Tilt Test in Essential Hypertension

Differential Responses in Heart Rate and Vascular Resistance

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AND MICHEL E. SAFAR

SUMMARY Changes in hemodynamic parameters following 50-degree head-up tilt were studied in a population of 56 men, including 35 subjects with sustained essential hypertension and 21 age-matched normotensive controls. The increase in heart rate following tilt was similar in both groups and exhibited the same reduction in response with age. The increase in vascular resistance following tilt was strongly and positively correlated with both age and baseline vascular resistance. The latter finding was observed mainly in hypertensive subjects. The study provided evidence that differentiated responses of heart rate and vascular resistance may be observed following orthostasis. In both normal and hypertensive subjects, the age dependence of heart rate response possibly reflected differences in baroreceptor reflex control of parasympathetic and sympathetic activity. In hypertensive subjects, the vascular response was amplified with age and baseline vascular resistance, suggesting a role for structural changes of the vessels in the increased vascular response. (Hypertension 10: 29–34, 1987)

KEY WORDS • essential hypertension • baroreceptor reflex mechanisms • orthostasis

WHEN a normal person changes from the recumbent to the erect position, the central blood volume and heart volume are decreased and the cardiac output (CO) is reduced by about 20%.1–3 Diminished CO accompanying reduced peripheral resistance should result in a sharp fall in arterial pressure unless reflex cardioacceleration and vasoconstriction occur at the same time because of the baroreceptor reflex compensatory mechanisms.3 For that reason, baroreceptor reflex mechanisms may be adequately evaluated using passive tilting on a tilt table from the horizontal to the erect position,4–8 during which muscular pumping action of the legs9 is minimal or absent.

The mechanisms resulting in the changes in heart rate and systemic vascular resistance on standing are complex, involving baroreceptors of the high and the low pressure systems and even ergoreceptors in the skeletal muscles.3,10–15 Furthermore, adequate studies have emphasized possible differential responses between heart rate and vascular resistance in normal subjects and hypertensive patients.1 This disparity may result partly from a difference in innervation: baroreceptor reflex control of heart rate involves both the sympathetic and the parasympathetic systems, while control of vascular resistance exclusively reflects sympathetic activity.3,11,14 However, the possible role of such differences in the hemodynamic changes observed during orthostasis has been poorly investigated in patients with hypertension.

The purpose of the present study was to evaluate the hemodynamic changes observed during tilting in a population of normal and hypertensive subjects. Special emphasis was given to the evaluation of differential responses between heart rate and vascular resistance in the upright position.

Subjects and Methods

The study group comprised 35 men with sustained hypertension (mean age, 33 ± 10 years [± 1 SD]) and 21 normotensive men (mean age, 34 ± 9 years) in whom extensive clinical and laboratory investigations revealed no evidence of cardiovascular disease. Mean weight, height, and body surface area were, respectively, 66 ± 8 and 72 ± 10 kg (p < 0.05), 171 ± 7 and 173 ± 7 cm, 1.77 ± 0.12 and 1.85 ± 0.14 m² (p < 0.05). Sustained hypertension was defined as a...
diastolic pressure consistently greater than 100 mm Hg in the absence of therapy. All diagnoses were based on outpatient blood pressure recordings. Hypertensive subjects were either untreated or had discontinued therapy at least 1 month before the study.

All subjects were hospitalized for 6 days and placed on a diet containing sodium, 110 mEq/day. Investigations included determination of blood and urinary electrolytes, endogenous creatinine clearance, and, in hypertensive subjects, urinary catecholamines and timed intravenous pyelography. All hypertensive subjects were diagnosed as having essential hypertension, with no evidence of renal, neurological or cardiological involvement. All had regular sinus rhythm without evidence of left or right bundle branch block. The protocol was approved by the Institut National de la Santé et de la Recherche Médicale (INSERM). All subjects freely consented to the investigation after a detailed description of the procedures was given.

