Aging and cardiac responses to epinephrine in humans: role of neuronal uptake

Frans H. H. Leenen, Elizabeth Coletta, Anne Fourney, and Roselyn White

Hypertension Unit, Division of Cardiology, University of Ottawa Heart Institute, Ottawa, Ontario, Canada

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Leenen, Frans H. H., Elizabeth Coletta, Anne Fourney, and Roselyn White. Aging and cardiac responses to epinephrine in humans: role of neuronal uptake. Am J Physiol Heart Circ Physiol 288: H2498–H2503, 2005. First published December 30, 2004; doi:10.1152/ajpheart.00793.2004.—In healthy humans, ganglionic blockade unmask a clear age-related decrease in cardiac responses to isoproterenol but not to epinephrine. We postulated that an age-related decrease in neuronal uptake (which affects epinephrine but not isoproterenol) may offset a parallel decrease in β-receptor-mediated responses. To test this concept, nine young (mean 29 ± 2 yr) and eight older (mean 61 ± 2 yr) healthy subjects were infused on three different study mornings with epinephrine at increasing rates either alone or combined with desipramine to eliminate differences in neuronal uptake or with desipramine and trimetaphan to induce ganglionic blockade and thereby also eliminate differences in arterial baroreflex activity. Epinephrine caused the expected rate-related increases in systolic blood pressure, heart rate, stroke volume, ejection fraction, and cardiac index. Except for the systolic blood pressure, the extent of the changes was similar in young and older subjects. After desipramine, cardiac responsiveness to epinephrine was markedly enhanced, although more (P < 0.01) in young vs. older subjects for heart rate and cardiac index (+14 vs. 7 beats/min and +1.6 vs. 1.1 L·min⁻¹·m⁻², respectively, at 20 ng·kg⁻¹·min⁻¹). Combined with desipramine and trimetaphan, cardiac responses to epinephrine were further enhanced, again more (P < 0.01) in young subjects, resulting in large differences in heart rate and ejection fraction increases (+29 vs. 17 beats/min and +14 vs. 7%, respectively, at 20 ng·kg⁻¹·min⁻¹). Here, we show that “healthy aging” in humans is associated with decreased cardiac responsiveness to the β-agonist epinephrine; however, this decrease can be balanced by concomitant decreases in buffering of these responses by neuronal uptake and the arterial baroreflex.

Address for reprint requests and other correspondence: F. H. H. Leenen, Hypertension Unit, Univ. of Ottawa Heart Institute, H360, 40 Ruskin St., Ottawa, Ontario, Canada K1Y 4W7 (E-mail: fleenen@ottawaheart.ca).
humans and that such a decrease in neuronal uptake of epinephrine may balance the decrease in β-receptor-mediated responses. To test this hypothesis, we evaluated the effects of age on cardiac responses to intravenous infusion of epinephrine at increasing rates alone, combined with infusion of desipramine to eliminate possible differences in neuronal uptake, or combined with desipramine as well as trimetaphan to induce ganglionic blockade to also eliminate differences in arterial baroreflex activity.

METHODS

Subjects. Nine young normotensive subjects (age 23–38 yr, mean 29 ± 2 yr, 5 men and 4 women, 72 ± 5 kg body wt) and eight older normotensive subjects (age 55–73 yr, mean 61 ± 2 yr, 7 men and 1 woman, 71 ± 3 kg body wt) participated in the study. All subjects had a weight within 25% of their ideal body weight, and all were nonsmokers and had a normal history, physical examination, and biochemistry profile, including fasting blood sugar and lipid profile. The body mass index was 24.8 ± 1.0 kg/m² in the young and 23.3 ± 0.6 kg/m² in the older group. Only subjects with excellent-quality echocardiograms and normal left ventricular (LV) function were enrolled in the study. Older subjects also underwent a treadmill exercise test, and four were excluded because of a positive test for myocardial ischemia. None of the eight older subjects participating in the study, however, exhibited any evidence for myocardial ischemia during the infusions of epinephrine. The subjects were instructed to refrain from caffeine and alcohol 24 h before each study morning and to not use medications during the study. The study was approved by the Human Research Ethics Committee of the University of Ottawa Heart Institute, and written, informed consent of subjects was obtained.

