Comparative Cardiovascular Effects of Tyramine, Ephedrine, and Norepinephrine in Man

By Jay N. Cohn, M.D.

The observation that tissues depleted of norepinephrine no longer respond normally to certain sympathomimetic amines led Burn and Rand to hypothesize that these amines exert their effect by releasing norepinephrine from storage sites in the postganglionic adrenergic nerve endings. On the basis of their effect on denervated or reserpine-pretreated tissues, the sympathomimetic amines have been classified into three groups: (1) those which have a direct action on receptor sites; (2) those which act indirectly by releasing norepinephrine; and (3) those with a mixed effect.

Although ephedrine was initially classified by Burn and Rand as having only indirect effects, more recent studies have demonstrated some direct myocardial action. Tyramine is considered to have purely indirect action, and the hemodynamic effects of this agent should therefore be attributed to release of stored norepinephrine.

The present investigation was undertaken to study the hemodynamic effects of tyramine and ephedrine in man and to compare their vascular effects with those of norepinephrine.

Methods

Studies were performed on hospitalized male patients without significant cardiac or vascular disease. Arterial blood pressure was measured directly from the brachial artery with a Statham P23Db transducer and Sanborn recording equipment. Mean pressure was obtained by electrical integration. Cardiac output was determined by the dye dilution method utilizing a central injection of indocyanine green. Blood was withdrawn at a constant rate through a continuously recording Gilford cuvette densitometer using a Harvard constant withdrawal pump. Values given for cardiac output are averages of two or more consecutive determinations. Total peripheral vascular resistance was calculated from the equation (atrial pressure assumed zero),

\[
TPR = \frac{\text{mean arterial pressure (mm Hg)}}{\text{cardiac output (ml/min)}}
\]

Forearm blood flow was measured during venous occlusion with a Whitney mercury-in-rubber resistance gage applied to the upper forearm and connected through a matching bridge circuit to a Sanborn direct-writing oscillograph. Circulation to the hand was occluded during forearm flow measurement by a wrist cuff inflated to pressures well above systolic blood pressure. Venous occlusion was produced in the upper arm by a cuff inflated rapidly by means of an air reservoir to a pressure 20 mm Hg below the subject's diastolic pressure. A polyethylene catheter was threaded into a large forearm vein and the rise of venous pressure during occlusion was recorded by means of a Statham P23Db strain gage. Vascular resistance in the forearm segment was calculated by dividing mean arterial pressure by forearm blood flow in ml/100 ml tissue/min. Venous tone was determined using the method of Sharpey-Shafer. The increment in forearm venous pressure in mm Hg/min was divided by the forearm blood flow in ml/100 ml tissue/min.

Intravenous infusions of tyramine hydrochloride, ephedrine sulfate and L-norepinephrine (Levophed bitartrate, Winthrop) were given at a rate resulting in a nearly equal blood pressure rise with each drug. In assessing the effects of systemic administration on forearm blood flow, the drugs were infused in the opposite arm. In studies of local effects in the forearm the drugs were infused by a Harvard pump through a Courand or Rochester needle in the brachial artery. Tyramine was given in concentrations of 84 and 320 μg/ml, ephedrine 320 and 1600 μg/ml and norepinephrine 0.1 and 0.4 μg/ml. Forearm blood flow was measured in both arms using a resistance gage on each arm. The effect...
### TABLE 1

#### Hemodynamic Effects of Tyramine and Ephedrine

<table>
<thead>
<tr>
<th>Subject no.</th>
<th>Mean arterial pressure</th>
<th>Cardiac output</th>
<th>Heart rate</th>
<th>Peripheral vascular resistance</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Control (mm Hg)</td>
<td>Change (ml/min)</td>
<td>Control (beats/min)</td>
<td>Change (units)</td>
</tr>
<tr>
<td>Tyramine, 2 mg/min</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>1</td>
<td>96</td>
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<td>+22</td>
<td>6250</td>
<td>+860</td>
</tr>
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<td>11</td>
<td>80</td>
<td>+23</td>
<td>8240</td>
<td>+330</td>
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<tr>
<td>Mean</td>
<td>94</td>
<td>+22 ± 11 sd</td>
<td>5999</td>
<td>+84 ± 844</td>
</tr>
</tbody>
</table>

