INFLUENCE OF WATER AND MANNITOL LOADS ON RADIO-HIPPURAN RENAL FUNCTION CURVES

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Several authors (*1–4*) have shown that in the dehydrated patient the descending portion of ^{131}I-Hippuran renal function curves is flatter than in hydrated patients and that the peak of the curve is reached later in dehydration. Wedeen and coworkers (*3*) showed a parabolic relationship between urine flow rate and an arbitrary index of the steepness of decline of the curves.

An analysis of ^{131}I-Hippuran curves (*5*) has shown that the descending as well as the rising curve is a permutation of the arterial blood concentration curve in dogs and men who have high urine flow rates and no mechanical obstruction to outflow. We have performed studies delineating the degree of dependence of the falling portion of the curve on urine flow rate. These studies indicate that at urine flows above 2–3 ml/min the curve is relatively independent of urine flow rate.

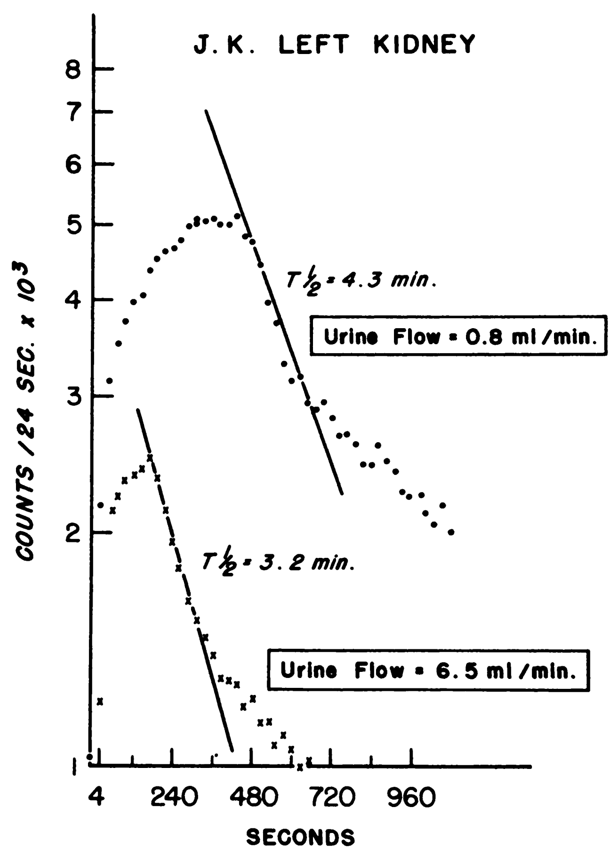

FIG. 1. ^{131}I-Hippuran studies in normal subject at urine flow rates of 0.8 and 6.5 ml/min. Counts/24 sec are replotted semilogarithmically and $T_{1/2}$ of initial descending slopes are determined.

METHODS

Seven normal subjects of both sexes ranging in age from 21 to 25 years were studied at varied urine flow rates produced by either withholding water overnight or administering sufficient water orally at 15-min intervals until a stable desired urine flow rate was achieved. Inasmuch as water loading increases urine flow only at the level of the distal nephron and collecting ducts and beyond, we also studied the effect of mannitol, an osmotic diuretic, which increases urine flow rate throughout the nephron, in five subjects. Mannitol was given by intravenous infusion of a 10% solution in water at rates which produced urine flow rates intermediate between two others achieved by water loading the same subject. In this manner the osmotic effect might be differentiated from distal urine flow-rate effects. Urine flow rates were determined by measuring voided urine volumes during timed intervals. When stable flow rates were achieved, an ^{131}I-Hippuran study was done in the seated position as previously described (*6*) with about 50 μCi in about 0.5-ml volume.

The pulses from three matched NaI(Tl) scintillation detectors (1½ × 1 in. recessed 2 in. in 20-deg flat-field collimator) directed at the kidneys and the left upper chest were recorded on magnetic tape. The pulses were subsequently replayed into a multiscaler to give counts per selected interval (usually 20 sec)

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(*6*). The data of each kidney and the chest were plotted on semilogarithmic paper. The initial descending portion of the curve is readily fitted by a straight line with little ambiguity (Fig. 1). The half-time of this line ($T_{1/2}$) was taken as a measure of the steepness of the curve. The half-time of the initial decline of the chest curve was measured similarly after the first minute when initial circulation effects had dissipated. The time to peak of each kidney curve was noted. Information from only one kidney was used in compiling the data.

RESULTS

The time to peak was plotted as a function of urine flow rate (Fig. 2). Above 2 ml/min urine flow rate produced by water loading, little change is noted in time to peak. The mannitol data suggest a continued but diminishing decrease in time to peak as urine flow rate—which in this situation reflects the degree of osmotic loading—increases.

