The Direct Renal Vascular Effects of Epi-
ephrine and Norepinephrine before and
after Adrenergic Blockade

By Merrill P. Spencer, M.D., Adam B. Denison, Jr., M.D., and Harold D. Green, M.D.

By use of a noncannulating electromagnetic flowmeter the direct vasoconstrictor response of the dog renal vasculature to intra-arterial epinephrine was found to be but slightly greater, weight for weight, than that of norepinephrine. No dilation phase to their reactions was found before or after Ildar, and this adrenergic blocking drug failed to dilate the renal vasculature in four out of five dogs in the anesthetized and operated state.

By direct intra-arterial injections, the response of the muscle vascular bed to L-epinephrine in dogs has been found to be a double one, that is, an initial vasoconstriction followed by vasodilation, while L-nor-
epinephrine and sympathetic nerve stimulation give essentially a vasoconstrictor response. These investigators found that the cutaneous vascular bed responds both to drugs and to sympathetic nerve stimulation by pure vaso-
constriction without reversal by the adrenergic blocking drugs. They report that all responses in both these vascular beds are blocked by the adrenergic blocking agents, Ildar, Dibenzyline, Regitine and Priscoline. So-called reversal of the epinephrine response in the muscle vascula-
ture arises because the constrictor response is blocked at a lower dose than the dilator re-
sponse.

This study was carried out, first, to deter-
mine the direct effects of L-epinephrine and L-norepinephrine on renal vasomotor tone. Second, we wished to study the blocking action of Ildar on these responses in regard to effi-
ciency of blockade and possible reversal ef-
fects. Third, we were interested in any direct dilator effect of adrenergic blockade which might indicate a tonic sympathetic vasocon-
striction in the kidneys of anesthetized dogs. Ildar, the newest member of the adrenergic blocking agents, was the drug of choice because in humans it has the fewest side effects of the four blocking drugs listed, yet in dogs it is capable of blocking completely the constrictor responses of epinephrine, norepinephrine and sympathetic nerve stimulation in skin and muscle and has a wide dose range between epinephrine reversal and norepinephrine block-
ade in muscle vascular beds.

METHODS

Left or right renal blood flow and femoral arterial pressure were measured directly and continu-
ously in 10 pentobarbitalized dogs (12 to 15 Kg.) during the intra-arterial injection of 1, 3 and 10 ug. doses of L-epinephrine (hydrochloride) and L-norepinephrine (base). In five dogs these doses were repeated after progressively increased intra-
arterial doses of Ildar.

For the measurement of blood flow a new de-
velopment of the electromagnetic flowmeter was

† The following drugs were kindly supplied to us by the companies indicated: Adrenaline hydro-
TABLE 1.—Comparison of Renal Vasocconstrictor Actions of Intra-arterial I-Epinephrine and I-Norepinephrine

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These observations were made in nine experiments, four of which were adrenergic blockade experiments reported here. Each norepinephrine injection was immediately prior to, or immediately following, the paired epinephrine injection of the same animal.

I-Epinephrine 3 µg.  I-Norepinephrine 3 µg.

Fig. 1. Records illustrating progressive blockade of renal vascular response to 3 µg. of l-epinephrine and l-norepinephrine by increasing doses of lidar. On each record, blood flow is indicated in milliliters per minute. Mean femoral arterial pressure in millimeters Hg marked at the top; time after injection in minutes, at the bottom of each segment. Zero flow, checked periodically by brief occlusion of renal artery, is indicated by sharp deflections in flow records.

RESULTS

Direct Effects of I-Epinephrine and I-Norepinephrine on the Renal Vasomotor Tone.

†Mepesulfate (Treburon) is a heparin-like anticoagulant obtained from Hoffmann-LaRoche, Inc., Nutley, N. J.
Table 2.—Adrenergic Blocking Doses of Ilidar in the Kidney

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Non-blocking = largest dose of Ilidar tried which failed to block completely. Blocking = smallest dose which completely blocked responses. Estimated = logarithmic average of doses which completely blocked response.

Both sympathetic amines gave pure vasoconstrictor responses so far as the net vasomotor tone was concerned, with no dilator phase being seen at any dose. Table 1 shows the degree of constriction brought about by paired 1, 3, and 10 µg. doses of l-epinephrine and l-norepinephrine previous to use of Ilidar. Since mean arterial pressure was unaffected by these doses, the effect on vasomotor tone was analyzed by integrating the change in the volume flow and response time into a single factor expressing the volume of blood shunted away from the kidney by each drug action. On the average, l-epinephrine had a slightly greater vasoconstrictor effect than l-norepinephrine, but calculations of the probabilities that the observed differences were not due to chance established statistical significance only to the 10 µg. doses.

