FUNCTIONAL IMAGING OF INTRARENAL BLOOD FLOW USING SCINTILLATION CAMERA AND COMPUTER

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In order to obtain spatial distribution of an index for regional blood flow at each element on a scintigraphic image of the kidney, we attempted the construction of the so-called functional image. After injecting a single bolus of ^{133}***Xe into a renal artery by means of a catheter, this objective was accomplished using digital computer processing for a sequence of scintillation camera recordings of the following washout process from the kidney. This is expressed in a form of matrix of disappearance rate constant. Calculation for the rate constant, the flow index of the functional image, was done using either the least squares (LS) method or height-over-area (H/A) method. Although the former method was considered to be theoretically suitable without undue participation of background activities, the latter was preferred because of stable results for image construction. On reviewing the functional image thus obtained from 22 patients representing a variety of renal diseases, the H/A gave specific information concerning regional distribution of the perfusion integrity mainly related to the cortical part of the kidney. This is often difficult to accomplish utilizing the conventional method of compartmental analysis of the xenon washout curve or selective renal angiography.***

During the past few years, attempts have been made to construct the so-called functional image (*1*) of various organs, which means some functional index such as turnover rate of a tracer transported by blood flow or ventilation to be expressed spatially in order to conform with the radionuclide scintigraphic image. Upon processing a serial recording of a scintillation camera using a digital computer, these objectives have been accomplished by observing the washout process of ^{133}Xe from lung (*2*) or brain (*3*). The functional image thus obtained proved to be useful both for evaluation of the overall function as well as its regional distribution.

Observing the washout process after introducing a single bolus of radioxenon into a renal artery, the intrarenal blood flow distribution is known to be heterogeneous not only in terms of concentric distribution from the outer part of cortex to the inner part of medulla (*4*) but also in terms of segmental distribution whenever there is focal ischemia (*5,6*). Our present concern is with construction of the functional visualization of these disturbances of the intrarenal blood flow.

The present study describes (A) technical feasibility of constructing the functional image, (B) physiologic implications deduced by comparing data analyzed by the conventional analysis for washout curves with data of angiography and renography, and (C) the functional image in various renal diseases.

SUBJECTS AND METHODS

Following selective renal angiography, 22 Japanese subjects with a variety of renal diseases were investigated. There were four patients with idiopathic hematuria, three patients with diffuse parenchymal disease including one with renovascular hypertension, one with primary hyperaldosteronism, and two with essential hypertension; the remaining fifteen had a variety of focal lesions in the kidney and included five with hydronephrosis, four with renal tuberculosis, two with polycystic kidney, two with renal cyst, and one with renal cell carcinoma.

Approximately 5–10 mCi of ^{133}Xe solution in less than 1 ml was injected as a rapid bolus with a quick saline flush through a green Kifa catheter into a renal artery following selective renal angiography. The washout process of ^{133}Xe was recorded using the scintillation camera, Searle Radiographics Pho/

Received Dec. 12, 1974; revision received April 10, 1975.

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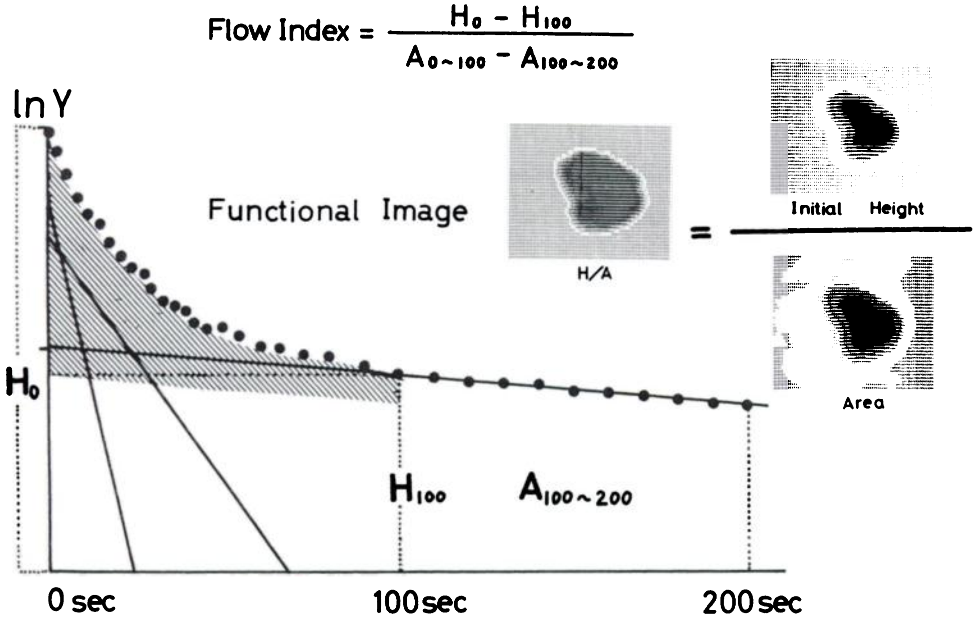


FIG. 1. Calculation for H/A method with background subtraction. Flow indices at each element, f, were derived as ratio of corrected initial height (H_0 — H_{100}) to subtracted area (A_{0-100} — $A_{100-200}$) of shaded washout process in figure. Functional image could be constructed by calculating these indices for every 1,600 40 × 40 image elements.

