

# Clinical study of liver blood flow in man measured by $^{133}\text{Xe}$ clearance after portal vein injection

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**SUMMARY** During the course of a clinical trial to assess the value of adjuvant liver perfusion of 5-fluorouracil after surgery for colorectal cancer, liver blood flow was measured in 14 patients. Access to the portal circulation was achieved by dilatation and cannulation of the obliterated umbilical vein. The clearance from the liver of a bolus of  $^{133}\text{Xe}$  was monitored using a gamma-ray camera so that blood flow from different areas of the liver could be calculated. The clearance curve of  $^{133}\text{Xe}$  was a double exponential of which the initial fast component accounted for a consistently high proportion of the total clearance. The perfusion studies have shown wide differences in blood flow to the various areas of the liver in the same patient, in addition to a wide variation in perfusion rate between the 14 patients. This technique of quantitative estimations of liver blood flow to different areas of the liver may have importance in planning operative procedures and understanding the haemodynamic mechanisms involved in liver disease.

Accurate measurement of liver blood flow in man has proved a difficult and elusive goal. The main problem has been difficulty in access necessitating indirect measurements and hence several assumptions. Clearance techniques using inert radioactive gases—for example,  $^{133}\text{Xe}$ —have been used in animals by injection *via* the portal vein (Darle, 1970), and into both portal vein and hepatic artery (Rees *et al.*, 1964; Groth *et al.*, 1968). In man, operative measurements have been performed by direct injection into liver parenchyma (Gelin *et al.*, 1968; Plengvanit *et al.*, 1972). These measurements, however, take no account either of the variation in blood flow from one region of the liver to another, or of the haemodynamic changes involved.

The importance of accurate quantitative measurements of liver perfusion in various pathological states in man is clear. This is particularly relevant to the problem of portal hypertension where haemodynamic relationships may affect the choice of operative procedure and influence the subsequent prognosis.

In the treatment of colorectal cancer, we have been assessing the value of adjuvant liver perfusion with the cytotoxic agent 5-fluorouracil in an attempt to reduce the incidence of hepatic metastases and,

hopefully, improve the five-year survival rate. Access to the portal vein circulation is available *via* the umbilical vein and accurate measurements of liver blood flow in the conscious subject can be determined.

## Methods

Fifty consecutive patients with colorectal cancer have so far entered the trial. Twenty-four were randomly allocated to receive adjuvant cytotoxic liver perfusion, which was started immediately after resection and continued by constant perfusion for seven days.

The left branch of the portal vein was entered by dilatation and cannulation of the 'obliterated' umbilical vein as previously described (Kessler and Zimmon, 1967; Lavoie *et al.*, 1967; Piccone and Leveen, 1967; Man *et al.*, 1974). Under the image intensifier the catheter was manipulated to lie in the main portal vein, so allowing perfusion of both lobes of the liver.

Blood flow studies were performed on 14 patients before removal of the catheter (between the fifth and seventh postoperative day). The patient was positioned supine under the gamma-camera (Nuclear Chicago, Pho-Gamma III), so that the anterior surface of the liver was in the field of view of the camera. 2 mCi of  $^{133}\text{Xe}$  dissolved in saline (Radio-

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chemical Centre, Amersham) was injected as a bolus through the catheter into the portal vein by flushing the catheter with 20 ml saline. The rate of clearance of the  $^{133}\text{Xe}$  from the liver was recorded by using an on-line computer system (Nukab) to collect the integrated counts over the field of view for 60 consecutive periods of 10 seconds and to store the resulting images on magnetic disc. Each image, which consisted of an array of  $64 \times 64$  elements, was reduced to an  $8 \times 8$  array by summing over 64 adjacent points, so that each new element represented a  $3.5 \times 3.5$  cm area. Any element which represented areas within the field of view but outside the liver and which also contained radioactivity—for example, the catheter and the lungs—was excluded from the subsequent analysis.