Hemodynamic Measurements and Tilt Test Technique

Hemodynamic indices were determined on the third day of hospitalization before intravenous pyelography. After overnight fasting, the subjects were brought to the hemodynamic laboratory without premedication. A percutaneous catheter was inserted through an antecubital vein into the right atrium for injection of indo-cyanine green dye and central venous pressure recording. A second catheter was inserted into the right brachial artery and positioned at the aortic root immediately distal to the aortic valves for measurement of intra-arterial pressure and withdrawal of blood for indicator-dilution curves. CO was measured at least twice with the subject in the supine position and during 3 and 5 minutes of 50-degree, weight-bearing, head-up tilt. Particular care was taken to ensure accurate blood pressure determinations by having the subject's arm extended, so that the pressure transducers, needles, and tubing were at the atrial level at all times. In addition, the pressure transducers were calibrated and referred to zero pressure during all supine, tilt, and posttilt testing. All tilt tests were performed at least twice with a 5-minute interval between tests. The first tilt was performed to provide a period of familiarization before the second tilt, in which the two CO determinations were made. The CO results were the mean value of these two CO measurements. The blood pressure response of the first tilt was never significantly different from that observed in the second tilt test. CO was determined by the Stewart-Hamilton method. Cardiac index was expressed as milliliters per minute per square meter by correcting for body surface area. Total peripheral resistance was calculated (dyn/sec·cm⁻²·m²) from the formula mean arterial pressure/cardiac index × 80. Cardiopulmonary blood volume (CPBV) was defined as the volume between the right atrium and the tip of the arterial catheter and was calculated by the Stewart-Hamilton method as follows: CPBV (ml/m²) = cardiac index (ml/sec/m²) × mean transit time (in seconds) from the right atrium to the tip of the arterial catheter. The correction for the sampling system was subtracted from the observed time in calculating mean transit time. Statistical Analysis

The significance of the differences between means ± 1 SD and paired averages of subjects between groups was determined by Student's t test, and the significance of means in each group between the initial and final examinations was determined by a paired t test. Correlation coefficients were calculated according to standard methods. A p value inferior to 0.05 was considered significant.

Results

Compared with normal subjects, hypertensive subjects had increased blood pressure, central venous pressure, and vascular resistance (p < 0.001) with normal values of cardiac index, heart rate, stroke index, and CPBV in both the supine and upright positions (Table 1). In both normal and hypertensive subjects, head-up tilt produced a significant increase in heart rate (p < 0.001) and vascular resistance (p < 0.001) and a significant decrease in cardiac index (p < 0.001), stroke index (p < 0.001), central venous pressure (p < 0.001), and CPBV (p < 0.001; see Table 1). Blood pressure did not change in normal subjects. In hypertensive subjects, systolic pressure did not change, while diastolic (p < 0.001) and mean arterial pressures (p < 0.01) increased slightly but significantly (see Table 1).

<table>
<thead>
<tr>
<th>Arterial pressure (mm Hg)</th>
<th>Normal subjects</th>
<th>Sustained hypertensive subjects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systolic</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Supine</td>
<td>126 ± 13</td>
<td>190 ± 35*</td>
</tr>
<tr>
<td>Upright</td>
<td>122 ± 17</td>
<td>188 ± 37*</td>
</tr>
<tr>
<td>Diastolic</td>
<td>78 ± 7</td>
<td>121 ± 20*</td>
</tr>
<tr>
<td>Supine</td>
<td>79 ± 9</td>
<td>128 ± 24*</td>
</tr>
<tr>
<td>Upright</td>
<td>94 ± 8</td>
<td>144 ± 24*</td>
</tr>
</tbody>
</table>

