Autonomic Response

Effects of Orthostatic Stress on Forearm Endothelial Function in Normal Subjects and in Patients With Hypertension, Diabetes, or Both Diseases

Marco Guazzi, Laura Lenatti, Gabriele Tumminello, and Maurizio D. Guazzi

Background: Sympathetically mediated vasoconstriction, to compensate for reduced venous return and cardiac output, characterizes the circulatory adaptation to head-up tilting (HUT). It has not been clarified whether this is coupled with a modulating endothelial vasorelaxation and whether diseases causing endothelial dysfunction, such as diabetes and hypertension, may impair this counterregulatory mechanism.

Methods: In patients with hypertension (group 1), diabetes (group 2), or both diseases (group 3) and in healthy control subjects (12 subjects per group) we investigated the brachial artery vasodilating response to the release of distal circulatory arrest (DCA) while they were supine and during 60° HUT.

Results: The supine increase in lumen was smaller ($P < .01$) in groups 1 (+4.5% ± 1.5%), 2 (+4.8% ± 1.4%), and 3 (+3.9% ± 1.3%) than in the control group (+8.6% ± 1.6%). Vasorelaxation by nitroglycerin was similar in each population. During HUT, the lumen response to DCA was enhanced ($P < .01$ supine) in control subjects (+15.4% ± 2.5%) and group 1 (+10.0 ± 2.4%) and was reduced ($P < .01$ supine) in groups 2 (+2.9% ± 0.5%) and 3 (+2.1% ± 0.4%), even though the hyperemic reaction to DCA was similar. The ratio of lumen changes to changes in flow (mm/mL/min × 1000) during reactive hyperemia to DCA increased ($P < .01$ supine) in control subjects (1.75 v 1.19) and group 1 (1.61 v 0.95), and decreased ($P < .01$) in groups 2 (0.62 v 0.87) and 3 (0.48 v 0.77).

Conclusions: The HUT posture is characterized by an increased endothelium-dependent, flow-mediated vasodilation as a possible modulator of the neural vasoconstriction. This effect is persistent but blunted in hypertension and is abolished in diabetes, either alone or in association with high BP. Thus, vasoconstrictor factors could remain unmodulated during an event such as orthostasis, making the risk posed by these disorders more critical. Am J Hypertens 2005;18:986–994 © 2005 American Journal of Hypertension, Ltd.

Key Words: Diabetes, endothelium, head-up tilt, hypertension.

It has been proved that for the maintenance of a physiological circulatory homeostasis, paracrine agents released by vascular endothelium significantly interact with the humoral and the neurogenic mechanisms. Exercise is one such example, being associated with an endothelium-mediated vasodilation despite the occurrence of intensive neurogenic vasoconstrictor activity. Orthostasis is another condition in which the neural control of circulation is predominant. Even though the cardiovascular regulation during orthostatic stress has been extensively investigated, exploration for a possible role for endothelium has long remained neglected. In a recent study performed in healthy subjects, we found an increase in flow-mediated brachial artery dilation during head-up tilting (HUT), which is consistent with an endothelium-dependent phenomenon. This suggests the possibility that for an optimal vascular adaptation to the upright posture in man, an endothelial–neural interplay may be required. A question that arises from this consideration is whether morbid conditions associated with endothelial dysfunction, such as high blood pressure (BP) and diabetes mellitus, may impair this endothelial modulating activity. The point is not of secondary importance because, in patients with these diseases, vasoconstrictor
factors could remain unmodulated during a condition—the assumption of the upright posture—that occurs countless numbers of times in an individual’s life. This may make more critical the cardiovascular risk associated with the systemic disorders.\textsuperscript{11,12}

The elucidation of these aspects was the aim of the present study. Healthy subjects, patients with hypertension or diabetes mellitus, and patients with both diseases to evaluate the possibility of an additive effect, were investigated.

