Liver Blood Flow in Man during Abdominal Surgery

I. Description of a method utilizing intrahepatic injections of radioactive xenon (^{133}Xe). Normal values and effect of temporary occlusion.*

L.-E. Gelin, D. H. Lewis and L. Nilsson

Department of Surgery I (Head: L.-E. Gelin, M. D., Prof. of Surgery), Sahlgrenska sjukhuset, Göteborg, Sweden

Liver blood flow in man has been measured in a number of ways (*Bradley,* 1963). These methods have all been based upon the clearance of some substance from the blood by the liver. In the now standard method developed by *Bradley, Ingelfinger, Bradley,* and *Curry* (1945) bromsulphonthalein (BSP) is infused intravenously at a rate to match the hepatic extraction. This extraction rate divided by the hepatic arterio-venous difference, the latter obtained by hepatic vein catheterization, yields a value for hepatic blood flow by the well-known Fick formula. These methods have contributed much to our knowledge of the hepatic circulation in man, and have found widespread acceptance in large part by virtue of the fact that they are safe and harmless to the patient.

As a part of a long-term shock project being carried out in this department, it was desired to measure liver blood flow in man at the time of abdominal surgery. The existing methods, despite the fact that they are non-injurious, were found unsuitable for a number of reasons. The development of a method for the measurement of skeletal muscle blood flow by the intramuscular injection of radioactive xenon (^{133}Xe) (*Lassen, Lindbjerg,* and *Munck,* 1964) suggested that this technique could be applied to our special situation. It will be shown that the intrahepatic injection of radioactive xenon meets the requirements of a method that is simple, rapid, and reproducible. Furthermore, in adapting the procedure to the operating room, the surgeon is not kept waiting for the result, since laboratory analyses of samples are not necessary.

These two companion papers deal with preliminary experiences in the application of the method. Specifically, this communication will consider certain aspects of the hepatic vascular physiology felt to be an important background to the shock investigation, while the other paper touches on the phenomenon of serendipity.

Methods and materials

Studies were carried out on 11 patients at the time of upper abdominal surgery, e. g. cholecystectomy, gastrectomy. To establish control values, the patients chosen were those with uncomplicated disease processes, and whose livers were normal by inspection, papation, and chemical

* The original research reported in this communication was made possible by the support of the United States Army through its European Research Office (Contract No. DA-91-591-EUC-3658).

tests. With relatively short, uncomplicated operations it did not seem to make a difference whether the blood flow was measured at the beginning or at the end. In those patients in whom temporary vascular occlusion was carried out, the hepatic artery and portal vein were identified and a short segment dissected free for subsequent occlusion. Care was taken to disturb the nerves accompanying the vessel as little as possible. The hilus of the liver was also explored to be sure that no collaterals or anomalies existed, and that the vessel to be clamped represented the total recognizable supply to the liver. In no case was any ill-effect of the vascular occlusion noted either during or after the surgery. It should also be noted that the post-occlusion values were of the same order of magnitude as the pre-occlusion values.

To measure liver blood flow usually 0.1 ml of radioactive xenon (^{133}Xe) (1–3 mc/ml) dissolved in saline* was injected into the substance of the liver with a small gauge needle. The volume of injectate was varied depending upon the strength of the isotope, so as to give an initial external count rate in the range of 20,000 to 50,000 cpm. For volumes larger than 0.1 ml, the injection was made over a correspondingly larger area through the same needle track so as to insure, as much as possible, that the isotope could come into diffusion equilibrium with the tissues. As recommended by *Lassen* (1964), the needle was held in place for approximately 30 sec after injection to minimize escape of xenon via the needle track. In some observations the needle was withdrawn immediately after the injection and a cotton pledget held at the injection site. Comparison of values with and without the 30 sec period of waiting revealed no significant differences. In most cases several injections were made and each disappearance slope followed for usually 5 to 10 minutes, in some cases longer.

