA. Increase in sympathetic activity with age. II. Role of impairment of cardiopulmonary baroreflexes. *Am J Physiol* 1991;260:H1121–H1127.

13. Ebert TJ, Morgan BJ, Barney JA, Denahan T, Smith JJ. Effects of aging on baroreflex regulation of sympathetic activity in humans. *Am J Physiol* 1992;263:H798–H803.

14. Van Merode T, Brands PJ, Hoeks APG, Reneman RS. Faster aging of the carotid artery bifurcation in borderline hypertensive subjects. *J Hypertens* 1993;11:171–176.

15. Hajduczok G, Chapleau MW, Abboud FM. Rapid adaptation of central pathways explains the suppressed baroreflex with aging. *Neurobiol Aging* 1991;12:601–604.

16. Itoh H, Bunag RD. Age-related reduction of reflex bradycardia in conscious rats by catecholaminergic nucleus tractus solitarius lesions. *Mech Ageing Dev* 1993;67:47–63.

17. Tanabe S, Bunag RD. Aging escalates baroreceptor reflex suppression by the posterior hypothalamus in rats. *Hypertension* 1991;17:80–90.

18. Bursztyn M, Bresnahan M, Gavras I, Gravas H. Effect of aging on vasopressin, catecholamines, and alpha2-adrenergic receptors. *Geriatr Soc* 1990;38:628–632.

19. Feldman RD, Limbird LE, Nadeau J, Robertson D, Wood AJJ. Alterations in leukocyte β-adrenergic sensitivity in the elderly. *N Engl J Med* 1984;310:815–819.

20. Mader SL, Downing CL, Van Lunteren E. Effect of age and hypoxia on β-adrenergic receptors in rat heart. *J Appl Physiol* 1991;71:2094–2098.

21. Ferrari AU, Daffonchio A, Gerosa S, Mancia G. Alterations in cardiac parasympathetic function in aged rats. *Am J Physiol* 1991;260:H647–H649.

22. Ferrari AU. Modulation of parasympathetic and baroreceptor control of heart rate. *Cardioscience* 1993;4:9–13.

23. Smith ML, Hudson DL, Graitzer HM, Raven PB. Exercise training bradycardia: the role of autonomic balance. *Med Sci Sports Exerc* 1989;21:40–44.

24. Katona PG, McLean M, Dighton DH, Guz A. Sympathetic and parasympathetic cardiac control in athletes and non-athletes at rest. *J Appl Physiol* 1982;52:1652–1657.

25. Ribeiro JP, Ibanez JM, Stein R. Autonomic nervous control of the heart rate response to dynamic incremental exercise: evaluation of the Rosenblueth-Simeone model. *EurJAppl Physiol* 1991;62:140–144.

26. Lakatta EG. Changes in cardiovascular function with aging. *Eur Heart J* 1990;11(suppl C):22–29.