**Methods**

**Study Population**

The study population consisted of 12 healthy subjects and equal numbers of patients with high BP (group 1), type 2 diabetes mellitus (group 2), or both diseases (group 3). Participants were matched for gender and approximate age, and none of them had taken part in previous studies in our laboratory. Their clinical characteristics are reported in Table 1. Written informed consent was obtained from each subject after explanation of the study’s nature and purposes. The protocol was approved by the hospital Ethics Committee for clinical research. General inclusion criteria were: age \( \leq 65 \) years (to limit the interference of aging with the endothelial function\textsuperscript{13}); life-long nonsmoking habit or smoking of \(< 10 \) cigarettes per day for \(< 10 \) years, abstinence from tobacco products for at least 9 months before enrollment,\textsuperscript{14} carboxyhemoglobin level not higher than 2%; absence of peripheral vascular or valvular heart diseases; no history of cerebral vascular disease, myocardial infarction, or unstable angina; no prescription of statins or other medications known to influence vascular function, with exception of conventional antihypertensive and antidiabetic therapies. Healthy volunteers selected as the control group were screened by clinical history, physical examination, routine chemical analyses, chest x-ray, and electrocardiography. None had evidence or history of diabetes mellitus, high BP, hyperlipemia, or any other systemic condition.

Patients with high BP alone (group 1) or high BP associated with diabetes (group 3) were enrolled if they had a clinical BP reading \( > 140/90 \) mm Hg (the average of three measurements in the sitting position after 15 min of rest, each performed on 3 separate days, with the diastolic pressure read as phase V of Korotkoff sounds), if they had a family history of high BP, and if they had no cause of secondary hypertension, according to the conventional criteria. The duration of hypertension averaged 6.5 \( \pm 2.7 \) years in group 1 and 5.9 \( \pm 3.2 \) years in group 3. One patient in group 1 and two patients in group 3 were not receiving antihypertensive treatment. The remaining patients had received one or more antihypertensive medications for at least 4 years before enrollment, and none was receiving \( \beta \)-blockers (Table 1). Treated patients were asked to discontinue all antihypertensive medications 2 weeks before the study, and during that period they were closely monitored for any evidence of accelerated hypertension (increase of diastolic pressure \( > 10 \) mm Hg). Patients in whom treatment withholding was deemed hazardous, mostly because of the poor response to the current therapy, were excluded from the study.

Diagnosis of diabetes mellitus was made according to the criteria of the Expert Committee on Diagnosis and Classification of Diabetes Mellitus.\textsuperscript{15} Patients with type 2

<table>
<thead>
<tr>
<th>Table 1. Characteristics of the study population</th>
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<tr>
<td><strong>Sex (male/female)</strong></td>
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<td><strong>Age (y)</strong></td>
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<td><strong>Body mass index (kg/m(^2))</strong></td>
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<td><strong>Serum glucose (mmol/L)</strong></td>
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<td><strong>Total cholesterol (mmol/L)</strong></td>
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<td><strong>LDL cholesterol (mmol/L)</strong></td>
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<td><strong>HDL cholesterol (mmol/L)</strong></td>
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<td><strong>Triglycerides (mmol/L)</strong></td>
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<td><strong>Glycosylated hemoglobin (%)</strong></td>
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<td><strong>Creatinine (( \mu \text{mol/L} ))</strong></td>
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<td><strong>Duration of diabetes (y)</strong></td>
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<td><strong>Duration of hypertension (y)</strong></td>
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<td><strong>Drug therapy distribution</strong></td>
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<td><strong>ACE inhibitors</strong></td>
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<td><strong>Diuretics</strong></td>
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<td><strong>Ca(^{2+}) channel blockers</strong></td>
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<td><strong>( \alpha )-Blockers</strong></td>
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<td><strong>Sulfonylurea</strong></td>
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<td><strong>Biguanide</strong></td>
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\* \( P < .01 \) v control subjects.
diabetes mellitus, either associated (group 3) or not associated with high BP (group 2), had stable weight and fasting glucose levels over a minimum of 4 weeks before enrollment. Diabetes control was achieved by diet alone in two patients in group 3 and by diet plus sulfonylurea or biguanide preparations in the other cases. Patients in groups 2 and 3 were not accepted if they had hypercholesterolemia (total cholesterol >6.2 mmol/L), hypertryglyceridemia (tryglycerides >2.3 mmol/L), macro- or microalbuminuria (two timed overnight samples), known diabetic retinopathy, clinically evident distal symmetric neuropathy, autonomic insufficiency (measured by variations in RR interval with cycled breathing and by the presence of a ≥20 mm Hg decrease of upright BP without a change in heart rate), or a glycosylated hemoglobin level ≥7% with treatment.