The data recorded was simply the rate at which the isotope disappeared from the injection site. No blood samples were taken. The gamma emissions from the xenon were detected with a 1½ inch sodium iodide crystal in a cylindrical collimater, placed as close to the injection site as possible. The detector led into a pulse height analyser**. Two methods of recording were used. In one, counts were recorded on a scaler unit for 30 sec intervals with 10 sec between them to reset the scaler. From these data the logarithm of cpm versus time was plotted to obtain the disappearance slope. Alternately, a count rate meter with a 3 sec time constant activated a logarithmic recorder*** which gave the disappearance slope directly. The results obtained with the two methods were identical.

The basis upon which the external detection of radiation from xenon can be used to measure blood flow may be considered briefly as follows: Xenon diffuses rapidly through tissues, and very shortly after injection can be considered to be in diffusion equilibrium with the tissues. If, as seems likely, blood leaving the capillaries and entering the venous return of an organ is in diffusion equilibrium with the tissues, then were the xenon has been injected, it is in equilibrium with the tissue and the venous blood leaving the tissue. Consider now that the detector sees all of the xenon which has been injected into the tissue. Blood flowing through the tissue and coming into equilibrium wiht it, picks up xenon from the tissue and carries it away in the venous return, out of sight of the detector. Since this xenon is virtually completely expired when it reaches the lungs, there is no recirculation of the radioactivity. Therefore, the activity seen by the detector declines progressively. The rate at which the xenon is carried away from the tissue, the disappearance slope, depends upon two factors, first, the rate of blood flow, and second, the relationship between tissue and blood concentration at equilibrium, that is, the proportionality constant. This constant, λ, has been measured for normal liver *(Conn,* 1961), so that in these normal patients disappearance slope can be converted to blood flow, using the following formula *(Lassen, Lindbjerg,* and *Munck,* 1964).

$$\underset{\text{(ml/min/100 g)}}{\text{Blood Flow}} = 100 \times \ln 10 \times \lambda \times \underset{\text{(log units/min)}}{\text{Disappearance slope}}$$

By recording the logarithm of activity, the disappearance slope then becomes merely the rate at which the curve declines, i. e. log units/min. For a more detailed and rigorous description

* Obtained from the Radiochemical Centre, Amersham, England.

** AB Nucleonics Instrument Co., Göteborg, Sweden.

*** Linear and Logarithmic Potentiometric Recorder, Beckman Instrument Co., Fullerton, Calif.

of the theoretical basis of this method, the reader is referred to the original publication of *Lassen, Lindbjerg,* and *Munck* (1964).

Several aspects of the technique deserve emphasis. First, it is essential that the conditions for diffusion equilibrium of the isotope be as optimal as possible. This requires small volumes of injectate administered slowly, and absolute certainly that no air bubbles are injected, since the xenon will preferentially enter the air bubble rather than the venous return. Second, since the calculations are based in part on the assumption that there is no recirculation of the xenon, the anesthetic system must always be changed from a closed one to an open one while these measurements are being carried out, to allow the xenon to escape. Third, since the lung is the pathway of exit for the xenon, the detector must be placed in such a way that while it sees liver, it does not see lung.

Results

Fig. 1 shows the disappearance slope of the xenon as obtained with the logarithmic recording technique in a typical case. The patient a 43 year old woman was operated upon for cholecystitis. At operation the gallbladder which was inflamed and contained several small stones was removed, and following that the liver blood flow was determined by the intrahepatic injection of radioactive xenon. The disappearance slope in this case was 0.341 log units/min. Using 0.7 for λ, one then obtaines a blood flow of 55 ml/min/100 g tissue.