| Ephedrine, 10 mg/min |                      |                |            |                                |
|----------------------|----------------------|----------------|------------|                                |
| 6                    | 79                   | +13            | 4600       | +760                           | 96              | +8              | .017            | .000             |
| 7                    | 72                   | +43            | 6820       | -160                           | 64              | -4              | .010            | +.007            |
| 8                    | 95                   | +7             | 4100       | +1160                          | 92              | +12             | .023            | -.004            |
| 9                    | 87                   | +10            | 5550       | +3270                          | 64              | +44             | .015            | -.005            |
| 10                   | 108                  | +10            | 6250       | +2520                          | 76              | +16             | .017            | -.004            |
| 11                   | 80                   | +18            | 8240       | +690                           | 80              | -16             | .010            | +.001            |
| Mean                 | 87                   | +17 ± 13 sd    | 5927       | +1373 ± 1276                   | 79              | +10 ± 20        | .015            | -.001 ± .004     |

*P values* | > .4 | < .05 | < .02 | < .05 |
of drug infusions on the flow in the test arm was compared with simultaneously determined flow in the control arm. The drugs were administered in random fashion in individual subjects. Some received a wide range of doses of only one drug while others were given all three drugs. Each infusion was continued for approximately five minutes. The flow reported for each infusion was that obtained from the third to fifth minute of the infusion when blood flow was quite stable. After the infusion was ended, the blood flow in the test arm was allowed to return to control levels for 15 minutes before another infusion was begun. Repeated large doses of tyramine or ephedrine were avoided because of the possibility of norepinephrine depletion. An intra-arterial infusion of norepinephrine was administered between test infusions whenever markedly vasoconstrictor doses of these amines were given.

Results

SYSTEMIC HEMODYNAMIC EFFECTS OF TYRAMINE AND EPHEDRINE

Intravenous infusions of tyramine or ephedrine were given 15 times to eleven subjects (table 1). Tyramine (2 mg/min) in nine subjects produced an average increase in mean arterial pressure of 22 mm Hg, a decrease in heart rate of 10 beats/min and no change in cardiac output. Ephedrine (10 mg/min) in six subjects resulted in average increases of 17 mm Hg in mean arterial pressure, 1260 ml/min in cardiac output and 15 beats/min in heart rate. Tyramine increased peripheral vascular resistance while ephedrine produced little mean change. The differences between the effects of tyramine and ephedrine on cardiac output, heart rate, and peripheral resistance were all significant (table 1).

Subjects 8 through 11 of table 1 were given both tyramine and ephedrine infusions. Because of its shorter duration of action, tyramine was given first, except in subject 8. After blood pressure had returned to control levels, ephedrine (or tyramine in subject 8) was administered. An attempt was made to give the drugs in equipressor doses; however, in three of the subjects ephedrine even in large doses did not increase arterial pressure to a level as high as that produced by tyramine. In each of the subjects, however, the blood pressure rise during ephedrine infusion was associated with a higher cardiac output, more rapid heart rate and lower peripheral resistance than during tyramine administration.

The rise in the minute volume of the heart during infusion of ephedrine was due in large part to the tachycardia, since cardiac output increased an average of 20.6% while stroke volume increased an average of only 11.5%. Since cardiac output was not significantly changed by tyramine, the bradycardia which occurred was associated with an increase of stroke volume averaging 24.9%.

VASCULAR EFFECTS IN THE FOREARM DURING INTRAVENOUS ADMINISTRATION

Forearm blood flow and venous tone were measured in seven subjects given successive intravenous infusions of norepinephrine, tyramine, and ephedrine in the contralateral arm. Tyramine or norepinephrine was administered first and ephedrine last because of its longer duration of action. Equipressor doses could not always be attained because of occasional difficulty in producing a comparable pressor effect with ephedrine. Average infusion rates required were 1.6 mg/min for tyramine, 8 mg/min for ephedrine and 8 μg/min for norepinephrine.

