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Attenuated peripheral vasoconstriction during an orthostatic challenge in older men

JAN T. GROOTHUIS[1,2], DICK H. J. THIJSSEN[1], MIRIAM KOOIJMAN[1,2], REBECCA PAULUS[1], MARIA T. E. HOPMAN[1]

[1]Department of Physiology, Institute for Fundamental and Clinical Human Movement Sciences, Radboud University Nijmegen Medical Centre, 6500 HB, Nijmegen, The Netherlands
[2]Department of Rehabilitation Medicine, Sint Maartenskliniek, Nijmegen, The Netherlands

Address correspondence to: Maria T. E. Hopman, Department of Physiology (143), Radboud University Nijmegen Medical Centre, Geert Grooteplein-noord 21, PO Box 9101, 6500 HB Nijmegen, The Netherlands. Tel: (+31) 24 3613650; Fax: (+31) 24 3540535. Email: M.Hopman@fysiol.umcn.nl

Abstract

Background: orthostatic hypotension is common in older men and associated with morbidity and mortality. During orthostatic challenges, older men maintain their blood pressure by an augmented increase in total peripheral resistance. Changes in the leg vascular bed contribute importantly to blood pressure regulation during orthostatic challenges, partly because of blood pooling in the legs. Little is known about the contribution of the leg vascular bed to the augmented increase in total peripheral resistance.
Objective: to examine tilt-induced peripheral vasoconstriction in the leg vascular bed of young and older men.
Methods: we measured forearm and calf blood flow in 12 young and 12 older men, using venous occlusion plethysmography during 30° head-up tilt (HUT). Forearm and calf vascular resistance were calculated as mean arterial blood pressure divided by blood flow.
Results: during HUT, calf and forearm vascular resistance increased in older and young men. The increase in forearm vascular resistance was similar between older (40 ± 6%) and young men (51 ± 12%). However, the increase in calf vascular resistance was lower in older (96 ± 15%) than in young men (175 ± 30%).
Conclusion: advancing age leads to an attenuated tilt-induced increase in calf vascular resistance, which may contribute to age-related orthostatic hypotension.

Keywords: *ageing, blood flow, head-up tilt, sympathetic nervous system, vascular resistance, elderly*

Introduction

Orthostatic hypotension is a common feature with advancing age, with a prevalence ∼17% in persons aged 65 years and older [1, 2], and is associated with falls [2], cognitive decline [3], cardiovascular morbidity [4] and mortality [2, 5, 6].

During orthostatic challenges, venous blood is pooled in the lower limbs and abdomen, leading to a decreased venous return and a transient decrease in cardiac output and blood pressure. The drop in blood pressure activates the baroreflex, resulting in an increase in sympathetic activity. As a consequence, heart rate and vascular resistance are increased to restore cardiac output and blood pressure [7]. In contrast to young men, during an orthostatic challenge, older individuals demonstrate an attenuated cardiac output [8–10] which is compensated by an augmented increase in total peripheral resistance in order to maintain blood pressure [8–11].

Because venous blood pooling plays a major role during orthostatic challenges, changes in vascular resistance in the splanchnicus and lower limb vascular bed contribute importantly to the blood pressure regulation during orthostatic stress [7]. Minson *et al.* [11] demonstrated an augmented increase in splanchnic vascular resistance during head-up tilt (HUT) in older compared with young men, which may account for the age-related augmented increase in total peripheral resistance. In addition, the lower limb vascular bed is also an important contributor to blood pressure regulation during orthostatic challenges [7]. Nonetheless, changes in leg vascular resistance during an orthostatic challenge in older men have never been measured.

The purpose of this study was, therefore, to examine the tilt-induced peripheral vasoconstriction in the leg vascular bed of healthy young and healthy older men. We tested the hypotheses that the tilt-induced leg vasoconstriction is

Table 1. General characteristics of young and older men

	Young men ($n = 12$)	Older men ($n = 12$)
Age (years)	24 ± 1	71 ± 1*
Height (cm)	182 ± 2	175 ± 3
Body mass (kg)	73 ± 3	78 ± 3
Systolic BP (mmHg)	124 ± 3	131 ± 4
Diastolic BP (mmHg)	74 ± 2	77 ± 2
MAP (mmHg)	90 ± 2	95 ± 2

Values represent mean ± SEM.
BP, blood pressure; MAP, mean arterial blood pressure.
*Significantly different from young men.

augmented in older men compared with young men, and thereby contributing to the previously reported augmented tilt-induced increase in total peripheral resistance.