Vascular Studies

Vascular assessments were performed according to guidelines of the International Brachial Artery Reactivity Task Force. Based on the technique described by Celermajer et al imaging studies of the brachial artery were performed with a high resolution ultrasound Philips 11-MHz linear-array transducer (Philips Medical Systems, DA Best, The Netherlands) that was held at the same point throughout the scan by a stereotactic clamp. The monitored, nondominant arm was positioned at the heart level with the distal forearm supinated and immobilized by support encompassing the limb. After the clearest view of the brachial artery was found, the skin was marked and the arm was kept in the same position. Measurements included brachial diameter and flow velocity by pulsed Doppler with the range gate (1.5 mm) in the center of the artery. Images were obtained in the control state, during arrest of forearm circulation and during reactive hyperemia. Measurements were averaged. Analyses of images and measurements were performed by one of the investigators (G.T.) who was blinded to the sequence.

Blood flow was calculated by multiplying the velocity–time integral of the Doppler signal by the cross-sectional area of the vessel and heart rate. Flow-mediated dilation and reactive hyperemia were calculated as absolute variation in brachial artery diameter and flow at maximal hyperemia compared with baseline (maximal dilation and maximal hyperemia were coincident). The ratios of lumen variations to flow variations were also determined. Sources of variability were studied for baseline measurement of brachial artery diameter (BAD) and flow-mediated dilation (FMD), in the supine position (S) and during 60° HUT. For reproducibility, coefficients of variation were: BADS = 2.3, BAD 60° = 2.5, FMDS = 1.2, FMD 60° = 1.9. For repeatability, coefficients of variation were: BADS = 2.9, BAD 60° = 3.6, FMDS = 2.1, FMD 60° = 2.0.

HUT Procedure

Each subject was familiarized with the operation of the tilt-table and with the sensation of moving from horizontal to a 60° upright position. Tests were administered at least 3 days after familiarization. Beat-by-beat measurements of heart rate (HR) were obtained from an electrocardiogram; BP was monitored from the contralateral arm with the Dinamap system (Critikon, Tampa, FL), which computes BP for a period of 15 sec.

Protocols

All Studies Brachial artery diameter and flow velocity were obtained in the control state, during arrest of forearm circulation and during reactive hyperemia. Measurements were started after subjects had remained relaxed on the table, until the heart rate in consecutive min varied by ≤3 beats/min. A second scan was taken in the last 60 sec of distal circulatory arrest (DCA) and in the 90 sec immediately after cuff deflation, with measurements taken 30 sec before deflation and 15, 30, 60, and 90 sec after deflation.