Gamma III, focusing on the kidney from the back with a 4,000-hole low-energy collimator. The exact location of the kidney was identified using a test dose of xenon in less than 0.5 mCi prior to the procedure. Signals from the camera could be stored into the videotape recorder (VTR) playback system of Searle Radiographics for reproducing scintiphotographic images on the cathode ray tube (CRT) and the persistence scope and for reproducing the washout curve on the pen chart recorder at a selected time and region. These were also transferred into the magnetic tape recorder serially in the form of 40 × 40 digitized matrix per frame to be analyzed by the digital computer, FACOM 230-60. The transfer proceeded at a time interval of 1.8 sec with transfer time of 0.3 sec during several initial frames, and accumulation of activities through the subsequent process up to 200–300 sec was followed. Using a sequence of frames, index for flow at every element of a 1,600 matrix was calculated point by point using the digital computer.

The flow index, which is the regional turnover of the radioxenon, can be represented by the disappearance rate constant at each point of the process in a unit of reciprocal of time.

In the initial 13 cases, the calculations of the flow index were done either by the least squares (LS) method (*2*) or the height-over-area (H/A) method (*3,7*) in order to investigate technical feasibility. The LS method was applied for the initial sequence of six frames, i.e., the logarithm of decreasing activities for each elemental matrix was fitted during a period of the initial 12.3 sec, assuming the process to be one term exponential with time. Although the desaturation process of the radioxenon from the kidney has been known to follow the multiexponential function (*4,8,9*), it has also been demonstrated that the initial slope of the process represents the average disappearance rate constant of these composite functions (*10*).

Without any precedent for a specific deterministic model such as the multicompartmental model, Zierler proposed the height-over-area (H/A) method (*7*) for the calculation of the turnover rate of the washout process, i.e., the flow index can be calculated by the ratio of the initial height (H) of the washout curve and the area (A) under the curve. The height was determined by lumping the initial three frames during 6.3 sec, the area under the curve was obtained by accumulation of the subsequent series of frames until 200–300 sec, and the ratio of these activities was calculated point by point at every elemental matrix.

After investigating the feasibility and validity of these two methods, we decided on the H/A method with background subtraction for the standard method, specifically, the latter part of the frames from 100 to 200 sec was regarded as the integration of the background activities and subtracted from the initial part of the integration up to 100 sec where the washout process of Components 1 and 2 of the composite exponential was already complete. The subtracted image thus obtained was then used to calculate the denominator of the H/A method. The numerator H was also corrected for the calculation as illustrated in Fig. 1. This is the approximated equation proposed by Bassingthwaithe (*11*).

To begin the calculation, a smoothing program of the nine-element bounding was applied to each frame. All images were depicted in the form of isocontour expression by symbols with nine levels of 90×40 matrix by a line printer. The kidney contour on the functional image was determined by cutting off the region which had less than 22% of the maximum activity of the initial frame which is the lower second level. Details of this processing have been previously described (*2,3*).

The washout curve obtained from the selected region including the entire kidney and excluding the other part such as lung was plotted on semilogarithmic graph paper and analyzed by the conventional peeling-off method (*8,9*). The percent distribution of the tracer was calculated from the intercept at zero time of each exponential function. The blood flow per 100 gm of tissue was calculated from the slope of the rate constant of the exponential function by multiplying the partition coefficient of 0.7. Since the analysis was applied to the process for up to 300 sec, the usual washout was shown to be the three terms of exponential functions.

The selective renal angiography done simultaneously was interpreted according to the grading criteria for the vascular abnormalities from the main renal artery to the cortical or interlobular arteries proposed by Hollenberg (*5*). The renal blood flow (RBF) and mean transit time (MTT) of the ^{131}I-labeled sodium iodohippurate through the kidney were derived by analyzing the conventional renogram by means of the analog computer simulation method (*10*). These angiographic and renographic findings were compared with the results in the present investigation.

RESULTS

Values for ^{133}Xe washout data. The value for the component of the washout curve by the compartmental analysis in the four patients with essential renal bleeding without additional evidence of renal disease was $77 \pm 4\%$ for Component 1 with the flow rate, determined from the slope of this component, of 408 ± 52 ml/min/100 gm; $16 \pm 2\%$ with 112 ± 28 ml/min/100 gm for Component 2; and $6 \pm 2\%$ with 10 ± 3 ml/min/100 gm for Component 3, respectively. These calculations are well within the accepted values for the normal (*8,9*).

