A PHYSIOLOGICALLY active vasodilator mechanism has not been described in the finger. Vasodilation in this cutaneous vascular bed has previously been ascribed solely to withdrawal of α-adrenergic sympathetic tone (Gaskell, 1956; Greenfield, 1960; Abramson, 1972). However, the digital vasospastic phenomena, experienced by patients treated with β-adrenergic-blocking agents (Greenblatt and Koch-Weser, 1974; Marshall et al., 1976; Eliasson et al., 1979), may imply that active β-adrenergic vasoconstriction has not been described in the finger. Vasodilation normally attenuates digital vasoconstrictor tone. β-adrenergic-blocking agents would then result in potentiation of vasoconstriction by unopposed α-adrenergic action.

Cobbold et al. (1960) reported that intra-arterial isoproterenol caused marked vasodilation in the forearm, but only slight or transient effects in the hand and foot. Since the forearm consists predominantly of skeletal muscle, and the hand and foot of skin, they concluded that a functional β-adrenergic vasodilator mechanism was not present in the cutaneous vascular bed. In preliminary studies, we confirmed that intra-arterial isoproterenol had no detectable effect on plethysmographic measurements of fingertip blood flow. However, this lack of effect might be due to the near maximal finger vasodilation present in the basal state. We therefore studied the effects of intra-arterial isoproterenol and pranopanol during digital vasconstriction. A β-adrenergic mechanism which can modulate the effects of intra-arterial vasoconstricting agents, but which has no apparent effect on reflex sympathetic vasconstriction, was identified in the fingertip.

Methods

Thirty-nine studies were performed in normal subjects. All studies were approved by the Institutional Review Board for Human Studies, and subjects gave informed consent. Subjects were supine in a controlled-temperature room. Fingertip total blood flow (FBF) was measured by air-displacement venous occlusion plethysmography. The hand was positioned slightly above heart level. The plethysmograph consisted of a finger cup sealed with caulk compound to the fingertip beyond the distal interphalangeal joint. A 25-mm-wide pneumatic cuff was applied proximal to the finger tip. The lowest venous occlusion pressure required to obtain the maximal rate of increase in fingertip volume was determined, and used throughout each study (average 58 mm Hg). Changes in fingertip volume were detected by a Sanborn pressure trans-
duced (268A) connected by stiff rubber tubing to the finger cup outlet. The system was calibrated by recording the pressure increase which occurred upon introduction of a measured volume of air. FBF was derived from the initial rate of rise in fingertip volume occurring with venous occlusion. The volume of the fingertip within the finger cup was determined by water displacement to express blood flow in ml/min per 100 ml tissue.

At the beginning of each study, an 18 gauge catheter was placed in the brachial artery and maintained patent with 0.5 ml/min infusion of 0.9% saline with 1 U/ml sodium heparin (Elkins-Sinn). All drugs were dissolved in the same heparinized saline just prior to use, and delivered intra-arterially by constant infusion pumps (Harvard Apparatus Company). At no time did the infusion rate exceed 2 ml/min.

In a 24°C room, we induced finger vasoconstriction by intra-arterial infusion of humoral agents and then studied the effects of isoproterenol or propranolol added to the intra-arterial infusion. After initiating infusion of each drug or drug combination, FBF reached a stable level within 3 minutes; then five measurements of FBF over 2 minutes were obtained and averaged to obtain a value for that dose. In 10 subjects, a dose of norepinephrine (levarenol bitartrate, Winthrop, 0.125–0.5 μg base/min) was chosen to reduce FBF to approximately 10–20 ml/min per 100 ml tissue. In two subjects, angiotensin amide (Ciba-Giegy, 0.1–0.2 μg/min), and in six subjects, tyramine hydrochloride (50–200 μg/min), were infused to produce vasoconstriction of similar degree to that caused by norepinephrine.

Isoproterenol hydrochloride (Winthrop, 0.025–0.1 μg/min) was then added to the infusion of norepinephrine, angiotensin, or tyramine. The dose of 0.1 μg/min isoproterenol was not exceeded to avoid systemic side effects. After isoproterenol was stopped and stable vasoconstriction was again present, propranolol hydrochloride (Ayerst, 0.5 mg in 3 ml saline) was infused through the arterial catheter over 2 minutes. When FBF reached a new stable level, the dose of isoproterenol, which prior to propranolol had produced maximal vasodilation, was readministered.

