The hemodynamic effects of sympathetic stimulation combined with parasympathetic blockade in man

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ABSTRACT To define the effects of circulating norepinephrine and epinephrine on cardiac function and to determine whether left ventricular function is influenced by parasympathetic mechanisms during catecholamine stimulation, hemodynamic changes were investigated in healthy young human subjects who were supine and awake during infusion of (1) intravenous norepinephrine alone (125 ng/kg/min) (n = 6), (2) norepinephrine (125 ng/kg/min) plus epinephrine (50 ng/kg/min) (n = 6), and (3) norepinephrine plus epinephrine plus parasympathetic blockade induced by atropine (2 mg intravenously) (n = 5). Ejection fraction and changes in cardiac volumes were measured by radionuclide ventriculography. During the infusion of norepinephrine plus epinephrine, plasma norepinephrine increased from 358 ± 35 to 1782 ± 123 pg/ml (mean ± SE) and plasma epinephrine increased from 31 ± 5 to 355 ± 90 pg/ml (both p < .01 vs baseline). These increases in plasma catecholamines were associated with increases in the heart rate (58 ± 3 to 67 ± 2 beats/min, p = NS), systolic blood pressure (113 ± 3 to 140 ± 6 mm Hg, p < .01), ejection fraction (0.64 ± 0.02 to 0.72 ± 0.02 ejection fraction units, p < .01), stroke volume (+41 ± 5%, p < .01), and cardiac output (+54 ± 8%, p < .01), and a decrease in systemic vascular resistance (−31 ± 3%, p < .01). Administration of atropine during the concurrent infusion of catecholamines led to additional increases in heart rate (127 ± 5 beats/min), systolic pressure (179 ± 10 mm Hg), ejection fraction (0.83 ± 0.05), stroke volume (+58 ± 5%), and cardiac output (+262 ± 18%), and a decrease in systemic vascular resistance (−63 ± 1%) (all p < .05 compared with baseline and with norepinephrine plus epinephrine alone). These findings define in part the range of hemodynamic changes controlled by sympathetic and parasympathetic mechanisms in normal subjects. The augmentation of ejection fraction and stroke volume by the infusion of atropine supports the concept that parasympathetic inhibition of ventricular performance occurs in man. Circulation 75, No. 5, 922–929, 1987.

IN A WIDE VARIETY of stress states, sympathetic augmentation and parasympathetic withdrawal modulate many of the cardiovascular responses. 1-3 Although the influence of circulating catecholamines on cardiovascular function has been studied in animal preparations, relatively little is known in man about the hemodynamic effects of defined increases in circulating epinephrine and norepinephrine, both of which are elevated in association with many physiologic and pathologic states. 3-10 The plasma levels of circulating norepinephrine or epinephrine have correlated with hemodynamic changes in some studies. 6, 11-14 More direct knowledge of their hemodynamic effects is available from infusion studies. In a prior study, increases in plasma epinephrine within the normal physiologic range caused highly significant changes in the ejection fraction, stroke volume, and cardiac output. 15 However, the hemodynamic effects of circulating norepinephrine alone or norepinephrine in addition to epinephrine have not been examined in detail. In man, although the effects of parasympathetic control on the heart rate are well known, it has not been determined whether parasympathetic activity has a significant effect on ventricular performance. Until recently, vagal influence on ventricular function was thought to be minimal. 16 However, several studies
in animals document that parasympathetic activation counterregulates the stimulatory effects of adrenergic activation on ventricular function.\textsuperscript{1, 16–20} Vagal inhibition of ventricular function is accentuated at higher levels of sympathetic activity in animal preparations.\textsuperscript{1, 16, 21, 22}

The purpose of the present investigation was to define the effects of circulating norepinephrine and epinephrine on cardiac function in normal intact humans. In addition, we sought to determine whether left ventricular function is influenced by parasympathetic mechanisms during elevated sympathetic stimulation caused by catecholamine infusions. Our results document in part the magnitude of hemodynamic changes that can result from autonomic mechanisms and suggest that parasympathetic inhibition of left ventricular function occurs in man.

