The Effect of Age and Sodium Depletion on Cardiovascular Response to Orthostasis

RICHARD P. SHANNON, JEANNE Y. WEI, ROBERT M. ROSA, FRANKLIN H. EPSTEIN, AND JOHN W. ROWE

SUMMARY To test the hypothesis that normal age-related limitations in cardiovascular homeostasis may become clinically significant under stress, the cardiovascular response to postural change was assessed in six young and six old healthy subjects before and after modest diuretic-induced sodium depletion. Before diuresis, systolic blood pressure was maintained (from 110 ± 4 to 113 ± 6 mm Hg) while heart rate increased 22% (from 67 ± 2 to 82 ± 5 beats/min) at 3 minutes after 60-degree upright tilt in young subjects. After a significant diuretic-induced weight reduction and natriuresis, the young again maintained systolic blood pressure (from 110 ± 4 to 110 ± 6 mm Hg) and increased heart rate 49% (from 68 ± 2 to 101 ± 5 beats/min; p < 0.05, compared with prediuresis values) in response to the same postural stimulus. During the prediuresis tilt, the older subjects showed no change in systolic blood pressure (from 132 ± 4 to 134 ± 6 mm Hg) and a 9% increase in heart rate (from 68 ± 3 to 74 ± 2 beats/min). After a similar significant weight reduction and sodium loss, the older subjects showed a significant reduction in systolic blood pressure (from 132 ± 6 to 108 ± 6 mm Hg; p < 0.05) and a 17% increase in heart rate (from 69 ± 4 to 81 ± 3 beats/min; p < 0.05) during tilt compared with values in young subjects. Three of six elderly subjects noted postural symptoms. These results suggest that, although the healthy old may appear well compensated under optimal conditions, decreased cardiovascular reserve renders them susceptible to postural change following mild sodium depletion. (Hypertension 8: 438-443, 1986)

KEY WORDS • blood pressure • orthostasis • sodium depletion • cardioacceleration • postural stress • hypotension • baroreflex function • age

ALTHOUGH aging diminishes baroreceptor reflex response in humans,1,2 the clinical significance of the blunted baroreflex response in the healthy elderly remains uncertain. Some studies suggest that this diminished baroreceptor reflex activity renders the elderly susceptible to falls and orthostatic hypotension, generally defined as a reduction in blood pressure of at least 20 mm Hg of systolic and 10 mm Hg of diastolic pressure on assumption of upright posture.3,4 However, these studies have been confounded by inclusion of subjects with varying degrees of illness in addition to advanced age.

To test the hypothesis that the normal age-related limitation in cardiovascular homeostasis may become clinically significant under stress, we characterized the time course and magnitude of blood pressure and heart rate response to upright tilt in carefully screened, healthy, community-dwelling young and old volunteers before and after mild diuretic-induced sodium depletion.

Subjects and Methods

Six young (age, 23–35 years) and six old (age, 65–80 years) healthy, community-dwelling subjects participated in this study. Nine subjects were men and three were elderly women. Eleven subjects were white and one young subject was black. The protocol was approved by the Human Experimentation Committee of the Beth Israel Hospital, and all participants gave informed consent before the study. All were thoroughly screened by history, physical examination, labora-
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Tory studies (including complete blood counts, determination of electrolyte levels, serum glutamic oxaloacetic transaminase levels, alkaline phosphatase levels, total bilirubin concentration, and 24-hour urinary creatinine clearance), glucose tolerance test, and resting electrocardiogram. All were normotensive, apparently free of cardiovascular disease, and took no medications. All subjects were normally physically active; none were participating in regular cardiovascular training or aerobic exercise programs.