| Mean                      |                 |                               |
| Supine                    | 94 ± 11         | 148 ± 27*                    |
| Upright                   | 122 ± 12*       | 95 ± 13†                     |
| Stroke index (m/min/m²)   |                 |                               |
| Supine                    | 46 ± 9          | 43 ± 9                       |
| Upright                   | 33 ± 6†         | 30 ± 7†                      |
| Total peripheral resistance (dyne/cm⁻²·m²) | 2236 ± 479 | 3577 ± 870* |
| Cardiopulmonary blood volume (ml/m²) | 565 ± 112 | 568 ± 102 |
| Cardiopulmonary pressure (mm Hg) | 3.1 ± 1.6 | 5.1 ± 1.9* |
| Central venous pressure    |                 |                               |
| Supine                    | 0.4 ± 1.81      | 2.1 ± 1.6‡                   |
| Upright                   |                 |                               |

Values are means ± 1 SD.
* p < 0.001, † p < 0.01, compared with values in normotensive subjects.
‡ p < 0.001, † p < 0.01, compared with supine values.
The change in vascular resistance following tilting was significantly higher in hypertensive than in normal subjects: +888 ± 712 versus 319 ± 242 dyn/sec · cm⁻¹ · m² when expressed as an absolute value (p < 0.001) and +25 ± 18% versus +16 ± 12% when expressed as a percentage of change (p < 0.02). The decrease in cardiac index following tilting was similar in both populations: −530 ± 406 versus −602 ± 736 ml/min/m² and −16 ± 11 versus −12 ± 13% (NS). Changes in central venous pressure were also not significantly different between hypertensive and normal subjects.

The decrease in CPBV during tilt was negatively correlated with the baseline value of CPBV (Figure 1). Normal and hypertensive subjects followed the same curve. Similarly, the change in heart rate during tilt was negatively correlated with age (Figure 2). Normal and hypertensive subjects followed the same curve. In neither of the two groups were the changes in heart rate significantly correlated with baseline heart rate.

The change in vascular resistance (absolute value) during tilting was positively correlated with baseline vascular resistance in the overall population (r = 0.42, p < 0.001) and in hypertensive subjects (r = 0.46, p < 0.01) but not in normal subjects (Figure 3). In the latter, the lack of correlation was not due exclusively to the narrower range of baseline vascular resistance. When the change in vascular resistance was expressed as a percentage, the correlation was significant (p < 0.02) but negative (r = −0.50). The change in vascular resistance during tilting was positively correlated with age in hypertensive subjects (r = 0.39, p < 0.05) but not in normal subjects (Figure 4).

**Discussion**

In the present study, 50-degree upright tilt was used to evaluate the integrated response to orthostasis. Both redistribution of intravascular volume and changes in hemodynamic parameters following tilting were determined. Although the decrease in intrathoracic volume was of similar magnitude in normal and hypertensive subjects (see Figure 1), important differences were observed when the heart rate and vascular resistance responses were compared.

The increase in heart rate in the upright position was indeed similar in hypertensive and control subjects. However, the study of correlations reflected two characteristics. First, the increase was not correlated with the baseline heart rate. Second, the degree of cardioacceleration was markedly reduced with age (see Figure 2). Age-related differences in the heart rate response to postural, hypotensive, and other physiological stimuli have been extensively described in the literature. Heart rate changes during tilting have been shown to depend mainly on neural influences involving both parasympathetic withdrawal and sympathetic stimulation. Diminished β-adrenergic responsiveness with age has been described, but limitations in the lessening of parasympathetic tone are not so well recognized. In the past, some studies in patients with essential hypertension have even shown that the parasympathetic component of the heart rate response is little influenced by age. Finally, whatever the mechanisms may be, the age dependence of heart rate responses were quite similar in normal and hypertensive subjects (see Figure 2).
Changes in vascular resistance following tilt were quite different from those seen in heart rate. The increase in vascular resistance following tilt was significantly higher in hypertensive than in normal subjects. Furthermore, the study of correlations revealed two characteristics. First, the increase in vascular resistance in the upright position either was not correlated (normotensive subjects) or was positively correlated (hypertensive subjects) with age, indicating a clear dissociation between the influence of age on the baroreceptor reflex response of heart rate and vascular resistance. Second, the increase in vascular resistance following tilt was strongly correlated with the baseline value of vascular resistance. The finding was noted in the overall population, but mainly in hypertensive subjects, a point we shall examine in further detail.