Figure 3 relates urine flow rate to the half-time of initial disappearance from the kidney. At given urine flow rates the mannitol values of $T_{1/2}$ are generally lower than those obtained during water loading. As in the data of Wedeen *et al* (*3*), above about 2 ml/min, the points could be fitted equally well by a straight horizontal line or a gentle curve. In either case the $T_{1/2}$ values do not *appreciably* shorten as urine flow increases above 2 ml/min.

In Fig. 4 the $T_{1/2}$ value obtained from a kidney is compared with the value determined from the simultaneously obtained left upper chest curve. With the exception of four values obtained at urine flow rates below 2 ml/min, the data indicate a very close relationship between these measurements. In Fig. 5, the $T_{1/2}$ of the kidney has been divided by the simultaneously obtained chest $T_{1/2}$. With the exception of the same four points noted above, it is clear that the ratio of these values is independent of urine flow rate over an 11-fold range of flow rates. The mannitol $T_{1/2}$ values are not distinguishable from the water-loading values when normalized by the chest $T_{1/2}$ values.

DISCUSSION

Much of the renography literature implies that the descending portion of the renogram curves reflects only urine flow rate. These conclusions were reached by comparing dehydrated patients, whose urine flow rates might reach small fractions of a ml/min, with hydrated patients. The paper by Wedeen *et al* clearly indicates that at urine flow rates below about 2 ml/min their index of the slope of the descending curve is highly dependent on urine flow rate. There is too great variability in both their data and ours to determine whether a threshold phenomenon occurs at about 2 ml/min or whether a continuing but slight urine flow-rate effect is present.

In this study we have assumed that the curve obtained from the upper chest reflects bodily clearance and is independent of intrarenal movement of radioisotope. The apparently linear correlation of $T_{1/2}$ from the chest with that from the kidney (Fig. 4), except at low urine flows, indicates that, indeed, variation of the kidney $T_{1/2}$, at urine flow rates above 2–3 ml/min, reflects altered clearance rather than the effect of urine flow. A previous study (*7*) has

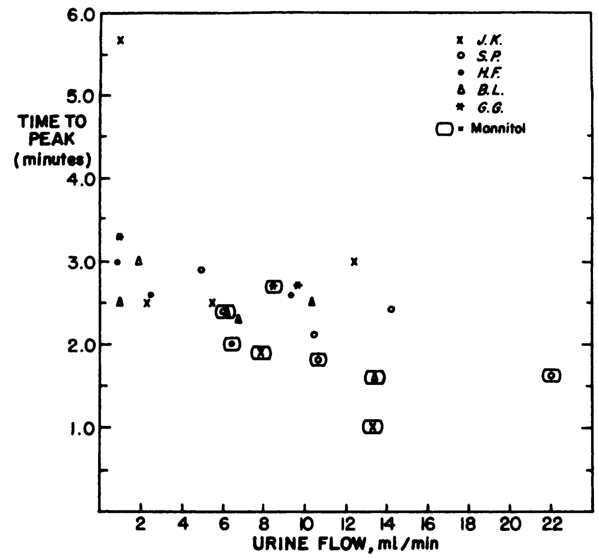

FIG. 2. Time to peak as a function of urine flow rate. Above about 2 ml/min there is little change in time to peak in water-loaded studies. Shorter times to peak at similar urine flow rates are present in mannitol studies.

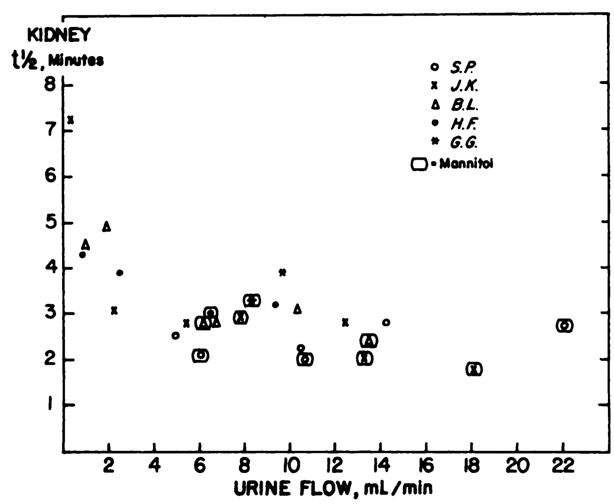

FIG. 3. Kidney $T_{1/2}$ related to urine flow rate. Above about 2 ml/min, $T_{1/2}$ is fairly constant in water-load studies. Mannitol values tend to be lower than water-load values.

shown that in dogs the initial slope of the descending curve reflects total renal clearance of PAH.