TABLE 1. CORRELATION COEFFICIENT OF ^{133}Xe WASHOUT STUDIES WITH RENOGRAPHIC AND ANGIOGRAPHIC FINDINGS

	Component 1 of ^{133}Xe washout	
	Blood flow rate (ml/min/100 gm)	Distribution (%)
Renogram		
RPF	0.5914†	0.8168*
MTT	−0.5581‡	−0.8158*
Renal		
Angiogram grading	0.5331‡	0.8162*

* $p < 0.001$.
† $p < 0.05$.
‡ $p > 0.1$.

Comparison of ^{133}Xe washout data with angiographic and renographic data. In order to interpret the clinical implication of the functional image, the xenon washout process should be examined primarily from the point of view of renal function together with morphology. For this reason, data derived from the washout curve were compared with angiographic findings in all cases according to the grading criteria proposed by Hollenberg, and with renographic findings, represented by the renal plasma flow (RPF) and mean transit time (MTT), in each patient.

By reviewing the correlation of the flow rate and the percent distribution for each component with these angiographic and renographic parameters, no definite correlation could be found except for that of Component 1. As shown in Table 1, there were good correlations between the percent distribution of Component 1 and the RPF, the MTT, or the vascular grading, respectively ($p < 0.001$). On the contrary, concerning the flow rate for this component, correlation between these parameters was less significant ($p < 0.05$ and $p > 0.01$), that is, absolute integrity of renal perfusion evaluated by the sodium iodohippurate clearance or the renal vascularity appeared to correlate linearly with the fractional blood supply for Component 1 which is considered to correspond with that for the outer cortex (*4,9*).

Comparison of the LS method with the H/A method. Total counting rate per frame with 1.8 sec accumulation at the initial peak was about 5,000 and in each element counts were less than 30. In a normal rapid washout process, the following sequence of counting rate decreased by half until the sixth frame at which time the LS method was applied. The counting rate of the subsequent integration was about 60,000 counts during the initial 100 sec and 30,000 counts during the latter 200 sec. Most of the ele-

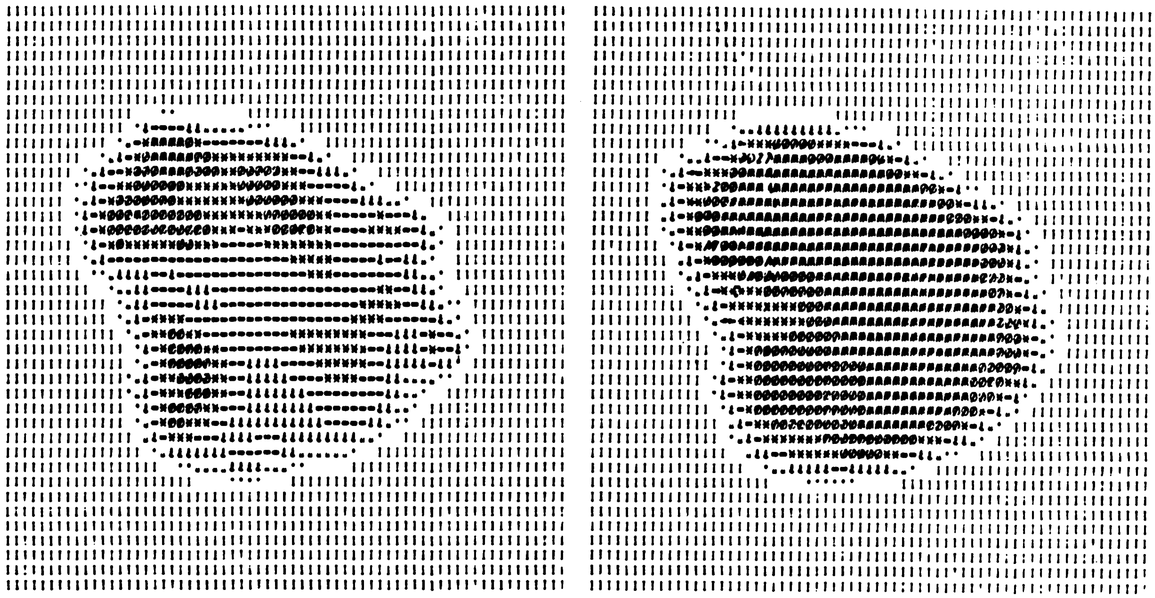


FIG. 2. Functional image either by LS method (left) or H/A method (right).

