A non-invasive \(\gamma\)-camera technique for the measurement of intrarenal flow distribution in man

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Summary

1. A new method, based on the transit time of \(\sigma\)-iodohippurate sodium (Hippuran) through the kidney, is proposed as an accurate non-invasive means of measuring the intrarenal flow distribution in man.

2. Data from \(^{123}\)Hippuran \(\gamma\)-camera renography are utilized in this method which employs region of interest selection, deconvolution, cross-correlation and curve subtraction to obtain the spectrum of transit times through the cortical and juxtamedullary nephrons.

3. In 12 normal subjects the mean percentage cortical flow was 83.9\% (SEM 0.7\%) which is approximately the anatomical proportion of cortical nephrons in the human kidney.

4. Cortical flow as a percentage of total was significantly reduced in 21 hypertensive patients, all of whom had no evidence of primary renal disease (mean 74.6\%, SEM 1.5\%).

5. In both the normotensive and hypertensive groups there was a good correlation between the results obtained from the left and right kidneys of the same patient showing the parallel physiological response of the two kidneys (mean difference 4\%, \(P < 0.001\)).

6. Reduction in the distribution of flow to the cortical nephrons in the essential hypertensive patients supports the hypothesis that renal autoregulation is important in this syndrome.

Key words: cross-correlation, deconvolution, \(\gamma\)-camera renography, Hippuran, intrarenal flow distribution, transit time.

Introduction

There is to date no generally accepted method of determining the intrarenal flow distribution in man. The importance of this measurement lies in the fact that overall renal blood flow may remain relatively constant while marked alterations are occurring in renal physiology. The intrarenal haemodynamic changes which alter the flow to the cortical and juxtamedullary nephrons, may be the physiological determinant of salt and water homeostasis [1], may have an important role in the pathogenesis of renal failure [2] and in the kidney's response to hypertension [3]. Many of the proposed techniques are not readily applicable in man [4, 5], and the only two claiming some support are the inert-gas washout [6] and the \(^{131}\)Hippuran transit-time methods [7–9].

Validation of the \(^{133}\)Xe-washout technique has been frequently attempted [10, 11], but only Schuler et al. [12] have shown a good correlation between the curve components and the distribution of microspheres in the kidney. They, however, studied a situation in which no change in intrarenal blood flow distribution was found. Other workers in the field have failed to show this correlation and the method has been subject to much criticism [4, 13–17]. Although requiring an arterial catheter, it is a reasonable method for measuring the total renal blood flow [11], but \(^{133}\)Xe-washout curves given the above criticism should not be used to estimate the intrarenal flow distribution with any justification.

The Hippuran transit-time method has been validated in man [18, 19]. The results of this method have been reproduced by Reeve &
Crawley [20] using a different deconvolution technique avoiding albumin injection and computer-assisted blood background subtraction. In experimental animals there was a highly significant correlation between the results of the Hippuran transit-time method and the distribution of radioactive microspheres [8]. Truniger [5] felt that the agreement between microsphere distribution data and the results of the deconvolution analysis of Britton et al. [21] was remarkable, but still not sufficient proof for its validation.

We propose a new method, based on the frequency distribution of Hippuran transit time, for determining intrarenal haemodynamics. The data from \(^{123}\)I-Hippuran \(\gamma\)-camera renography is utilized to determine the fractional cortical flow of the total renal flow by means of the mathematical processes of region of interest selection, deconvolution, cross-correlation, normalization and curve subtraction. The use of the \(\gamma\)-camera avoids the disadvantages of probe renography which include the difficulty of renal localization and the inability to separate renal pelvis from parenchyma. In the course of these studies evidence has been obtained that calyceal and/or distribution of transit-times and can contribute an additional mode to this distribution.

Methods

The patient is seated reclining in a modified dentists' chair with the \(\gamma\)-camera (Ohio Nuclear series 100) fitted with a diverging collimator set up over his back so that both kidneys and the lower chest are in the field of view. After a rapid intravenous injection of \(^{123}\)I-Hippuran [22] into a medial antecubital vein, 64 \(\times\) 64 resolution frames are recorded initially at 1 s interval for 100 s followed by 90 frames at 10 s intervals to complete the 20 min study with an on-line Varian V76 computer programmed to record and process the data.

An image of the data at 2 min is reconstructed and displayed and from this image regions of interest (ROI) are defined for the whole left and right kidneys, background regions and the heart region.

