The Response of the Renal Circulation in Man to Constant-Speed Infusions of \( l \)-Norepinephrine

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The effects of constant-speed intravenous infusions of \( l \)-norepinephrine in man have been studied with reference to the changes produced in the renal circulation. The responses to four rates of infusion were studied both qualitatively and quantitatively in each of nine normal men. As dosage was increased glomerular filtration rate changed little if at all, effective renal plasma flow diminished, and filtration fraction rose. Both afferent and efferent glomerular arteriolar resistances sharply increased, but the latter did so much more markedly than the former.

NOREPINEPHRINE, a naturally occurring pressor amine with potent vasoconstrictor properties, has recently been the subject of much study and investigation. This hormone has been shown to constrict the peripheral arterioles\(^4\)\(^-\)\(^7\) both in cutaneous vessels and in skeletal muscle,\(^8\) to increase the pressure in the pulmonary circuit\(^1\) (although this is primarily due to an increase in pulmonary venous pressure rather than to a constriction of the pulmonary arterioles\(^9\)), to diminish the cerebral blood flow,\(^6\)\(^-\)\(^7\) to reduce slightly the hepatic blood flow,\(^9\) to dilate the coronary arteries,\(^9\) and to produce splenic contraction.\(^9\) It also causes a rise in peripheral venous pressure\(^3\) and constricts the arterial segments of the terminal capillary loops in the nailfold.\(^10\) Its pharmacodynamics has been thoroughly reviewed in recent publications.\(^11\),\(^12\)

Studies on the effects of norepinephrine upon the renal circulation have been far less extensive. Barnett and co-workers\(^13\) showed that this hormone reduced renal blood flow in six subjects were studied, each at a single dose of 20 to 30 micrograms per minute. Although all six men showed a reduction in renal blood flow, the experimental observations were confined to a single clearance period in each subject. In the dog, norepinephrine has been reported to diminish the renal blood flow\(^14\) and also to produce no change in it.\(^15\) Our own observations\(^16\),\(^17\) and those of Werkö and associates\(^18\) support the assertion that norepinephrine is a renal vasoconstrictor in man. Both of these research groups have shown that the hormone increases renal resistance. However, in the latter investigation,\(^19\) the segmental resistances were calculated by formulas\(^19\) in which a value for the renal venous pressure enters into the computation. In the study of Werkö and his colleagues, this parameter was apparently not measured and an assumed value would have to have been used in the calculations. Since norepinephrine\(^4\) as well as other vasoconstrictors\(^20\) have been shown to alter venous pressure, the assignment of an assumed and constant value to the venous pressure seems invalid to us. At any rate, the detailed relation between dose and response was not the subject of Werkö's study.

On the glomerular filtration rate in man, norepinephrine has been reported to produce "small changes in both directions,"\(^18\) slight falls,\(^13\) and no change.\(^13\),\(^21\) In the dog, filtration rate has been reported to show no change,\(^15\) or a depression.\(^14\)

In view of these discrepancies, and because of the suggestion\(^1\) that norepinephrine plays an important role in the pathogenesis of essential
hypertension, it seemed advisable to us to attempt to ascertain definitively, both qualitatively and quantitatively, the renal hemodynamic effects of norepinephrine in man. Further impetus for physiologic quantitation in this regard stems from the clinical therapeutic use of norepinephrine in a variety of hypertensive conditions, such as surgical, hemorrhagic, and traumatic shock, after sympathectomy, after excision of pheochromocytomata, and after acute myocardial infarction.

We have attempted, therefore, to define the effects in man of constant speed l-norepinephrine infusions upon glomerular filtration rate, effective renal plasma flow, afferent glomerular arteriolar resistance, and efferent glomerular arteriolar resistance in normal man and to quantitate the dose-response relationships.

Methods

Experimental Procedure

The subjects were nine clinically normal young men. Glomerular filtration rate was measured by inulin clearance, and effective renal plasma flow by para-aminohippurate (PAH) clearance. Each subject was placed on a normal diet of constant and known composition a week before the experiment was to take place. All studies were made in the morning after a ten-hour fast. After a suitable priming injection, a solution of inulin and para-aminohippurate in 0.85 per cent saline was administered intravenously by a Bowman constant speed infusion pump at a rate calculated to produce an inulin concentration in serum of about 30 mg. per 100 ml. and a para-aminohippurate concentration of 1 to 2 mg. per 100 ml. Urine was collected through a multieyed catheter, and the bladder rinsed with distilled water or inflated with air at each emptying. In order further to minimize errors in urine collection, the studies were performed under water diuresis, each subject drinking 200 ml. of tap water every 20 minutes, starting two to three hours before the beginning of the experimental observations. Femoral arterial blood samples were collected at midperiod under oil by means of an indwelling Cournand needle. All blood was centrifuged and the serum separated with minimum possible delay.