Experimental protocol. The study was conducted on four study mornings at least 4 days apart. On the first morning, a run-in study protocol was used for infusion of the drugs, and BP was measured automatically in each forearm. A blood pressure (BP) cuff was applied to the arm not used for infusion of the drugs, and BP was measured automatically during the infusions of epinephrine. The subjects were instructed to refrain from caffeine and alcohol 24 h before each study morning and to not use medications during the study. The study was approved by the Human Research Ethics Committee of the University of Ottawa Heart Institute, and written, informed consent of subjects was obtained.

Analysis of data. Baseline hemodynamic parameters in the two groups of subjects were compared by unpaired t-test. The dose-response curves were analyzed by multivariate general linear model. After we tested the homogeneity of slopes, analysis of covariance was used to compare the group effect adjusted for the covariate (infusion rate). Variables with nonlinear responses were analyzed by ANOVA with repeated measures. A P value of <0.05 was considered statistically significant. Data are expressed as means ± SE.

RESULTS

Baseline hemodynamics and plasma catecholamines. Baseline hemodynamics are shown in Table 1, and plasma catecholamines are shown in Table 2.

The older subjects had somewhat higher resting BPs and lower resting heart rates on each of the 3 study days. Parameters of LV function did not differ significantly between the young and older subjects.

Desipramine increased BP and heart rate similarly in the two groups and caused only minor changes in LV function. This pattern of changes was similar for the two study days with desipramine, and the increases in BP persisted throughout the morning on the study day with desipramine alone.

Infusion of trimetaphan after desipramine caused a different pattern of change in young vs. older subjects. In young subjects, trimetaphan significantly lowered total peripheral resistance and markedly increased cardiac index with little change in BP. In the older subjects, trimetaphan caused a smaller decrease in total peripheral resistance, no change in cardiac index, and a clear decrease in (particularly systolic) BP. In the young subjects, the increase in cardiac index was due to a marked increase in heart rate, whereas LV volumes and stroke volume were decreased. In the older subjects, LV volumes and stroke volume decreased similarly, but heart rate showed a less marked increase compared with the young group.

Resting plasma norepinephrine was significantly higher in the older vs. young subjects on all three study days. Infusion of
versus older subjects on study morning 3

Table 1. Hemodynamic parameters at baseline and changes induced by infusions of desipramine and trimetaphan in young versus older subjects on study morning 3

<table>
<thead>
<tr>
<th></th>
<th>SBP, mmHg</th>
<th>DBP, mmHg</th>
<th>HR, beats/min</th>
<th>LVEDVI, ml/m²</th>
<th>LVESVI, ml/m²</th>
<th>SVI, ml/m²</th>
<th>EF, %</th>
<th>CI, l·min⁻¹·m⁻²</th>
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<tbody>
<tr>
<td><strong>Baseline</strong></td>
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<tr>
<td>Young (n = 9)</td>
<td>111 ± 1</td>
<td>63 ± 2</td>
<td>59 ± 3</td>
<td>70 ± 4</td>
<td>21 ± 2</td>
<td>49 ± 3</td>
<td>70 ± 1</td>
<td>2.9 ± 0.2</td>
</tr>
<tr>
<td>Older (n = 8)</td>
<td>127 ± 5*</td>
<td>71 ± 4*</td>
<td>51 ± 1*</td>
<td>76 ± 8</td>
<td>24 ± 6</td>
<td>52 ± 2</td>
<td>71 ± 4</td>
<td>2.6 ± 0.1</td>
</tr>
<tr>
<td><strong>Changes by desipramine</strong></td>
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<td></td>
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<tr>
<td>Young</td>
<td>9 ± 2</td>
<td>6 ± 2</td>
<td>4 ± 2</td>
<td>-1 ± 1</td>
<td>-1 ± 1</td>
<td>0 ± 2</td>
<td>1 ± 0</td>
<td>0.2 ± 0.1</td>
</tr>
<tr>
<td>Older</td>
<td>11 ± 3</td>
<td>3 ± 2</td>
<td>3 ± 1</td>
<td>-1 ± 2</td>
<td>1 ± 1</td>
<td>-2 ± 2</td>
<td>-2 ± 1</td>
<td>0.1 ± 0.1</td>
</tr>
<tr>
<td><strong>Changes by trimetaphan after desipramine</strong></td>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Young</td>
<td>1 ± 4</td>
<td>3 ± 3</td>
<td>39 ± 4</td>
<td>-13 ± 2</td>
<td>-3 ± 1</td>
<td>-10 ± 2</td>
<td>3 ± 2</td>
<td>0.7 ± 0.3*</td>
</tr>
<tr>
<td>Older</td>
<td>-19 ± 5*</td>
<td>-5 ± 2*</td>
<td>19 ± 4*</td>
<td>-15 ± 3</td>
<td>-4 ± 1</td>
<td>-11 ± 2</td>
<td>-1 ± 1</td>
<td>0.1 ± 0.1</td>
</tr>
</tbody>
</table>