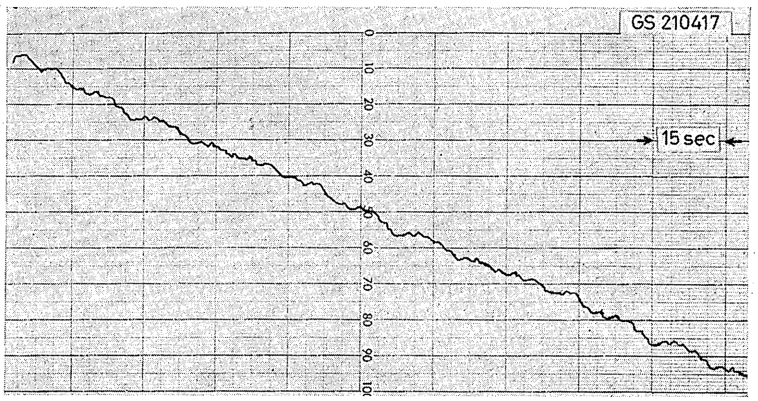

Fig. 1 (GS 210417) Representative tracing of disappearance slope of radioactive xenon from liver. Full scale (0 to 100) is one decade, i. e. 1,000 log units. Value shown is 0.341 log units/min or blood flow of 55 ml/min/100 g.

In 4 of the patients it was possible to investigate the effect of temporary occlusion of the main hepatic artery. Fig. 2, for purposes of demonstration, shows the effect of a brief occlusion. The flow is reduced immediately upon occlusion of the vessel, and increased immediately upon release. In Fig. 3 is demonstrated the effect of a short-term occlusion of the portal vein, carried out in this and one other patient. As with arterial occlusion, the responses are immediate. In all instances studied thus far there has been no readily recognizable reactive hyperemia following release of the occlusion, even for periods of occlusion in excess of 5 min.

Table 1 lists the disappearance slopes and calculated blood flows obtained with all succesful injections in all 11 patients studied.

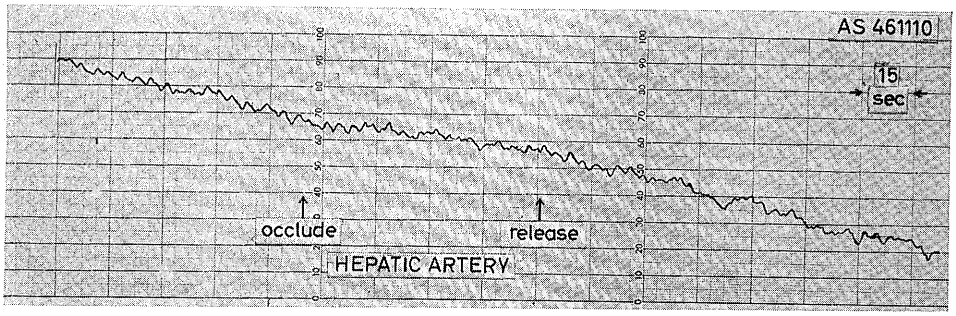

Fig. 2 (AS 461110) Effect of temporary hepatic artery occlusion on disappearance slope. Occlusion decreases flow from 27 to 15 ml/min/100 g, with a value of 32 after release of occlusion.

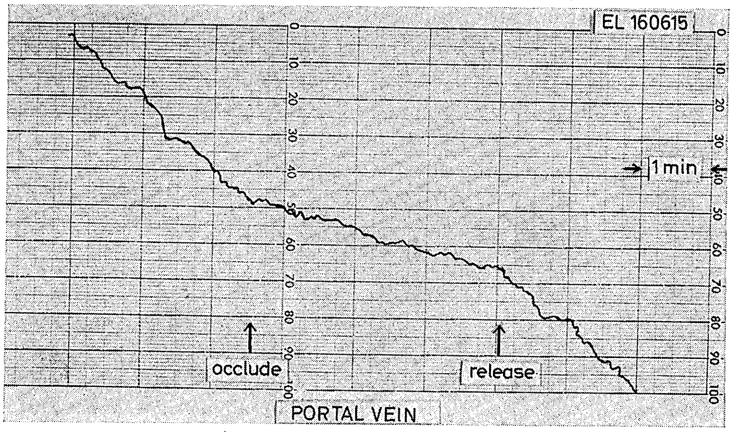

Fig. 3 (EL 160615) Effect of temporary portal vein occlusion on disappearance slope. During occlusion the flow was reduced to 8 ml/min/100 g from a pre-occlusion value of 29. With release of occlusion flow returns to 27.