Subjects received instruction for a no-added-salt diet, which they were asked to initiate 3 days before admission. Subjects were then admitted to the Clinical Research Center where baseline body weight and serum electrolyte levels were determined. After resting quietly for 30 minutes in the supine position, the subjects underwent a standardized upright tilt to 60 degrees using the Circu-electric Bed (Stryker, Kalaramoz, MI, USA). The subjects were loosely strapped to the Stryker bed with their feet abutting a footboard. The tilt was entirely passive, although once upright, subjects were required to support their weight with their legs. Subjects were given notice just before tilt was initiated to avoid startling them. Heart rate was recorded continuously using lead II electrocardiographic recording, and blood pressure determinations were recorded at 60-second intervals using an automatic sphygmomanometer (Critikon Dinamapp Vital Sign Monitor, Model 1846; Tampa, FL, USA) with an oscillometric sensing method that compares favorably (0.8–1.8% error) with intra-arterial recordings. These variables were recorded for 3 minutes before tilting (basal) and at 1, 2, and 3 minutes after assumption of upright posture.

After completion of baseline studies, subjects began a supervised, isocaloric, 3-g sodium (7.5 g sodium chloride; i.e., no-added-salt) diet and received hydrochlorothiazide, 100 mg/day, po, for 2 days. A 24-hour urine collection was used to quantify sodium losses. Sodium loss was measured as the difference between daily 24-hour urinary excretion of sodium and the measured 3-g sodium intake. On the morning of the third day, subjects again underwent a tilt study as described. All studies were conducted between 0700 and 0900 after an overnight fast. Serum sodium and potassium concentrations were determined by the hospital clinical chemistry laboratory. In this study, we did not measure neurohumoral changes (vasopressin, renin, norepinephrine) because we were interested in the acute physiological response to a brief stimulus (3-minute tilt), and it is not clear that plasma neurohumoral levels are indicative of activity at the receptor site under such acute conditions.

The rate of cardioacceleration during the first 60 seconds after upright tilt was determined. To minimize the influence of respiratory variation, heart rate was calculated at 6-second intervals using the mean of five consecutive RR intervals measured around each sixth second (the first two RR intervals occurred before, the third coincided with, and the fourth and fifth RR intervals occurred after each sixth second). These patterns were analyzed by linear regression techniques. The slope of the relationship (ΔRR/Δt) over the first 18 seconds was compared with that of the period between 18 and 60 seconds in an effort to analyze the initial effects of parasympathetic withdrawal and sympathetic stimulation, respectively.

The changes in systolic and diastolic pressures, the magnitude of heart rate response, and the rate of cardioacceleration following postural provocation were analyzed for the influence of age and the effect of modest sodium depletion.

Results

In response to the 2-day diuresis, the young and old subjects experienced similar significant weight reductions: a mean of 2.1 (2.7%) and 1.8 kg (3.1%), respectively. This reduction was associated with similar urinary sodium losses (young, 182 ± 16; old, 166 ± 34 mEq/day) and net negative sodium balance (young, −54 ± 18; old, −41 ± 36 mEq/day). There was also a small but significant increase in serum albumin level and a small but significant decrease in sodium and potassium concentration of similar magnitude in both young and old subjects (Table 1).

To investigate the possibility that dietary salt restriction may have altered sodium balance and contributed to the sodium depletion observed after diuresis, four of the six young and four of the six elderly subjects underwent similar urine sodium measurements, made over 2 days while on a 3-g sodium restriction diet, but subjects received placebo instead of diuretics. Net sodium balance was actually positive (young, 18 ± 12; old, +43 ± 20 mEq/day), and sodium losses were significantly less compared with the postdiuresis values (young, 101 ± 18; old, 67 ± 20 mEq/day). Diet alone

<table>
<thead>
<tr>
<th>TABLE 1. Body Weight and Serum Sodium and Potassium Concentrations Before and After 2 Days of Diuretic Therapy in Old and Young Subjects</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Group</strong></td>
</tr>
<tr>
<td>---------</td>
</tr>
<tr>
<td>Young (n=6)</td>
</tr>
<tr>
<td>Old (n=6)</td>
</tr>
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<td></td>
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</tbody>
</table>

Values are means ± SEM.

* p < 0.001, † p < 0.01, compared with prediuresis values.
resulted in insignificant weight loss in both groups (young, 0.7 ± 0.4; old, 0.5 ± 0.3 kg), and there was no difference in the response of either group to 60-degree postural tilt under these conditions. Thus, diet restriction alone did not influence the cardiovascular response to orthostasis.