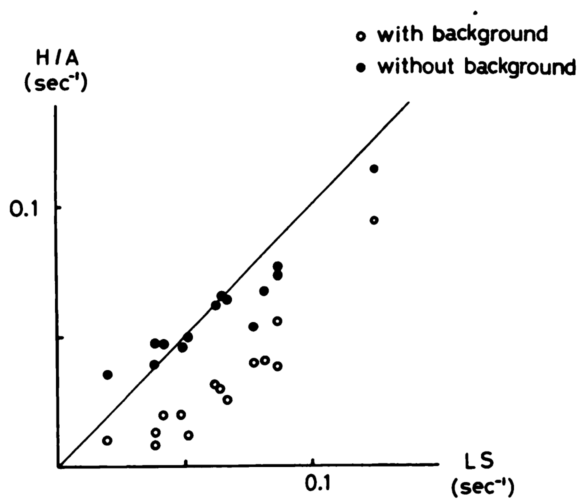


FIG. 3. Comparison of overall flow index derived from LS method with that from H/A method (open circles). Closed circles represent comparison with that from H/A method with background subtraction.

mental counts after the subtraction were more than 100. Division of the counting rate into so many elements gives rise to considerable statistical variation so that the elements of each frame were smoothed by a nine-element bounding. However, even with this program, the image constructed by the LS method often resulted in an unstable one owing to the application of the least squares fit for an initial sequence of frames without the sufficient activity of less than 30 counts at each elemental matrix (Fig. 2). On the other hand, the H/A method always resulted in a stable image as the processing was applied to the frames with sufficient activity. The average of the initial three frames with maximum activities was the initial height and a frame of subsequent integration of the washout process was considered to be the area (Fig. 2).

As shown in Fig. 3, the average flow index was calculated by these methods and the results were compared. As indicated by open circles in this figure, the flow index calculated by the H/A method revealed systematic underestimation compared with the index by the LS method. This may be attributed to the background from the nonfunctional areas of the kidney apparent in the latter part of the curve (*4*), which produced high values of the subsequent integration of the washout process as the demominator of the H/A. The H/A method proved disadvantageous as an absolute value since the longer the recording, the lower the resulting index value.

In short, the H/A method is superior to the LS method with respect to stability of the image but lacks virtue with respect to absolute evaluation of the flow index. The H/A method with background subtraction which was established for our standard method may, however, prove to be a kind of compromise for this dilemma. In fact, as shown in Fig. 3, the underestimation of the flow index was indeed eliminated.

Criteria for interpretation of functional image. The flow index calculated by the H/A method with background subtraction can be approximated to be a composite of Components 1 and 2 of the compartmental analysis. Moreover, the overall perfusion integrity of the kidney is thought to be dependent mainly upon the extent of participation of Com-

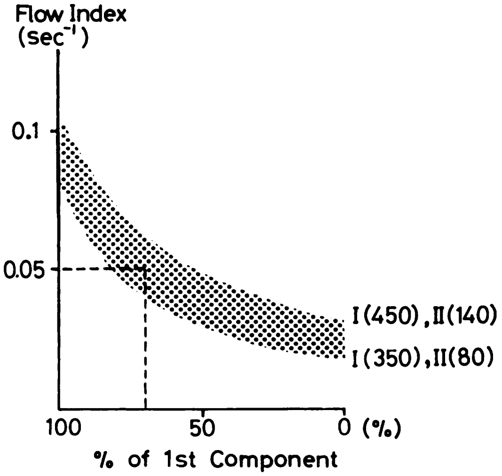
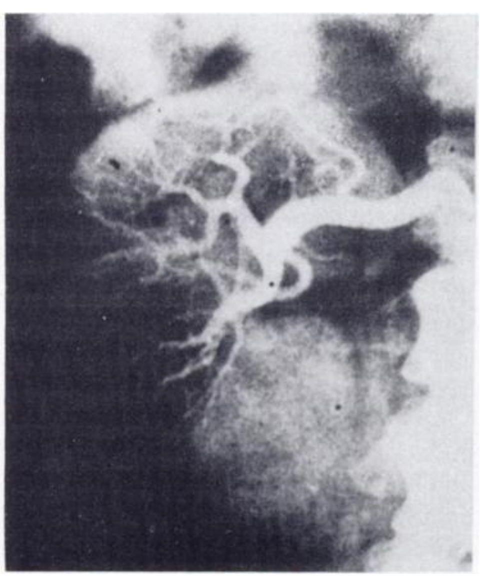


FIG. 4. Relationship between flow index (ordinate) and plausible combination of Components 1 and 2 (abscissa). If element of image consists of Component 1 exclusively, flow index will be around 0.1 sec^{-1} with range, depending on flow rate for this component, from 450 ml/min/100 gm to 350 ml/min/100 gm. If it consists of 70% of Component 1 and 30% of Component 2, it will be approximately 0.05 sec^{-1} as indicated by dotted line. If there is no Component 1, flow index will be less than around 0.02 sec^{-1} depending on flow rate for Component 2 which would range from 140 ml/min/100 gm to 80 ml/min/100 gm.