In six subjects, nutritional blood flow as reflected by radioisotope clearance was measured simultaneously with plethysmographic flow measurements during infusion of norepinephrine and during the addition of isoproterenol to the infusion of norepinephrine. Approximately 0.02 ml of Na131I in saline was injected with a 27-gauge needle into the skin of the pad of the fingertip adjacent to the finger with the plethysmograph. The clearance was monitored by a scintillation probe, ratemeter (time constant = 10 seconds), and linear recorder. The scintillation probe contained a thallium-activated sodium iodide crystal, 2.5 × 2.5 cm. The dose of radioisotope was about 2 μCi. The finger injection was made after plethysmographic measurements indicated stable vasoconstriction, resulting from an intra-arterial infusion of norepinephrine. No baseline clearance rates before starting norepinephrine were obtained in these tests. In previous studies (Coffman, 1972), a similar group of subjects under the same environmental conditions had iodine-131 clearance rates that were biphasic with the average half-time during the first rapid phase of disappearance equal to 5 minutes. In that study, lower doses of intra-arterial norepinephrine caused a reduction in both total and nutritional finger blood flow, and the clearance rates remained biphasic. In the present tests, larger doses of norepinephrine were used and resulted in greater reduction of both total and nutritional flow, and the clearance rates became nearly mono-exponential and remained stable for periods of 20 minutes. After injection, clearance was monitored for 8 minutes, after which isoproterenol (0.05–0.1 μg/min) was added to the norepinephrine infusion and measurements continued for an additional 8 minutes. Radioisotope activity was plotted on semilogarithmic paper after subtraction of the background counts, and half-times were estimated during the 6 minutes before, and 6 minutes after, adding isoproterenol to the infusion.

Reflex sympathetic vasoconstriction was induced in 10 subjects by exposure to a 20°C environment for 1 hour. At this time, there was a stable reduction of FBF to a degree similar to that produced by intra-arterial humoral agents. Five measurements of FBF were averaged to obtain a control value. In six subjects, intra-arterial isoproterenol (0.1 μg/min) and in four subjects, histamine phosphate (Lilly, 1–2 μg/min) was then infused for 5 minutes, and five flow measurements in the last 2 minutes were averaged. In the isoproterenol experiments, 15 minutes after stopping the isoproterenol, propranolol (0.5 mg) was given intra-arterially and flow measurements were repeated.

In five subjects, we studied the effect of propranolol on the finger vasoconstriction which occurs during another sympathetic stimulus, mental stress. FBF was measured simultaneously in the third finger of each hand in a 24°C room. When FBF became stable, an intra-arterial infusion of propranolol (10 μg/min) was started; this dose of propranolol has been shown to block the forearm vasodilation caused by intra-arterial isoproterenol (Brick et al., 1966). After 8 minutes, the subjects were asked to serially subtract a 2-digit number from a 4-digit number in time with a metronome for a period of 6 minutes. FBF was recorded continuously for 3 minutes before, during, and for 2 minutes after the arithmetic task, and flows were averaged during each period.

Intra-arterial blood pressure was monitored with a Hewlett-Packard pressure transducer (1280C), and heart rate was recorded during all studies. Mean blood pressure was calculated by adding one-third of the pulse pressure to diastolic pressure.
Finger vascular resistance (FVR) was calculated by dividing mean blood pressure by average blood flow. Statistical analyses were made by the Wilcoxon signed rank test (Colton, 1974) or with Student's t-test for paired data where n was less than six (mental stress and histamine tests). Data are presented as mean ± standard error.

Results

In a 24°C room, baseline FBF was high, averaging 61 ± 9.5 ml/min per 100 ml tissue. Intra-arterial norepinephrine reduced FBF to an average of 13 ± 5.9 ml/min. Isoproterenol, added to the norepinephrine infusion, caused a large fingertip vasodilation in each of 10 subjects (Table 1). After isoproterenol was stopped, finger vasoconstriction due to continued norepinephrine infusion returned to near its former value.

Infusion of propranolol potentiated the vasoconstriction caused by norepinephrine. When isoproterenol was readministered following propranolol, there still was a significant increase in FBF and decrease in FVR. However, the isoproterenol-induced increase in FBF after propranolol was significantly less than prior to propranolol (before propranolol, 168 ± 30%; after propranolol, 67 ± 20%, P < 0.01) and the fall in FVR was also smaller (before propranolol, 56 ± 4.6%; after propranolol, 31 ± 8.9%; P < 0.01).

In six subjects, we simultaneously monitored radioisotope clearance and total fingertip blood flow before and after adding isoproterenol to infusions of norepinephrine (Fig. 1). In these subjects, addition of isoproterenol to norepinephrine infusion caused an average of 54 ± 12% increase in total fingertip blood flow. However, the clearance rates were unchanged by the addition of isoproterenol (half-times: norepinephrine, 24 ± 5.2; norepinephrine + isoproterenol, 28 ± 7.2 min; P > 0.2).