Methods

Subjects

Twelve healthy young (20–28 years) and twelve healthy older men (67–80 years) volunteered to participate in this study (Table 1). Subjects never smoked or stopped smoking at least 2 years ago. All subjects were normotensive (<140/90 mmHg), had no signs of varicose veins and were free of overt chronic cardiovascular diseases as assessed by medical history and physical examination and did not report orthostatic hypotension. None of the subjects used medication known to interfere with the cardiovascular system. Individuals with a ankle-brachial pressure index <0.90, and/or abnormalities in a 12-lead resting ECG were excluded. The study was carried out in accordance with the Declaration of Helsinki (2000) and approved by the medical ethical committee of our institution. All subjects gave written informed consent.

Experimental procedures and protocol

All subjects refrained from caffeine-containing food and beverages, vitamin C supplements and alcohol for at least 12 h prior to the experiment and refrained from heavy physical activity for at least 24 h prior to the experiment. Room temperature was controlled at 23 ± 1°C. After completing a health questionnaire, subjects were positioned comfortably on a tilt table in the supine position. The experimental procedures started after a supine resting period of at least 30 min.

First, baseline forearm and calf blood flow were measured for 5 min in the supine position. Subsequently, subjects were tilted manually, within 5 s, to a 5 min passive 30° HUT position in order to induce a significant cardiovascular response [12].

Measurements

Heart rate and arterial blood pressure were measured continuously using a non-invasive portable blood pressure device (Portapres, TNO, Amsterdam, The Netherlands). A finger cuff was attached to the middle phalanx of the left third finger in order to measure finger arterial blood pressure. Finger arterial blood pressure measurements accurately reflect intra-arterial blood pressure changes during orthostatic stress [13]. Data were collected during the experiment at a rate of 100 Hz. Mean arterial blood pressure (MAP) values were derived beat to beat, and heart rate was the inverse of the interbeat interval.

Blood flow in the forearm and calf was measured using venous occlusion plethysmography. In the supine position, the right arm and leg were supported to ensure that they were positioned ~5 cm above heart level. A standard blood pressure cuff (10 cm width) was placed around the right upper arm, and a 12 cm width occlusion cuff was placed just above the right knee. Mercury-in-silastic strain gauges (Hokanson, Inc., Bellevue, WA, USA) were placed at the widest girth of the right forearm and calf. Both cuffs were inflated simultaneously with a rapid cuff inflator (Hokanson, Inc., Bellevue, WA, USA), within 1 s, to 50 mmHg in the supine position [14] and to 65 mmHg in the 30° HUT position to correct for changes in hydrostatic pressure [15]. The occlusion pressure was sustained for 7 s after which the cuffs were deflated instantaneously (for 9 s). Venous occlusion plethysmography is suggested to requisite an empty venous system to guarantee full venous compliance. Recently, it was shown that venous occlusion plethysmography measurements of calf blood flow during supine and up to 30° HUT correlate well ($r^2 = 0.86$, $P < 0.001$) with superficial femoral artery blood flow measured with Doppler ultrasound [16]. This indicates that venous occlusion plethysmography during 30° HUT represents arterial inflow and is not significantly affected by venous compliance.

Data analysis

Blood flow (in ml/min/dl) was calculated from the slope of the volume change over a 4 s interval. To avoid artefacts, the initial first second was excluded from analysis. Vascular resistance was calculated as MAP divided by blood flow. For the calculation of vascular resistance, we assumed that venous pressure was approximately zero in the supine position. Furthermore, we assumed that hydrostatic pressure made an identical contribution to leg venous pressure as to leg arterial pressure during 30° HUT. Blood flow, vascular resistance, MAP and heart rate were averaged over the last 2 min of the supine and 30° HUT positions.