Values are means ± SE, either as absolute values for the baseline or as changes induced by desipramine and trimetaphan. CI, cardiac index; DBP, diastolic blood pressure; EF, ejection fraction; HR, heart rate; LVEDVI, left ventricular end-diastolic volume index; LVESVI, left ventricular end-systolic volume index; SBP, systolic blood pressure; SVI, stroke volume index. *P < 0.05 young vs. older.

desipramine did not significantly affect resting plasma norepinephrine, whereas subsequent infusion of trimetaphan resulted in significant decreases of plasma norepinephrine in both groups. Resting plasma epinephrine tended to be higher in the older subjects. Infusion of desipramine and trimetaphan did not change plasma epinephrine levels.

Cardiac effects of epinephrine. Epinephrine alone caused the expected dose-related increases in systolic BP, heart rate, stroke volume, and cardiac index (P < 0.01 for all). The increase in stroke volume was related to minor increases in LV end-diastolic volume, a significant decrease in LV end-systolic volume, and therefore an increase in ejection fraction. The extent of the increases in heart rate (Fig. 1), stroke volume (Table 3), ejection fraction (Fig. 2), and cardiac index (Fig. 3) did not differ significantly between the young and older subjects. Only the increase in systolic BP (Table 3) was significantly less in the older vs. young subjects.

After desipramine, epinephrine caused a similar pattern of changes, but cardiac responsiveness was markedly enhanced (see Figs. 1–3). The extent of this enhancement was larger in young vs. older subjects for systolic BP, heart rate, LV end-diastolic volume, and cardiac index, but this was not different for ejection fraction and stroke volume. Epinephrine alone at 20 ng·kg⁻¹·min⁻¹ increased heart rate (Fig. 1) by 4 ± 1 vs. 6 ± 1 beats/min in young vs. older subjects, respectively; after desipramine, this was increased by 14 ± 3 vs. 7 ± 1 beats/min (P < 0.01). Cardiac index (Fig. 3) was increased at this rate by 0.5 ± 0.1 l·min⁻¹·m⁻² in both groups; after desipramine, this was increased by 1.6 ± 0.2 vs. 1.1 ± 0.2 l·min⁻¹·m⁻² in young vs. older subjects, respectively (P < 0.01).

Combined with desipramine and trimetaphan, cardiac responses to epinephrine were further enhanced, again more in young vs. older subjects, resulting in larger differences in the increases in heart rate and now also in ejection fraction. With combined blockade, epinephrine at 20 ng·kg⁻¹·min⁻¹ increased heart rate (Fig. 1) by 29 ± 3 vs. 17 ± 3 beats/min in young vs. older subjects, respectively (P < 0.01), and ejection fraction (Fig. 2) by 14 ± 2 vs. 7 ± 1% (P < 0.01). Both LV end-diastolic and end-systolic volumes now decreased in parallel (Table 3), although significantly (P < 0.01) more in young vs. older subjects (Table 3), whereas cardiac index (Fig. 3) now only tended to increase more in young vs. older subjects.