To outline the pelvi-calyceal area, the computer constructs a mean time picture which is a functional image displaying the mean tracer time for each pixel of the 64 \(\times\) 64 matrix so that pixels with long mean times, i.e. calyces and pelvis, have high intensities. It is now possible to draw an ROI parallel to the outer lateral edge of the kidney so as to include all areas of high intensity leaving an outer zone of cortex. A third ROI is constructed from the 15 min image corresponding to the renal pelvis (inner zone).

Thus these ROI form three zones in each kidney. These zones are not specifically anatomical, but help to emphasize the dominant component in each zone to aid subsequent mathematical analysis. The outer zone may be taken as representative of the cortical nephrons; the middle zone contains mainly medullary and calyceal region, but in addition cortical components from over- and under-lying cortex; and the inner zone is representative of the renal pelvis with only a small renal parenchymal contribution.

With the heart curve as the renal input and the curves from the outer and outer-and-middle zones separately, deconvolution analyses by the direct matrix-algorithm method are performed to give the retention of activity in each zone (impulse retention function), which would have resulted from a theoretical spike injection into the renal artery without recirculation. The early vascular component now has to be removed from these impulse retention functions by detecting the subsequent plateau level of the retention function followed by back extrapolation from the shoulder of this curve.

Differentiation of these corrected retention functions gives the spectra of transit time through the outer and outer-and-middle zones respectively, but there is a high statistical noise contribution. To reduce this noise and recover the signal, the transit time spectra are cross-correlated with a Gaussian function. The assumptions and mathematical basis of this procedure have been discussed by Nimmon et al., [23].

If one makes the assumption (see the Discussion section) that the transit-time spectrum of the cortical nephrons is not appreciably lengthened during flow through the collecting system then tracer transit through the outer zone will represent flow mainly through the cortical nephrons alone. This outer zone cross-correlation curve is normalized to the value of the outer and middle zone cross-correlation curve by means of a proportionality factor arrived at by comparing the leading edges of the two curves. Subtraction of the two cross-correlation curves results in a new curve, which represents the second mode originating from the middle zone. In the absence of pelvi-calyceal holdup, this curve is due to tracer transit through the juxtamedullary nephrons. By comparing the heights of these cortical and juxtamedullary cross-correlation curves, one obtains the percentage cortical flow from the total flow through the nephrons [21] and
simulation studies have shown that the standard deviation for these results is 6-8% when \(^{123}I\)-Hippuran is used in a dose of 1.5-2.0 mCi, provided that the renal function is near normal.

Results

Twelve normotensive patients on no medication and referred for renography for various reasons (e.g. transplant donor) were studied by the above method if their routine renogram analysis revealed a normal result. They were found to have a mean arterial blood pressure (diastolic and \(\frac{1}{2}\) pulse pressure) of 93 mmHg with a range of 83-100 mmHg and their percentage cortical flow (Table 1) had a mean value of 83.9% (SEM 0.7%).

Twenty-one patients with mild essential hypertension, on no treatment and without pelvi-calyceal tracer retention on renography, were also studied (Table 2) and their mean blood pressure was 118 mmHg (range 105-150 mmHg) and percentage cortical flow was 74-6% (SEM 1.5%).

The difference between these means is statistically significant \((P < 0.002)\). Comparing the percentage cortical flow between the left and right kidneys of each patient in the total group of 33 patients, there was a good correlation between the two sides \((r = +0.88, P < 0.001)\).

Discussion

Assumptions inherent in the Hippuran transit-time method are that the mean rate of Hippuran uptake into the kidney, transfer through the cells of the proximal tubule and rate of removal from the renal pelvis must be rapid relative to the mean rate of Hippuran transit along the lumens of the nephrons of each population. In the normal kidney with a normal pelvis these assumptions have been shown to be true [7].

What then accounts for the difference between the transit times of Hippuran through the cortical nephrons and juxtamedullary nephrons? In both populations of nephrons the Hippuran is secreted into the proximal tubule and thereafter is not reabsorbed. The greatest contribution to the transit time is the time taken for the Hippuran to pass through the respective loops of Henle. The collecting ducts, calyces and pelvis are common to both cortical nephrons and juxtamedullary nephrons and, because transit times through these parts of the nephron are of the same order as the sampling time (10-20 s), they will cause no appreciable delay to the passage of tracer.

Thus it might be expected that the cortical nephrons with their short loops would have a faster transit time than the juxtamedullary nephrons whose long loops penetrate deeply into the renal medulla, where the high osmolality causes fluid reabsorption and therefore slows movement of the intratubular non-reabsorbable Hippuran. A high osmolality is required in the

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renal medulla in order for the kidneys to concentrate solutes and conserve water. This can only be maintained if flow through the non-autoregulating juxtamedullary nephrons is slow.

