Effects of age on cardiovascular responses to adrenaline in man

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Aims Whereas the effects of ageing on β-receptor mediated responses have been extensively studied in vitro and in vivo using the β-adrenoceptor agonist isoprenaline, little is known regarding ageing induced changes in responses to endogenous catecholamines. In the present study, we assessed age-related changes in cardiac responses to the endogenous β-adrenoceptor agonist adrenaline and the influence of age-related changes in arterial baroreflex function on these responses.

Methods Adrenaline alone was infused in 14 young subjects, age 30±2 years (eight males, six females), and 18 older subjects (six males, 12 females), age 60±2 years, and together with ganglionic blockade (trimetaphan) in seven young and 11 older subjects. Adrenaline was infused at 3–4 incremental rates, each rate for 8 min. Cardiac function was assessed by echocardiography.

Results Adrenaline alone, at infusion rates 20–160 ng kg⁻¹ min⁻¹ caused similar increases in heart rate in the two groups. In contrast, adrenaline caused larger increases in stroke volume, ejection fraction, cardiac index and systolic blood pressure and larger decreases in end-systolic wall stress and diastolic blood pressure in the young compared with older subjects. Older females exhibited the smallest increases in stroke volume index and ejection fraction. With concomitant ganglionic blockade, all above cardiovascular responses to adrenaline were similar in the young and older group. Plasma adrenaline increased similarly in the two groups.

Conclusions We conclude that ganglionic blockade does not unmask an age-related decrease in cardiovascular responses to adrenaline (in contrast to isoprenaline). A concomitant ageing induced decrease in neuronal uptake (which applies to adrenaline, but not isoprenaline) may explain such a differential effect.

Keywords: ageing, adrenaline, haemodynamics, adrenoceptor responsiveness, arterial baroreflex, gender

Introduction

Both in animals and in humans ageing is associated with a decrease in β-adrenoceptor mediated responses of the cardiovascular system [1]. Nearly all studies on the interaction of ageing and β-adrenoceptor mediated responses have employed the synthetic agonist isoprenaline. Little is known regarding the effects of ageing on the cardiovascular responses to the endogenous neurotransmitters noradrenaline and adrenaline. In the intact organism, several differences between isoprenaline and the endogenous catecholamines preclude extrapolation of findings obtained with isoprenaline to the endogenous agonists. In contrast to isoprenaline, both endogenous agonists have substantial α-receptor agonistic activity, both pre- and post-synaptically, which will influence the final haemodynamic responses. There are no consistent reports on an age-related decrease in α-adrenoceptor mediated vasoconstrictor responses [2], whereas presynaptic autoregulation of noradrenaline release via α2-adrenoceptors appears to decrease with age [2, 3]. Secondly, in contrast to isoprenaline endogenous catecholamines are taken up by the adrenergic nerve terminals [4]. This uptake represents one of the major mechanisms for removal of the endogenous agonists out of the synaptic cleft. Decreased/absent uptake will lead to higher effective concentrations in the synaptic cleft at similar rates of (endogenous) release or of exogenous infusion for the endogenous agonists but will not affect the concentrations of isoprenaline. Cardiac transplant patients have no cardiac neuronal uptake and this probably explains why, compared with control patients, they show increased cardiac responses to intravenous infusion of adrenaline but not of isoprenaline [5, 6]. Changes in cardiac neuronal uptake occur with ageing although these changes have not yet been assessed in humans. The rat heart shows a degeneration of sympathetic nerve terminals with ageing [7], as well as decreased neuronal uptake of noradrenaline [3, 8], although one study reported increased uptake [9].

In humans, only one study [10] has so far evaluated the effects of ageing on cardiovascular responses to the endogenous catecholamine adrenaline. In this study responses of blood pressure (BP), heart rate and leg vascular resistance to adrenaline at increasing infusion rates were evaluated in young and older healthy normotensive subjects. Plasma adrenaline concentrations achieved in the two groups were similar. Increases in heart rate, and decreases in diastolic BP
and leg vascular resistance were also similar. Only systolic BP showed a difference, i.e., an increase in the young, but not the older subjects, possibly indicating decreased inotropic responses in the elderly. However, cardiac function was not evaluated, nor whether differences in arterial baroreflex activity masked differences in responsiveness to adrenaline. Ageing decreases the buffering capacity of the arterial baroreflex [11, 13], and this difference between young and older subjects clearly determines the extent of the responses to a β-adrenoceptor agonist [e.g. 13]. In the present study, we therefore evaluated the effects of age on cardiac responses to adrenaline at increasing infusion rates without and with concomitant ganglionic blockade to eliminate differences in arterial baroreflex activity.