ponent 1 as indicated by the preceding results. The flow index at each elemental area, therefore, may be interpreted as the degree of the regional preservation of this component to other components, mostly Component 2. On this basis, as shown in Fig. 4, a nomogram was constructed to predict a realistic combination of Components 1 and 2 as a fractional participation of the cortex at a specific level of the flow index. The shaded range of flow rate (ml/min/100 gm) appearing in the nomogram was derived from the normal range as referred to in the results of those with idiopathic hematuria. This nomogram provides clues for clinical interpretation of functional images.

Functional image. According to the nomogram and the functional image, all cases were classified as follows.

1. The first group is the high perfusion one with maximum flow index of more than 0.1 sec^{-1}. In this group, there was one patient with hyperaldosteronism where the washout curve showed a four compartmental flow characteristic with supernormal Component 1 of 1,078 ml/min/100 gm for flow rate. The functional image revealed that the outer part of the kidney was occupied with the region of more than 0.1 sec^{-1} of the flow index with a maximum of 0.131 sec^{-1} (Fig. 5).
2. The second group is that of normal perfusion with maximum flow index of more than 0.05 sec^{-1} with homogeneous image. There were four patients including three with idiopathic hematuria and one with hydronephrosis. The well-preserved flow index of the entire region indicated rapid and homogeneous washout of xenon from the kidney with normal combination of the compartmental flow (Fig. 6).
3. The third group is the normal perfusion one



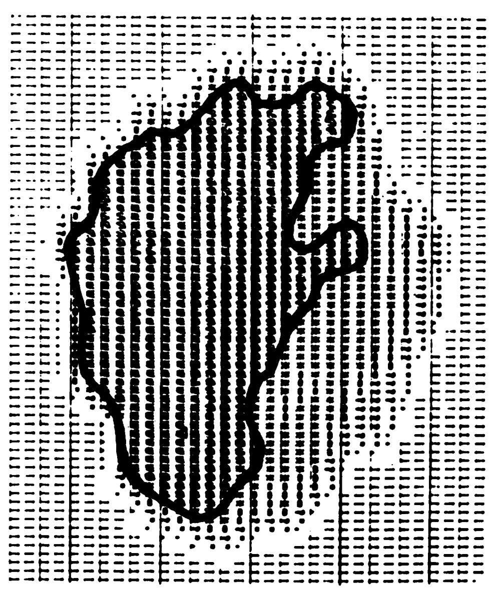


FIG. 5. Functional image and selective renal angiography of patient with primary aldosteronism, an example of high perfusion group. Isocontour line in image indicates line of flow index with 0.1 sec^{-1}. Washout data of this case showed that Component 1 was 1,078 ml/min/100 gm with 56%, Component 2 was 647 ml/min/100 gm with 37%, and Component 3 was 100 ml/min/100 gm with 30%.