Methods

Subjects. Eight normal male subjects from 24 to 35 years old were studied after an overnight fast. Normal cardiovascular function was documented by cardiovascular history, results of physical examination, the resting electrocardiogram, and M mode and two-dimensional echocardiograms. No subject had taken any medication or smoked cigarettes within the week before the study. None were highly trained athletes. All subjects gave informed consent.

Study protocol. An intravenous catheter was inserted in the forearm or antecubital fossa of each subject. Each then rested supine for 30 min before the collection of baseline data. Studies were performed with the subjects supine. All eight subjects received an infusion of 125 ng/kg/min norepinephrine for 16 min followed by a combination of norepinephrine (125 ng/kg/min) plus epinephrine (50 ng/kg/min) for the next 8 min. Due to technical errors, data from two of the eight subjects who received the infusions of norepinephrine and norepinephrine plus epinephrine were not available. Five subjects continued to receive the norepinephrine plus epinephrine infusion along with an intravenous bolus injection of a total of 2 mg of atropine sulfate (Eli Lilly, Indianapolis) (1 mg at both 24 and 34 min from the onset of initial infusion of norepinephrine. Therefore, data are reported from six subjects who received infusions of norepinephrine alone and of norepinephrine plus epinephrine and from five subjects who received norepinephrine plus epinephrine plus atropine.

The solutions of norepinephrine and epinephrine for infusion were prepared by the dilution of a sufficient amount of norepinephrine and epinephrine (Parke-Davis, Detroit) in 0.9% saline (100 ml final volume for each) to achieve the proper dose. Ascorbic acid (0.5 mg/ml) was added to prevent oxidation of the epinephrine and norepinephrine. Infusion solutions were loaded into 50 ml syringes and placed on Harvard infusion pumps (Harvard Apparatus Co., South Natick, MA). All infusions were into the left arm. The infusion rates were designed to achieve plasma norepinephrine and epinephrine levels similar to those we have previously noted at symptom-limited supine bicycle exercise in a healthy population of similar age.\textsuperscript{9} No complications occurred.

Data collection and processing. For the subjects who received only norepinephrine and norepinephrine plus epinephrine, data were recorded until completion of the combined infusion (24 min from the onset of infusion). For the remaining subjects, data were recorded until 10 min after the subject had received a total of 2 mg of atropine (44 min from the onset of infusion). During the infusions, cardiac blood pool images, heart rate, right arm sphygmomanometer blood pressure, and plasma catecholamine concentrations were determined at rest and at 16 and 24 min in all subjects, and at 44 min in the subjects who received atropine. Mean arterial pressure was defined as the diastolic pressure plus $\frac{1}{3}$ (systolic-diastolic pressure). All blood pressures were recorded by a single investigator. Venous samples (2.5 ml) for catecholamine determinations were drawn from the right arm through an indwelling catheter and promptly placed into prechilled glass tubes containing EGTA and reduced glutathione (5 mmol/liter final concentration). The samples were immediately placed on ice and the plasma was subsequently separated by double centrifugation at 4°C and then frozen at $-20^\circ$C until its assay. Plasma epinephrine and norepinephrine concentrations were measured by a single-isotope radioenzymatic assay.\textsuperscript{21} The mean basal plasma levels in 95 normal subjects at supine rest were 252 ± 138 pg/ml (± SD) for norepinephrine and 50 ± 22 pg/ml for epinephrine by this method in this laboratory.\textsuperscript{8} The intra-assay and interassay variabilities are 10% and 12%, respectively, for samples above 100 pg/ml.