Mannitol diminishes tubular water reabsorption and thereby increases bulk flow in the tubules. It shortens passage time through the kidney as indicated by shorter times to peak (Fig. 2) compared to water-loaded subjects with similar urine flow rates. Mannitol may also shorten the $T_{1/2}$ of the descending slope compared to water loads at comparable urine flow rates (Fig. 3). This difference at similar urine flow rates indicates that a factor other than urine flow rate is operative. Mannitol is known to alter renal blood flow. The differences in $T_{1/2}$ noted above reflect changes of total renal clearance of ^{131}I-Hippuran rather than some effect on urine flow or tubular "washout" of the radioisotope, as evidenced by the similarity of values normalized by chest $T_{1/2}$.

Data obtained from intrarenal artery injections of ^{131}I-Hippuran in dogs indicated that mannitol loads had no major effect on transrenal passage in dogs with intact renal circulation but significantly shortened passage time in dogs with partially clamped renal arteries (*8*). The realization that the descending slope ($T_{1/2}$) of the renogram in a nonobstructed kidney with high urine output is a measure of total renal function has suggested a prognostic index of the curability of renovascular hypertension by surgery (*7*).

Several authors have indicated the sensitivity of prolonged retention of radioisotope seen in the descending portion of the renogram for detecting renal

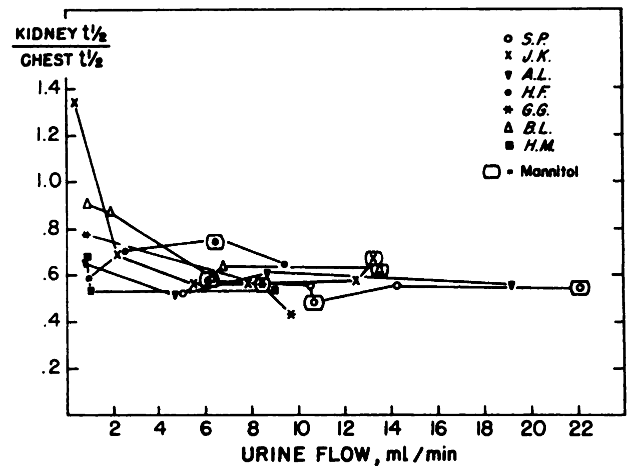

FIG. 5. Kidney $T_{1/2}$ to chest $T_{1/2}$ related to urine flow rate. Above about 2 ml/min ratio of kidney to chest $T_{1/2}$ is constant suggesting that variations in $T_{1/2}$ seen in Fig. 3 reflect differences in clearance rather than transrenal passage phenomena.

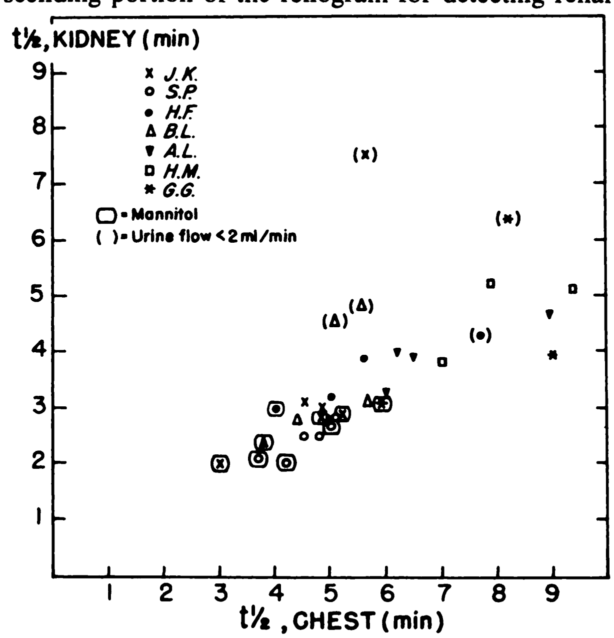

FIG. 4. Kidney $T_{1/2}$ related to chest $T_{1/2}$. Excluding four points obtained at low urine flow rates, correlation of two measurements is excellent indicating that at high urine flows kidney $T_{1/2}$ reflects rate of fall in blood and tissues.

arterial stenosis (*9–11*). This unilateral retention is produced by unilateral low urine flow and/or prolonged transtubular passage in the affected kidney. Performing renography in the dehydrated state will result in occasional unilaterally predominant retention of radioisotope which may be mistaken for unilateral renal disease. It should be noted that occasionally at quite low urine flow rates the initial descending slope of the kidney curve is, however, not prolonged unduly (HF, Fig. 4). Differences in retention which may be quite significant in diagnosis of renovascular disease may be masked by low flow rates. Also at low urine flow rates the curves cannot be used to evaluate total renal function. The data indicate that flow rates above 2 ml/min are desirable to avoid distortion of the renal area curve. The urine flow rate should be determined with each renogram to aid in interpretation.