It is well accepted that initial resistance can condition the magnitude of vasomotor responses to superimposed vasoconstrictor stimuli under various clinical and experimental conditions. According to the law of initial value, the increase in vascular resistance with tilting is expected to be lower in subjects with a higher baseline resistance, thus producing a negative relationship between baseline resistance and its change. Indeed, as shown by Wilder, "the outcome of an autonomic reaction depends on the already existing state of excitation of the autonomic nerves: the higher the state of excitation . . . prior to the influence exerted, the lower is the stimulatory, the stronger the inhibitor reaction." In the present investigation, the increase in vascular resistance following tilt was strongly correlated with the baseline value of vascular resistance in the overall population, in the group of hypertensive subjects but not in the group of normal subjects. In the latter group, the lack of significant correlation could not be due to the narrow range of vascular resistance. Such an interpretation does not fit with the negative correlation observed when the change in vascular resistance was expressed as a percentage. However, the dominant finding of our study was that the relationship
observed between baseline resistance and the change in vascular resistance during tilting was positive. The result does not fit with the simple law of initial value, and indicates that the magnitude of the increase in vascular resistance in the upright position was enhanced with the severity of hypertension. Since hypertrophy of the vessel wall is known to markedly amplify the changes in resistance that occur in response to smooth muscle contraction, the observed finding may suggest the contribution of such a structural component in the mechanisms of increased vascular resistance in hypertensive subjects. Indeed, in hypertensive humans, structural arteriolar changes have been noted on the basis of studies of both forearm vascular resistance at maximal dilatation and computer simulations resulting from introduction of clinical data into cardiovascular models of the circulation.

Although the relationship between initial resistance and the magnitude of its increase with tilting was significant in hypertensive subjects (see Figure 3), the correlation coefficient was relatively low, indicating that factors other than structural vascular changes could amplify the vascular response. Reduced \( \beta \)-adrenergic responsiveness with age may be responsible for a parallel increase in unopposed \( \alpha \)-adrenergic constriction. However, such an interpretation would require a negative correlation between vascular resistance and the magnitude of its change with tilting. An alternative hypothesis results from the possible role of mechanoreceptors in the low pressure system. Arterial baroreceptor control of the circulation is modulated by reflexes originating in cardiopulmonary receptors with vagal afferent pathways. Normally, these receptors exert an inhibitory influence on arterial baroreceptor reflex control of the cardiovascular system. Arterial baroreceptor-mediated circulatory effects increase when CPBV or pressure, or both decrease, as occurs during standing. Subsequently, removing the cardiopulmonary baroreceptor reflex inhibition of arterial baroreceptor centers favors an increase in sympathetic activity and vascular resistance. In our study, the decrease in central venous pressure and in CPBV following tilt was identical in normal and hypertensive subjects. The magnitude of the CPBV decrease was exclusively related to the baseline value of CPBV, with similar relationships in both groups of subjects (see Figure 1). Thus, it is possible that an increased inhibition of vasomotor centers by cardiopulmonary receptors could effectively exist in essential hypertension but this also cannot explain the amplification of the vascular response to standing in hypertensive subjects.

In conclusion, this study of the orthostatic baroreceptor reflex mechanisms showed differences in the heart rate and vascular response. In normal and hypertensive subjects, the heart rate responses were similar and equally influenced by age. The heart rate response decreased with age, whereas the vascular response increased with age. In addition, the increase in vascular resistance following tilting was amplified with the severity of hypertension, suggesting that arteriolar structural changes participated in the increased contraction of vessels.

Acknowledgment

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