Statistical analysis

Results are expressed as mean ± SEM. A paired Student's *t*-test was used to determine the effect of 30° HUT in young and in older men, and an unpaired Student's *t*-test was used to compare the changes upon 30° HUT between young and in older men. The level of statistical significance was set at $\alpha = 0.05$.

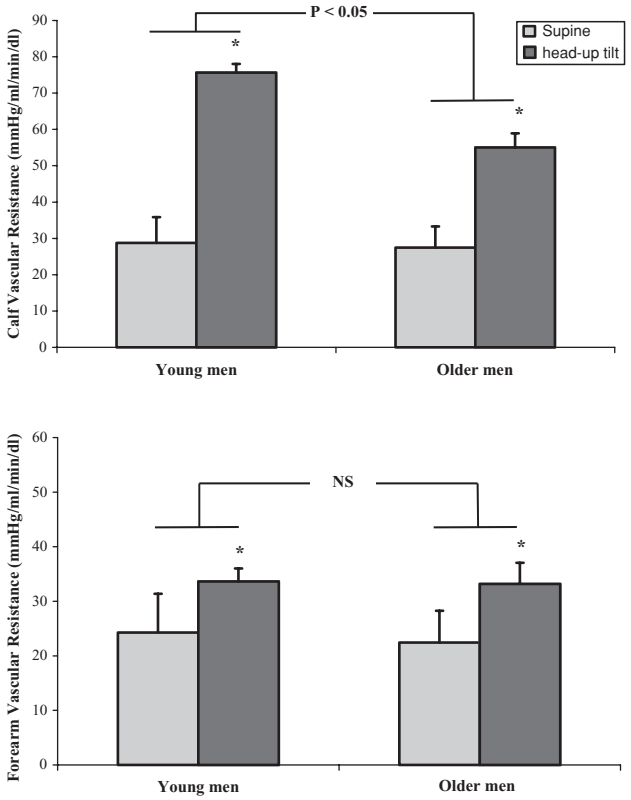

Figure 1. 30° head-up tilt-induced differences in calf and forearm vascular resistance in young and older men. Values represent mean + SEM. *Significantly different from supine; NS, not significantly different.

Results

No differences in physical characteristics between young and older men were present, with the exception of the significant age difference (Table 1).

Central cardiovascular responses

Young and older men demonstrated a significant increase in MAP during 30° HUT, which was significantly larger in young than in older men. During 30° HUT, heart rate increased significantly in young men only (Table 2).

Peripheral cardiovascular responses

In young and older men, calf and forearm blood flow demonstrated a significant decrease during 30° HUT, which were not different between both groups. Calf and forearm vascular resistance increased significantly during 30° HUT in young and older men. The increase in forearm vascular resistance was not different between both groups. However, the increase in calf vascular resistance was affected by age. A significantly larger increase in calf vascular resistance was found in young (175 ± 30%) compared with older men (96 ± 15%) (Table 2 and Figure 1).

Table 2. Central and peripheral parameters during supine and 30° head-up tilt (30° HUT) in young and older men

	Supine	30° HUT	*P*-value
Young men ($n = 12$)			
MAP (mmHg)	85 ± 4	92 ± 4	<0.001
Heart rate (bpm)	60 ± 2	66 ± 3	<0.001
Calf BF (ml/min/dl)	3.3 ± 0.4	1.4 ± 0.1	<0.001
Calf VR (mmHg/ml/min/dl)	28.8 ± 3.1	75.7 ± 8.7	<0.001
Forearm BF (ml/min/dl)	4.9 ± 0.8	3.7 ± 0.6	<0.001
Forearm VR (mmHg/ml/min/dl)	24.3 ± 4.2	33.7 ± 6.1	0.001
Older men ($n = 12$)			
MAP (mmHg)	87 ± 3	90 ± 3	0.010
Heart rate	61 ± 4	63 ± 4	0.326
Calf BF (ml/min/dl)	3.4 ± 0.2	1.9 ± 0.2	<0.001
Calf VR (mmHg/ml/min/dl)	27.5 ± 2.5	55.0 ± 7.9	<0.001
Forearm BF (ml/min/dl)	4.8 ± 0.6	3.5 ± 0.5	<0.001
Forearm VR (mmHg/ml/min/dl)	22.4 ± 2.9	33.2 ± 4.4	0.003

Values represent mean ± SEM.
MAP, mean arterial blood pressure; BF, blood flow; VR, vascular resistance.