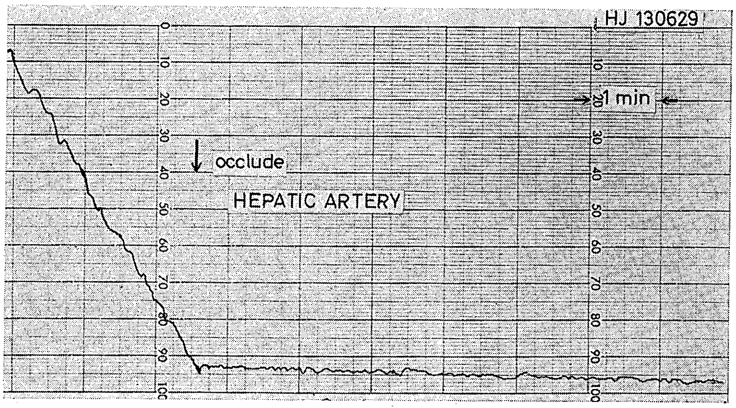

Fig. 4 (HJ 130629) Effect of temporary hepatic artery occlusion on the disappearance slope in a patient with complete occlusion of the portal vein by tumor. During occlusion the flow is reduced virtually to zero.

Table I Liver Blood Flow Measurements

Pt	Sex	Age	Diagnosis	Disappearance Slope, Log units/min	Flow ml/min/100 g	Remarks
JM	F	62	Ca Pancreas	0.158	25	
				0.169	27	
BB	F	30	Cholelithiasis	0.427	69	
				0.380	61	Hept. Art. occluded
				0.391	63	Hep. art. open
BO	M	43	Cholelithiasis	0.098	16	low BP which cont. to fall, measurements not continued
MK	F	62	Duodenal ulcer	0.072	12	flow measured after
				0.037	6	gastrectomy
FL	M	57	Cholelithiasis	0.460	74	
AC	M	76	Adenoma of stomach	0.216	35	after gastrectomy
				0.177	29	
EL	F	34	Duodenal ulcer	0.194	31	after gastrectomy
				0.240	39	
IP	F	39	Cholelithiasis	0.080	13	low BP
				0.043	7	Hep. art. occluded
				0.075	12	Hep. art. open
				0.054	9	Hep. art. occluded
				0.075	12	Hep. art. open
GS	F	43	Cholelithiasis	0.286	46	
				0.341	55	
AS	F	18	Cholelithiasis	0.170	27	low BP
				0.094	15	Hep. art. occluded
				0.199	32	Hep. art. open
				0.064	10	Portal vein occluded
				0.181	29	Portal vein open
EL	F	49	Cholelithiasis	0.144	25	Hep. art. occluded
				0.178	29	Hep. art. open
				0.052	8	Portal vein occluded
				0.168	27	Portal vein open

One additional case, not a "normal", seems worthy of special mention. H. J. (130629) was a 61 year old man who had had progressively deepening, painless, jaundice for several months. The laboratory data were consistent with extrahepatic biliary obstruction. At exploration it was demonstrated that the patient had a carcinoma of the gallbladder with extensive local invasion. The portal vein was of normal caliber but was enmeshed in carcinomatous tissue. The diameter of the hepatic artery was several times greater than normal, while the pulsations seemed normal. Fig. 4 demonstrates that occlusion of this vessel reduced liver blood flow virtually to zero. These was prompt restoration to the control value following release of the occlusion. The physiological evidence that the blood supply to the liver in this patient was solely by way of the hepatic artery was confirmed anatomically subsequently at autopsy by demonstration of complete obstruction of the portal vein by tumor.