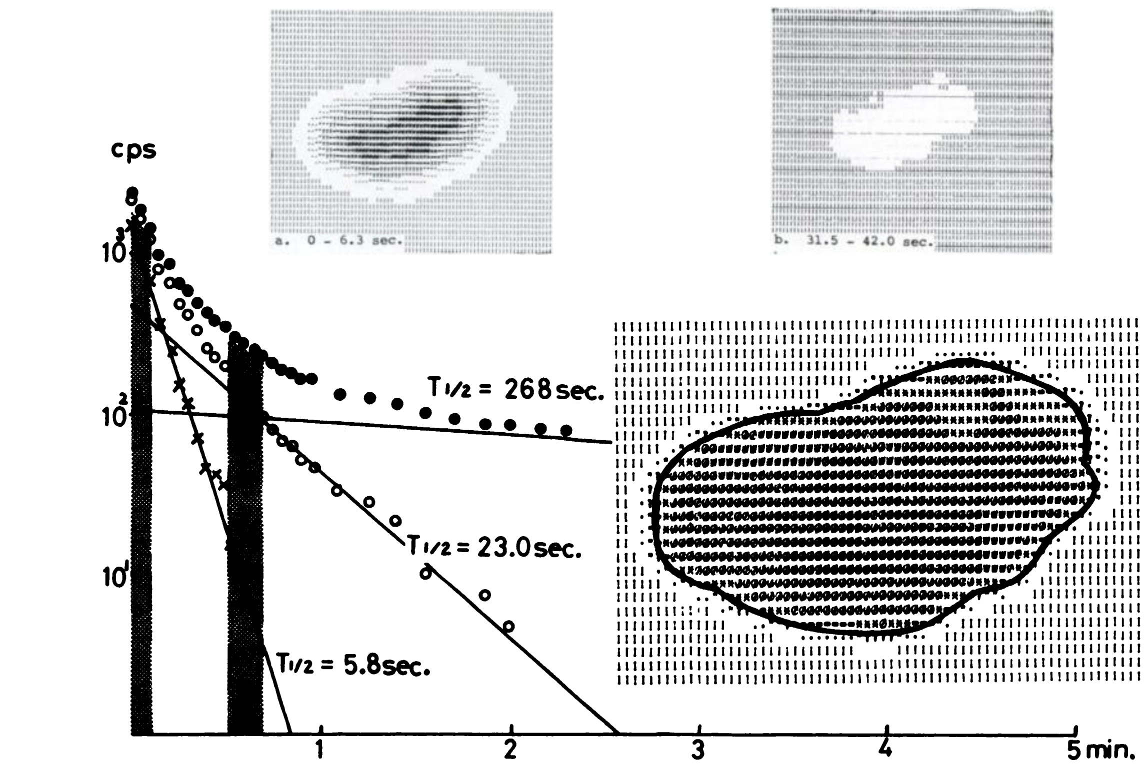


FIG. 6. Functional image of patient in normal perfusion group with homogeneous image. Xenon washout curve shows rapid washout as indicated by initial image (upper left) and later image at 30 sec (upper right). Isocontour line indicates line with flow index 0.055 sec^{-1}.

with maximum flow index of more than 0.05 sec^{-1} without a homogeneous image. Here, there were nine patients including six with apparent focal lesions (two with renal cyst, two with renal tuberculosis, one with polycystic kidneys, and one with renal cell carcinoma) and, in addition, there were three without appreciable focal lesion (two with essential hypertension and one with idiopathic renal hematuria). In the former group of six patients, decreased areas of the flow index less than 0.05 sec^{-1} corre-

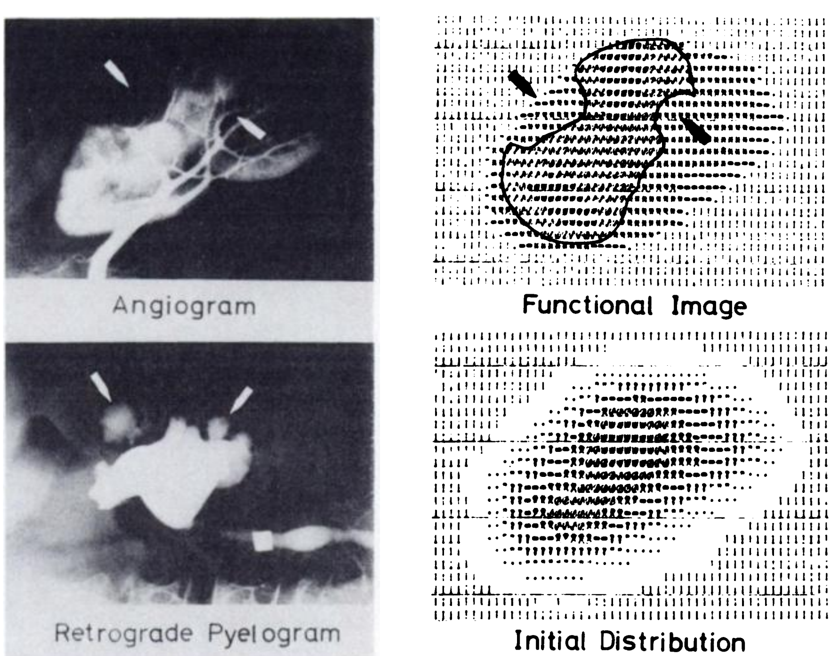


FIG. 7. Images of patient with two tuberculous cavities as shown by retrograde pyelogram, an example of normal perfusion with nonhomogeneous image. Isocontour line on functional image indicates line of flow index with 0.05 sec^{-1}, outlining two focal ischemic regions (arrows) due to cavitary lesions with diameter of 2 cm and 1 cm, respectively. Smaller lesion could hardly be identified on angiogram or image of initial distribution.