Methods

Subjects
Adrenaline without trimetaphan was administered to 14 young normotensive subjects (age 21–40 years, mean 30 ± 2; eight males and six females) and 18 older normotensive subjects (age 50–73 years, mean 60 ± 2; six males and 12 females). Of these subjects, seven young (four males/three females) and 11 older (five males/six females) received adrenaline with concomitant trimetaphan. All subjects had weight within 20% of the ideal body weight. They all had a normal history, physical examination and biochemistry profile. Only subjects with excellent quality echocardiograms were enrolled in the study. The subjects were instructed to refrain from caffeine and alcohol 24 h before each study morning and not to use any medication during the study. The study was approved by the Human Ethics Committee of the University of Ottawa and written informed consent was obtained. Most of the subjects were also infused with isoprenaline alone or combined with ganglionic blockade. The effects of age on cardiovascular responses to isoprenaline have already been reported [13]. For comparison, the heart rate response to isoprenaline has been presented in Figure 1.

Figure 1. Changes in heart rate in response to isoprenaline (b) or adrenaline (a) infusion with or without trimetaphan in young and older subjects. Values represent changes (mean ± S.E. mean) from baseline. Data on isoprenaline from White & Leenen [13]. Pre-trimetaphan (young ■ old □), Post-trimetaphan (young ● old ○).

Experimental protocol

Following a run-in study morning to acquaint the subjects with experimental procedures and personnel, on the first study-morning adrenaline alone was administered and on the second study-morning adrenaline with concomitant trimetaphan. Study mornings were at least 4 days apart. Each study-morning, following a standardized liquid breakfast the subjects remained supine until completion of the study. Two indwelling intravenous catheters were inserted, one in each forearm. A blood pressure cuff was applied to the arm that was not used for infusion and blood pressure was measured automatically with a Roche Arteriosonde (Roche Medical Electronics Inc., Cranbury, NJ). ECG electrodes were attached to measure heart rate by a Tektronic 414 monitor (Tektronic Inc, Beaverton, Oregon).

On the first study-morning, following a rest period of at least 60 min adrenaline was started at 20 ng kg \(^{-1}\) min \(^{-1}\) and increased to 40, 80, 120 or 160 ng kg \(^{-1}\) min \(^{-1}\) until the heart rate had increased by 20–25 beats min \(^{-1}\) or the diastolic blood pressure decreased by 15 mm Hg. Each dose was infused for 8 min. On the second study-morning, subjects were first titrated with trimetaphan (Arfonad). The latter was started at 20 ng kg \(^{-1}\) min \(^{-1}\) for 10 min, then increased to 50 ng kg \(^{-1}\) min \(^{-1}\) again for 10 min and subsequently increased to 100 ng kg \(^{-1}\) min \(^{-1}\). The rate was not further increased if the systolic BP decreased below 90 mm Hg. In the young subjects, two continued on normal history, physical examination and biochemistry profile. For comparison, the heart rate had increased by 20–25 beats min \(^{-1}\) or the diastolic blood pressure decreased by 15 min Hg. Each dose was infused for 8 min. On the second study-morning, adrenaline with concomitant trimetaphan. All subjects had weight within 20% of the ideal body weight. They all had a normal history, physical examination and biochemistry profile. Only subjects with excellent quality echocardiograms were enrolled in the study. The subjects were instructed to refrain from caffeine and alcohol 24 h before each study morning and not to use any medication during the study. The study was approved by the Human Ethics Committee of the University of Ottawa and written informed consent was obtained. Most of the subjects were also infused with isoprenaline alone or combined with ganglionic blockade. The effects of age on cardiovascular responses to isoprenaline have already been reported [13]. For comparison, the heart rate response to isoprenaline has been presented in Figure 1.

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Ageing and haemodynamic responses to adrenaline

Baseline and peak infusion rate, and measured according to Sole & Hussain [14].