SUMMARY

Urine flow rate was altered in normal subjects by dehydration, water loading and administration of mannitol. The ^{131}I-Hippuran studies were performed in each condition. The time to peak and the half-time of the initial portion of the descending renal curve ($T_{1/2}$) were related to the urine flow rates. Above about 2 ml/min urine flow rate, changes in $T_{1/2}$ could largely be ascribed to changes in total renal clearance as determined from the half-time of a curve simultaneously obtained from the upper chest rather than to any effect of urine flow *per se* or of renal "washout." Urine flow rate should be determined in clinical renography to properly interpret retention of radioisotope by a kidney. Flow rates above 2 ml/min are recommended to avoid distortion of the renal area curves.

REFERENCES

1. WAX, S. H. AND MCDONALD, D. F.: Analysis of the I^{131} sodium-o-iodohippurate renogram. *J. Am. Med. Assoc.* **179**:140, 1962.

2. MEADE, R. C. AND SHY, C. M.: The evaluation of individual kidney function using radiohippurate sodium. *J. Urol.* **86**:163, 1961.

3. WEDEEN, R. P., GOLDSTEIN, M. H. AND LEVITT, M. F.: The radioisotope renogram in normal subjects. *Am. J. Med.* **34**:765, 1963.

4. O'CONNOR, V. J., JR., LIBRETTI, J. V. AND GRAYHACK, J. T.: The early differential diagnosis of post operative anuria using the radioactive renogram: An experimental study. *J. Urol.* **86**:276, 1961.

5. FARMELANT, M. H., SACHS, C. E., GENNA, S. AND BURROWS, B. A.: A physiological model for the renal excretion of labeled compounds. *J. Nucl. Med.* **10**:664, 1969.

6. HINE, G. J., FARMELANT, M. H., CARDARELLI, J. A. AND BURROWS, B. A.: Four channel magnetic tape recording and digital analysis of radio-hippuran renal function tests in normal subjects. *J. Nucl. Med.* **4**:371, 1963.

7. FARMELANT, M. H., SACHS, C. E. AND BURROWS, B. A.: Prognostic value of radioisotopic renal function studies for selecting patients with renal arterial stenosis for surgery. Submitted to *J. Nucl. Med.*

8. FARMELANT, M. H., BAKOS, C. AND BURROWS, B. A.: Physiological determinants of renal tubular passage times. *J. Nucl. Med.* **10**:641, 1969.

9. BURBANK, M. K., HUNT, J. C., TAUXE, W. N. AND MAHER, F. T.: Radioisotopic renography. Diagnosis of renal arterial disease in hypertensive patients. *Circulation* **27**:328, 1963.

10. FARMELANT, M. H., LIPITZ, C. A., BIKERMAN, V. AND BURROWS, B. A.: Radioisotopic renal function studies and surgical findings in 102 hypertensive patients. *Am. J. Surg.* **107**:50, 1964.

11. MEADE, R. C., HORGAN, J. D. AND MADDEN, J. A.: Comparison of methods for renogram evaluation. *J. Nucl. Med.* **10**:40, 1969.

SECTION ON SPECIAL TOPICS: SESSION ON NUCLEAR MEDICINE CLINICAL APPLICATIONS OF NUCLEAR MEDICINE FOR THE PRACTICING PHYSICIAN

AMA ANNUAL CONVENTION
Chicago, June 1970
Monday, June 22, 2–5 P.M.
International Amphitheatre
Room J

1. William S. Maxfield, M.D., New Orleans, La.
   "The Camera Renogram Compared with Intravenous Pyelography."
2. Salvador Treves, M.D., New Haven, Conn.
   "Use of High Photon Yield Radionuclides in Kidney and Bladder Studies."
3. Milo M. Webber, M.D., Los Angeles, Calif.
   "Thrombophlebitis—Demonstration by Radionuclide Scanning."
4. James J. Conway, M.D., Chicago, Ill.
   "Radionuclide Studies of Pediatric Chest Diseases."
5. E. James Potchen, M.D., St. Louis, Mo.
   "The Radioisotopic Assessment of Regional Pulmonary Function."
6. Malcolm R. Powell, M.D., San Francisco, Calif.
   "Clinical Correlation of Liver Gamma Photography Findings."
7. Ernest Greenberg, M.D., New York, N.Y.
   "Kinetics of Bone Seeking Radionuclides Used for Bone Scanning."
8. Richard E. Peterson, M.D., Iowa City, Ia.
   "Screening for Metastatic Bone Lesions with Whole Body Scanning."
9. James J. Smith, M.D., New York, N.Y.
   "Treatment of Hyperthyroidism with Low Dose ^{131}I."