Comparison of the blood pressures produced by these drugs suggested a difference in their hemodynamic effects (table 2). The average control blood pressure for the seven subjects was 128/82 mm Hg. Norepinephrine raised this to an average of 167/106 mm Hg, tyramine to 174/95 mm Hg, and ephedrine to 165/94 mm Hg. Thus ephedrine and tyramine both produced a smaller rise of diastolic pressure with the same or a greater increase of systolic pressure than was the case following norepinephrine. Heart rate during the control period averaged 75 beats/min; during infusion of norepinephrine it averaged 57 beats, tyramine 66 beats, and ephedrine 83 beats/min. Differences between the means of the heart rates were significant with P values of less than 0.05. In each of the seven subjects norepinephrine produced the smallest rise of diastolic pressure with the same or a greater increase of systolic pressure than was the case following norepinephrine. Heart rate during the control period averaged 75 beats/min; during infusion of norepinephrine it averaged 57 beats, tyramine 66 beats, and ephedrine 83 beats/min. Differences between the means of the heart rates were significant with P values of less than 0.05. In each of the seven subjects norepinephrine produced the slowest heart rate and ephedrine the fastest. The forearm vascular effects during intravenous infusions in the seven subjects are summarized in table 2. Norepinephrine produced a marked in-
crease in forearm segment vascular resistance and a marked increase in venous tone in each subject. The arterial constriction was simultaneous with the rise of blood pressure, while the onset of venoconstriction was delayed until two or three minutes after the infusion was begun. Tyramine produced a lesser mean increase in vascular resistance, the paired analysis of this difference between norepinephrine and tyramine being significant (P<0.01). During ephedrine infusion, mean vascular resistance was slightly decreased. Paired analysis also demonstrated a significant difference between the effects of tyramine and ephedrine on venous tone was significant (P<0.02).

In two subjects (14 and 17), tyramine infusion was associated with a slight fall in vascular resistance, suggesting little or no forearm vasoconstriction. One subject (12) responded to ephedrine with a marked increase in forearm resistance, indicating that occasional individuals may be sensitive to its vasoconstrictor effect.

BRACHIAL ARTERIAL INFUSIONS

Changes in vascular resistance observed during the pressor response to a drug may result from both the direct and reflex hemodynamic
effect produced by the agent and the passive dilator effect of an increased transmural arterial pressure. In order to assess the local vascular effects of these drugs, 30 subjects were given infusions at varying rates into the brachial artery in doses insufficient to affect systemic arterial pressure. The mean per cent change in forearm blood flow produced by various infusion rates in all the subjects studied is shown in figure 1.

Norepinephrine infused into the brachial artery at a rate of 0.025 μg/min had very little local constrictor effect, producing a mean increase of 1 ± 11% (SD) in forearm blood flow. Norepinephrine in larger doses produced constriction in all subjects. Infusion rates of 0.05 μg/min decreased forearm flow by an average of 35 ± 13%; 0.1 μg/min, -32 ± 10%; and 0.5 μg/min, -68 ± 13%. A nearly straight line relationship was noted between the log-dose and the constrictor effect (fig. 1).

Arterial infusions of tyramine at a rate of 16 μg/min produced no significant vascular effects in most subjects. Infusions of 32 μg/min decreased flow by 34 ± 8%; 80 μg, -41 ± 28%; 160 μg, -21 ± 38%; 400 μg, -27 ± 68%; and 800 μg, -5 ± 72% (table 1). The great variability of response to the higher doses of tyramine occurs because some patients demonstrated vasoconstriction comparable to that produced by 80 μg doses and others developed vasodilatation.

Ephedrine infused at 40 μg/min reduced forearm flow by an average of 7 ± 10%, while doses of 80 and 160 μg/min produced more vasoconstriction, decreasing flow by 30 ± 14% and 22 ± 13%, respectively. Larger doses again were associated with variable effects, producing moderate vasoconstriction in some subjects and definite vasodilatation in others. Infusion rates of 400 μg/min increased flow by an average of 7 ± 33%; 800 μg, -23 ± 20%; and 2000 μg, +11 ± 33% (fig. 1).

Phentolamine, (Regitine, Ciba) 2.5 to 5 mg was injected in the brachial artery of 15 subjects after which the local infusions of the test drugs were repeated. Doses of norepinephrine, tyramine, and ephedrine which were constrictor prior to phentolamine, produced no effect on forearm blood flow immediately after phentolamine. In no case was a constrictor effect reversed to a dilator effect during adrenergic blockade.