Radionuclide left ventricular angiography was performed by electrocardiographically synchronized blood pool imaging of $^{99m}$Tc-labeled red blood cells.\textsuperscript{24, 25} Images were acquired in the left anterior oblique projection that offered the best septal definition with the use of a low-energy, high-sensitivity, parallel-hole collimator and a gamma scintillation camera (Ohto Nuclear, Series 100, Solon, OH) interfaced to a computer (Medical Data Systems, Trinny, Ann Arbor). Images were acquired for three 2 min baseline periods in subjects at rest and then every 2 min during the infusions, and analyzed as previously described by our laboratory.\textsuperscript{24, 25} The background-subtracted, composite time-activity curve data for each 2 min image were corrected for isotope decay and used to obtain or derive end-diastolic counts (EDC), end-systolic counts (ESC), stroke counts (SC = EDC-ESC), ejection fraction (EF = SC/ESC), and radionuclide cardiac output counts (RNCO = SC × heart rate), where heart rate is the number of cardiac cycles during the period of data collection. Systemic vascular resistance was defined as mean arterial pressure/radionuclide cardiac output counts. Radionuclide-determined changes in end-diastolic count volume, end-systolic count volume, stroke count volume, systemic vascular resistance, and cardiac output are expressed as a percent change from baseline: \[ \text{Observed counts} - \text{baseline counts} \times 100 \]

Baseline counts

Only the relative changes in cardiac volumes and output and systemic vascular resistance compared with baseline were determined. Absolute cardiac volumes and cardiac outputs in milliliters of blood were not measured. The radionuclide techniques used for measurement of changes in cardiac output and stroke volume have been previously validated in our laboratory against cardiac output and stroke volume measured by direct Fick techniques in normal subjects at rest and during maximal exercise.\textsuperscript{25} Only the catecholamine and hemodynamic data obtained during the final 2 min of each infusion period will be presented since there were no significant differences in catecholamine or hemodynamic measurements obtained at the middle and those obtained at the end of the infusions.

For comparison with the results of infusion of norepinephrine alone, hemodynamic responses during the infusion of epinephrine alone at 100 ng/kg/min in five similar young healthy subjects are also presented. The results of the infusion of epinephrine were obtained by methods similar to those described above and have been previously reported.\textsuperscript{15}
Results

**Norepinephrine infusion.** The infusion of norepinephrine increased plasma levels of norepinephrine from 358 ± 35 to 1681 ± 200 pg/ml (p < .01) (table 1), while plasma epinephrine was unchanged. Norepinephrine caused a modest 14 ± 5% decrease in heart rate (p < .05), a 22 ± 2% increase in systolic pressure (p < .01), a 19 ± 1% increase in mean arterial pressure (p < .01), no significant change in the pressure-rate product, and a 30 ± 10% increase in systemic vascular resistance (p < .01). End-diastolic volume, end-systolic volume, ejection fraction, stroke volume, and cardiac output were not significantly changed (figures 1 and 2).

**Norepinephrine plus epinephrine infusion.** Epinephrine in addition to norepinephrine led to a plasma concentration of norepinephrine of 1782 ± 123 pg/ml and plasma epinephrine of 355 ± 90 pg/ml (both p < .01 vs baseline). Compared with baseline, infusion of norepinephrine plus epinephrine did not change the heart rate or mean arterial pressure, and increased the systolic pressure and pressure-rate product (both p < .01). Systemic vascular resistance was reduced by 31 ± 3%.

### Table 1

<table>
<thead>
<tr>
<th></th>
<th>Plasma norepinephrine (pg/ml)</th>
<th>Plasma epinephrine (pg/ml)</th>
<th>Heart rate (beats/min)</th>
<th>Mean BP (mm Hg)</th>
<th>SBP (mm Hg)</th>
<th>HR-SBP (mm Hg/min) × 10²</th>
<th>EDV counts</th>
<th>ESV counts</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>358 ± 35</td>
<td>31 ± 5</td>
<td>58 ± 3</td>
<td>88 ± 4</td>
<td>113 ± 3</td>
<td>66 ± 4</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Norepinephrine</td>
<td>1681 ± 200</td>
<td>52 ± 8</td>
<td>52 ± 3</td>
<td>106 ± 6</td>
<td>140 ± 7</td>
<td>73 ± 5</td>
<td>6 ± 5</td>
<td>6 ± 7</td>
</tr>
<tr>
<td>Norepinephrine + epinephrine</td>
<td>1782 ± 123</td>
<td>355 ± 90</td>
<td>67 ± 2</td>
<td>93 ± 5</td>
<td>140 ± 6</td>
<td>93 ± 5</td>
<td>16 ± 6</td>
<td>1 ± 7</td>
</tr>
<tr>
<td>Norepinephrine plus epinephrine plus atropine</td>
<td>1760 ± 174</td>
<td>388 ± 14</td>
<td>127 ± 5</td>
<td>112 ± 6</td>
<td>179 ± 10</td>
<td>228 ± 18</td>
<td>4 ± 6</td>
<td>-31 ± 9</td>
</tr>
</tbody>
</table>