Table 2. Plasma catecholamines at baseline and changes induced by infusions of desipramine and trimetaphan in young versus older subjects

<table>
<thead>
<tr>
<th></th>
<th>Plasma Norepinephrine, pg/ml</th>
<th>Plasma Epinephrine, pg/ml</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Young (n = 9)</td>
<td>Older (n = 8)</td>
</tr>
<tr>
<td>Day 1 (baseline)</td>
<td>144 ± 27</td>
<td>30 ± 12</td>
</tr>
<tr>
<td>Day 2</td>
<td>153 ± 30</td>
<td>45 ± 20</td>
</tr>
<tr>
<td>Day 3</td>
<td>185 ± 44</td>
<td>30 ± 12</td>
</tr>
<tr>
<td>Change by desipramine</td>
<td>11 ± 15</td>
<td>14 ± 9</td>
</tr>
<tr>
<td>Change by desipramine + trimetaphan</td>
<td>-78 ± 18†</td>
<td>4 ± 6</td>
</tr>
</tbody>
</table>

Values are means ± SE, either as absolute values for the baseline or as changes induced by desipramine and trimetaphan. *P < 0.05, young vs. older; †P < 0.05 for change from baseline.

Changes in Heart Rate

![Fig. 1. Changes in heart rate in response to epinephrine either alone, after infusion of desipramine, or after infusion of desipramine and trimetaphan in young and older subjects. Values represent changes (means ± SE) from baseline.](http://ajpheart.physiology.org/DownloadedFrom)
subjects (by 1.3 ± 0.5 vs. 0.9 ± 0.3 l·min⁻¹·m⁻² at 20 ng·kg⁻¹·min⁻¹).

Epinephrine alone at infusion rates of 40 and 120 ng·kg⁻¹·min⁻¹ caused modest increases in plasma norepinephrine in both groups of subjects (Table 4). When combined with desipramine and trimetaphan, only minor changes were found. Infusion of epinephrine caused the expected dose-related increases in plasma epinephrine (Table 4). Plasma epinephrine concentrations tended to increase more in the older subjects after desipramine and in both groups of subjects when combined with desipramine and trimetaphan. The extent of the increases in plasma epinephrine levels showed only minor differences between young and older subjects.

**DISCUSSION**

The present study confirms our previous findings (26) that young and older subjects exhibit similar cardiac responses to intravenous infusion of epinephrine. As a significant new

### Table 3. Cardiac responses to epinephrine in young versus older subjects

<table>
<thead>
<tr>
<th>Agonist, ng·kg⁻¹·min⁻¹</th>
<th>ΔSBP, mmHg</th>
<th>ΔLV EDVI, ml/m²</th>
<th>ΔLV ESVI, ml/m²</th>
<th>ΔSVI, ml/m²</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Epi alone</td>
<td>Desip + Epi</td>
<td>Desip + Trim + Epi</td>
<td>Epi alone</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>0 ± 1</td>
<td>2 ± 2 (9)</td>
<td>-9 ± 2 (9)</td>
<td>-1 ± 3</td>
</tr>
<tr>
<td>20</td>
<td>-1 ± 2 (9)</td>
<td>4 ± 1</td>
<td>-7 ± 4 (8)</td>
<td>-1 ± 1</td>
</tr>
<tr>
<td>40</td>
<td>3 ± 1</td>
<td>16 ± 3 (8)</td>
<td>-11 ± 7 (7)</td>
<td>-2 ± 1</td>
</tr>
<tr>
<td>80</td>
<td>13 ± 2</td>
<td>29 ± 7 (7)</td>
<td>-11 ± 7 (7)</td>
<td>-4 ± 1</td>
</tr>
<tr>
<td>120</td>
<td>21 ± 3</td>
<td>5 ± 1</td>
<td>-12 ± 4</td>
<td>-3 ± 1</td>
</tr>
<tr>
<td>10</td>
<td>0 ± 1</td>
<td>2 ± 2 (8)</td>
<td>-4 ± 3 (8)</td>
<td>0 ± 1</td>
</tr>
<tr>
<td>20</td>
<td>-4 ± 2 (8)</td>
<td>-4 ± 3</td>
<td>-11 ± 7 (7)</td>
<td>0 ± 1</td>
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<tr>
<td>40</td>
<td>-5 ± 2</td>
<td>-2 ± 5</td>
<td>-11 ± 7 (7)</td>
<td>0 ± 1</td>
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<tr>
<td>80</td>
<td>-1 ± 3</td>
<td>6 ± 8 (7)</td>
<td>-11 ± 7 (7)</td>
<td>0 ± 1</td>
</tr>
<tr>
<td>120</td>
<td>9 ± 4</td>
<td>1 ± 2</td>
<td>-12 ± 4</td>
<td>0 ± 1</td>
</tr>
</tbody>
</table>