In the young subjects, systolic blood pressure did not change significantly during the postural stimulus before or after diuresis (Figure 1). There was a significant increase in resting diastolic pressure after diuresis (mean, 6 mm Hg) and further significant increases in diastolic pressure during the postdiuresis tilt (mean, 5–7 mm Hg), which were greater than those observed before diuresis (mean, 1–4 mm Hg; Table 2).

Resting heart rate in the young subjects was similar before and after diuresis (Table 3). Before diuresis, the young subjects showed a 22% increase in heart rate in the 3 minutes after tilt. This response was enhanced to a 49% posttilt increase after the diuretic-induced sodium loss.

The rate at which cardioacceleration (ΔRR/Δt) occurred in the young subjects was also examined (Table 4). Cardioacceleration during the first 18 seconds after tilt was greater after diuresis than before (Figure 2). The rate of cardioacceleration in the latter portion of the first minute was also greater after diuresis, but the difference did not reach statistical significance. Thus, the young subjects not only increased the magnitude of heart rate response to a postural stimulus, but did so quite abruptly after modest sodium losses. None of the young subjects showed symptoms during the tilt before or after diuresis.

Although resting systolic blood pressure was maintained during postural stimulus under basal (prediuresis) conditions in older subjects, there was a significant postural drop in systolic pressure after diuresis (mean, −22 mm Hg). Before diuresis, the old subjects demonstrated a significant increase in diastolic pressure (mean, +15 mm Hg) in response to tilt (see Table 2). After modest diuresis, although the old subjects still manifested an increase in supine resting diastolic pressure (mean, +6 mm Hg), they failed to mount a significant increase in diastolic pressure in response to tilt (see Figure 1).

Heart rate in the old subjects increased significantly in response to tilt under basal conditions and was further augmented after diuretic-induced sodium depletion.

Following equivalent sodium depletion, significant age differences became apparent in the cardiovascular response to tilt. In response to upright posture, the old subjects showed a marked decline in systolic pressure and failed to augment heart rate or cardioacceleratory response to the same degree as the young subjects. Figure 3 illustrates the age difference in the pattern and magnitude of RR interval changes. Under prediuresis conditions, the young subjects displayed substantial short-term variability in the rate of change of RR inter-

| Table 2. Blood Pressure Response to 60-Degree Upright Tilt Before and After Diuretic-Induced Volume Depletion in Six Old and Six Young Subjects |
|---------------------------|-----------------|-------------------|-------------------|-----------------|-----------------|-------------------|
|                           | Systolic (mm Hg) | Diastolic (mm Hg) |
|                           | Minutes after tilt | Minutes after tilt | Minutes after tilt |
| Group                     | −1   | 1     | 2     | 3              | −1   | 1     | 2     | 3              |
| Young                     |      |       |       |                |      |       |       |                |
| Prediuresis               | 110 ± 4 | 108 ± 6 | 109 ± 5 | 113 ± 6 | 69 ± 1 | 70 ± 4 | 73 ± 5 | 72 ± 4 |
| Postdiuresis              | 110 ± 4 | 109 ± 5 | 109 ± 4 | 110 ± 6 | 75 ± 2* | 83 ± 5 | 83 ± 5 | 80 ± 5† |
| Old                       |      |       |       |                |      |       |       |                |
| Prediuresis               | 132 ± 4 | 133 ± 4 | 134 ± 5 | 134 ± 6 | 68 ± 3 | 76 ± 4 | 75 ± 3 | 83 ± 2† |
| Postdiuresis              | 132 ± 6 | 112 ± 4 | 108 ± 6 | 115 ± 6† | 74 ± 2† | 74 ± 4 | 75 ± 4 | 79 ± 3 |

Values are means ± SEM.