Echocardiography

Echocardiograms were obtained in the supine position using a Toshiba 2-D sonographer SSH-60A. Tracings were recorded at 30 mm s$^{-1}$ paper speed. The measurements were made to the nearest millimetre on at least four cardiac cycles during quiet respiration and the results averaged for statistical analysis. The measurements were made by the same observer according to the guidelines of the American Society of Echocardiography. All echocardiograms were obtained by the same research assistant with the subject in the same position, and by the same observer in the same intercostal area, in the same left ventricular (LV) area, just below the tip of the ventral leaflets. The following parameters were measured or calculated: LV end-diastolic and end-systolic dimensions. The end-diastolic and end-systolic volumes were estimated by the cube function formula. The stroke volume index, cardiac index and left ventricular ejection fraction were calculated accordingly. The end-systolic pressure was estimated from the dicrotic notch pressure determined from a calibrated carotid pulse recording at baseline and peak infusion. The end-systolic stress was calculated as previously described [15].

Results

Baseline haemodynamics

Young and older subjects had similar resting heart rates and blood pressure. The young group had significantly larger LV end-diastolic, end-systolic and stroke volumes compared with the older group (Table 1). These differences were mainly a result of significantly larger volumes in younger males compared with older male or female subjects (Table 2). Trimetaphan decreased blood pressure, total peripheral resistance (TPR), LV volumes and stroke volume, but increased heart rate thereby maintaining cardiac index (Table 3). Heart rate increased more ($P<$0.05) in the young (from 60±2 to 83±4 beats min$^{-1}$) compared with older (from 64±2 to 70±3 beats min$^{-1}$) subjects.

Analysis of data

Baseline haemodynamic parameters in the two groups of subjects were compared by unpaired $t$-test. The dose-response curves were analysed by multivariate general linear model. After testing the homogeneity of slopes, analysis of covariance was used to compare the group effect adjusted for the covariate (infusion rate). Variables with non linear responses were analysed by ANOVA with repeated measures. A $P$ value less than 0.05 was considered statistically significant. The SYSTAT/SYGRAPH software (SYSTAT Inc., Evanston, IL) was utilized. Data are expressed as mean ± s.e. mean.

Blood pressure and cardiac effects of adrenaline alone

In response to increasing rates of adrenaline systolic BP increased more and diastolic BP decreased more in young compared with older subjects. Mean arterial pressure showed