BP = blood pressure; EDV = end-diastolic volume; ESV = end-systolic volume; HR = heart rate; SBP = systolic blood pressure.
(p < .01). End-diastolic volume increased by 16 ± 6% (p < .05), end-systolic volume was unchanged, ejection fraction increased to 0.72 ± 0.02 (p < .01), cardiac output increased 54 ± 8% (p < .01), and stroke volume increased 41 ± 5% (p < .01).

Compared with the norepinephrine infusion alone, the addition of epinephrine caused a significant increase in heart rate (p < .01), no change in systolic pressure, a decrease in mean arterial pressure (p < .01), an increase in pressure-rate product (p < .01), and a decrease in systemic vascular resistance (p < .01). End-diastolic and end-systolic volume were unchanged, but there were highly significant increases in ejection fraction, stroke volume, and cardiac output (all p < .01).

**FIGURE 2.** Changes in cardiac output induced by infusion of norepinephrine (NE), norepinephrine plus epinephrine (NE + E), and norepinephrine plus epinephrine plus atropine (NE + E + A) in normal subjects.

**TABLE 1**

(Continued)

<table>
<thead>
<tr>
<th>Stroke volume counts (p change)</th>
<th>Ejection fraction</th>
<th>Systemic vascular resistance (p change)</th>
<th>Cardiac output (p change)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0.64 ± 0.02</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>9 ± 2</td>
<td>0.65 ± 0.02</td>
<td>30 ± 10</td>
<td>−7 ± 7</td>
</tr>
<tr>
<td>41 ± 5</td>
<td>0.72 ± 0.02</td>
<td>−31 ± 3</td>
<td>54 ± 8</td>
</tr>
<tr>
<td>58 ± 5</td>
<td>0.83 ± 0.05</td>
<td>−63 ± 1</td>
<td>262 ± 18</td>
</tr>
</tbody>
</table>

Norepinephrine plus epinephrine plus atropine infusion. Compared with baseline, the infusion of catecholamine combined with parasympathetic blockade induced by atropine increased the heart rate by 130 ± 14%, the systolic pressure by 64 ± 7%, the mean pressure by 112 ± 6%, and the pressure-rate product by 404 ± 70% (tables 1 and 2) (all p < .01 vs baseline). Systemic vascular resistance decreased by 63 ± 1% (p < .01). End-diastolic volume was unchanged, and end-systolic volume was reduced by 31 ± 9% (p = NS). The ejection fraction increased to 0.83 ± 0.05, stroke volume increased by 58 ± 5%, and cardiac output increased by 262 ± 18% (all p < .01 vs baseline).

Compared with sympathetic stimulation with norepinephrine plus epinephrine infusion, the addition of parasympathetic blockade by atropine caused no change in plasma catecholamine levels but led to significant additional increases in heart rate, systolic pressure, mean arterial pressure, and pressure-rate product and a further decline in systemic vascular resistance (all p < .01 compared with norepinephrine plus epinephrine infusion). End-diastolic volume was unchanged, while end-systolic volume was marginally reduced. However, stroke volume (p < .05), ejection fraction (p < .01), and cardiac output (p < .01) all increased significantly with the addition of atropine to norepinephrine plus epinephrine.