Discussion

What is being measured here is the rate of disappearance of xenon from the liver. While there can be little argument with this, there is the question as to what extent this reflects blood flow. The most important requirement for this is that the xenon be in diffusion equilibrium with the tissues. It was noted that with a large injection bolus one obtained a constantly decreasing disappearance rate, suggesting that equilibrium had not been obtained. Using small volumes of injectate in one area resulted in a single disappearance slope for at least 7 min. suggesting though not proving that an equilibrium state had existed. While it is true that the bile and the lymph represent two additional pathways of disappearance for the xenon, their rates of flow are so low compared with the blood flow, that the error thus induced must be small indeed. If then the disappearance rate of the xenon can be said to be proportional to the blood flow, conversion to actual flow values depends upon knowing the tissue/blood partition coefficient, λ. This coefficient varies from tissue to tissue for xenon, particularly as regards fat. Since the fat content of the liver can vary from person to person, it would be expected that there would be a degree of uncertainty concerning λ. In these patients no one had a fatty liver, and the value for normal liver has been used. However, until such time as the range of spread for λ for liver in patients at operation can be determined, no attempt can be made seriously to defend this value. In point of fact, the most important reason for developing this method was to detect changes in blood flow over relatively short periods of time. For this purpose exact knowledge of λ, while undoubtedly of value, is not essential.

If one can accept the major premises set forth, then it can be said that liver blood flow has been measured. Two points are relevant here. First, the blood flow measured is only that where the injection has been made, that is to say, regional or local blood flow. It may not, and indeed probably does not reflect the flow in all parts of the liver. It should be clear, therefore, that one can neither compare this method with the BSP method, nor consider that it can replace it. Undoubtedly one can inject xenon precutaneously into the liver, and excluding the lung from the sight of the detector obtain liver blood flow in the intact, unanesthetized patient, as with the BSP method. It is still a local flow and not a total flow as measured with BSP. The fact that it is local flow method gives it certain possibilities not heretofore available with liver blood flow methods. One such is discussed in the following paper. Injecting the isotope into the vascular supply as done by *Rees, Redding,* and *Ashfield* (1964) in dogs brings the radioactive inert gas method closer to the BSP method. We have used injection into the vascular supply more for measurement of renal blood flow than of hepatic blood flow *(Lewis* and *Bergentz,* 1966). Second, since the xenon must leave the tissue via the capillary this method measures only that flow in which blood is in diffusion equilibrium with the tissues. Blood passing through the organ but not coming in contact with the tissue, i. e. shunts, is not measured with this method. In this respect it can be said to measure nutritional flow rather than total perfusion.

As expected, occlusion of the portal vein caused a more profound decrease in blood flow than occlusion of the hepatic artery, which is in agreement with previous data on this point *(Bradley,* 1963). The question as to extent of acute adaptation to vascular occlusion in man remains to be settled by further investigations. Concerning long-term adaptation, the observation in patient H. J. indicated that here the hepatic artery had taken over for what must have been a gradual occlusion of the portal vein. It is also known that the normal human liver can withstand permanent complete occlusion of the hepatic artery *(Brittain, Marchioro, Hermann, Waddell,* and *Starzl,* 1964). It is doubtful, however, if sudden permanent occlusion of the portal vein could be tolerated.

Of interest too is the observation that in each case with release of the occlusion, the flow returned promptly to the control region. There appeared to be no significant phase of reactive hyperemia as is seen in skeletal muscle. Since a reactive hyperemia must be associated with vascular dilatation, its absence in the liver would suggest that the vessels are maximally dilated.

Summary

1. A method for the measurement of regional liver blood flow in man at the time of abdominal surgery has been described, and the results in a series of 11 patients presented. Values of from 6 to 74 ml/min/100 g tissue have been observed.

2. The method is based upon the measurement of the rate of disappearance of radioactive xenon (^{133}Xe), externally detected, from the liver following intrahepatic injection. The method is rapid, simple, and does not require the analysis of blood samples.

3. The effect of hepatic artery occlusion (4 patients and portal vein occlusion (2 patients) has been noted. In one additional patient, complete obstruction of the portal vein by tumor invasion was demonstrated physiologically by the observation that temporary hepatic artery occlusion reduced the flow to zero.

4. The advantages and limitations of the method are discussed.

Zusammenfassung

1. Eine Methode für die Messung des menschlichen regionalen Leberblutstroms im Verlauf von abdominellen Operationen wird beschrieben. Die Resultate von Untersuchungen an 11 Patienten werden angeführt, Werte von 6–74 ml/min/100 g Gewebe wurden beobachtet.