In two subjects, angiotensin was used to produce finger vasoconstriction. Isoproterenol caused a decrease in FVR during angiotensin infusion in both subjects (baseline: 0.9 ± 0.2, angiotensin: 3.6 ± 1.5, isoproterenol + angiotensin: 2.5 ± 1.3 mm Hg/ml per min per 100 ml tissue).

In 10 subjects, finger vasoconstriction was induced by a 1-hour exposure to a cool environment. The increased FVR was of the same degree as that induced by norepinephrine (P > 0.3). Isoproterenol infusions did not attenuate, and propranolol did not potentiate this sympathetic reflex finger vasoconstriction in six subjects (Table 2). However, histamine infusions in four subjects caused a large increase in FBF (6.0 ± 1.0 to 22.3 ± 5.8 ml/min per 100 ml, P < 0.05) and decrease in FVR (14.7 ± 2.0 to 4.4 ± 0.9 mm Hg/ml per min per 100 ml tissue).

TABLE 1  Effect of Intra-arterial Isoproterenol and Propranolol on Finger Blood Flow and Vascular Resistance in Fingers Preconstricted with Intra-arterial Norepinephrine

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>NE</th>
<th>NE + ISO</th>
<th>NE</th>
<th>NE + P</th>
<th>NE + P + ISO</th>
</tr>
</thead>
<tbody>
<tr>
<td>FBF</td>
<td>61 ± 9.5</td>
<td>13 ± 5.9*</td>
<td>37 ± 7.5*</td>
<td>14 ± 3.6*</td>
<td>7.0 ± 1.1†</td>
<td>12 ± 2.9†</td>
</tr>
<tr>
<td></td>
<td>(ml/min per 100 ml)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FVR</td>
<td>1.9 ± 0.3</td>
<td>8.0 ± 1.3*</td>
<td>3.4 ± 0.7*</td>
<td>9.6 ± 2.0*</td>
<td>17 ± 3.7†</td>
<td>11 ± 1.9†</td>
</tr>
<tr>
<td></td>
<td>(mm Hg/ml per min per 100 ml)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean BP</td>
<td>87 ± 1.8</td>
<td>87 ± 2.0</td>
<td>89 ± 1.7</td>
<td>91 ± 1.8</td>
<td>94 ± 2.3</td>
<td>94 ± 2.0</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>60 ± 2.5</td>
<td>69 ± 2.5</td>
<td>58 ± 2.4</td>
<td>57 ± 2.8</td>
<td>57 ± 2.8</td>
<td>58 ± 2.3</td>
</tr>
</tbody>
</table>

Each value represents the mean ± SE of 10 subjects. NE = norepinephrine, ISO = isoproterenol, P = propranolol, FBF = finger blood flow, FVR = finger vascular resistance, BP = blood pressure.

* Significant difference from preceding column are denoted by *P < 0.01; †P < 0.02.


**Table 2**  Effect of Intra-arterial Isoproterenol and Propranolol on Finger Blood Flow and Vascular Resistance in a Cool Environment

<table>
<thead>
<tr>
<th></th>
<th>Control 1</th>
<th>ISO</th>
<th>Control 2</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>FBF (ml/min per 100 ml)</td>
<td>25 ± 11</td>
<td>20 ± 8.0</td>
<td>14 ± 5.6</td>
<td>16 ± 12</td>
</tr>
<tr>
<td>FVR (mm Hg/ml per min per 100 ml)</td>
<td>14 ± 7.4</td>
<td>13 ± 5.2</td>
<td>19 ± 7.7</td>
<td>24 ± 8.1</td>
</tr>
<tr>
<td>Mean BP (mm Hg)</td>
<td>76 ± 3.8</td>
<td>74 ± 4.6</td>
<td>81 ± 3.2</td>
<td>81 ± 2.8</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>52 ± 3.1</td>
<td>52 ± 3.9</td>
<td>52 ± 3.2</td>
<td>51 ± 3.6</td>
</tr>
</tbody>
</table>

Each value represents the mean ± SE of six subjects. Abbreviations are the same as in Table 1. No significant changes from control periods occurred when ISO or P was infused.

*P* < 0.005). Control blood flows were measured in a finger of the opposite arm in these experiments and showed no significant change (FBF 4.3 ± 0.7 to 3.7 ± 1.6, *P* > 0.5; FVR 20.4 ± 2.1 to 32.2 ± 8.0, *P* > 0.1).