Table 2. Heart rate and blood pressure in the supine position and during head-up tilting (HUT)

<table>
<thead>
<tr>
<th></th>
<th>Normal control subjects</th>
<th>Hypertensive patients (group 1)</th>
<th>Diabetic patients (group 2)</th>
<th>Patients with both diseases (group 3)</th>
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<tr>
<td><strong>Supine position</strong></td>
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<tr>
<td>Heart rate (beats/min)</td>
<td>68 ± 2.4</td>
<td>67 ± 3.1</td>
<td>69 ± 2.2</td>
<td>65 ± 2.0</td>
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<tr>
<td>Blood pressure (mm Hg)</td>
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<tr>
<td>Systolic</td>
<td>129 ± 3.1</td>
<td>166 ± 1.5*</td>
<td>127 ± 2.2</td>
<td>170 ± 2.2*</td>
</tr>
<tr>
<td>Diastolic</td>
<td>83 ± 2</td>
<td>99 ± 2.8*</td>
<td>82 ± 1.7</td>
<td>101 ± 1.9*</td>
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<tr>
<td><strong>60° HUT</strong></td>
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<td></td>
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<tr>
<td>Heart rate (beats/min)</td>
<td>81 ± 1.8†</td>
<td>79 ± 2.3†</td>
<td>85 ± 2.2†</td>
<td>84 ± 2.0†</td>
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<tr>
<td>Blood pressure (mm Hg)</td>
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<tr>
<td>Systolic</td>
<td>121 ± 1.7</td>
<td>163 ± 2.2†</td>
<td>120 ± 2.8</td>
<td>166 ± 1.9†</td>
</tr>
<tr>
<td>Diastolic</td>
<td>95 ± 2.2†</td>
<td>108 ± 16.4†</td>
<td>97 ± 1.7†</td>
<td>111 ± 2.3†</td>
</tr>
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* P < .01 v control subjects; † P < .01 v supine position.

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Protocol 1  These studies were performed to determine whether orthostatic displacement affects flow-mediated brachial artery vasodilation, compared with values in the horizontal position, and to determine the existence of any group difference in the responses to DCA in the two positions. The responses were determined by measuring brachial flow and lumen variations in the horizontal position, during the 60° HUT, in random order. A 30-min supine rest was allowed between the stimulus applications. At the end of these procedures, 0.3 mg nitroglycerin was administered sublingually,20 and brachial artery recordings were obtained again in the supine position and soon afterward at 60° HUT.

Protocol 2  These assessments were carried out in 16 participants selected randomly among patients and control subjects to determine whether systemic factors might have a role in the results. In these subjects, measurements were made in the dominant arm, whereas distal circulatory arrest was applied in the contralateral arm. Investigators performing vascular studies were blinded to patient status.

Statistical Analysis

Data are expressed as means ± SD. When appropriate, the comparisons were made by using paired or unpaired two-tailed t test, using the Bonferroni correction for multiple comparisons, one-way or two-way repeated-measures analysis of variance (ANOVA). A P value < .05 was considered significant.

Results

Control subjects and patients had, by selection, normal levels of triglycerides, total and LDL cholesterol, and normal renal function, and they were matched for gender and approximate age. Fasting blood sugar and glycosylated hemoglobin were higher in groups 2 and 3 than in group 1 and the control group (Table 1). As expected, BP in groups 1 and 3 was raised (Table 2).

Brachial Artery Lumen and Flow

Supine Position  Changes in brachial artery lumen induced by varying blood flow through the vessel were studied in all subjects in the supine position. Values of arterial diameter in the control state, during distal circulatory arrest, and after cuff deflation are reported in Fig. 1. In the control state, brachial diameter was similar among all four patient groups, and in each population diminished to a comparable extent with DCA. During reactive hyperemia, the increase in diameter was comparable in the three patient groups and was smaller (P < .01 by ANOVA) than in healthy subjects. Maximal dilation averaged 0.17 ± 0.02 mm in hypertensive patients, 0.16 ± 0.03 mm in diabetic patients, 0.15 ± 0.03 mm in patients with both diseases, and 0.34 ± 0.03 mm in healthy subjects.

Reactive hyperemia was less (P < .01 by ANOVA) in all patient groups compared with the healthy control subjects, and maximal increase (in milliliters per minute) averaged 141 ± 13 in group 1, 160 ± 40 in group 2, 153 ± 36 in group 3, and 204 ± 96 in the control subjects (Fig. 2). Differences among the patients groups were not significant. As shown in Fig. 3, the ratio of lumen changes to flow changes in the horizontal position in control subjects and group 1 were similar, and those in group 2 and 3 were reduced.