Table 1 Haemodynamic changes in response to adrenaline

<table>
<thead>
<tr>
<th>SBP (mm Hg)</th>
<th>DBP (mm Hg)</th>
<th>MAP (mm Hg)</th>
<th>LVESVI (ml m$^{-2}$)</th>
<th>LVEDVI (ml m$^{-2}$)</th>
<th>CI (l min$^{-1}$ m$^{-2}$)</th>
<th>LVET (ms)</th>
<th>MNSER (l min$^{-1}$)</th>
<th>ESS (mm Hg)</th>
<th>P value</th>
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<tbody>
<tr>
<td>Baseline</td>
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<tr>
<td>Young (14)</td>
<td>111 ± 3</td>
<td>75 ± 2</td>
<td>87 ± 2</td>
<td>81 ± 2</td>
<td>21 ± 1</td>
<td>3.6 ± 0.2</td>
<td>0.33 ± 0.01</td>
<td>2.3 ± 0.1</td>
<td>&lt;0.01</td>
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<td>Old (18)</td>
<td>159 ± 3</td>
<td>99 ± 2</td>
<td>105 ± 3</td>
<td>14 ± 2</td>
<td>3.3 ± 0.2</td>
<td>0.38 ± 0.01</td>
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<td>91 ± 3</td>
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<td>Adrenergic dose (ng kg$^{-1}$ min$^{-1}$)</td>
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<tr>
<td>20 (14)</td>
<td>1 ± 1</td>
<td>−6 ± 2</td>
<td>−4 ± 1</td>
<td>1 ± 1</td>
<td>−3 ± 1</td>
<td>0.5 ± 0.1</td>
<td>−0.01 ± 0.01</td>
<td>0.2 ± 0.1</td>
<td>&lt;0.01</td>
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<td>40 (14)</td>
<td>3 ± 1</td>
<td>−9 ± 2</td>
<td>−5 ± 2</td>
<td>2 ± 2</td>
<td>−6 ± 1</td>
<td>1.0 ± 0.1</td>
<td>−0.02 ± 0.01</td>
<td>0.4 ± 0.1</td>
<td>&lt;0.01</td>
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<tr>
<td>80 (14)</td>
<td>13 ± 2</td>
<td>−13 ± 2</td>
<td>−4 ± 2</td>
<td>3 ± 2</td>
<td>−9 ± 1</td>
<td>1.5 ± 0.2</td>
<td>−0.03 ± 0.01</td>
<td>0.6 ± 0.1</td>
<td>&lt;0.01</td>
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<tr>
<td>120 (13)</td>
<td>21 ± 2</td>
<td>−14 ± 2</td>
<td>−3 ± 1</td>
<td>4 ± 2</td>
<td>−10 ± 1</td>
<td>1.9 ± 0.2</td>
<td>−0.04 ± 0.01</td>
<td>0.8 ± 0.1</td>
<td>&lt;0.01</td>
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<td>160 (13)</td>
<td>28 ± 3</td>
<td>−14 ± 3</td>
<td>−1 ± 2</td>
<td>7 ± 2</td>
<td>−10 ± 1</td>
<td>2.3 ± 0.3</td>
<td>−0.05 ± 0.01</td>
<td>0.9 ± 0.1</td>
<td>&lt;0.01</td>
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<td>P value</td>
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<td>20 (10)</td>
<td>0 ± 1</td>
<td>−4 ± 1</td>
<td>−3 ± 1</td>
<td>−1 ± 1</td>
<td>−2 ± 1</td>
<td>0.5 ± 0.1</td>
<td>−0.01 ± 0.01</td>
<td>0.2 ± 0.1</td>
<td>&lt;0.01</td>
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<td>40 (10)</td>
<td>4 ± 2</td>
<td>−7 ± 2</td>
<td>−3 ± 1</td>
<td>1 ± 1</td>
<td>−4 ± 1</td>
<td>0.7 ± 0.1</td>
<td>−0.03 ± 0.01</td>
<td>0.4 ± 0.1</td>
<td>&lt;0.01</td>
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<tr>
<td>80 (10)</td>
<td>11 ± 2</td>
<td>−9 ± 2</td>
<td>−2 ± 1</td>
<td>2 ± 1</td>
<td>−5 ± 1</td>
<td>1.3 ± 0.2</td>
<td>−0.04 ± 0.01</td>
<td>0.6 ± 0.1</td>
<td>&lt;0.01</td>
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<tr>
<td>120 (10)</td>
<td>17 ± 2</td>
<td>−8 ± 1</td>
<td>−0 ± 1</td>
<td>4 ± 2</td>
<td>−5 ± 1</td>
<td>1.6 ± 0.2</td>
<td>−0.05 ± 0.01</td>
<td>0.7 ± 0.1</td>
<td>&lt;0.01</td>
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<tr>
<td>160 (10)</td>
<td>23 ± 3</td>
<td>−8 ± 2</td>
<td>−2 ± 2</td>
<td>2 ± 2</td>
<td>−8 ± 1</td>
<td>1.6 ± 0.3</td>
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<tr>
<td>P value</td>
<td>&lt;0.01</td>
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</tbody>
</table>

SBP=systolic blood pressure; DBP=diastolic blood pressure; MAP=mean arterial pressure; LVEDVI=left ventricular end-diastolic volume index; LVESVI=left ventricular end-systolic volume index; CI=cardiac index; LVET=left ventricular ejection time; MNSER=mean normalized systolic ejection rate; ESS=end-systolic stress.

Number of observations after each dose. Data are mean ± s.e. mean. $P$ values refer to differences in baseline or to differences in the changes by adrenaline in young vs. old.
Max (140 ± 40 ng kg⁻¹ min⁻¹) and peak infusion for male and female subjects.

