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, 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. 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-
EFFECT OF AGE AND SODIUM DEPLETION ON ORTHOSTASIS/SHANNON ET AL.

TABLE 1. Body Weight and Serum Sodium and Potassium Concentrations Before and After 2 Days of Diuretic Therapy in Old and Young Subjects

<table>
<thead>
<tr>
<th>Group</th>
<th>Age (yr)</th>
<th>Time</th>
<th>Body weight (kg)</th>
<th>Albumin (g/dl)</th>
<th>Na⁺ (mEq/L)</th>
<th>K⁺ (mEq/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Young (n = 6)</td>
<td>31 ± 2</td>
<td>Prediuresis</td>
<td>74 ± 3</td>
<td>4.3 ± 0.2</td>
<td>142 ± 1.0</td>
<td>4.2 ± 0.1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Postdiuresis</td>
<td>72 ± 3*</td>
<td>4.6 ± 0.2*</td>
<td>137 ± 0.7</td>
<td>3.6 ± 0.1</td>
</tr>
<tr>
<td>Old (n = 6)</td>
<td>74 ± 4</td>
<td>Prediuresis</td>
<td>64 ± 5</td>
<td>3.9 ± 0.1</td>
<td>142 ± 0.7</td>
<td>4.4 ± 0.1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Postdiuresis</td>
<td>62 ± 5*</td>
<td>4.1 ± 0.1*</td>
<td>138 ± 0.6†</td>
<td>3.7 ± 0.1†</td>
</tr>
</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 (∆RR/∆t) 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 interval.

### Table 2. Blood Pressure 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>Systolic (mm Hg)</th>
<th>Diastolic (mm Hg)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Minutes after tilt</td>
<td>Minutes after tilt</td>
</tr>
<tr>
<td></td>
<td>−1</td>
<td>1</td>
</tr>
<tr>
<td>Young</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prediuresis</td>
<td>110 ± 4</td>
<td>108 ± 6</td>
</tr>
<tr>
<td>Postdiuresis</td>
<td>110 ± 4</td>
<td>109 ± 5</td>
</tr>
<tr>
<td>Old</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prediuresis</td>
<td>132 ± 4</td>
<td>133 ± 4</td>
</tr>
<tr>
<td>Postdiuresis</td>
<td>132 ± 6</td>
<td>112 ± 4</td>
</tr>
</tbody>
</table>

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 3 min</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Minutes after tilt</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Young</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prediuresis</td>
<td>67 ± 2</td>
<td>77 ± 3</td>
</tr>
<tr>
<td>Postdiuresis</td>
<td>68 ± 2</td>
<td>90 ± 2</td>
</tr>
<tr>
<td>Old</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prediuresis</td>
<td>68 ± 3</td>
<td>77 ± 3</td>
</tr>
<tr>
<td>Postdiuresis</td>
<td>69 ± 4</td>
<td>80 ± 5</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.

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.

vals with tilting (initial decrease followed by subsequent increase in RR interval during the first 18 seconds). These patterns were not apparent when sodium depletion was superimposed, and they were not observed in the elderly subjects under either circumstance. (This age difference is also noted in Table 4 as the difference in *ARR/Δt*.) After diuresis, there was less variability within young subjects as well as for the group as a whole.

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.
degree upright tilt as a postural stimulus because it is designed to defend against the moment-to-moment alterations in arterial pressure to assess cardiovascular response. In the elderly, such 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 vasococontract 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 posture, 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 complicated 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 non-osmotic 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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