In five subjects, a brief period of sympathetic reflex finger vasoconstriction was induced during mental stress produced by an arithmetic task (Table 3). Prior to mental stress, an infusion of propranolol (10 μg/min) was started in one brachial artery. This dose of propranolol caused no significant change in FVR (control, 2.0 ± 0.5; propranolol, 1.8 ± 0.6 mm Hg/ml per min per 100 ml tissue). Before, during, and after mental stress, the degree of finger vasoconstriction in the hand treated with propranolol was not significantly different from the contralateral hand. Mean FVR of both hands, blood pressure, and heart rate rose significantly during mental stress.

In six subjects, we caused finger vasoconstriction with intra-arterial infusion of tyramine (Table 4). Tyramine produced finger vasoconstriction that was not significantly different from that produced by norepinephrine infusions or environmental cooling. Neither isoproterenol nor propranolol changed FVR when vasoconstriction was caused by tyramine infusion. A small but significant fall in mean blood pressure occurred when isoproterenol was added to intra-arterial infusions of tyramine.

Except for the one exception noted during tyramine infusions, no significant change in heart rate or blood pressure occurred with each change of intra-arterial drug infusion. A small but significant gradual increase in systemic blood pressure occurred during the studies with humoral agents, probably as a result of the prolonged intra-arterial infusion of vasoconstrictor agents.

**Discussion**

We have shown that the β-adrenergic agonist, isoproterenol, dilates and the β-adrenergic antagonist, propranolol, potentiates the fingertip vasodilation produced by intra-arterial norepinephrine. This is the first direct evidence that a local β-adrenergic vasodilator mechanism can affect blood flow in a human cutaneous vascular bed.

The fingertip circulation consists of arteriovenous anastomoses in parallel with the fingertip capillaries. In previous work, intra-arterial norepinephrine was shown to reduce both fingertip arteriovenous shunt and nutritional blood flow (Coffman, 1972). In the present study, isoproterenol caused a marked increase in the fingertip total blood flow during norepinephrine-induced vasoconstriction, but the nutritional clearance was not affected. This suggests that the β-adrenergic vasodilator mechanism acts solely on the arteriovenous shunt vessels.

Isoproterenol also caused vasodilation in fingers preconstricted with intra-arterial angiotensin. Scroop and Whelan (1966) showed that intra-arterial angiotensin causes vasoconstriction by a direct action on vessels which was not modified by α-adrenergic blockade. Thus, the dilator response to isoproterenol is not restricted to an interaction with

**Table 3**  Effect of Intra-arterial Propranolol on Finger Vascular Resistance during and Immediately after Mental Stress

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>During mental stress</th>
<th>Following mental stress</th>
</tr>
</thead>
<tbody>
<tr>
<td>Propranolol-treated digit FVR (mm Hg/ml per min per 100 ml)</td>
<td>1.8 ± 0.6</td>
<td>5.1 ± 0.9*</td>
<td>1.6 ± 0.4</td>
</tr>
<tr>
<td>Control digit FVR (mm Hg/ml per min per 100 ml)</td>
<td>1.5 ± 0.3</td>
<td>5.2 ± 0.7*</td>
<td>1.7 ± 0.5</td>
</tr>
<tr>
<td>Mean BP (mm Hg)</td>
<td>75 ± 0.9</td>
<td>90 ± 5.0†</td>
<td>79 ± 2.0</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>61 ± 6.5</td>
<td>76 ± 8.3†</td>
<td>61 ± 5.8</td>
</tr>
</tbody>
</table>

Each value represents the mean ± SE of five subjects. Abbreviations are the same as in Table 1. No significant differences occurred between control and propranolol-treated digits. Significant changes from baseline are denoted by *P* < 0.05; †*P* < 0.01.
the α-adrenergic vasoconstrictor mechanism because it modulates other humorally produced vasoconstriction.

No effect of isoproterenol on FBF was observed when vasoconstriction was produced by environmental cooling. Finger vasoconstriction during our relatively mild environmental cooling stimulus is mediated primarily via sympathetic nerves, although an increase in circulating catecholamines and local digital cooling might have contributed to the reduction in flow. This inability of isoproterenol to oppose reflex sympathetic nerve stimulation is probably specific for β-adrenergic agonists, since histamine, a nonadrenergic agonist, produced a large increase in FBF and decrease in FVR in all four subjects tested. To further ascertain the effect of isoproterenol on sympathetic nerve-mediated vasoconstriction, FBF was reduced with intra-arterial tyramine infusions. In these tests, done in a warm environment, no sympathetic vasoconstriction reactions to cold or effects of local cooling were present. Tyramine has little direct vasoconstrictor action, but induces vasoconstriction by causing the release of stored norepinephrine largely from sympathetic nerve endings (Trendelenberg, 1961). The lack of effect of isoproterenol on tyramine-induced finger vasoconstriction also suggests an inability of the β-adrenergic vasodilator mechanism to affect sympathetic nerve-mediated vasoconstriction.