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Participants</th>
<th>Adrenaline Dose (ng kg⁻¹ min⁻¹)</th>
<th>HR (beats min⁻¹)</th>
<th>SBP (mm Hg)</th>
<th>MAP (mm Hg)</th>
<th>LV EDVI (ml m⁻²)</th>
<th>LV ESVI (ml m⁻²)</th>
<th>EF (%)</th>
<th>CI (l min⁻¹ m⁻²)</th>
<th>MNSER (µl dyn cm⁻¹)</th>
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<tbody>
<tr>
<td>Young</td>
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<tr>
<td>Young male</td>
<td>10</td>
<td>59 ± 2</td>
<td>114 ± 3</td>
<td>79 ± 2c</td>
<td>86 ± 1b,c</td>
<td>23 ± 2</td>
<td>63 ± 4b,c</td>
<td>74 ± 1c</td>
<td>3.7 ± 0.3</td>
<td>2.3 ± 0.1</td>
</tr>
<tr>
<td>Young female</td>
<td>12</td>
<td>61 ± 5</td>
<td>107 ± 4</td>
<td>69 ± 2</td>
<td>75 ± 3</td>
<td>18 ± 2</td>
<td>57 ± 2</td>
<td>77 ± 2</td>
<td>3.5 ± 0.2</td>
<td>2.3 ± 0.1</td>
</tr>
<tr>
<td>Older male</td>
<td>6</td>
<td>66 ± 4</td>
<td>117 ± 6</td>
<td>74 ± 3</td>
<td>64 ± 4</td>
<td>16 ± 2</td>
<td>48 ± 2</td>
<td>76 ± 2</td>
<td>2.9 ± 0.2</td>
<td>2.1 ± 0.1</td>
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<tr>
<td>Older female</td>
<td>6</td>
<td>65 ± 1</td>
<td>114 ± 3</td>
<td>77 ± 2</td>
<td>60 ± 4</td>
<td>13 ± 2</td>
<td>52 ± 3</td>
<td>81 ± 2</td>
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</table>

Young male (A) 59 ± 2 114 ± 3 79 ± 2c 86 ± 1b,c 23 ± 2 63 ± 4b,c 74 ± 1c 3.7 ± 0.3 2.3 ± 0.1
Young female (B) 61 ± 5 107 ± 4 69 ± 2 75 ± 3 18 ± 2 57 ± 2 77 ± 2 3.5 ± 0.2 2.3 ± 0.1
Older male (C) 66 ± 4 117 ± 6 74 ± 3 64 ± 4 16 ± 2 48 ± 2 76 ± 2 2.9 ± 0.2 2.1 ± 0.1
Older female (D) 65 ± 1 114 ± 3 77 ± 2 60 ± 4 13 ± 2 52 ± 3 81 ± 2 3.4 ± 0.2 2.4 ± 0.1

Max (150 ± 10) 17 ± 3 29 ± 4 17 ± 3 4 ± 3 11 ± 1c 15 ± 3c 14 ± 2c 23 ± 0.4 1.0 ± 0.1
Max (160 ± 9) 16 ± 1 25 ± 3 11 ± 3 7 ± 2 7 ± 1 10 ± 2 9 ± 1 1.2 ± 0.3 0.4 ± 0.1
Max (170 ± 8) 19 ± 3 23 ± 5 9 ± 2 4 ± 4 8 ± 2 12 ± 3 13 ± 2 18 ± 0.2 1.1 ± 0.1
Max (180 ± 7) 20 ± 2 32 ± 5 7 ± 2 3 ± 1 3 ± 1 4 ± 1 0.7 ± 0.2 0.3 ± 0.1
Max (190 ± 6) 19 ± 2 18 ± 3 8 ± 2 2 ± 1 5 ± 1 8 ± 3 9 ± 2 1.6 ± 0.2 0.7 ± 0.1

Adrenaline dose (ng kg⁻¹ min⁻¹)

Young
0 (8) 105 ± 3 74 ± 3 84 ± 2 86 ± 3 18 ± 3 41 ± 0.1 0.31 ± 0.01 2.4 ± 0.1 48 ± 2

Old (11) 97 ± 3 66 ± 3 77 ± 3 59 ± 3 13 ± 2 34 ± 0.2 0.30 ± 0.01 2.4 ± 0.1 33 ± 4

P value <0.05 <0.05 <0.01

Adrenaline effect (µg kg⁻¹ min⁻¹)