HUT Results  Brachial artery diameter and flow were measured after subjects had remained relaxed for at least 10 min on the table rotated to a horizontal angle of 60° (control state), during DCA, and after deflation of the occluding cuff. Compared with values in the supine position, the baseline brachial artery diameter showed a trend toward reduction with HUT (Fig. 1). With cuff deflation...
after 5 min of occlusion, brachial lumen increased more in the control group than in the patient groups ($P < .01$ by ANOVA). Compared with the supine position, head-up tilting was associated with a greater increase from the control state of the brachial artery lumen in healthy subjects ($+0.53 \pm 0.03$ mm, $P < .01$ vs vertical value of $+0.34 \pm 0.03$ mm) and in patients with high BP ($+0.40 \pm 0.02$ mm, $P < .01$ vs vertical value of $+0.17 \pm 0.02$ mm) and with a smaller increase of the arterial dimensions in patients with diabetes alone ($+0.12 \pm 0.01$ mm, $P < .01$ vs supine value of $+0.19 \pm 0.02$ mm) or with both diseases ($+0.10 \pm 0.01$ mm, $P < .01$ vs supine value of $+0.17 \pm 0.02$ mm). Remarkably, in control subjects and patients with high BP, the vessel diameter reached during reactive hyperemia in the upright position was significantly greater than the corresponding diameter in the horizontal position; on the contrary, it was significantly smaller in the presence of diabetes or both diseases (Fig. 1). In healthy subjects, reactive hyperemia was similar to that in each patient population; in fact, the increase in brachial artery flow (in milliliters per minute) averaged $272 \pm 43$ in control subjects, $260 \pm 40$ in patients with hypertension, $248 \pm 31$ in patients with diabetes, and $254 \pm 22$ in patients with both diseases (Fig. 2).

Figure 3 shows that in control subjects and in group 1 patients the ratio of changes in lumen to changes in flow during reactive hyperemia in the supine position and at 60° head-up tilting (HUT) was significantly increased with HUT compared with the horizontal position, and the pattern was the opposite in patients with diabetes or diabetes plus hypertension. The vasorelaxing effects of nitroglycerin in each patient population were similar to those in normal control subjects in the supine position and did not vary with upright displacement.

The 60° HUT was invariably associated with a significant increase in heart rate and diastolic BP, as compared with values in the horizontal position. As shown in Fig. 4, in normal subjects and in patients with hypertension alone, but not in patients with diabetes or diabetes plus hypertension, there was a significant correlation between increase in heart rate with HUT and increase in brachial artery dilation after DCA compared with values in the horizontal position.

Arterial Lumen and Flow in the Contralateral Arm Brachial artery diameter and flow were measured in the contralateral arm in 12 participants, who were randomly selected among control subjects and patients, during DCA and reactive hyperemia, in the horizontal and upright positions. Both DCA and hyperemia in the nondominant arm did not affect the brachial artery flow or diameter in the dominant arm.

![FIG. 2. Brachial artery flow in the control state (immediately before cuff inflation) and during distal circulatory arrest (30 sec before cuff release), and time course of reactive hyperemia (15, 30, 60, and 90 sec after cuff release) in the supine position and during head-up tilting (HUT) at 60°. Values in hypertensive patients (upper), diabetic patients (middle) and patients with both diseases (lower) are compared with those in normal control subjects. *$P < .01$ vs supine; #*$P < .01$ vs control subjects.](https://academic.oup.com/ajh/article-abstract/18/7/986/221433)
Discussion

This study confirms that in normal individuals there is an increased brachial artery vasodilation during post-ischemic hyperemia during orthostatic stress.\(^5\) It also shows that this effect is blunted or abolished in disorders associated with attenuation of the flow-mediated vasodilation in the supine position.