The work of Abboud et al. (1965, 1966) offers an explanation for the inability of isoproterenol to affect sympathetic nerve-mediated vasoconstriction. These investigators found that the dilation caused by isoproterenol in the dog paw occurred in the distal small vessel segment where intra-arterial norepinephrine also exerted its vasoconstrictor effect. There was little, if any, effect of isoproterenol on the large arteries and veins where sympathetic nerve stimulation produced the greatest resistance to flow. Similarly, isoproterenol may not affect cold or tyramine reduced fingertip blood flow if sympathetic nerve-mediated vasoconstriction occurs in proximal larger vessels without affecting the α-adrenergic vasoconstrictor mechanism in the fingertip arteriovenous shunts. Activating the β-adrenergic mechanism in the arteriovenous shunts, which remain vasodilated, would then have little effect on fingertip blood flow. If basal levels of vascular tone produced by sympathetic nerves also occur in the vascular segment proximal to the fingertip arteriovenous shunts, the inability of isoproterenol to affect resting fingertip blood flow may be explained.

Propranolol potentiated the finger vasoconstriction caused by norepinephrine infusions. Similar potentiation by β blockers of norepinephrine-induced vasoconstriction has been demonstrated in other vascular beds in animals (Glick et al., 1967) and in humans (Glover and Hutchinson, 1964; Lowe and Robinson, 1964; White and Udwadia, 1975) and has been interpreted as representing blockade of the β-adrenergic agonist behavior of norepinephrine, resulting in unopposed α-adrenergic action.

In contrast, propranolol had no effect on primarily sympathetic vasoconstriction produced by cooling, mental stress, or tyramine. Glick et al. (1967) demonstrated similar differences in the dog hind-limb between the effects of β blockade on intra-arterial norepinephrine and norepinephrine released from sympathetic nerves. They concluded that neurally released norepinephrine does not reach vascular β receptors in concentrations large enough to produce physiologically significant stimulation. Moran et al. (1980) found that propranolol slightly augmented the dog skeletal muscle vasoconstrictor response to nerve stimulation. This potentiation was blocked by pretreatment with cocaine, and was therefore ascribed to propranolol-induced inhibition of neuronal reuptake of norepinephrine. In our studies of the fingertip circulation, propranolol had no apparent pre-synaptic or postsynaptic effect on responses mediated by sympathetic nerves. Our finding that neither isoproterenol nor propranolol affects sympathetic digital vasoconstriction further suggests a spatial dissociation of the site of β-adrenergic vasodilation from the site of sympathetic nerve-mediated vasoconstriction. A previous conclusion has been that peripheral vascular beta receptors are not innervated, but are "hormonal" receptors responding to circulating catecholamines (Glick et al. 1967; Rosell and Belfrage, 1975; Russell and Moran, 1980).

Our data indicate that a β-adrenergic mechanism is capable of causing vasodilation of fingertip arteriovenous shunts constricted by humoral agents.

![Table 4: Effect of Intra-arterial Isoproterenol and Propranolol on Finger Blood Flow and Vascular Resistance in Fingers Preconstricted with Intra-arterial Tyramine](http://circres.ahajournals.org/figure/1981/49/5/1200.jpg)
The role of this newly discovered cutaneous vasodilator mechanism in the physiological control of finger circulation is, as yet, unknown. Three to six (Greenblatt and Koch-Weser, 1974; Eliasson et al., 1979), or possibly a greater percentage (Marshall et al., 1976), of hypertensive patients on propranolol therapy develop Raynaud’s phenomenon or cold hands and feet. These side effects have previously been ascribed to the central cardiovascular depressant effects of β blockade, inducing increased reflex sympathetic vasoconstriction (White and Udwadia, 1975; Marshall et al., 1976; Eliasson et al., 1979) or to a propranolol-induced decrease in the plasma volume (Julius et al., 1972). We have presented evidence that intra-arterial propranolol causes no local potentiation of cold or mental stress-induced fingertip vasoconstriction in normal subjects. However, the possibility that propranolol could potentiate finger vasodilatation caused by increased levels of circulating catecholamines in some hypertensive patients has been postulated (Hansson and Hökfelt, 1979), and our findings would provide a physiological basis for such a mechanism.

Acknowledgments

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