Young
20 (7) 2 ± 2 −3 ± 2 −1 ± 2 −2 ± 1 −4 ± 1 0.7 ± 0.1 −0.02 ± 0 0.3 ± 0.1 −7 ± 1
40 (7) 10 ± 2 −5 ± 2 0 ± 2 −1 ± 2 −6 ± 1 1.5 ± 0.1 −0.04 ± 0.01 0.7 ± 0.1 −10 ± 1
60 (5) 23 ± 4 −3 ± 2 6 ± 3 1 ± 2 −9 ± 2 2 ± 0.4 −0.06 ± 0.1 1.2 ± 0.2 −14 ± 3
Old
20 (11) −1 ± 3 −5 ± 1 −4 ± 2 0 ± 1 −3 ± 1 0.7 ± 0.1 −0.02 ± 0.01 0.3 ± 0.1 −8 ± 2
40 (11) 12 ± 5 −3 ± 2 2 ± 3 1 ± 1 −5 ± 1 1.6 ± 0.2 −0.04 ± 0.01 0.6 ± 0.1 −8 ± 2

Data represent mean ± s.e. mean. For abbreviations see Table 1. Number of observations after each dose. None of the dose-response curves differ between the two groups. Since in the older group adrenaline at 80 ng kg⁻¹ min⁻¹ was only infused in two subjects, results for this rate are not included in the older subjects.

only small decreases, not different between the two groups (Table 1). The larger decrease in diastolic BP was restricted to the small group (Table 2).

Whereas heart rate increased similarly in the two groups (Figure 1), parameters of LV function showed different responses. LV end-diastolic volume showed similar minor increases, but LV end-systolic volume decreased more in the young (Table 1). This led to larger increases in stroke volume (Figure 2), ejection fraction (Figure 2), and cardiac index (Table 1) in the young. Older females tended to have the least increase in end-diastolic volume index and the least decrease in end-systolic volume index. As a result, older females exhibited the smallest increases in stroke volume index and in ejection fraction.

Blood pressure and cardiac effects of adrenaline with concomitant trimetaphan

Adrenaline with concomitant infusion of trimetaphan was administered in seven young and 11 older subjects. The older subjects received significantly less trimetaphan but exhibited larger decreases in systolic and diastolic blood pressure (Figure 1).
pressures. Nine of the 11 older subjects could not tolerate adrenaline 80 ng kg\(^{-1}\) min\(^{-1}\) because of symptomatic hypotension and only two older subjects received this dose of adrenaline. The data acquired at this higher dosage in the aged were therefore not included in the analysis.

In contrast to the findings without trimetaphan, with concomitant ganglionic blockade adrenaline caused similar BP and cardiac chronotropostic and inotropic changes in young and older subjects (Table 3, Figures 1–2). Thus, systolic and diastolic BP, heart rate, LV end-systolic and stroke volume as well as cardiac index, ejection fraction, systolic ejection rate and end-systolic wall stress all changed to a similar extent in the two groups. Trimetaphan caused a leftward shift of the adrenaline dose-response relationship for heart rate (Figure 1), systolic blood pressure and—to a less extent—most parameters of LV function. Figure 3 (left panel) illustrates the changes in heart rate at the maximum dose of adrenaline without and with concomitant administration of trimetaphan. The mean maximal dose of adrenaline was 134 ± 6 [young] compared with 138 ± 7 ng kg\(^{-1}\) min\(^{-1}\) [old] (P = NS) without trimetaphan, and 69 ± 7 [young] compared with 45 ± 5 ng kg\(^{-1}\) min\(^{-1}\) [old] with concomitant infusion of trimetaphan (P = 0.02). Adrenaline infused under ganglionic blockade resulted in a significantly greater chronotropic response at a lower dose of adrenaline, but similar for young and older groups.