*p < 0.05, compared with prediuresis values in young subjects; †p < 0.02, compared with values at −1 minute. ‡p < 0.02, compared with prediuresis values in old subjects.
TABLE 3. Heart Rate Response to 60-Degree Upright Tilt Before and After Diuretic-Induced Volume Depletion in Six Old and Six Young Subjects

<table>
<thead>
<tr>
<th>Group</th>
<th>Heart rate (beats/min)</th>
<th>% change over Minutes after tilt</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0-18</td>
<td>18-60</td>
</tr>
<tr>
<td>Young</td>
<td>Prediuresis</td>
<td>67 ± 2</td>
</tr>
<tr>
<td></td>
<td>Postdiuresis</td>
<td>68 ± 2</td>
</tr>
<tr>
<td>Old</td>
<td>Prediuresis</td>
<td>68 ± 3</td>
</tr>
<tr>
<td></td>
<td>Postdiuresis</td>
<td>69 ± 4</td>
</tr>
</tbody>
</table>

Values are means ± SEM. *p < 0.02, compared with postdiuresis values in old subjects; †p < 0.05, compared with prediuresis values in young subjects.

TABLE 4. Initial Heart Rate Response to Tilt and Change in RR Interval After 60-Degree Upright Tilt in Six Old and Six Young Subjects

<table>
<thead>
<tr>
<th>Group</th>
<th>ΔRR/Δt (msec/sec) 0-18 sec</th>
<th>ΔRR/Δt (msec/sec) 18-60 sec</th>
</tr>
</thead>
<tbody>
<tr>
<td>Young</td>
<td>Prediuresis</td>
<td>$-1.4 ± 1.2$</td>
</tr>
<tr>
<td></td>
<td>Postdiuresis</td>
<td>$-5.4 ± 0.6*$</td>
</tr>
<tr>
<td>Old</td>
<td>Prediuresis</td>
<td>$-2.28 ± 0.8$</td>
</tr>
<tr>
<td></td>
<td>Postdiuresis</td>
<td>$-3.4 ± 0.6*$</td>
</tr>
</tbody>
</table>

Values are means ± SEM. *p < 0.05, †p < 0.01, compared with prediuresis values; ‡p < 0.05, $ p < 0.01$, compared with postdiuresis values in young subjects.

Discussion

In the present study, healthy, community-dwelling elderly subjects demonstrated sufficient cardiovascular reserve to maintain blood pressure during a 60-degree upright tilt under basal conditions. After 2 days of modest sodium depletion, however, the elderly subjects uniformly showed significant declines in systolic pressure following postural provocation. The younger subjects were able to maintain blood pressure despite similar provocation. Thus, a limitation in blood pressure homeostasis was unmasked in healthy elderly subjects after a modest physiological stress.

Figure 2. Change in RR interval over time during the first 60 seconds after upright tilt (ΔRR/Δt). Single asterisk indicates significant difference compared with values in old subjects (p < 0.05) and with prediuresis values in young subjects (p < 0.05). Double asterisks indicate significant difference compared with values in old subjects (p < 0.01).

Figure 3. Influence of age and sodium depletion on RR interval during the first 60 seconds after upright tilt. Substantial variability in the rate of change in RR interval present in the young subjects’ response curve before diuresis (PRE) disappeared after mild sodium depletion (POST). The elderly group did not manifest such variability at any time.
Other studies have employed pharmacological manipulations of arterial pressure to assess cardiovascular response in the elderly. We chose to use the 60-degree upright tilt as a postural stimulus because it simulates more closely the physiological changes associated with orthostasis yet allows for a controlled, reproducible experimental condition. This sudden postural stimulus is an acute test of baroreflex function designed to defend against the moment-to-moment alterations in blood pressure imposed by forces such as gravity. Failure of this system to respond rapidly and adequately may predispose to syncope. We imposed a modest physiological stress, diuretic-induced sodium loss, to further test the functional reserve of the cardiovascular system. Although we did not measure fluid volume directly, the diuretic-induced negative sodium balance, coupled with the observed weight reduction and significant increase in serum albumin concentration, suggests a reduction in extracellular volume.