Discussion

The major finding of the present study is that, in contrast to our hypothesis, an attenuated increase in calf vascular resistance during 30° HUT in older men is present compared with young men. The attenuated peripheral vasoconstriction in older men is present in the calf, but not in the forearm.

The lower limb vascular bed importantly contributes to the blood pressure regulation, especially during orthostatic stress [7]. Hence, our results suggest that the age-related attenuated vasoconstriction in the calf vascular bed may be part of the explanation of orthostatic hypotension in older men.

We did not find a difference in baseline vascular tone between young and older men, which is in agreement with some studies [17–19], but in contrast with others [20, 21]. Studies which reported no difference in vascular tone used plethysmography to measure calf [17, 18] or upper leg blood flow [19]. Interestingly, studies that reported a difference in leg vascular tone [20, 21] used Doppler ultrasound to measure whole leg blood flow. In contrast to plethysmography, Doppler does not correct for the differences in leg volume, which are likely to be present between these groups [22]. In addition, Fu *et al.* [18] found no difference in calf blood flow between older and young men, although a higher sympathetic activity level was present in older men. This suggests that sympathetic activity can be increased, without an attenuated calf blood flow.

The augmented increase in total peripheral resistance during orthostatic challenges with advancing age is a well-documented characteristic [8–11]. In these studies, total peripheral resistance was studied, including the splanchnic vascular bed that accounts for approximately one-third of the total peripheral resistance; we have assessed peripheral vascular responses of the calf and forearm that also account for approximately one-third of the total peripheral resistance. Minson *et al.* [11] demonstrated that older men increased their splanchnic vascular resistance to a greater extent than

young men during 60° HUT, which was hypothesised to be a compensation for the attenuated cardiac output and diminished the increase in vasoconstriction of the forearm vascular bed. In contrast, we found no differences in forearm vascular resistance in young and older men during 30° HUT. Interestingly, we demonstrated a lower ability to increase calf vascular resistance during 30° HUT in older compared with young men. Although a different tilt angle was used, this has no effect on leg blood flow [16]. The attenuated increase in calf vascular resistance, therefore, may initiate or contribute, at least partly, to the orthostatic intolerance observed in older men.

We can only speculate about the possible mechanisms that explain the attenuated vasoconstriction response in the calf during 30° HUT in older men compared with young men. Recently, Smith *et al.* [23] demonstrated that leg post-junctional α-adrenergic vasoconstrictor responsiveness to noradrenalin is reduced with advancing age, and thereby can impede sympathetic control of vascular resistance and negatively influence blood pressure control to orthostatic challenges. In young men, a larger response in the calf to α-adrenergic receptor stimulation is present than in the forearm [24]. Accordingly, it is possible that the lower limb is prone, especially with advancing age, to the reduction in α-adrenergic vasoconstrictor responsiveness and could explain the difference in a tilt-induced calf vascular resistance increase between older and young men.

Another possible explanation for the tilt-induced attenuated increase in calf vascular resistance could be the attenuated vasoconstrictor reserve [25] in advancing age, possibly caused by an increase in basal sympathetic activity [18, 26]. In other words, older men cannot increase their calf vascular resistance during an orthostatic challenge to the same extent as young men, who have a larger vasoconstrictor reserve.

In addition, arterial and venous blood vessel stiffening may contribute to the orthostatic hypotension in older men [2, 27]. Blood vessel stiffening with advancing age is associated with decreased baroreflex sensitivity [2, 28]. The attenuated heart rate response during orthostatic challenges in older men [8, 28], as present in our study, supports the decreased baroreflex sensitivity. In contrast, blood vessel stiffening could also blunt venous pooling and thereby limit the fall in venous return [27] during orthostatic challenges. However, since cardiac output in older men during orthostatic challenges is compromised [8–10], the vascular stiffening clearly is not sufficient enough to prevent venous pooling.