The method described here uses initial regions of interest to separate cortical, medullary and pelvic zones so that the outer zone contains predominantly cortical nephron glomeruli and loops of Henle, but excludes juxtamedullary glomeruli and the long loops of their nephrons. The transit time measured through this outer zone represents predominantly cortical nephron transit. About 85% of the total nephron population are cortical nephrons [24] and in the normal subject one would expect that approximately this percentage of the total flow will be passing through the cortical nephrons at any time under resting conditions. These expectations have been borne out by this pilot study of left and right kidneys of the 12 normotensive patients (mean 83.9%, SEM 0.7%).

The problem of measuring the distribution of transit times is not straightforward. The spectra obtained by deconvolution with matrix algorithm are the sum of the true solution and an oscillatory noise component. It is the oscillatory nature of this component which makes quantitation and recognition of statistically significant modes difficult, when simple smoothing algorithms are applied either pre- or post-deconvolution. An alternative scheme of utilizing only mean time and variance of spectra (Reeve et al. [25]) suffers from two main disadvantages. The variance is heavily dependent, as shown by the authors, on the state of diuresis; it fails to give a measurement of percentage 'modal' contribution. Further any errors in judging the point of truncation of the spectra will give a significant contribution to the variance and possible erroneous identification of further 'modes'. A comparison of deconvolution methods for model resolution of spectra has been made [23]. The correlation technique used in the present study was found to give more accurate results than either the matrix algorithm with simple 1-2-1 smoothing or a more sophisticated iterative technique. The simulation data used in these studies had a statistical noise level comparable with that obtained from patient data in this clinical study.

The main limitation of analysis of probe renograms is that it is not possible to separate out the effect of calyceal-pelvic transport on the transit spectra. Further no information is obtainable on the site of origin within the kidney of a particular mode. Probe methods for renographic analysis have been used for a long time [7]. It has been found wanting because the renal pelvis is included in the field of view of a probe and may well be contributing to a multimodal distribution of transit time. By using a γ-camera and the technique described, the pelvis is excluded as a possible source of the extra modes described by Reeve et al. [25] in hypertensive patients for, in the present study, a slightly dilated calyx or renal pelvis was the commonest cause of multimodal data. The use of regional renography with the γ-camera overcomes the above shortcomings of probe renography which is essential for a serious attempt at measuring nephron transit times.

A reduction in renal blood flow is common in patients with essential hypertension [26]. It has been shown angiographically that this decrease is not uniform in distribution, but that cortical flow is reduced out of proportion to the other parts of the kidney [3]. In the present study the mildly hypertensive patients likewise showed a reduction in the percentage cortical flow (mean 74.6%, SEM 1.5%).

This can be looked at in two ways. If the essential hypertension comes first, the reduction in cortical nephron flow represents a normal autoregulatory response reducing perfusion pressure to the glomeruli of the outer cortex to maintain a normal filtration rate [27]. At the same time the non-autoregulating juxtamedullary nephrons receive an increased perfusion pressure. Both actions tend to reduce distribution to cortical nephrons and increase that to juxtamedullary nephrons. Alternatively, alteration of autoregulatory control might be a primary phenomenon in essential hypertension leading to increased salt and water retention increasing cardiac output, after the hypothesis of Ledingham & Cohen [28] or else the autoregulatory control disturbance would be associated with local renin release subserving autoregulation [27] and also systemic renin release initiating hypertension or both. Some of the patients with essential hypertension have a normal intrarenal flow distribution (Table 2), making a primary role less likely. However, there is evidence that there is a subgroup of essential hypertensive patients where a normal or high percentage distribution to cortical nephrons is associated with a high cardiac output and normal effective renal plasma flow [29].

In normal subjects one would expect the two kidneys to differ very little in their distribution of blood flow. Similarly in hypertensive patients without renal disease one would expect a parallel response by each of the two kidneys to the raised blood pressure. The good correlation between
percentage cortical flow in the left and right kidney of the total group confirms these expectations and provides essential evidence of the validity of the technique.

With this method the contributions of cortical nephrons and juxtamedullary nephrons to total nephron function can be measured with only a small standard deviation which was also found with simulation studies [23]. The method is readily applicable to the data available from routine [131I]Hippuran γ-camera renography. Patients with gross pelvi-calyceal tracer retention and/or moderate-to-severe impairment of renal function have to be excluded, since their data are not susceptible to this analysis.

The present non-invasive method of determining the percentage cortical flow by deconvolution, cross-correlation and curve subtraction forms a basis for the further investigation of human intrarenal blood flow distribution.

References