The counts from the same element of successive images were arranged in time sequence and analysed as a double exponential function by a simple curve stripping and linear regression technique. The results were expressed as liver perfusion in ml/min/100 g of liver tissue, by multiplying the exponential rate constant of the fast clearance component by the partition coefficient of liver tissue to blood. The value of this partition coefficient was taken as 0.74 (Conn, 1961). The results were presented as  $8 \times 8$  numerical printouts of the liver perfusion and of the initial percentage of  $^{133}\text{Xe}$  being cleared by the fast component.

Immediately after the  $^{133}\text{Xe}$  study, 2 mCi of  $^{99\text{m}}\text{Tc}$  sulphur colloid was administered intravenously and static views of the liver obtained.

The studies were performed in the fasting state, and the  $^{133}\text{Xe}$  clearance measurements were repeated in one patient to assess the accuracy of the technique, the time intervals between the two studies being less than 20 minutes. In addition, three patients were studied approximately 30 minutes after eating a meal consisting of meat, peas, and mashed potatoes, the total weight being 250 g.

## Results

### INITIAL $^{133}\text{Xe}$ DISTRIBUTION

The distribution of  $^{133}\text{Xe}$  within the liver was found by summing the first 12 images of the study—that is, time 0 to two minutes. In general, it was found that the initial distribution of  $^{133}\text{Xe}$  reflected the distribution of contrast media in the portogram, rather than the sulphur colloid image of functioning liver tissue.

### CLEARANCE CURVES

In each of the 14 patients studied, a double exponential function of the  $^{133}\text{Xe}$  clearance curve was observed from all regions of the liver (Fig. 1).

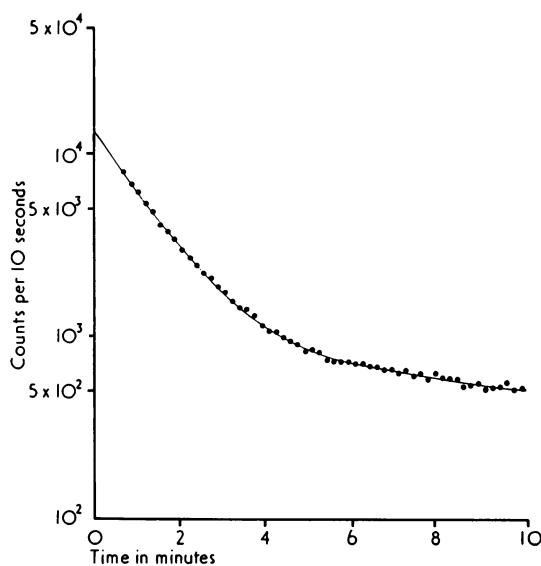


Fig. 1 Clearance curve from one element of the  $8 \times 8$  array. The data are displayed on log/linear axes and the continuous line shows the computer fit of the double exponential function to the data points. The calculated perfusion was 64 ml/min/100 g and the initial percentage of the fast clearance was 94%.

In all regions of the liver in all patients a high proportion of the  $^{133}\text{Xe}$  was cleared by the fast component (Table 1).

### PERFUSION RATES

The mean perfusion rates over the liver in each patient were obtained by averaging the local perfusion rates and are shown in Table 2. There was a wide variation in the average perfusion between

Table 1 Initial percentage of  $^{133}\text{Xe}$  cleared by fast component giving limits of the initial percentage values obtained from areas  $3.5 \text{ cm} \times 3.5 \text{ cm}$  across liver, and average of these local values\*

Patient	Mean $\pm$ SD	Range
C.B.	84.6 $\pm$ 8.4	58-96
V.B.	90.1 $\pm$ 7.5	72-98
H.H.	87.4 $\pm$ 11.6	53-96
I.H.	92.6 $\pm$ 6.2	76-98
E.M.	97.5 $\pm$ 2.0	91-98
H.M.	94.0 $\pm$ 4.3	83-98
B.P.	91.8 $\pm$ 6.7	72-97
N.P.	87.4 $\pm$ 5.1	74-94
F.S.	92.2 $\pm$ 3.7	85-97
G.S.	95.2 $\pm$ 4.1	85-99
L.S.	78.5 $\pm$ 12.3	45-89
M.S.	94.9 $\pm$ 2.5	91-98
N.S.	93.7 $\pm$ 5.7	78-98

\* These data are not available for patient B. P. i.