After about 30 minutes (to allow for equilibration), a second slow intravenous infusion of 0.85 per cent saline was started in a different vein. The bladder was then emptied, and, after two control periods, a solution of 5 to 10 micrograms per mil-

litter of l-norepinephrine* in 0.85 per cent saline was substituted for the control saline. This solution was freshly made up just before use and was also administered by constant speed infusion pump. Four successive pairs of clearance periods were then performed, stepwise increments in rate of norepinephrine infusion being made at the end of each pair of periods. The dosage range studied varied from 2.0 micrograms per minute to 37.6 micrograms per minute. The period of administration at each dosage rate was approximately 20 minutes. Blood pressure was determined once a minute by sphygmomanometer.

An additional subject was studied in a somewhat different manner. After four control clearance periods (employing the same technics as outlined above), an intravenous infusion of l-norepinephrine was started and the rate of flow adjusted by a 4 cm. channel clamp. The rate was adjusted so as to maintain an approximately constant blood pressure of 210/110. The dose thus administered was calculated by a running count of the number of drops passing per minute through the calibrated Murphy drip.

Chemical Methods

Inulin was determined in cadmium sulfate filtrates of serum and urine by the method of Roe.22 Par-aminohippurate was determined in the same filtrates by the method of Smith and associates.20 Hematocrits were determined on alternate blood specimens, with dried heparin as anticoagulant. Serum proteins† were determined by a modification of the Howe precipitation and Kjeldahl digestion.

Calculations

Inulin clearance was calculated in the conventional way as the product of the urine flow (milliliters per minute) and the concentration of inulin in urine (milligrams per 100 ml.) divided by the concentration in serum (milligrams per 100 ml.). All clearance values were corrected to a surface area of 1.73 square meters. Afferent and efferent arteriolar resistances were calculated according to the formulas of Lamport.25, 26

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† We are indebted to the Billings Hospital Clinical Chemistry Laboratory under Dr. Richard L. Landau for the serum protein determinations.
‡ Subsequent to the completion of a major portion of this work, Gómez27 presented a new method for calculating resistance in various segments of the renal vascular tree. While not intending to render judgment upon the relative merits and validity of the two derivations, we have retained the Lamport formulas instead of those of Gómez because the latter require that renal venous pressure either be known or
FIG. 1. Dose-response curves for glomerular filtration rate, effective renal plasma flow, and filtration fraction in nine normal men receiving graded constant-speed infusions of l-norepinephrine. Infusions were started at a low initial rate and then gradually increased in stepwise fashion. Each point represents the average of two clearance periods during which the l-norepinephrine infusion rate remained constant. The points representing the values thereby obtained in each subject are connected by straight lines.

RESULTS

The dose-response curves for all nine subjects are illustrated in figure 1. The glomerular filtration rate (GFR) changed little, if at all. One individual, who exhibited an unusually high tolerance to norepinephrine in terms of pressor response, showed a tendency towards diminution in glomerular filtration rate as higher infusion rates were achieved, but percentage-wise this change was not great.

The effective renal plasma flow (ERPF) showed a clear-cut and progressive decrease with increasing norepinephrine dose (fig. 1). One individual failed to exhibit further decrease in renal venous pressure after the second increase in infusion rate.*

The filtration fraction (FF) rose as norepinephrine infusion rate was increased. As with the first two functions, percentile change was linearly related to the logarithm of the dose.

The results obtained on the subject who was started abruptly on a rapid rate of infusion of norepinephrine, rather than on a low rate with successive gradual increases, were quite different (fig. 2). When the norepinephrine infusion was started, both the glomerular filtration rate and the effective renal plasma flow fell sharply with a concomitant rise in filtr-

* The anomalous behavior of this subject is apparent in figures 1, 3, and 4. Since the experimentally determined effective renal plasma flow is employed in the calculation of the filtration fraction and the afferent and efferent arteriolar resistances, variations in the first of these parameters are reflected in the others. The experiment was repeated on this subject because his response was at variance with the other eight men. The data derived from the duplicate study were entirely in accord with those for the other subjects. However, since no experimental error could be found in the first run, either in the procedure itself or in the chemical laboratory, the data from this experiment have been retained and appear in the graphs in unaltered form.
tion fraction. As the infusion continued, the glomerular filtration rate returned to control values, but although the effective renal plasma flow also rose, it remained well below the range observed before the norepinephrine infusion was begun.