**Comparison of hemodynamic effects of circulating norepinephrine and epinephrine.** The comparative net circulating hormonal hemodynamic effects of infused norepinephrine and infused epinephrine are listed in table 3. Epinephrine alone infused at a rate of 100 ng/kg/min in five subjects caused an increase in plasma epinephrine from 30 ± 4 to 484 ± 69 pg/ml, as previously reported. Although the plasma epinephrine levels were considerably lower than the norepinephrine levels, circulating epinephrine caused a significantly greater reduction in mean blood pressure and systemic vascular resistance and significantly greater increases in stroke volume, ejection fraction, cardiac output, and heart rate than did circulating norepinephrine (all p < .01).

**Discussion**

The purposes of the present study were to determine the net hemodynamic effects of circulating norepinephrine and epinephrine and to investigate the hemodynamic effects of parasympathetic blockade during the infusion of catecholamines in man. The observed hemodynamic changes in these unanesthetized normal subjects who were receiving no medications represent...
both the primary effects of the infused agents and secondary reflex responses. It is highly likely that the infusion triggered the arterial baroreceptor reflex and led to reduced endogenous efferent sympathetic traffic and to augmented vagal traffic. The relative contributions of the primary and secondary effects to the observed hemodynamic changes cannot be determined.

Although the observed effects of atropine were likely due primarily to cholinergic blockade, atropine may exert other effects. For example, Rigel et al.\textsuperscript{27} demonstrated in dogs that atropine caused an "excess tachycardia" of approximately 26 beats/min that could not be attributed to cholinergic blockade. In addition, an atropine-induced alteration of either catecholamine disposition or of adrenergic responsiveness cannot be excluded.

Nevertheless, the marked changes in hemodynamics induced by the infusions document in part the range of hemodynamic responses under autonomic nervous system control. The findings also strongly suggest that parasympathetic inhibition of left ventricular function occurs in man, at least during states of increased sympathetic stimulation.

\textbf{Parasympathetic inhibition of ventricular function.} Canine studies have documented that various indexes of ventricular contractility are depressed by vagal stimulation.\textsuperscript{1, 16-20} The inhibitory effects of vagal activity are more pronounced when sympathetic activity or baseline contractility is elevated,\textsuperscript{1, 16, 21, 22} a phenomenon that Levy and Martin\textsuperscript{16} have termed accentuated antagonism, which is mediated at both the presynaptic and postsynaptic levels. To date, we are unaware of evidence that documents the existence of parasympathetic depression of ventricular function in man. Although the finding that the infusion of atropine caused pressor hyperresponsiveness in a prior study was compatible with a vagal-induced negative inotropic effect, no direct measurement of ventricular function was made.\textsuperscript{25} Isolated infusion of atropine in young normal subjects in another study did not lead to evidence of parasympathetic inhibition of ventricular function; infusion of atropine (2 mg) alone resulted in a 25%
reduction in stroke volume, a fall in central venous pressure, a 70% increase in heart rate, a 6% increase in mean arterial pressure, a 28% increase in cardiac output, and a 16% fall in peripheral resistance. To study parasympathetic inhibition of ventricular function, we increased sympathetic stimulation by the infusion of norepinephrine and epinephrine to augment potential vagal effects. In this setting, parasympathetic blockade with atropine produced significant additional increases in stroke volume (from 41% to 58%) and ejection fraction (from 0.72 to 0.83).

The increase in stroke volume occurred while two of its determinants, arterial pressure and end-diastolic volume, were changing in directions that would be predicted to decrease the stroke volume; the extent of parasympathetic inhibition of ventricular performance may have been even more apparent had these factors been held constant. The increased stroke volume and ejection fraction after atropine cannot be ascribed simply to the twofold increase in heart rate, since doubling the heart rate by atrial pacing in humans caused no increase in the stroke volume, but a 40% to 50% reduction; in addition, doubling the heart rate by itself caused no change in ejection fraction, cardiac output, or mean arterial pressure. Thus, the current data are compatible with the interpretation that parasympathetically-induced depression of ventricular performance was present during the norepinephrine plus epinephrine infusion, since blockade of vagal activity by atropine led to an augmentation of ventricular function. Stated differently, atropine "unmasked" the vagal depression of ventricular function that occurred during the infusion of catecholamines.