2. Die Methode basiert sich auf der Messung der Abfallrate von radioaktivem Xenon (^{133}Xe) in der Leber bei externer Messung. Die Methode ist schnell, einfach und erfordert keine Untersuchung von Blutproben.

3. Der Effekt des Verschlusses der Arteria hepatica (4 Patienten) und der Vena portalis (2 Patienten) wurde beschrieben. Bei einem weiteren Patienten konnte ein totaler Verschluß der Vena portalis durch Tumorinvasion aufgewiesen werden. Es zeigte sich, daß ein temporärer Verschluß der Arteria hepatica den Blutstrom auf Null reduzierte.

4. Die Vorteile und Grenzen dieser Methode werden diskutiert.

Résumé

1. Description d'une méthode pour la détermination du débit sanguin dans le foie de l'homme au cours d'interventions abdominales. Présentation des résultats des examens effectués chez onze malades; les auteurs ont observé des valeurs de 6 à 74 ml/min par 100 gr. de tissu.

2. La méthode repose sur la détermination du taux de désintégration du xénon radioactif (^{133}Xe) dans le foie par des mesures externes. Elle est rapide, simple et ne nécessite aucun examen de plusieurs prélèvements sanguins.

3. Description de l'effet produit par une oblitération de la veine porte (deux malades) et de l'artère hépatique (quatre malades). Chez un autre malade, les auteurs purent constater une oblitération totale de la veine porte par l'envahissement tumoral. Ils ont en outre observé une supression totale du courant sanguin à la suite d'une oblitération momentanée de l'artère hépatique.

4. Discussion des anvantages et des limites de cette méthode.

Resumen

1. Se describe un método de medida de la irrigación sanguínea en diversas zonas hepáticas durante operaciones de abdomen. Se exponen los resultados de ensayos con once pacientes. Se observaron valores de 6–74 ml/min/100 g de tejido.

2. El método se basa en la medida de la velocidad de disminución de xenon radiactiva (^{133}Xe) en el hígado por medición desde el exterior. El método es sencillo, rápido y no se precisa el ensayo de diversas muestras de sangre.

3. Se describe el efecto de la oclusión de la arteria hepática (4 pacientes) y de la vena porta (2 pacientes). En otro paciente se pudo demostrar una oclusión total de la vena porta por invasión tumoral. Se observó que la oclusión temporal de la arteria hepática reduce a cero la corriente sanguínea.

4. Se discuten las ventajas y límites de este método.

Literature

Bradley, S. E.: The hepatic circulation, in Hamilton, W. F., P. Dow (ed) Handbook of Physiology. Section 2 Circulation, Volume II, p. 1387. Washington, D.C.. Amer. Phys. Soc. 1963

Bradley, S. E., F. J. Ingelfinger, G. P. Bradley, J. J. Curry: The estimation of hepatic blood flow in man. J. clin. Invest. 24 (1945), 890

Brittain, R. S., T. L. Marchioro, G. Hermann, W. R. Waddell, T. E. Starzl: Accidental hepatic artery ligation in humans. Amer. J. Surg. 107 (1964), 822

Conn, H. L. jr.: Equilibrium distribution of radioxenon in tissue: xenon-homoglobin association curve. J. Appl. Physiol. 16 (1961), 1065

Lassen, N. A., F. Lindbjerg, O. Munck: Measurement of blood-flow through skeletal muscle by intramuscular injection of Xenon-133. Lancet 1964/I, 686

Lewis, D. H., S.-E. Bergentz: Renal blood flow measurement with Xenon,133 at the time of operation for renal artery stenosis. Surgery 59 (1966), 1043

Rees, J. R., V. J. Redding, R. Ashfield: Hepatic blood flow measurement with Xenon 133. Lancet 1964/II, 562

Prof. Dr. L.-E. Gelin, Dr. D. H. Lewis, L. Nilsson, M. D. Göteborgs Universetet Medicinska Fakulteten Kir. klin. I Sahlgrenska Sjukhuset Göteborg/Schweden