Another hypothesised mechanism is the decreased total blood volume in advancing age [29]. During orthostatic challenges, a translocation of blood into the compliant peripheral venous system occurs, leading to a decreased cardiac filling [7]. In older men the lower total blood volume could lead to a relatively exaggerated decrease in cardiac filling during orthostatic challenges.

The objective of the present study was not to elucidate the mechanism causing the differences in tilt-induced responses between young and older men, for this additional research is needed. Nonetheless, the attenuated increase in calf vascular resistance during 30° HUT in older men seems to be part of the explanation of orthostatic hypotension in older men.

Clinical relevance

Individuals who suffer from severe orthostatic hypotension can promote venous return and thereby raise cardiac output by applying physical counter-manoeuvres [2, 7, 30]. These physical counter-manoeuvres exist of leg crossing and/or leg muscle tensing, which are typically directed towards the lower limb vascular bed and have been demonstrated to be beneficial to counteract orthostatic hypotension. Based on our findings of an attenuated increase in calf vascular resistance in older men during 30° HUT, we suggest that applying these physical counter-manoeuvres could be helpful in counteracting orthostatic hypotension, especially with advancing age. Additional research is needed to evaluate the efficacy of these counter manoeuvres in the ageing population.

Conclusion

In conclusion, the present study demonstrates that 30° HUT leads to an attenuated increase in vascular resistance of the calf, but not of the forearm in older compared with young men. The lower ability to increase calf vascular resistance in older men during orthostatic challenges cannot explain the augmented total peripheral resistance during orthostatic challenges, but may be part of the explanation of orthostatic hypotension with advancing age.

Key points

- Older men have a lower ability to increase calf vascular resistance during HUT compared to their younger counterparts.
- Attenuated leg vasoconstriction during an orthostatic challenge in older men may be part of the explanation of orthostatic hypotension in older men.
- Applying physical counter-manoeuvres could be helpful in counteracting orthostatic hypotension in older individuals.

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Conflicts of interest

None.