The dose-response curves for the afferent and efferent glomerular arteriolar resistances are shown in figure 3. Although both these parameters rose with increasing dosages, the efferent resistances did so more sharply. In order to indicate the differential in responsiveness to norepinephrine of the afferent and efferent arterioles in each individual subject, the graphic method of figure 4 has been employed. In this figure, the difference between the percentile increments in efferent and afferent resistance are plotted for each subject against the corresponding dose. Thus, for any particular infusion rate, when the ordinate is positive and greater than zero, the percentage increment in efferent resistance exceeds that of the afferent. For any particular individual, when the dose-response curve has a positive slope, the percentage increase in efferent resistance is increasing more rapidly with increase in dosage than is that of the afferent resistance. As can be seen from figure 4, the response of the efferent arteriolar resistance to increasing doses of norepinephrine is clearly greater than that of the afferent resistance.

**DISCUSSION**

It has seemed to us a refinement of dubious value to subject these data to exhaustive mathematical analysis, since simple inspection of the curves in figure 1 and figure 3 indicates a rough linearity between percentile change and the logarithm of infusion rate. This is in accord with Goldenberg's assumptions and observations that blood pressure bore a roughly rectangular hyperbolic relationship to norepinephrine infusion rate.1

There is general agreement that norepinephrine reduces renal blood flow in man while producing slight or inconstant changes in glomerular filtration.16, 18, 13, 21 Recently, Moyer...
and Handley\textsuperscript{14} have reported a decrease in glomerular filtration rate in dogs receiving intravenous norepinephrine. These dogs weighed from 10 to 20 Kg, and the doses employed were 10 micrograms and 30 micrograms per minute. A proportional dose for a 70 Kg. man would be much greater than those employed in establishing the dose-response curves herein reported. They may be considered more analogous to our experiment (fig. 2) in which a rapid rate of infusion of norepinephrine was started abruptly. If it is assumed that the rapidity with which a certain rate of norepinephrine administration is achieved influences the effect on glomerular filtration rate, some of the existing discrepancies in the available data are clarified.

The establishment of dose-response curves for normal human subjects makes possible investigations on the effects of various agents upon the responsiveness of the renal circulation to norepinephrine. Studies along these lines have been made in this laboratory with cortisone and desoxycorticosterone.\textsuperscript{27}

\textbf{Summary and Conclusions}

1. The effects of constant speed infusions of \textit{l}-norepinephrine upon renal hemodynamics in normal men have been studied, and the responses of glomerular filtration rate, effective renal plasma flow, filtration fraction, afferent glomerular arteriolar resistance, and efferent glomerular arteriolar resistance have been established for varying rates of norepinephrine administration. Four rates of infusion were studied in each of nine subjects.

2. With increasing norepinephrine dose, the glomerular filtration rate remained essentially unchanged, the effective renal plasma flow decreased, the filtration fraction increased, and both afferent and efferent glomerular arteriolar resistance increased (the latter change exceeding the former). Percentile change in the parameters affected by norepinephrine showed an approximately linear relation to the logarithm of the rate at which the hormone was being administered.

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\textbf{Sumario Español}

1. Los efectos de infusiones rápidas constantes de \textit{l}-norepinefrina en la hemodinámica renal en hombres normales han sido estudiados y las respuestas en el promedio de filtración glomerular, circulación plasmática renal efectiva, fracción filtración, resistencia arteriolar glomerular aferente y resistencia arteriolar glomerular eferente han sido establecidas para variables velocidades de administración de norepinefrina. Cuatro velocidades de infusión fueron estudiadas en cada uno de nueve sujetos.

2. Con aumento en la dosis de norepinefrina, la filtración glomerular promedio permaneció esencialmente sin cambio, la circulación plasmática efectiva disminuyó, la fracción de filtración aumento, y ambas resistencias arteriolas glomerulares aferentes y eferentes aumentaron (la última más que la primera). Cambios en porcentaje en los parámetros afectados por la norepinefrina demostraron una relación aproximadamente lineal al logaritmo...
de la velocidad a la cual la hormona se administra.

REFERENCES
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