Table 2 Liver perfusion showing average of local perfusion rates, and limits of perfusion values obtained from areas 3.5 cm  $\times$  3.5 cm across liver

Patient	Mean $\pm$ SD (ml/min/100g)	Range
C.B.	58.0 $\pm$ 12.3	35-74
V.B.	60.4 $\pm$ 13.2	34-83
H.H.	68.6 $\pm$ 12.3	52-87
I.H.	70.2 $\pm$ 17.1	40-98
E.M.	97.4 $\pm$ 11.0	77-116
H.M.	101.5 $\pm$ 19.7	69-131
B.P.i.	66.3 $\pm$ 10.3	49-83
B.P.	122.6 $\pm$ 22.2	96-187
N.P.	55.1 $\pm$ 12.1	32-85
F.S.	70.9 $\pm$ 9.9	56-85
G.S.	80.6 $\pm$ 10.3	55-100
L.S.	52.8 $\pm$ 9.2	37-62
M.S.	98.6 $\pm$ 24.9	49-128
N.S.	100.0 $\pm$ 24.0	55-127

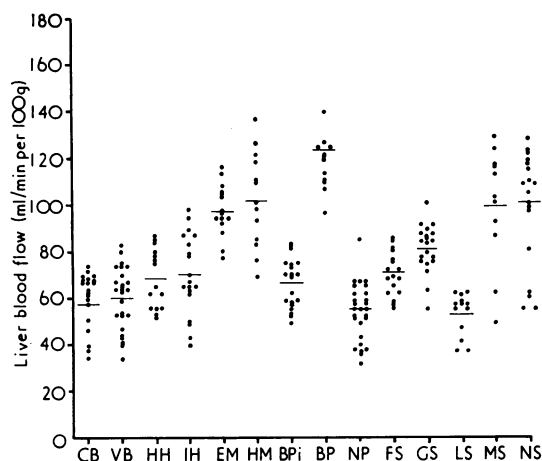


Fig. 2 Distribution of the perfusion rates of each individual element of the liver for each subject to illustrate the wide range of values obtained.

patients, varying from 52.8 ml/min/100g to 122.6 ml/min/100 g.

Similarly, the rate of perfusion to different areas of the liver varied considerably (Fig. 2). An example of this variation for a particular patient is given in Fig. 3a and b. However, it can be seen in Fig. 3c that the percentage cleared because of the fast component in this patient does not show the same magnitude of variation.

#### REPEATED STUDIES

##### Accuracy

In the subject in whom the  $^{133}\text{Xe}$  clearance was repeated, the perfusion rates from 17 elements

showed a high degree of consistency; the average deviation from the mean was found to be 7.1%

##### Post-prandial

In the three patients in whom the studies were repeated after feeding, the average changes in blood flow were + 0.9, + 5.9, and + 1.1 ml/min/100 g. These changes did not represent a statistically significant difference from the fasting state.