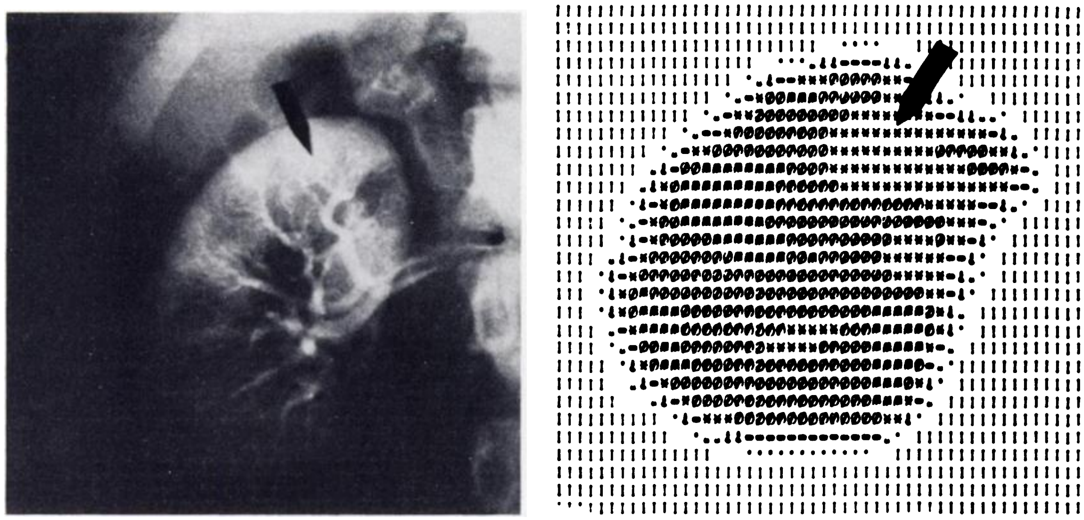


FIG. 8. Image of patient with essential hypertension revealed a slight focal ischemia at upper region (arrows), where a minimum of vascular tortuosity was seen on angiogram.

sponded well with these focal lesions (Fig. 7). In the last-mentioned group of three patients, as exemplified in Fig. 8, decreased area of the flow index was noted even when minimum changes were observed on the renal angiogram. It is apparent that morphologic findings by the conventional method would not always reflect regional status of the function as does the flow index. In general, the focal decreases of the flow index for this group were hardly predictable and might be represented by decreased percent distribution of Component 1 only if the percent distribution were markedly decreased.

4. The fourth group is the low perfusion one with maximum flow index of less than 0.05 sec^{-1} with homogeneous image. There were three patients including two with hydronephrosis and one with renovascular hypertension. These were characteristic with the decreased percent distribution as well as flow rate of Component 1 and especially typical in renovascular hypertension.
5. The fifth group is one of low perfusion with maximum flow index less than 0.02 sec^{-1}. This group included four patients: two with renal tuberculosis and two with hydronephrosis. As shown in Fig. 9, the washout data showed minimum preservation of both Components 1 and 2, suggesting an almost complete abolition of the cortical part of the kidney.

DISCUSSION

The limit of resolution for the tracer ^{133}Xe with an emission of 81 keV was found to be approximately 1.4–1.8 cm in terms of FWHM for a point source in water medium ranging from 1 to 10 cm depth. This was considered to be a critical resolution as applied to the present study, assuming that the average thickness of the renal cortex was 1.2 cm. However, spatial limitation of this resolution problem might not stand up to the dynamic process, as a focal perfusion reduction with a size even smaller than the limit of this resolution can emerge by integrating the washout process as a visible spot and thus calculate it to be a discernible spot with a low flow index. For example, as seen in Fig. 7, a tuberculous lesion with a diameter of less than 1 cm could be discerned from the neighboring region as a decreased spot of the flow index. Hence, the resolution problem seems to be somewhat different in the case of functional imaging from ordinary static imaging where additional information of the time domain is involved in the spatial domain. Alternatively, the statistical reliability of the calculated functional index at each elemental point would be of greater importance.

Using the LS method in presenting the disappearance constants of ^{133}Xe washout from lung, MacIntyre, et al (*2*) calculated the standard deviation of each rate constant to give an indication of the statistical reliability. It is usually less than 30% for regions of the lung and for the most part it varies between 10 to 25%. On the other hand, however, since the washout process from the kidney is usually twice as rapid as that from the lung, this method proved to be impractical in the present study, failing to collect sufficient counts during the short period of the initial sequence that would be sufficient to calculate with statistical reliability. In the case of the kidney, the H/A method is therefore preferable