References

1. Rutan G, Hermanson B, Bild D, Kittner S, LaBaw F, Tell G. Orthostatic hypotension in older adults. The Cardiovascular

Health Study. CHS Collaborative Research Group. Hypertension 1992; 19: 508–19.
2. Gupta V, Lipsitz LA. Orthostatic hypotension in the elderly: diagnosis and treatment. Am J Med 2007; 120: 841–7.
3. Elmstahl, S, Rosen I. Postural hypotension and EEG variables predict cognitive decline: results from a 5-year follow-up of healthy elderly women. Dement Geriatr Cogn Disord 1997; 8: 180–7.
4. Rose KM, Tyroler HA, Nardo CJ *et al.* Orthostatic hypotension and the incidence of coronary heart disease: the Atherosclerosis Risk in Communities study. Am J Hypertens 2000; 13: 571–8.
5. Luukinen H, Koski K, Laippala P, Kivela SL. Prognosis of diastolic and systolic orthostatic hypotension in older persons. Arch Intern Med 1999; 159: 273–80.
6. Masaki KH, Schatz IJ, Burchfiel CM *et al.* Orthostatic hypotension predicts mortality in elderly men: the Honolulu Heart Program. Circulation 1998; 98: 2290–5.
7. Smit AA, Halliwill JR, Low PA, Wieling W. Pathophysiological basis of orthostatic hypotension in autonomic failure. J Physiol 1999; 519: 1–10.
8. Laitinen T, Niskanen L, Geelen G, Lansimies E, Hartikainen J. Age dependency of cardiovascular autonomic responses to head-up tilt in healthy subjects. J Appl Physiol 2004; 96: 2333–40.
9. Shannon RP, Maher KA, Santinga JT, Royal HD, Wei JY. Comparison of differences in the hemodynamic response to passive postural stress in healthy subjects >70 years and <30 years of age. Am J Cardiol 1991; 67: 1110–6.
10. Youde J, Panerai R, Gillies C, Potter J. Reproducibility of circulatory changes to head-up tilt in healthy elderly subjects. Age Ageing 2003; 32: 375–81.
11. Minson CT, Wladkowski SL, Pawelczyk JA, Kenney WL. Age, splanchnic vasoconstriction, and heat stress during tilting. Am J Physiol 1999; 276: R203–12.
12. Matalon S, Farhi L. Cardiopulmonary readjustments in passive tilt. J Appl Physiol 1979; 47: 503–7.
13. Imholz BPM, 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.
14. Groothuis JT, van Vliet L, Kooijman M, Hopman MTE. Venous cuff pressures from 30 mmHg to diastolic pressure are recommended to measure arterial inflow by plethysmography. J Appl Physiol 2003; 95: 342–7.
15. Stewart JM. Pooling in chronic orthostatic Intolerance: arterial vasoconstrictive but not venous compliance defects. Circulation 2002; 105: 2274–81.
16. Kooijman M, Poelkens F, Rongen GA, Smits P, Hopman MT. Leg blood flow measurements using venous occlusion plethysmography during head-up tilt. Clin Auton Res 2007; 17: 106–11.
17. Leithe ME, Hermiller JB, Magorien RD, Unverferth DV, Leier CV. The effect of age on central and regional hemodynamics. Gerontology 1984; 30: 240–6.
18. Fu Q, Iwase S, Niimi Y *et al.* Age-related changes in vasomotor reflex control of calf venous capacitance response to lower body negative pressure in humans. Jpn J Physiol 2002; 52: 69–76.
19. Thijssen DH, Rongen GA, van Dijk A, Smits P, Hopman MT. Enhanced endothelin-1-mediated leg vascular tone in healthy older subjects. J Appl Physiol 2007; 103: 852–7.
20. Dinenno FA, Seals DR, DeSouza CA, Tanaka H. Age-related decreases in basal limb blood flow in humans: time course, determinants and habitual exercise effects. J Physiol (Lond) 2001; 531: 573–9.
21. Dinenno FA, Jones PP, Seals DR, Tanaka H. Limb blood flow and vascular conductance are reduced with age in healthy humans : relation to elevations in sympathetic nerve activity and declines in oxygen demand. Circulation 1999; 100: 164–70.
22. Frontera WR, Hughes VA, Fielding RA, Fiatarone MA, Evans WJ, Roubenoff R. Aging of skeletal muscle: a 12-yr longitudinal study. J Appl Physiol 2000; 88: 1321–6.
23. Smith EG, Voyles WF, Kirby BS, Markwald RR, Dinenno FA. Ageing and leg postjunctional alpha-adrenergic vasoconstrictor responsiveness in healthy men. J Physiol 2007; 582: 63–71.
24. Pawelczyk JA, Levine BD. Heterogeneous responses of human limbs to infused adrenergic agonists: a gravitational effect? J Appl Physiol 2002; 92, 2105–13.
25. Fu Q, Witkowski S, Levine BD. Vasoconstrictor reserve and sympathetic neural control of orthostasis. Circulation 2004; 110: 2931–7.
26. Kingwell B, Thompson J, Kaye D, McPherson G, Jennings G, Esler M. Heart rate spectral analysis, cardiac norepinephrine spillover, and muscle sympathetic nerve activity during human sympathetic nervous activation and failure. Circulation 1994; 90: 234–40.
27. Vaitkevicius PV, Fleg JL, Engel JH *et al.* Effects of age and aerobic capacity on arterial stiffness in healthy adults. Circulation 1993; 88: 1456–62.
28. Monahan KD, Dinenno FA, Seals DR, Clevenger CM, Desouza CA, Tanaka H. Age-associated changes in cardiovagal baroreflex sensitivity are related to central arterial compliance. Am J Physiol 2001; 281: H284–9.
29. Davy KP, Seals DR. Total blood volume in healthy young and older men. J Appl Physiol 1994; 76: 2059–62.
30. Ten Harkel AD, van Lieshout JJ, Wieling W. Effects of leg muscle pumping and tensing on orthostatic arterial pressure: a study in normal subjects and patients with autonomic failure. Clin Sci 1994; 87: 553–8.

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