Despite the increase in mean arterial pressure after atropine, systemic vascular resistance fell, as has previously been reported. Although the current study was not designed to clarify the mechanism of the reduction in systemic resistance, a possible explanation is baroreflex inhibition of neurally mediated vasoconstrictor tone. In this context, the finding by Goldstein and Keiser that the infusion of atropine caused a fall in plasma norepinephrine from 182 ± 105 to 109 ± 48 pg/ml in normal subjects is concordant with a baroreflex-mediated reduction in systemic resistance after atropine. Studies in conscious dogs indicate that arterial baroreceptors attenuate the vascular responses to vagal blockade.

Hemodynamic effects of circulating norepinephrine and epinephrine. Apart from heart rate and blood pressure responses, the hemodynamic effects of physiologic concentrations of circulating norepinephrine have not been defined in detail in normal man. In prior studies, plasma norepinephrine concentrations greater than 1800 pg/ml were required to produce measurable changes in heart rate and systolic blood pressure, and no change in cardiac output occurred at doses of 60 to 340 ng/kg/min. In a third study, infusions to plasma levels of approximately 2000 pg/ml increased systolic and diastolic arterial pressure and decreased heart rate. At a mean plasma norepinephrine level of 1681 pg/ml, we found changes in heart rate and blood pressure similar to those previously noted. In addition, we found no change in end-diastolic volume, end-systolic volume, ejection fraction, stroke volume, or cardiac output.

There are limited data regarding the comparative hemodynamic effects of circulating norepinephrine and epinephrine in humans. The present study confirms the findings of Hjermdahl et al. regarding the effects on blood pressure and heart rate, and allows a more extensive comparison of the net circulating hormonal hemodynamic effects. As shown in table 3, the net responses were widely divergent, with epinephrine causing greater increases in stroke volume, ejection fraction, cardiac output, and heart rate, and greater reductions in mean arterial pressure, end-systolic volume, and systemic vascular resistance. These differing effects are likely due in part to the preferential action of epinephrine in causing $\beta_2$-adrenoreceptor-mediated vasodilatation.

The addition of epinephrine to the norepinephrine infusion in the current study caused increases in heart rate, end-diastolic volume, stroke volume, ejection fraction, and cardiac output and a fall in mean arterial pressure and systemic vascular resistance. Thus, as would be predicted, the effects of the combination of norepinephrine and epinephrine were intermediate between those of norepinephrine alone and epinephrine alone.

Hemodynamic effects of sympathetic stimulation combined with parasympathetic withdrawal. The hemodynamic effects of sympathetic stimulation combined with parasympathetic blockade have not been previously described in detail in man. Despite the small numbers of subjects studied, the combined infusion produced highly significant changes in all hemodynamic measurements, with the exception of end-diastolic volume. The magnitude of the hemodynamic effects induced by the combined infusion was large. In fact, most measurements (mean arterial pressure, stroke volume, ejection fraction, heart rate, systemic vascular resistance, and cardiac output) changed to an extent similar to that noted during maximal supine bicycle exercise, which causes greater hemodynamic
changes than most other types of stress. Haidet et al. also noted that the combined infusion of norepinephrine plus epinephrine plus atropine in dogs led to changes in cardiac output, heart rate, and myocardial blood flow similar to those induced by submaximal exercise; however, increases in skeletal muscle and tongue blood flow were greater with exercise than with infusion.

In summary, the current study documents in part the wide range of hemodynamic control exerted by the autonomic nervous system in man. Sympathetic stimulation with parasympathetic blockade produced major changes in all indexes of left ventricular function. The net hemodynamic effects of circulating norepinephrine and epinephrine differed markedly. Parasympathetic blockade during elevated sympathetic activity resulted in enhanced ventricular function, which suggests that parasympathetic inhibition of ventricular performance occurs in man.

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