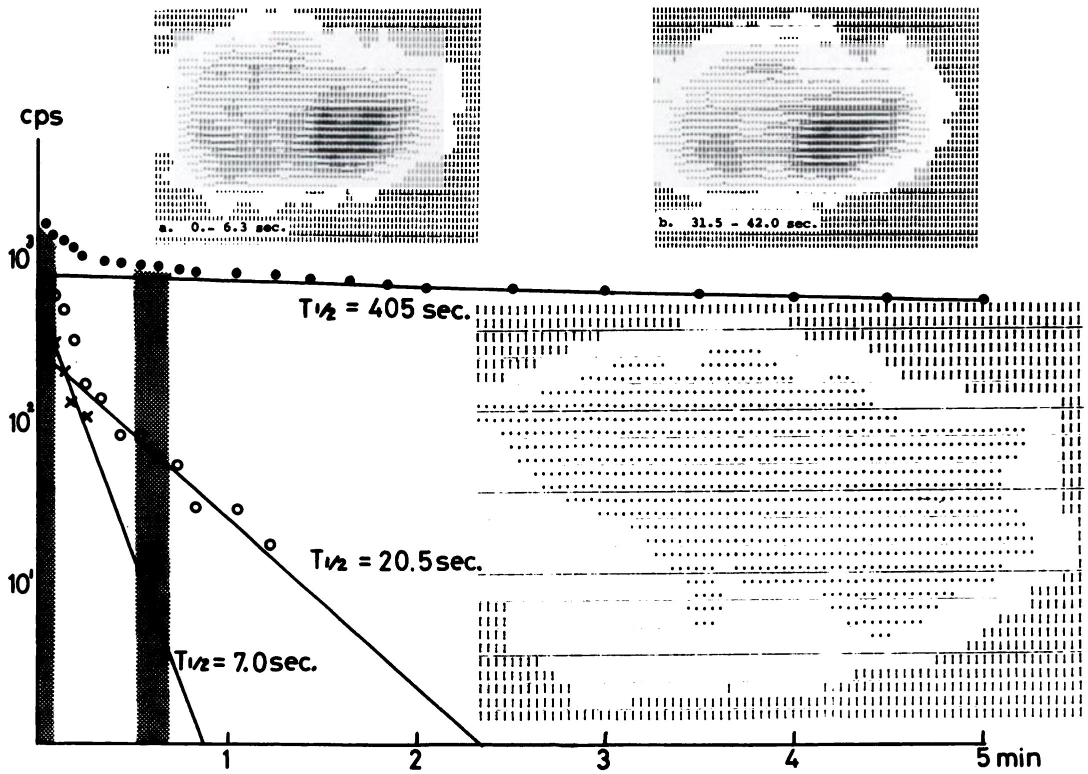


FIG. 9. Functional image of patient with hydronephrosis, an example of low perfusion with maximum flow index less than 0.020 sec^{-1}. Xenon washout curve shows slow washout as indicated by the initial image (upper left) and later image at 30 sec (upper right).

to the LS method. In fact, even on the outermost contour line of the organ, the standard deviation for the statistical reliability at each element after applying the H/A method was estimated to be about 15% whereas within the contour line of the organ, the greater part varied betweeen 5 to 10%.

The H/A method, however, proved to have shortcomings as already pointed out by another investigator (*10*) who suggested the same type of background subtraction to overcome this defect (*12*). For xenon, the partition coefficient for fat may be as high as 8.0 (*13*) and may produce a ridiculously large diluting volume for the compartment including perirenal fat, making a long tail formation in the washout curve. Furthermore, the counter-current exchange of the xenon gas in the ascending and descending vasa recta caused the same effect (*14*). The recirculating xenon in the body fat stores must also have important implications for the tail components (*6*). In contrast, since the application of the LS method to the initial part of the curve is an expression of the average of composite compartmental slopes (*10*), which is thought to be weighted not by the diluting volume but by the quantity of radioactivity initially transported by arterial flow as verified by Sapirstein (*15*), the underestimation resulting from a falsely large diluting volume might be avoided. The different results of these two methods suggest that the instantaneous diffusion dominated by the volume can hardly be attained at the initial introduction of the tracer but rather the deposition dominated by the flow may be actual (*15*). From this point of view, efforts to obtain the functional image using the LS method may still prove beneficial and should be the first choice if sufficient activities can be collected from such organs as the lung and brain.

The most characteristic feature of the intrarenal blood flow is the fact that the cortex is supplied by a large fraction of renal blood flow at a high flow rate of 4 ml/min/gm, which is eight times greater than the coronary blood flow, whereas the medulla has a much lower flow rate (*4,6,8,9*). For this reason, it is pertinent to assume that the flow index in the functional image is the spatial expression of the degree of preservation of the cortical blood flow in diseased kidney regardless of the complexity of the vascular structure of the kidney (*16,17*). This type of expression seems of particular value in assessing localization of the ischemic area which is hardly predictable when depending upon the washout curve alone. The situation presumably occurs even in diffuse parenchymatous disease such as essential hypertension in which segmental ischemia in the presence of patchy renal microvascular disease may exist (*5,6,18*).

Since cortical perfusion plays an essential role in renal functions such as sodium balance (*19,20*), the extent of its preservation both in terms of overall and regional perfusion may provide a basis for evaluating the intrarenal physiology. If so, this type of presentation will become the status quo for the future.

ACKNOWLEDGMENT

Thanks are due to M. Ohara of Kyoto University for assistance with preparation of the manuscript.

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