**Plasma catecholamines (Table 4)**

Baseline values for plasma noradrenaline tended (NS) to be higher in the older compared with young subjects. Infusion of adrenaline caused a clear increase in plasma adrenaline and lesser increase in plasma noradrenaline. The increase in adrenaline levels was similar for the two groups but noradrenaline levels increased to a larger extent in the older subjects. Combined with ganglionic blockade, the young subjects tended to receive a higher maximal dose of adrenaline (69 ± 7 [young] compared with 45 ± 5 ng kg\(^{-1}\) min\(^{-1}\) [old]; P = 0.02). Both groups exhibited similar increases in plasma adrenaline by adrenaline with trimetaphan compared with adrenaline alone, but at lower infusion rates for adrenaline with or without trimetaphan (Table 4). Figure 3 (right panel) illustrates the changes in heart rate at the maximal dose of adrenaline relative to the plasma concentrations of adrenaline obtained. Adrenaline alone caused similar increases in plasma adrenaline and in heart rate in the young and older groups. With ganglionic blockade, adrenaline again caused similar increases in heart rate and plasma adrenaline in the two groups. Comparison of the findings without and with trimetaphan showed enhanced responses to adrenaline combined with trimetaphan in both the young (P < 0.01) and older (P < 0.05) group.

**Discussion**

The present results show that ageing causes changes in cardiovascular responses to systemic infusion of adrenaline.

<table>
<thead>
<tr>
<th></th>
<th>noradrenaline</th>
<th>adrenaline</th>
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<tr>
<td></td>
<td>(pg ml(^{-1}))</td>
<td>(pg ml(^{-1}))</td>
</tr>
<tr>
<td>Basal</td>
<td>Peak</td>
<td>Basal</td>
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</table>

<table>
<thead>
<tr>
<th>Age group</th>
<th>Basal</th>
<th>Peak</th>
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<tbody>
<tr>
<td>Young</td>
<td>255 ± 18</td>
<td>395 ± 30(^*)</td>
</tr>
<tr>
<td>Old</td>
<td>266 ± 16</td>
<td>602 ± 56(^*)</td>
</tr>
</tbody>
</table>

Data represent mean ± s.e. mean.

\(*P < 0.05\) peak vs basal

\(\dagger P < 0.05\) young vs old.
which are distinctly different from the changes in responses to infusion of isoprenaline. Thus, ageing did not affect the increase in heart rate by adrenaline, either alone or with concomitant ganglionic blockade. On the other hand, ageing blunted the increases in systolic BP and LV performance as well as the decreases in diastolic BP caused by adrenaline, but these differences were no longer present with concomitant ganglionic blockade. In contrast, responses of heart rate and LV function to the non-selective β-adrenoceptor agonist isoprenaline are clearly decreased in older subjects, when combined with ganglionic blockade [13].

The cardiovascular effects of adrenaline in man have been well documented. For example, Harris et al. [16] showed that adrenaline at a rate of 5 μg min⁻¹ increased heart rate, stroke volume, cardiac output and systolic BP. The increase in LV function relates at least in part to direct effects on myocardiual contractility [17], although effects on venous return [18] likely contribute. We previously reported the rate-related changes in above parameters by adrenaline [19] and the present data are similar in this regard. β₁-receptors appear to play a major role in the increase in heart rate caused by adrenaline, whereas effects on LV function appear to be mediated primarily via β₂-receptors [19].

Without ganglionic blockade, adrenaline and isoprenaline cause rather similar cardiovascular responses. With ganglionic blockade, isoprenaline decreases LV end diastolic volume, and stroke volume and systolic BP no longer increase [13]. In contrast, adrenaline maintained LV end-diastolic volume, still increased stroke volume and systolic BP, and actually increased cardiac index even more than adrenaline alone. This pattern of changes suggests that in the presence of ganglionic blockade adrenaline has a larger effect on venous return, but isoprenaline less. This difference may relate to α-receptor stimulation by adrenaline.

Whereas the effects of the arterial baroreflex on the hemodynamic responses to isoprenaline have been studied extensively [13], as far as we are aware of, no studies have addressed this interaction for adrenaline. As shown in Figure 1, ganglionic blockade clearly enhances the heart rate responses to infusion of both adrenaline and isoprenaline. The effects on LV function by adrenaline are enhanced as well, but to a less extent (Figure 2, Tables 1, 3). This pattern of changes may suggest that both agents activate the arterial baroreflex, resulting in an increase in vagal tone and decrease in cardiac sympathetic tone, thereby blunting the increases in heart rate and LV function. However, combined with trimetaphan adrenaline causes higher plasma concentrations (Table 4) of circulating adrenaline compared with infusion of adrenaline alone, which also explains part of the enhanced responses (Figure 3).