The first questions raised by these results are whether endothelial activation is part of the vascular adaptation to orthostatic displacement and whether its involvement in this response is limited by morbid conditions known to be associated with endothelial dysfunction, such as hypertension\(^6\)–\(^8\) and diabetes mellitus.\(^9,10\)

Use of flow-mediated vasomotion as an index of paracrine vasodilator release requires that the vasodilating stimulus (ie, flow) remains the same. Orthostatic displacement in normal subjects in this study, however, was associated with a significant increase in post-ischemic flow. Yet, flow-mediated vasodilation is inversely related to baseline arterial diameter,\(^21\) because paracrine agents, mainly nitric oxide, act as functional antagonists in vascular smooth muscle, and efficacy of relaxation depends on the preceding degree of activation of the contractile process. Theoretically, upright displacement, even if the associated brachial constriction is negligible, could affect the measured responses without a true impact on endothelial function. It is important to note, however, that in normal individuals the changes in ratio of diameter to flow during reactive hyperemia were significantly increased with HUT, reflecting vasodilating reactivity, for an increase in flow, greater than observed in the supine position. In addition, during HUT, post-ischemic changes in brachial artery diameter significantly exceeded changes in the horizontal position; and even though, 60 sec after cuff release, post-ischemic flow had reverted to values similar to those in the supine position, brachial artery diameter increase remained significantly greater. On the other hand, an intervention of ischemic metabolites and an increase in paracrine vasodilator sensitivity do not explain the HUT effects on the forearm vasomotor response, because arterial flow or caliber did not change in the contralateral arm, and results with nitroglycerin stimulation were unchanged.

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FIG. 4. Plot of changes in pulse rate vs changes in brachial artery vasodilation with orthostatic displacement in normal control subjects and in the three patient groups.
In our opinion, these considerations are valid enough to support the concept that an enhanced endothelial activity occurs as a physiologic response to upright displacement in human beings.

Compared with values in the horizontal position, there was an increase (even if significantly less than normal) in flow-mediated dilation with HUT in patients with high BP, and a decrease in patients with diabetes alone or with diabetes and hypertension. Sex, age, body mass index, serum cholesterol and triglyceride concentration, smoking habit, and reactive hyperemia to the release of DCA during vertical displacement in the three patient groups were similar to those in healthy subjects. During HUT, patients also showed no changes in flow or caliber of the contralateral brachial artery and in the vasomotor response to nitroglycerin. Yet, the orthostatic stimulus in hypertensive patients caused an increase in arterial diameter for an increase in flow that was greater than in the horizontal position but smaller than normal. In patients with diabetes alone or diabetes and hypertension, the increase in diameter for an increase in flow was reduced in the upright compared with the supine posture. Altogether, these observations point to the interpretation that the endothelial reaction during orthostatic stress is abnormal in patients with high BP, and even more in those with diabetes mellitus.

Another main point to be addressed in this study concerns of the mechanisms involved in the physiologic endothelial response to orthostasis and in the abnormalities associated with hypertension and diabetes. Because in normal individuals endothelial activation is present soon after HUT, our discussion is focused on factors that could affect the release of paracrine agents without delay after changes in posture. Theoretically, several features could be involved in the increased vasodilating response, such as an augmented flow velocity because of an enhanced cardiac contractility caused by cardiopulmonary receptor deactivation,22,23 cholinergic stimulation of the vascular endothelium, elicitation of a systemic adrenergic reflex, increase in pulse frequency, and shear stress–mediated NO release produced by tachycardia. Flow velocity, however, was reduced by vertical displacement, and cholinergic innervation of blood vessels in human forearm is apparently absent.24 On the contrary, a systemic adrenergic reflex and tachycardia hold the potential of stimulating release of endothelial paracrine agents.