Discussion

Systemic administration of norepinephrine to man increases the contractile force of the heart, but the pressor effect is associated with an increase of peripheral resistance, slowing of the heart, and either no change or a slight fall of cardiac output. Thus the peripheral vasoconstrictor effect leads to reflex bradycardia which obscures the direct myocardial effect of the drug. Forearm blood flow is altered not only by the direct vascular effect of the amine, but also by the influence of reflex baroreceptor activity and by the passive effect of an increased transmural pressure. Barcroft and his associates reported an increase of forearm blood flow in some subjects during intravenous administration of norepinephrine and they implicated an indirect vasodilator effect of the drug. When forearm blood flow was related to arterial perfusion pressure, all subjects in the present series showed a considerable increase of vascular resistance. In most subjects forearm blood flow fell despite the
rise of arterial pressure. The pronounced vasoconstrictor effect of norepinephrine was confirmed by brachial arterial infusions, which caused a dose-dependent decrease of forearm flow in all subjects.

The increase of venous tone observed during the intravenous infusion of norepinephrine confirms previous studies which have demonstrated a vasoconstrictor effect of norepinephrine using a plethysmographic method in man, and a decrease of vascular capacity in response to norepinephrine in animals. Because of the maintenance of cardiac output in the face of a marked bradycardia and increased arterial pressure, ventricular stroke work is greatly increased. This increased work may be accomplished in part by the direct myocardial effect of norepinephrine and in part by virtue of the vasoconstrictor effect which may increase diastolic filling and diastolic stretch of the ventricle.

The hemodynamic effects of tyramine differed from those of norepinephrine. Tyramine produced a smaller rise in diastolic pressure with a wider pulse pressure and a less striking bradycardia. The average increase of forearm vascular resistance during intravenous infusion was significantly less than that associated with norepinephrine, and venous tone was not significantly altered. In some individuals (subjects 1, 9, 10, 14, and 17), tyramine had weak vasoconstrictor activity and the myocardial stimulating effect was more important in raising the blood pressure. This became manifest either by a rise in cardiac output with a fall in peripheral resistance or by a fall in forearm vascular resistance during systemic administration. The absence of significant vasoconstriction during the tyramine effect suggests that an increment in diastolic stretch of the ventricle was not needed for maintenance of the augmented stroke work.

Ephedrine had weak vasoconstrictor activity, as evidenced by an increase in cardiac output, tachycardia, and a fall in total peripheral resistance and in forearm vascular resistance, during intravenous infusion. The pressor effect of this drug was dependent therefore in large part on its ability to increase the rate and strength of myocardial contraction. Two subjects (7 and 12) showed a marked increase of total peripheral resistance or forearm vascular resistance during systemic administration of ephedrine, indicating that some individuals may be particularly responsive to the vasoconstrictor effect of this drug.

Since blood pressure was not altered by the brachial arterial infusions of the drugs, the local vascular effects could be studied without the modifying effect of increased transmural pressure or of baroreceptor reflex activity. The appearance of an occasional dilator response to doses of tyramine over 80 μg/min and the frequent dilator effect of ephedrine in doses of 400 μg/min or more were distinctly different from the effect of larger doses of norepinephrine, which uniformly produced vasoconstriction.

In order to relate the local vascular effects studied by arterial infusions to the systemic effects of the drugs, it would be important to estimate what concentrations of these sympathomimetic amines exist locally during intravenous infusions. Since about one-half to one per cent of the cardiac output is delivered to the forearm, it might be assumed that this fraction of the intravenous dose infused in the brachial artery should produce similar local blood levels. However, since the rate of inactivation of tyramine and particularly ephedrine is much slower than that of norepinephrine, it is likely that the systemic doses used in the present study resulted in brachial arterial concentrations in the higher dose ranges shown in figure 1, where tyramine occasionally, and ephedrine frequently, produced vasodilation.