Aging and cardiovascular responses to adrenaline
Whereas ganglionic blockade unmasks the decreased chronotropic responses to β-receptor stimulation by isoprenaline with ageing (Figure 1), such a decrease does not become apparent for adrenaline (Figure 1 and 3). Assuming that decreased β-receptor mediated responses are indeed present [20], at least two explanations are possible for this difference in response to the two agonists. Whereas isoprenaline stimulates both β₁ and β₂ receptors in the sinus node, adrenaline mainly stimulates β₂-receptors [19]. Although in ventricles both β₁- and β₂-mediated responses decrease with ageing [20, 19], it is possible that the sinu node ageing preferentially affects β₁-mediated responses and to a less extent β₂-responses, thereby maintaining heart rate responses to adrenaline. Alternatively, neuronal uptake of adrenaline may have been decreased in the older subjects. This would—at similar plasma concentrations (Table 4)—result in higher concentrations around the synaptic cleft, which would compensate for a decrease in β₂-receptor mediated responses. However, there is no consensus about the effect of ageing on pre-synaptic neuronal uptake of catecholamines [3, 8, 9]. The older subjects exhibited a similar increase in circulating levels of adrenaline despite a somewhat lower dose of exogenous adrenaline suggesting that decreased clearance and uptake may indeed occur with ageing. A decrease in clearance with ageing has previously been demonstrated for noradrenaline [21].

Regarding the effects of adrenaline on LV function, compared with the older subjects the young subjects showed an enhanced LV emptying (i.e., larger decrease in LV end-
systolic volume, and larger increases in stroke volume, ejection fraction and cardiac index) in response to adrenaline. Since systolic ejection rate increased similarly in the two groups and afterload as assessed by diastolic blood pressure and end-systolic wall stress decreased more in the young subjects, it appears that the enhanced LV emptying is primarily related to a larger decrease in afterload in the young subjects. Consistent with this conclusion, with concomitant ganglionic blockade adrenaline caused similar decreases in afterload in young compared with older subjects and also similarly improved LV emptying. These findings are in marked contrast to our previous results with isoprenaline [13], showing with ganglionic blockade an age-related decrease in ejection fraction and systolic ejection rate in response to isoprenaline. We conclude that in humans an age-related decrease in β-receptor mediated chronotropic and inotropic responses does occur, but that in the case of adrenaline this decrease appears to be compensated by other mechanisms such as a decrease in neuronal uptake of adrenaline. If so, then one may expect that inhibition of neuronal uptake will unmask ageing-induced decreases in responses to adrenaline.

Without trimeptaphan circulating noradrenaline levels were increased in response to adrenaline more in the aged compared with younger subjects whereas circulating levels of adrenaline increased similarly. In humans adrenaline can increase muscle sympathetic nerve activity and noradrenaline overflow most likely by pre-synaptic β2-receptor stimulation [22]. The larger increase in plasma noradrenaline in the older subjects may relate to a relative decrease in pre-synaptic α2-receptors [2, 3] or a decrease in neuronal uptake, either leading to enhanced noradrenaline release and/or levels in response to adrenaline.

Gender and cardiovascular response to adrenaline

Some age and gender specific changes in response to adrenaline were found, although the conclusions are limited by small sample sizes especially in the young female and older male groups. Overall, the older females tended to have a smaller increase in LV inotropic function than the other groups in response to adrenaline. These findings are in agreement with preliminary data from Bristow and coworkers showing that the age-related downregulation in myocardial β1-receptors is more pronounced in women than in men [Bristow M, unpublished data]. Since the adrenaline-mediated increase in LV inotropic function appears to be mediated primarily via β1-receptors [19], this finding is consistent with a reduction in LV inotropic responses to adrenaline in older women.

In conclusion, the present study shows that ageing affects cardiovascular responses to adrenaline distinctly different than to isoprenaline. After ganglionic blockade young and older subjects showed similar responses to adrenaline, whereas decreased cardiac responses to isoprenaline become more prominent in the elderly. Effects of ageing on neuronal uptake of adrenaline may explain this difference.

The study was supported by a Grant-in-Aid from the Heart and Stroke Foundation of Ontario. FHHL is a Career Investigator of the Heart and Stroke Foundation of Ontario.

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(Received 20 December 1993, accepted 12 November 1996)