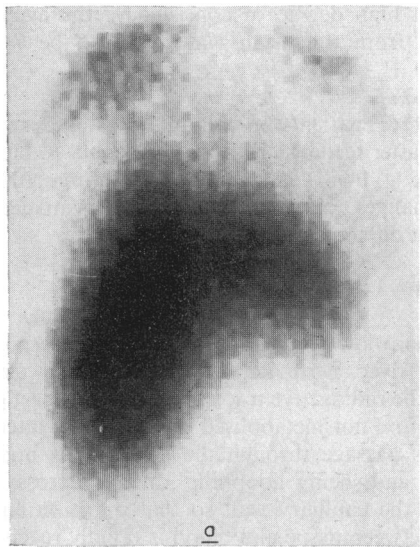
##### Discussion

Liver blood flow studies in 14 patients undergoing adjuvant liver perfusion were performed using  $^{133}\text{Xe}$  as the radioactive tracer. Xenon is an inert gas and therefore not metabolised or chemically altered during its passage through the tissue. It is highly diffusible and, being lipophilic, diffuses across the whole of the capillary wall so that diffusion equilibrium between tissue and blood is rapidly reached. Removal of xenon from the field of view is dependent upon the venous outflow. The high permeability of xenon means also that on reaching the lungs it rapidly diffuses across the alveolar membrane and is completely expired so that little recirculation of radioactivity occurs.

The  $^{133}\text{Xe}$  clearance technique is based on the Fick Principle in which the flow through an organ is related to the amount of tracer removed from the circulation by the organ and the arterial concentration of the tracer. It can be shown that the perfusion rate—that is, the blood flow per unit volume of tissue ( $F/V$ )—is given by the formula  $F/V = K\lambda$ , where  $K$  is the clearance rate constant and  $\lambda$  is the partition coefficient (Kety, 1951). We have assumed a constant partition coefficient of 0.74, although experimental work is in progress to establish the consistency of this value.

Several workers using this technique to measure liver blood flow in animals have found a double exponential clearance curve (Hollenberg and Dougherty, 1966; Danielson and Karlmark, 1970; Darle, 1970).

We have assumed that the fast component reflects intrahepatic blood flow. The origin of the second slow component is obscure. Hollenberg and Dougherty (1966) supposed that the existence of two components could be explained by two types of sinusoids with different perfusion. However, Darle (1970) postulated that the slow component reflected extrahepatic activity emanating partly from the lungs, 'rest activity' from the injection catheter, and recirculating tracer. This hypothesis is supported by their experiments where the outflow from the liver was diverted outside the body of the animal and the  $^{133}\text{Xe}$  activity detected in this outflowing blood



	68	65			85	86		
76	84	75	69		93	90	93	94
85	81	62	72	56	95	91	90	95
80	72	58	62		96	97	87	90
68	57	<u>b</u>			85	93	<u>c</u>	

Fig. 3 (a) Distribution of  $^{133}\text{Xe}$  in the liver.  $^{133}\text{Xe}$  within the lungs can be observed at the top of the image as a result of clearance from the liver. (b) Computer printout of the spatial distribution of liver perfusion in this patient (in ml/min/100 g). (c) Computer printout of the spatial distribution of the initial percentage of the fast component in the same patient.

gave rise to a monoexponential curve. Darle (1970) also showed good accordance between the blood flow calculated from the fast component and directly measured total blood flow from the liver. Gelin *et al.* (1968), reported that measurements of blood flow obtained by direct injection of  $^{133}\text{Xe}$  into the liver parenchyma gave a single exponential curve. However, in our own experience of direct parenchymal injection at operation, a double exponential curve was recorded with  $^{133}\text{Xe}$  in six of seven patients tested, suggesting that, whatever technique of  $^{133}\text{Xe}$  administration one uses, a double exponential curve is found.

Using the computerised system with the gamma camera, we have been able to make quantitative measurements of the perfusion to different areas of the liver over a 10 minute period. The results indicate a marked difference in perfusion to each element of the liver and the range in the individual is surprisingly wide. Nevertheless, we have found that a constant high proportion of Xenon is cleared by the initial fast component of the clearance curve and the second slow component, whatever it may represent, accounts for, on average, less than 10% of liver blood flow.

Liver perfusion in man, measured by direct injection of  $^{133}\text{Xe}$  into the portal vein, is similar to observations made in animal studies. A fast and slow component exist in the clearance curve, the former being predominant. The data on the wide

variation of perfusion to individual elements of the normal human liver may have implications in the planning of surgical procedures.

We would like to thank Mr J. T. Rowling, consultant surgeon, Sheffield, for allowing us to study patients admitted under his care.

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