Values are means ± SE; numbers in parentheses are numbers of observations after SBP responses to the first dose unless stated otherwise. If the number of subjects for a given infusion rate decreased below 3, no mean value has been provided, but the individual observations were included for statistical analysis. Desipr, desipramine; Epi, epinephrine; Trim, trimetaphan. P values refer to differences in the changes by epinephrine in young vs. older.

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**Changes in Ejection Fraction**

Fig. 2. Changes in ejection fraction in response to epinephrine either alone, after infusion of desipramine, or after infusion of desipramine and trimetaphan in young and older subjects. Values represent changes (means ± SE) from baseline.

**Changes in Cardiac Index**

Fig. 3. Changes in cardiac index in response to epinephrine either alone, after infusion of desipramine, or after infusion of desipramine and trimetaphan in young and older subjects. Values represent changes (means ± SE) from baseline.
finding, the study demonstrates that aging does decrease intrinsic cardiac responses to epinephrine; however, this decrease may be compensated for by concomitant decreases in neuronal uptake and arterial baroreflex control of the heart.

**Cardiac responses to epinephrine.** The cardiovascular effects of epinephrine in humans have been well documented (11, 14). The present study confirms these effects, showing rate-related increases in systolic BP, heart rate, stroke volume, ejection fraction, and cardiac index. These hemodynamic effects by intravenous infusion of epinephrine represent the composite of several mechanisms. We previously demonstrated that β₂-receptors play a major role in the increase in heart rate caused by epinephrine, whereas effects on LV function appear to be mediated primarily via β₁-receptors (16). Besides direct postsynaptic β₁- and β₂-receptor stimulation, presynaptic β₂-receptor stimulation results in enhanced norepinephrine release and an increase in plasma norepinephrine (9, 19). On the other hand, activation of the arterial baroreflex by an increase in BP blunts the extent of the cardiac responses, particularly of heart rate and to a lesser extent of LV function (26). The extent and duration of these effects are influenced by the effectiveness of neuronal uptake, which, particularly in the heart, controls synaptic cleft concentrations of norepinephrine and, to a lesser extent, of epinephrine (4, 6–8). The present study provides new insights into the relative role of some of these mechanisms.

Ganglionic blockade by trimetaphan eliminates the arterial baroreflex buffering, which would enhance cardiac responses to epinephrine, whereas the resulting low sympathetic firing rates decrease the extent of presynaptic stimulation by epinephrine, leading to less cardiac and systemic norepinephrine release (9, 26) and thereby lower cardiac responses. On balance, removal of the inhibitory arterial baroreflex effects appears to predominate because, with ganglionic blockade, the cardiac responses to epinephrine become markedly enhanced (26).

Desipramine causes blockade of norepinephrine and epinephrine neuronal (re-)uptake (6); therefore, one may expect increased responses to exogenously administered epinephrine. Indeed, cardiac responses to epinephrine after desipramine were substantially enhanced with clear leftward shifts and higher “maxima” of the dose-response relationships for heart rate, ejection fraction, stroke volume, and cardiac index. On the other hand, desipramine causes inhibition of central sympathetic outflow (6), and the resultant lower sympathetic firing rate makes presynaptic stimulation less effective, likely explaining the absent increase in plasma norepinephrine by epinephrine after desipramine. Addition of trimetaphan to the desipramine effects will further eliminate sympathetic activity and indeed significantly lowered plasma norepinephrine, but it will also remove vagal regulation of cardiac function. In this setting, one may see the postsynaptic effects of epinephrine per se. The results further demonstrate the leftward shifts in the dose-response curves with marked increases, particularly in heart rate at low infusion rates, likely reflecting the absent buffering of vagal tone.