One possible explanation for the age-related differences in cardiovascular response is related to differences in the magnitude of the diuretic-induced sodium losses. Although the magnitude of weight reduction was equivalent between groups, it represented a slightly higher percent reduction in the elderly (3.2% vs 2.7%). However, net negative sodium balance was slightly less in the elderly subjects in response to diuresis. Thus, differences in stress were unlikely to account for the observed cardiovascular differences. The young subjects showed a trend toward increased diastolic pressure that did not reach statistical significance under basal conditions. Of interest is the low baseline diastolic pressure seen in the old subjects. The diastolic pressure did not fall in the elderly subjects after diuresis at a time when systolic pressure fell by as much as 20 mm Hg. This finding suggests that the diuretic-induced, orthostatic blood pressure change may not involve failure to vasoconstrict in these healthy elderly subjects.

Reductions in the extracellular sodium concentration may have contributed to the blunted cardiovascular response in the elderly subjects. Studies in animals have suggested that the carotid and aortic baroreceptors are sensitive to small changes in sodium concentration. However, there was no difference in the decline in sodium concentration between the two groups, and no data are currently available regarding the influence of senescence on baroreflex attenuation associated with decreased sodium concentration.

Age-related differences in heart rate response to postural, hypotensive, as well as other physiological stimuli have been well described. The present study also found a notable difference in rate of cardioacceleration during upright tilt. Under basal conditions, both groups showed similar rates of cardioacceleration during the early (0–18 seconds) and later (18–60 seconds) phases. After diuresis, the young subjects showed a significantly greater rate of cardioacceleration during both phases. It has been suggested that the initial phase of cardioacceleration depends on parasympathetic withdrawal, while subsequent increases involve sympathetic stimulation. Our data suggest that the elderly subjects showed a diminished response during both the initial and later stages. Diminished β-adrenergic responsiveness in the elderly is well described, but limitations in the withdrawal of parasympathetic tone are less well recognized, although this phenomenon has been observed in disease states such as diabetes mellitus and Chagas' disease.

The substantial variability in heart rate response in the young subjects (ΔRR/Δt), which disappeared after diuresis and was absent altogether in the old subjects, may relate to differences in intrinsic parasympathetic tone. Such age-related differences in heart rate variability have been noted with respiration. The parasympathetic system may be more prominent in the young under basal conditions but may be withdrawn rapidly in response to tilting after sodium depletion. The relative lack of variability in the elderly subjects suggests that the prompt withdrawal of parasympathetic tone is a less prominent feature of the cardiovascular response to postural stimulus in advanced age, even in the face of sodium depletion. The predominating influence of even weak, vagal activity over strong, sympathetic stimulation to cardioacceleration has been well described.

The clinical implications of these observations are important. First, the healthy elderly appear to be able to maintain their blood pressure against gravity under usual circumstances. This is accomplished by less reliance on heart rate and perhaps greater dependence on peripheral vasoconstriction, as manifested by the increase in diastolic pressure during tilting. It has been shown that the elderly are similarly less reliant on heart rate in their cardiovascular response to exercise but maintain cardiac output by augmenting end-diastolic volume. If extracellular sodium is diminished, dependence on Starling's mechanism may be compromised and cardiac output reduced. Thus, sodium depletion may be a particularly serious insult to the adaptive cardiovascular response to posture in the elderly. Second, the elderly are at greater risk of sodium and volume depletion due to age-related decreases in thirst, renin response, and urinary concentrating ability. The diuretic-induced sodium and volume changes in these subjects were mild and similar to those seen with diarrhea, vomiting, or short-term renal losses. Thus, the morbidity of such intercurrent illness may be compounded by unrecognized cardiovascular limitations unmasked by sodium depletion. This point underscores the importance of attention to weight and fluid balance in the sick elderly. Third, limitations in the cardiovascular response to posture may serve as a nonspecific stimulus to vasopressin release predisposing to hyponatremia, which is seen with increasing frequency in the elderly under the stress of illness or drugs such as diuretics.

Although further studies are needed to explore the possible mechanisms, our results provide support for
the view that age-related changes in adaptive cardiovascular capacity occur in the absence of disease and contribute to the vulnerability of the elderly to orthostatic symptoms.

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