First, the importance of the reflex sympathetic nervous reaction in maintaining BP during upright displacement is well established,25,26 and a forearm vasoconstriction with HUT has been described. In this study, the heart rate and diastolic BP increase is consistent with an adrenergic activation by baroreceptor unloading. Second, an interaction between the adrenergic nervous system and NO release and activity27,28,29 as well as an endothelium-dependent component of \( \beta_2 \)-adrenoceptor–mediated vasodilation in the human forearm28 have been described in several reports. The inhibition of peripheral sympathetic vasoconstriction has been proposed as an important mechanism of vasodilation mediated by NO,29 and an increase in adrenergic activity has been suggested to facilitate the vascular NO release, both by increasing shear stress and by stimulating direct agonistic activity.30 Similarly, the influences of adrenergic stimulation on endothelium during orthostatic stress might, at least in part, be mediated by changes in wall shear stress because of a higher pulse frequency.31,32 Hutcheson and Griffith31 have found that when a rat aortic preparation is perfused at low pulse pressure amplitudes, increases in pulse frequency (a hemodynamic situation reminiscent of that with HUT) were associated with vessel dilation, which was attenuated by NO synthase inhibition. Increases in pulse rate and in flow-mediated dilation with upright displacement in this study were related to each other in normal and hypertensive subjects, and not in diabetic subjects, in whom flow-mediated dilation in the upright position was depressed. This is significant, although it is hard to discern whether an increase in pulse frequency has a role or simply reflects an augmented adrenergic activity. Third, previous reports have repeatedly provided evidence that NO,27,28 prostaglandins,33 and endothelium-derived hyperpolarizing factor34 act in several ways as feed-back inhibitors of the sympathetic vasoconstrictor activity in a variety of models including the human forearm. Thus, a paracrine counter-regulatory activity, hypothetically related to the autonomic nervous system, could be viewed as a modulator of the neurally mediated vasoconstriction during orthostatic stimuli.

Among the factors that promote endothelial dysfunction in hypertensive and diabetic individuals, a decrease in NO synthesis34 or NOS bioactivity,35 or an increase in NO synthesis inhibition,36 superoxide anion production and oxidative stress,37,38 NO degradation,20,39 have been indicated. These same factors could impede the response to orthostasis in the same disorders. Diabetic subjects, however, showed a paradoxical response, namely, flow-mediated brachial artery dilation reduced by the upright displacement. The reasons are unknown. A possibility may be the release of vasoconstrictors, such as endothelin40 or angiotensin II. Hyperglycemia is critical in causing endothelial dysfunction, but in our patients glycemia was fairly well controlled. In regard to the hypothesis of an adrenergically mediated endothelial activation with orthostasis, it may be speculated that, in diabetes, endothelium has lost its responsiveness to this stimulus, thus causing imbalance in favor of the vasoconstrictor effect. The interpretation of an autonomic dysfunction producing a weaker endothelial activation, although reasonable, is not supported by clinical data. Diabetes presented with the same endothelial abnormalities also when associated with high BP, and no additive affect of the two diseases was evident.

A significant limitation of this study are that the hypothesis of the sympathetic system as an elicitor of endothelial activity during orthostatic stress has not been
probed with adrenergic receptor blockade (this was considered hazardous in individuals undergoing the orthostatic maneuver). Another limitation is that the recruited patients were not representative of hypertensive or diabetic populations at large. The possibility cannot be ruled out that subsets of individuals with hypertension or diabetes who were not represented in our study populations may have different responses.

In conclusion, this study shows that the physiologic vascular adaptation to orthostasis includes an increased endothelial responsiveness. This effect is persistent but blunted in high BP and is abolished in diabetes mellitus. In patients with these disorders, vasoconstrictor factors could remain poorly or totally unmodulated during an event, ie, orthostasis, which occurs countless numbers of times in an individual’s life, thus making more critical the cardiovascular risk associated with these disorders, and becoming a hypothetical link between risk factors and atherosclerosis burden.

References