**Aging and cardiac responses to epinephrine.** Similar to the findings of our previous study (26), infusion of epinephrine caused fairly similar increases in heart rate, ejection fraction, stroke volume, and cardiac index in the young and older subjects. Only the increase in systolic BP was significantly less in the older group. Desipramine enhanced cardiac responses to epinephrine in both age groups, but this enhancement was significantly more pronounced in the young subjects for heart rate, LV end-diastolic volume, and cardiac index. These differences appeared at similar increases in plasma epinephrine concentrations in the two age groups. With combined desipramine and ganglionic blockade, differences between the two age groups became larger for heart rate and now also became apparent for ejection fraction. Together, these findings therefore suggest that decreases in both neuronal uptake and arterial baroreflex buffering offset the intrinsically decreased cardiac responsiveness to epinephrine in older subjects. At the particular age of the subjects studied (mean age of 61 yr), the impact of the age-induced changes in these mechanisms appears to offset each other. However, the age of onset of these mechanisms may vary, and the extent of the change may be influenced by further aging. The balance may therefore be different in younger (e.g., ~40–60 yr old) or older (e.g., ~70–90 yr old) subjects.

Larger cardiac responses to epinephrine in young vs. older subjects emerged after blockade of neuronal uptake by desipramine. One may conclude from this finding that aging decreases neuronal uptake of epinephrine and that therefore at the same infusion rate higher concentrations of epinephrine in the synaptic cleft compensate for an aging-induced decrease in postsynaptic β-receptor responsiveness. As such, this would be
a different conclusion than the one reached by Esler et al. (7). The present study reflects a functional evaluation of cardiac responses, which particularly for heart rate can be considered very accurate and sensitive. In contrast, the study by Esler et al. (7) was a kinetic study in small groups of subjects and may have missed modest but functionally important differences in neuronal uptake between young and older subjects. Alternatively, this finding may reflect a decrease in aging-induced neuronal uptake of norepinephrine, demonstrated by Esler et al. (8), if norepinephrine release as a result of presynaptic β-receptor stimulation by epinephrine plays a major role in the cardiac responses to epinephrine.

Previously, our group (26) showed that ganglionic blockade alone does not result in a differential cardiac response to epinephrine in young vs. older subjects. This and our previous study combined suggest that removal of the different buffering by the arterial baroreflex alone does not reveal significant differences in cardiac responsiveness to epinephrine by age but does so after blockade of neuronal uptake. It is not readily apparent why this may be so.

Limitations of study. Infusions of tritiated epinephrine at tracer doses together with the biologically active doses would have enabled correlations between the effects of aging on functional responses and on actual epinephrine kinetics. However, whole body kinetics do not reflect the heart (4, 7). Repeated invasive approaches would be needed to obtain specific cardiac kinetic data for the three study days, which is ethically difficult to justify. Trimetaphan was infused at rates up to 100 μg·kg⁻¹·min⁻¹. The actual degree of ganglionic blockade was not assessed, but the significant decreases in resting plasma norepinephrine and BP, as well as the increases in heart rate, are consistent with substantial ganglionic blockade.

In conclusion, the present study indicates that “healthy aging” in humans is associated with decreased cardiac responsiveness to the β-agonist epinephrine, but this decrease can be offset, even balanced, by concomitant decreases in buffering of these responses by neuronal uptake and the arterial baroreflex. It is tempting to speculate that aging-associated changes in these cardiovascular regulatory mechanisms do not happen to occur as co-phenomena but represent an integrated response to maintain cardiovascular homeostasis, particularly in response to stress.

GRANTS

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