The method used for measuring forearm blood flow cannot distinguish between skin, and muscle flow, although placing the gage on the upper forearm, as was done in this study, probably measures predominantly muscle flow. If the responses of the forearm vascular bed can be taken as representative of overall systemic vascular responses, then the atypical effects noted for tyramine and eph-
The occasional subject whose blood vessels constricted very little or even dilated during arterial infusion of tyramine explains the results for individuals (subjects 1, 9, and 10) in whom systemic administration increased cardiac output without increasing peripheral resistance. The occasional subject who showed constriction even at high doses of ephedrine intra-arterially may account for the response noted in subjects 7 and 12, whose vascular resistance rose markedly during systemic administration of ephedrine. The difficulty of obtaining a satisfactory pressor effect in some subjects despite large doses of ephedrine can be explained by the dose-response curve. Increasing the infusion rate in these subjects may have resulted in less peripheral constriction or more dilatation.

If the vascular actions of tyramine and ephedrine were exerted exclusively by release of norepinephrine, it might be expected that these drugs would have identical vascular effects. From the dose-response curves (fig. 1), it would appear that tyramine and ephedrine in small doses have local vasoconstrictor actions very similar to those of norepinephrine. However, systemic administration of these drugs resulted in hemodynamic effects significantly different from norepinephrine, and larger doses infused locally did not produce the dose-dependent vasoconstriction noted with norepinephrine. The possibility exists that the larger intra-arterial doses of tyramine and ephedrine depleted norepinephrine, despite the replenishing norepinephrine infusions, and that the vasodilatation observed in some individuals represents unmasking of a direct action. However, if norepinephrine stores were depleted by these "therapeutic" doses, then a similar depletion would be expected after even a short intravenous infusion of these drugs.

Since endogenously released norepinephrine may act only near its storage site, while norepinephrine administered exogenously may gain access to any available receptor sites, their hemodynamic effects may not be identical. However, the demonstration of differences in the vascular effects of tyramine, ephedrine, and norepinephrine suggests that alternatives to the Burn and Rand hypothesis should be considered. Several possible proposals could reconcile previous observations with those of the present study: (1) Ephedrine in most individuals and tyramine in some are more effective in releasing norepinephrine from the heart than from peripheral vascular stores. Increases of coronary sinus norepinephrine levels have been demonstrated following tyramine and ephedrine in dogs. (2) Tyramine and particularly ephedrine cause local release of epinephrine or dopamine as well as norepinephrine. Epinephrine produces forearm vasodilatation, and both ephedrine and dopamine increase cardiac output and decrease peripheral resistance when infused in normal subjects. Both dopamine and epinephrine exist in storage sites in association with adrenergic neurones and Lockett and Eakins have demonstrated increased aortic blood concentrations of epinephrine as well as norepinephrine after administration of tyramine to cats. (3) Tyramine and ephedrine exert their sympathomimetic effects directly without the intervention of norepinephrine. The subsensitivity to these amines associated with catecholamine depletion might indicate a role for the catecholamines as a permissive factor, although the effect of reserpine could also be explained as a direct antagonism between reserpine and tyramine-like agents. (4) The sympathomimetic amines, rather than falling into three distinct groups, all have both direct and indirect actions of varying degrees.

Summary

The systemic hemodynamic and forearm vascular effects of tyramine, ephedrine, and norepinephrine were studied in normal male subjects. The pressor effect of tyramine was associated usually with bradycardia, unchanged cardiac output, and moderate arteriolar constriction in the forearm. A similar pressor effect of ephedrine was characterized by an increase of heart rate and output, with a slight fall in forearm vascular resistance. Occasional
subjects responded to tyramine with an increase of cardiac output and a fall in forearm vascular resistance, and to ephedrine, with a marked increase of vascular resistance. The pressor effect of norepinephrine was associated always with bradycardia and with marked arteriolar and venous constriction in the forearm. Brachial arterial infusions of the drugs in nonpressor doses confirmed the vascular effects. Norepinephrine produced dose-dependent forearm constriction in all subjects, while vasodilatation was observed occasionally with tyramine and frequently with ephedrine.

The demonstrated differences in local vascular and systemic hemodynamic effects of these drugs suggest some inconsistency in the hypothesis that the effect of either ephedrine or tyramine is mediated exclusively by norepinephrine release.

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References


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