**The Blocking Action of Ilidar on the Renal Vasomotor Tone.**

Our method of studying rapid responses of renal blood flow to the intra-arterial injection of drugs eliminates reflex neurogenic and hormonal effects which obscure the direct action of pressor and depressor drugs injected intravenously. In addition, renal autonomous vasomotor mechanisms resulting from changes in the systemic arterial pressure are eliminated.

Our finding that epinephrine has but little more direct renal vasoconstrictor effect than norepinephrine is apparently in disagreement with Ahlquist’s finding that “it required five to ten times more levarternol than epinephrine to produce an equivalent degree of renal vasoconstriction by intra-arterial injection.” Two factors help to resolve this and other discrepancies reported by various investigators who compared these two drugs. First, we compared norepinephrine base with equal weights of epinephrine hydrochloride while Ahlquist made his injections on an equimolar basis. This factor could, however, reduce the apparent strength of epinephrine, compared with

**Vasoconstrictor Effects of l-Epinephrine and l-Norepinephrine.** From the original records from one experiment (fig. 1) it is apparent that stepwise increases in the dose of Ilidar progressively blocked the vasoconstrictor actions of both adrenergic drugs. As expected, progressively larger doses were required to block the larger doses of the sympathetic amines. Table 2 shows the doses necessary to effect complete blockade. In no experiment did Ilidar unmask any vasodilator effect of either l-epinephrine or l-norepinephrine.

**Discussion**

Our method of studying rapid responses of renal blood flow to the intra-arterial injection of drugs eliminates reflex neurogenic and hormonal effects which obscure the direct action of pressor and depressor drugs injected intravenously. In addition, renal autonomous vasomotor mechanisms resulting from changes in the systemic arterial pressure are eliminated.

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that of norepinephrine, by only 23 per cent.
The second and more important explanation
of the discrepancy comes from an analysis of
the dosage response curves of the two sympa-
thetic amines. When the molar doses are plotted
against the average volume of blood shunted
away from the kidney, the epinephrine re-
response is consistently greater, but it is also
apparent that, when stating the magnitude of
the difference, it matters greatly whether one
compares doses necessary to give the same re-
response, as Ahlquist did, or whether one com-
pares the responses obtained at the same dose,
as our experiments do. This factor is most ap-
parent at the lower dose ranges used. Thus with
0.045 micromols of epinephrine base (1 µg.
epinephrine hydrochloride or 0.846 µg. epi-
nephrine base) it requires 300 per cent more
norepinephrine to give the same response, but
0.045 micromols of norepinephrine base (0.70
µg.) will give 60 per cent of the response given
by 0.045 micromols of epinephrine. Because
of the variability of individual responses, the
difference between the drugs measured by the
latter method does not appear statistically
significant. At the 10 µg. dose level, the differ-
bence between the two drugs by the latter
method becomes greater and that of the former
becomes smaller.

Since intra-arterial Ilidar, in doses capable
of blocking strong adrenergic constriction of
ejpinephrine and l-norepinephrine, caused no
vasodilation following its injection into four
out of five dogs, these results fail to demon-
strate consistent tonic sympathetic effect on
the renal vasculature during the anesthetized
and operated state. There is no reason to sus-
pect that the renal nerves were not functional
in each experiment, since the application of the
flowmeter was far from a denervation proce-
dure.

**Summary and Conclusions**

The actions of Ilidar on the innervated renal
vasculature and on the direct renal responses
to intra-arterial injections of l-epinephrine and
l-norepinephrine were studied in five pento-
obarbitalized dogs. Renal blood flow was mea-
sured with a noncannulating development of
the electromagnetic flowmeter, the magnet-
electrode assembly of which was applied di-
rectly to the surgically exposed artery. Doses
of 1, 3 and 10 µg. of the two catechol amines
were administered intra-arterially before and
after progressively increasing doses of the
adrenergic blocking agent. The following con-
clusions are reached:

When injected directly into the arteries of
innervated kidneys, l-epinephrine has a greater
vasoconstrictor action than that of l-norepi-
nephrine. This difference is more apparent at
10 µg. than at 1 and 3 µg. doses.

The adrenergic blocking drug, Ilidar blocks
but does not reverse the constrictor reactions
of epinephrine and norepinephrine.

Neither sympathomimetic amine has a renal
vasodilator effect either manifest or latent.
It is therefore concluded that the renal vas-
culature is incapable of responding directly to
the vasodilator potentiality of epinephrine.

Intra-arterial injections of Ilidar cause no
vasodilation in the renal vascular circuit of
anesthetized and operated dogs when blood
loss has not been large.

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The Direct Renal Vascular Effects of Epinephrine and Norepinephrine before and after Adrenergic Blockade

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